Pregnancy outcomes of women with Type 2 and gestational diabetes mellitus (GDM): specific focus on client engagement with health professionals, diagnosis of GDM and supplementation with omega 3 fatty acids.

A thesis submitted in fulfilment of the requirements of the London Metropolitan University for the degree of Doctor of Philosophy (PhD)

by

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Dedication

This thesis is dedicated to ‘mummy Cilma’ and late ‘daddy Indian’ who have sacrificed to give me the education which I have. Mummy, you have been exceptional. You have taught me a lot for which I am profoundly grateful and will forever be indebted to you.

Also, this is dedicated to my adorable husband Brian whose love and support has brought me to the end of this journey.

Author's statement

I wish to certify that I am the author of this thesis entitled 'Diabetes and Pregnancy: Client engagement, diagnosis and lipid nutrition' which is submitted in support of my PhD work.

The data supporting this thesis is my original work which I have used to undertake the statistical analyses, interpretation of the results and writing up of the thesis.

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Abstract

Background:

Maternal nutrition is essential to the well being of mother and baby during pregnancy and beyond. It is necessary for effective placental accretion, foetal growth and development and optimal pregnancy outcomes. Adequate nutrition becomes even more critical when pregnancies are complicated with diabetes of any type which includes type 2 diabetes mellitus (T2 DM) and gestational diabetes mellitus (GDM). Complementary to other lifestyle factors, nutrition forms the cornerstone for achieving euglycemia to reduce potential maternal and foetal risks associated with diabetes in pregnancy such as macrosomia, hypertensive disorders and preterm birth.

T2 DM and GDM are characterised by insulin resistance which affects effective beta cells function in the secretion and synthesis of insulin. Additionally, reduced levels of arachidonic acids (AA) (omega 6 fatty acids) and docosahexaenoic acids (DHA) (omega 3 fatty acids) have been found in maternal red blood cells in pregnancies complicated with diabetes. AA and DHA cannot be produced by the body and must be ingested by the mother. Foetal demands for these fatty acids are high and these are transferred by placental selection from maternal to placental circulation. It is reported that diabetes impairs the activity of delta-6 and delta-5 desaturases which are enzymes necessary for the synthesis of AA & DHA. Recent studies have reported significantly lower levels of AA & DHA in the red blood cells of pregnant women with GDM and T2 DM, resulting in a depletion in placental uptake and transfer of these fatty acids to the foetus and adequate supply for the mother, which if remains untreated, may have adverse impact on maternal, foetal and neonatal health in the short- and long-term. Therefore, women in these high risk groups need to effectively engage with health care professionals (HCPs) involved in their care and the services offered to them.

Insulin therapy and supplementation with these essential fatty acids may correct this depletion. However, the impact on pregnancy outcome remains unknown. Newham is one of the most deprived boroughs of London and has a high prevalence and incidence of diabetes. Therefore, by evaluating the pregnancy outcomes of women with T2 DM and GDM after supplementation with essential fatty acids (EFAs), the local service needs would be better understood, and vital answers would be provided to optimise the pregnancy outcomes for this client-group which already has complex health needs.

Aims

This study investigated: -

(1) Socio-cultural and economic factors which influence engagement of pregnant women with health care professionals; (2) The impact of early detection of gestational diabetes mellitus (GDM) on pregnancy outcome and postnatal maternal health; and (3) The effect of omega-3 fatty acid supplementation on the outcome of pregnancy in women with GDM and (4) type 2 diabetes.

Method

Pregnant women 17-45 years with diabetes (T2 DM and GDM) and without diabetes and booked at Newham University Hospital were recruited during antenatal or home visits.

In Phase 1 of the study, diabetic (n=594) and non-diabetic (n=243) pregnant women were recruited during antenatal or home visits in the first, second and third (up to 32 weeks gestation) trimesters. Detailed demographic, socio-cultural and economic data and the interactions of women with HCPs and reasons given by women for their engagement or non-engagement with HCPs were collected using a questionnaire developed for the study.

In Phase 2, pregnant women diagnosed with GDM before 24 (n=212) and after 24 (n=226) weeks of gestation were recruited after diagnosis on OGTT and up to 32 weeks gestation. Demographic, socio-cultural, economic and clinical and obstetric data were collected from hospital records and from the participants with the use of a questionnaire.

One hundred fifty (n=149) women diagnosed with gestational diabetes were recruited up to 32 weeks gestation and randomised and given DHA (n=75) or high oleic acid sunflower seed oil placebo (n=74) supplement until delivery, in Phase 3. Comprehensive data was collected on diabetes management regimen, pregnancy complications (preeclampsia, miscarriage, preterm labour, etc.), foetal outcome (prematurity, macrosomia, low birth weight, neonatal admission to special care baby unit, etc.) and postnatal glycaemic status. Also, detailed demographic, socio-cultural and economic information was gathered with a questionnaire designed for the study.

In Phase 4, pregnant women with type 2 diabetes (n=96) were recruited up to 17 weeks gestation during their antenatal visits. They were randomised into two groups and given DHA (n=47) or high oleic acid sunflower seed oil placebo (n=49) capsules until delivery. Similarly, their matching controls (non-diabetics) (n=89) were also recruited in the first trimester on their maternity booking appointments or on antenatal clinic visits, and randomised and given DHA (n=40) and placebo

(n=49). Demographic, socio-cultural, economic and maternal and foetal outcomes were collected and documented rigorously, using a questionnaire designed for the study.

Results

Phase 1

Socio-economic, cultural and demographic factors are influential in a pregnant woman's decision on whether or not to engage with HCPs. For Asian Muslims, strong decision-making indicators were their ability to speak English (***p <0.001***), husband and/or family involvement (***p <0.000***) and adequate time to make a decision. Being a singleton (***p <0.001***), non-Asian (***p <0.002***) Christian (***p <0.001***) enabled a prompt response to engage. Professional women and those in intermediate jobs (***p <0.026***) and women whose partners were similar jobs (***p <0.006***) engaged better with HCPs.

Engagement with HCPs reduced the development of complications in pregnancy (***p <0.001***) but had no positive effect on birth outcome. Stillbirth, neonatal death and miscarriages were more common among engaged women. Non-engaged women had more term babies and reduced incidence of preterm births and hypertensive disorders (PIH, pre-eclampsia or eclampsia) (***p <0.006***) Engagement made no difference to onset of labour (***p < 0.283***), mode of delivery (***p < 0.366***), and neonates admission to special care baby unit (***p < 0.400)***. Low birth weight infants and macrosomia was approximately two-fold higher among non-engaged women (***p < 0.037***).

Phase 2

Family history and BMI ≥30 were strong indicators for screening for gestational diabetes mellitus (GDM) (***p <0.291***). Women diagnosed with GDM <24 weeks gestation had better pregnancy outcomes than women diagnosed >24 weeks gestation. Women who were diagnosed <24 weeks gestation, premature birth was 13% (26), other groups 3.6% (7) {stillbirth 1% (2), neonatal death 0.5% (1), miscarriages 2% (4)} and the remaining 83% (163) delivered at full term. For those who delivered after 24 weeks, 84% (182) delivered at full term with 17% (36) delivered prematurely (***p <0.014***). Of those diagnosed before and after 24 weeks gestation, 1% / 2% had macrosomia, 12% / 8% low birth weight and the remainder were normal 88% / 90%, respectively (***p <0.380***). Post-delivery, of women with GDM diagnosed <24 weeks, 25% had abnormal OGTT of which 12 % were diagnosed with T2 DM. In the ≥24 weeks group, 4% had T2 DM and 9% had either impaired glucose tolerance (IGT) (blood glucose between 7.8 & 11.1mmol/l after 2 hours glucose load) or impaired fasting glucose (IFG) (fasting glucose >6.1mmol/l). Overall, twenty-five (16 %) were diagnosed with T2 DM and 23% had either IGT or IFG on postnatal OGTT (***p <0.010***).

Phase 3

The demographic and clinical characteristics of the women in the supplemented and non-supplemented groups were similar. Omega-3 fatty acid supplementation had no effect on maternal and foetal health and pregnancy outcomes and postnatal glycaemic control of women with GDM. There was no difference in onset of labour (***p <0.328***), **i**nduction of labour (***p <0.368***), reasons for induction (***p <0.616***), caesarean section rates (***p <0.294*)**, prolonged pregnancy (***p <0.285***), reduction in pre-term birth (***p <0.096***), macrosomia (***p <0.124***), low birth weight infants (***p <0.124***), hypertensive disorders of pregnancy (***p <0.826***) and postpartum glycaemic control (***p <0.485***). The incidence of stillbirth (n=1), miscarriage (n=1) and neonatal death (n=1) was found only in women without active treatment, but this was not statistically significant (***p <0.096***).

Phase 4

Fish oil supplementation had a positive impact on birth maturity (***p <0.005***) and reduced pre-term births (***p <0.011***). Less neonates were admitted to SCBU among women with T2 DM (***p <0.017***), and had elective caesarean sections (***p<0.007***). The overall caesarean section rate was also reduced and this was nearing significant ***p <0.060***. Fish oils supplementation had no impact on reducing the rate of induction (***p <0.129***) and admission to SCBU (***p <0.678***) and birth weight (***p <0.932***). Glycaemic control was also not impacted by fish oils supplementation ***(p<0.255)***.

<u>Conclusion:</u>

The findings of this study have demonstrated that NICE current guidelines on screening for the early detection of GDM are inappropriate for use in communities like Newham with a high disposition of DM. In communities like Newham which are genetically susceptible to T2 DM, risk factors for early screening for GDM should be family history of diabetes and BMI $\geq$30kg/m^2 , as well as previous history of GDM. Early detection of GDM within these groups will facilitate the reduction of adverse birth outcomes.

Results from this study also demonstrated that some benefits can be achieved from taking fish oils in pregnancy, particularly among women with T2 diabetes. Although some pregnancy outcome measures were not improved, fish oils supplementation as an adjunct management option for diabetics should be considered but further evidence is needed to substantiate these findings.

To optimise maternal and foetal outcomes, women with diabetes in pregnancy need adequate and flexible holistic care options, to enable them to make informed choices that would be in the best interest of them and their babies.

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Abbreviations

AA	arachidonic acid
BAME	Black, Asian and Minority Ethnic
BG	blood glucose
BGLs	blood glucose levels
BMI	body mass index
CS	caesarean section
DCCT	diabetes control and complications trial
DHA	docosachexaeonic acid
DSM	diabetes specialist midwife
DSN	diabetes specialist nurse
EASD	european association for the study of diabetes
EFAs	essential fatty acids
EPA	eicosapentaenoic acid
GBP	great British pounds
GDES	gestational diabetes education session
GDM	gestational diabetes mellitus
GPs	general practitioners
HAs	health advocates
HLE	healthy life expectancy
HBA1c	glycaeted haemoglobin
HDL	high density lipoprotein

HCPs	health care professionals
IFCC	international federation of clinical chemistry
IOL	induction of labour
IUGR	intrauterine growth retardation
LA	linoleic acid
LCPUFA	long chain polyunsaturated fatty acids
LDL	low density lipoprotein
LMU	London Metropolitan University
MMR	Maternity mortality ratio
NEFAs	non-esterified fatty acids
NICE	National Institute for Health and Care Excellence
NUH	Newham University Hospital
O^2	oxygen
ONS	office of national statistics
OGTT	oral glucose tolerance test
PE	pre-eclampsia
PI	ponderal index
PIH	pregnancy induced hypertension
PIL/s	patient information leaflet/s
PUFA	polyunsaturated fatty acids
RCTs	randomised controlled trials
SADC	specialist antenatal diabetes clinic
SBGM	self blood glucose monitoring

SCBU	special care baby unit
SD	standard deviation
SFA	saturated fatty acids
SFD	small for dates
T1 DM	type 1 diabetes mellitus
T2 DM	type 2 diabetes mellitus
WHO	World Health Organisation
UK	United Kingdom

Operational Definitions

Abstract	A brief description of a completed or proposed study; usually located at the beginning of the study/journal article.
Advocacy	Help given to patients by an advocate who can be a family member, friend or independent representative, to enable them to know the services that are available to them, their rights and entitlement and support to enable them to express their opinions and make informed decisions.
Advocate	A family member, friend or independent representative who has been given the authority to act on behalf of patients.
Afro-Caribbean	Refers to women of African or Caribbean origin.
Alpha-linoleic acid	An omega-3 fatty acid found in plant-based seeds and oils from foods like flaxseed, walnut, soy, chia and hemp.
Amino acids	The building blocks of proteins.
Anabolic state	A state where the body builds and repairs muscle tissues.
Anaemia	Refers to iron deficiency anaemia. Anaemia is the reduced level of red blood cells in the blood to carry oxygen to the tissues of the body. The deficiency can be treated with iron.
Analysis	A process of organising and synthesizing data in such a way that research questions can be answered, and hypotheses tested.
Antenatal	Refers to the period of pregnancy form conception and throughout to before birth.
Antepartum	Refers to the period of pregnancy form conception and throughout to before birth.
Apgar scores	Scoring system used to assess newborn at interval of 1, 5 & 10 minutes after they are born. The maximum score is 10. A total of 2 is awarded for each for the following: A- appearance, P- pulse, G- grimace, A- activity, R- respiration. Low APGAR may indicate that the baby needs special care intervention.
Applications	The tasks that computers can be used to perform (e.g. word processing, database management, statistical analysis).
Arachidonic acid	A polyunsaturated omega-6 fatty acid found in the phospholipids of membranes of the cells of the body. It is abundant in the brain, muscles and liver. It can be synthesised by linolenic acid.
Asian	Refer to women of Pakistani, Bengali, Indian, Chinese and any other Asian background.
Assisted delivery	Any delivery conducted vaginally, aided by the use if instruments, such as vacuum extractor or forceps. Any delivery conducted vaginally, without the aid was considered normal.
Autoimmune	Relating to disease caused by antibodies or lymphocytes produced against substances naturally produced in the body.

Bias	Any influence that produces a distortion in the results of a study.
Birth maturity	Delivery or birth from 37 to 42 weeks of gestation.
Blinding	The concealment of the trial drug the subject of a study is taking from one or more individuals eg. research subjects and investigators/researchers.
Booking	Also referred to as the booking appointment in which the women enters the maternity care pathway. The first antenatal appointment a pregnant woman has with her midwife in which comprehensive history is taken from the woman to plan her pregnancy care.
Caesarean section	A surgical procedure used to deliver a baby through incision in the abdomen and uterus.
Caesarean section - planned / elective	Booked dated for delivery by caesarean section, whatever the reason/s.
Caesarean section - emergency	Delivery by caesarean section resulting from women status requiring immediate intervention.
Candidiasis	A fungal infection caused by a yeast candida
Cardiotocograph	An electronic foetal heart monitor
Cellulitis	An infection caused by bacteria getting in the deep layer of the skin.
Clinical Commissioning Group	Formed in 2010 and consists of several GPs and other health professionals who are responsible for the purchasing of healthcare.
Co-morbidity	The relationship between two or more diseases or conditions.
Congenital abnormality	Any malformation(s) discovered prior to or immediately after birth.
Constructivist	One who believes that people actively construct or make their own knowledge and that reality is determined by your experiences as a learner.
Cortisol	A steroid hormone often described as the 'fight and flight hormone' which is designed to sense and alert danger.
Data collection	The gathering of information needed to address a research problem.
Data entry	The process of entering data onto an input medium for computer analysis.
Deductive Reasoning	The process of developing specific predictions from general principles.
Delivery	The birth of the baby.
Demography	The make-up of a population. Often includes one's age, sex, religion, nationality, culture, etc.
Dependent Variable	The outcome variable of interest; the variable that is hypothesized to depend on or be caused by another variable, the independent variable.
Deprivation	The state of poverty

Descriptive Research	Research studies that have as their main objective the accurate portrayal of the characteristics of persons, situations, or groups and/or the frequency with which certain phenomena occur.
Diabetic fetopathy	Features seen in the hyperinsulinemic foetus of a diabetic mother which includes macrosomia, postnatal hypoglycaemia, polycythemia etc.
Diabetic status	The type of pre-existing diabetes condition (Type 1 or Type 2) or whether developed during pregnancy.
Docosachexaeonic acid	An omega-3 fatty acid that is a primary structural component of the human brain, cerebral cortex and retina. It can be synthesised by alpha-linolenic acid.
Double blind	A randomised clinical study in which the subjects and the researchers are unaware of what group the subjects are allocated, that is, the experimental treatment (standard treatment) or the placebo group.
Eligibility criteria	The criteria used by a researcher to designate the specific attributes of the target population and by which participants are selected for participation in a study.
Embryo	The unborn infant in the process of development in utero.
Empirical evidence	Evidence that is rooted in objective reality and that is gathered through the collection of data using one's senses; used as the basis for generating knowledge.
Empiricist	One who believes that knowledge is based on experience derived from the senses.
Epigenetics	The study of changes in organisms caused by modification of gene expression rather than the genetic code itself.
Epistemological	Relates to all aspects of validity, scope and methods of acquiring knowledge.
Essential fatty acids	Fatty acids that must be ingested because the body requires them for good health but cannot synthesize them.
Ethics	A system of moral values that is concerned with the degree to which research procedures adhere to professional, legal and social obligations to the study participants.
Ethnography	A branch of human inquiry, associated with the field of anthropology that focuses on the culture of a group of people, with an effort to understand the world view of those under study.
Euglycemia	A normal concentration of glucose in the blood
Experiment	A research study in which the investigator controls (manipulates) the independent variable and randomly assigns subjects to different conditions.
Foetal gene expression	The expression of specific genes in the foetus to a particular genotype
Foetal programming	Foetal programming is also referred to as prenatal programming and occurs during the embryonic and foetal developmental stages during pregnancy. It is theorised that the environment surrounding the foetus during the

	developmental phase determines the disease risk during the later stages of pregnancy and throughout to adulthood.
Findings	The result of the analyses of the research data; in quantitative studies, the results of the hypothesis tests.
Functional illiterates	Patients with reading and writing skills that are inadequate to manage daily living and employment tasks requiring reading skills beyond basic level.
Further education	Refers to education at A levels up to Diploma levels.
Generalizability	The degree to which the research procedures justify the inference that the findings represent something beyond the specific observations on which they are based; in particular, the inference that the findings can be generalized from the sample to other settings or an entire population.
Glucose	A simple sugar which is an important energy source. It is a component of carbohydrates.
Glycaemia	The presence of glucose in the blood
Glycaemic control	Refers to the level of blood glucose control in someone with diabetes
Glycogen	Glucose stored as carbohydrates in the tissues of the body.
Gluconeogenesis	A pathway used by the body to create glucose from other molecules. Through this process, the body stores energy for the brain in the form of glucose.
Haemorrhage	Bleeding from a blood vessel
HBA1c	Refers to glycated haemoglobin which identifies average plasma glucose concentrate in one's blood.
Health advocate	A translator of direct service to non-English speaking pregnant women to assist and support them to make health care decisions that is appropriate to their individual needs.
Health care professionals	Refer to the clinicians and allied health professionals involved in the care of the women in this study. They include obstetricians, diabetologists, midwives, dieticians & health advocates.
Hepatic	Relates to the liver
Higher education	Refers to education at degree level and above.
High density lipoprotein	Commonly referred to as 'good' cholesterol.
Homeostasis	Characteristics of a system that regulates its internal environment to a level of stability.
Hormone	A chemical substance produced in the body that controls and regulates the activity of certain cells or organs.
Human placental lactogen	A hormone produced by the placenta. It breaks down fat from the mother to provide fuel for the growing foetus and this can lead to insulin resistance and carbohydrates intolerance in the mother.

Hyaline membrane disease	A condition in the newborn in which the lungs are deficient in surfactant, which prevents their expansion and causes the formation of hyaline material in the lung spaces.
Hyperglycaemia	Blood sugar level much higher than normal range. ≥5.6 mmol/l on fasting and ≥7.8 mmol/l post meals.
Hypoglycaemia (neonatal)	Measurement of blood glucose levels lower than 2.5mmols/l during the first 48hrs of life.
Hyperinsulinemia	Excessive levels of insulin circulating in the blood relative to the blood glucose level.
Incidence	Refers to the number of new cases diagnosed with a disease in a given area over a given period of time.
Induction of labour	The use of local prostaglandins with or without the use of intravenous infusion of oxcytocin to induce labour. This could follow the artificial or spontaneous rupture of membranes.
Interpretivist	A tradition from qualitative research. Combines qualitative data with propositions that can be tested into systems of beliefs whose manifestations are specific to a case.
Intrapartum	The period of pregnancy from onset of labour and throughout to the birth of infant/s.
In utero	In the woman's womb; before birth.
Ketogenesis	The biochemical process through which organisms produce ketone bodies through the breakdown of fatty acids and ketogenic amino acids.
Level of Significance	Is the probability of rejecting the null hypothesis when it is true; for example, a significance level of 0.05 indicates a 5% risk of concluding that a difference exists when there is no actual difference.
Linoleic acid	An omega-6 fatty acid found mainly in plant-based oils eg vegetable oils. It is used in the biosynthesis of prostaglandins and cell membranes.
Lipogenesis	The metabolic formation of fat.
Lipolysis	The breakdown of fats and other lipids by hydrolysis to release fatty acids. Hydrolysis is the chemical breakdown of a component due to reaction with water.
Longitudinal study	A study designed to collect data at more than one points over short of long periods of time.
Low density lipoprotein	Commonly referred to as 'bad' cholesterol.
Macrosomia	Birth weight greater than 4000g regardless of the gestational age.
Macro-vascular diseases	Diseases causing damage to the larger blood vessels.
Manipulation	An intervention or treatment introduced by the researcher in an experimental or quasi-experimental study' the researcher manipulates the independent variable to assess its impact on the dependent variable.

Mean	Often refers to the average of occurrence of a variable. A measure of central tendency, computed by adding all scores and dividing by the number of subjects.
Measurement	The assignment of numbers to objects according to specified rules to characterize quantities of some attribute.
Median	A descriptive statistic that is a measure of central tendency, representing the exact middle score or value in a distribution of scores; the median is the value above and below which 50% of the scores lie.
Metabolite	A substance formed in or necessary for metabolism.
Metabolise	The process by metabolism
Metabolism	The chemical processes which occur within a living organism in order to maintain life.
Methods (research)	The steps, procedures and strategies for gathering and analysing the data in a research investigation.
Micro-vascular diseases	Diseases causing damage to the smaller blood vessels.
Migration	The movement of people in and out of an area.
Miscarriage	Defined as any spontaneous onset of delivery before 24 weeks gestation.
Mode of delivery	Refers to the means by which the baby was born.
Molecule	The smallest particle in a chemical element or compound that has the chemical properties of that element or compound.
Monounsaturated fatty acids	Essential fatty acids that help develop and maintain the body's cells. They must be ingested because they cannot be synthesized by the body. They are classified as good fats and they help to lower bad cholesterol levels.
Morbidity	An alternative way of describing death.
Morphology	The study of how things are put together.
Mortality	The occurrence of an illness or disease.
Multigravida	A woman with one or more children.
Myoinositol	A vitamin-like compound structurally similar to glucose which is involved in the way the cells of the body communicate.
Naturalistic	Imitating real life or nature
Neonatal	A newborn infant under 28 days of age.
Neonatal death	Death of babies under four weeks of life.
Neonatal jaundice	Yellow discoloration of the baby's skin up to ten days of baby's life due to high bilirubin levels.

Nephropathy	Disease of the kidney caused by damage to the small blood vessels or the units of the kidneys that clean the blood.
Neuropathy	Disease or dysfunction of one or more peripheral nerves typically causing weakness or numbness.
Nominal Measure	The lowest level of measurement that involves the assignment of characteristics to categories (e.g., males = 1; females = 2).
Non-alcoholic fatty liver	A build up of fat in the liver which should otherwise have very little or no fat.
Non-esterified fatty acids	Molecules released from triglycerides and are transported to the blood bound to albumin. They provide a large part of the body's energy but only form a small part of body fat.
Normal Delivery	Any delivery conducted vaginally, without the use of instrumental aid.
Oestrogen	The primary female sex hormone responsible for the development and regulation of the female reproductive system and secondary sex characteristics.
Oligouria	The production and passing of small amount of urine. It measures <1ml/kg/hr.
Ontological	The study of the concept of existence or reality
Outcome Variable	A term sometimes used to refer to the dependent variable in experimental research; that is, the measure that captures the outcome of the experimental intervention.
Pancreas	A large gland in the stomach which secretes digestive enzymes into duodenum. In the pancreas is the islet of Langerhams which secretes hormones insulin and glycagon in the blood stream.
Paresthesia	An abnormal sensation, typically tingling or pricking, caused chiefly by pressure on or damage to peripheral nerves.
Patient engagement	Refers to the process of building the capacity of patients, families, carers professionals to facilitate and support the active involvement in their care to enhance the delivery of safe and quality care services.
Patient involvement	Where patients are actively involved in their care.
Patient participation	Involvement of patients in decision making.
Peripheral artery disease	A common circulatory problem in which the arteries become narrow reducing blood flow to the extremities of the body, usually the limbs but mainly the legs.
Peptidases	An enzyme which breaks down peptides to amino acids.
Perinatal	Pertaining to the time around birth.
Persistent pulmonary Hypertension	The failure of the normal circulatory transition that occurs after birth. This syndrome is characterised by pulmonary hypertension that causes hypoxemia secondary to right to left shunting of blood at the foramen ovale and ductus arteriosus.

Pharmacotherapy	Medical treatment by means of drugs.
Phenomenon	The abstract entity or concept under investigation in a study, most often used by qualitative researchers in lieu of the term variable'.
Phospholipids	A type of lipid molecule that is the main component of the cell membrane.
Placenta	Placental development starts during the implantation of the blastocyst. The trophoblast cells form the placenta and the inner cell mass forms the foetus and foetal cell membranes.
Ponderal Index	An indicator of relative fatness at birth measured by weight/length. Type 1 indicates that baby is proportionate while Type 2 is a low PI indicating a disproportionate measurement.
Polyuria	Excessive production of urine.
Polyunsaturated fatty acids	Essential fatty acids that help to develop and maintain cells of the body. They must be ingested because they cannot be synthesized by the body. These are considered as good fats.
Polypeptide	A linear chain of amino acids linked together. Amino acids are the basis building blocks of proteins.
Population	Number of individuals having some common characteristics, illness or disease.
Positivist	A tradition from qualitative research. A Positivist seeks to identify qualitative data with propositions that can be tested or identified in other cases.
Post maturity	Babies born after 42 weeks gestation.
Postnatal	Occurring after birth.
Postpartum	Refers to the period of pregnancy immediately after delivery and up to 6 weeks thereafter.
Prenatal	Occurring before birth.
Preterm delivery	Defined as delivery before 37 weeks gestation.
Prevalence	The number of people in a given population with a particular condition in a given time. The prevalence of a disease is calculated based on data collected and held on national registers.
Primagravida	A woman pregnant for the first time.
Progesterone	A hormone produced by the corpus luteum of the ovary. It plays an important part in the menstrual cycle and maintaining the early stages of pregnancy.
Prospective Study	A study that begins with an examination of presumed causes (e.g., cigarette smoking) and then goes forward in time to observe presumed effects (e.g., lung cancer).
Proteases	An enzyme which breaks down proteins to peptides.
Public engagement	Involves activities that bring researcher and the public

	together. It is a process of two-way communication in which there is shared learning and both groups benefit from each other.
Public involvement	Working in collaboration with patients, service users or the general public.
Qualitative research	Research using data obtained by the researcher from direct observation, focus groups, interviews, questionnaires and recordings made in natural settings.
Quantitative research	The process of objectively collecting numerical data to describe, predict or control variables of interest eg to test causal relationships.
Randomisation	The assignment of subjects to treatment conditions in a random manner (i.e., in a manner determined by chance alone); also known as random assignment.
Reliability	The degree to which a test consistently measured what it sets out to measure. It is to do with whether a test when applied repeatedly to the same objects gives the same results every time. Reliability is therefore concerned with consistency, stability and dependability. However, it is not necessarily concerned with accuracy.
Research	The attempt to obtain new and transferable knowledge. It involves systematic inquiry that uses orderly, disciplined methods to answer question or solve problems.
Research design	The plan for addressing a research question, including specifications for enhancing the integrity of the study.
Research Question	A statement of the specific query the researcher wants to answer to address the researcher problem.
Research team	Individuals involved in the conduct of the research study.
Results	The answers to research questions, obtained through an analysis of the collected data; in a quantitative study, the information obtained through statistical tests.
Retinopathy	Damage to the retina caused by abnormal blood flow. Often refers to as retinal vascular disease.
Retrospective Study	A study that begins with the manifestation of the dependent variable in the present (e.g., lung cancer) and then links this effect to some presumed cause occurring in the past (e.g. cigarette smoking).
Saturated fats	These are bad fats. They contain a high proportion of fatty acid molecules without double bonds considered to be less healthy than unsaturated fatty acids.
Significant level	The probability that an observed relationship could be caused by chance (i.e., as a result of sampling error); significance at the .05 level indicates the probability that a relationship of the observed magnitude would be found by chance only 5 times out of 100.
Socio-economic	Relating to or involving social and economic factors.
Sponsor	The organisation or partnership which takes overall

	responsibility for proportionate and effective arrangement for the set-up, running and reporting of a research project.
Spontaneous delivery	Defined as any delivery occurring naturally without any external aid.
Standard deviation	Used statistic for measuring the degree of variability in a set of scores or dispersion of statistical population.
Statistic	An estimate of a parameter, calculated from sample data.
Statistical analysis	The organisation and analysis of quantitative data using statistical procedures, including both descriptive and inferential statistics.
Statistical Significance	A term indicating that the results obtained in an analysis of sample data are unlikely to have been caused by chance, at some specified level of probability.
Statistical test	An analytical procedure that allows a researcher to determine the probability that obtained results from a sample reflects true population parameters.
Stillbirth	Birth after 24 weeks gestation and no signs of life at birth.
Subject	An individual who participates and provides data in a study; term used primarily in quantitative research.
Supplementation	The addition of an extra element – omega-3 & -6 and placebo.
Target population	The entire population in which the researcher is interested and to which he or she would like to generalise the results of a study.
Transient tachypnea	Breathing disorder seen shortly after delivery in the newborn in early term or late preterm. The condition is characterised by rapid abnormal breathing which is short-lived.
Trans fats	A form of unsaturated fat created by hydrogenation where liquid oils are converted to semi-solid fats. Trans fats can also be found in meat and dairy products.
Treatment	The experimental intervention under study; the condition being manipulated – omega 3 & omega 6.
Triacylglycerols	Known as triglycerides which are simple types of lipids consisting of 3 long chain fatty acids esterified to glycerol
Thrombocytopenia	A condition characterised by low platelets in the blood. Platelets are necessary for clotting of the blood.
Unblinding	The process by which the allocation code of the intervention or treatment are broken (revealed) and become known to the trial team /subjects etc.
Unsaturated fats	These are good fats. They contain a high proportion of fatty acid molecules with one or double bonds in the fatty acid chain and are considered to be healthier than saturated fatty acids.
Variable	The degree to which values on a set of scores are widely different or dispersed.
White	Refers to indigenous British women and Whites from Europe and other countries.

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Chapter 1:

Introduction

1.1 Introduction and structure of the thesis

1.1.1 Background

Diabetes Mellitus (DM) is one of the most common medical disorders in pregnancy (Diabetes UK, 2014). Pregnant women can present with either pre-existing DM {Type 1 diabetes mellitus (T1 DM) or Type 2 diabetes mellitus (T2 DM)} or develop the condition during pregnancy {gestational diabetes mellitus (GDM)}. A complex interplay between genetic and environmental factors can determine the aetiology of the disease type to be discussed in forthcoming chapter 2. T2 DM and GDM form the focus of this study.

Women who present in pregnancy with T2 DM and GDM pose a huge challenge for clinicians who are constantly striving to optimise the care they receive in order to reduce potential risks such as miscarriage, pre-eclampsia, macrosomia, pre-term birth, stillbirth and birth injury resulting in poorer pregnancy health and outcomes (maternal and foetal) compared to non-diabetic women (CEMACH, 2007). Consequently, the cost implications of diabetes management to the National Health Service (NHS) and society as a whole are vast (Whicher et al, 2020). To narrow this disparity, new and evolving management strategies are employed to provide the best possible care by achieving optimal glycaemic control. Management includes lifestyle advice on healthy eating and exercise. Individualised pharmacological interventions may also be necessary to normalise blood glucose control, but achieving this can at times be challenging (Antonio Negrato et al, 2012).

Adequate maternal nutrition contributes to effective glycaemic control and is essential for foetal growth and development (Ji et al, 2017; Palmer, 2011). Infant growth and development, the short- and long-term health of offspring and pregnancy outcomes can be affected by dietary fat intake during pregnancy (Koletsko et al, 2007). Long chain

polyunsaturated fatty acids (LCPUFAs) {(arachidonic acid (AA) and docosahexenoic acid (DHA)} are structural components of the cell and sub-cellular membranes and are necessary for optimal function of the immune, vascular and neuro-visual systems (Martinez 1992 & Clandinin et al, 1980). Foetal demand for these fatty acids is high, particularly in the third trimester when the brain is growing and rapidly accruing fat (Cetin et al, 2009). As the foetus has limited ability of synthesizing AA & DHA, foetal demand must be met by the mother through ingestion of foods rich in omega-3 fatty acids or supplements (Singh, 2005). LCPUFAs cannot be manufactured by the body and are often referred to as essential fatty acids (EFAs) because they must be obtained through oral intake (Greenberg et al 2008). Recommended guidelines on oral intake during pregnancy vary from 200mg (Koletzko et al, 2007), 250mg (EFSA, 2010) to 300mgs (ISFAAL). In the United Kingdom (UK), two to three (2-3) portions of fish with at least 1 portion of oily fish (eg. salmon, sardines and mackerel) are recommended weekly (European Food Safety Authority Scientific Committee, 2014) as fish consumption in pregnant women and women of childbearing ages are consistently low as shown in a European cohort study (1996-2004) (Leventakou et al, 2014).

Previous observational studies have shown possible benefits of fish oils on specific maternal and neonatal outcomes. For example, omega-3 fatty acid can prolong pregnancy by 4 days (Olsen et al, 1992 & Makarides et al, 2010), which in obstetrics is a huge accomplishment which can be the difference between prematurity and maturity of babies and their subsequent health and wellbeing. However, most observational studies and randomised controlled trials (RCTs) which examined supplementation of pregnant women with omega-3 fatty acids, focused only on specific outcomes such as IUGR (Horvath et al, 2007 & Olsen et al, 2000), preterm birth (Horvath et al, 2007 & Olsen et al, 2000), pregnancy induced hypertension (PIH) (Horvath et al, 2007), pre-eclampsia (Olsen et al,

1990 & 2000) and infant and child health in areas such as neurological development (Crawford et al, 1976 & Crawford, 1993) and visual acuity (Clandinin et al, 1980). A systematic review on pregnancy outcome data (up to March 2006) on high risk women after supplementation with omega-3 fatty acid has shown a reduction in pre-term delivery but no significant difference in infant birth weight, rate of low birth weight, recurrence of IUGR, rate of caesarean section and pre-eclampsia (Horvath et al, 2007). However, those studies on pregnancy outcome were done on non-diabetic women.

Earlier diabetic studies have shown depleted AA & DHA levels in pregnant women with T1 DM and their neonates (Ghebremeskel et al, 1998 & 2004), possibly resulting in poorer outcomes. The depletion of AA and DHA might be similar for women with T2 DM and their neonates as the activity of delta-6 and delta-5 which are necessary for the synthesis of AA and DHA were found to be impaired in individuals with T1 and T2 DM (Brenner et al, 2000 & El Boustani et al, 1989). Reduced plasma fatty acid levels of AA & DHA were found in neonates of women with GDM compared to non-diabetics (Thomas et al, 2004; Wijendran et al, 2000 & Min et al, 2004), and the depletion of those fatty acids was greater in obese and overweight gestational diabetic women (Min et al, 2004). Regardless, women of childbearing age have a great capacity of synthesising DHA (Burdge & Wotten, 2002 & Pawlosky et al, 2003) and possibly AA, as these fatty acids share the same synthetic pathway (Thomas et al, 2004). Also, the depletion of AA & DHA can be corrected by insulin therapy (Shin et al, 1995). Combined, these factors could have a positive impact on the fatty acid status of women with GDM and T2 DM and their subsequent pregnancy outcomes.

Two sub-set studies have been conducted on women with T2 DM and GDM of which I was involved. They have since been published (*appendix 1.1*). These studies have shown promising results. Supplementation with 600mgs DHA enhanced both maternal and foetal

DHA status in women whose pregnancies were complicated with T2 DM (Min et al, 2014) and maternal DHA status in women diagnosed with GDM (Min et al, 2016). Based on these findings, participation in the nutritional study may have benefited women who received active supplements and their babies. Although this preliminary data has shown an improvement in maternal/foetal DHA status, what remains unknown is the impact that improved DHA status had on maternal and foetal wellbeing and pregnancy outcomes. More robust research was needed to demonstrate cause and effect. To date, no study has examined maternal and foetal outcomes measures (as described in chapter 3 – section 3.4) which come in line with other pregnancy outcome studies, following supplementation with omega-3 fatty acids. This study was conducted with this aim. The study results will contribute to filling that gap. It would be useful to evaluate the pregnancy outcomes of supplemented groups with and without diabetes to establish whether supplementation with omega-3 fatty acids had any effects on and within the various sub-groups and this was explored in chapters 6 & 7. The findings will be invaluable when caring for pregnant women with GDM and T2 DM and will act as the 'pioneer' of many more research studies in the future.

1.1.2 Justification

1.1.2.1 Personal Interest

For many years, I have worked as part of the multi-disciplinary team in the specialist antenatal diabetes clinic (SADC) at Newham University Hospital as an Advanced Clinical Practice Midwife in the role of diabetes specialist midwife (DSM). During this time, I have worked alongside obstetricians, diabetologists/endocrinologists and dieticians caring for women with diabetes in pregnancy and I have witnessed first-hand the adverse impact of diabetes on maternal and foetal health and well-being. Those poor outcomes were at times cyclical; believed to be associated to the many complex health needs with which some women presented. At times, I was consumed by feelings of helplessness. I strongly felt that there were several issues that needed to be addressed to optimise the pregnancy outcome of the Newham's pregnant diabetic population which is socio-economically deprived, highly diverse and predominantly from South Asia (Pakistan, Bangladesh, India etc).

Also, I recognised the higher prevalence of diabetes related problems among this high-risk group of pregnant women, particularly due to lack of engagement or inadequate levels of engagement with health care professionals (HCPs) and the care they provided. From observation, it appeared that the more engaged women were with HPs involved in their care, the more positive the impact on their and their babies' health and pregnancy outcomes. Evidence from a review has shown a correlation between effective physician-patient communication and improved health outcomes (Stewart, 1995). Effective communication is critical for client engagement. Therefore, one can conclude that client engagement is critical for optimising maternal and foetal outcomes; but strong empirical data through systematic review and meta-analysis within maternity are lacking. Therefore,

this aspect of care needed to be studied to have a better understanding of why these high-risk women were not fully engaging with HCPs to optimise their and their babies' health and wellbeing. The findings can then be used to better help and support women in this part of East London. This hypothesis was explored in the first phase of this study.

Secondly, I have seen a significant number of women who are diagnosed with GDM on a weekly basis. The incidence seemed to be increasing over time and the gestational ages at which diagnosis was made appeared to be decreasing. That trend caused me concern. I was baffled as to why this was particularly as many of those women had no previous history of GDM but had other risk factors like raised body mass index (BMI) $\geq 30 kg/m^2$ and family history of diabetes. The National Institute of Health and Care Excellence (NICE) (2015) guidance recommends that women with a previous history of GDM should be screened early and if the result is normal, repeat testing should be done at 24-28 weeks gestation. Women with other risk factors should be screened between 24-28 weeks gestation. From observation, it appeared that women with risk factors other than previous history of GDM were detected early (within first and second trimester of pregnancy) with GDM. Therefore, I wanted to establish the predominant risk factors for early detection of GDM and evaluate whether gestational age at diagnosis impacted on pregnancy outcomes. It was also critical to examine the appropriateness of NICE's GDM screening guidance for use within a borough like Newham where there is a high multi-ethnic community and a high prevalence of diabetes. This area needed to be studied and has led to the second phase of the study which has explored the predominant risk factors for the early detection of GDM (<24 weeks gestation) and the subsequent impact on pregnancy outcomes. The findings of this phase could have significant impact on strategic planning with appropriate and adequate resource allocation to improve the maternal and foetal health and wellbeing, and pregnant

outcomes of local women at risk of GDM, who tend to be obese/ overweight (NICE, 2015 & Chu et al, 2007) and / or have first degree relatives with diabetes (NICE, 2015).

As mentioned above, previous evidence has demonstrated that women with diabetes in pregnancy have poorer outcomes compared to non-diabetic women. The London borough of Newham is ethnically diverse and has a high prevalence of diabetes which resulted in women presenting in pregnancy with many co-morbidities which were either diabetes-related or not. This has led me to believe that the pregnancy health and outcomes of diabetic women within my local hospital might be significantly worse compared to other boroughs within England where different population profiles exist and where the prevalence and incidence of DM vary.

Also, care of women with GDM upon discharge seemed fragmented. There was no tight structure in place to manage women's postnatal diabetes health following discharge from hospital. Prior to discharge, an oral glucose tolerance test (OGTT) appointment for 6-8 weeks post-delivery was given to women with lifestyle advice. Upon discharge, women were re-referred to their general practitioners (GPs) who were responsible for chasing up and attending the OGTT results and subsequent annual reviews should T2 DM was not detected. Yet, some women with a previous history of GDM were presenting with high blood glucose levels in the first trimester in subsequent pregnancies, having not received appropriate follow-up care. Follow up care was like a lottery. Some women received annual diabetes screening from their GPs while others did not. Post-discharge quality of care was GP-dependent and whether women spoke English and were proactive to chase their GPs for annual diabetes screening appointments. Previous evidence has shown that up to 70 per cent of women with GDM would develop T2 DM within 5-10 years and earlier in some cases (Metzger et al, 2002). Therefore, it was critical to establish the postnatal prevalence of T2 DM after GDM. With that hard data, adequate resources can hopefully be

generated to organise appropriate screening and preventative programmes for the postnatal care of women diagnosed with GDM. This can lead to huge cost savings for Women's Health Directorates and the wider National Health Service (NHS) in the immediate and long-term.

As a senior midwife who always strives to provide quality care, I had a keen interest to research the areas highlighted above, but I did not have the financial capability and research experience to conduct the research. But, when the opportunity presented itself when the London Metropolitan University (LMU) collaborated with Newham University Hospital (NUH) to conduct a nutritional study among the pregnant diabetic women and offered the co-ordinator of that study to register to do a PhD, I positively embraced the opportunity. I was then tasked with leading and managing this project from set-up to study close-out.

This nutritional study was conducted because no other well designed study has previously been done to evaluate the pregnancy health and outcomes of women with diabetes mellitus (DM) after supplementation with fatty acids. This study fills that gap. Also, for factors like lack of resources, research into this local client-group has not been conducted. To date, assumptions are being made about the pregnancy outcome of clients attending the SADC. Care provision is based on observation, intuition, findings from general research evidence and directives from bodies like the World Health Organisation (WHO) and NICE. While all these directives and measures have their place, true empirical evidence to answers vital questions is necessary to optimise the pregnancy outcome for diabetic women within the borough of Newham. My thesis also works towards this aim.

1.1.2.2 Why Newham?

Newham is one of the most deprived boroughs in London (NCCG, 2017a) and deprivation may drive women and their families to engage in cheap and easy food options which can be detrimental to their health. Healthy eating forms part of the local Clinical Commissioning Group (CCG) agenda. Food vouchers which include fruits and vegetables are provided to the less privileged as part of that drive. But, throughout the borough, within close proximity to each other, there are many fast-food shops selling mainly 'chicken and chips' and other foods high in saturated fats and this is likely to inhibit the success of promotional work on healthy eating within the borough. However, engaging with women during pregnancy; a time when they are more likely to be motivated to care for their and their baby's well-being, could have been beneficial.

Local women may simply not have the financial means of having a daily nutritional diet and many could be starting pregnant in poor nutritional health. Diets high in saturated fats, eaten over a considerable length of time can be detrimental to one's health, likewise during pregnancy. Healthy eating which includes a reduction of saturated fats but an intake of polyunsaturated fats from oily fish are encouraged in pregnancy. Adequate nutrition is particularly important to promote positive pregnancy health and outcomes and achieve optimal glycaemic control in pregnant diabetic women. Saturated fats can impair insulin sensitivity which is already a metabolic challenge for diabetics (Riserus et al, 2009). Although that impairment may be corrected by insulin therapy (Shin et al 1995), which forms part of the management strategy for women with T2 DM and GDM, its effect on maternal and foetal pregnancy health and outcome remained unknown and needed exploring.

Therefore, this nutritional study can be justified, particularly as women in the borough do not live as long as other women in London and England as a whole (Newham London, 2017). Women within the borough are predominantly non-Whites and are affected disproportionally by local deprivation factors of low income, overcrowding, fuel poverty and concern for crime (Newham London, 2017). Consequently, they tended to have poorer general health (Newham London, 2017) and presented in pregnancy with much co-morbidity. Also, the co-morbidities associated with DM in a deprived area like Newham would suggest that women could have been starting pregnancy with depleted stores of AA & DHA.

In prospective studies which investigated whether diabetes during pregnancy affected maternal and foetal AA and DHA status in women with T1 DM, T2 DM and GDM and their babies, it was revealed that the levels of both fatty acids were significantly reduced in red cell choline phosphoglycerides of mothers and in red cell and plasma choline phosphoglycerides of their neonates (Ghebremeskel et al 2004, Thomas et al 2005). In a pilot study of Korean women with GDM and their neonates, compromised red cell AA and DHA was found among those mothers, at levels similar to their British counterparts. Conversely, among the Korean women, their neonates had normal levels of plasma and red cell DHA. Since foetal DHA status is enhanced by increased maternal intake of DHA in pregnancy and Korean women had high daily intake of fish (75g/day vs 13-34g/day in European) (Ghebremeskel, 2000), it seems intuitive to assume that the normal DHA level found in the neonates could be due to the high intake of DHA from fish consumed by Korean gestational diabetics women. Therefore, it seemed reasonable to assume that pregnant diabetic women within the borough of Newham could have benefited from the effects of fish oils supplementation in pregnancy to rectify their possible depleted stores of AA & DHA which in turn could have had a positive impact on their pregnancy health and

outcomes. Also, with the high prevalence of pregnant women with T2 DM and GDM within the borough and women from the Black and minority ethnic (BAME) groups disproportionally having poorer maternal and birth outcomes (Knight et al 2018, Garcia et al 2015 & Office of National Statistics 2013), the effects of omega-3 supplementation could have been more discernible and impacted on a wider cross-section of women than if the study was conducted in a wealthier borough. Ethnically-related differences in maternal omega-3 and omega-6 fatty acid intake during pregnancy may exist due to varied levels of fish consumption which may lead to disparity in birth outcomes (van Eijsden et al, 2009). However, baseline data taken for Min et al (2014 & 2016) studies did not reveal any difference in omega-3 fatty acid level between Caucasians & other ethnic groups. An overview of each chapter follows.

1.1.3 Overview of each chapter

Chapter 2

This chapter has provided a broad overview of the current literature available on T2 DM, GDM and the impact of these conditions on pregnancy and pregnancy outcomes. Also, current available evidence is provided on essential fatty acids (EFAs) (AA & DHA) supplementation during pregnancy and impact on pregnancy outcome. The prevalence (global, national and local) of T2 DM (prior to and during pregnancy) and GDM, their associated risk factors, aetiology, pathophysiology, diagnosis, complications and management with specific focus on supplementation with essential fatty acids (AA & DHA) are areas covered within this chapter. This background information sets the scene for all four experimental chapters 4, 5, 6 and 7.

Chapter 3

This chapter has outlined the materials and procedures used to conduct the study which encompassed the study design including the inclusion/exclusion criteria, recruitment and follow up process of participants, intervention and blinding, data collection and analysis. These elements provided clarity to the research process and formed the foundation on which experimental chapters (4 – 7) were conducted.

Chapter 4

Chapter 4 explored the socio-cultural, economic and demographic factors that influenced a pregnant woman's decision on whether or not to engage with HCPs on the nutritional study and the impact that level of engagement / lack of it had on pregnancy outcomes. Adequate nutrition is considered critical to diabetes management and women with T2 DM and GDM are considered 'high risk' and being offered the opportunity to engage with HPs to improve their nutritional status could have been beneficial to maternal and foetal wellbeing. This chapter formed the bedrock for this study, has set the scene for the upcoming 3 phases of the study in chapters 5 - 7 and has influenced the distribution of subjects in each of those phases.

Particularly, for the RCTs conducted in chapters 6 & 7 to be successful, it was necessary to provide women with the information in the language that they understood, preferably face to face. Supported by health advocates (HAs) and patient information leaflets (PILs) translated into 5 different languages, a better understanding of the factors which fostered engagement with HCPs were established. Findings from this chapter were invaluable to

HCPs on the approach to take for the recruitment and follow-up processes to be successful. For example, offering women the choice of hospital or home visits seemed beneficial.

Chapter 5

Women with GDM form the largest group of women who attended the specialist pregnancy antenatal diabetes clinic (SADC). Therefore, this group would have an overwhelming impact on the results of any research conducted on the local SADC. It was therefore imperative to assess the local screening programme in meeting the needs of those with risk factors of GDM, in order to identify women early and provide optimal care management for women at risk and those confirmed with the condition. Predominant risk factors for the early detection of GDM were examined and NICE's recommendation on screening for GDM has also been evaluated in the context of its appropriateness for use within a highly diverse population like Newham's. These formed the focus for this chapter. This study is the first large scale study to evaluate the pregnancy outcomes of the SADC and this result would add to the findings of chapters 6 and 7 in future development of the service.

Chapter 6

This chapter has utilized data from women who were recruited into the nutritional study to evaluate the maternal and foetal health and pregnancy outcomes after supplementation with omega-3 fatty acid in women whose pregnancies were complicated with GDM. Maternal outcome measures were onset of labour, mode of delivery, pregnancy loss and hypertensive disorders in pregnancy while foetal/neonatal outcomes were gestational ages

at delivery, low birth weight, prematurity and admissions to special care baby unit (SCBU). Pregnancy outcomes were also evaluated in the context of diabetes management. Demographic (age, ethnicity, language parity, BMI) and clinical (chronic medical problems & pregnancy complications) characteristics were also examined. This chapter forms a central part of the thesis and the findings can have huge implications for future midwifery practice and research. A comprehensive evaluation of maternal and foetal outcomes would therefore be highly beneficial for the nutritional advice provided to women at booking and throughout pregnancy.

Chapter 7

The focus of this chapter was similar to that of chapter 6 except that maternal and foetal outcomes were of women with T2 DM and women without any form of diabetes after supplementation with omega-3 fatty acid. Demographic and clinical data as outlined in chapter 6 were also examined. Women with T2 DM formed the second largest group of women who attend the SADC and the results of this chapter coupled with the evidence from the two previous chapters on GDM would afford a comprehensive evaluation of the SADC and provide invaluable data for future care planning of these high risk groups. This chapter also forms a central part of the thesis.

Chapter 8

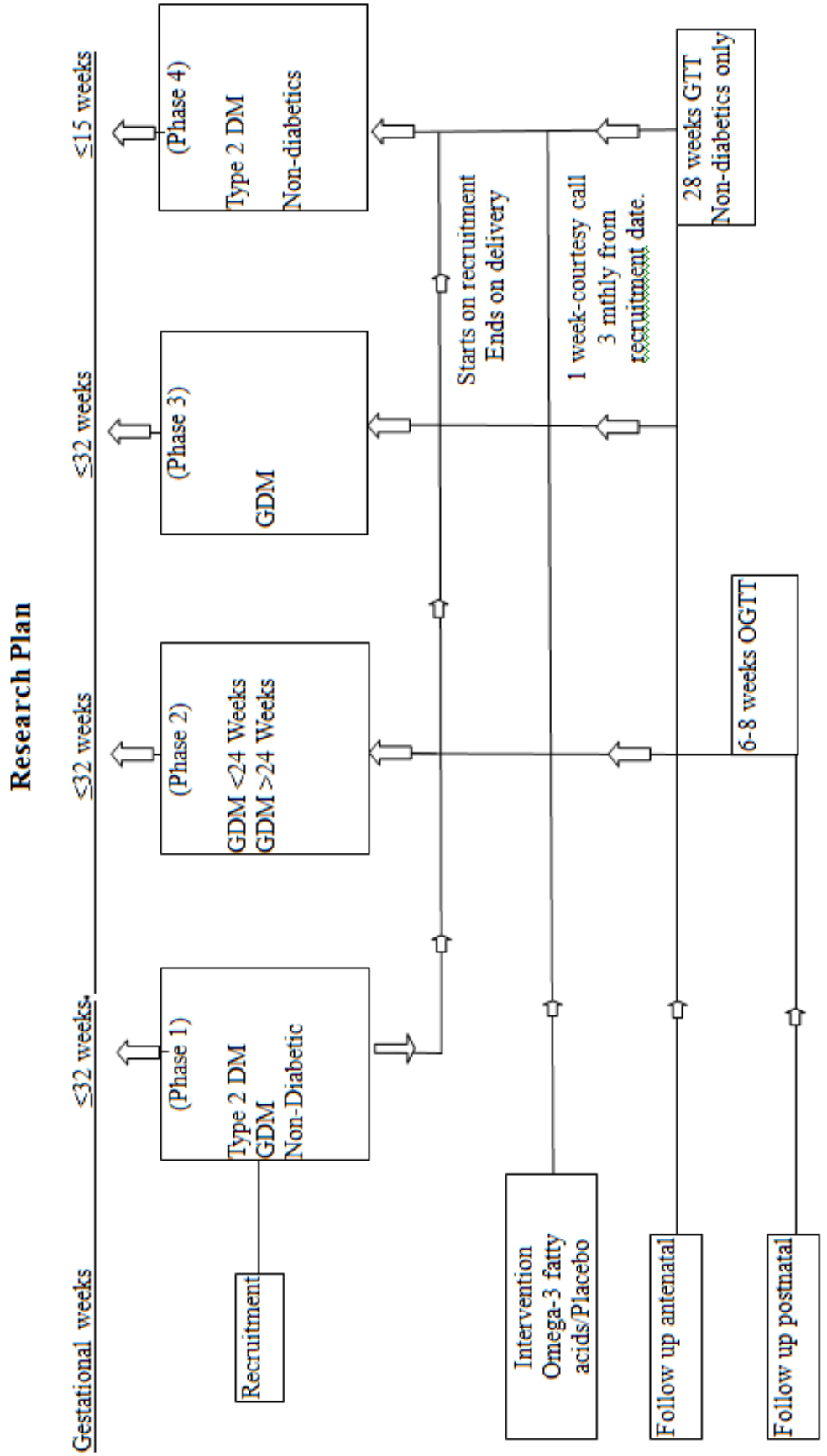
Chapter 8 has summarised the main findings of this thesis and the unique contribution this thesis has made. Also, I have highlighted the strengths and limitations of each phase of the study and the overall implications and areas for future investigations.

In summary, I have established the factors which have influenced women's decision on whether or not to engage with HCPs on the nutritional study and evaluated the impact of engagement /non-engagement on maternal and foetal outcomes. The dominant risk factors responsible for early detection of GDM and the impact of those factors and the time of diagnosis on maternal and foetal outcomes were examined. Supplementation with fish oils in women with GDM and T2 DM on pregnancy outcomes was also explored.

1.1.4 Structure of the theses

This thesis is presented over eight chapters and has four phases. This first chapter details the purpose of the study and provides an overview which includes my personal and professional motivation and how these have influenced the area of study. The process of this study is as demonstrated in (***flow chart 1.1***). The structure of this thesis is as described hereunder.

Prior to the exploration of the experimental chapters to address the above issues raised, an introduction to the research problem will be made encompassing a brief study overview followed by an extensive literature search which draws on previous empirical data to outline the research background to this study. This feeds into the chapter on the conduct of the study (chapter 3) followed by the experimental chapters (as described in 1.1.3) and culminating with the final chapter which revisited the aims to establish whether the data presented supported the hypotheses. This was done through a process of reflection on each experimental chapter. The strengths and limitations of the study are then described followed by recommendations for future research.



Flow chart 1.1: Research Plan

Chapter 2:

Literature review

2.1 Chapter overview

Information pertinent for this thesis is critically examined within this chapter. It sets the scene with background information for all preceding chapters of this study. I will also attempt to identify gaps in the literature which my study will try to address.

An overview of the epidemiology, aetiology, complications, management and pregnancy outcomes of women with T2 DM and GDM is provided with the latest insight into the global and UK epidemic. Information on pregnant women's (with T2 DM & GDM) engagement with HCPs, risk factors associated with early detection of GDM and nutritional supplementation with omega-3 and omega-6 fatty acids and their impact on maternal and foetal outcomes also form the background of this chapter.

2.2 Search strategy

2.2.1 Aim and process

A comprehensive literature review was undertaken for this study. Accuracy and precision were aimed for from mainly biomedical published evidence, to achieve a quality search from literature written in English but inadequacies in the indexing of research papers, human frailty, spelling differences and time constraints were possible limitations to capturing all available literature.

The literature search started from the research idea to put the research problem in context. It continued throughout the period of the research study to keep abreast with and facilitate the use of newly published relevant data. However, the main bulk of the search was conducted in the early stages of the research process.

The aim was to obtain evidence which focused on pregnancy outcomes of women with T2 DM and GDM with reference to client engagement with HPs, risk factors of GDM and omega-3 and omega-6 fatty acids supplementation. The postnatal health of women with GDM with and without supplementation with fish oils was also included in this aim.

The objectives while conducting this review were to describe the epidemiology of GDM and T2 DM with reference to pregnancy, current screening guidelines and diagnosis of GDM, pregnancy complications and management of GDM and T2 DM, factors which influence client engagement / lack of engagement with HCPs, the impact of omega-3 and omega-6 fatty acids on maternal and foetal wellbeing and the pregnancy outcomes of women with GDM and T2 DM with reference to client engagement, early detection of GDM and supplementation with omega-3 and omega-6 fatty acids in women with T2 DM and GDM; all within the context of the population and health profile of pregnant women within the borough of Newham.

2.2.2 Participants

Participants were pregnant women of any gestational age, parity, demographic and socio-economic background, regardless of their medical and/or obstetric history. All observational studies, RCTs, systematic reviews and meta-analysis of RCTs and RCTs of pregnant women with or without GDM and T2 DM and supplemented with omega-3 and omega-6 fatty acids regardless of time and duration of intervention and dose regimen, were included. All RCTs on GDM were included despite the screening criteria.

2.2.3 Data Sources

Data sources included Pubmed, Elsevier, Medline, Cinahl, Embase, the Cochrane Library databases including the Pregnancy and Childbirth's Trial Register. Google Scholar searches provided most electronic academic journals and hard copies from the local library were reviewed as these provided past and recent peer-reviewed articles which denoted quality having gone through a rigorous review process. Related articles from references list directed searches in a variety of journals and books. The Cochrane database including the Pregnancy and Childbirth's Trial Register provided the best available evidence through the reviews of results from RCTs.

2.2.4 Search terms

Search terms used subjects and text words searches using simple Bolean logic. For example, for experimental chapter 1, search terms included client/patient engagement and health professional/clinicians, client/patient engagement with NHS / health service, client/patient engagement with pregnancy diabetes services / maternity services, barriers / influential factors to engagement of women with GDM/T2 DM, deprivation/ethnicity and client engagement and client/patient engagement and pregnancy outcomes. Search terms used for experimental chapter 2 included gestational diabetes mellitus/ GDM, prevalence of gestational diabetes mellitus / GDM, risk factors of gestational diabetes mellitus / GDM, ethnicity and risk factors of gestational diabetes mellitus / GDM, screening for gestational diabetes mellitus / GDM, screening criteria for gestational diabetes mellitus / GDM, NICE guidance on screening and management of gestational diabetes mellitus / GDM, early/late detection/diagnosis of gestational diabetes mellitus / GDM, effects of gestational diabetes mellitus / GDM, obstetric / midwifery complications {macrosomia, IUGR, birth weight,

hypertensive disorders (high blood pressure, pre-eclampsia, eclampsia), prematurity, hypoglycaemia, respiratory distress syndrome, prolonged pregnancy, modes of delivery, admission to special care baby unit} and gestational diabetes mellitus / GDM and management of gestational diabetes mellitus / GDM. Similarity existed in the search terms used for phases 3 and 4 except for the diabetes type (GDM / T2 DM) except where specific peculiarities existed with each group eg. postpartum glycaemic status for women with GDM and not for women with T2 DM. Search terms included, fish oils, omega-3 fatty acids, long chain polyunsaturated fatty acids (LCPUFA) in and outside pregnancy, obesity and pregnancy complications / outcomes in GDMs/ T2 diabetics, obesity and fatty acids absorption, effects of fish oils on mother / baby (foetus)/neonate. Pregnancy complications / outcomes were as listed above with focus on maternal (hypertension, pre-eclampsia, eclampsia, miscarriages, induction rate, gestational length, reasons for and caesarean section rate) and foetal / neonatal (congenital abnormality, stillbirth, neonatal death, gestational ages at birth, birth weight, apgar scores, macrosomia, low birth weight, admission to special care baby unit and reasons for admission).

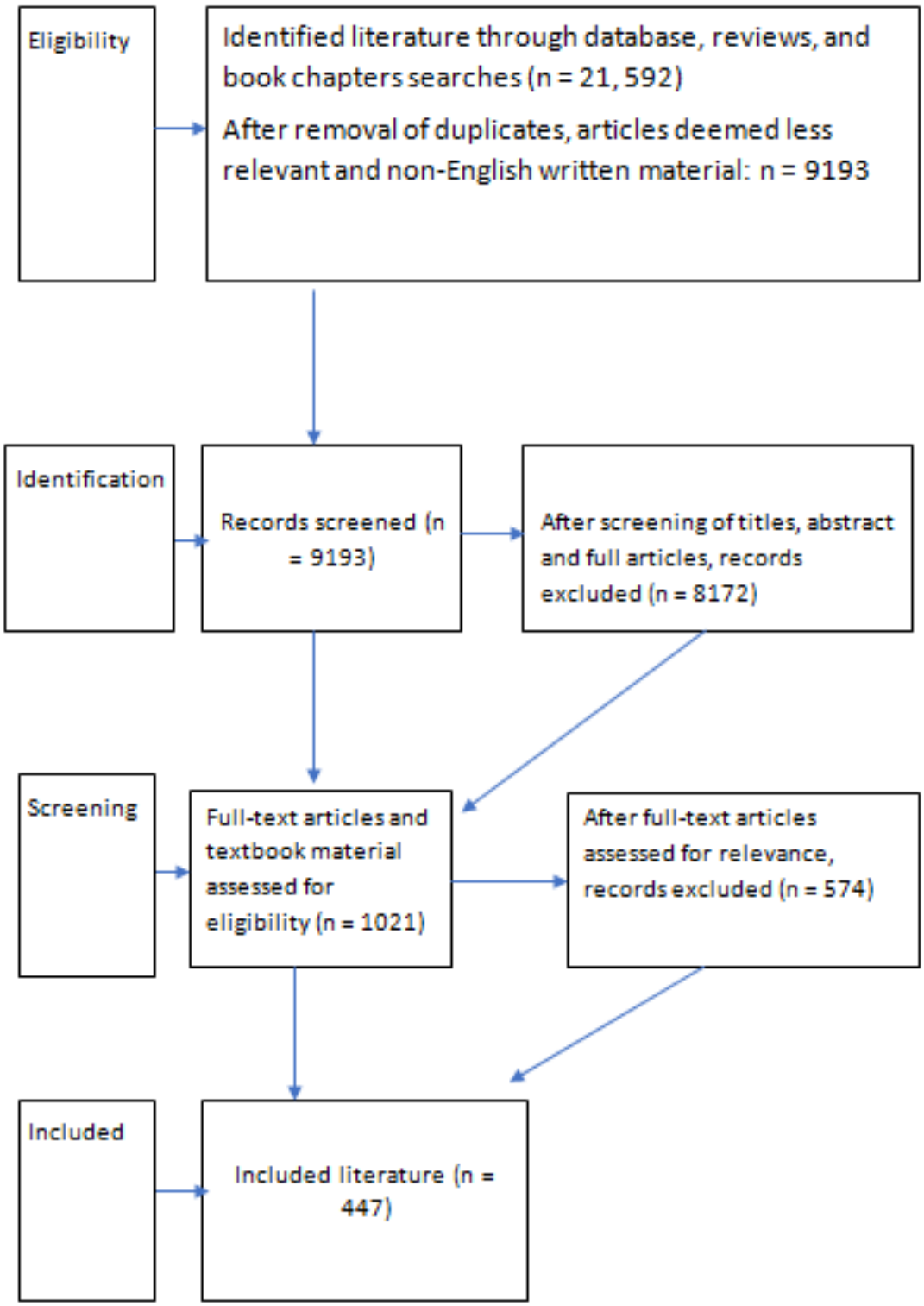
2.2.5 Search results

The literature screening process and results are described in **flow chart 2.1**. An overwhelming number of results were found on T2 DM and GDM (n=17,435). The results included literature on prevalence, incidence, screening, diagnosis, management, impact on health outside (T2 DM) and during pregnancy (T2 DM and GDM) on maternal and foetal health and wellbeing and their pregnancy outcomes. Some articles also covered both conditions, particularly when discussed within the context of pregnancy. The sheer volume of articles found meant that it was impossible to include all relevant article so only the most pertinent were included.

The results on omega 3 fatty acid in pregnancy was also substantial (n=4157) but when screened within the context of pregnant women with T2 DM and GDM, very little literature was found deemed appropriate (n=78). This meant that references within this thesis were primarily of data on supplementation of pregnant women without diabetes. Also, no trials were found on comprehensively evaluating maternal and foetal outcomes (as identified under study design and methods). Rather, specific aspects of pregnancy outcomes measures such as pre-eclampsia, birth weight and IUGR were evaluated after fish oil supplementation. Other articles were found on the prevention of T2 DM and GDM and were used as supporting evidence within this thesis.

Finding literature on pregnant women's engagement with HCPs was challenging. Only 1 article was found on the primary outcome measure of client engagement with HCPs. Most results found were on patient engagement which described service users' involvement in committees including at strategic levels in the formulation of health policies as opposed to the way clients/patients engaged with HPs and the services made available to them and the subsequent impact on their health and wellbeing, following engagement.

When screened for appropriateness, the most relevant literature was selected and used (n=447) as referenced within this thesis. Other literature on areas such as research, pre-eclampsia, obesity, health inequalities, the demographic and health profile of Newham and local and national policies and directives were also used as supporting evidence and contributed to this total.



Flow chart 2.1: Literature screening process

2.3 The Evidence

2.3.1 Overview

Globalisation has impacted on the increasing size and diversity of the UK population with 1 in 4 births of women born oversees (Higginbottom, 2019). Disparities exist between the birth outcomes of Black, Asian and Ethnicity Minority (BAME) women and those of the indigenous group, with adverse outcomes more common among the former group (Garcia et al, 2015).

Ethnicity is a key characteristic of developing pre-existing diabetes (Type 1 & Type 2) (Buschur et al, 2018 & Vora, 2010) and GDM (Buschur et al, 2018; Mc Donald et al, 2015). Risk factors of pre-existing diabetes and GDM are the same and they also share same metabolic abnormalities (insulin resistance and hyperinsulinemia (Ben Slama, 1997). Women with these conditions have poorer birth outcomes than women without the condition (Abu-Heija et al, 2017). This poses a huge challenge for HCPs. Planning and delivering services that are culturally specific in and within the various ethnic groups, to optimise maternal and foetal outcomes are critical (Higginbottom, 2019). An adequate and effective screening programme for GDM and an effective management strategy for this condition and T2 DM throughout pregnancy and the immediate postnatal period should form the nucleus of all service planning.

The experience of pregnancy and childbirth is very complex and multidimensional. Various emotions are experienced, but pregnancy is primarily a time of happiness for most women, their partners, family members and friends. Women's hope is for 'everything to go well' for them and their babies from booking and throughout to the postnatal period and beyond. HCPs need to provide the bedrock on which that positivity can thrive through adequate and appropriate information provision and individualised woman-centred care and support. Women can then feel empowered to positively engage with the services

available to them to enhance their pregnancy health and pregnancy outcomes (National Midwifery Review, 2016 & WHO, 2015).

Previous reductionist paradigm that the foetus is not affected by its environment is eroding as new evidence on epigenetics (Kluny & Dillard, 2014) and foetal origins hypotheses (Barker, 2007) emerge. For example, maternal stress can adversely impact on the foetus and can have long-term consequences (Kluny & Dillard, 2014). Likewise, it is postulated that coronary heart disease and T2 DM may originate from maternal nutrition during intra-uterine development (Barker, 2007). Paul (2010) in her work on foetal origins of adult disease supports these views.

Similarly, maternal nutrition determines the intrauterine environment (foetal programming) and is critical for maternal and foetal well being (Myatt & Powell, 2010), placental transfer of long chain polyunsaturated fatty acids (Larque et al, 2011), foetal growth and neural development (Innis, 2007; Crawford, 1993 & Crawford et al, 1993), pregnancy outcomes (Salvig & Lamonth, 2011) and the long-term health of the offspring (McNarara & Carlson, 2006). Nevertheless, as fatty acids cannot be synthesised by the body, they need to be ingested in the maternal diet through foods and/or supplements. Previous work has shown that through a physiological mechanism, an appropriate balance exists between AA and DHA which can be beneficial for cell membrane stability and function (Ghebremeskel et al, 1999). This is an important phenomenon since a balance of both AA and DHA is required for adequate supplementation in pregnancy (Monique et al, 2000). Combined, current data suggest that LCPUFAs in pregnancy is critical for optimal maternal and foetal health, and possibly their pregnancy outcome. As limited work is done on women supplemented with fatty acids in diabetic pregnancies, further work of this phenomenon is needed to explore the impact on maternal and foetal outcomes in a deprived borough like Newham, where no previous work has been done and where pregnant women can present

with various co-morbidities, which may or may not be related to DM. More detailed explanation on the rationale for conducting this study can be found in chapter 1 under 'justification'.

2.3.2 Background

2.3.2.1 Diabetes Mellitus (DM)

2.3.2.1.1 Prevalence globally and in UK

The global prevalence and incidence of diabetes mellitus (DM) have met epidemic proportions. In 2014, the number of people living with diabetes had risen from 100 million to 422 million and that increase was more rapid in middle- and lower-income countries. Among adults age 18 and over, there was an increase from 4.5% to 8.7% {(World Health Organisation (WHO) (2018)}. In 2011, the estimated prevalence of diabetes globally was 366 million and it was forecasted to affect 642 million by 2040 (Diabetes UK, 2019).

In the UK, the prevalence in 2012 was 5.8 % of the population and this figure had increased to 6.0 % in 2013 and 6.2 % in 2014. More recently, this number has doubled to 3.9 million, which when added to the near million undiagnosed T2 diabetics who are unknowingly living with the condition, this equates to 4.8 million (Diabetes UK, 2020). Of this total 8 per cent has T1DM and the remaining 90 per cent has T2DM (Diabetes UK, 2020) and about 44 per cent are women (Diabetes UK, 2015).

2.3.2.1.2 Prevalence of diabetes in pregnancy

Diabetes is the most common pre-existing medical disorder complicating pregnancy in the United Kingdom (UK) (Diabetes UK, 2014). In the UK, approximately 700,000 women give birth each year and up to 5% of these women have either pre-existing diabetes or GDM. Of the women who have diabetes during pregnancy, approximately 5% have T2 diabetes and 87% have GDM which may not resolve after pregnancy (NICE, 2015).

Since 1989, the St. Vincent declaration stated as a five-year goal that the 'outcome of the diabetic pregnancy should approximate that of the non-diabetic pregnancy' (Balen, 2007). Changes in management strategies in areas of pre-conceptual, antenatal and neonatal care were acclaimed to that achievement, as combined, they were believed to contribute to the reduction in the morbidity and mortality rates of infants of diabetic mothers. However, despite the notion that care delivered within a multi-disciplinary context is paramount to reduce adverse outcomes (NICE, 2015), all high-risk pregnancies, including those with abnormal blood glucose levels, continue to pose significant challenges to health care professionals.

Consequently, management of the pregnant diabetic women is continuously an evolving process, which takes into account the aetiology of the disease, one's demographic, socio-economic and lifestyle factors which include adequate nutrition. Also, the political bias of one's environment at local and national levels can be influential. Therefore, health care professionals need to face these issues head-on in order to provide equity to all for whom they care.

2.3.2.1.3 Definition and Concept

Diabetes Mellitus (DM) is 'a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances in carbohydrate, fat and protein metabolism resulting from deficiencies in insulin secretion, insulin action, or a combination of both' (WHO, 1999). DM occurs when normal glucose metabolism becomes impaired. The pancreas does not produce enough insulin that the body needs or when the body is unable to effectively utilize the insulin produced by the pancreas (WHO, 2018). This defect in insulin secretion is 'caused by autoimmune destruction of the beta cells of the pancreas, insulin action due to insulin resistance, or both'. Insulin resistance is the inability of the body to respond to and utilise available insulin (Matthews, 2008).

2.3.2.1.4 Signs and symptoms

The signs and symptoms of diabetes (***Table 2.1***) vary considerably in the rate of onset, the severity of the condition and the type of diabetes (Holt, 2009). T1 DM can present acutely with individuals being unwell and ketoacidosis without recognising initial symptoms or subacutely with polyuria, weight loss, thirst and polydipsia (Meeking, 2011). T2 DM has a latent, asymptomatic period of sub-clinical stages and remains undiagnosed for many years (Ramchandran, 2014; Meeking, 2011). Symptoms for T2 DM can include thirst, polyuria, fatigue and blurred vision and individuals can present with skin infections, cellulitis, genital candidiasis or urinary tract infection and / or microvascular and macrovascular complications (***Table 2.2***) (Meeking, 2011).

2.3.2.1.5 Cost to the National Health Service (NHS)

DM is a huge public health concern. Data recently synthesized by Diabetes UK has shown that DM places a significant burden on the UK society and specifically the NHS. The NHS spends approximately £10 billion annually on the disease and of that total, 80% is spent treating diabetic related complications and accounted for 1:6 hospital inpatients' admissions. At the time of diagnosis of T2 DM, one-third of individuals have suffered a microvascular complication. Complications included 530 myocardial infarctions and 175 amputations, weekly. Additionally, nearly 40% of people living with DM have some form of psychological ill-health. Despite these complications, 57% and 42% individuals with Type 1 and T2 diabetes, respectively, do not attend all their annual diabetes review appointments (Whicher et al, 2020).

Table 2.1: Features of Type 1 and Type 2 Diabetes Mellitus

Features	**Type 1 DM**	**Type 2 DM**
Age of onset	Any age, mostly adolescent	Mostly in adults
Pattern of onset	Sudden/Abrupt	Slow/Gradual
Body habitus	Usually thin or normal weight	Often obese or overweight
Ketoacidosis	Common	Rare
Auto antibodies	Usually present	Absent
Genetic predisposition	Moderate	Very strong
Biochemical defect	Autoimmune destruction of the β cells in 90% of cases. Cause unknown in other 10% but there is impaired production of insulin.	Insulin resistance combined with inability of the β cells to produce adequate amounts of insulin.

Table 2.2 Micro- and macrovascular complications of diabetes

Micovascular complications	**Presentation**
Retinopathy	Visual impairment or a chance discovery
Nephropathy	Proteinuria, hypertension or nephrotic syndrome
Neuropathy	Painful sensory peripheral neuropathy, mononeropathy, carpel tunnel syndrome, amyotrophy or foot ulceration
Macrovascular complications	**Presentation**
Coronary	Angina or myocardial infarction
Cerebral	Stroke, transient ischaemic attacks
Peripheral	Intermittent claudication, rest pain, ischaemic leg

Extracted from Meeking, D. (2011) Understanding Diabetes and Endocrinology – A problem-solving approach. p23

2.3.2.1.6 Diagnosis

The diagnosis of DM is made on either a fasting blood glucose of ≥7.0mmol/l and / or two-hour blood glucose of ≥11.1mmol/l after using the World Health Organisation (WHO) screening tool of 75g oral glucose load. With signs and symptoms of diabetes (as listed above), a random blood glucose level of ≥11.1mmol/l was also be used to make a diagnosis of diabetes. Additionally, in 2011 WHO declared that HBA1c can also be used for the diagnosis of the condition, but this group was excluded from this study. Glucose levels ≥48mmol/l (6.5%) confirms a diagnosis of DM, although it is stated that values below this value does not exclude diabetes. Nevertheless, more scientific evidence is needed to make that diagnosis (Diabetes UK, 2015; WHO, 2011). Alternatively, many complications of the disease have been known to present with detrimental effects of hyperglycaemia with specific micro-vascular (diabetic retinopathy, nephropathy and neuropathy) and macro-vascular (coronary heart disease, peripheral heart disease and stroke) diseases (Fowler, 2008) which often led to diagnosis of the disorder (NICE, 2008).

2.3.2.1.7 Types of Diabetes Mellitus

Various factors have influenced the classification of diabetes which has changed over time. As the aetiology of the disease became better understood, it became more difficult to categorise diabetes (Todd, 2010). T1 DM was renamed from insulin dependent diabetes mellitus (IDDM) which was previously referred to as juvenile diabetes. Similarly, T2 DM was redefining from non-insulin dependent diabetes mellitus (NIDDM) previously called mature onset diabetes. Gestational diabetes mellitus (GDM) which is diabetes detected during pregnancy following screening of women with risk factors (NICE, 2015) will be explored further in chapters 5 & 6. Additionally, other classifications of glucose regulation

which are less common and less understood exist (American Diabetes Association, 2010 & 2015; 2008) (***Table 2.3***). Categorizing an individual into a diabetes type depends on the circumstances at the time of diagnosis and therefore many diabetic individuals do not fit solely into a single type (American Diabetes Association, 2010). The Expert Committee on Diagnosis and Classification of Diabetes Mellitus has recognised individuals who fit into two groups whose plasma glucose levels are above normal values but not high enough to be classified as having diabetes. These are impaired fasting glucose (IFG) (fasting plasma glucose between 6.1 – 6.9 mmol/l) and impaired glucose intolerance (IGT) (2-hour value of OGTT, ≥7.8 – 11.0 mmol/l) which are often referred to as pre-diabetes (Expert Committee on Diagnosis and Classification of Diabetes Mellitus, 1997).

Below, a brief overview of T1 DM will be provided for an umbrella view of DM but T2 DM and GDM form the focus for this study and will be explored in detail.

Table 2.3: Classification of other causes of diabetes mellitus

Endocrinopathies • acromegaly • Cushing's syndrome • pheochromocytoma • hyperthyroidism • glucagonoma, somatostatinoma **Drug-induced** • glucocorticoids • combined antiretroviral therapy for HIV • nicotinic acid • pentamidine • diazoxide • thyroxine and others **Infections** • congenital rubella • cytomegalovirus	**Genetic syndromes associated with diabetes** • Down's syndrome • Klinefelter's syndrome • Turner's syndrome • Wolfram's syndrome • Friedrichs ataxia • Prader-Willi syndrome **Pancreatic disease** • pancreatitis • cystic fibrosis • hemochromatosIs • pancreatic carcinoma **Transplantation-associated diabetes**

*Adapted from American Diabetes Association (2008) in Scobie & Samaras (2009)

2.3.2.1.7.1 Type 1 Diabetes Mellitus (T1 DM)

2.3.2.1.7.1.1 Prevalence

In 2015, approximately 542,000 children were living with T1 DM worldwide and regional differences exist. That figure was forecasted to increase when adults living with the condition were added. In the UK, the incidence is approximately 10% of all people diagnosed (Diabetes UK, 2016).

2.3.2.1.7.1.2 Risk factors

Numerous studies have shown a link between T1 DM and familial (Stefan et al, 2014) and environmental (Gillespie et al, 2004; Kaila et al, 2003 & Metcalf et al, 2001) factors and viral infections (Rodriguez-Calvo & von Herrath, 2015), but the latter remains debatable (Shaheen et al, 2020, Scobie and Samaras, 2010 & Petzold et al, 2015).

2.3.2.1.7.1.3 Aetiology

Type 1 DM is a metabolic condition in which the beta cells of the pancreas produce no insulin. The rate of destruction varies between individuals but tend to be rapid in infants and children and slower among adults (Zimmer et al, 1994). Beta cell destruction is marked by production of antibodies. Over ninety per cent of the beta cells destruction would have occurred before signs and symptoms of T1 DM are manifested. This type of diabetes is more common among children and young adults, but as the architecture of T1 DM becomes better understood, this type can be detected in a wider spectrum of ages (American Diabetes Association, 2003). Individuals with T1 DM will require daily insulin injections to manage their lifelong condition (Holt & Kumar, 2015).

2.3.2.1.7.2 Type 2 Diabetes Mellitus

2.3.2.1.7.2.1 Prevalence

Type 2 diabetes mellitus (T2 DM) has met epidemic proportions, particularly in developing countries where approximately 80% of diabetics live (Nanditha, et al, 2016). Worldwide (WHO, 2018) and nationally (ONS, 2019), T2 DM is the most common form of diabetes. In the UK, the prevalence is between 90-95% (ONS, 2019), estimated to be 1:6 (6% of the population). There are nearing one million individuals unknowingly living with undiagnosed T2 DM (Diabetes UK, 2019), which can have an impact on the prevalence and incidence of the disease.

2.3.2.1.7.2.2 Risk factors

Risk factors of DM (***Box 2.1***) can be complex and varied. With the proliferation in the prevalence and incidence, promotional work increases to raise awareness of the risk factors, some of which are considered preventable (Ramchandran, 2014).

Age >35years
Family history of diabetes
Sedentary lifestyle
Recent weight gain
Overweight / Obesity
Presence of hypertension
Gestational diabetes
Central obesity or upper body obesity

Adapted from Ramchandran, 2014

Box 2.1: Risk factors of type 2 diabetes mellitus

2.3.2.1.7.2.3 *Age*

The prevalence of diabetes increases with age. In the UK, one in twenty individuals over the age of sixty-five years has diabetes compared to one in five in the eighty-five years and over age group (DOH, 2002). Recent figures by Diabetes UK (2015) have shown a similar trend. People in the most deprived areas of the UK are 1.5 times more likely than the average to have DM, whatever the age (DOH, 2002).

2.3.2.1.7.2.4 *Ethnicity*

Significant inequalities exist in the risk of developing T2 DM which is more prevalent among the less affluent population (Nanditha et al, 2016; DOH, 2002). A prevalence study

has shown a higher incidence of T2 DM among South Asians than among their Caucasian counterparts (Akhter et al, 1996). T2 DM among South Asians is estimated to be more than 150% between 2000 and 2035. Age, urbanisation and lifestyle factors were described as major determinants with adverse intra-uterine environment and subsequent epigenetic changes labelled as contributory factors (Nanditha et al, 2016). South Asians (Bangladeshis, Pakistanis and Indians) are the largest ethnic groups in urban locations in the UK (Khuti et al, 2009), and T2 DM is 6 times more common among this group (Khuti et al, 2009; Akhter et al, 1996) and up to three times more common in Afro-Caribbeans, compared to the indigenous population (Akhter et al, 1996).

Individuals in South Asian ethnic groups develop diabetes earlier and with lower BMIs (He at al, 2001 & Deurenberg et al, 1998). It is hypothesised that evolutionary changes are believed to be responsible for this. Traditionally, consumption of foods high in carbohydrates among these ethnic groups was considered necessary for dealing with difficult nutritional provisions and arid conditions in which they or their fore parents lived. This in turn developed a high efficiency in the metabolism of carbohydrates. However, as individuals from these ethnic groups become westernised; habits have changed to a more sedentary lifestyle with the consumption of high-sugar, high-fat foods and processed foods. The beta cells then become unable to cope with the dietary changes, resulting in hyperglycaemia and the diagnosis of T2 DM (Holt, 2009). The change in lifestyle is presumably seen as symbols of positive achievements. However, generalisation should be avoided because dietary preferences among ethnic groups can be diverse.

A similar phenomenon is that the risk of diabetes in adult life is highest among those who were exposed to intra-uterine under nutrition and subsequent exposure to an affluent diet resulting in a metabolic challenging environment and increased rates of T2 DM among individuals in Asia and the Pacific (Li et al, 2010).

2.3.2.1.7.2.5 *Obesity and sedentary lifestyle*

In the UK, approximately twenty-five per cent of the female population are obese and thirty-two percent are overweight (National Obesity Observatory, 2012). Individuals with T2 DM are often obese or overweight (Holt & Kumar, 2015; Meeking, 2011). T2 DM is often described as a lifestyle disease because environmental factors like sedentary lifestyle and increasing weight are inextricably linked to the development of the disease state (Boffetta et al, 2011). Approximately, 75-80% of individuals with T2 DM are obese. For every 1kg increase in body weight, there is a 9% relative risk of developing T2 DM (Mokdad et al, 2000). T2 DM and obesity result in insulin resistance (Ben Slama, 1997). The infiltration of fat cells into the pancreatic islet cells exacerbates the effects of insulin resistance. This results in premature and rapid decline in the function of the beta cells in maintaining an increased insulin output (Haslam & James, 2005).

Boffetta et al (2011) in a cross-sectional study found a strong correlation between BMI and prevalence of DM among Asians by age, country and other risk factors. Genetics also has a strong link to T2 DM; stronger than that of T1 DM (Scobie & Samaras, 2010). An epidemiological study among the Pima Indians has shown an increased risk of obesity and T2 DM in offspring exposed to maternal obesity and diabetes (Ma et al, 2015; Pettitt et al, 2004). Socio-economic factors are determinants of health and well-being (Psaltopoulou et al, 2017). Low educational attainment, absence of wealth and living in low-income areas and countries are believed to be predictors of weight gain and obesity (Cohen et al, 2013; Kunst et al, 1998). Independent of BMI, central obesity is strongly associated with the risk of developing DM. However, the debate continues as to whether obesity is a problem of the lower- middle- or higher income households and countries (Dinsa et al, 2012).

As diabetes and obesity reach worldwide epidemic proportions, the concept of insulin resistance and its impact on health are gaining more prominence to inform health policy (Wilcox, 2005). Other metabolic risk factors of raised blood pressure and hyperlipidaemia are derivatives of hyperinsulinaemia developed from insulin resistance (Broom, 2006). Obesity is often associated with an increased risk of hypertension (Greenstein & Wood, 2011).

2.3.2.1.7.2.6 *Aetiology*

T2 DM is more common in the middle- to older-aged individuals but it is becoming more common among younger children (Haslam & James, 2005), notable in younger adults ≤ 40 years (Dabelea et al, 2009). This shift is attributed to a worldwide obesity epidemic (Boffetta et al, 2011) resulting in the dramatic increase in obesity in children and adolescents over recent decades (Tilenius, 2018 & Hammond et al, 2005).

The onset of T2 DM is very subtle in nature, in that, a person can unknowingly have the condition for a considerable length of time before they experience symptoms (as described earlier) and the diagnosis being made (Holt & Kumar, 2015).

2.3.2.1.7.2.7 Complications of T2 DM

The complications of T2 DM can be debilitating and life-threatening. **Table 2.2** has outlined the micro- and macro-vascular complications of T2 DM. These complications can worsen if blood glucose levels are not well-controlled. Retinopathy can lead to blindness, nephropathy to renal failure and neuropathy to leg and foot ulcers, limb amputation and

sexual dysfunction/impotence. Cardiovascular disease and strokes are also common among diabetics (Meeking, 2011).

Cardiovascular disease is among the long-term complications of T2 DM (Vora, 2010) and is more common among Asians (Jalal et al, 2019). This disease type can be inherited (Scobie & Samaras, 2010) but can be mitigated by lifestyle factors like healthy eating and exercise. Diabetes is one of the leading causes of deaths. Globally, in 2016, an estimated 1.6 million deaths were attributed to diabetes (WHO, 2018). In the UK, 24000 deaths have been reported as associated with diabetes (Diabetes UK, 2019).

2.3.2.1.7.3 Gestational diabetes mellitus (GDM)

2.3.2.1.7.3.1 *Definition* and concept

Gestational diabetes mellitus is 'any degree of glucose intolerance first diagnosed during pregnancy, regardless of the gestation and whether or not medication is used for treatment and the condition persists following pregnancy' (Metzer et al, 1998; Buchanan & Xiang, 2010). GDM develops at any time, but most commonly during the second and third trimester (Pickup & Williams, 1991). This intolerance is of varying degrees of severity. This definition of GDM applies regardless of the management option and whether or not the condition persists after pregnancy and/or if the glucose intolerance was undetected prior to the pregnancy. So, a renowned problem of GDM is to clarify if this condition is only a clinical sign or a distinct clinical entity – with implications for the mother and the baby (Hawthorne et al, 1993).

2.3.2.1.7.3.2 Prevalence and incidence of GDM

The prevalence and incidence of GDM varies between populations. The true prevalence of GDM is unknown but its prevalence is increasing worldwide (Wan et al, 2019; Guariguata et al, 2014). The incidence of the condition is increasing in parallel with the increase in rates of obesity, physical inactivity and pregnancy in older women (Hunt & Schuller, 2007, NICE, 2015; Assaf-Balut et al, 2016, Farrar et al, 2016). This prevalence has further increased with the use of new diagnostic criteria (Moses et al, 2011) and universal screening which can increase the prevalence fourfold (Chamberlain et al, 2015).

The current estimate of GDM is between 13% and 30% (Wong et al, 2017) but is dependent on the population studied and the diagnostic method used (Zhu & Zhang, 2016). Reported prevalence are India 27.5%, Sri Lanka 9.9%, Bangladesh 9.8% (Guariguata et al, 2014), Canada 8-18%, (Bhattacharyya et al, 2008) with the highest believed to be in South East Asia. Hirst et al (2012) reported a prevalence of 6.8-10.4% in China and in 2006 China was classified as the second highest in the world (Enquobahrie et al, 2015). Saudi Arabia is 12.5% and 3.8% by WHO criteria and American Diabetes Association criteria, respectively (Al Rowaily & Abolfotouh, 2010).

Previously, a large multi-ethnic study conducted by Dornhorst et al (1992) has shown a higher incidence of GDM in the non-indigenous population, with a relative risk of 3.1 for blacks, 7.6 for South East Asians and 11.3 for women from the Indian subcontinent. A retrospective study by Akhter et al (1996) among Pakistani women living in Karachi showed an incidence of 3.3%. Also, GDM was more likely in pregnancies of Tunisian women older than 35 years for reasons such as obesity (Ben Slama, 1997). GDM was evidenced in most of the patients studied by Ben Slama et al (1997), after the 20th week of

gestation. But early diagnosis was made in 20% of that group and might be suggestive of pre-gravid undiagnosed types 2 diabetics.

More recently in the USA, the prevalence is believed to range between 1 and 14% of all pregnancies, depending on the population studied and the screening tests used. This equates to 7% of all pregnancies (Wang et al, 2015). In the UK, diabetes affects 5% of all pregnancies with 87.5% having GDM (National Institute of Health and Care Excellence (NICE, 2015). In 2008, this figure equated to approximately 3.5% (National Collaborating Centre for Women and Children's Health, 2008), suggestive that a common trend is that most diabetic pregnancies are GDMs and that that trend is increasing.

2.3.2.1.7.3.3 Aetiology

Pregnant women develop GDM when the body cannot produce enough insulin to meet the extra need of pregnancy (Diabetes UK, 2014). GDM occurs when insulin secretion fails to compensate for the elevated insulin resistance as gestation advances (Horie et al, 2015).

GDM arises during pregnancy; usually in the second or third trimester. A correlation exists between GDM detected at late gestation and changes in the placental function. Changes are noted in the utero-placental circulatory system whereby there is increased intervillous diffusion causing a mismatch due to distancing of the immature villi and placental size perfusion. Subsequently, the foetus may be exposed to chronic/acute changes in gas and nutrients resulting in a change of function of the placenta from being 'foetus protector' to a potential source of adverse outcome. It is therefore not surprising that placentas from GDM pregnancies can differ from the non-diabetic pregnancies by an increased foetal placental ratio and villous fibrinoid necrosis and low-grade hypoxia due to blood flow (Gabbay-Benziv, 2015).

2.3.2.1.7.3.4 Risk factors

The most recognised risks factors of GDM are previous large babies (equal to or greater than 4500 grams), previous history of GDM, family history of diabetes, obesity (BMI $\geq$30kg/m^2), ethnic origin especially of the South Asian, Black Caribbean and Middle East groups (***Box 2.2***).

Early detection through screening is of great importance because early intervention is necessary to reduce the maternal and foetal morbidity associated with the condition.

Box 2.2: Risk factors of gestational diabetes mellitus

- BMI above 30 kg/m^2
- previous gestational diabetes
- previous macrosomic baby weighing $\geq$4.5 kg
- family history of diabetes (first degree relative with diabetes)
- minority ethnic family origin with a high prevalence of diabetes

2.3.2.1.7.3.5 Screening and diagnosis

The need for screening at risk women for GDM has been highlighted by early researcher like O'Sullivan et al (1973) and since then the criteria has evolved over the years. In 2008, the UK National Clinical guidelines have recommended that all women are screened by assessment of specific risk factors at their first pregnancy appointment. Any pregnant

woman (not previously identified as having type 2 diabetes) with one or more risk factors should be offered an Oral Glucose Tolerance Test (OGTT) between 24- and 28-weeks gestation (Farrar et al, 2015). OGTT involves a fasting blood test followed by a glucose drink then two hours later another blood sample is taken. Diagnosis is made when either the fasting plasma glucose level is ≥5.6mmol/litre or if the blood level reading after analysis is ≥7.8mmol/litre on the hour blood glucose test (NICE, 2015). NICE (2015) supports this screening practice and has identified the risk factors as outlined in ***Box 2.2***. However, screening practices for GDM vary between health institutions (Kennedy, 2017) countries, regions and year (Zhu & Zhang, 2016). Following the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study, recommendations were made by the International Association for Diabetes and Pregnancy Study Group (IADPSG) to address the inconsistencies (Kennedy, 2017).

Historically, as seen in the North of England which has high levels of deprivation with a significant number of births of women of South Asian origin and a fifth of White British women being obese, only women with risk factors were offered an OGTT at 26-28 weeks gestation. However, blanket screening was introduced, whereby all pregnant women were screened at 26-28 weeks of pregnancy after a study conducted in that area highlighted a rising number of infant mortality due to poor health of pregnant women in that city (Hospital in North of England, 2012).

The screening approaches for GDM are universal or routine screening for all pregnant women or selective screening for women with risk factors or a combination of both. Universal screening should detect most high-risk women, while selective screening adopts a more specific focus on high-risk women only to detect the condition (Zhu & Zhang, 2016). Hence, the latter is deemed more cost-effective (Berger & Sermer, 2009) but may not detect approximately 40% of cases (Ostlund & Hanson, 2003), particularly among

women deemed ‘low-risk’ as women with GDM are usually asymptomatic and may not have associated risk factors (Kennedy, 2017).

Based on World Health Organisation (WHO) 75g of glucose was used for the OGTT test in the North of England study for women between 26-28 weeks of pregnancy. The fasting plasma glucose level for diagnosis was ≥6.1mmol/litre or two-hour glucose ≥7.8mmol/litre (WHO, 1999). The results of the study showed that the proportion diagnosed with GDM increased almost fourfold after the introduction of the policy of offering a diagnostic OGTT to all women compared to selectively offering the test. The proportion of women having severe hyperglycaemia doubled following the change in policy (Farrah et al, 2015). Another finding was that offering universal OGTT was linked to a reduction of admissions to the neonatal unit for the whole obstetric population amongst those diagnosed with GDM. There were similarities in the rates of Elb's palsy and fractures before and after the policy change. Regardless, the rates of these conditions were exceptionally low, and the ratio estimates had very wide confidence intervals which included any association from a marked reduction to a marked increase in risk (Farrar et al, 2015).

The benefits of offering universal testing and treatment of cases were also weighed against the cost of the service and the possible adverse effects to the woman herself. The criteria for the GDM diagnosis did not change during the study period, though it was evident that before the introduction of universal testing three women were tested and each of them was diagnosed with GDM, whereas with the introduction of universal screening, each of the ten women tested positively for GDM. This meant that if it was possible to increase the uptake of testing with the universal invitation, the difference was likely to increase. Similarly, this difference was likely to increase with the uptake of testing with universal screening (Farrah et al, 2015).

Conclusion of the study suggests that offering all women an OGTT was associated with increased identification of women with GDM and severe hyperglycaemia and neonatal benefits were evident for those diagnosed with GDM. However, there were no differences in neonatal outcomes in the obstetric population. It was therefore not surprising that 6% was identified as having GDM when OGTT was offered to all women and GDM diagnosis made based on the WHO criteria (NICE, 2008).

2.3.3 Complications of T2 DM & GDM: maternal and foetal/neonatal

2.3.3.1 Effects on mother, foetus & neonate

Normal pregnancies are non-pathological events characterised by multiple complex hormonal adaptations to ensure a continuous supply of essential metabolites to ensure the growth and development of the foetus (Zeng et al, 2017). Glucose in adequate amounts is supplied to the growing foetus without causing hyperglycaemia and creating a risk environment (Antonio Negrato et al, 2012). Hyperglycaemia, a common feature of diabetes, is an indication of uncontrolled diabetes. Poorly controlled diabetes, particularly pre-conceptually (CEMACH, 2007) and during the first trimester of pregnancy (Knock et al, 1997 & Steel, 1990) are associated with an increased risk of obstetric and neonatal complications, morbidity and mortality (Easmin et al, 2015; Garcia-Vargus et al, 2012; CEMACH, 2007; Ben Slama et al, 1997; Hod, 1996). Hence, pregnancies complicated with T2 DM and GDM are considered high risk. Generally, pregnancy outcomes of women with diabetes are poorer than that of women without diabetes (CEMACH, 2007).

A plethora of evidence has shown an association between GDM (Hosseini, et al, 2018; Kennedy, 2017; Gabbay-Benziv & Baschat, 2015; et al, 2014) and DM (Antonio Negrato et al, 2012; CEMACH, 2007) and increased risks for the mother, foetus and neonate. The

landmark HAPO 2008 study has confirmed this association with GDMs (Kennedy, 2017) and for the pre-gestational diabetics (type 1 & 2), the findings of CEMACH 2002-2003 Diabetes Programme unmasked the public health issue concerning pregnancy outcomes within these groups (CEMACH, 2007). Better screening and antenatal surveillance, including pre-pregnancy care, particularly for pre-existing diabetics (NICE, 2015), the introduction of insulin (Ben Slama et al, 1997) and a better understanding of the conditions, have the potential for improved management of pregnant diabetic mothers and the achievement of a more positive maternal, foetal and perinatal outcome (Nishikawa et al, 2017; CEMACH, 2007).

2.3.3.1.1 Morbidity / Mortality

Diabetes in pregnancy can have immediate or long-term effects to the mother, the developing foetus and the neonate. A hyperglycaemic environment is responsible for not only significant short-term morbidity in the foetus and the neonate but an increased risk of developing diabetes and other chronic, non-communicable diseases in adulthood life (Mitanchez et al, 2015 & Hod, 1996). Congenital malformations, stillbirth, macrosomia, birth injury and postnatal adaptations (such as hypoglycaemia) are more common in babies born to mothers with diabetes. To the mother, miscarriage, pre-eclampsia, preterm labour and injuries during labour are common CEMACH report (2007). These complications are not exclusive to those with pre-existing diabetes, but some are found to be associated with GDM (Horvath et al, 2019; Garcia-Vargus et al, 2012). Women with GDM are prone to prenatal mortality and development of future diabetes. In the UK, thirty per cent (30%) of women with GDM develop T2 DM (Fahami et al, 2015).

2.3.3.1.1.1 Foetal loss

Foetal loss can be categorised into three main groups: those who spontaneously abort for unknown reasons or possibly diabetes-related problems, those who opt for a termination for reasons of foetal abnormalities and otherwise, and thirdly, those who continue the pregnancy but experience a late loss prior to or following delivery. The losses can occur at any time, but the first two seems more common in the first trimester and the latter during the last trimester. Congenital abnormality is one of the reasons for spontaneous foetal loss (Pickup & Williams, 1991)**.** The magnitude of the increased risk of late foetal loss was reported to have increased to approximately fourfold in perinatal death and a fivefold increase in stillbirths (Casson et al, 1997).

The increased risk of stillbirth, in diabetic pregnancies is well documented. Although stillbirth rates for these pregnancies have decreased due to screening, treatment and antenatal surveillance of these mothers, about 4% of all stillbirths remain attributable to diabetes, and diabetic pregnancies continue to be at risk of prenatal mortality (Weissgerber & Mudd, 2015). Overall, increasing age is associated with adverse pregnancy outcome and the risk of stillbirth is increased after thirty-five (35) years even after exclusion of conditions like hypertension and diabetes (Ben Slama et al, 1997).

The incidence of pregnancy loss has had a rapid declined since the introduction of insulin during the 20th century (Ben Slama et al, 1997) and is considered the medicine of choice for treatment of diabetics during pregnancy and labour and delivery (de Valk & Visser, 2011).

2.3.3.1.1.2 Congenital Malformations

The reduction of perinatal mortality in pregnancies complicated with pre-existing diabetes mellitus remain one of the most common measures used to qualify the success of a pregnancy outcome. Yet, the risk of having an infant with congenital abnormality remains significantly high in diabetic pregnancies (Reece & Homko, 2000; Carta et al, 1997; Hod, 1996). Tight glycaemic control in the early weeks of pregnancy, facilitated by good blood glucose control from the pre-conceptual period can reduce the incidence of congenital abnormality in infants born to women with pre-existing diabetes (Steel, 1990). Prevention of malformation was first recognised in offspring of diabetic rats which achieved good glucose control during organogenesis (Ericksson et al, 1984). Also, as the teratogenic process of the diabetic pregnancy is multi-factorial (Albert Reece, 1996), similar outcome may be achieved in a hyperglycaemic state, provided that restoration of normalisation of free radicals and EFAs/phospholipid deficiency state are rectified through dietary supplementation with polyunsaturated fatty acids, myoinositol or antioxidants (Reece at al, 1996 & Albert Reece, 1996).

The incidence of congenital malformation varies between clinical populations (Carta et al, 1997) and ethnic groups (Garcia et al, 2015; Kheder, 1992). Congenital malformation increased with age and affected 2.7% of Tunisian pregnancies of women ≥40 years (Kheder, 1992). Also, raised HBA1c values are associated with a significant increase in congenital malformations and foetal macrosomia (Visser & de Valk, 2015).

The rates submitted to the Office for Neonatal Statistics remains under-reported and may result in surveillance bias. The Diabetes Control and Complications Trial reported a prevalence of 4.7% among controls, compared to only 1.1% among the children of women in the intervention group. This may explain why in a randomised controlled trial with well-

motivated, self-selected diabetic women who received intensive treatment before pregnancy, the prevalence of congenital malformation in infants was similar to that of non-diabetic women (NICE, 2008).

Pregnancy outcomes for women with T1 DM and T2 DM are similar (NICE, 2015). In Casson et al (1997) study, five per cent (5%) of infants born to women with pre-existing Type 1 diabetes had a 10-fold greater risk of congenital abnormality and a five-fold risk of having a stillbirth. The prevalence of malformation in Casson, et al (1997) study was similar to that in comparable studies. Of the seven deaths noted, exclusive of miscarriages and stillbirths that totalled 19% (87), all except one of those infants had congenital abnormality. No difference of congenital malformations was observed between Type 2 diabetics and those with GDM (Ben Slama et al, 1997). Also, no incidence was reported in GDM pregnancies in Pima Indians (Pettit et al, 1980). Botta (1997) in her study showed that the percentage of malformation in offspring of Type 2 diabetic mothers was higher than of women with Type 1 diabetes, despite the former having had better metabolic control. However, it is important to note that oral hypoglycaemic drugs were used by the former group during their pregnancies unlike more intensive treatment in the latter group.

2.3.3.1.1.3 Macrosomia

The definition of macrosomia, like many issues related to ‘diabetes in pregnancy’, remains controversial and is an area for further debate. Whatever that definition, it refers to birth-weight that approximates 4000g and over, irrespective of the sex of the baby (Jardim et al, 1997).

Macrosomia may be due to an increase maternal body mass index, increased body weight gain during pregnancy, absence of adequate placentation and cardiovascular complications (Visser & de Valk, 2015).

Macrosomia is also correlated to time of insulination (Ben Slama et al, 1997). Early insulination is highly significant in the reduction of macrosomia in GDMs. Compared to the non-GDM woman, women with GDM have a higher incidence of macrosomia, regardless of receiving treatment to manage their condition and when corrections were made for gestational ages at birth (Jensen et al, 2000). However, the incidence of macrosomia between GDMs and Type 2s is similar (Cundy & McBride, 1993). Additionally, intensive insulin regimen significantly decreased macrosomia rate in GDM pregnancies from 29% to 10% but monitoring of fasting and pre-meal glycaemia had no impact on preventing macrosomia (Langer et al, 1994). In Casson et al (1997) study, only 13.7% (43/344) of the study sample weighed less than the median birth weight for gestational age of the referenced cohort. Hence, the result has indicated that infant macrosomia remains a problem in diabetic pregnancies.

2.3.3.1.1.4 Intrauterine growth restriction (IUGR) and Pre-eclampsia

Pre-eclampsia and IUGR can have detrimental effects on the mother and the foetus. These complications are associated with reduced placental perfusion (Dessi et al, 2015). Consequently, when a woman presents with either one of these conditions in pregnancy, both are monitored particularly as pre-eclampsia is a major cause of IUGR, pre-term births and perinatal deaths (Sibai et al, 2005). Similarly, IUGR is associated with stillbirth, neonatal death and perinatal morbidity which include cerebral palsy (Jacobson et al, 2008; Kady & Gardosi, 2004 & Barker et al, 1993). Additionally, abnormal placentation is a

causal effect of pre-eclampsia (Dessi et al, 2015) with congenital abnormities, infections and drug and substance misuse identified as causal effects of IUGR (Figueras & Gardosi, 2010).

Much controversy remains about the definition of IUGR, but more accepting is that a baby with an estimated foetal weight below the 10th customised centile has an increased risk of mortality and morbidity even without an abnormal artery Doppler (Figueras et al, 2008).

Pre-eclampsia is characterised by hypertension and proteinuria and tend to occur after 20 weeks gestation (Lopez-Jaramillo, 2018). Adequate nutrition is essential in the prevention of pre-eclampsia. Deficiency in EFAs and other nutrients which include calcium, proteins and vitamins are believed to play a key part in the development of pre-eclampsia (Vasiljevic et al, 1996). Also, increasing maternal age (Phipps et al, 2016) and/or being over-weight/obese (Levine et al, 2000) increase a woman's risk of developing pre-eclampsia. Pre-eclampsia is more common among women with diabetes compared to non-diabetics and the incidence and severity of the condition increases with the severity of the diabetes (Garner et al, 1990).

IUGR and pre-eclampsia, when combined with GDM, where metabolic and blood vessels adaptations to pregnancy are sub-optimal, the morbidity and mortality on mother and baby can be detrimental (Dessi et al, 2015; Gabbay-Benziv et al, 2015). Placental blood perfusion can worsen resulting in failure to respond adequately to hormones such as insulin leading to hyperglycaemia. Subsequently, the effects cannot only have immediate consequences to the health of the mother and baby but may also impact on their future health (Dessi et al, 2015; Gabbay -Benziv et al, 2015). As the effects of T2 DM can be worse or in some cases similar to women with GDM, one can conclude that the incidence and severity of IUGR and pre-eclampsia can be equally measured for the type 2's.

Early detection and management are critical to improve maternal and foetal outcomes and reduce long-term morbidity which includes cardiovascular, respiratory, central nervous system, renal and hepatic diseases which are more common to women diagnosed early with pre-eclampsia compared to women diagnosed late (Lisonkova et al, 2014).

2.3.3.1.1.5 Gestational Ages at Birth

Compared to non-diabetic women, the offspring of GDM women tend to be delivered at an earlier gestational age (Jensen et al, 2000). In Jenson's study, there was also a trend towards a more pre-term delivery in the GDM group although not statistically significant.

In a Tunisian study, pre-maturity rate was 24% (Zanina, 1985) and trend was similar in Ben Slama et al's (1997) study. In Ben Slama et al (1997) study, no case of pre-maturity was observed in women whose mean fasting glycaemia was <5.5mmols whereas it concerned 33% of women whose mean fasting glycaemia exceeded 6.6mmols and that was highly significant. Prematurity rate was 9% for Type 1 diabetic mothers and 14% for mothers with GDM. The mean gestational age at delivery was 38 +/- 2.3 weeks for Type 1 diabetics and 38.6 +/- 1.5 weeks for GDMs (Ben Slama et al, 1997).

The overall incidence of pre-term delivery in Akhter et al's (1996) study was 19.1% (10.6% in excellent control, 19.1% in moderate and 35.2% poorly controlled) and that was highly significant. Therefore, there was a greater significance with the poorly controlled group's control. Early gestational delivery was more common in the GDM group compared to the non-GDM; that was 10.5% GDM and 4.9% non-GDM (Jensen et al, 2000).

2.3.3.1.1.6 Mode of delivery

Jang et al (1997) in their study reported a significantly increased incidence of caesarean section in the GDM group, despite good blood glucose control during pregnancy. In a prospective study carried out by Sermer et al (1995), increasing carbohydrate intolerance was found to be associated with higher incidence of caesarean section rates even though the incidence of macrosomia was reduced with treatment. In Naylor et al (1996) study, the caesarean section rate remained high in the sub-group with GDM.

A Tunisian study by Zanina (1985) found rates of caesarean section at 22% while the study by Ben Slama et al (1997) had an increased rate at 48%. Caesarean section delivery rates of 32.9% for the GDM group compared to 21.0% in non-GDM were reported by Jensen et al (2000). In other studies, the caesarean section delivery rate was 62% (Hawthorne et al, 1993) and 25.9% (Akhter et al, 1996). In the former study, nineteen pre-term labour started spontaneously (Hawthorne et al, 1993). In Jensen et al (2000) study 61% of GDMs compared with 24% of non-GDM were induced. Regardless, foetal outcomes and the frequency of various obstetric complications were reported as the same in GDM and non-GDM groups (Lucas et al, 1993).

2.3.3.1.1.7 Admission to SCBU

SCBU admission rate of infants born to women with diabetes are higher compared to infants of non-diabetic women. In Jensen et al (2000) study, 46% GDM and 12% Non-GDM were admitted to SCBU for reasons like hypoglycaemia and jaundice. In another study, 46.2% of babies delivered by GDM mothers were admitted to the neonatal unit

compared with 11.9% of non-diabetic women (Ben Slama et al, 1997). Of those, nine per cent (9%) infants received intensive neonatal care.

2.3.4 Management of women with T2 diabetes and GDM

2.3.4.1 *Overview*

GDM and T2 DM share the same risk factors and metabolic abnormalities (insulin resistance and hyperinsulinemia) (Ben Slama, 1997). Therefore, their management would be similar depending on the severity of the conditions. For the GDMs, gestational age at diagnosis would be highly significant whereas for the type 2's, medical management on confirmation of pregnancy would indicate where an individual is on the treatment spectrum. Whatever the diabetes type, a positive pregnancy outcome can be determined by an individual's commitment, motivation and self-empowerment. Potential risks can also be minimised with high dose folic acid (5mgs daily), optimal glycaemic control combined with close monitoring of mother and baby during the antenatal period (CEMACH, 2008).

2.3.4.2 Structured education

Pregnancy complications are in part directly or indirectly related to some degree of metabolic control, regardless of the type of diabetes. Reducing complications to a minimum requires that women have near to normoglycaemia during pregnancy. This can be achieved through the joint effort of the specialist team and women themselves. Diabetologic education which involves the provision of adequate knowledge, skills and motivation is the cornerstone to effective management of individuals with diabetes (Roura, 2003).

Various health educational/promotional strategies need to be in place to effectively manage women with pre-existing diabetes from the pre-conceptual period and throughout pregnancy. The Diabetes National Service Framework has recommended structured education programmes for all diabetics and the DESMOND trial has shown the benefits of such programmes for newly diagnosed Type 2s (Davies et al, 2007).

Women with GDM will benefit from similar programmes from screening to the postnatal period and beyond. All health professionals working with diabetic women should be able to support women to go through the various stages of pregnancy from the pre-pregnancy stage feeling confident and empowered to effectively manage their condition and maintain a healthy lifestyle.

Adequate screening and having an appropriate referral system in place following diagnosis of GDM is crucial to the management strategies to be employed, to optimise maternal and foetal outcomes (NICE, 2015). For known diabetic women, it is postulated that pre-conceptual care followed by rigorous management throughout pregnancy until the postnatal period are believed to be the most appropriate measures/strategies to improve the pregnancy outcome of both mother and baby (Casson et al, 1997). Appropriate dietary advice and/or intensive self-home blood glucose monitoring and frequent adjustments of insulin doses are also believed to be important requirements to achieve a positive pregnancy outcome. Additionally, early and appropriate referral of all clients with abnormal blood glucose levels to a multi-disciplinary team (MDT) clinic is considered paramount and essential to reduce the perceived risks associated with maternal and foetal morbidity and mortality (Pickup & Williams, 1991, NICE, 2015). This MDT approach is also required for women diagnosed with GDM to obtain tight control of their diabetes and promote positive outcomes for mothers and their babies (NICE, 2015).

NICE guidelines further recommend that all women of child-bearing age with a history of previous GDM should be empowered through education on lifestyle factors during pregnancy and upon discharge to plan for their future pregnancies. Women should be advised on spacing their pregnancies and how best to lead their lives through healthy eating and exercise to prevent the disease transcending into T2 DM (NICE, 2015). Although the advice is similar on spacing their family, women with overt diabetes are usually advised to aim to complete their family while young because as they get older, the morbidity associated with diabetes can increase and/or become more severe and can complicate future pregnancies.

2.3.4.3 Oral and insulin therapy

Diet and lifestyle modification are usually the first line treatment for women with GDM and if this fails in controlling blood glucose levels, oral and/or insulin therapy is used. Women with T2 DM and starting pregnancy on oral medication would often be started on insulin therapy and a more intensive regimen is started for those already on insulin (Antonio Negrato et al, 2012).

Insulin therapy is the gold standard for treatment and prevention of hyperglycaemia during pregnancy, when lifestyle measures have not maintained glycaemic control. Hypoglycaemic agents such as metformin and glyburide are safe and acceptable alternatives. Metformin crosses the placenta but compared to the benefits of reducing neonatal and maternal hypoglycaemia, there are no serious concerns around tetrogenesis. Compared to metformin, glibenclamide is better tolerated and more effective in lowering blood glucose in women with GDM resulting in lower treatment failure rates than metformin. However, metformin remains the drug of choice as glibenclamide is believed to

be associated with higher rates of pre-eclampsia, neonatal jaundice, longer stay in the neonatal care unit, macrosomia and hypoglycaemia (Kaira et al, 2015).

2.3.4.4 Ultrasound scans

Serial scans for the detection of foetal structural abnormalities are recommended. This should include foetal umbilical artery Doppler before 38 weeks. In women with insulin-treated diabetes who are receiving steroids for foetal lung maturation, additional insulin should be given according to an agreed local protocol and should be monitored closely with scans (NICE, 2008 & 2015 & Albert-Reece et al, 1994).

2.3.5 Maternal nutrition and placental function

Rapid physiological changes occur in pregnancy from the time of conception until birth. Nutritional requirements increase during pregnancy (Blumfield et. al, 2013) and micronutrients and macronutrients need to be tailored to individual needs to optimise maternal and foetal outcomes (Mousa et al, 2019). Increasingly, maternal nutrition from preconception and throughout to lactation is shown to be critical to foetus survival (Ji et al, 2017) growth and development (Ji et al, 2017; Palmer, 2011) and the homeostatic pathways of the offspring (Palmer, 2011). Maternal nutrition determines the intrauterine environment – a phenomenon referred to as 'foetal programming', indicating that the long-term health of the infant is determined by the internal environment in which the foetus has developed (Ji et al, 2017; Myatt & Powell, 2010; Wu et al, 2004). Therefore, good maternal nutrition from conception and throughout is vital to have a positive impact on pregnancy outcome and future health of the newborn. Pregnancy outcome can be deemed successful when the wellbeing of both mother and baby are optimal. Effective synergy between the maternal, placental and foetal systems is critical for this success which can be

facilitated through good maternal health (Myatt & Powell, 2010). Therefore, maternal over-nutrition & under-nutrition can be detrimental to the developing foetus (***Figure 2.1***) (Herring et al, 2017; Wu et al, 2004).

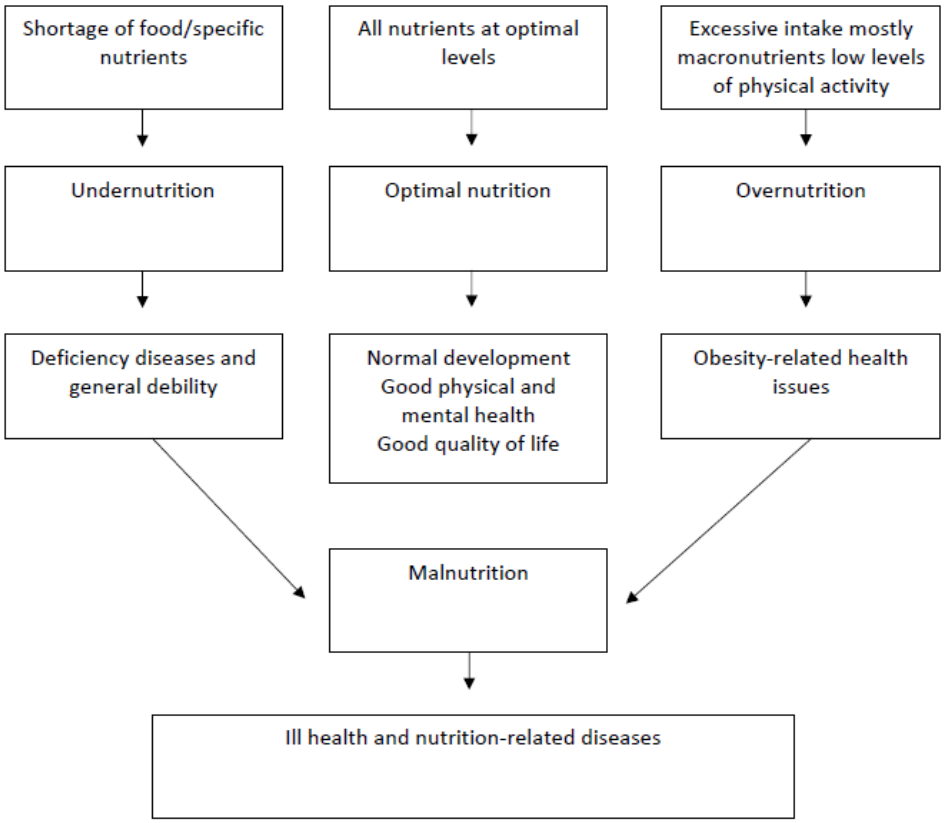


Figure 2.1 Spectrum of nutritional adequacy

2.3.5.1 Placental transfer of nutrients

The foetus receives its nutrition from the mother via the placenta. Placental function depends on the nutritional wellbeing of the mother and subsequently, its supply to the foetus. Substances required by the foetus are selected by the placenta and complex nutrients are broken down into compounds which can be utilised by the foetus. Proteins are

transferred as amino acids, carbohydrates as glucose and fats as fatty acids. Placental capacity increases as pregnancy advances and its size is determined by maternal nutrition (Bell & Ehrhardt, 2013). Therefore, size can impact on placental function and any reduction in the placental foetal blood flow can lead to conditions like intra-uterine growth retardation (IUGR) (Wu et al, 2004). Consequently, adequate maternal nutrition is critical to maternal and foetal wellbeing, particularly as some epigenetic events, modified by diet can impact more than one generation (Danielewicz et al, 2017).

2.3.5.2 Metabolic changes in non-diabetic and diabetic pregnancies

Maternal metabolism changes significantly during pregnancy. The key changes of lipid metabolism during pregnancy are increase in maternal fat deposits and hyperlipidemia (Herrera & Ortega-Senovilla, 2014), characterised by a rise in plasma triacylglycerols in response to an increase in maternal energy requirement (Hummel et al, 1976). Multiple adaptations occur to ensure a continuous supply of essential metabolites (glucose and amino acids) for the growth and development of the foetus (Zeng et al, 2017) and meeting the increased physiological demands of the woman during pregnancy, labour and lactation (Tucker Blackburn, 2013). Total metabolism increases 30% higher than in the non-pregnant woman (Hamzah, 2015). Early pregnancy (up to 20 weeks) is described as the anabolic state and is marked by an increase in maternal fat stores and accelerated placental growth (Tucker-Blackburn, 2013).

Maternal protein nutrition plays a critical part in improving embryonic survival, growth and development, foetal programming and alteration in foetal genes expression. Low levels can result in embryonic losses, intrauterine growth retardation (IUGR) and reduced post-delivery growth due to the absence of specific amino acids responsible for cell metabolism and function. Embryonic death and IUGR are also caused by an increase in maternal

nutritional protein due to amino acid excesses and toxicity derived from amino acids catabolism (Herring et al, 2018). Total concentration of protein decreases by approximately 0.1g/dl during pregnancy due to increased utilisation and excretion (Hamzah, 2015). Approximately 900g of new protein is synthesised by the mother, foetus and the placenta (Tucker Blackburn, 2013).

Maternal carbohydrate is metabolised into glucose which is also critical for maternal and foetal wellbeing. Insulin is necessary for regulation of these processes and the activity of the beta cells increase during early pregnancy (Zeng et al, 2017). Hyperinsulinemia during the first two trimesters of pregnancy is deemed responsible for promoting maternal lipogenesis and fat deposition (Zeng et al, 2017). Approximately 3-4 kilograms of fats are stored in the abdomen wall, breasts, hips and thighs (Hamzah, 2015).

Placental growth is overtaken by foetal growth in the second trimester. In response, the placenta starts producing anti-insulin hormones (oestrogen, cortisol, progesterone and human placental lactogen). As pregnancy progresses, there is a progressive decline in maternal insulin sensitivity (insulin resistance) (Sivan et al, 1999; Buchanan, 1990), increasing to 45-70% by the 3rd trimester (Kuhl, 1991). This triggers a cessation of fat accretion and an increase in adipose lipolysis, hepatic gluconeogenesis and ketogenesis (Catalano et al, 2006; Boaden, 1996), which the foetus utilises in later pregnancy. To compensate, two- to three-fold insulin secretion occurs (Cousins, 1991).

However, if beta cells are defective, women may present with hyperglycaemia in early pregnancy (possible undiagnosed T2 diabetes), and/or GDM may manifest in late pregnancy (Boaden, 1996). This adaptive mechanism is ineffective in diabetic pregnancies where maternal insulin resistance and defect in beta cell reserves and function already exist. Consequently, due to hyperglycaemia, maternal and foetal outcomes may be adversely affected (Homko et al, 2001).

2.3.5.3 *Long chain polyunsaturated fatty acids (LCPUFAs) supply in pregnancy*

Long chain polyunsaturated fatty acids (LCPUFA) are essential fatty acids (EFAs) and include linoleic acid (LA) (omega 6) and alpha-linoleic acid (ALA) (omega 3) (Leaf, 1992). The major metabolites of LA and ALA are arachidonic acids (AA) and docosahexaenoic acids (DHA), respectively. Like DHA, eicosapentaenoic acids (EPA) are the most important metabolites of ALA. Omega 3 and omega 6 fatty acids are required for the growth and development of many organs, particularly the brain and eyes. Other physiological functions include transportation of oxygen, energy storage, cell membrane function, and regulation of cell proliferation (Innis & Friesen, 2008). Also, some markers of inflammation have been associated with anti-inflammatory action with omega 3 fatty acid supplementation and a possible link to maternal-foetal fatty acid transfer (Simopoulos, 2002 & Calder, 2002). The role of LCPUFAs, particularly AA and DHA in relations to pregnancy health and outcomes has received great interest in recent decades, particularly in areas of neuro-visual development (Crawford et al, 1989; Leaf et al, 1992; Colletta et al, 2010) and in optimising the health of pregnancies complicated with diabetes (Min et al, 2016, Min et al, 2014 & Thomas, 2005; Ghebremeskel, 2004; Ghebremeskel, 1998).

2.3.5.3.1 *Foetal and neonatal supply of essential fatty acids (EFAs)*

From conception, EFAs (AA and DHA) foetal demands are high because they are needed for incorporation into the lipids of proliferating membranes (Lauritzen et al, 2001). AA is supplied mainly for foetal growth and development and DHA for development and function of the nervous system (Lauritzen et al, 2001)), which includes the eyes and particularly the brain which has accelerated growth during the second trimester (Colletta et al, 2010; Martinez, 1992; Min & Crawford, 2004; Catalano et al, 1998).

The foetus and neonate can synthesize AA & DHA (Poisson et al, 1993) but at possibly too slow a rate to match its demand (Koletzko et al, 1996). The foetus depends on the mother for optimal supply of these nutrients (AA & DHA) due to its limited ability of synthesising these fatty acids. It is estimated that the foetus accumulates about 70 mg/day of omega-3 fatty acids; both AA & DHA but mainly the latter (Clandinin et al 1980, Martinez 1992).

LCPUFAs mainly AA, DHA, eicosapentaenoic acids form 10-15% of the volume of the cell membrane. Any reduction of this amount may lead to conditions related to prematurity (Crawford, 1993 a & b), low birth weight and neurological impairment (Connor et al, 1992 & Crawford et al, 1976). Gestational length and foetal growth trajectory may also be affected (Myatt & Powell, 2010). AA and DHA increase three-fold in human cerebellum and cerebrum in latter pregnancy and the immediate postnatal period (birth to week 12) (Clandinin et al, 1980). Therefore, reduction of AA at full term (Leaf et al, 1992) and up to the first few weeks following birth, may suggest that maternal supply of fatty acids is critical for optimal foetal and the neonatal wellbeing (Koletzko et al, 1996).

2.3.5.3.2 *Maternal supply of EFAs*

Compared to the non-pregnant woman, pregnant women have lower levels of blood and tissue fatty acids (Ghebremeskel et al, 2000). From week 10 of pregnancy, there is a marked decline in maternal levels of AA & DHA (Otto et al, 1999 & Min et al, 2000). Increased parity (Al et al, 1997) and lactation (Otto et al, 1999 & Min et al, 2000) are associated with depleted stores of AA & DHA.

Maternal supplementation is necessary because AA & DHA are higher in the foetus than in the maternal circulation. Like other nutrients, AA & DHA are selectively transferred from

the mother to the foetus via the placenta (Haggarty et al, 1997). Therefore, the placenta needs to have an adequate supply of these nutrients for uptake, particularly in the latter stage of pregnancy when the foetal demand increases. Any deficiency may compromise pregnancy outcomes (Min & Crawford, 2004). At times of high foetal demand, AA & DHA are met by maternal stores leading to depletion in the maternal stores (Otto et al, 1999). Therefore, EFAs must be eaten by pregnant mothers through foods or supplements because they cannot be synthesized by the body (Bell et al, 1997; Min & Crawford, 2004). Foods rich in omega 3 are fish (such as salmon, tuna, mackerel & sardines) nuts and seeds (such as walnuts, chia seeds & almonds) and plant oils (such as flaxseed oil). Pulses, poultry, green leaves and vegetables are some foods rich in omega 6 (Bourre, 2005).

2.3.5.3.3 *LCPUFAs supply in diabetic pregnancies*

Pre-gestational T2 DM (Hadden et al, 2003; Balsells et al, 2000 & Cundy et al, 2000) and GDM (Wu, 2018 & Sweeting et al, 2016) are associated with increased risk of perinatal and maternal morbidity. These metabolic conditions can affect maternal LCPUFAs status and this in turn can have an adverse impact on the supply of these fatty acids to the foetus (Crawford, 2004).

Experimental studies on diabetes have shown that the enzymes involved in the regulation and synthesis of LCPUFAs are impaired. In other words, diabetes impairs the activity of delta-6 and delta-5 desaturases – enzymes necessary for synthesis of AA and DHA (Brenner et al, 2000; Poisson et al, 1992; El Boustani et al, 1989).

In non-diabetic pregnancies, DHA is taken up preferentially by the placenta and transferred from the maternal to foetal circulation resulting in an increased supply in venous cord blood levels in the foetus compared to the mother (Innis, 1991). In diabetic pregnancies this process of DHA transfer becomes affected (Min et al, 2005a; Thomas et al, 2005;

Wijendran et al, 2000). Compared to women without diabetes, previous studies have found that AA and DHA were significantly lower in the red blood cells membranes of women with GDM (Min et al, 2016, Thomas et al, 2005) and T2 DM (Min, et al, 2014; Min et al, 2004 & 2005a, Min, 2006) and in the plasma and red blood cell of their children (Min, et al, 2014; Thomas et al, 2005; Min 2005a & 2005b).

Also, infants born to mothers with T2 DM and GDM have shorter attention span and motor function (Ornoy et al, 1999), low cognitive performance (Levy-Shiff et al, 2002 & Hod et al, 1999) and a higher risk of language impairment compared to women without diabetes, (Dionne et al, 2008)

Insulin therapy has the corrective ability by normalising fatty acids distribution in the cell membranes through enhancement of the activity of delta-6 and delta-5 desaturases or by improving the incorporation of LCPUFAs (Shin et al 1995; Poisson, 1989 & Poisson et al, 1992). Although this impairment may be corrected by insulin therapy, its effect on maternal and foetal pregnancy outcome remains unknown and would be explored within this study.

Strong evidence exists to support supplementation with LCPUFAs to enhance both maternal and foetal well-being in women whose pregnancies are complicated with diabetes (Min et al, 2016; Min, et al, 2014; Gould et al, 2013; Thomas et al, 2005; Ghebremeskel et al, 2004; Ghebremeskel et al, 1998).

2.3.6 Omega-3 fatty acids and pregnancy outcomes (maternal and foetal)

The search the impact of omega-3 fatty acid supplementation on pregnancy outcomes has yielded very little that was relevant to answer the research enquiries in Phases 3 and 4 because the pregnancy outcome studies were done on women without diabetes. Although

pregnancy outcomes of women with T2 DM and GDM have long been studied, a possible explanation for this was the management complexities which these conditions present may have deterred researchers from conducting studies which added another management dimension to an already challenging situation. Also, pregnancy outcome data was from observational studies and RCTs were on specific aspects of pregnancy, for example pre-eclampsia (Chen et al, 2015) and preterm birth (Olsen, 2000). Consequently, no systematic reviews or meta-analysis were found on the pregnancy outcomes of women with T2 DM and GDM after supplementation with omega-3 fatty acids. Phases 3 and 4 of this study hope to fill this gap.

An early review by Olsen et al (1986) indicated that supplementation with omega-3 fatty acid during pregnancy may increase foetal birth weight by prolonging gestational age. A RCT later followed to assess the efficacy of supplementation in the reduction of preeclampsia, preterm birth and IUGR. Conclusions were that fish oil supplementation reduced the risk of preterm birth but had no effect on preeclampsia and IUGR (Olsen et al, 2000). A Cochrane review conducted by Makrides et al (2006) showed a consistent small increase in mean gestational length but no significant effect in preventing preeclampsia following fish oils supplementation.

Two reviews from the Cochrane Library on fish oil supplementation in T2 DM outside pregnancy have demonstrated that supplementation had no effect of glycaemic control in T2 diabetics but lowered triglyceride and may raise LDL cholesterol particularly in hypertriglyceridemic patients on higher doses of fish oils (Farmer et al, 2007 & Hartweg et al, 2009).

No reviews were found on postpartum diabetic status of women with GDM after fish oils supplementation but a recent meta-analysis on omega-3 fatty acid supplementation during

second and third trimesters has shown no effect on the reduction of developing GDM (Chen et al, 2015) and this was supported by a systematic review conducted by Saccone et al (2016). Also, a RCT conducted by Wu et al (2012) showed no relationship between omega-3 fatty acids and fish/seafood intake nor eicosapentaenoic (EPA) and DHA in the reduction of T2 DM although a modestly lower risk with alpha-linolenic acid (ALA) was suggested. More recently, a systematic review conducted by Ostadrahimi et al, (2016) has purported that enough evidence did not exist to confirm whether or not omega-3 fatty acid should be routinely used in pregnancy to prevent or treat diabetes; indicating that further research is needed.

Another systematic review and meta-analysis of RCTs conducted by Saccone et al (2015) has concluded that in women with a previous history of IUGR and uneventful singleton pregnancy, fish oil supplementation during pregnancy does not prevent the recurrence of IUGR. Saccone et al (2016) in a subsequent systematic review found that there was slightly improved serum-creative protein concentrates in pregnant women who received omega-3 fatty acid, and reduced incidence of hyperbilirubinemia and hospital admission in the newborn. Regardless, they concluded that there was not enough evidence to recommend routine supplementation of omega-3 fatty acid in pregnancy since supplementation had no effect on the prevention of pre-eclampsia (PE), GDM, preterm birth, small for gestational age infants, neonatal development and postpartum depression. More research was suggested as there was a significant reduction in perinatal death in women who started taking omega-3 fatty acid $\leq$ 20 weeks gestation. Similarly, a meta-analysis has shown that there was no effect on the reduction of PE, pregnancy induced hypertension (PIH) and GDM (Chen et al, 2015).

The most recent systematic reviews conducted by Middleton et al (2018) on the use of omega 3 fatty acid during pregnancy has found reduced incidence of preterm birth (<37

weeks), very preterm birth (<34 weeks), low birth weight babies and a possible increased incidence of prolonging pregnancy beyond 42 weeks, reduction of sick babies and neonatal intensive care admission. There was no difference in induction of labour for postmaturity and postnatal depression. In child development and growth, very few differences existed. Conclusion from that study was that very little or no difference existed between the supplemented and non-supplemented groups. That has raised the question on whether an increased dosage could be more beneficial in the reduction of pre-term birth, low birth weight babies and prolonging pregnancies. The need for more empirical studies was suggested to establish if and how outcomes may vary between indifferent populations of women with different increasing doses of omega-3 fatty acid during pregnancy. Having reviewed the overall guidance on fish oil consumption in pregnancy, Taylor et al (2018) have found great variations and have suggested that to achieve impact, guidelines need to be clear and memorable and presented in visual format, supported by technology for the logging of fish oil consumption in real time.

Regardless, conclusions from reviews by Saccone et al, (2016), Ostadrahimi et al, (2016), Middleton et al, (2018) and others which are also of the same ilk have indicated that there is not enough evidence to support or refute the use of fish oil supplementation in pregnancy. This study hopes to contribute to answering the research questions around fish oil supplementation in pregnancies complicated with T2 DM and GDM.

2.3.7 Client engagement

Adequate nutrition and exercise form the cornerstone for effective diabetes management and these lifestyle measures are critical for optimising glycaemic control for the reduction of cardiovascular risk (Holt & Kumar, 2015) and pregnancy related maternal and foetal

diabetes complications (NICE, 2015). Effective management can be facilitated through adequate engagement with the services that are available to pregnant women coupled with professional help and support from HCPs (NICE, 2015).

In deprived boroughs like Newham, diabetic women could have been starting their pregnancy in poor nutritional health. By women participating in the nutritional trial, they would have had additional advice on healthy eating and could have benefited from fish oils consumed and the likely benefits which supplementation offered. Combined, these factors could have enhanced women's nutritional health, possibly resulting in optimal maternal and foetal outcomes. Therefore, it was necessary to obtain existing quality data to have a better understanding of the socio-cultural and economic factors that facilitate engagement. That information was critical for the success of the RCTs (Phases 3 & 4) in areas of client recruitment and follow-up care provision.

For decades, research evidence has highlighted ethnic health inequalities in areas like nutrition and chronic illnesses such as diabetes and pregnancy outcomes. Complex socio-economic and political factors may in part, be responsible for this. Lack of investment in researching the health needs of women from ethnic minority groups may also have contributed to this inequality and may have denied this group which may have the greater capacity to benefit from being researched (Sheikh, 2006).

Empirical evidence published between 2006 and 2016 in a systematic review on Black, Asian and Minority Ethnic (BAME) patient and public involvement in social research and found that ethnic minority patients' involvement usually stopped at the study design phase and rarely progressed to the data analysis and interpretation phases (Dawson et al, 2018). Ethnic minority patients' involvement throughout the research cycle can generate new

learning and a broader research interest which can be influential among and within their cultural groups, resulting in better research engagement.

Pregnancy is ideal for addressing the complex and challenging needs of ethnic minorities (Aquino et al, 2014) and promote positive engagement with HCPs. Current trend is that increasingly, a higher proportion of pregnant women are seeing midwives as their first contact when pregnancy is confirmed (Care Quality Commission, 2018). Therefore, midwives are in a privileged position to 'get it right from the start' by making that first contact a very positive one and using it to form the building blocks on which to form meaningful, trustworthy, enriched and lasting relationships. Such relationships can thrive by keeping women positively engaged with the services available while encouraging them to make informed choices that would make their pregnancy experience a positive and lasting one. This requires that women are provided with adequate and appropriate information about the services that are available to them and through support and guidance, gain the confidence to access those services and be engaged in their personalised woman-centred care plans in meeting the requirements of NICE (2015) and 'Better Births' (National Maternity Review, 2016).

2.3.7.1 Policy strategies: equity in care provision and delivery

Local and national guidance have evolved to improve general health and well-being and maternal and foetal outcomes among disadvantaged women. Management of the pregnant diabetic women is continuously an evolving process, which takes into account one's environment, culture, socio-economic and nutritional factors. The political bias of one's environment at local and national levels is also crucial.

Since 1989, the St. Vincent declaration by the World Health Organisation stated as a five-year goal that the 'outcome of the diabetic pregnancy should approximate that of the non-diabetic pregnancy'. Changes in management strategies in areas of pre-conceptual, antenatal throughout to include neonatal care were acclaimed to that achievement, as combined, they were believed to contribute to the reduction in the morbidity and mortality rates of infants of diabetic mothers. However, despite the notion that care delivered within a multi-disciplinary context is perceived to be paramount to reduce adverse outcomes, all high-risk pregnancies, including those with abnormal blood glucose levels, continue to pose a significant challenge to HCPs.

Quality maternity care service and provision remain at the heart of the NHS which is constantly striving for improvement (Care Quality Commission, 2018). Local governments through strategic planning have similar goals to promote the wellbeing of their local population. In pursuit of achieving that objective, Changing Childbirth was launched over two decades ago and the quality of maternity care and pregnancy outcomes had improved. More recently, as part of the NHS Five Years Forward View, NHS England in 2015 announced a major review of the maternity service. In response to this, the National Maternity Review Report 'Better Births' was published a year later with focus on becoming 'safer, more personalised, kinder, professional and more family friendly; where every woman has access to information to enable her to make decisions about her care; and where she and her baby can access support that is centred around their individual needs and circumstances' (National Maternity Review, 2016).

The Care Quality Commission survey (2017) on women's experiences of the maternity service reported small incremental improvements in all aspects of care including the postnatal period. Obstetric and midwifery teams were then tasked with ensuring that systems were in place and services were provided in such a way as to encourage pregnant

women to positively engage with HCPs and that services should be constantly evolving to meet the changing needs of women (Care Quality Commission, 2018).

By the end of the First World War, life expectancy in the UK increased by 1 year every 4 years but by 2010, that rate slowly decreased. Socio-economic factors contributed to the decline which was manifested through inequalities in health. This has led to the Marmot Review which was published as 'Fair Society, Healthy Lives'. That review found striking differences in health between people living in wealthier and deprived communities. Central to that review was the recognition that a child could be disadvantaged before birth and that accumulates throughout that child's life. For equity, recommendations were made to address the social determinants of health which included education, housing, income, social isolation and disability. A framework of action embedded within six policy objectives (***Table 2.4***) was presented for action by national and local governments, but primarily the latter (Marmot et al, 2010).

Table 2.4: Marmot review 6 policy objectives

Nos.	Policy objectives
1	Giving every child the best start in life
2	Enabling all children, young people and adults to maximise their capabilities and have control over their lives
3	Creating fair employment and good work for all
4	Ensuring a healthy standard of living for all
5	Creating and developing sustainable places and communities
6	Strengthening the role and impact of ill-health prevention

Ten years on and the review has shown that things have become worse, especially for women. The health gap has become wider between the wealthy and deprived (Dixon, 2020). Compared to our European counterparts, the UK has poorer outcomes in some areas and women from disadvantaged backgrounds are more likely to have the worse outcomes (Marmot, 2019). We await the report on 'Better Births' which aimed to address some of those shortcomings within its 5 years plan by providing more personalised and safer care for women and their babies while reducing inequalities and improving birth outcomes (National Maternity Review, 2016). The recent Ockendon report (2020) has shown that we still have a long way to go in achieving safe midwifery care but we remain hopeful.

A woman's pregnancy experience stretches beyond social interactions between her and her baby's life but to the lives of family members, friends, their wider social network and their life-long interaction with health services and their providers. This in turn can determine the immediate and long-term health and well-being of households, the wider population and cost implications for the NHS and local governments (Care Quality Commission, 2018).

Further result of the literature search to support the phenomenon of client engagement can be found in chapter 4.

2.4 The Borough of Newham

2.4.1 *Population profile*

2.4.1.1 Sex, age and ethnic distribution

The borough of Newham has a population of approximately 353,134 (ONS, 2019). In 2019, forty-seven percent (47%) were females with (68%) of the population between ages 18-64 and 24.4% ≤18 years. Ethnic distribution was Asians (45.2%), Whites (27.7%), Blacks (17.7%) and other ethnic groups (9.3%) (Newham London, 2020).

This ethnic mix presents many challenges for health care service providers especially as Newham has one of the highest birth rates in the country which is primarily from a younger population (Newham London, 2015). The average age of an individual living in Newham is 31 with a median of 29 (Newham Census Demographics United Kingdom, 2011).

2.4.1.2 Religion

Religious groups within the borough were Christians 40%, Muslims 8.8%. Hindu 2.1%, Sikh, 9.5% had no religion, 6.4% stated no religion and 1.2% belonged to other religious groups (Newham Census Demographics United Kingdom, 2011).

2.4.1.3 Language

Two percent (2%; 863,000) of the population across England and Wales either spoke little or no English as shown in 2011 census. This figure reduced to 1% in most local authorities except in areas like Brent, Tower Hamlets and Newham where there was a substantial increase to 8% - 9% of the population (ONS, 2015). The diversity of the borough means that over 200 languages and dialects spoken in the borough which explains the increase. In

2017, 59% of the Newham population did not speak English as their first language. People living in the borough who spoke English were 41%, followed by Bengali (13%), Urdu (6%), Gujarati (5%), Punjabi (3%), Portuguese (2%), Hindi (2%), Somali (2%), Polish (2%) and other European languages (13%) (Ipsos MORI Social Research Institute, 2018). The population in Newham is constantly mobile and has become more Asians and moving into the borough as seen in the shift of languages spoken in previous data where people living in the borough were English-speaking (59%), Bengali (7.4%), Urdu (4.4%), Gujarati (3.3%), Lithuanian (2.7%), Tamil (2.3%), Polish (2.0%), Punjabi (1.8%), Romanian (1.6%) and Portuguese (1.4%) (Newham Council Communication, 2006).

2.4.1.4 Language and Health

Data collected from the 2011 census has shown a correlation between non-proficiency in language and poor health. Only 65% of those who were not proficient in English enjoyed good health compared to 88% of those who spoke English well. Also, access and utilization of the available services can also be affected by non-proficiency in English (Newham Council Communication, 2006).

2.4.1.5 Language and Employment

In the 2011 census, non-proficiency in English was linked to unemployment. Employed non-proficient females were 34% compared to 58% who were proficient at speaking English (Newham Council Communication, 2006).

2.4.1.6 Prevalence of diabetes

Approximately 10% of the adult population (26,500) are diagnosed with Type 2 diabetes mellitus (T2 DM). Newham has a very diverse population which has contributed to this high prevalence (NCCG, 2017a; NCCG, 2017b). This has impacted on the number of GDMs locally and subsequently, the future prevalence of T2 DM since up to 50% of GDMs will be diagnosed with overt diabetes within ten years (Wu et al, 2016). Consequently, the obstetric / midwifery challenges are varied and include diabetes in pregnancy.

2.4.1.7 Birth rate

The population of the UK at mid-2018 was estimated to be approximately 66.4 million (66,435,550) – an increase by 395,000 (0.6%); a similar increase to the previous year. The number of births occurring in that year was 744,000 a decrease by 2% (1800.00) compared to the previous year and the lowest since 2006. In mid-2012, birth rate peaked by 813,000 but has subsequently decreased by 69.000 (Office of National Statistics, 2018a). In 2015, the birth rate in Newham was the 4th highest in UK and second highest in London (Aston-Mansfield, 2017). In that year, there were 6226 live births (Aston-Mansfield, 2017) but by 2016 crude live birth rate was 18.7 per 1000 (Clark, 2018). Overall, most births were to women between 25 – 29 years (Public Health England, 2013).

2.4.1.8 Healthy life expectancy **(HLE)**

In the UK, life expectancy in 2017 for males was 79.2 years and 82.9 for females. These figures have remained unchanged in England (between 2014 – 2016) unlike other parts of the UK (Office of National Statistics, 2018b). Historically, the HLE of borough of

Newham is low compared to other local authorities and in 2015-2017 it remained low at 60.7 for females and 65.3 for males (Office of National Statistics, 2018c) indicating that a woman living within the borough has poorer health compared to national average. Recent data has shown a fall in life expectancy in women living in deprived areas in England compared to those in wealthier areas of the country, but this is in contrast to those living in more deprived areas like Newham (Office of National Statistics, 2018c).

2.5 Summary

'Diabetes' and 'diabetes in pregnancy' are not new 'illnesses'. Yet, they continue to pose challenges to HCPs for many years. In the quest for HPs to address these challenges, references are continually made to early empirical evidence for strong clinical decision making. It is therefore not surprising that much early work, like that performed by O'Sullivan (1973) on 'screening for GDM' is still used by many practitioners to inform practice. Similar studies are still being used by researchers as a basis from which to work when conducting relevant studies. More recently, the International Association of Diabetes and Pregnancy Study Group (IADPSG) study (IADPSG Consensus Panel, 2010) is used as the benchmark for screening, supported by NICE guidance (2015) while pregnancy outcome of this group is benchmarked on the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) (HAPO Study Cooperative Research Group, 2008). The lack of consistency probably explains why confusion still exists around the screening criteria for GDM and other issues related to diabetes in pregnancy and the need for future research using these benchmarks.

The search revealed that there was lack of clarity on the screening criteria for GDM. NICE had provided guidance that women with a previous history of GDM should be screened

early after booking and if the result was normal, at 24-28 weeks gestation. However, it remains uncertain whether in boroughs like Newham with a highly diverse population and a high prevalence and incidence of diabetes, whether women with other risk factors like family history and raised BMI are screened too late. From the evidence, there is a strong association with these risk factors and the development of GDM. Therefore, it was pertinent to question whether other risk factors other than a previous history of GDM were responsible for the early detection of GDM and to evaluate the impact of early (≤24 weeks gestation) and late (≥24 weeks gestation) diagnosis of GDM on maternal and foetal outcomes.

The results of the literature search have shown that pregnancy outcomes of women with T2 DM and GDM to be sub-optimal when compared to women without diabetes. Therefore, it would be worthwhile to explore whether fish oil supplementation had any impact on maternal and foetal outcomes, particularly as previous evidence has shown that most pregnant women do not meet the UK recommended dose of at least 2-3 portions of fish weekly with at least 1 portion of oily fish. Fish oil supplementation may therefore be beneficial to meet this shortfall and improve maternal and foetal health and outcomes and was therefore worth exploring.

Prior to embarking on the RCT, it was necessary to establish what factors impacted on a woman's decision on whether to engage with HCPs. It was intended that the results of that question would have helped to facilitate a successful RCT. No high quality data was found on client engagement with HPs within the midwifery fraternity and on pregnancy outcomes of women with T2 DM and GDM after supplementation with fish oils. Regardless, these predictors were used to assess maternal and foetal health and evaluate their pregnancy outcomes using the themes generated and identified below. Consequently, data generated from this study will provide new knowledge in those areas.

Various themes were derived from the literature search and will soon follow. The research paradigms adopted will also be described.

2.6 The philosophical framework and research paradigms adopted

2.6.1 Thematic approach

A thematic approach is the utilization of recurring ideas and thoughts to guide the research under study. When applied to the analysis of research, themes are recurring regularities emerging from analyses of previous studies which help to structure the analysis and findings of one's research study (Blaxter et al, 1997).

Having explored the literature various themes were reoccurring, For example, on 'outcomes of diabetic pregnancies', foetal loss, congenital abnormalities, macrosomia, low birth weight infants, preterm birth, IUGR, hypertensive disorders (PIH, PE, eclampsia), time and mode of delivery and admission to SCBU were common reoccurring themes. It followed naturally that the best line of research enquiry was one of replication, thereby focusing on similar maternal and foetal outcomes based on those themes previously highlighted and discussed, and to establish how findings from this study compared with previous data. As no previous research has been done on the local SADC, utilising existing themes enabled me to draw on the work of other researchers to support or refute my own arguments and draw conclusions based on the findings derived from each phase of this study (Blaxter et al, 1997). It was simply a case of not 're-inventing the wheel'.

The objective of scientific and academic writing is clear communication (Reardon-Castles, 1987). A thematic approach was deemed an appropriate analytic framework to provide adequate contextualization for this study. It has afforded structure in the way the research was conducted, written and findings reported by adding clarity, and hopefully it would provide clear communication for the reader. The research paradigms adopted follows.

2.6.2 Research paradigms

Midwifery care is constantly evolving. Various initiatives have been launched from Changing Childbirth in 1993, the National Midwifery Review (2016) throughout to present day Ockendon report (Ockendon, 2020); all with the focus on safety and the provision of the best possible individualised care to women. Quality care has its foundation from evidence-based midwifery research which informs strong clinical decision making. Midwifery research follows a systematic line of inquiry to answer questions generated from problems faced in clinical practice as I have described in the personal interest section in chapter 1 under 'justification'. Various constructions and interpretations of reality exist within midwifery. These are characterised by the unique way of working within the discipline and conceptualisation of all related phenomena. It is from that philosophical framework that research questions are generated and the methodological approach of any study is driven as I have demonstrated in chapters 1 and 3, respectfully.

Research paradigms more associated with nursing are Positivist (Empiricist) and Naturalistic (Interpretivist / Constructivist / Post-positivist). Commonly used nursing / midwifery research methods are qualitative and quantitative in design and are characterised by ontological and epistemological differences to understand and conduct research (Gortner 1993, Parahoo 1997, Sapsford & Abbott 1992, & Polgar & Thomas 2000).

The construct of the qualitative design meant that this approach was adopted for experimental chapter 1 (chapter 4). This chapter explored the factors which influenced pregnant women's decision to engage with HPs on the nutritional study. This design allowed for an interactive, subjective and systematic approach to describe women's views on engagement gave meaning to those experiences by establishing the rationale for their decision. A non-reductionist approach was conducted to explore women's reality in thoughts, beliefs, behaviours, expectations and perceptions (Foss & Ellefsen, 2001, Polgar & Thomas 2000 & Halcomb, 2021). Through questioning, it was imperative to allow women to explain their reasons for engaging or not engaging and to gather as much information as possible on women's reality in their responses after which the data was categorised for analysis. By allowing women to share their reality, a true conceptualisation of the influential factors to client engagement with HCPs could have been captured and shared. As the data is subjective and open to interpretation, it is associated with the Naturalistic/Interpretivist paradigm (Schalk–Thomas, 1990 & Halcomb, 2021).

The quantitative design was adopted for chapters 5, 6 & 7 where relationships were examined; cause and effect evaluated or test for effectiveness conducted (Halcomb, 2021 & Reaves, 1992). For example, in chapters 6 & 7, the effect of omega-3 and omega-6 on the health and wellbeing and pregnancy outcomes of women with GDM and T2 DM, respectively, were examined. This design lends itself to the reductionist paradigm where the research concept is broken down into parts to be studied to provide concise data after evaluation (Halcomb, 2021). It afforded measurability of the phenomena studied using numerical data which was coded and evaluated in a systematic way with the SPSS statistical analysis tool. Consequently, a more accurate account of the findings was presented within these chapters. This design emerges from the Positivist paradigm which places value on objectivity, rationale, prediction and control (Halcomb, 2021). Also, the

quantitative design was used for evaluation of the maternal and foetal outcomes in all experimental chapters. The quantitative and qualitative issues under inquiry were coded according to themes. This afforded clarity in data collection and analysis, the results obtained and the discussion of the issues raised throughout (Foss & Ellefsen, 2001).

The aims and specific aims are outlined hereunder.

2.7 Aims

The aims of the research programme were to investigate (1) Socio-cultural and economic factors which influence engagement of pregnant women with health care professionals; (2) Comparative pregnancy outcomes and postnatal health of women diagnosed with gestational diabetes mellitus (GDM) in early, and mid to late, gestations periods and (3) The effect of omega-3 fatty acid supplementation on the outcome of pregnancy in women with type 2 diabetes and GDM and the postnatal health of women with GDM.

2.8 Specific aims:

1. Diabetic (n=594) and non-diabetic (n=243) pregnant women aged 17 to 45 were recruited during antenatal appointments or home visits in the first, second and third (up to 32 weeks gestation) trimesters. Detailed demographic, socio-cultural and economic data and the interactions of the women with health care professionals were collected using a questionnaire developed for the study.
2. Pregnant women diagnosed with GDM before 24 (n=212) and after 24 (n=226) weeks of gestation were recruited after diagnosis and up to 32 weeks gestation. Demographic, socio-cultural, economic and clinical, obstetric data were meticulously collected from hospital records and from the participants with the use of a questionnaire.
3. One hundred fifty (n=149) women diagnosed with gestational diabetes were randomised and given DHA (n=75) or high oleic acid sunflower seed oil placebo (n=74) supplement until delivery. Comprehensive data was collected on diabetes management regimen, pregnancy complications (preeclampsia, miscarriage,

preterm labour, etc.), foetal outcome (prematurity, macrosomia, low birth weight, neonatal admission to special care baby unit, etc.) and postnatal glycaemic status. Also, detailed demographic, socio-cultural and economic information was gathered with a questionnaire designed for the study.

4. Pregnant women with type 2 diabetes (n=96) were recruited during their antenatal visits in the first trimester. They were randomised into two groups and given DHA (n=47) or high oleic acid sunflower seed oil placebo (n=49) capsules until delivery. Similarly, their matching controls (non-diabetics) (n=89) were also recruited in the first trimester on their maternity booking appointments or on antenatal clinic visits, and randomised and given DHA (n=40) and placebo (n=49). Demographic, socio-cultural, economic and maternal and foetal outcomes were collected and documented rigorously, using a questionnaire designed for the study.

This literature review provided context for the following chapters. Chapter 3 which follows describes the design of the study which involves the materials and procedures used to conduct the study.

Chapter 3:

Study design and methods

3.1 Chapter overview

Chapter 3 builds on chapter 2 and provides the overall conduct of the study. In this chapter I have described the study design/method which included the study participants' selection process for all phases of the study, the definitions specific for this study, the study intervention, and monitoring and data collection processes, and the ethical considerations (e.g. informed consent) and approval obtained for the study. The statistical analysis tool used is also described.

I was responsible for co-ordinating all aspects of the study from set-up to study close-out. My role also involved training support staff {staff midwife x 1 (full-time) and administrative staff x 1 (full-time)} on the conduct of the study using the study protocol with local guidelines. Supervision was provided throughout the research process. I actively led on screening for eligibility, recruitment, consenting and follow-up of women. I was single-handedly responsible for data collection and evaluation. The supporting midwife focused mainly on recruitment while administrative duties were conducted mainly by the administrator with my help and support. However, this was a multi-disciplinary study which was supervised by staff (Professor and Doctor) from London Metropolitan University and local Professor and Obstetrician, and combined these senior and experienced staff provided me with the supervision and support that I needed to successfully co-ordinate this study project.

3.2 Study participants

3.2.1 Inclusion criteria

This was a double-blind placebo-controlled, randomised, nutritional trial which was conducted between 2007 & 2016 within the borough of Newham; an inner city area of London with predominantly a young and mobile population which is highly diverse and of mainly Afro-Caribbean and South Asian ethnic groups.

Singleton pregnant women who were non-diabetics or had either T2 DM or GDM and ages between 17 and 45 were recruited at Newham University Hospital (NUH). Ages were grouped loosely based on the Office of National Statistics age grouping, the fertile periods in a woman's life and for ease of data analysis. Eligible type 2 diabetics and their matching healthy controls (non-diabetics) were recruited <17 weeks. All women with GDM were recruited up to 32 weeks gestation. Non-diabetic women were offered an oral glucose tolerance test (OGTT) at 28 weeks gestation to exclude GDM (***flow chart 1.1***).

After assessing for eligibility and prior to meeting to discuss the study in detail, a letter of invitation (*appendix 3.1*) and a small patient information leaflet (PIL) (*appendix 3.2*) were posted to clients with their antenatal appointment letters. PILs were posted routinely with booking appointment letters for pre-gestational diabetics and with the invitation letter to the GDES, for those with GDM. For the healthy controls, PILs were given when first approached by the researchers. Therefore, most women would have already received the PIL in the post prior to their first meeting with the researcher/s. The PIL was translated into five different languages (Bengali, Somali, Urdu, Punjabi and Tamil) and therefore the appropriate PIL was given. A sample of the leaflet in Bengali language (*appendix 3.3*) and the order form are enclosed (*appendix 3.4*). The main PIL (*appendix 3.5*) was given to each

woman on first meeting. For detailed discussion of the study and subsequent recruitment, all women were given the choice of home or antenatal appointments (usually ≥ 1 week), at which time the study was explained in detail while giving women and/or their family members the opportunity to ask questions and address any concerns.

Non-diabetic women (healthy controls) were referred from the maternity booking centre and routine antenatal clinics while diabetic (T2 DM & GDM) women were from the specialist multi-disciplinary antenatal diabetes clinic (SADC) where all women with diabetes in pregnancy were cared for by a multi-disciplinary team comprising of a lead Obstetrician and Diabetologist and their supporting colleagues of similar and lower grades, Diabetes specialist midwives (DSM) and nurses (DSN) and a dedicated dietitian. Women with GDM were also referred from the weekly gestational diabetes education sessions (GDES) which were run by specialist staff {DSMs (including the researcher**),** a DSN and dedicated dietitian}.

After the initial meeting, women who showed interest were offered a follow-up appointment on their subsequent antenatal visit/s to the hospital or in their homes. Several episodes of communication and visits were often necessary to initiate recruitment but these were guided by women's informed choice on whether they were to be followed-up. Although time consuming, it was necessary primarily for clients' informed decision making to be respected and was critical to promote client engagement, compliance and continuation on the study. Follow-up appointments with family members and/or their friends were encouraged, offering women the choice to be supported and their decisions respected.

Women recruited were T2 diabetics (n=136), GDMs (n=458) and non-diabetic women (n=243). All subjects (n=837) were included in the first arm of the study (chapter 4) (Phase

1) (*Graph 4.1*) while only women who had a diagnosis of GDM on OGTT (n=438) (Phase 2) and women with a diagnosis of GDM and consented to the nutritional arm of the study (n=149) (***Figure 6.1***) were included in Phase 2 (chapter 5) and Phase 3 (chapter 6), respectively. Subjects with pre-gestational T2 DM (n=96) and consented to participate in the nutritional arm of the study were matched with consenting women without diabetes (n=88) and included in the final arm of the study as indicated in chapter 7 (Phase 4) (***Figure 7.1***) (***Flow chart 1.1 & Figure 3.1***.).

Pre-gestational diabetics with T2 DM were referred to the SADC from their general practitioners (GPs), outreach diabetic clinics and some women self-referred. Women diagnosed with GDM were referred to the GDES within one to two weeks of diagnosis with the condition. Please refer to 'clinical pathway' in section 3.8 for further information on this aspect.

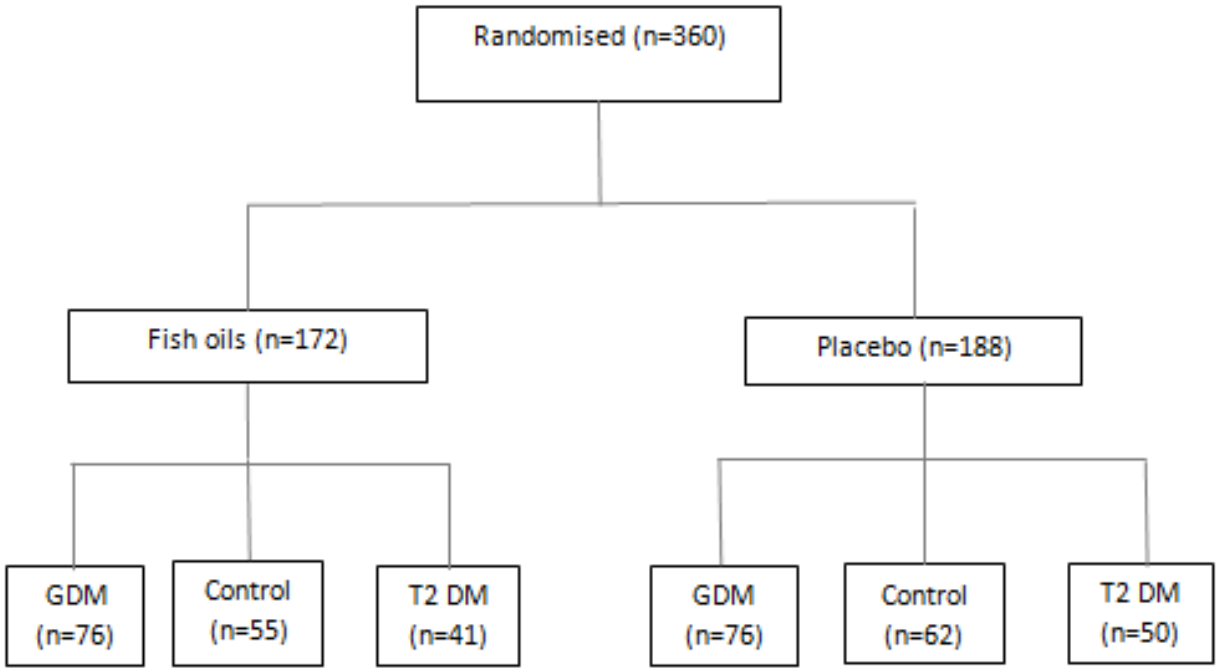


Figure 3.1 Distribution of subjects

3.2.2 Exclusion criteria

Women diagnosed with GDM on random blood glucose and HBA1c were excluded from the study to reduce variations in screening regimen and conflict when evaluating outcomes measures. Also, these tests were not considered robust enough to make a confirmed diagnosis of GDM. Women were excluded if they were pregnant with more than one foetus, had known major foetal abnormalities in the index pregnancy, and chronic medical conditions such as sickle cell, kidney and heart diseases and HIV/AIDS. Women were also excluded if they were planning to receive tocolytic or corticosteroids therapy, taking omega 3 supplements, allergic to fish and/or fish products and those who were vegetarians

had a choice of whether or not they wanted to be included into the study. After re-evaluation, women with T1 DM (n=19) were excluded from the analysis as recruitment of subjects within this group was small and could have affected credible statistical analyses.

3.3 Screening and diagnosis

Local screening and diagnostic criteria were broadly based on NICE 2008 guidance and the European Association for the Study of Diabetes (EASD) criteria (1979).

3.3.1 *Gestational Diabetes Mellitus (GDM)*

Women who were deemed high risk had a random blood glucose at booking and an OGTT at 16 weeks (or soon after booking appointment, if a late booker) and at 28 weeks gestation, if that early result was normal. Risk factors of GDM were a previous history GDM, macrosomia (birth weight of ≥4 kilograms), previous unexplained stillbirth and a family history of diabetes (first degree relative with Type 1 or Type 2 diabetes), maternal age ≥40 and either overweight or obese (BMI ≥30 kg/m^2). Non-indigenous women were also considered to be in the high-risk category as currently specified in NICE (2015) guidance, but at the time of conducting the study, ethnicity was not a risk factor for screening; yet it was used when evaluating all outcome measures.

Diagnosis of GDM was made with a fasting glucose concentration of ≥6.1mmol/l and /or a 2-hour value ≥7.8mmol/l after 75g glucose challenge. An OGTT was regarded as the gold standard for screening for diabetes. The test involved overnight fast followed by taking blood at 0 and 120 minutes with a glucose load of 75 grams of glucose given to the woman after taking the blood samples. Women who were diagnosed with GDM and who met the WHO criterion of T2 DM were still classified and treated as GDMs. This criterion follows.

3.3.2 *Type 2 diabetes mellitus (T2 DM)*

At Newham, a diagnosis of T2 DM was made on either a fasting blood glucose of ≥7.0mmol/l and / or two-hour blood glucose of ≥11.1mmol/l after using the WHO screening tool of 75g oral glucose load. With symptoms of diabetes, a random blood glucose level of ≥11.1mmol/l was also used to make a diagnosis of T2 DM. Women with T2 DM were included in the study regardless of how the diagnosis was made but that diagnosis should have been made pre-pregnancy.

3.3.3 *Glycaeted haemoglobin (HBA1c) and blood glucose levels*

HBA1c measures glycaeted haemoglobin which identifies average plasma glucose concentrate in one's blood. HBA1c test results provide an overview of blood glucose control or lack of it, when used in conjunction with blood glucose (BG) readings and an individual's state of health and well-being. Target value during pregnancy was 43mmol/mol (6.1%) (NICE, 2008 & 2015) and measured 4-weekly according to local policy to provide an estimate of glycaemic control. As pregnancy progresses, HBA1c values are usually low due to increased erythropoietin and the decreased lifespan of the red blood cells to 90 days (from 120 days) (Lurie & Mamet, 2000). HBA1c drops between 12-16 weeks gestation, drops even further between 20-24 weeks (Hanson et al, 1983 & Lind & Cheyne, 1979) and increases during the third trimester (Phelps et al, 1983). Consequently, HBA1c screening throughout pregnancy is no longer encouraged as routine practice.

3.3.4 *Self blood glucose monitoring*

All women with T2 DM & GDM were taught self blood glucose monitoring **(**SBGM) and asked to record their blood glucose readings in a diary four times daily; on waking (pre-breakfast) and 2 hours post meals (breakfast, lunch & dinner). Normal BG values pre-meals were 4.0 mmol/l – 6.0 mmol/l and 4.0 mmol/l - 7.7 mmol/l 2-hours post-meals (NICE, 2008) unlike current target values of 4.0 mmol/l – 5.5 mmol/l and 4.0 mmol/l – 7.7 mmol/l, respectively, as recommended by NICE (2015).

3.3.5 *Definition of Overweight and Obesity*

The World Health Organisation's definition for overweight and obesity were adopted for this study, regardless of ethnicity. Overweight is classified as a body mass index (BMI) ≥25 – 29.9 kg/m^2 and obese and BMI ≥30 kg/m^2. According to local hospital protocol, women with BMI>30 kg/m^2 were referred to a dietician for lifestyle advice on healthy eating and exercise.

3.4 Data collection

Written informed consent forms designed for the study (*appendix 3.6*) and based on the principles of the Declaration of Helsinki and ethically approved (*appendix 1.2*) were obtained prior to data collection. Detailed demographic, socio-cultural, economic and clinical information were obtained from subjects during one-to-one interviews at the time of recruitment. Questionnaires designed for the study (*appendices 3.7 & 3.8*) were used for data collection. Questionnaires were developed based on discussion with investigators and stakeholders eg. obstetricians, diabetologists, midwives, nutritionists and researchers and they were piloted and modified.

Maternal outcome measures included pregnancy complications, early (miscarriages) or late (stillbirth) pregnancy loss and neonatal death. Data on hypertensive disorders in pregnancy (pre-eclampsia / eclampsia, or systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg), onset of labour (induction of labour, spontaneous vaginal delivery & elective caesarean section), mode of delivery (vaginal, assisted / instrumental or caesarean section) and postpartum glycaemic status were also collected. Other outcome measures included ante-partum haemorrhage, postpartum haemorrhage, cholestasis, anaemia, ante-partum thrombocytopenia and non-alcoholic fatty liver but due to their small numbers, they were grouped together as 'other pregnancy complications'. Clinical data included maternal diabetes status, and glycaemic treatment and control.

Foetal/ neonatal outcomes included birth maturity (extremely preterm <28weeks, very preterm 28-31weeks, moderate preterm 32-36weeks, term 37-40 weeks & post-maturity ≥41weeks), Apgar scores (1 minute, 5 minutes & 10 minutes), low birth weight (birth weight ≤2499grams), macrosomia (birth weight ≥4500grams), intra-uterine growth restriction (confirmed on ultrasound - maternal age and ethnicity - and gestational age specific birth weight <90th centile), congenital abnormality, admission to special care baby unit, reasons for admission (hypoglycaemia, respiratory distress syndrome, prematurity, suspected infection and poor feeding/jaundice) and stillbirth and neonatal death.

Confounding factors included maternal characteristics of age, marital status, ethnicity, religion, ability to speak English, body mass index (BMI) and parity. Socio-economic factors of employment status of subjects and partners and pre-existing medical conditions and obstetric complications developed in the index pregnancy were also collected.

Predictors of pregnancy outcomes were factors which influenced women's decision to engage or not to engage with HCPs (experimental chapter 1), risk factors for early

detection of GDM and the gestational ages at time of diagnosis of GDM (experimental chapter 2), and omega-3 and omega-6 fatty acids supplementation or placebo intake in women with GDM (experimental chapter 3) and T2 DM (experimental chapters 4) and establish how these have impacted on maternal and foetal outcomes (as outlined earlier).

Baseline data which included socio-demographic, medical and obstetric data were taken at the time of recruitment of women for all phases of the study, using the fore-mentioned questionnaires (*appendices 3.7 & 3.8*). For the index pregnancy, obstetric data was collected prospectively from subjects through questioning and examination of women's maternity hand-held records, the hospital case notes and electronic patient records (EPR). The EPR system was also used to collect supporting clinical obstetric (past and current), medical (past and current) history and biochemical (eg. haematology and OGTT) measurements.

Follow up of subjects and timing of data collection varied. They were study-phase-specific. For subjects in Phase 1 (chapter 4) and Phase 2 (chapter 5), additional data on maternal and foetal health and pregnancy outcome were extracted following delivery. Following baseline data collected for subjects in Phases 4 (chapter 6) and 5 (chapter 7), all subjects received a courtesy call one week after recruitment to assess how they were having started the study and taking the supplements and any relevant data was collected at that time. Thereafter, subjects were followed up 3-monthly from the date of recruitment until the postnatal period. At 28 gestational weeks, non-diabetic women (only) attended for an OGTT to exclude GDM and all women were reviewed at 34-36 weeks (when they attended for a scan for a sub-study). Postnatal OGTT results were collected following the tests which were offered 6-8 weeks after delivery, for women in Phases 2 (chapter 5) and 3 (chapter 6) of the study. Intervals for data collection were at recruitment and on follow-up visits as indicated in ***flow chart 1.1***.

Data collected was categorised and labelled into variables and coded for analysis. For example, study groups 'Control-T2 DM and T2 DM' (experimental chapter 4) and gestational ages at time of diagnosis of GDM {< 24 weeks (early) and ≥ 24 weeks (late)} (experimental chapter 2) were used with the view of testing the hypotheses and achieving the research aim/s. As detailed below in the ethical approval and informed consent sections, the services of health advocates / translators employed and approved by the Trust were utilised for interviews and data collection from women who spoke little or no English.

3.5 Ethical approval and informed consent

Application for ethical approval for this study was sought by collaborators from the London Metropolitan University. Ethical approval was granted by the East London and the City HA Local Research Ethics Committee 3 (REC reference number 06/Q0605/89) and registered with ISRCTN Register (REC reference no. ISRCTN68997518) (*appendix 3.9*). Local approval was also granted from the hospital (*appendix 3.10*) which provided insurance cover for the study (*appendix 11*). The principles of the Declaration of Helsinki and Good Clinical Practice were applied throughout and formed the basis for written informed consent from participants. Informed consent forms, PILs and questionnaires were approved by the ethics committee. PILs were translated in five commonly spoken languages (Tamil, Punjabi, Bengali, Urdu, and Somali) within the borough. Non-English speaking women were supported by health advocates (translators) employed by the Trust (Newham University Hospital Trust) and were complemented by 'language line' which was an external translation services approved by the Trust. All investigators, researchers

and subjects were blinded to the allocation of supplements during recruitment and unblinding occurred only after the completion of the study.

The supplements used within this study are licensed and on sale in health shops, supermarkets and chemists in the UK and other countries. Women were informed of this and advised to report any possible side effects. Checks were also made one week after recruitment and on follow-up appointments as indicated above in flow chart 1.1. A dedicated mobile telephone number linked to myself was given to women for use at anytime of the day including out of hours.

3.6 Intervention and blinding

After recruitment, women were randomly assigned to either treatment or placebo group. The treatment group received two gelatine capsules a day containing DHA enriched formula totalling 600mg DHA and 200mg AA from the time of recruitment until delivery. For the same period, the control (placebo) groups received two gelatine capsules containing mainly oleic acid (721 mg) for daily use. Capsules for both groups were encapsulated in identical oblong soft gelatin (75 mg in size) and to prevent oxidation, 10μg of vitamin E (d-alpha tocopherol) per gram polyunsaturated fatty acids was added to each capsule. Allocation of supplements was as outlined in the supplement protocol (*appendix 3.12*). To maintain the quality of the supplements, they were stored in a cool and dry cupboard, away from direct sunlight. Daily temperature checks were done at varied times during the day to ensure that the temperature remained within the guided range of 4-20 degrees to monitor the stability of the supplements. In adherence to research governance, the cupboard, was kept locked at all times and was accessible only by the research team.

Supplements were provided by Equazen/Vifor Pharma Ltd. (Glattbrugg, Switzerland) which was responsible for randomisation generated through a random code. Only the Data Manager knew the randomisation codes which were assigned in batches of nine bottles per subject and distributed three bottles at a time which was planned around routine antenatal follow-up appointments. Unblinding of allocation was made available to investigators, researchers and subjects after data analysis.

Non-diabetic women received dietary advice on healthy eating in pregnancy, initially by the booking midwife and this was reinforced by research staff on recruitment. All T2 diabetic women received more targeted individualised advice and a supporting healthy eating advice sheet (*appendix 3.13*) was given at booking and they were monitored throughout till delivery. For this group (T2 DM) one-to-one consultation with the dedicated dietitian in the SADC continued based on individual need, if blood sugar levels were unstable. Women diagnosed with GDM received similar dietetic input as women with T2 DM from the point of diagnosis of the condition and education received on their visit to the GDES and throughout till delivery.

Contemporaneous records of the supplements were kept to ensure the correct code allocation to subjects on recruitment and on follow-up visits. Each subject was allocated an individual distribution record sheet and all supplements dispensed were logged on an electronic spreadsheet. That rigorous process allowed for ease and accuracy of distribution and monitoring of compliance.

3.7 Compliance

3.7.1 Self blood glucose monitoring

As previously mentioned, target values for blood glucose values pre-breakfast and post meals were 4.0-6.0mmol/l and 4.0-7.7mmol/l, respectively. Women's blood glucose levels (BGLs) were reviewed individually and holistically with their activity/exercise, diet and the general health and wellbeing of women and their babies. Lifestyle advice on healthy eating and exercise were provided by a dedicated dietician for pregnant diabetic women and by the DSN & DSM. For women with unstable BGLs, they received dietetics input throughout pregnancy until delivery; based on need. Lifestyle advice was reassessed and individual care plans put in place. Where necessary, women were re-taught SBGM. A diary was given to each woman to record their glucose readings which were reviewed on each antenatal visit. A weekly telephone clinic run by a DSN for women considered high risk with unstable BGLs also proved beneficial.

3.7.2 Supplements

Compliance was monitored on follow-up visits, through courtesy calls and keeping comprehensive records of supplements taken. Regular phone calls (including out-of-office hours) were made, and follow-up visits were at the hospital and/or home visits. Following the initial dispensing of the supplements at recruitment, women were given further supply at 3 months and 6 months (from the date of recruitment) and monitoring also occurred at those times. Supplements were discontinued at delivery.

Women were encouraged to bring their supplement bottles (including empties) on their follow-up appointments and a count was made and documented. For those who did not

bring their bottles, a home visit was done, or women were asked to provide via text or telephone call, a count of the sealed bottles and the remainder of supplements in the bottle in use.

Food diaries were given to women for completion, but the return rate of the completed forms was low, and the quality of the returned forms was poor. Consequently, the decision was made to omit data from food diaries from the analysis.

3.8 Clinical pathway

3.3.1 *Overview*

All pregnant women with diabetes (GDM and T2 DM) were monitored in the combined specialist antenatal diabetic clinic (SADC) throughout until delivery by a specialist multidisciplinary team as previously described. Women were given access to the direct line for the specialist team and bleep numbers for the DSM and DSN were also made available to them with the view of optimising BGLs at the earliest opportunity to minimise any likely adverse events. Teaching was provided for women to become informed about diabetes on pregnancy and pregnancy on diabetes. Also, women were provided with relevant information on care provision within the SADC to enable them to engage with the specialist team and make informed decisions about their care.

Follow up appointments were dependent of diabetes type, BG control and maternal and foetal and health and wellbeing. A weekly telephone clinic service was also provided to review the BGLs of all women who were extremely ‘high risk’ and/or who caused concern, regardless of their diabetes type.

3.8.2 *Pregnant diabetic and non-diabetic women*

Women were referred by their GPs to NUH maternity department for booking soon after a pregnancy diagnosis was made. Some women also self-referred. The aim was to book all women before 10 weeks gestation. Early booking was necessary to collect information on current and past medical, clinical and non-clinical information for early identification of risk factors, to effectively plan women's care and increase the likelihood of positive maternal and foetal outcomes (NICE, 2016). Follow up appointments were then planned and women and their babies monitored during antenatal visits with blood tests, physical examinations and scans. All diabetic women were followed up in the SADC and non-diabetic women in routine antenatal clinics or in specialised clinics for conditions like hypertension. The non-diabetic women for this study were recruited from the maternity booking centre and routine antenatal clinics.

3.8.3 *Pregnant women with GDM*

At booking, women with risk factors of GDM were offered an OGTT at 16 and/or 28 weeks gestation. Once a diagnosis of GDM was made as outlined above, women were offered an appointment within 1-2 weeks period to attend the GDM education session which adopted a multidisciplinary approach with a diabetes specialist midwife (DSM), diabetes specialist nurse (DSN) and a dietician, and in keeping with NICE (2015) recommendations; the national body by which the SADC is governed.

GDM and its potential risks to mother and baby were explained. Teaching on lifestyle factors of healthy eating and exercise were discussed within the context of women managing their diabetes and the vital role those factors play in optimising maternal and

their foetal health and wellbeing. Education was supported by a healthy eating leaflet for reference (*appendix 5*). Women were advised to walking for at least 20-30 minutes daily as physical exercise during pregnancy have shown benefits in improving glycaemic control and in preventing and treating complications during pregnancy such as GDM and obesity (Filhol et al, 2014).

Women were taught self blood glucose monitoring (SBGM) on a 1:1 basis to empower them to take control of their health and well-being. They were advised to monitor blood glucose levels (BGLs) four times daily; on waking (pre-breakfast) and 2 hours post breakfast, lunch and dinner and they were advised to contact the specialist team if their reading were outside the normal ranges (4.0mmol/l – 6.0mmol/l on fasting and 4.0mmol/l – 7.7mmol/l 2-hours post meals). Local values were formulated based on NICE (2008) recommendations and with consideration given to the local clientele. The acceptable normal ranges of BGLs and the interval between food consumption and testing remain historical debatable issues.

At the end of each teaching session, individuals were given the opportunity to evaluate their results within the context of the normal ranges and advice was given on the actions necessary when results were abnormal. Additional practical help was provided at the end of each session to women who expressed anxieties around SBGM.

Teaching sessions were opened to partners, family members and/ or friends to enable them to provide support to the newly diagnosed women with GDM, at a time which can be most daunting and stressful. Also, the wider family circle would have received the teaching and should have benefited personally and be better able to support women to successfully manage their condition and ultimately improve their pregnancy outcomes and postnatal health.

Women with GDM were offered a follow up appointment in the SADC a week after attendance to the education session and were reviewed on an average of 2-3 weeks intervals and weekly if BGLs were unstable. SBGM was stopped during the immediate postnatal period provided that their BGLs were stable. SBGM continued if their BGLs were out of range and women were reviewed on their follow-up appointments 6-8 weeks later by members of the diabetes MDT.

3.8.4 *Pregnant women with T2DM*

Pregnant women with T2 DM were given the earliest appointment once the pregnancy was confirmed. On the first appointment in the multidisciplinary specialist SADC, women were seen by a Consultant Diabetologist who reviewed their blood glucose readings and a plan put in place for future follow-up appointments. On the initial appointment, women were also reviewed by an Obstetrician with whom a Diabetologist would have conferred prior to devising an individualised plan of care. This was deemed necessary to embrace the multidisciplinary approach to care to achieve to perceived benefits of this notion and in keeping with recommendations from NICE (2008 & 2015) and local guidelines.

Women with T2 DM were taught SBGM prior to being referred to the SADC and their skills were re-assessed by the DSMs or DSNs on arrival to the clinic. Any issues related to SBGM were addressed and clients were monitored through review of their BGLs and questioning during 1-2 weekly antenatal clinic appointments. Women were also encouraged to call the specialist midwives/nurses if BGLs were out of range and/or they had any concerns with SBGM, and where issues were raised, one to one teaching ensued. Women with T2 DM continued SBGM beyond discharge from hospital as that activity formed part of their daily routine.

3.9 Pharmacotherapy

Pharmacotherapy (oral anti-diabetic medication and/or insulin therapy) was commonly used in the management of glycaemic control for women with T2 DM, pre-pregnancy and during pregnancy. Women with GDM and whose BGLs were not controlled by lifestyle modification during the antenatal period, also received similar treatment. Oral pharmacological agent was metformin which was considered the effective non-insulin drug of choice during pregnancy. An individualised sliding scale regimen was provided for the intra-partum period for all women on medication.

Post-delivery, anti-diabetic medication was stopped for all women with GDM and their diabetes control was reviewed. A six to eight weeks OGTT was offered, and lifestyle modification behaviour was encouraged. Women with abnormal BGLs at this stage were followed up in the outreach diabetes clinics and those with normal results were to have annual diabetes review; arranged by their GPs. Women with T2 DM were returned to their pre-pregnancy medication regimen, unless otherwise indicated. Also, they were followed-up in the outreach diabetes clinic within six to eight weeks.

3.10 Statistical Analysis

Methods used to analyse the data will be described in each chapter, but independent variables were used to assess their impact/effect on women's participation or lack of participation in research, early and late diagnosis of GDM and maternal and foetal outcomes with and without supplementation with omega 3 fatty acids, throughout to the postnatal period. Variables included women's ages, booking BMI, ethnicity, religion, employment status, their ability to speak English, gravida/parity, gestation at time of

approach, chronic medical history, and pregnancy complications developed. HBA1c levels at recruitment and pre-delivery and anti-diabetes treatment (pre- and during pregnancy) were recorded. Occupation was classified using the Registrar General Social Class Scale (1911-present).

Pearson's Chi square analyses were used to establish any relationship between the confounding variables and predictors. For example, to establish the relationship between lack of engagement and pregnancy outcomes, the Pearson's Chi square crosstabulation test was used. Also, Chi square test was used to evaluate any differences in pregnancy outcome data.

Independent T-test analyses were performed to compare identified predictors with confounding factors and predictors and pregnancy outcomes. The independent samples T-test was used to assess whether the means of those in the active and placebo groups differ in terms of birth weight and Apgar scores, in keeping with McCormick et al (2015) model on hypothesis testing. Based on theory of variance as outlined by (McCormick et al, 2015), the assumption made was that birth weight and Apgar scores which are continuous dependent variables, are normally distributed and of similar variations within the active and supplemented groups (homogeneity of variance). Therefore, the Independent T-test is deemed appropriate for use in testing whether the means of women who received fish oils and placebo differ in their babies' weight and Apgar scores at 1, 5 and 10 minutes.

Anova test of homogeneity of variance was used to test if there were differences between the fish oils and placebo groups with e.g., birth weight and Apgar scores were statistically significant.

IBM SPSS for Windows (version 25) (IBM Corporation, Armonk NY, USA) was used to perform all statistical analyses. Statistical significance was defined as **$p<0.05$**.

In each chapter, the statistical analyses relevant to those chapters will be discussed further.

The following chapter 4 has examined the factors that influence a pregnant woman's decision on whether or not to engage with HCPs on the nutritional study and the impact that that level of engagement or lack of engagement had on pregnancy outcomes.

Chapter 4:

Factors that influence engagement of pregnant women with health professionals: impact on pregnancy outcomes

4.1 Chapter overview

In this chapter, I have explored the factors which influenced women's decision on whether or not to engage with HCPs and the impact of their decision on maternal and foetal outcomes. To do this, women with T2 DM, GDM and without diabetes were approached by random selection and offered the opportunity to take part in the nutritional study and information on their decision, socio-cultural, economic and clinical data collected using questionnaires *(appendices 3.7 & 3.8).* This chapter is the first phase of the study and laid the foundation for chapters 5 – 7 (Phases 2-4), particularly around subjects' selection and participation. Please refer to chapter 3 for further details on subjects and methods.

4.2 Introduction

4.2.1 Concept of engagement / non- engagement

Engagement is defined as "actions individuals take to obtain the greatest benefit from the health care services available to them" (Gruman et al, 2010 p 351). Engagement and non-engagement are terms use mainly within this first phase of the study. Lack of engagement and non-engagement mean the same and are used interchangeably within this study. Women were described as non-engaged when they didn't show interest or ask questions about the study even though the PILs would have been offered in their spoken language and non-English speaking women would have been supported by health advocates on their initial meetings. Non-engagement extended to include when women declined accepting the PIL, offered no response when approached by researchers who were HCPs, declined hearing about the study and declined participation. Lack of engagement was measured by women declining to become part of the study when first approached or after being followed up. A positive level of engagement described when women showed interest in the

study and was later recruited after providing written informed consent, irrespective of the number of encounters with HCPs. Partial engagement referred to the 'considerers' who showed interest and were given time to decide whether or not they wanted to become part of the study. Final outcome refers to the final decision made by women whether they engaged or not engaged with HCPs, regardless of whether or not they showed interest and/or were followed up.

4.2.2 Health inequality and access

The experience of pregnancy and childbirth is very complex and multidimensional. Local health authorities are tasked with making the journey along the trajectory from the antenatal period to the postnatal period as pleasant and risk-free as possible. The quantity and quality of resources invested along this pathway to reduce the mortality and morbidity associated with pregnancy and childbirth vary depending on where in the world women are cared for and by whom.

Globally, approximately 289,000 deaths occurred in 2013, a 49% decrease from 1990 (WHO, 2014). Disparities exist between the developing countries and the Western world in the maternal mortality ratio (MMR). For example, in 2015, the rate in the Philippines was 114:100,000 compared to 12:100,000 in countries like the UK (WHO, 2015). Disparities also exist among BAME women who tend to have poorer birth outcomes compared to their White counterparts (Garcia et al, 2015). Additionally, as DM is more prevalent among this group (Diabetes UK, 2020 & 2016), and pregnant diabetics have poorer birth outcomes compared to non-diabetic women (Hosseini, et al, 2018; Kennedy, 2017; Gabbay-Benziv & Baschat, 2015; Antonio Negrato et al, 2012 & CEMACH, 2007), BAME women with diabetes would be severely disadvantaged in terms of their birth outcomes. Regardless, to

reduce this disparity, women can benefit from health care if they have considerable knowledge and are motivated to actively engage with the care available to them (Gruman et al, 2010).

Only 58% of women can access prenatal care worldwide (UNICEF, 2017). This is postulated to be due to 'proximity to services, transportation cost, availability of skills, knowledge of availability services, knowing when to seek care, underlying gender inequality and cultural hierarchy that can affect decision making', which individually or combined can result in morbidity and/or mortality (Public Health England, 2017).

In the UK, the national drive is to reduce the Maternity Mortality Ratio and this can be achieved by services tailored to meet the needs of its local populations and women engaging with HCPs involved in their care and accessing care in a timely fashion. This is based on a philosophy of putting women, their babies and their families at the centre of care planning and delivery (National Maternity Service Review, 2016 & NICE, 2016).

4.2.3 Maternity service provision: Newham University Hospital (NUH)

Almost 50% of the population of Newham in East London are female with nearing 70% between ages 18-64, as previously shown in chapter 2 (section 2.4.1) and combined these factors have impacted on the high birth rate within the borough. The ethnic distribution is vast with the indigenous group being in the minority (Newham London, 2015 & 2020). Asians remain the dominant cultural group (Newham London, 2015 & 2020) but the population is still rapidly changing with the arrival of Europeans now residing in the area and with an explosion of regeneration projects which started prior to and continued since London 2012 Olympics (ONS, 2019). Deprivation and cultural diversity result in complex

medical and social issues and a high incidence of morbidity and co-morbidities (O'Driscol 2018, Dawson et al 2018, Jayaweera 2010, Cumberlegde 2015 & DOH 2013}, possibly the cause of Newham having one of the highest death rates in London (ONS, 2017).

In pregnancy, women can present with complex health needs comprising of pre-existing conditions like hypertension while others are diagnosed during (gestational diabetes mellitus - GDM) and/or after pregnancy (postnatal depression). Individually or combined, these can have adverse effects on women's and their babies' health and pose a huge challenge for healthcare policy makers to provide equitable access for all (Szczepura, 2005). Therefore, it is paramount that care services embrace the notion of a multi-dimensional, multi-faceted and all-encompassing approach to ensure that holistic high care quality care is available for local pregnant women to reduce potential morbidity and mortality.

The local midwifery services embrace this framework which incorporates specialist midwifery provision in areas, for example, mental health, diabetes and when caring for teenage and vulnerable women. The primary aim of these services is to promote engagement of women with specialist HCPs for help and support, through an accessible service with continuity of care for their client groups and to optimize the quality of care provided.

Additionally, Newham has one of the highest annual birth rates compared to other UK hospitals (Aston Mansfield Community investment Unit, 2017 & ONS, 2015) and this has formed the cornerstone for the recent rebuild of the maternity wards and facilities following consultation with the local community and stakeholders in order to develop services that match the needs of its local service users. Other new and improved services include community birthing centre facilities, a low-risk birthing unit, and a 24-hours

telephone helpline. Women can also self-refer for booking and access the 24-hours assessment unit. On one hand, the availability of these services to meet the needs of local women is good but on the other hand, women need to engage with the services made available to them, for those services to become meaningful.

4.2.4 Possible reasons for non-engagement: local and national measures taken

Despite the availability of local services, women are not adequately engaging, and this is believed to be due to traditional ways in which health service is delivered {Blunt, 2014; National Institute for Clinical Excellence (NICE), 2014a} and possibly, structural and population characteristics (NICE, 2014b). Positive and negative women's experience at the reception desk may have similar impact on their engagement with HCPs throughout their pregnancy journey. In recognition of this shortfall, some work through patients and public engagement programs has commenced to encourage active engagement in the decision-making around the tendering and procurement of services (Newham Clinical Commissioning Group, 2017). NICE (2014b) has provided guidance on the use of community engagement for care delivery. In 2016, 'Better Birth' was launched by the National Maternity Service Review to reduce variations of quality of care and encourage women to be partners in care planning. Based on this notion, local needs can be tailored and delivered with local women being at the nucleus to promote equity in accessing services.

A cross sectional analysis of routine data was conducted at the local hospital to evaluate the initiation of engagement with maternity services for antenatal care. Conclusions were that late engagement was predominantly among non-Whites who were born outside the UK and were non-English speaking. Women of Afro-Caribbean origin were more likely to

engage with services late compared to their White counterpart. Other factors included high parity, maternal age younger than 20 and living in temporary accommodation (Cresswell et al, 2013).

Despite this information, the scientific evidence remains outstanding for the Newham specific needs on the core factors responsible for engagement and/or lack of it, particularly as Newham is more research active. One may argue that it is futile having the best high-quality resources if (a) disconnect exists between service providers and users it purports to embrace and (b) a lack of understanding exists as to why that it.

Therefore, only by addressing the problem through research, the factors responsible for the lack of uptake of services can be effectively addressed and maternity services restructured to form the bedrock for engagement with local pregnant women who can then benefit significantly from the services available to them. Subsequently, potential morbidity and mortality can be reduced. A plethora of evidence has demonstrated a strong link between deprivation and adverse nutritional health (Marmot, 2019; Marmot, 2012; Marmot, 2005) and pregnancy outcomes (Min et al, 2016). With deprivation being significantly high in the borough of Newham, this study provided women with the opportunity to improve their nutritional health with omega-3 fatty acid (Min et al, 2016; Colletta et al, 2010).

4.3 Aims

The aim of this phase of the study is to investigate: -

Socio-economic, cultural, religious and demographical factors which hinder effective engagement of pregnant women with health professionals in the London Borough of Newham. It was therefore necessary to: -

- Establish the level of engagement of local women with HCPs.
- Elucidate factors which may influence or hinder effective engagement with HCPs.
- Evaluate possible ramifications of patients' lack of engagement on maternal and foetal outcomes.

4.4 Subjects and Methods

This was an observational cross-sectional study of pregnant women who were willing to participate or not participate in a nutritional study. Women were ages between 17 and 45 and booked at Newham hospital. They were randomly approached at the hospital's specialist antenatal diabetes clinic (SADC), gestational diabetes education sessions (GDESs), and routine maternity booking and antenatal clinics and offered the opportunity to improve their nutritional health.

All subjects approached were included in this phase of the study. Women with T2 DM and their matching comparisons without diabetes were recruited before 17 weeks gestation while women with gestational diabetes mellitus (GDM) were recruited when the diagnosis was made and up to 32 weeks gestation. Women without diabetes were also recruited up to 32 weeks gestation (***Figure 4.1***).

A questionnaire designed for the study (*appendix 3.8*) was used for data collection on reasons given by women for their engagement or non-engagement with HCPs on the nutritional study. Other information collected included women's ages, ethnicity, religion, employment status, ability to speak English, parity, gestation at time of approach, past and present medical and/or obstetric history and/or complications and whether or not women had support with their decision on engagement or lack of engagement with HCPs. Please refer to chapter 3 for further details.

4.5 Statistical Analysis

As mentioned in the Subjects and Methods Chapter (3), the IBM SPSS Statistics for Windows (Version 25) analysis framework was used. The levels of measurements used for this chapter were nominal and categorical data. The number of cases which appeared in each category was counted to either accept or nullify the hypotheses and descriptive statistics were used to establish frequencies in data, for example, to establish how many women were in the different study groups and engaged when first approached and after follow-up. Data are reported as mean and standard deviation (mean ± SD). Two different unpaired samples were compared and therefore the independent T test was used, for example, to test the statistical mean between birth weight, gestational ages at delivery and levels of engagement.

The Chi-square (cross tabulation), Pearson's correlation test for independent samples was used to analyse any pattern of observed frequencies which may suggest a correlation between variables tested (Foster 2001 & Kinnear & Gray 2008), for example, whether there was an association between marital status and engagement and engagement and pregnancy outcomes. Statistical significance was defined as $\mathbf{p < 0.05}$.

4.6 Results

4.6.1 Characteristics of subjects

4.6.1.1 Study subjects distribution

Of the total number of subjects studied (n=837), women diagnosed with GDM was 458 (55%) while healthy controls and T2 diabetics were 243 (29%) and 136 (16%) respectively (***Graph 4.1***). Overall, the level of engagement within these groups was 120 (33%) controls, 151 (42%) GDMs and 90 (25%) T2 diabetics.

4.6.1.1.1 Age, marital status, parity, BMI and folic acid use

Baseline characteristics of the participants are provided in ***Table 4.1***. Most engaged pregnant women (n=370) were married (n=326, 88%) (**p < 0.001**) with a mean age of 31 years and between 21- 40 years (n=339, 92%) (**p < 0.002**). Mean BMI was 28.51kg/m^2 with 131 (35%) and 139 (38.0%) being overweight and obese, respectively while 86 (23%) were of normal weight (**p < 0.939**). Mean parity was 2.08 with similar distribution of women being first time mothers (n=127, 34%) and those having had 2 - 4 children (n=129, 34%). Of all women studied, 50% (429) used folic acid during pregnancy and 72% (256) users were among those who engaged.

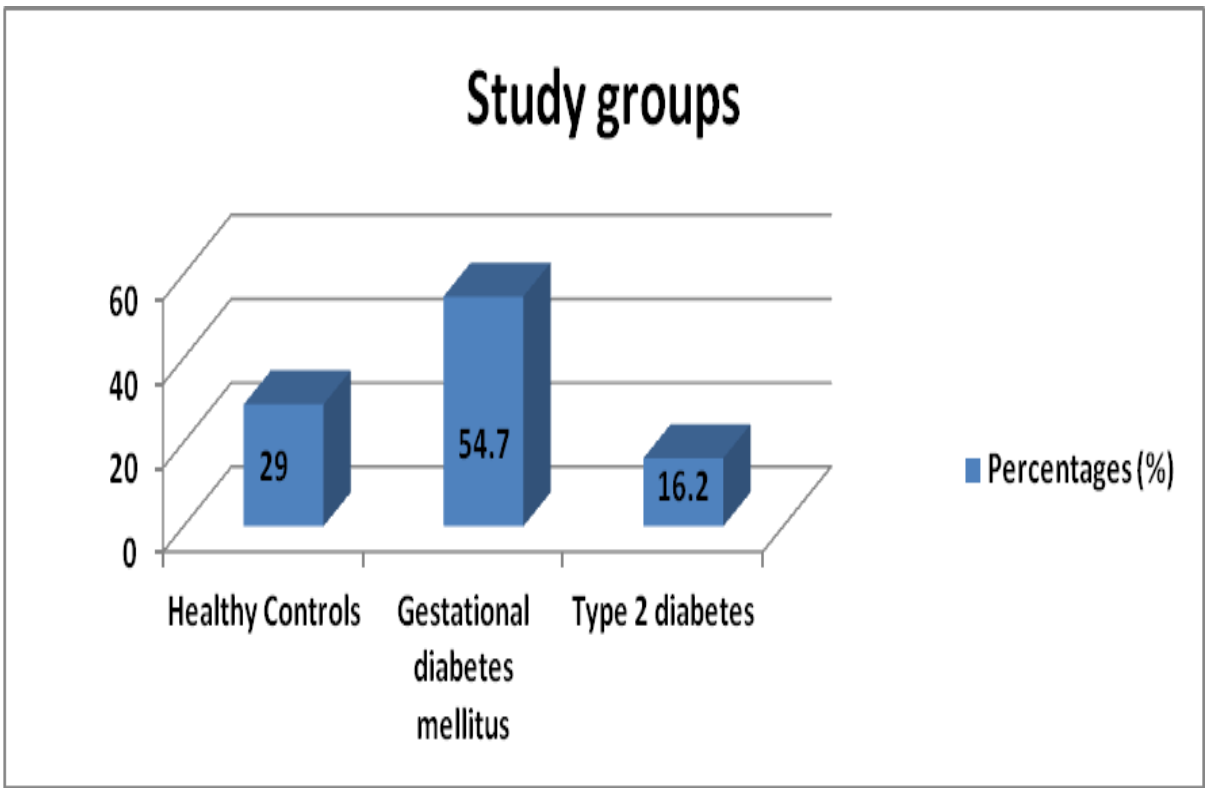
4.6.1.1.2 Ethnicity, Language & Religion

Two hundred and one (54.3%) of engaged women were Asians, 113 (31.0%) were Afro-Caribbeans and 55 (15%) were Whites (**p < .002**). Two hundred and eighty-one (70%) were English-speaking (**p < .001**). Most women were Muslims (n=182, 58%), followed by Christians (n=149, 33%) and Hindus & Sikhs (n=29, 9%) (**p < .002**) (***Table 4.1***).

4.6.1.1.3 *Employment status: engagement and ethnicity*

Most women were unemployed (n=204, 41%); very few occupied managerial positions (n = 39, 10%) and for the remaining who worked (n=127, 29%), they were in the middle to lower economic groups (**p = .026**). Most partners did routine manual jobs (n=134, 36%) while 62 (17%) were managers and the remaining (n=174, 24% each) equally distributed between intermediate jobs and the unemployed (***Table 4.1***).

Combined, patients in the managerial / intermediate occupations, and those who were either students, unemployed or had routine / manual jobs were 17 (31%) / 38 (69%) Whites, 42 (37%) / 71 (63%) Afro-Caribbeans and 39 (19%) / 162 (81%) Asians, respectively, for the engaged 17 (31%) / 38 (70%) Whites, 42 (37% / 71 (63%) Afro-Caribbeans and 39 (19%) / 162 (81%) Asians (**p < .000**). Respectively, for the non-engaged, there were 15 (30%) / 28 (70%) Whites, 28 (27%) / 75 (73%) Afro-Caribbeans and 57 (19%) / 250 (81%) Asians (**p < .000**). For the partners, combined in professional jobs and for those who were either lower paid jobs and the unemployed were 11 (20%) / 44 (80%) Whites, 46 (41%) / 67 (59%) Afro-Caribbeans and 86 (44%) / 109 (54%) Asians, respectively (**p < 008**). For the non-engaged, there were 11 (22%) / 39 (78.0) Whites, 29 (28%) / 74 (72%) Afro-Caribbeans and 19 (39%) / 188 (61%) Asians (**p < .001**), respectively, combined in professional jobs and for those who were either lower paid jobs and the unemployed (***Table 4.2***).



Graph 4.1: Distribution of subjects

Table 4.1: Characteristics of participants

	Levels of engagement on 1st approach				Final levels of engagement after follow-up		
	Engaged	Non-Engaged	Considerers	P value {Standard deviation (df)}	Engaged	Non-Engaged	P value {Standard deviation (df)}
No. of Subjects (n)	226	310	255		370	460	
Age, (years) (mean 31.0) n (%)				.941 (6)			.875 (3)
≤ 21	6 (24.0)	10 (40.0)	9 (36.0)		12 (45.2)	14 (53.8)	
21 – 30	99 (28.3)	140 (40.0)	111 (31.7)		158 (43.2)	208 (56.8	
31 – 40	109 (29.0)	142 (37.8)	125 (33.2)		181 (45.5)	218 (54.6)	
≥ 40	12 (30.0)	18 (45.0)	10 (25.0)		19 (48.7)	20 (51.3)	
Body mass index (BMI) (kg/m2), (mean 28.51) n (%)				.936 (6)			.939 (3)
Underweight (<18.5)	5 (27.8)	8 (44.4)	5 (27.8)		8 (42.1)	11 (57.9)	
Normal weight (18.5-24.9)	53 (26.6)	83 (41.7)	63 (31.7)		86 (43.4)	112 (56.6)	
Over weight (25.0-29.9)	79 (30.2)	88 (33.6)	95 (36.3)		131 (46.1)	153 (53.9)	
Obese (≥30)	84 (28.8)	115 (39.4)	93 (31.8)		139 (45.0)	170 (55.0)	
Marital status, n (%)				.000 (2)			.001 (1)
Married	191 (26.1)	296 (40.4)	245 (33.5)		326 (42.3)	445 (57.7)	
Single	33 (58.9)	13 (23.2)	10 (17.9)		42 (75.0)	14 (25.0)	
Ethnicity, n (%)				.000 (4)			.002 (2)
All Whites	41 (40.6)	36 (35.6)	24 (23.8)		55 (52.4)	50 (47.6)	
Afro-Caribbeans	74 (35.7	78 (37.7)	55 (26.6)		113 (52.3)	103 (47.7)	
Asians	110 (22.8)	196 (40.7)	176 (36.5)		201 (39.6)	307 (60.4)	
Religion, n (%)				.000 (4)			.000 (2)
Hindu & Sikh	23 (31.5)	31 (42.5)	19 (26.0)		29 (38.2)	47 (61.8)	
Muslim	90 (20.5)	182 (41.5)	167 (38.0)		182 (39.4)	280 (60.6)	
Christian	106 (42.1)	85 (33.7)	61 (24.2)		149 (56.9)	113 (43.1)	
Language, n (%)				.002 (2)			.001 (2)
English	180 (32.3)	207 (37.2)	170 (30.5)		281 (48.4)	300 (51.6)	
Non-English	46 (19.7)	103 (44.0)	85 (36.3)		89 (35.7)	160 (64.3)	
Parity, (mean 2.08) n (%)				.559 (6)			.783 (3)
No previous child	72 (25.6)	117 (41.6)	92 (32.7)		127 (43.2)	167 (56.8)	
1 child	65 (33.0)	73 (37.1)	59 (29.9)		97 (47.1)	109 (52.9)	
2-4 children	81 (29.1)	107 (38.5)	90 (32.4)		129 (43.6)	167 (56.4)	
≥ 5 children	7 (20.6)	13 (38.2)	14 (41.2)		16 (48.5)	17 (51.5)	
Employment status - Subjects, n (%)				.075 (6)			.026 (3)
Managerial & professional	26 (33.3)	24 (30.8)	28 (35.9)		39 (50.6)	38 (49.4)	
Intermediate	40 (33.9)	44 (37.3)	34 (28.8)		59 (48.8)	62 (51.2)	
Routine & Manual	46 (35.7)	44 (34.1)	39 (30.2)		68 (53.1)	60 (46.9)	
Unemployed, student, not classified / stated	114 (24.5)	198 (42.5)	154 (33.0)		204 (40.5)	300 (59.5)	
Employment status - Partners, n (%)				.083 (6)			.006 (3)
Managerial & professional	35 (25.9)	50 (37.0)	50 (37.0)		62 (44)	79 (56)	
Intermediate	53 (33.3)	50 (31.4)	56 (35.2)		87 (52.1	80 (47.9)	
Routine & Manual	82 (31.3)	104 (39.7)	76 (29.0)		134 (47.9)	146 (52.1)	
Unemployed, student, not classified / stated	56 (23.8)	106 (45.1)	73 (31.1)		87 (36)	155 (64)	
Folic acid use, n (%)							.000 (1)
Yes					257 (60.5)	168 (39.5)	
No					102 (27.6)	267 (72.4)	
Support present when engagement decision made, n (%)							.000 (2)
Alone					67 (91.8)	6 (8.2)	
Husband and/or relative					196 (77.2)	58 (22.8)	
Unknown					105 (24.4)	326 (75.6)	

Table 4.2: Employment: engagement / non-engagement and ethnicity

	Ethnic groups			
Employment status (Patients)	**Whites**	**Afro-Caribbean**	**Asians**	**P value / standard deviation (df)**
***Engaged*, n (%)**	**55**	**113**	**201**	.000 (6)
Managerial & professional	5 (12.8)	24 (61.5)	10 (25.6)	
Intermediate	12 (20.3)	18 (30.5)	29 (49.2)	
Routine & Manual	13 (19.1)	17 (25.0)	38 (55.9)	
Unemployed, student, not classified / stated	25 (12.3)	54 (26.6)	124 (61.1)	
***Non-Engaged*, n %**	**50**	**103**	**307**	.000 (6)
Managerial & professional	6 (15.8)	10 (26.3)	22 (57.9)	
Intermediate	9 (14.5)	18 (29.0)	35 (56.5)	
Routine & Manual	14 (23.3)	19 (31.7)	27 (45.0)	
Unemployed, student, not classified / stated	21 (7.0)	56 (18.7)	223 (74.3)	
Employment status (Partners)				
***Engaged*, n (%)**	**55**	**113**	**201**	.008 (6)
Managerial & professional	7 (11.3)	19 (30.6)	30 (58.1)	
Intermediate	4 (4.6)	27 (31.0)	56 (64.4)	
Routine & Manual	29 (21.6)	34 (25.4)	71 (53.0	
Unemployed, student, not classified / stated	15 (17.5)	33 (38.4)	38 (44.2)	
***Non-Engaged*, n %**	**50**	**103**	**307**	.001 (6)
Managerial & professional	4 (5.1)	9 (11.4)	66 (83.5)	
Intermediate	7 (8.8)	20 (25.0)	53 (66.3)	
Routine & Manual	22 (15.1)	25 (17.1)	99 (67.8)	
Unemployed, student, not classified / stated	17 (11.0)	49 (31.6)	89 (57.4)	

4.6.2 Engagement at first and final meetings

The level of engagement on first and final meetings was similar, regardless of demographic profiling. Of all women studied, approximately a third (n = 229, 29%) consented when first approached while 255 (32%) agreed to be followed up to participate in the nutritional arm of the study. Of those considerers, 14 (5.6%) were lost to follow-up and 12 (4.8%) exceeded the gestational age and were therefore no longer eligible to making a decision on whether or not to engage. Approximately two-thirds (n = 140, 61%) engaged when they were followed up totalling an overall recruitment of 370 (43.2%) and non-engagement 460 (53.7%) (***Tables 4.1 & 4.2***). Sixty-seven (18%) women were alone and 196 (53%) received social support when the decision was made whether or not to engage (**p < .000**).

The reasons given for women's lack of engagement are outlined in ***figure 4.1***. These reasons were varied and included no research interest 90 (22.6 %), time constraints 39 (9.8%) and family members influence 41(10.3%). That level of persuasion was apparent among the 'considers' (n = 255), as 140 (55%) wanted 'more time' to make a decision while the remaining 115 (45%) stated that they needed to discuss the study with their husbands and/or family members prior to making that decision.

There was some reluctance to disclose the reasons for lack of engagement and this accounted for nearly a third (n = 121, 30.3%) of non-participants. For women who engaged, the likely benefits to their baby were the main reason given as can be surmised in ***Box 4.1***. Other reasons were religious, altruistic (wanting to do good for others) and use of little of their time.

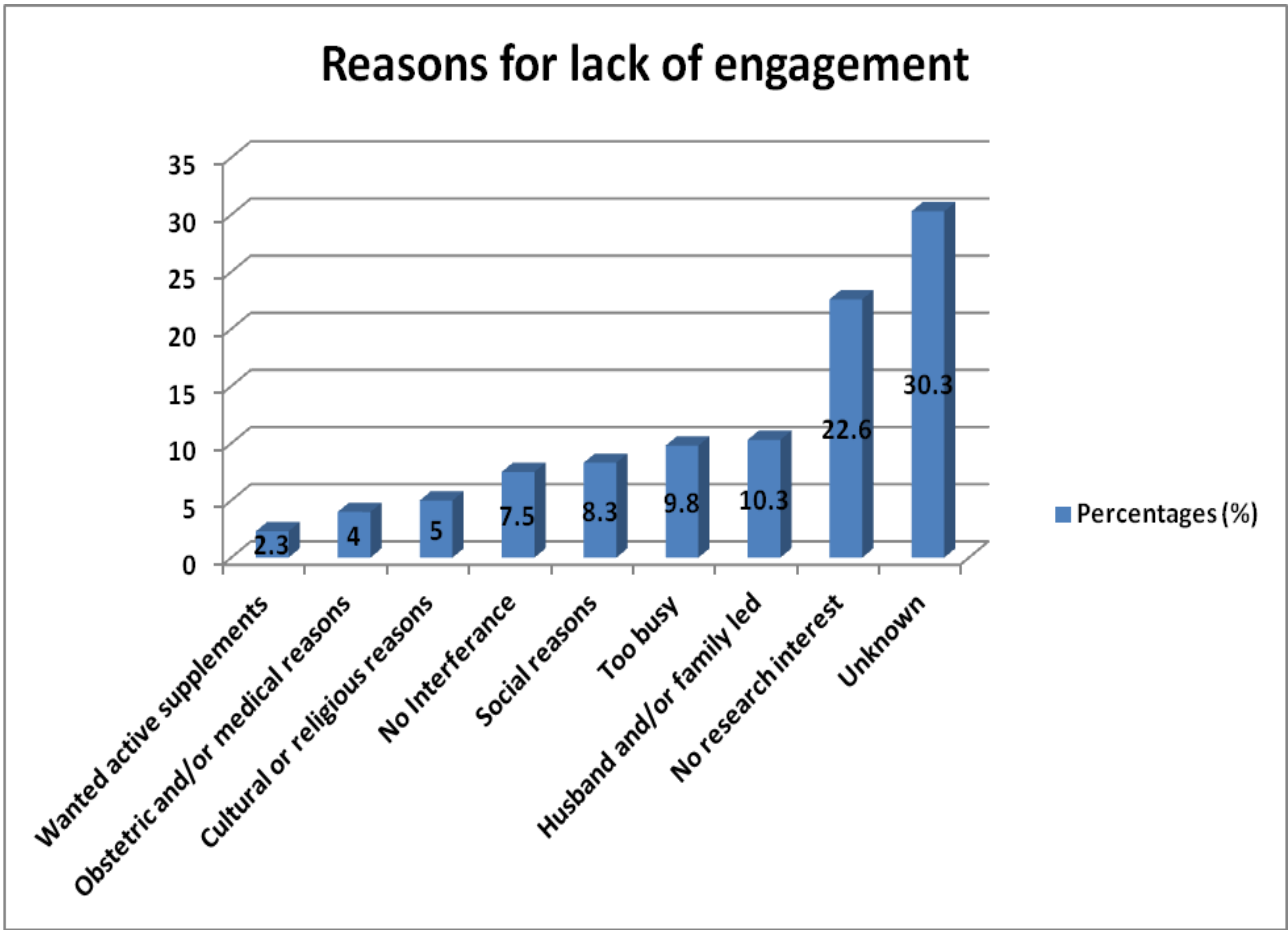


Figure 4.1**: **Reasons for lack of engagement

Box 4.1: Influential factors to engagement

- ‘If it can be good for my wife and baby’
- ‘Anything that might help me and my baby …and help others’
- ‘Maybe I will have some good out of it’
- Only if it’s Halal
- ‘Sounds good …..although other children did not have it’
- ‘Sounds great but I need to discuss it with my husband / family first’
- ‘My family is a doctor (overseas) so let me discuss it and I will let you know’
- ‘Want the best for baby’
- ‘If it can help others’
- ‘I’ve got too much on ……but I will…..benefit to baby’
- ‘If I don’t have to take time off work …I will’
- ‘I don’t like taking tablets….. but I’ll try…help baby’
- ‘I hate taking tablets. But if it can be good for my baby…’
- ‘Only if it is free’
- ‘Only if it doesn’t take too much of my time’

4.6.3 Factors which impact on engagement / lack of engagement

The implications of demographic and socio-economic factors and the impact of these on engagement and folic acid use in pregnancy were examined.

4.6.3.1 Demographic and socio-economic factors on engagement

4.6.3.1.1 Age:

Engagement was similar in all age groups with a slight increase among those ages forty and above (***Table 4.1***). The difference was **p < 0.875**.

4.6.3.1.2 Marital Status:

Seventy-five percent (75%) of singletons engaged compared to forty-two percent (42%) of those who were married (***Table 4.1***). The difference was **p <0.001**.

4.6.3.1.3 Language:

Forty-eight percent of women who spoke English engaged compared to thirty-six percent (36%) of those who did not speak English (***Table 4.1***). The difference was **p < 0.001**.

4.6.3.1.4 Ethnicity:

Approximately half Whites and Afro-Caribbean engaged (52%) compared to Asians (40%) (***Table 4.1***). The difference was **p < .002**.

4.6.3.1.5 BMI:

Participation was similar regardless of women's BMI (***Table 4.1***). The difference was **p < 0.939**.

4.6.3.1.6 Religion:

Of the Christians approached, fifty-seven percent (57%) engaged compared to Muslims and Hindus & Sikhs among whom there was no difference in engagement (39%) (***Table 4.1***). The difference was **p < 0.001**.

4.6.3.1.7 Parity:

Engagement was similar whatever a woman's parity although there was a slight increase among multiparous women and those with one previous child (***Table 4.1***). The difference was (**p < 0.783)**.

4.6.3.1.8 ***Employment status: Women***

Professionals and those with managerial and intermediate jobs had 51% and 49% level of engagement, respectively, compared to those who had routine and manual jobs (54%). Students and the unemployed demonstrated a lower level of engagement (41%) (***Table 4.1***). The difference was **p < 0.026**.

4.6.3.1.9 ***Employment status: Partners***

Similarly, women of partners who were students or unemployed had a lower level of engagement (36%) compared to those who had intermediate occupations (52%), professionals (44%) and manual workers (48%) (***Table 4.1***). A difference of **p < 0.006** existed.

4.6.3.1.10 ***Support received***

Engagement was higher among those who were alone (92%) compared to those whose husbands and/or relatives were involved (***Table 4.1***). The difference was (**p < 0.000)**.

4.6.3.2 Demographic and socio-economic factors and folic acid use

4.6.3.2.1 *Marital status:*

Folic acid use was higher among singletons (65%) compared to married women (51%) (***Table 4.1***). The difference was **p < 0.050**.

4.6.3.2.2 Language:

The use of folic acid among English-speaking women was fifty-seven percent (57%) compared to those who did not speak the language (40%) (***Table 4.1***). The difference was **p < 0.0001**.

4.6.3.2.3 Ethnicity:

Folic acid use among the Whites, Afro-Caribbeans, and East Asians was similar (56-57%) unlike the South Asians (50%) (***Table 4.1***). The difference was **p < 0.472**.

4.6.3.2.4 BMI:

In the various BMI categories, folic acid use was underweight 47%, normal 53.5%, overweight 56.2% and obese 49.7% (***Table 4.1***). The difference was **p < 0.436**.

4.6.3.2.5 Religion:

Muslims had a forty-seven percent (47%) uptake of folic acid compared to other religions (***Table 4.1***). The difference was **p < 0.002**.

4.6.3.2.6 Parity:

More than half of singletons (54.4%) and women with one previous child (57.1%) used folic acid compared to women with 2 – 4 children (48.0%) and those with five or more children (45.5%) who had under 50% usage (***Table 4.1***). The difference was (**p < 0.155**).

4.6.3.2.7 Employment status:

4.6.3.2.7.1 Employment status of clients

Women in managerial/professional and intermediate jobs had an uptake of folic acid use of approximately sixty (60%) compared to routine/manual (55%) and students and the unemployed (48%) (***Table 4.1***). The difference was **p < 0.014**.

4.6.3.2.7.2 Employment status of client's partners

The use of folic acid of women whose partners were in managerial/professional jobs was 58% compared to the unemployed (49%) (***Table 4.1***). The difference was **p < 0.253**.

4.6.4 Implications of engagement / lack of engagement on maternal and foetal outcomes

Pregnancy outcome data is presented in **Table 4.3.** In women who engaged and did non-engaged, 172 (47%) vs 249 (54%) developed pregnancy complications. The statistical difference was **p < 0.001**. The incidence of IUGR 14 (4%) vs 14 (3%) and hypertensive disorders (PIH, pre-eclamsia or eclampsia) 33 (10%) vs 34 (8%) were similar in both groups. On scan, detection of big babies was 22 (6%) and 49 (12%) while presumed foetal compromise and other pregnancy complications were 29 (9%) vs 41 (10%) and 21 (7%) vs 66 (16%) in women who engaged and did non-engaged, respectively. Furthermore, in the engaged group, stillbirths 4, neonatal death 1, miscarriages 24 compared to stillbirth 1, miscarriages 9 and congenital abnormality I in women who did not engage.

Premature birth was 59 / 65 in the engaged and non-engaged women (excluding stillbirths, miscarriages and neonatal death), respectively (**p < 0.001**). Of those engaged and non-

engaged women had, 2 / 5 macrosomia and 46 / 36 low birth weight infants, respectively (**p < 0.037**). Onset of labour for women recruited and not recruited were 145 (45%) / 206 (49%) spontaneous, 110 (34%) / 143 (34%) induced and 67 (21%) / 69 (17%) elective caesarean section, respectively (**p < 0.283**) and mode of delivery 149 (46%) / 206 (49%) vaginal, 17 (5%) / 29 (7%) instrumental and 156 (48%) / 183 (44%) caesarean section, respectively (**p < 0.366**). Thirty-one (10%) babies of engaged and 35 (8%) of non-engaged were admitted to special care baby unit (**p < 0.400**) (***Table 4.3***).

With use of the independent sample t-test, birth weight mean = 3082.53 grams (df = 615.06) and for those who were not recruited mean = 3187.85 grams, (df = 591.30); t (735) = -2.36, respectively **(p < 0.019).** Gestational ages at birth for those who engaged (n = 323) and those who did not (n = 418), mean = 37.49 grams, df = 2.58) and mean = 37.88 grams, df = 2.13); t (739) = -2.30, respectively (**p < 0.022**).

Table 4.3: Impact of engagement and non-engagement on pregnancy outcomes

	Levels of engagement		P value / (df)
Pregnancy outcome measures	**Engaged**	**Non-Engaged**	
Pregnancy complications, n (%)	***370***	***460***	***.001 (7)***
None	*198 (61.9)*	*211 (49.9)*	
IUGR by scan	*14 (4.4)*	*14 (3.3)*	
Big baby by scan	*22 (6.9)*	*49 (11.6)*	
Congenital abnormality	*0 (0.0)*	*1 (0.2)*	
Malpresentation	*3 (0.9)*	*7 (1.7)*	
PIH, Pre-eclampsia or Eclampsia	*33 (10.3)*	*34 (8.0)*	
¤ Presumed foetal compromise	*29 (9.1)*	*41 (9.7)*	
✤Other pregnancy complications	*21 (6.6)*	*66 (15.6)*	
Onset of labour, n (%)	***322***	***418***	***.283 (2)***
Spontaneous	*145 (45.0)*	*206 (49.3)*	
Induced	110 (34.2)	143 (34.2)	
Elective caesarean	67 (20.8)	69 (16.5)	
Mode of delivery, n (%)	***322***	***418***	***.366 (2)***
Vaginal	149 (46.3)	206 (49.3)	
Instrumental	17 (5.3)	29 (6.9)	
Caesarean section	156 (48.4)	183 (43.8)	
Birth outcome, n (%)	**347**	**427**	**.006 (5)**
Full term birth live	258 (74.4)	353 (82.7)	
Preterm birth live	59 (17.0)	63 (14.8)	
Stillbirth	4 (1.2)	1 (0.2)	
Neonatal death	1 (0.3)	0 (0.0)	
Miscarriages	24 (6.9)	9 (2.1)	
Medical TOP	1 (0.3)	1 (0.2)	
Gestational ages at birth, n (%)	***347***	***427***	***.001 (2)***
Full term birth	258 (74.4)	351 (82.2)	
Preterm birth	59 (17.0)	65 (15.2)	
***Other outcomes	30 (8.6)	11 (2.6)	
Birth Weight, n (%)	***319***	***417***	***.037 (2)***
Low birth weight (≤2499grams)	46 (14.4)	36 (8.6)	
Normal birth weight (2500 - 4449grams)	271 (85.0)	376 (90.2)	
Macrosomia (≥4500grams)	2 (0.6)	5 (1.2)	
Admission to Special care baby unit (SCBU), n (%)	***313***	***416***	***.400 (2)***
Yes	31(9.9)	35 (8.4)	
No	281 (90.1)	381 (91.6)	

***Other outcomes comprise of stillbirth, miscarriages and neonatal deaths. ¤ Presumed foetal compromise: suspicious cardiotocograph, spontaneous rupture of membranes, premature rupture of membranes, prolonged premature rupture of membranes, meconium-stained liquor and reduced amniotic fluid index. ✤Other pregnancy complications: cholestasis, anaemia, ante-partum haemorrhage, postpartum haemorrhage, thrombocytopenia, non-alcoholic fatty liver & unstable blood sugars

4.7 Discussion:

4.7.1 Influential factors to engagement/non-engagement

4.7.1.1 Key factors

The likely benefits to the baby were the main reason given for women's engagement with HCPs. Pregnancy is usually a time of excitement for the woman, her friends and family members. However, amidst the euphoria, mothers are usually more concerns about the wellbeing of their babies and therefore it is not surprising that this factor was highly influential in their decision to engage with HCPs. Most pregnancies are usually very much 'wanted pregnancies' and women would do what it takes in the best interest of their babies. Conversely, women declined primarily because they had no research interest, were pressed for time and needed family involvement in their decision making. This is in keeping with the evidence which has shown that non-Whites are less likely to participate in research (Shavers et al, 2002) and a family-centred approach to decision making being adopted by Asians (Hussain-Gamble et al, 2004) who formed the predominant ethnic group studied.

4.7.1.2 Socio-cultural, economic and demographic factors

4.7.1.2.1 Impact of social influences and client-focused approach on decision making

Nearly one-third of the women approached engaged with HCPs on first meeting. The level of engagement after follow-up had doubled leading to an overall engagement rate of forty-three percent. The co-ordination of women's appointments with their antenatal follow-up visits and the offer of home visits would have saved women considerable time and money

travelling to and from appointments and may have contributed to the engagement rate nearing fifty per cent. Most women and their partners were either unemployed or low earners and money saved on transportation would have been invaluable.

Compared to hospital visits, many more family members and friends frequently got involved and supported women with their decision making on home visits. Bearing in mind the main reasons given for delay in women's choices were 'time for decision making' and 'discussion with husband and/or family', the offer of home visits would have been highly beneficial to both parties (pregnant woman and HCP) and should be considered as an option to promote positive engagement of high risk women.

As most women were married Asians who are culturally family oriented (Hussain-Gambles et al, 2004), one can appreciate those reasons given by the 'considerers' and that further explained why a third of women studied needed time to provide a feedback on whether or not to engage with HCPs. In this study, ten percent husbands / family members openly influenced the decision about lack of engagement while fifty-three percent were involved in the decision-making process of all who engaged. These high numbers could have been derived from the fact that Asian men tend to be paternalistic, particularly towards non-English speaking partners. Regardless, the benefits of holistic care are well documented (Cumberlege, 2016) and women's partners should be involved in all aspects of women's care, be it the women's choice for their (partner's) involvement. Gorelic et al (1998) supports this holistic view of embracing the wider family circle which they purport to be critical to engagement since the combined efforts of individuals and their families can impact on women's health and wellbeing. Subsequently, their pregnancy outcomes may be optimised.

4.7.1.2.2 Language and religion

A woman's ability to speak English was a highly significant factor in whether or not she engaged. This was reflected in the results on folic acid use which has now become synonymous with pregnancy. It was felt that if women were willing to use folic acid for the potential benefits which are now established, they might be willing to engage with HCPs on the nutritional study. The non-English speaking women were Asian Muslims who had a low uptake of folic acid. This could be due to language barriers which resulted in their lack of understanding about folic acid and its use to reduce the risk of neural tube defect in the infants as recommended by NICE (2015). An Australian epidemiological study and survey on refugees from sub-Saharan Africa has confirmed that language barrier, poor health information on how to access services have contributed to that client group not accessing care (Sheik-Mohammed et al, 2006), suggesting that the effect of engagement might have been similar.

Locally, health advocates employed by the Trust, support non-English-speaking women, and the latter should have had adequate information to make an informed decision, despite their language difficulties. Therefore, one may argue that because some non-English-speaking women did not want to engage, it was their informed choice to have no interference, leaving everything to 'Allah' as mentioned by some women when they declined engagement. A highly significant number of Christians engaged compared to the Muslims. As Christians tend to be predominantly non-Asians, one may conclude that help from partners and family members was not as important as among Asians, resulting in higher levels of engagement. A strong correlation was demonstrated between religion and engagement.

4.7.1.2.3 Time constraints

Like religion, time constraints, cultural and personal reasons were factors highlighted for client's lack of engagement. Often when individuals are approached to engage in available services, time constraints are usually raised and can be a deterrent. Women within the borough had an average of 2-4 children and this comes with huge commitments. Activities like the school run and managing a home full-time, particularly as many were unemployed, can be demanding on a woman's time. This demand can be further challenged when ill-health is present as women living within the borough of Newham had poorer health compared to the national average (Office of National Statistics, 2018c). With T2 DM and other chronic medical such as hypertension and cardio-vascular disease at high levels within the borough (Newham London, 2017), some women were possibly carers, particularly as many Asians tend to live with extended families and needed to fully embrace their roles as dutiful daughters-in-law.

HCPs should ensure that women's social circumstances are considered to reduce the frequency and length of appointments. Preparatory work should be done prior to meeting clients and home visits should be offered as an alternative to hospital appointments, where possible.

4.7.1.2.4 Health behaviours

One's view of health and illness and the emphasis that one places on one's health and well-being when considering other hierarchy of needs, can be varied. In a deprived borough like Newham, survival may take precedence over 'living a healthy lifestyle' and therefore

actively participating in research with the view of improving health in the future may not be a concept which some pregnant women may find of great interest and urgency. Conversely, some may have grown tired of stereotypes and engaged, and this could have impacted on the overall engagement rate.

Regardless, health promotional work falls within the remit of HCPs who are duty bound to provide healthy life style advice and support to all pregnant women and particularly those deemed high risk, as women with T2 DM and GDM. Behavioural change requires self-discipline and motivation. Motivation is a psychological construct which can be promoted and supported by HCPs with the appropriate psychological skills-set to effect behavioural change. The MAPS behavioural change technique which includes motivation, action, prompts and cues are believed to be effective in lifestyle behaviour change and can be delivered as part of clinical care by HCPs to improve health outcomes in individuals with diabetes (Swanson & Maltinsky, 2019).

4.7.1.2.5 Employment status

Most women and a third of their partners were either unemployed or did routine manual jobs. This possibly accounted for the low level of engagement among this group particularly as professional/managerial women and those with intermediate jobs had a high level of engagement compared to those who had routine and manual jobs. A health education survey demonstrated that South Asians contribution to the labour market varies. Women of Pakistani and Bangladeshi origins are less economically active and Indian men are more likely to be in employment compared to Pakistani men resulting in the employment rate being twice as high in this group compared to the local population (Hussain-Gambles et al, 2004).

In this study, there was a strong correlation between employment status and ethnicity. Whites and Afro-Caribbeans were more in employment unlike South Asians (***Table 4.2***). The use of folic acid was lower when they and their partners were unemployed, and this may be due to financial constraints; a factor which could have been a deterrent for some women living in a deprived borough like Newham with they and their partners being unemployed or in lower paid jobs. Overall, the use of folic acid during pregnancy was low as only half the women studied took it during pregnancy. Regardless, a high percentage of women who used folic acid also engaged indicating that this group of women may have felt generally motivated to do what was necessary to maintain good health to optimise their pregnancy health and particularly that of their neonates.

4.7.1.2.6 Ethnic groups

A significant difference strongly existed in the levels of engagement between ethnic groups whereby Whites and Blacks engaged more than women of Asians descent, despite the latter being the more dominant group. After the Whites, Afro-Caribbeans was the second largest group studied which was better at engaging. The evidence from Shavers et al (2002) study has, in part, supported these findings having demonstrated that Whites are more likely to participate in medical research when compared to people from the ethnic minority groups.

A systematic review conducted to evaluate whether ethnic minorities are less likely to engage in research has found that the issue was that individuals from this group were less likely to be approached and invited to take part, but when they were, they engaged on similar levels as their White counterparts (Wendler et al, 2006). Therefore, the onus is on HCPs and not the marginalised (Sheikh, 2006). A well coordinated collective approach

through networking and alliance building is critical to overcome deeply entrenched divisions. Likewise, understanding the causes of exclusion of the marginalised can help with the engagement process. Implementing participatory local structures with links to local and national Government can enable women to access the political stream and have a voice in the decision-making process (O'Driscoll, 2018).

As most women studied were non-Whites, lack of engagement could have related to trust issues (Psarros, 2018). Also, some women, particularly Asians, may have needed to consult with husbands and family members prior to deciding and they may not have openly shared that with HCPs for fear of reprisal, and combined, these factors may have contributed to the high rate of undisclosed reasons for lack of engagement among approached subjects.

4.7.1.2.7 Perceived discrimination

Perceived discrimination may have existed among this group as demonstrated in a US study. This phenomenon which is very powerful prevented African Americans from accessing treatment for symptoms of cancer in a timely manner (Mullings et al, 2019). If patients can defer accessing health care for conditions as serious as cancer, engagement with pregnancy services may seem lower in the prioritisation of health needs as pregnancy is not an illness. Therefore, perceived discrimination could also have been a deterrent for reduced levels of engagement among non-Whites who are more likely to report feelings of discrimination (Cumberlege, 2016). There is a strong interconnectedness between poverty, marginalisation and political exclusion and a multifaceted approach is required to address this shortfall. Combined, poverty and marginalisation have led to shortfalls in an

individual's livelihood, education, access to basic needs (Hedstrom and Smith, 2013) and these in turn can determine their access to and ability to optimise local health services.

4.7.1.2.8 Historical factors

Many myths and misunderstanding of research exist. These have caused concerns and lack of trust between the general public and researchers (Mills et al, 2006). Lack of motivation to engage may simply have been due to historical effects of bad press on research studies as far back as the Tuskegee Study of Untreated Syphilis (1932-1972) in USA and more recently the Northwick Park Hospital cancer trial (2006) in UK; both of which resulted in significant harm to patients who participated in those studies. Undoubtedly, some women approached by HCPs involved in this study would have shared some misunderstanding of and/or lack of trust and these factors may have contributed to non-engagement. These were probably women who provided no reason for non-engagement, showed no research interest and wanted no interference unless there was guarantee that they were having the active supplements.

Motivational work is needed to regain trust in the public by promoting engagement on all levels. Work has begun by institutions such as National Institute for Health and Research and NICE on patient and public engagement, including at strategic levels, to ensure that services are truly patient-focused. This change of focus embraces the notion that patients are partners and their contributions are critical to 'getting things right from the start'. Having representation of people from the public and of BAME background who 'look like you' could act as a catalyst for pregnant women of all ethnic groups to feel that they can trust policy makers who would want the best for them and their babies. Hopefully, as this work flourishes, trusting relationships can be re-built and women feel encouraged to

engage positively and early especially when diabetes is present, to optimise their health in pregnancy and subsequently their pregnancy outcomes.

Apart from the public engagement initiatives work needs to be done within disciplines including maternity, to promote research as part of the package of women's routine care as opposed to viewing research as an 'additional extra'. Stakeholders and managers need to embrace this notion and lead from the front to drive this change in the provision of true woman-centred holistic care.

4.7.1.2.9 Caring responsibilities

In 2011, 5,800,246 people identified as carers nationwide. Within that same year, the number of reported carers in Newham was 24,604; an increase of 19% from 2001. This increase was higher than the national average of 11% (Newham Clinical Commissioning Group, 2015). This disparity is not surprising since the reported morbidity and co-morbidities within the borough was shown to be extremely high when the Joint Strategic Needs Assessment was conducted (Information Centre for Health and Social Care GfK NOP, 2011). Furthermore, as local carers are more likely to be women (Information Centre for Health and Social Care GfK NOP, 2011), some non-engaged local pregnant women would have also been primary carers. Also, as that 2011 report demonstrated that fifty-two percent local carers reported that their own health needs had been compromised by caring for others (Newham Clinical Commissioning Group, 2015), some women studied would have been primary carers who suffered ill health. Some women may not have engaged for social reasons which accounted for 8% of non-engagers. Women's caring duties could have meant them overlooking the potential benefits to their and their babies' health by engaging with HCPs on the nutritional study. Pathways for information sharing between

primary and secondary care sectors need to be improved. Effective communication between HCPs needs to be increased and where necessary appropriate inter-referrals made. These sectors need to work more cohesively to ensure that pregnant mothers who are carers do not feel marginalised and get lost within the care system, but have their needs met and those for whom they care, as outlined in the Newham Joint Carers' Strategy 2015 -2018 (Newham Clinical Commissioning Group, 2015).

4.7.1.2.10 Cultural and linguistic diversity

Cultural and linguistic diversity is a real phenomenon in East London and certainly within Newham. In this study there was a significant difference in women who did and did not speak English and engaged. Cultural and language barriers may prevent pregnant women from engaging because women's ability and willingness to engage with HCPs in seeking and understanding advice can be affected (Sheik-Mohammed et al, 2006; Harper Bulman et al, 2010). One's inability to speak English can have an adverse impact on one's health, likewise the perception of HCPs during pregnancy (Harper Bulman et al, 2010). Subsequently, this could have had an adverse impact on pregnancy outcomes and is an area of significance worth exploring in the future.

A retrospective Australian study which examined whether cultural (country of birth, race & refugee status) and linguistic (primary language spoken & use of interpreters) diversity were independent predictors of maternal and foetal outcomes when at least one adverse event occurred, has found a reduced likelihood of an adverse pregnancy outcome of those born outside Australia and New Zealand and/or those who used interpreting service. Those findings did not support the model for having a multi-faceted / professional approach when caring for this group but emphasised the need for use of interpreting services. It is believed

that continuity of care provider was more important for areas of communication and compliance. Having the same interpreter as practised within Newham, may have given women the confidence and provided additional support and encouragement to adequately engage and to better communicate their needs, if or when needed (Thomas et al, 2010). Being surrounded by people of similar culture and religious background should instil confidence in individuals to make informed decisions about their care.

Conversely, some interpreters live within the locality and may be familiar with women, their wider family and friends leading to some women being reluctant to disclose information which is critical for their care planning and delivery. Regardless, it is important to use the hospital approved health advocates. The use of informal interpreters may prevent open dialogue between women and HCPs by women withholding critical information (eg. domestic abuse) and not receiving appropriate counselling and support as a result (Harper Bulman et al, 2010). This practice should be discouraged because care pathways may not match the true needs of women resulting in adverse impact on pregnancy outcomes and the long-term maternal and foetal / neonatal well-being.

*4.7.1.2.*11 Migrants, Gypsy, Roma and Traveller's population and engagement/non-engagement

4.7.1.2.11.1 Mobile migrant population

Newham has a very mobile population partly due to the increase of migrants within the locality; some of whom may not have had the necessary documents to reside in the UK. A recent study which looked at the experiences of migrant women accessing maternity care has found that among the reasons given for non-engagement were communication

difficulties (Shortall et al, 2015; Parry et al, 2004) and having to pay for care received (Shortall et al 2015, Aston 2014 & Taylor 2013). Similar findings were found in a project commissioned by Public Health England which evaluated factors which contributed to inequalities in maternal and child health of Black and ethnic minorities in low-income households. Access and effective use of health services were examined, and barriers identified included registration refusal due to migration, language and communication difficulties and prejudice and discrimination (Psarros, 2018). Taylor (2013) supported those disclosures and further stated that lack of engagement can result in some women avoiding antenatal care and can be forced to deliver at home or present in labour with complications. Also, fear of being arrested and having to provide documents for administrative purposes were also deterrents. Combined, those factors resulted in only 38% receiving care before 12 weeks gestation, and of the remaining who booked late, 34% booked after 20 weeks in Shortall et al, 2015's study and that level of engagement contravenes NICE (2015) antenatal care guidelines. The population profile of Newham bears similar resemblance and similar factors could have contributed to lack of engagement and accounted for nearing fifty per cent of local women having developed complications during pregnancy. However, one needs to be careful of generalizing since an Australian study has found no significant correlation between refugee status and adverse pregnancy outcomes (Thomas et al, 2010).

4.7.1.2.11.2 Gypsy, Roma and Traveller's population

A large Gypsy, Roma and Traveller's population reside in Newham. This group which is among the most deprived in the UK (Women and Equalities Committee, 2019) takes pride in being tough and self-reliant (Parry et al, 2004) and these and other lifestyle factors such

as low educational attainment, overcrowding and caring responsibilities (Burchardt et. al, 2018) may have prevented women from this community accessing maternity services and engaging with HCPs. Non-engagement may also be derived from mistrust formed from perceived racism, discrimination, hate and violence against women and girls in this group (Women and Equalities Committee, 2019). Also, Gypsies, Roma and Travellers live within close communities with the characteristics of an extended family (similar to the Asians) and therefore good and bad experiences with HCPs will be shared (Parry et al, 2004). This practice can determine the health care choices that are made and the level of engagement within this group and local maternity services, over generations. This community is also very private, and their way of life may not comply with the philosophy of positive engagement whereby women are encouraged to communicate freely and form strong partnerships with HCPs. Consequently, the principles of positive engagement go against the social and cultural norms of Gypsies, Roma and Travellers.

4.7.1.2.12 Age and engagement/non-engagement

Age was not a factor as to whether or not to engage. Nevertheless, as one advances in years, one tends to strive to do what one thinks is right as responsible citizens. Women who engaged early or on the first follow-up meeting possibly fell within this category. This notion could have influenced women's decision to engage with pregnancy services available to demonstrate their acceptance and compliance with health advice. Also, that yearning could have been to exonerate oneself of being blamed should 'things go wrong' during pregnancy and/or after delivery. Therefore, as a portrayal of responsible behaviour, one can engage with HCPs by 'doing what's right by the baby'; the main reason given for engaging with HCPs.

4.7.1.2.13 Engagement/non-engagement: the unknown factors

All previous issues raised could have contributed to lack of disclosure of the reason for non-engagement. Some of those issues are discussed below.

4.7.1.2.13.1 Social influences

Approximately a third of all women approached did not disclose their reasons for non-engagement. Lack of coercion or women simply expressing their informed choice could have been among the reasons for women not engaging. Ultimately, women's decision needed to be respected in keeping with research ethics as outlined in the protocol which is embedded in the UK policy framework for health and social care research (formerly Research Governance Framework) (Department of Health, 2015).

One reason given by the 'considerers' was 'time to make a decision'. Yet, some considerers were 'alone' and presumed unsupported when they made their final decision. The conclusion from that could have been that some women who were within that category may have needed time to get their husband and / or family members' approval but that was not openly shared. Therefore, social influence could have been more profound than that stated among those being 'alone' when the decision on engagement or non-engagement was made. If that theory is true, the need for having an inclusive approach with women's social support system becomes even more profound and should always be respected by HCPs in critical healthcare decision making.

4.7.1.2.13.2 Attributes of HCPs

Follow-up of the 'considerers' involved a significantly high level of activities which were costly in terms of time for repetition of activities and financial (travelling) cost for home visits. Nevertheless, despite the extra resources required, it was clear that doggedness contributed positively to high levels of engagement especially when subjects were followed up. One may argue that successful engagement could have been further influenced by the interest, motivation, approachability and dedication of researchers and the emphasis that they placed on client engagement and the likely benefits to clients through research engagement. Good communication, effective listening skills, respect for client's autonomy and awareness of the health related matters within the locality (Newham) could have individually or combined, had a positive impact on engagement and should form the cornerstone of any research project. In the absence of these attributes, non-engagement among clients could escalate and may have an adverse impact on pregnancy outcomes.

4.7.1.2.13.3 Complacency

Complacency could have been another reason as was reflected in low folic acid use despite Government guidelines based on the need to reduce neural tube defects as shown in previous studies (NICE, 2016). For example, although there was no significant difference in folic acid use based on parity, the higher the parity, the less likely women were to use folic acid in pregnancy, and this may have contributed to only approximately 50 per cent of all women approached having taken it in pregnancy. After having had previous complications-free pregnancies, women may have internalised that they wanted 'no interference' and this may have been another reason for non-disclosure.

4.7.1.2.13.4 Lack of trust

Lack of trust, as previously explained, may have been another possible reason. Women communicating to HCPs that they were not trusted would not have been easy for fear of reprisals that the care they subsequently received would have been affected and this may have prevented women from disclosing a reason for non-engagement.

4.7.2 Pregnancy outcomes (maternal and foetal)

4.7.2.1 Maternal outcomes

4.7.2.1.1 Social inequalities

Having explored ethnic and social inequalities of women's experiences of maternity care in England, it was found that single mothers, ethnic minority women and those who completed education earlier in their lifetime, accessed maternity care late, experienced complications during pregnancy and birth, had poorer pregnancy outcomes and felt less satisfied with some aspects of care received (Raleigh et al, 2010). In this study, it was highly significant that the singletons were better at engaging possibly because they do not feel the need to have to consult with their partners and/or family members prior to making a decision in the same way as Asians who historically embrace the notion of a family approach to decision making (Hussain-Gambles et al, 2004). Contrary to Rayleigh's study, non-engaged women had better birth outcomes and this was significant. Women within that group had more full term live births and less preterm births, stillbirths, miscarriages and low birth weight infants compared to women who engaged. A possible explanation for this could be that women without diabetes were among those who were non-engaged

because they felt that they had uncomplicated pregnancies and were more likely to have had better pregnancy outcomes compared to those with diabetes (CEMACH, 2007).

4.7.2.1.2 *Hypertensive disorders and related conditions*

Hypertensive disorder complicates approximately 5-10% of all pregnancies and is the second most common cause of direct maternal deaths. Pre-eclampsia, eclampsia and HELLP syndrome represent different severity of the disease on the spectrum (Vest & Cho, 2014). Combined, these hypertensive disorders accounted for 10% (engaged) and 8% (non-engaged) of all complications in this study. Women who engaged developed less complications and enjoyed healthier pregnancies than those who did not engage, and this was highly significant. Yet, hypertensive disorders were slightly increased among those who engaged.

Women with essential hypertension need early engagement and regular antenatal follow-ups to reduce the morbidity and mortality associated with this medical condition. If not managed effectively, mild to moderate hypertension can develop into severe hypertension which can have devastating consequences for the mother and baby. Equally, foetal growth restriction can develop if blood pressure is too tightly controlled so a balance needs to be had (Nabhan & Elsedawy, 2011).

Timely delivery of the foetus is critical in the presence of hypertensive complications (Vest & Cho, 2014). Hence, hypertensive disorders are among the strongest predictors of preterm delivery (World Health Organisation, 2012), which was 17% and 15% in the engage and non-engaged, respectively, and was highly significant. Other adverse effects of hypertensive disorders include low birth weight infants, perinatal deaths and placental

abruption (Nabhan & Elsedawy, 2011). In this study, there was a higher incidence of low-birth-weight infants in the engaged group, among which was the only case of neonatal death. Anaemia and placental abruption were grouped under 'other obstetric complications'. As these conditions are associated with poor neonatal outcomes, it would have been useful to explore the impact of those conditions on pregnancy outcomes in the engaged and non-engaged groups.

Hypertensive disorders are in part related to inactivity which can be manifested through obesity. Maternal obesity increases the risk of complications in pregnancy which includes gestational hypertension, pre-eclampsia and gestational diabetes (Office of National Statistics, 2019).

A recent study by Domingues et al (2015) on physical activity on maternal-foetal health during pregnancy has shown that activity in pregnancy was extremely low, but the study was ongoing. Exercise intervention programmes are believed to be beneficial but a recent study on obese and overweight women at risk of gestational diabetes has shown no improvement in fasting blood glucose insulin sensitivity and birth weight, but this was believed to be associated with non-compliance (Oostdam et al, 2012).

A significantly high number of women in this study were either over-weight or obese, but the result was insignificant. Being overweight or obesity is a precursor for increased incidence of hypertensive disorders (Greenstein & Wood, 2011), T2 DM (Mokdad et al, 2000 & Boffetta et al, 2011) and GDM (Hunt & Schuller, 2007) which was high among this study group. The distribution of women who did and did not engage was similar. This was reflective of Newham's population which is highly diverse with many Asians who tend to live sedentary lifestyles impacting on a high prevalence of DM (Nayamdorj et al, 2010).

Poverty is a derivative of socio-economic factors and a predictor of obesity (Cohen et al, 2013) which is widespread within the borough of Newham. Women who are less motivated to manage their own health may not positively engage with HCPs due to socio-economic factors including poor housing and employment in lower paid jobs. Therefore, optimal health may not a priority. Also, in some cultures, being obese and overweight can be seen as a sign of wealth, attraction to the opposite sex and fertility (Naigaga et al, 2018). Enabling women to look beyond this cultural view may be a challenge for HCPs in areas of diabetes education and management.

4.7.2.1.3 *Onset of labour and mode of delivery*

Engagement had no impact on onset of labour. In keeping with local policy on diabetes management in pregnancy, supported by NICE, 2008 & 2015 guidance, women with T2 DM and GDMs on insulin were induced between 37 and 40 weeks of pregnancy to optimise the pregnancy outcomes of mothers and their babies. The rate of induction was similar in both groups. More non-engaged women went into spontaneous labour compared to the engaged but this was not significant. The homogeneity in both groups of women's demographic profile of age (mean, 31 years) and BMI (mean, 28.51kg/m^2), parity (mean, 2.08 children) and disease type (T2 DM and GDM) were all non-significant. This coupled with local and national guidance on the management of women with DM in pregnancy, would have impacted on the similarity seen in onset of labour in each group.

For the reasons highlighted above, homogeneity in both groups of women could also have impacted on mode of delivery which was not significant, but accounted for a slightly increased number of births by caesarean section among those who engaged. That slight increase may have been attributable to maternal request and/or a slightly decreased number

of women without DM among the engaged. The morbidity and mortality associated with a diabetic pregnancy are high (Assaf-Balut et al, 2016; Reece & Homko, 2000 & CEMACH, 2007) and delivery by elective caesarean section may have also been necessary to promote the wellbeing of mother and baby. Cumulatively, this would have also contributed to almost fifty percent of all women approached in each group being delivered by caesarean section which may have been exacerbated by the high rate of induction.

Approximately a quarter of women studied were primips. There was an equal distribution of first-time mothers and multi-parous women who were delivered by caesarean section. It is a preconception that failed IOL is more common among first-time mothers following induction. A population based cross-sectional study has shown that induction of primips with uncomplicated histories resulted in an increased incidence of failed spontaneous onset of labour and increased emergency caesarean section rate (Davey & King, 2016). Conversely, a recent study has shown that the induction of fist time mother at 39 weeks did not increase the caesarean section rate but resulted in a lower frequency (Grobman et al, 2018).

Women in NUH present in pregnancy with many co-morbidities increasing the likelihood of being induced, delivered by caesarean section and having a pre-term birth. Although the difference was not significant, planned caesarean section was offered to approximately one-fifth of all patients in the engaged group and a slightly reduced number among those who did not engage. A plausible explanation for this could be the high incidence of morbidity with which some subjects presented in early pregnancy and complications developed throughout.

4.7.2.2 Foetal/Neonatal outcomes

Engagement had no impact on foetal outcomes. Women who engaged were more likely to have a preterm birth and were worse for other pregnancy complications such as spontaneous, premature and prolonged rupture of membranes and suspicious cardiotocograph. Effective clinical management of high-risk women with T2 DM and GDM would have required that some women were delivered early and this would have contributed to the premature birth rate which was highly notable, and significant.

The incidence of macrosomia was small, but it was two-fold higher for non-engagers than for those who engaged with HCPs. Considering that the pregnancy outcomes were better for the non-engaged, and pregnancy complications were worse in that group, could it be that most mothers within that group had heavier babies due to slightly raised BMIs, impacting on that marginal difference in macrosomic babies? A systematic review and meta-analysis conducted on maternal obesity and foetal macrosomia has found a correlation between both entities (Gaudet et al, 2014).

Overall, the detection of big babies on scan was significantly high and should have resulted in a higher detection rate of macrosomia in both groups, with a high likelihood of being mainly among those who did not engage. A plausible explanation is that clinical management of women whose babies were confirmed as large for gestational age on scan were offered an early induction based on maternal and foetal health and wellbeing. Approximately a third of engaged and non-engaged women were induced and therefore based on local protocol, women detected with big babies on scan could have been among those induced. Subsequently, this could have impacted on the reduced detection rate of macrosomia but may have likely increased the incidence of large for gestational age infants

and premature births; the latter which was greater among women who engaged (17%) than the non-engaged (15%), which was significant.

The CQC 2017 survey on women's experience of the maternity service has reported that in 2013 and 2015, 17% of births were premature while the remaining 93% delivered at maturity (37-weeks gestation) (Care Quality Commission, 2018). For this study, the overall preterm birth rate was 15% and above the national average of 7.8% in 2019 (Office of National Statistics, 2020). Preterm birth is often associated with neonatal death (Domingues et al, 2015) but was not indicative of the case in this study since delivery was at term. This woman's inability to communicate English, process complex information about her care and her health prior to and during pregnancy were possible contributed to the cause of death.

4.8 Conclusion

The findings of this study have shown that socio-cultural, economic and demographic factors have impacted on a pregnant woman's decision on whether or not to engage with HCPs. Strong decision-making indicators were ethnicity, marital and employment status, social support system and women's ability to speak English. The likely benefits to the baby were the overarching reason given for positive engagement.

Engagement with HCPs reduced complications in pregnancy but had no effect on onset of labour, mode of delivery and the reduced incidence of hypertensive disorders, premature births, macrosomia, low birth weight infants, neonates admission to SCBU. Further large scale trials are needed in this area.

Ethnic minorities from deprived areas like Newham can present with complex health issues which can provide substantially rich data for local research. Locally, ethnic minorities' participation in research is under-reported. This might be due to the under-representation of this group in research due to the challenges that their involvement might pose in areas such as language difficulties, lack of trust and feelings of not belonging which can prevent women from engaging. Despite resources being limited within the NHS, HCPs need to embrace a holistic approach when engaging with all pregnant women, particularly those who are 'high risk' even when they may present with complex social, cultural, financial and challenging health needs, amidst discussion on research participation.

For positive client engagement to become successfully embedded within the NHS culture and subsequently flourish, HCPs need to acknowledge that issues with non-engagement do not lie solely with pregnant women from ethnic minority groups. Also, HCPs need to examine their own prejudices through self-reflection, and this could be a positive way forward to provide a truly respectful and equal service to all pregnant women within our locality. By so doing, women may feel encouraged to positively engage with HCPs and the services available to them. Among and within each ethnic group there are certain nuances and unless service providers acknowledge, respect and embrace this notion, service engagement in pregnancy will continue to be problematic, possibly resulting in increased morbidity and mortality.

This chapter has set the scene for all experimental chapters (5-7) (Phases 2-4) and has influenced the distribution of subjects and in each of those chapters. Particularly, for the RCTs conducted in chapters 6 & 7 to be successful, it was necessary to provide women with the information in the language that they understood, preferably face to face.

Supported by health advocates and PILs translated into 5 different languages, a better understanding of the factors which fostered engagement with HCPs were established. Findings from this chapter were invaluable to HCPs on the approach to take when recruiting and following up participants in the other phases.

In chapter 5, predominant risk factors for the early detection of GDM were examined and the implications of gestational age at diagnosis on maternal and foetal outcomes. NICE's recommendation on screening for GDM has also been evaluated in the context of its appropriateness for use within a highly diverse population like Newham.

Chapter 5

Screening high-risk women for gestational diabetes mellitus at different gestational weeks: Implications for management of maternal and foetal health

5.1 Chapter overview

In chapter 5, I have explored the risk factors for the early detection of GDM and evaluated the impact of early (≤24 weeks) and late (≥24 weeks) diagnosis on maternal and foetal outcomes. Women with GDM are at increased risk of sub-optimal pregnancy outcomes and recurrent GDM. Early identification of 'at risk' women can improve pregnancy outcomes in the index pregnancy and provide women with the education and support for proactive behavioural changes for their long-term health benefits and future pregnancies.

5.2 Introduction

5.2.1 Gestational diabetes mellitus (GDM)

5.2.1.1 Definition

Gestational diabetes mellitus is 'any degree of glucose intolerance first diagnosed during pregnancy, regardless of the gestation and whether or not medication is used for treatment and the condition persists following pregnancy' (Metzer et al, 1998). GDM is further defined as a condition which forecasts future overt diabetes in mothers and the long-term metabolic health of their offspring through foetal programming effects (Krishnaveni et al, 2010).

5.2.1.2 Risk factors and aetiology

Commonly identified risk factors of GDM are family history of diabetes, past GDM pregnancy, BMI ≥30kg/m^2, previous large baby (≥4.5kg) and ethnicity particularly women from South Asia, Black African/Caribbean and the Middle East (NICE, 2015) as outlined in ***Box 2.2***. Other risk factors include age, parity, hypertension, stillbirth and/or neonatal

death in previous pregnancies (Teede et al, 2011) and polycystic ovaries syndrome (PCOS) (Tomlinson et al, 2012 & Teede et al, 2011).

GDM is marked by abnormal glucose metabolism and insulin resistance (Ben Slama, 1997). In non-diabetic pregnancies, insulin resistance is marked by compensatory increases in insulin secretion by the pancreatic bêta cells (Richardson and Carpenter, 2007). In the presence of GDM, relative insulin deficiency is derived from beta cells dysfunction. GDM is also associated with obesity. Women starting pregnancy who are already overweight or obese are at high risk of developing GDM (Chu et al, 2007). Also, ethnicity may determine the effect of obesity on insulin resistance in pregnancy as BMI has greater insulin resistance in pregnancies among Asians, (Retnakaran et al, 2006).

5.2.1.3 Prevalence

The true prevalence of GDM is unknown but its prevalence is increasing worldwide (Wan et al, 2019; Guariguata et al, 2014). Current estimate of GDM is believed to be between 13% and 30% (Wong et al, 2017) but is dependent on the population studied and the diagnostic method used. GDM affects 87.5% of all diabetic pregnancies (National Institute of Health and Care Excellence (NICE, 2015).

5.2.1.4 Effects of GDM

The adverse effects of GDM on foetal/neonatal and maternal health are well documented (Benhalima et al 2015, Dessi et al 2015, Billionet et al 2017 & Kwik et al 2007). The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study is often referred to as a landmark study which described the adverse impact on both mothers and their babies' health (HAPO Study Cooperative Research Group, 2008). Increased placental transfer of glucose to the foetus due to maternal hyperglycaemia results in adverse foetal and neonatal

outcomes which include macrosomia, small for gestational age, hypoglycaemia, congenital abnormality, increased admission to special care baby unit, stillbirth and neonatal death (Benhalima et al, 2015). Infants born to women diagnosed with GDM are at risk of impaired glucose regulation leading to obesity (Wu et al, 2016 & Damm, 2009), T2 DM (Mitanchez et al, 2015 & Wu et al, 2016) and autisms (Xiang et al, 2015). Effects related to the mother include preterm births, increased caesarean section rates, pre-eclampsia, maternal trauma and post-partum haemorrhage. Micro/macrovascular complications are associated with chronic hyperglycaemia (Kawahito et al, 2009). Additionally, diagnosis of GDM can lead to a 70% risk of developing the condition in subsequent pregnancies and T2 DM within 10 years after delivery (Schwartz et al, 2015). Consequently, any preventative measures can have huge cost benefits (Hex et al, 2012). Early identification of 'at risk' women can improve pregnancy outcomes and provide women with the education and support for proactive behavioural changes for their long-term health and subsequent pregnancies.

5.2.1.5 Management

5.2.1.5.1 Overview

Early intervention is critical to reduce the morbidity associated with the condition (Görig et al, 2015). After diagnosis, women should be referred for multi-disciplinary review where teaching is provided on GDM, its likely implications on maternal and foetal health in the immediate and long-term, importance of blood glucose control and likely treatment. Women should also be taught to self-monitor blood glucose and reviewed regularly in MDT clinic until delivery. Individualised plans of care should be implemented during

labour and delivery and women discharged with lifestyle advice and screened postnatally to establish their diabetes status (NICE, 2015).

5.2.1.5.2 S*trategies employed on diagnosis*

On diagnosis of GDM, women were referred to the multi-disciplinary (MDT) education session where the condition and potential risks to their and their babies' health were explained. Dietary advice was given using the 'Eat well plate' (***Figure 5.1***) and they were taught self-monitoring of blood glucose levels. Advice was given to contact the specialist team if their blood glucose levels exceeded the targeted levels (pre-prandial ≤6mmol/l and 2 hours post-meals <7.8mmol/l). They were also encouraged to increase their daily physical activity, particularly post-meals to contribute to normalising their blood glucose levels without emphasis on weight-loss. An appointment was given for the following week to attend the MDT (Obstetricians, Endocrinologist/Diabetologists, Nurse and Midwife specialists and dietician) clinic for antenatal diabetes review. Subsequent follow-up appointments were given throughout till delivery based on individual assessments of mothers' and babies' health and well-being. Individualised plans of care were implemented during labour and delivery.

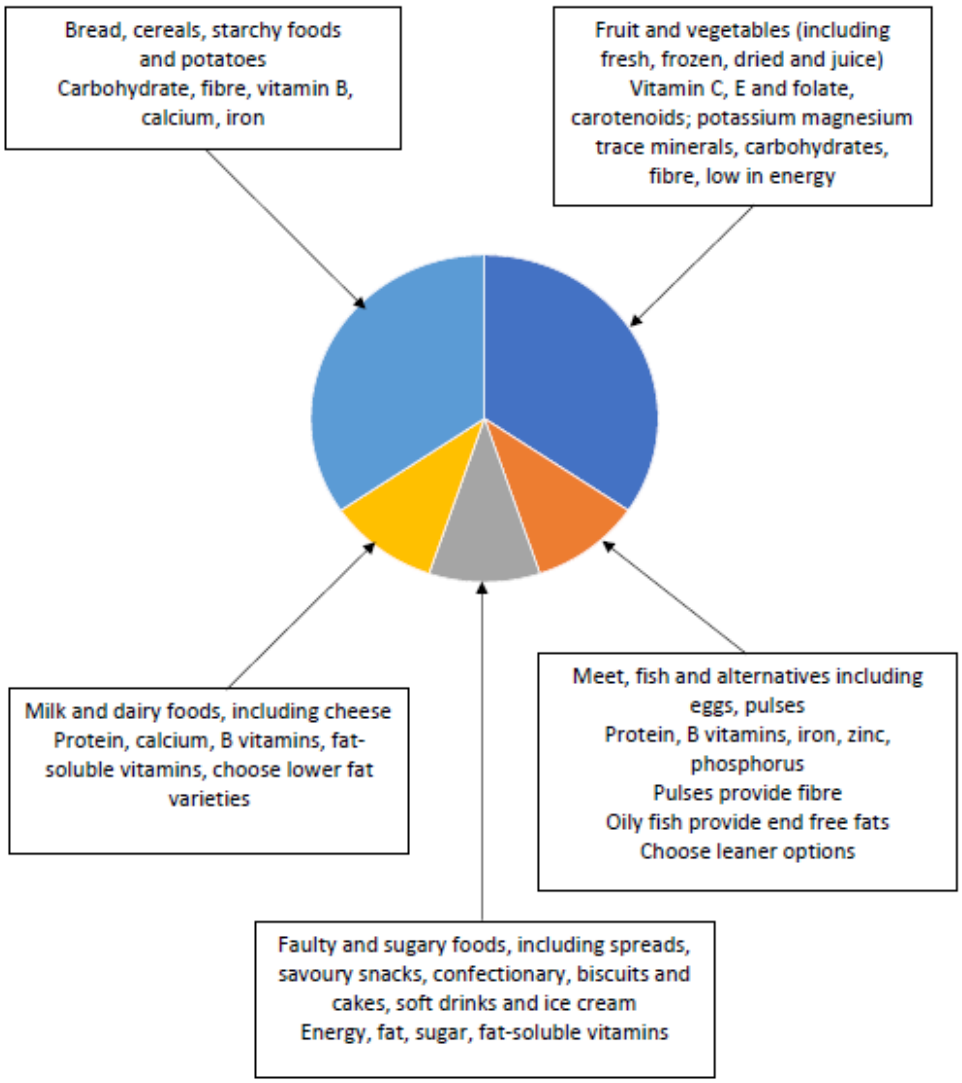


Figure 5.1. Diagrammatic representation of the Plate Model

5.2.1.5.3 Strategies employed post-delivery

All women diagnosed with GDM were offered an OGTT 6weeks post-delivery and a follow-up appointment for diabetes review after that appointment in the MDT postnatal clinic. Women with normal results were referred to their General Practitioners (GPs) with advice for yearly screening. Women with abnormal results were referred to the Outpatients clinic for specialist care by the Endocrinologist/Diabetologist and Diabetes Nurse Specialist.

Before discharge, women are encouraged to continue with healthy eating and to increase their level of activity to maintain a healthy lifestyle. They are also encouraged to have an early antenatal booking in subsequent pregnancies to enable early screening for the condition if overt diabetes was not confirmed

5.2.1.6 *Screening*

5.2.1.6.1 *What is the guidance?*

There is no consensus with regards to the time of screening (Leary et al, 2010; Gilmartin et al, 2008 & Bottalico, 2007). However, in response to the HAPO study (HAPO Study Cooperative Research Group, 2008) and the need to promote standardised quality care, the International Association of Diabetes and Pregnancy Study Group (IADPSG) recommended universal screening between 24-28 weeks for pregnant women not known to be diabetic (IADPSG Consensus Panel, 2010), as some women may be asymptomatic (Cundy et al, 2014); but despite this, ambiguity remains (Benhalima et al, 2015). Consequently, there is ongoing and increasing debate on effective screening for GDM (Feghal et al, 2018; Moncrieff, 2018 & Hanna et al, 2007), but most support universal screening between 24- and 28-weeks gestation for women with risk factors such as previous history of GDM, previous macrosomic baby, obesity, family history of

diabetes and age 35 and above and polycystic ovaries syndrome (Standards of Medical Care in Diabetes - 2017 (2017).

As pregnancy advances, insulin resistance increases (Catalano et al 1993). Screening at 24-28 weeks gestation is recommended at the time of peak insulin resistance to get an accurate diagnosis of GDM while allowing time for intervention and management benefit (Feghal et al, 2018). However, due to Type 2 diabetes meeting epidemic proportions outside of pregnancy, women may present with undiagnosed pre-existing diabetes or may develop GDM below 24 weeks gestation (Feghal et al, 2018). Hence, blanket screening at the antenatal booking visit is recommended by some organisations. For women with risk factors (as previously described) the recommendation for early screening varies but more common is screening between 24-28 weeks (Standards of Medical Care in Diabetes - 2017 (2017), NICE, 2015). If changes to GDM screening are to be made, the level of uncertainty and heterogeneity should be considered (Chamberlain et al 2015).

Current NICE's guideline (2015) recommends early testing for pregnant women with a previous history of GDM and repeat testing between 24-28 weeks gestation if the initial result was normal. Women with other risk factors should be screened between 24-28 weeks.

Intensive MDT management is critical once the diagnosis is made and appropriate follow-up care is necessary post-delivery. However, the evidence suggests that communication between the primary and secondary sectors are fragmented resulting in fewer than fifty percent of women not attending for their postnatal screening. Adequate postnatal care is therefore ineffective, and a substantial number of women can develop T2 DM which in turn can have huge cost implications on the health care system (Bernstein et al, 2016).

5.2.1.6.2 *Demographics of the local population*

The borough of Newham has a population of approximately 353,134 (ONS, 2019). In 2019, forty-seven percent (47%) were females with (68%) of the population between ages 18-64 and 24.4% ≤18 years. Ethnic distribution was Asians (45.2%), Whites (27.7%), Blacks (17.7%) and other ethnic groups (9.3%) (Newham London, 2020). Further details on the Borough of Newham can be found in chapter 2 (2.4).

This ethnic mix presents many challenges for health care service providers especially as Newham has one of the highest birth rates in the country which is primarily from a younger population. Gestational diabetes mellitus (GDM) poses a huge challenge for obstetricians and midwives. The local prevalence of GDM is unknown but is presumed very high as approximately 26,500 people are diagnosed with Type 2 diabetes mellitus (T2 DM) and this is about 10% of the adult population (NCCG, 2017a). Therefore, it is critical to have appropriate local and national screening guidelines which incorporate identifiable risk factors of GDM which will identify women who need to be screened and in a timely manner; considering the potential morbidity and mortality associated with the condition. This chapter is conducted with this aim.

5.3 Aims

- To assess whether NICE national guideline is appropriate for screening women at risk of gestational diabetes with risk factors of raised BMI and first degree relatives with diabetes.
- To assess whether there are any differences in maternal and foetal outcomes with women who are diagnosed before 24 weeks gestation and women diagnosed after this gestation.

5.4 Research questions

- Does adherence to the recommendations of current NICE's guidelines on screening for GDM, result in delayed diagnosis and intervention in women with other risk factors who develop the condition early in their pregnancy?
- Are there differences in pregnancy and post-pregnancy outcomes between early and late diagnosis of GDM?

5.5 Hypotheses

- Current NICE guideline on early screening for GDM is appropriate to detect women most at risk of developing the condition.
- There is no difference in pregnancy and post-delivery outcomes between women diagnosed early (<24 weeks) with GDM and those diagnosed late (≥24 weeks).

5.6 Subjects & Methods

5.6.1 *Study population and design*

This study was conducted at Newham University Hospital on pregnant women between ages 17 to 45. Women diagnosed with GDM ≤ 24 weeks gestation (n=212) and ≥ 24 weeks gestation (n=226) were identified at the hospital's SADC and GDESs (previously discussed) and were recruited during the first to third trimester at their homes or on antenatal visits. Data of only women with a confirmed diagnosis of GDM following an oral glucose tolerance test (OGTT) were included and detailed demographic, socio-cultural, economic and clinical data collected. Diagnosis of GDM was made when the fasting plasma glucose was ≥6.1mmol/litre and/or two hours ≥7.8mmol/litre (NICE, 2008). Women with a previous history of GDM, family history of diabetes, BMI ≥30 kg/m2, previous babies weighing ≥4kg, maternal age ≥40 and raised random blood glucose ≥7.0mmol/l and <11.1mmol/l had an OGTT at 16 weeks and if negative repeated at 28 weeks gestation. Eligible women were recruited up to 32 weeks gestation.

A questionnaire (*appendix 3.7*) was used to collect data on (a) gestational age at the time of diagnosis of GDM (<24weeks gestation & > 24weeks gestation) (b) antenatal and postnatal OGTT results, (c) pregnancy complications (eg. hypertensive disorders and pregnancy loss), (b) diabetes management and (d) maternal and foetal outcomes (eg. prematurity, post-maturity, macrosomia and low birth weight, neonatal admission to special care baby unit). Detailed demographic, socio-cultural and economic data was also collected. Further details can be found in chapter 3.

5.7 Statistical analysis

Data analysis was conducted using the SPSS Statistics for Windows (Version 25) analysis framework. Data collected were labelled, coded and inputted into the SPSS tool. The level of measurement was nominal data. The number of cases that appeared in each category was counted to either accept or nullify the hypotheses and descriptive statistics were used to establish frequencies in data, for example, to establish how many women were diagnosed before and after 24 weeks gestation. The Chi-square (cross-tabulation), Pearson's correlation coefficient test for independent samples was used to analyse any pattern of observed frequencies which may suggest an association between variables tested, for example, whether there was an association between ethnicity and women diagnosed with GDM. Values of $\mathbf{p < 0.05}$ were considered significant.

5.8 Results:

5.8.1 *Characteristics*

The demographic and clinical information of the participating subjects are outlined in ***Table 5.1***. Women aged 21-30 and 31-40 diagnosed with GDM <24 weeks gestation were 84 (40%) and 119 (56 %) and ≥24 weeks gestation 100 (44%) & 108 (48%) respectively (**p < 0.206**). The mean age was 25.9. The rate of diagnosis <24 weeks and ≥24 weeks gestation in Asians was 71% and 68% respectively and 26% and 23% (respectively) in Afro-Caribbeans (**p < 0.025**). GDM diagnosis <24 and ≥24 weeks were 38% & 34% respectively in overweight women and 42% in obese women in both screening groups (**p < 0.494**). For those diagnosed <24 weeks, 20% presented having had previous chronic medical conditions while 14% was in the latter group (≥24 weeks gestation) (**p < 0.74**).

Table 5.1: Demographic and medical information and gestational weeks at diagnosis

Demographic & medical information	**<24 weeks of gestation**	**≥24 weeks of gestation**	**Totals**	**P value**
Ages	***(n=212)***	***(n=226)***		***0.206***
≤ 20 years	2 (0.9%)	5 (2.2%)	7 (1.6%)	
21-30 years	84 (39.6%)	100 (44.2%)	184 (42.0%)	
31-40 years	119 (56.1%)	108 (47.8%)	227 (51.8%)	
≥ 41 years	7 (3.3%)	13 (5.8%)	20 (4.6%)	
Ethnicity	***(n=212)***	***(n=226)***		***0.025***
All Whites	7 (3.3%)	22 (9.7%)	29 (6.6%)	
Afro-Caribbean	54 (25.5%)	51 (22.6%)	105 (24.0%)	
Asians	151 (71.2%)	153 (67.7%)	304 (69.4%)	
Booking BMI	***(n=208)***	***(n=220)***		***0.494***
Underweight (<18.5)	3 (1.4%)	1 (0.5%)	4 (0.9)	
Normal weight (18.5-24.9)	41 (19.7%)	53 (24.1%)	94 (22.0%)	
Overweight (25.0-29.9)	77 (37.0%)	74 (33.6%)	151 (35.3%)	
Obese (≥30)	87 (41.8%)	92 (41.8%)	179 (41.8%)	
Chronic medical conditions	***(n=193)***	***(n=220)***		***0.740***
Yes	39 (20.2%)	30 (13.6%)	69 (16.7%)	
No	154 (79.8%)	190 (86.4%)	344 (83.3%)	

Table 5.2 shows the interrelationship between age, BMI, ethnicity and chronic medical conditions. Of those between ages 21-30 and 31-40, 77% and 63%, respectively, were Asians and 18% and 29% (respectively) Afro-Caribbeans and the remaining 5% and 8% (respectively), were Caucasians (**p < 0.053**). Within those age groups, 42% and 49% respectively were overweight and 33% and 61% (respectively) were obese (**p < 0.000**). In the overweight category, 3% were Caucasians, 20% Afro-Caribbeans and 77% were Asians, while 11%, 37% and 52% respectively were obese (**p < 0.000).** Of the 72 women who presented with chronic medical conditions, 93% were between ages 21-40 (**p < 0.604**); 35% were of Afro-Caribbean and 60% of Asian descent (**p < 0.059**), and they were either overweight (31%) or obese (44%) (**p < 0.909**).

Table 5.2: Interrelationship between age, BMI, ethnicity and chronic medical conditions

	≤ 20 years	**21-30 years**	**31-40 years**	**≥ 41 years**	**P value**
Age distribution of ethnic groups	(n=7; 1.5%)	(n=195; 42.6%)	(n=234;51.1%)	(n=22; 4.8)	**0.053**
All White	0 (0.0%)	10 (5.1%)	19 (8.1%)	2 (9.1%)	
Afro-Caribbean	3 (42.9%)	35(17.9%)	67 (28.6%)	3 (13.6%)	
Asians	4 (57.1%)	150 (76.9%)	148 (63.2%)	17 (77.3%)	
Age distribution and BMI	(n=7; 1.6%)	(n=190; 42.4%)	(n=231; 51.6%)	(n=20; 4.5%)	**0.000**
Underweight (<18.5)	0 (0.0%)	4 (66.7%)	1 (16.7%)	1 (16.7%)	
Normal weight (18.5-24.9)	0 (0.0%)	58 (59.2%)	38 (38.8%)	2 (2.0%)	
Overweight (25.0-29.9)	6 (3.8%)	66 (41.8%)	78 (49.4%)	8 (5.1%)	
Obese (≥30)	1 (0.5%)	62 (33.3%)	114 (61.3%)	9 (4.8%)	
BMI and ethnicity	**Underweight (<18.5)**	**Normal weight (18.5-24.9)**	**Over weight (25.0-29.9)**	**Obese (≥30)**	**0.000**
	(n=6; 1.3%)	**(n=98; 21.9%)**	**(n=158; 35.3%)**	**(n=186; 41.5%)**	
All White	0 (0.0%)	4 (4.1%)	4 (2.5%)	21 (11.3%)	
Afro-Caribbean	0 (0.0%)	6 (6.1%)	32 (20.3%)	68 (36.6%)	
Asians	6 (100.0%)	88 (89.8%)	122 (77.2%)	97 (52.2%)	

	Chronic medical conditions		
	(n=72)	**(n=360)**	**0.604**
Age	**Yes**	**No**	
≤ 20 years	1 (1.4%)	5 (1.4%)	
21-30 years	25 (34.7%)	156 (43.3%)	
31-40 years	42 (58.3)	181 (50.3%)	
≥ 41 years	4 (5.6%)	18 (5.0%)	
Ethnicity	**(n=72)**	**(n=360)**	**0.059**
All White	4 (5.6%)	22 (6.1%)	
Afro-Caribbean	25 (34.7%)	78 (21.7%)	
Asians	43 (59.7%)	260 (72.2%)	
BMI	**n=71**	**n=358**	**0.909**
Underweight (<18.5)	1 (1.4%)	5 (1.4%)	
Normal weight (18.5-24.9)	17 (23.9%)	78 (21.8%)	
Overweight (25.0-29.9)	22 (31%)	127 (35.5%)	
Obese (≥30)	31 (43.7%)	148 (41.3%)	

5.8.2 Risk factors

5.8.2.1 Risk factors of GDM and gestational ages at diagnosis

Of those women who consented to take part in the study, 203 {38 (18.7%) previous GDM vs. 165 other risk factors} and 218 {27 (12.4%) previous GDM vs. 191 other risk factors} were GDM positive at <24 and ≥24weeks respectively (**p <0.291**) (***Table 5.3***).

Table 5.3: Risk factors of GDM at different gestational weeks

	Family History	BMI ≥30	Previous GDM	Other Groups*	P value
Gestational weeks	**n=229**	**n=88**	**n=65**	**n=39**	**0.291**
<24 (n=203)	108 (43.2%)	41 (20.2%)	38 (18.7%)	16 (7.9%)	
≥24 (n=218)	121 (55.5%)	47 (21.6%)	27 (12.4%)	12 (10.6%)	

***Other groups comprise of previous macrosomia, ages 40+, previous poor obstetric outcome (SB & ND), raised random blood glucose (≥7.0 & ≤11.1mmol/l) and glucosuria

The interrelationship between the risk factors and age, ethnicity and BMI are outlined below in ***Table 5.4***. Age 21-30 was 67%, 16% and 9% respectively and 31-40 were 45%, 24% and 21% respectively (**p <0.001**); ethnicity was all White 21%, 55% and 17% respectively, Afro-Caribbean 36%, 32% and 20% respectively and Asians 65%, 13% and 13% respectively (**p <0.000**). For BMI, the values were 76%, 6%, and 10% respectively; 64%, 3% and 17% and 34%, 47% and 17% respectively (**p <0.000**).

Table 5.4: Risk factors and maternal age, ethnicity and BMI

	Family History	BMI ≥30	Previous GDM	Other Groups*	P value
Age	**n=237**	**n=89**	**n=65**	**n=41**	**0.001**
≤ 20 years	6 (85.7%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	
21-30 years	121 (66.5%)	29 (15.9%)	16 (8.8%)	16 (8.8%)	
31-40 years	101 (45.3%)	54 (24.2%)	47 (21.1%)	21 (9.4%)	
≥ 41 years	9 (45.0%)	5 (25.0%)	2 (10.0%)	4 (20.0%)	
Ethnic groups					**0.000**
All White	6 (20.7%)	16 (55.2%)	5 (17.2%)	2 (6.9%)	
Afro-Caribbean	37(35.6%)	33 (31.7%)	21(20.2%)	13 (12.5%)	
Asians	194 (64.9%)	40 (13.4%)	39 (13.0%)	26 (8.7%)	
BMI					**0.000**
Underweight (<18.5)	5 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Normal weight (18.5-24.9)	68 (75.6%)	0 (0.0%)	9 (10.0%)	13 (14.4%)	
Overweight (25.0-29.9)	96 (64.4%)	4 (2.7%)	25 (16.8%)	24 (16.1%)	
Obese (≥30)	61 (34.3%)	84 (47.2%)	30 (16.9%)	3 (1.7%)	

5.8.3 Pregnancy outcomes

5.*8.3.1 Pregnancy outcomes and gestational ages at diagnosis of GDM*

In ***Table 5.5*** women who were diagnosed <24 weeks gestation, premature birth was 13% (26), other groups 3.6% (7) {stillbirth 1% (2), neonatal death 0.5% (1), miscarriages 2% (4)} and the remaining 83% (163) delivered at full term. For those who delivered after 24 weeks, 84% (182) delivered at full term with 17% (36) delivered prematurely (**p <0.014**). Of those diagnosed before and after 24 weeks gestation, 1% / 2% had macrosomia, 12% / 8% low birth weight and the remainder were normal 88% / 90%, respectively (**p <0.380**). Eighty-three per cent (83.3%) of babies with macrosomia were born to mothers who were obese and (16.7%) overweight. Mode of delivery of those diagnosed <24 weeks was 41.5%

vaginal, 7.7% instrumental and 50.8% caesarean section and 45.2%, 7.8% and 47.0%, respectively ≥24 weeks of gestation (**p <0.735**).

Table 5.5: Pregnancy outcomes and gestational ages at diagnosis of GDM

	Gestational ages at diagnosis of GDM		**P value**
Pregnancy outcomes	**<24 weeks of gestation**	**≥24 weeks of gestation**	
Gestational ages at birth	**(n=196)**	**(n=218)**	**0.014**
Full term birth	163 (83.2%)	182 (83.5%)	
Preterm birth	26 (13.3%)	36 (16.5%)	
***Other outcomes	7 (3.6%)	0 (0.0%)	
Birth Weight	¤(***n=193***)	(***n=218***)	**0.380**
Low birth weight (≤2499grams)	22 (11.4%)	17 (7.8%)	
Normal birth weight (2500 - 4449grams)	169 (87.6%)	197 (90.4%)	
Macrosomia (≥4500grams)	2 (1.0%)	4 (1.8%)	
Mode of delivery	**n=195**	**n=219**	**0.735**
Vaginal	81 (41.5%)	99 (45.2%)	
Instrumental	15 (7.7%)	17 (7.8%)	
Caesarean	99 (50.8%)	103 (47.0%)	

***Other outcomes comprise of stillbirth, miscarriages and neonatal deaths ¤miscarriages x 4

5.8.3.2 Obstetric complications and gestational ages at diagnosis of GDM

Within the index pregnancy, 21% and 31% developed maternal and foetal/neonatal complications <24 weeks gestation, respectively, and19% and 32% (respectively) ≥24 weeks **(p <0.925)** (***Table 5.6***).

***Table 5.6**: Obstetric complications and gestational weeks at diagnosis of GDM*

	Gestational ages at diagnosis of GDM		**P value**
	<24 weeks of gestation	**≥24 weeks of gestation**	
Obstetric complications	**(n = 155)**	**(n = 190)**	**0.925**
No complications	75 (48.4%)	94 (49.5%)	
Maternal complications	32 (20.6%)	36 (18.9%)	
Foetal / neonatal complications	48 (31.0%)	60 (31.6%)	

Gestational ages at birth for those with maternal and foetal/neonatal complications were 17.7% / 26.3% full term live and 28.1% / 54.4% preterm, respectively (**p <0.000**). Birth weight for maternal and foetal/neonatal complications were 27.3% / 46% low birth weight, 18.4% / 29.4% normal weight and 18.4% / 29.4% macrosomia, respectively (**p <0.046**). Deliveries vaginally 15.8% / 32.1%, instrumentally 22.2% / 48.1% and by caesarean section 22.0% / 28.0% were of women with maternal and foetal/neonatal complications, respectively (**p < 0.120**) (***Table 5.7***).

Table 5.7: Obstetric complications and pregnancy outcomes

	Obstetric complications			P value
Pregnancy outcomes	**No complications**	**Maternal complications**	**Foetal / neonatal complications**	
Gestational ages at birth	**(n=178)**	**(n=69)**	**(n=113)**	**0.000**
Full term birth	168 (56.0%)	53 (17.7%)	79 (26.3%)	
Preterm birth	10 (17.5%)	16 (28.1%)	31 (54.4%)	
***Other outcomes	0 (0.0%)	0 (0.0%)	3 (100.0%)	
Birth Weight	**(n=177)**	**(n=69)**	**(n=112)**	**0.046**
Low birth weight (≤2499grams)	9 (27.3%)	9 (27.3%)	15 (45.5%)	
Normal birth weight (2500 - 4449grams)	167 (52.2%)	59 (18.4%)	94 (29.4%)	
Macrosomia (≥4500grams)	1 (20.0%)	1 (20.0%)	3 (60.0%)	
Mode of delivery	**(n=178)**	**(n=69)**	**(n=113)**	**0.120**
Vaginal	86 (52.1%)	26 (15.8%)	53 (32.1%)	
Instrumental	8 (29.6%)	6 (22.2%)	13 (48.1%)	
Caesarean	84 (50.0%)	37 (22.0%)	47 (28.0%)	

5.8.4 Ethnic categories and consanguinity

Consanguinity was found only among the Asians (6.8%) (**p <0.001**) accounting for approximately 10% of all Asians screened (***Table 5.8***).

Table 5.8: Ethnic categories and consanguinity

	Consanguinity		P value
	Yes	**No**	
Ethnic categories	**(n=31)**	**(n=*424*)**	**0.001**
All Whites	0 (0.0%)	31 (100.0%)	
Afro-Caribbean	0 (0.0%)	108 (100.0%)	
Asians	31(9.8%)	285 (90.2%)	

5.8.5 Diabetes management and gestational ages at diagnosis

Diabetes management in <24 weeks gestation was diet only 42.5%, 62.1% diet and oral medication and 53.4% diet and insulin or combination therapy, compared to 57.5%, 37.9% and 46.6% respectively in ≥24 weeks (**p <0.034**) (***Table 5.9***).

Table 5.9: Gestational ages at diagnosis and diabetes management

	Gestational ages at diagnosis		**P value**
	<24 weeks of gestation	**≥24 weeks of gestation**	
Diabetes management	**n = 193**	**n = 214**	**0.034**
Diet only	105 (42.5%)	142 (57.5%)	
Diet and Oral medication	18 (62.1%)	11 (37.9%)	
Diet and Insulin and Combination therapy	70 (53.4%)	61 (46.6%)	

5.8.6 Diabetes management and pregnancy outcomes

Pharmacological therapy of diet only, diet and oral therapy and diet and insulin / combination therapy were 61.2%, 7.5% and 31.3%, respectively for full term births and 51.6%, 4.8% and 43.5%, respectively for preterm birth (**p < 0.0269**); 63.2%, 10.5% and 26.3% respectively, low birth weight, 59.7%, 6.5% and 33.8% respectively for normal birth weight. Macrosomia was 83.3% diet only and 16.7% diet, insulin and combination therapy (**p < 0.589**). Deliveries vaginally 70.2% / 7.2% / 22.7%, instrumentally 48.4% / 12.9% / 38.7% and by caesarean section 53.2% / 5.9% / 41.0% were managed with diet only, diet and oral therapy and diet, insulin or combination therapy, respectively (**p < 0.002**) (***Table 5.10***).

Table 5.10: Diabetes management and pregnancy outcomes

	Diabetes management			P value
Pregnancy outcomes	**Diet only**	**Diet and Oral Medication**	**Diet and Insulin and Combination therapy**	
Gestational ages at birth	**(n=250)**	**(n=29)**	**(n=137)**	**0.0269**
Full term birth	213 (61.2%)	26 (7.5%)	109 (31.3%)	
Preterm birth	32 (51.6%)	3 (4.8%)	27 (43.5%)	
***Other outcomes	5 (83.3%)	0 (0.0%)	1 (16.7%)	
Birth Weight				**0.589**
Low birth weight (≤2499grams)	24 (63.2%)	4 (10.5%)	10 (26.3%)	
Normal birth weight (2500 - 4449grams)	220 (59.7%)	25 (6.5%)	125 (33.8%)	
Macrosomia (≥4500grams)	5 (83.3%)	0 (0.0%)	1 (16.7%)	
Mode of delivery				**0.002**
Vaginal	127 (70.2%)	13 (7.2%)	41 (22.7%)	
Instrumental	15 (48.4%)	4 (12.9%)	12(38.7%)	
Caesarean	109 (53.2%)	12 (5.9%)	84 (41.0%)	

5.8.7 Post-delivery outcomes and gestational ages at diagnosis

Post-delivery, of those with GDM diagnosed <24 weeks, 25% had abnormal OGTT of which 12 % had T2 DM. In the ≥24 weeks group, 4% had T2 DM and 9% had either impaired glucose tolerance (IGT) (blood glucose between 7.8 & 11.1mmol/l after 2 hours glucose load) or impaired fasting glucose (IFG) (fasting glucose >6.1mmol/l). Overall, twenty-five (16 %) were diagnosed with T2 DM and 23% had either IGT or IFG on postnatal OGTT (**p <0.010**) (***Table 5.11***). Post-partum blood glucose status for Afro-Caribbeans and Asians were 87.8% / 78.0% normal, 6.8% / 12.6% IGT/IFG and 5.4% /

9.3% Type 2 DM, respectively. Whites were 83.3% normal and 16.7% Type 2 DM (**p <0.144**) (***Table 5.12***).

Table 5.11: Postpartum glycaemic status and gestational ages at diagnosis

	Normal	**Impaired Glucose Tolerance (IGT) / Impaired Fasting Glucose (IFG)**	**Type 2 diabetes mellitus**	**P value**
Gestational ages on GDM diagnosis (weeks)	**(n=262)**	**(n=36)**	**(n=25)**	**0.010**
< 24/40	112 (74.7%)	20 (13.3%)	18 (12.0%)	
≥ 24	150 (86.7%)	16 (9.2%)	7(4.0%)	

Normal = <6.1mmol/l on fasting and <11.1mmol/l two hours after glucose load; Impaired Glucose Tolerance (IGT) = normal fasting plasma glucose with 2-hour value ≥7.8mmol/l and ≤11.1mmol/l and Impaired Fasting Glucose (IFG) = fasting glucose ≥ 6.1mmol/l but below 7.0mmol/l with a normal 2-hours value <7.8mmol/l

Table 5.12: Postpartum glycaemic status and ethnic groups

	Normal	**Impaired Glucose Tolerance (IGT) / Impaired Fasting Glucose (IFG)**	**Type 2 diabetes**	**P value**
Ethnic groups	**(n=272)**	**(n=36)**	**(n=30)**	**0.144**
All Whites	15 (83.3%)	0 (0.0%)	3 (16.7%)	
Afro-Caribbeans	65 (87.8%)	5 (6.8%)	4 (5.4%)	
Asians	192 (78.0%)	31 (12.6%)	23 (9.3%)	

5.9 Discussion

5.9.1 Prevalence of GDM

In this study, GDM was more common among the Asians, followed by the Afro-Caribbeans with the indigenous group less likely to have the condition and this was highly significant. Although the Asians were the more dominant group detected with GDM, there were a similar number of women detected early and late gestation, likewise for the Afro-Caribbeans. Compared to the Whites, Afro-Caribbean were 4 times and Asians 10 times more likely to develop GDM. This prevalence exceeds national figures (NICE, 2015) but is reflective of the ethnic distribution of the local population. In support of the findings of this study, GDM was found to be more prevalent among Asians than Whites (Ferrara, 2007; Yang et al, 2002 & Dornhurst et al, 1992).

Obesity, sedentary lifestyle and changes in dietary habits 'superimposed on genetic/epigenetic' predispositions are believed to contribute to the high prevalence of diabetes in general among Asians (Hu, 2011). Also, the incidence and prevalence can be rapidly increased when further complicated with consanguineous marriages. Consanguinity is more common among Asians and this was reflected in this study which showed no incidence in the other ethnic groups. Therefore, a significant number of local women were presenting in pregnancy with other confounding factors, which at booking, make their pregnancy 'High Risk', even without the complications of diabetes.

In 2012, a West Indian study conducted to assess the effects of family history of diabetes and consanguinity on the siblings of T2 diabetics found a positive correlation between these factors and metabolic disturbance within this group (Shahid et al, 2012). This study

was conducted on a non-diabetic population and should GDM have been present in the study group, one can conclude that there could have been a stronger correlation, and this coupled with the aetiology of the condition, could be partly responsible for the cyclical effect of diabetes among and within this group.

5.9.2 Family history and BMI

In this study, family history and BMI ≥30 were strong indicators of developing GDM early in pregnancy with the latter being as strong as those having had a previous history of GDM and the former being over twice the strength. Over one-third of the women screened were either overweight or obese and they were mainly Asians followed by Afro-Caribbeans. These findings suggest a link between familial factors and increasing BMI and GDM within the local population.

Our findings are substantiated in a systematic review with meta-analysis on pre-pregnancy BMI and the risk of GDM, which found that compared to women of normal weight, women who were overweight and moderately/severely obese were at higher risk of developing GDM and that risk increased for every 1kg/m increase in BMI (Torloni et al, 2009).

Recently, a study had revealed that the incidence of GDM increased, the higher the pre-pregnancy BMI (Abu-Heija et al, 2017). A systematic review which examined maternal anthropometrics on pregnancy outcomes of South Asians found that pre/early pregnancy weight and body fat were associated with anthropometric changes, mode of delivery, birth weight and GDM, suggesting an increased risk of adverse pregnancy outcome among this ethnic group (Slack et al, 2018). Additionally, in a large-scale population-based study, a strong correlation was established between a woman's birth weight and her subsequent risk

of developing GDM suggesting that early life factors contributed to the aetiology of the condition (Innes et al, 2002).

Also, when BMI ≥25.0 kg/m2 was used as a screening tool for the detection of GDM, the incidence was highest among African Americans (76%), followed by Latinas (58%), Caucasians (46%) with Asians (25%) least at risk (Shah et al, 2011). In a large London-based study, BMI was found to be associated with diabetes in pregnancy, regardless of ethnicity. However, the application of BMI cut-off of 30.0 kg/m2 is believed to fail detection of East and South Asian women who have shown to be at higher risk of diabetes at a lower BMI threshold as low as 21 kg/mg2. It is therefore suggested that universal screening for all Asians might be the way forward (Nishikawa et al, 2017).

An Australian study that compared ethnicity with GDM diagnosis have demonstrated similar low BMI thresholds in South East Asians in the diagnosis of GDM based on elevated 2-hr values compared to Anglo-American and women from the Pacific who had higher BMIs and GDM diagnosis on elevated fasting values (Wong, 2012). Other studies have shown similar association between low BMI and the detection of diabetes among Asians (Ma & Chan, 2013 & Nyamdori et al, 2010). Having used BMI ≥30.0 kg/m2 as a cut-off for this study may prove to be of a disservice to Asians in particular. Hence, ethnic specific BMI thresholds for the diagnosis of GDM may be necessary for more accurate risk identification with a more targeted approach for intensive care including during the postnatal period (Mukerji et al, 2012). Nevertheless, obesity prevention among all ethnic groups may be necessary for the reduction of the prevalence of the disease (Shin et al, 2012).

Like BMI, advancing maternal age is also a risk factor in the detection of GDM and this is more of a concern among South Asians and Black Africans (Makgoba et al, 2011). Makgoba et al (2011) also found that the interaction of age and BMI with racial groups can determine the prevalence of GDM. Also, Black Caribbeans were less likely to develop GDM compared to Black Africans, suggesting inaccuracies of reporting epidemiological findings among and within these groups. Despite these findings, having a shift in separating these groups may be avoided to provide larger sample sizes for strong statistical analyses for the understanding of the aetiology of diseases like GDM/diabetes. Nevertheless, as Afro-Carribeans were the second largest group in this study, consideration must be given to separate the Black Caribbeans from the Black Africans for future work.

A recent study which looked at the prevalence of GDM and associated risk factors among Chinese women found that there was a high prevalence of GDM within this group with key risk factors being advanced maternal age, pre-pregnancy BMI and a history of first degree relative with diabetes (Wu et al, 2018). Likewise, there was a direct link between increasing maternal age and developing GDM with a family history of diabetes and previous history of GDM being the main predictors of the condition. There was also a strong correlation between increasing maternal age and having a positive oral glucose challenge test (OGCT) when screened between 24-28 weeks (Abu-Heija et al, 2017). In the Northern California Kaiser Permanente study, the prevalence of GDM increased in all age groups with the highest increase among the youngest group (Ferrara et al, 2004). The population studied was predominantly young and age was not a major risk factor for this study.

In a Saudia Arabian study, multiparous women were approximately 8 times more likely than nulliparous women to develop GDM and the latter group had an increased risk of 2-21% when age was increased from 20 to 40 years (Al Rowaily MA & Abolfotouh MA, 2010). In this study, age was not a determinant factor with regards to early or late diagnosis of GDM. However, as Al Rowaily & Abolfotouh (2010) and Abu-Heija et al (2017)'s studies only evaluated the late-onset GDM, it is difficult to make wholesome comparisons. Nevertheless, it would have been useful to explore parity in relation to the time of diagnosis as this factor seems to have some correlation to GDM diagnosis. Likewise, with our local population being predominantly young, this information would have been invaluable for future care planning.

5.9.3 Early and late diagnosis of GDM

NICE (2015) recommends that early screening should be offered only to those with a previous history of GDM. However, this study has demonstrated that almost 50% of the women developed GDM before week 24 and a considerable number of these high-risk pregnant women, nearing 80% had no previous history of gestational diabetes.

These findings concur with previous studies which concluded that selective screening may fail to detect about one-third of women with GDM (Benhalima et al, 2015) whereas universal screening has a higher detection rate (Tieu et al, 2017; Benhalima et al, 2015). This is despite a Cochrane review demonstrating insufficient evidence to conclude a positive impact on maternal and foetal health (Tieu et al, 2017).

NICE's (2015) current guidelines may have its foundations from similar origins. However, based on the evidence of this study whereby a considerable number of high-risk pregnant

women without previous histories of gestational diabetes developed GDM before week 24, a strict adherence to the NICE guidelines may be inappropriate if the target population is genetically predisposed to metabolic abnormalities.

Therefore, in regions of the UK, such as the London Borough of Newham which have a significant number of residents of Asian origin, pregnant women with a family history of diabetes and raised BMI should be screened for gestational diabetes as early as possible. Furthermore, universal screening in an area like this which is highly multi-cultural may have a high detection rate and further research may be needed to explore this area. Additionally, the fasting value on OGTT (≥6.1mmol/l) used for the diagnosis of GDM for this study were based on NICE's (2008) guidelines. This value is significantly higher than current recommendations of ≥5.6mmol/l and should the latter have been used, there would have been an increased detection rate, with these tighter guidelines.

This is of concern because poorly controlled gestational diabetes is associated with adverse maternal and foetal outcomes (Billionnet et al, 2017). Moreover, there is evidence that women with a history of gestational diabetes have a high risk of developing type 2 diabetes (Kwak et al, 2013) and their children type 2 diabetes in later life (Garcia-Vargus et al, 2012) and autism (Xiang et al, 2015).

5.9.4 Diabetes management

In this study, approximately 61 percent of all women were managed on diet only and this form of management was more common among those diagnosed ≤24 weeks gestation. Of those who received pharmacotherapy, the main form of treatment was diet and insulin therapy, and the incidence was similar in both early and late diagnosed GDM groups.

Although the number of women on combination therapy was small the incidence was three times greater in those diagnosed <24 weeks gestation compared to those diagnosed later. However, for statistical analysis, this group was combined with those receiving the next intensive form of treatment - insulin. Overall, those diagnosed early needed more intensive pharmacotherapy, possibly impacting on nearing half the number of preterm births and instrumental and caesarean section deliveries.

A recent study which evaluated pregnancy outcome in early and late-onset GDM with risk factors of BMI and family history of diabetes has shown that the insulin requirement was 85 percent and 55 percent in early and late-onset GDM, respectively (Easmin et al, 2015).

It is difficult to postulate whether the limitation of using only two risk factors and insulin as the only form of pharmacological therapy, coupled with the clinician's preference in treatment modalities and the environment in which treatment was administered, could have impacted on the pharmacotherapy regimen and the subsequent impact on pregnancy outcomes. Additionally, as the subjects studied were of Bangladeshi origin living in their native country, genetic predisposition may have been a factor necessitating intensive therapy resulting in higher use of insulin therapy compared to this study which studied a wider cross-section of ethnic groups living in the UK with four treatment options.

Nevertheless, most recently, a systematic review on the effects of treatment on pregnancy outcomes of women diagnosed with GDM has shown no significant difference except for a reduction in shoulder dystocia in intensive versus less intensive treatment in the former group (Hovath et al, 2019).

5.9.5 Pregnancy outcomes (maternal and foetal)

In this study, although nearing half of the women presented having had previous obstetric problems (adjusting for the primagravidas) and almost half had no clinical problems within the existing pregnancy. One can argue that early intervention may have contributed to that positive outcome, having had extensive screening before 24 weeks of pregnancy to include women with risk factors other than a previous history of GDM. Obstetric complications which were mainly associated with the foetus/neonate developed at any stage of pregnancy regardless of gestational age when GDM was diagnosed. A significant number of these women with complications delivered prematurely compared to healthy women.

Macrosomia was more common among women diagnosed ≥24 weeks and whose babies had ante- and intrapartum complications but with no statistical significance. Low birth weight was higher in diagnosed GDMs <24 weeks gestation. Fifty percent of those who developed complications were delivered by caesarean section while approximately one-third of those who had an instrumental delivery also had complications.

A possible explanation for the higher incidence of macrosomia in ≥24 weeks gestation could be due to the very nature of the late diagnosis and possible late specialist intervention. It is well documented in previous evidence the benefits of early intervention to promote optimal well being for mother and baby (Görig et al, 2015). Conversely, IUGR in those diagnosed <24 weeks could be as a result of intensive treatment requirements due to insulin resistance and a possible causal effect reflective of likely undiagnosed T2 diabetics.

In a prospective Austrian study which examined clinical and pathophysiological characteristics of women with early and late diagnosis of GDM (using the IADPSG criteria), a higher degree of insulin resistance in the early onset group was found implicating that pre-existing insulin resistance and beta cell dysfunction during pregnancy may determine early onset of GDM diagnosis. Conversely, a manifestation of beta-cell dysfunction was found in early pregnancy of women diagnosed with GDM later in pregnancy, suggesting possible compensatory mechanisms during later pregnancy (Bozhurt et al, 2015).

Compared to Caucasians, Asians and South Asians have increased insulin resistance in late pregnancy. Also, pre-pregnancy BMI has greater insulin resistance in pregnancies in Asians compared to Caucasians and this may have resulted in the great disparity between the former and latter ethnic groups in this study. When these factors are combined, ethnicity may determine the effect of obesity on insulin resistance in pregnancy (Retnakaran et al, 2006).

There were a similar number of full-term births within the two groups (83% vs 84%). However, the number of stillbirths, neonatal death and miscarriages although small was found only amongst those diagnosed <24 weeks gestation. This reinforces the notion that the earlier the diagnosis of GDM, the more detrimental the likely impact on both mothers and their babies' health, and the need for early screening and specialist support and management to reduce the morbidity associated with the condition (Kennedy 2017, NICE 2015).

Although stillbirth rates among GDMs have decreased due to screening, treatment and antenatal surveillance of these mothers, about 4% of all stillbirths remain attributable to diabetes, and diabetic pregnancies continue to be at risk of prenatal mortality (Weissgerber & Mudd, 2015). Ben Slama et al (1997) estimated that the risk of stillbirth is increased after thirty-five (35) years even after the exclusion of conditions like hypertension and diabetes. In our study, age was not a contributory factor, and the adverse pregnancy outcome may have been associated with early onset of GDM or the likelihood of undiagnosed Type 2 DM pre-pregnancy, and morbidity associated with those conditions. Findings from Hosseini et al's (2018)'s study confirm that pregnancy outcomes are poorer in early-onset GDMs compared to the late-onset group.

A retrospective study has demonstrated that pre-pregnancy overweight and obesity are linked to large for gestational age infants, even without a diagnosis of GDM (Black et al, 2013). Almost ninety percent of the babies had normal birth weight in this study. Of those diagnosed with macrosomia, their mothers were either obese or overweight. One can postulate that local guidance on extensive screening of those other than with a previous history of GDM has not only been effective in detecting high-risk women early, but with early intervention, the incidence of macrosomia and related co-morbidities may have been prevented or reduced. However, despite pre-pregnancy overweight and obesity being linked to GDM and poor pregnancy outcomes (Catalano et al, 2012; Perez-Ferre et al, 2012), even without a diagnosis of GDM (Black et al, 2013), it can be argued that excess weight and GDM share similar physiopathological characteristics of insulin resistance and therefore it is difficult to isolate the effects of each on maternal and neonatal outcomes (Assaf-Balut et al, 2016).

High first-trimester fasting glucose levels, even when below the values of diagnostic diabetes, increase the risk of macrosomia, LGA birth weight and caesarean (Riskin-Mashiah et al 2009). When combined these factors may suggest that women who present before 24 weeks gestation may have had advanced pathophysiology and this may have resulted in poorer maternal and neonatal outcomes (Feghal et al, 2018).

High rates of adverse pregnancy outcomes were detected in women diagnosed with GDM before 24 weeks with the highest risk in those diagnosed less than 12 weeks but after accounting for maternal characteristics like obesity and timing of diagnosis, there was no longer associated with macrosomia and LGA birth weight (Sweeting et al 2016).

A recent study which looked at the timing of diagnosis of GDM and pregnancy outcome confirmed that those with a history of previous GDM were more likely to have an early diagnosis before 24 weeks gestation. They were also more likely to be older, less likely to have a college education and be nulliparous. They were also more likely to be obese but had a reduced chance of having excess gestational weight gain (Feghal et al, 2018).

Women diagnosed before 24 weeks gestation were more at risk of adverse outcomes compared to those after 24 weeks. Macrosomia was more common in the earlier diagnosed group, but only a slight difference was reported in gestational age at delivery. In terms of diabetes management, women diagnosed before 24 weeks were more likely to be treated with oral therapy or insulin. This group of women diagnosed before 24 weeks is believed to have unique features and therefore a targeted approach to therapy is recommended (Feghal et al, 2018).

Preterm birth was higher in women diagnosed ≥before 24 weeks gestation with no statistical significance. This is unlike the finding of a most recent retrospective study which showed a high incidence of preterm birth in those diagnosed early. This study evaluated the pregnancy outcomes of women with early (< 24 weeks) and late (≥24 weeks) diagnosis of GDM using the WHO 2013 screening criteria (75g OGTT) and found a higher incidence of preterm birth and caesarean section rate in the former group compared latter, supporting the notion of early screening and diagnosis of high-risk women. Also, there was an association between gestational age at GDM diagnosis and macrosomia and neonatal hypoglycaemia (Bashir et al, 2019). Conversely, no significant difference was found in neonatal outcomes, in another retrospective study which used both the WHO 2013 screening criteria (75g OGTT) versus fasting plasma glucose ≥92mg/dl and HBA1c ≥5.7% at ≤24 weeks gestation. However, women diagnosed early had a greater need for pharmacotherapy and BMI was highly significant in the prediction of this need (Alunni et al, 2015).

Nevertheless, it is argued that despite early detection of GDM (<12 weeks gestation) and best treatment, the pregnancy outcome of these women remains poor and is comparable to women with type 2 diabetes. Therefore, it is suggested that alternative approaches to management are necessary to improve the pregnancy outcomes in these high-risk pregnancies (Sweeting et al, 2016). It is postulated that this could be due to the early establishment of foetal hyperinsulinaemia thus supporting the need for pre-pregnancy planning and early establishment of maternal glycaemic control (Desoye & Nolan, 2016). These researchers have described this phenomenon as ‘fetal glucose steal’ which is also responsible for some foetuses having the characteristics of diabetic fetopathy despite their mothers having normal glucose tolerance.

In a large retrospective Australian pregnancy study, it was found that compared to Caucasians, Chinese women had a higher risk of developing GDM but with fewer risk factors which included lower BMI. Caucasians had poorer pregnancy outcomes while there was no difference in outcome in those diagnosed with GDM and those without the condition. Consequently, ethnicity needs to be considered when screening for GDM and managing the potential risks associated with the condition. Hence, the 'precision medicine risk prediction approach' has been suggested (Wan et al, 2019).

5.9.6 Postnatal Outcomes

In this study, there was a significant increase in those diagnosed with T2 DM <24 weeks compared to those diagnosed after 24 weeks. As there was an additional 115 who were not screened because they forfeited their appointments for postnatal testing, one can conclude that an additional 12% could have had T2 DM, if the same percentage is applied. Of those diagnosed with overt diabetes, 77% were Asians, although not statistically significant. Thirteen percent (13%) were Afro-Caribbeans and the remaining 10% were Whites.

A previous study which evaluated the impact of GDM on postpartum diabetes has shown that 6.5% were of South Asians origin and a third developed diabetes within 8 years, although they and women of Chinese origin were at decreased risk of postpartum diabetes (9-10 -fold) compared to Whites in whom the risk was 13-fold (Mukerji et al, 2012).

Post-GDM, women are at risk of developing T2DM within 5-10years and their children, the condition in their early years because they have a higher risk of being obese (Metzger et al, 2002). Obesity is a known contributory factor to GDM but root causes relate to

socioeconomic factors (Chu et al, 2007). In a cross-sectional USA study, central obesity was common among Asians and the prevalence increased over time and was associated with increased risk of T2 DM (Liu et al, 2017). It is postulated that this obesity epidemic is fuelled by increased calorific intake and decreased physical activity (Assaf-Balut et al, 2016; Hunt & Schuller, 2007) and has now become a public health issue.

Follow-up of this lost group is critical if future morbidities associated with GDM in subsequent pregnancies and T2 DM are to be reduced or even prevented; as women diagnosed with GDM have a 70% risk of developing GDM in subsequent pregnancies and T2 DM within 10 years post-delivery (Schwartz et al, 2015). 15-50% of women diagnosed with GDM develop T2 DM post-delivery (Wu et al, 2016). Having a postnatal OGTT and consultation are critical to the follow-up program (Beischer et al 1997; McClean et al, 2010) which needs to be unambiguous (McClean et al, 2010) and could be best organised by team administrators than clinicians (Beischer et al, 1997).

In a descriptive qualitative US study, women described being motivated to manage their GDM condition for their babies and not for themselves. Most believed that their future health would not be affected, and they were unaware of their risk of early-onset T2 DM (Bernstein et al 2016) – a condition that could be prevented with reduced portion sizes and increased activity (Hunt & Schuller, 2007).

To reduce the morbidity associated with the long-term effects of GDM, having a health education model can be useful to improve knowledge, and related beliefs and practices for prevention and early detection of T2 DM (Tawfik, 2017). Community engagement programmes offering increased activity are also necessary for all ethnic groups but

particularly Asians, as most women diagnosed were within this group. However, care must be taken when conducting any health research because Asians are a heterogeneous group and should be studied and evaluated within sub-groups (Chu et al, 2009). In an Australian randomised controlled trial of a postnatal diabetes prevention program, it was concluded that as little as1kg weight loss has the potential to be significant in the reduction of diabetes risk (O'Reilly et al, 2016).

A study conducted to evaluate the effectiveness of the prevention of Type 2 diabetes presented by a commercial weight management provider using a primary pathway has achieved a significant reduction in weight loss and subsequent diabetes risk (Piper et al, 2017 b). However, one may argue that one needs to cautious because commercial interest can be seen as a bias and may influence the findings. Nevertheless, due to the economic constraints that the NHS is under, this could be a viable option to curb the obesity crisis and reduce the explosion of T2 DM following childbirth and in general.

5.10 Conclusion

Our findings demonstrated that in communities like Newham which are genetically susceptible to T2 DM, early screening should be offered to pregnant women with BMI ≥30 and with a family history of diabetes as these risk factors are strong predictors for early detection of GDM. Early detection of GDM within these groups will facilitate the reduction of adverse birth outcomes and postnatal risks.

GDM remains a challenge for clinicians. Screening for the condition remains ambiguous and debatable. Current NICE guidelines appear to be limited in its offer for early screening to only those with a history of previous GDM. Adherence to these guidelines would be inappropriate in highly diverse populations with a family history of diabetes and BMI ≥30. Therefore, current NICE guidance on screening for GDM may need to be re-evaluated to assess its efficacy of use and application in areas with a high prevalence of diabetes. Further research is needed in this area.

Oral supplementation with omega-3 fatty acids in pregnant women is believed to one way of improving the health and well-being of mothers and their offspring. This will be explored in the next chapter (6) with particular focus on women with GDM.

Chapter 6:

The beneficial effects of omega 3 fatty acids on maternal and foetal health and birth outcomes of women diagnosed with gestational diabetes mellitus

6.1 Chapter overview

5 In this chapter, I have explored the beneficial effects of omega-3 fatty acids on maternal and foetal health and birth outcomes of women diagnosed with GDM. To do this, women with GDM were approached by random selection and offered the opportunity to take part in the nutritional study. For women who consented to be part of the nutritional study, they were randomised into two groups and given DHA or high oleic acid sunflower seed oil placebo capsules from recruitment until delivery.

6.2 Introduction

Maternal nutrition at the time of conception and throughout pregnancy is critical to a woman's health during pregnancy and pregnancy outcomes for her and her baby (Myatt & Powell, 2010). Included in the recommendation for a balance and health diet, are essential fatty acids (EFAs) {(arachidonic acids (AA) and docosahexaenoic acids (DHA)}. EFAs have been shown to be essential components in the foetal placental unit (Crawford et al, 1989) with implantation, vascular growth and organogenesis (Demetris et al, 2005), and subsequent embryonic morphology (Hammiche et al, 2011). Both mother and baby benefit from enhanced levels of omega 3 fatty acids supplementation (Dunstan et al, 2004).

For the foetus, newborn and infant, EFAs, particularly AA are necessary for foetal growth and development (Innis, 2007; Crawford, 2004). DHA is an important component of the developing central nervous system and is vital for cognitive and visual development (Connor et al, 1992, Crawford et al, 1976). DHA accumulates rapidly in the brain and retina during the 2nd (Martinez, 1992; Min & Crawford, 2004) and 3rd trimester and soon after delivery (Jensen, 2006). A child's behaviour, level of concentration and learning

improve with supplementation with EFAs (Perera et al, 2012; Yui et al, 2012 & Gustafsson et al, 2010). Increased birth weight and reduction in preterm births (Onwude et al, 1994 & Olsen et al, 1986), low levels of hyperbilirubinemia and hospitalisation are other potential benefits.

For the mother, likely benefits include prolonged gestational age (Olsen et al, 1991), reduction of preeclampsia (Dyerberg & Bang, 1985 & Romeo et al, 1988) and anti-hypertensive properties (Miller et al, 2014 & Hartweg et al, 2007) and lowering effects of cardiovascular disease (Chowdhury et al, 2014 & Von Schacky & Haris, 2004).

During pregnancy, the foetus demands its requirement of AA & DHA from the mother (Clandinin et al, 1980; Martinez 1992) sometimes leaving the mother with depleted stores, particularly at the end of pregnancy (Ghebremeskel et al, 2000 & Otto et al, 1995). AA & DHA cannot be synthesized by the body (Otto et al, 1999). Therefore, adequate maternal stores of these EFAs through ingestion of foods or supplements are necessary for their selective and efficient placental transfer to meet the demands of the foetus during the pre- and post-natal periods (Dutta-Roy, 2000 & Haggarty et al, 1997).

However, experimental (human & animal) studies into diabetes have shown impairment in the delta-5 and delta-6 desaturases which are responsible for the synthesis of LCPUFAs (El Boustani et al, 1989). Additionally, since GDM is characterised by possibly short-term insulin resistance, which has an adverse effect on LCPUFAs (Min et al, 2006), and not adequately compensated by insulin hyper-stimulation due to defective beta cells function (Davis, 1990), added supplementation may be required to improve insulin sensitivity and subsequent pregnancy outcomes.

6.3 Aims

The aims are to investigate the:

a) Effects of maternal supplementation with arachidonic and docosahexaenoic acids on maternal and foetal wellbeing during pregnancy and on pregnancy outcomes of women diagnosed with GDM.

b) Effects of supplementation with arachidonic and docosahexaenoic acids on maternal postpartum glycaemic status.

6.4 Subjects and methods

This was a placebo-controlled, randomised nutritional trial conducted at Newham University Hospital. Women ages 17 to 45 were recruited from the hospital's SADC and GDESs (previously discussed). Eligible pregnant women diagnosed with GDM were recruited up to 32 weeks gestation and randomly allocated either omega-3 fatty acids or placebo, taken from the time of recruitment up until delivery.

A questionnaire (*appendix 3.7*) was used to collect data on pregnancy complications (eg. hypertensive disorders and pregnancy loss), diabetes management and maternal and foetal outcomes (eg. prematurity, post-maturity, macrosomia and low birth weight, neonatal admission to special care baby unit). Women were also asked about their and their babies health and wellbeing, supplement use which included how, when, quantity taken, side effects, storage of supplements and women's decision on whether or not they wanted to continue on the study. Further details can be found in chapter 3.

6.5 Statistical analysis

Data on age, parity and BMI are presented as mean ± standard deviation (df), median (range) and n (%) as number of occurrences with percentages, where appropriate. Pearson's Chi square test was used to test demographical and clinical characteristics with the study groups which received placebo or active (fish oils) supplements. The Chi square test was also used to evaluate the similarities and differences in maternal and foetal outcomes of women supplemented with AA and DHA and those without. Independent t-test was used to compare the effects of differences in age, parity and BMI between the groups. Statistical significance equated to $\mathbf{p < 0.05}$. The IBM SPSS Statistics version 25 was used to conduct all analyses.

6.6 Results

6.6.1 Subjects recruited

Maternal demographic and clinical characteristics of subjects are provided in ***Table 6.1*** and ***Figure 6.1***. Of the women diagnosed with GDM and randomised (n = 149), supplemented with fish oils were (n = 75) and placebo (n = 74). In the placebo group, withdrawn were (n = 7), moved out of the area (n = 4), miscarried (n=1), stillbirth (n = 1), neonatal death (n = 1) resulting in full term live births (n = 53) and preterm births (n = 6) completing the study and 1 lost to follow up. Full term and preterm live births in the active group were 49 and 15, respectively after accounting for withdrawals (n = 7) and women who moved out of area (n = 4) (***Figure 6.1***).

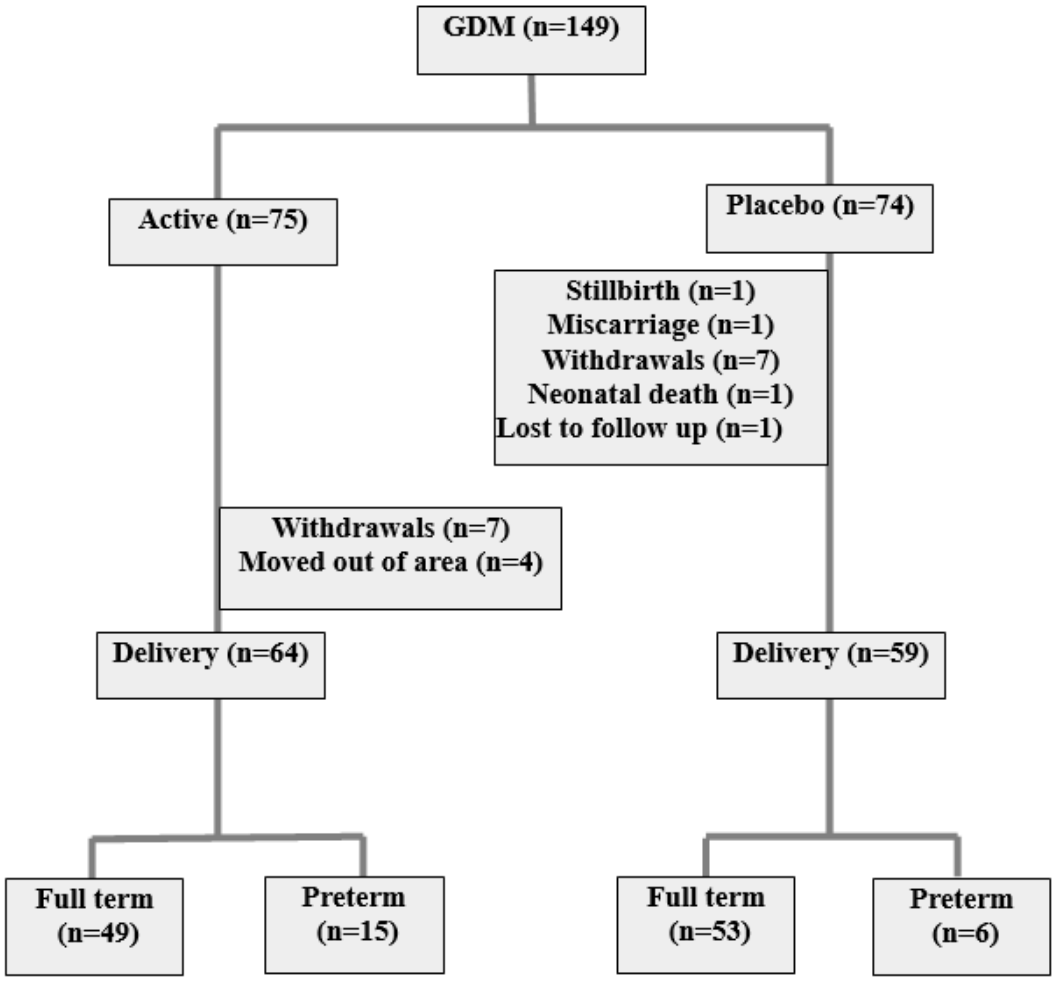


Figure 6.1: Flow chart of recruits

Subjects in the active and placebo groups had similar characteristics. Overall, the women studied were between ages 21 – 40 (n = 141; 95%) (Mean age 31.23; range 19-44 years) (**p < .277**). The majority were of Asian descent (n = 98; 66%) followed by Afro-Caribbeans (n = 37; 25%) with an average BMI of 28.99 kg/m^2 (range 16-48 kg/m^2) and an average of 2 (mean, 1.4; range 0-6) children. Most women (n = 104; 70%) were English speaking. Subjects starting the study with chronic medical problems were 16 (23%) and 9 (13%) in the active and placebo groups (**p < .132**), respectively; while others developed maternal (n

= 9, 17% / n = 6, 10%) and foetal (n = 29, 54% / n = 37, 62%) complications in the active and placebo groups (**p < .525**), respectively. Pregnancy complications developed in the index pregnancy were intrauterine growth retardation (IUGR) on ultrasound scan (USS) 4 (6.3%) / 2 (3.2%), big baby on USS 6 (9.4%) / 6 (9.7%) hypertensive disorders 7 (10.9%) / 4 (6.5%) presumed foetal compromise 4 (6.3%) / 4 (6.5%) in the fish oils and placebo groups, respectively. Other complications also developed in the active (n = 15, 23%) and the placebo group (n = 13, 21%) with 1 incident of malpresentation in the latter group (**p < .826**) (***Table 6.1***).

6.6.2 Diabetes management and control at recruitment and pre-delivery

Diabetes management among women in the active and placebo groups was diet only (n = 35, (57.4%) / n = 37 (61.7%), diet and oral medication (n = 6, (9.8%) / n =4, 6.7%), diet and insulin (n =18, (29.5%) / n = 14, (23.3%), and combination therapy (n= 2, (3.3%) / n = 5, 8.3%) (**p < .525**), respectively (***Table 6.2***). In the active and placebo groups, average HBA1c on recruitment and pre-delivery was 6.0% (42 mmol/l) / 6.1% (43 mmol/l) and 5.9% (41 mmol/l) / 5.8% (40mmol/l), respectively. Average gestational age on recruitment was 23 weeks in both groups and pre-delivery was 33 weeks / 32 weeks in the fish oils and placebo groups, respectively (***Table 6.2***).

Table 6.1: Demographic and clinical characteristics of subjects

Study groups	**Gestational diabetics**		
Intervention	**Active**	**Placebo**	**P value {Standard deviation (df)}**
No. of Subjects (n)	75	74	
Age, (years) n (%)	mean 30.73; minimum 20 - maximum 44	mean 31.74; minimum 19 - maximum 43	**.277 (3)**
≤ 21	1 (1.3)	1 (1.4)	
21 - 30	41 (54.7)	29 (39.2)	
31 - 40	31 (41.3)	40 (54.1)	
≥ 40	2 (2.7)	4(5.4)	
Ethnicity, n (%)			**.990 (2)**
All Whites	7 (9.3)	7 (9.5)	
Afro-Caribbeans	19 (25.3)	18 (24.3)	
Asians	49 (65.3)	49 (66.2)	
Language, n (%)			**.630 (1)**
English	51 (68.0)	53 (71.6)	
Non-English	24 (32.0)	21 (28.4)	
Parity, n (%)	mean 1.27, minimum 0 - maximum 6	mean 1.53, minimum 0 - maximum 6	**.263 (3)**
No previous child	33 (44.0)	24 (32.4)	
1 child	17 (22.7)	14 (18.9)	
2-4 children	21 (28.0)	32 (43.2)	
≥ 5 children	4 (5.3)	4 (5.4)	
Body mass index (BMI) (kg/m2), n (%)	mean 28.77; minimum 16 - maximum 48	mean 29.21; minimum 19 - maximum 42	**.570 (3)**
Underweight (<18.5)	2 (2.7)	0 (0.0)	
Normal weight (18.5-24.9)	17 (22.7)	17 (23.0)	
Over weight (25.0-29.9)	26 (34.7)	26 (35.1)	
Obese (≥30)	30 (40.0)	31 (41.9)	
Chronic medical problems, n (%)			**.132 (1)**
Yes	16 (22.9)	9 (13.0)	
No	54 (77.1)	60 (87.0)	
Complications- Index pregnancy, n (%)			**.525 (2)**
None	29 (53.7)	37 (61.7)	
Maternal	9 (16.7)	6 (10.0)	
Foetal/Neonatal	29 (53.7)	37 (61.7)	
Pregnancy complications, n (%)	**64**	**62**	**.826 (6)**
None	28 (43.8)	32 (51.6)	
IUGR by scan	4 (6.3)	2 (3.2)	
Big baby by scan	6 (9.4)	6 (9.7)	
Congenital abnormality	0 (0.0)	0 (0.0)	
Malpresentation	0 (0.0)	1 (1.6)	
PIH, Pre-eclampsia or Eclampsia	(10.9)	----4 (6.5)	
¤ Presumed foetal compromise	4 (6.3)	4 (6.5)	
✤Other pregnancy complications	15 (23.4)	13 (21.0)	

¤ Presumed foetal compromise: suspicious cardiotocograph, spontaneous rupture of membranes, premature rupture of membranes, prolonged premature rupture of membranes, meconium-stained liquor and reduced amniotic fluid index. ✤Other pregnancy complications: cholestasis, anaemia, ante-partum haemorrhage, postpartum haemorrhage, thrombocytopenia, non-alcoholic fatty liver & unstable blood sugars

Table 6.2: Diabetes management and HBA1c values

	GDMs			P value (df)
Clinical management		**Active**	**Placebo**	
Diabetes management (at recruitment), n (%)	**121**	61 (50.4)	60 (49.6)	**.525 (3)**
Diet only	72	35 (57.4)	37 (61.7%)	
Diet & Oral medication	10	6 (9.8%)	4 (6.7%)	
Diet & Insulin	32	18 (29.5%)	14 (23.3%)	
Combination therapy	7	2 (3.3%)	5 (8.3%)	
Diabetes management (during pregnancy), n (%)	**121**	61 (50.4)	60 (49.6)	**.525 (3)**
Diet only	72	35 (57.4)	37 (61.7%)	
Diet & Oral medication	10	6 (9.8%)	4 (6.7%)	
Diet & Insulin	32	18 (29.5%)	14 (23.3%)	
Combination therapy	7	2 (3.3%)	5 (8.3%)	
Active		**DCCT (%) (df) (minimum / maximum)**	**IFCC (mmol/l) (df) (minimum / maximum)**	
HBA1c (at recruitment) (mmol/l) mean (df)	61	6.0, df .91 (4.4 – 9.8)	42.05, df 9.94 (25 - 84)	
HBA1c (at recruitment) (mmol/l) mean, df (gestational weeks - range)		23, df 5.9 (10 – 32)		
HBA1c (pre-delivery) (mmol/l)	44	5.9, df .95 (4.3 – 10.1)	41.0, df 10.54 (23.0 – 88.0)	
HBA1c (pre-delivery) (mmol/l) mean, df – (gestational weeks, range)		33, df 3.4 (21 – 37)		
Placebo		**DCCT (%) (df) (minimum / maximum)**	**IFCC (mmol/l) (df) (minimum / maximum)**	
HBA1c (at recruitment) (mmol/l) mean (df)	61	6.1, df 1.14 (4.6 – 11.0)	43.2, df 12.5 (27 - 97)	
HBA1c (at recruitment) (mmol/l) mean, df (gestational weeks - range)		23, df 6.5 (7 – 32)		
HBA1c (pre-delivery) (mmol/l) mean, (df)	43	5.8, df .57 (4.6 – 7.2)	40.4, df 6.21 (27 - 55)	
HBA1c (pre-delivery) (mmol/l) mean, df – (gestational weeks, range)		32, df 4.7 (21 – 40)		

HBA1C – glycated haemoglobin (A1c) DCCT – Diabetes Control and Complications trial – units measured in (%)

IFCC – International Federation of Clinical Chemistry – units measured in mmol/l

6.6.3 Pregnancy outcomes – maternal and foetal / neonatal

6.6.3.1 Maternal outcomes

Pregnancy outcome data is provided in ***table 6.3***. In the active and placebo groups, 64 (100%) / 62 (98%) respectively, completed the study, with 1 stillbirth and 1 neonatal death in the latter group.

Modes of delivery were vaginal 25 (39%) / 28 (44%), assisted 8 (13%) / 3 (5%) and caesarean section 31 (48%) / 32 (51%) in the active and placebo groups (**p < .294**), respectively. Compared to women who received omega 3 & 6 supplements and those who received placebo, spontaneous onset of labour was 25 (39%) / 17 (27%), caesarean section before the onset of labour was 8 (13%) / 11 (18%), and induction of labour (IOL) 31 (48%) / 35 (57%) (**p < .328**), respectively. The reasons given for IOL were varied as outlined in table 5.2. Diabetes related complications (n = 12 (39%) / n = 19 (54%) and hypertensive disorders (n = 9 (29%) / n = 10 (29%) were the main reasons for IOL in the fish oils and placebo groups (**p < .616**), respectively.

6.6.3.2 *Foetuses / Neonates Outcomes*

The clinical outcome data of the foetuses and neonates are outlined in ***table 6.4***. Of the live births, the incidence of prematurity was 6 (10%) among those who were in the placebo group compared to those who received fish oils (n = 15; 23.4%) (**p < 0.96**). Of the babies born prematurely in the active group, the distribution was 1 (1.6%) extremely premature, 1 (1.6%) very premature and the remaining 20% moderately premature compared to 1(1.6%) extremely premature and the remaining 10% moderately premature in the placebo group (**p < 0.285**).

No macrosomia was noted in either of the groups but low birth weight (n =11; 17%) was twice more common among the active group than women in the placebo group (**p < 0.124**) (**table 6.4**), although not significant.

When birth weight was examined using the Levene's test of variance, mean = 2971 grams (df = 648.53) for women who received fish oils and 3046 grams (df = 546.48); t (137) = -0.74 for women in the placebo group, respectively (**p < 0.15**). Apgar at 1-, 5- and 10-minutes mean were = 8.2 (df = 1.77) / 9.46 (df = 1.33) / 9.27 (df = 2.16) for women who received fish oils and 9.14 (df = 1.53) / 8.29 (df = 2.16) / 9.49 (df = 2.05); t (138) = -0.26 / 0.45 / 0.54 for women in the placebo group, (**p < 0.66 / 0.31 / 0.54**), respectively.

Of the babies born to mothers who had fish oils, 8 (13%) were admitted to special care unit compared to 2 (3.3%) of babies born to mothers in the placebo group (**p < 0.057**) and the reasons given were varied with hypoglycaemia and respiratory distress recorded as the main reasons (**p < 0.586**) and significant.

6.6.4 Diabetes management and pregnancy outcome

Of 71 women who were on 'diet only' management for their GDM condition, birth outcome was prematurity 10, stillbirths 1, miscarriage 1 and low-birth weight 8. Mode of delivery was vaginal 37, instrumental 6 and caesarean section 28. For those on medication, the birth outcomes and modes of delivery for women on oral medication, insulin and combination therapy were pre-term birth 2, 5 & 2 respectively; low-birth weight 2, 4 and 1 respectively; vaginal 4, 9 & 1 respectively; instrumental delivery 2, 2 & 0, respectively and caesarean section 4, 21 & 6 respectively (***Table 6.5***).

6.6.5 Postnatal glycaemic status

Postnatally, 4 (8%) were diagnosed with Type 2 diabetes with 3 (5.9%) having either IGT/IFG among those who received fish oils compared to 6 (13%) and 1 (2.2%), respectively, among women in the placebo group (**p < 0.485**) (***Table 6.6***).

Table 6.3: Pregnancy outcomes - maternal

Study groups	**GDM**		
Pregnancy outcome measures (Maternal)	**Active**	**Placebo**	**P value {Standard deviation (df)}**
No. of Subjects (n)	**64**	**63**	
Pregnancy complications, n (%)			**.826 (6)**
None	28 (43.8)	32 (51.6)	
IUGR by scan	4 (6.3)	2 (3.2)	
Big baby by scan	6 (9.4)	6 (9.7)	
Congenital abnormality	0 (0.0)	0 (0.0)	
Malpresentation	0 (0.0)	1 (1.6)	
PIH, Pre-eclampsia or Eclampsia	7 (10.9)	4 (6.5)	
¤ Presumed foetal compromise	4 (6.3)	4 (6.5)	
✤Other pregnancy complications	15 (23.4)	13 (21.0)	
Onset of labour, n (%)			**.328 (2)**
Spontaneous	25 (39.1)	17 (27.0)	
Induced	31 (48.4)	35 (55.6)	
Elective Caesarean	8 (12.5)	11 (17.5)	
Induction of labour (IOL), n (%)			**.368 (1)**
Yes	31 (50.0)	36 (58.1)	
No	31 (50.0)	26 (41.9)	
Indications for IOL, n (%)	**31**	**35**	**.616 (5)**
Postdates	1 (3.2)	0 (0.0)	
Premature / Prolonged Rupture of membranes	2 (6.5)	2 (5.7)	
Diabetes related	12 (38.7)	19 (54.3)	
Hypertension, PIH, Pre-eclampsia or Eclampsia	9 (29.0)	10 (28.6)	
Foetal Reasons	4 (12.9)	3 (8.6)	
Other Reasons	3 (9.7)	1 (2.9)	
Mode of delivery, n (%)	**64**	**63**	**.294 (2)**
Spontaneous Vaginal (normal)	25 (39.1)	28 (44.4)	
Assisted (ventouse / forceps)	8 (12.5)	3 (4.8)	
Caesarean section (CS)	31 (48.4)	32 (50.8)	

¤ Presumed foetal compromise: suspicious cardiotocograph, spontaneous rupture of membranes, premature rupture of membranes, prolonged premature rupture of membranes, meconium-stained liquor and reduced amniotic fluid index. ✤Other pregnancy complications: cholestasis, anaemia, ante-partum haemorrhage, postpartum haemorrhage, thrombocytopenia, non-alcoholic fatty liver & unstable blood sugars

Table 6.4: Pregnancy outcomes - foetal/neonatal

Study groups	GDM		
Pregnancy outcome measures (foetal/neonatal)	**Active**	**Placebo**	**P value {Standard deviation (df)}**
No. of Subjects (n) (%)	**64**	**63**	
Birth Outcome (n) (%)			**.096 (4)**
Full Term live	48 (75.0)	54 (85.7)	
Preterm live	16 (25.0)	6 (9.5)	
Stillbirth/IUD	0 (0.0)	1 (1.6)	
Neonatal Death	0 (0.0)	1 (1.6)	
Miscarried	0 (0.0)	1 (1.6)	
Birth maturity (b) (weeks) (n) (%)	**64**	**62**	**.285 (4)**
Extremely Preterm (<28)	1 (1.6)	1 (1.6)	
Very Preterm (28-31)	1 (1.6)	0 (0.0)	
Moderate Preterm (32-36)	13 (20.3)	6 (9.7)	
Term (37-40)	48 (75.0)	55 (88.7)	
Post-maturity (≥41)	1 (1.6)	0 (0.0)	
Birth Weight, n (%)	**64**	**62**	**.124 (1)**
Low birth weight (≤2499grams)	11 (17.2)	5 (8.1)	
Normal birth weight (2500 -4449grams)	53 (82.8)	57 (91.9)	
Macrosomia (≥4500grams)	0 (0.0)	0 (0.0)	
Admission to Special Care Baby Unit (SCBU) (n) (%)	**64**	**61**	**.057 (1)**
Yes	8 (12.5)	2 (3.3)	
No	56 (87.5)	59 (96.7)	
Reasons for admission to SCBU (n) (%)	**8**	**2**	**.586 (5)**
Hypoglycaemia	2 (25.0)	2 (100.0)	
Respiratory Distress Syndrome	2(25.0)	0 (0.0)	
Prematurity	1 (12.5)	0 (0.0)	
Poor feeding/ Jaundice	1 (12.5)	0 (0.0)	
Suspected Infection	1 (12.5)	0 (0.0)	
Abnormality	1 (12.5)	0 (0.0)	

Table 6.5: Diabetes management and pregnancy outcomes

	Diabetes management				
Pregnancy outcomes	**Diet only**	**Diet and Oral Medication**	**Diet and Insulin**	**Combination therapy**	**P value {Standard deviation (df)}**
Birth outcome n (%)	**71**	**10**	**32**	**7**	**.951 (12)**
Full term birth	59 (83.1)	8 (80.0)	26 (81.3)	5 (71.4)	
Preterm birth	10 (14.1)	2 (20.0)	5 (15.6)	2 (28.6)	
Stillbirth	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	
Neonatal death	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	
Miscarriage	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	
Birth Weight	70	10	32	7	**.896 (3)**
Low birth weight (≤2499grams)	8 (11.4)	2 (20.0)	4 (12.5)	1 (14.3)	
Normal birth weight (2500 - 4449grams)	62 (88.6)	8 (80.0)	28 (87.5)	6 (85.7)	
Macrosomia (≥4500grams)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Mode of delivery	**71**	**10**	**32**	**7**	**.062 (6)**
Vaginal	37 (52.1)	4 (40.0)	9 (28.1)	1 (14.3)	
Instrumental	6 (8.5)	2 (20.0)	2 (6.3)	0 (0.0)	
Caesarean	28 (39.4)	4 (40.0)	21 (65.6)	6 (85.7)	

Table 6.6: Postnatal diabetes status: GDMs (fish oils supplemented)

	No. of Subjects (n) (%)		
Glycaemic status (n) (%)	**GDM (Omega 3 & 6)**	**GDM (Placebo)**	**P value {Standard deviation (df)}**
	51	**46**	**.485 (2)**
Normal	44 (86.3)	39 (85.8)	
IGT & IFG	3 (5.9)	1 (2.2)	
T2 DM	4 (7.8)	6 (13.0)	

IFG = Impaired fasting glucose; IFG = Impaired Fasting Glucose; T2 DM = type 2 diabetes mellitus

6.7 Discussion

6.7.1 *Demographic and clinical characteristics of subjects*

In this study, the average gestational age at recruitment was 23 weeks which was nearing the gestational age of 24 weeks when true gestational diabetes can begin to develop. Of the women diagnosed with GDM, Asians were the predominant ethnic group, followed by Afro-Caribbeans then Whites and there was an equal distribution of women of those ethnic groups who engaged with the study in the active and placebo groups. Asians were 3 times and 7 times more likely than the Afro-Caribbeans and Whites, respectively, to develop GDM. The incidence and distribution of GDM was similar to that detected in previous studies where GDM was more common among Asians and Afro-Caribbeans compared to Whites (Diabetes UK, 2016 & 2018). Most women who were between ages 21 – 40 spoke English. However, age, ethnicity and language had no impact on whether or not women chose to engage with the study. Also, the majority of women were either over-weight or obese and had an average of 2-4 children, but these factors had no influence on women's decision on whether or not to participate in the study and this was regardless of their general health and well-being, as previously demonstrated in Chapter 4.

6.7.2 Maternal Outcomes

6.7.2.1 Onset of labour and mode of delivery

Spontaneous onset of labour was higher among women in the active group, but the number of women induced in the placebo and fish oils groups was similar. Diabetes related issues were the main reasons for women being induced and this is common practice when caring

for pregnant women with this condition to promote optimal maternal and foetal pregnancy outcomes (Gorig et al, 2015 & National Institute for Clinical Excellence, 2015). This may be suggestive that regardless of whether or not women received fish oils, the decision for induction was made purely for clinical reasons and taking fish oils was not an influential factor in the decision making. From the women induced, the majority failed to deliver vaginally, resulting in a high caesarean section rate and in some cases the need for instrumental delivery. Again, these modes of delivery are not uncommon within this group (Bernstein et al, 2016 & Billionnett et al, 2012). Similar number of women had a vaginal delivery in both groups, and this accounted for only a third of the deliveries overall and supports this evidence.

Approximately half the women in both groups had an emergency caesarean section and a similar distribution of elective caesarean section. A higher number of women started their pregnancy with chronic problems and many developed complications during the index pregnancy. Combined those factors would have impacted on the high caesarean section rate. A high incidence of caesarean section deliveries is common among diabetic pregnancies which are considered 'high risk' and this would have also been another factor.

Most study subjects were either overweight or obese. Lifestyle interventions are usually recommended when managing GDM, but previous studies have demonstrated the lack of effectiveness of this strategy. Omega-3 PUFAs have been shown to have beneficial effects on glucose metabolism, lipid fractions, and inflammatory factors in women with GDM (Garmendia et al, 2018). However, a systematic review and meta-analyses by (Brown et al, 2019) has found no effect of increasing Omega-3 & -6 and total PUFAs on glucose metabolism. A RCT which examined the effectiveness of home-based dietary counselling with and without various strengths of DHA on pregnant mothers and their off-spring's metabolic control has shown that effect (Garmendia et al, 2018). But, perceived benefits of

the fish oils may not have been achieved because women with diabetes and are overweight or obese have a greater incapacity of synthesizing DHA. Obesity can adversely affect the red blood cell membranes AA & DHA levels of GDMs (Min et al, 2004) and the effects of pre-gestational BMI insulin insensitivity is well documented (Catalano et al, 2012, & 1999 & 1998). Subsequently, these factors combined may have exacerbated the problem. They may have impacted on pregnancy outcome measures including the postnatal glycaemic status, where there was no difference in women who received omega 3 & 6 compared to those who received placebo. Obesity is also associated with spontaneous abortion (Conway, 2011; Lashen et al, 2004) and could have contributed to the incidence of miscarriage (n=88.2%) – overweight & obese) and preterm birth (n=81.1% - overweight & obese) (**$p < 0.026$**) within the study group, with the result been significant. A meta-analysis of 16 studies on obese women has reported an overall OR of 1.67 for miscarriages and can justify this result (Metwally et al, 2008).

Also, singleton pregnant local women had an average of 2-4 children and usually in quick succession. This is a trend which is common among Asians, which represented the predominant ethnic group in the study. Previous evidence has shown that women with short durations between pregnancies may be starting with depleted stores of fatty acids, particularly as quick successions of pregnancies can contribute to low birth weight and preterm births (Rawlings et al, 1995). Combined, these factors may have affected the placental supply of fatty acids available for transportation to the foetus impacting adversely on the maternal and foetal outcomes, although not proven. This may suggest that depending on ethnicity and duration between pregnancies, supplementation of essential fatty acids during pregnancy may be necessary to meet the ongoing demand from the foetus and primarily the shortfall as some women would have started pregnancy with

depleted stores. Nevertheless, long chain polyunsaturated fatty acid concentrates are higher after a singleton pregnancy than multiple pregnancies (Ziejdner et al, 1997) and could have been beneficial.

6.7.2.2 Prolonged pregnancy

In this study, fish oils had no impact on prolonging the pregnancies of women with GDM. When compared to women who received fish oils, approximately 14% more women in the placebo group delivered at term, but the result was not significant. Also, only one woman supplemented with fish oils delivered beyond 41 weeks and twice the number of women who received fish oils had pre-term delivery. These findings were contrary to that of a multicentre RCT pregnancy study which found prolonged pregnancy in fish consumers (low - middle) after fish oils supplementation and dietary fish consumption in women with previous pregnancy complication (Olsen et al, 2007). A recent review by Middleton et al (2018) which demonstrated that supplementation with fish oils may reduce the incidence of premature births and may prolong pregnancy. Our local population with a high morbidity rate and being predominantly from the lower social class may not have been able to afford a daily balanced diet and that may have contributed to the disparity in findings, which could have adversely impacted on the pregnancy outcomes. Conversely, one may argue that the incidence of pre-maturity may have been reduced based on the finding of Olsen et al's study.

Also, a similar number of women in each group was induced and had a spontaneous delivery, suggesting that fish oils supplementation was not influential in any way in those two areas of care. Additionally, another RCT conducted on primagravidas who were supplemented in early pregnancy (17-19 weeks) until post delivery (3 months) showed a

likely correlation between DHA concentration and gestational length, but this was found from supplementation with cod liver and corn oils (Helland et al, 2001), which were different from the supplements used in our study.

6.7.2.3 Hypertensive disorders

In this study, there was no association between PIH, pre-eclampsia and eclampsia and fish oils supplementation. These findings were similar to findings from a meta-analysis conducted by Chen et al (2015) and a European multi-centre study by Olsen et al (2000) which evaluated the effects of fish oils supplementation during pregnancy and found no association with supplementation and the risk reduction of PIH. One could argue that should early supplementation be introduced immediately after conception or early in the first trimester, the results could have been different. GDM (Ben Slama, 1997) and hypertensive (Zhou et al, 2014) disorders share the same metabolic pathways which are characterised by insulin resistance and they often coexist. Insulin resistance can be corrected with insulin therapy (Shin et al, 1995). Therefore, early supplementation may have improved the effects of hypertensive disorders, particularly in women treated with insulin therapy.

6.7.3 Foetal and Neonatal Outcomes

6.7.3.1 Foetal and neonatal loss

Although not significant, there was slightly worsening birth outcome in the GDM placebo compared to the fish oils group in term of miscarriage (n=1), stillbirth (n=1) and neonatal death (n=1). Based on these findings, one may argue that supplementation with AA &

DHA may have made slightly positive contributions to the wellbeing of infants of mothers who received fish oils. Similar results have been found in previous systematic review conducted by Saccone et al (2015) which demonstrated no reduction in perinatal death. A larger sample size would have given a better overview of whether supplementation could reduce the incidence of miscarriages, stillbirths and neonatal deaths.

6.7.3.2 Low birth weight

There was no macrosomia in any of the groups, but low birth weight infants were higher (two-fold) among GDM women who received fish oils compared to women in the placebo group, although the result was not significant. Previous reported evidence supported the view that the use of fish oils has no positive impact on reduction of low birth weight (Onuwude et al, 1995). But, could the lack of benefits be associated to the low dose strength of supplements (1.62g of eicosapentaenoic acid (AA) and 1.8g of DHA) used? However, since that study was a double-blind placebo controlled randomised trial of fish oils in pregnancies complicated with intrauterine growth retardation and pregnancy induced hypertension, those factors may have impacted on the lack of benefits. GDM is a metabolic syndrome and when complicated by characterised hypertension the degree of insulin resistance could have worsened, adversely impacting on fish oils absorption. But, considering that half of the women recruited into this study started with medical and/or obstetric complications, those findings may be considered applicable for this group of women, but still need to be explored. Nevertheless, as a higher strength supplement was used for this study, the morbidity of the local population comes into question as presumed benefits may have been noted. Low levels of AA & DHA were shown to be associated with low-birth weight and gestational age (Leaf et al, 1992).

6.7.3.3 Prematurity

The prematurity rate, although high, was sporadic in both groups; those who received fish oils and placebo. These findings are dissimilar from an RCT conducted on high-risk pregnancies which showed supplementation reduced the recurrence risk of preterm birth, although not IUGR, preterm delivery and PIH (Olsen et al, 2000). Preterm babies are believed to have little fat stores and are more susceptible to reduction in AA and DHA (Min & Crawford 2004).

6.7.3.4 SCBU admission

Although most babies were born in good condition, four-fold those in the active group needed admission to special care baby unit compared to those in the placebo group. Therefore, supplementation of fish oils had no effect on the reduction of babies being admitted to SCBU. It was difficult to correlate taking of fish oils with the wellbeing of those infants, particularly as the incidence of admission appeared to match the norm of babies born to diabetic mothers are more likely to be admitted to SCBU for reason such as hypoglycaemia, respiratory distress syndrome and hyperbilirubinemia. Regardless, a RCT conducted by Jamilian et al, (2015) has shown a reduction in hospitalisation and hyperbilirubinemia.

6.7.4 Diabetes management

Management of diabetes for GDMs was mainly diet only and this was similar for those who received fish oils supplements and placebo. However, when treatment was introduced, it appeared to be aggressively managed with mainly insulin therapy, in both groups with a

slight increase in number among those in the active group, although that increase was not significant. Oral medication (metformin) was the next drug of choice and its use was more common among the active group compared to those in the placebo group which had above twice the incident of usage of combination therapy compared to those in the active group.

As GDM is diagnosed during pregnancy, there is a short period of time for the condition to be controlled and therefore having good diabetes control may require aggressive treatment and can justify the decision for intensive treatment with insulin therapy to reduce the morbidity associated with the condition (Gorig et al, 2018 & Billionnett et al, 2012). Also, some women may have been among the millions of undiagnosed type 2 diabetics (Diabetes UK, 2018 & 2014) and presented early in pregnancy with characteristics / symptoms like women with T2 DM which included high levels of blood sugars. It is well documented that the pregnancy outcomes of women with T2 DM are poorer than women without the condition and, as the pregnancy outcomes of women diagnosed with GDM can be similar to those with overt diabetes, intensive treatment would have been necessary to reduce the potential morbidity and mortality associated with the condition.

6.7.5 Diabetes management and pregnancy outcomes

Intensive treatment coupled with lifestyle factors of healthy eating and exercise can help to normalise HBA1c values and optimise maternal and foetal well-being. HBA1c values should be below 48 mmol/l (6.5%) to reduce the risk of miscarriages, birth defects, stillbirths and neonatal deaths (NICE, 2015). Local diabetic women were extremely high risk because of their complex health needs and therefore, according to local policy, the aim was to get HBA1c < 41 mmol/l (5.9%) by 16 weeks of pregnancy because it is difficult to interpret that test result after that gestation. Regardless, the average HBA1c at booking was

42 mmol/l (6.0%), reducing slightly pre-delivery to where it should have been at 16 weeks (41 mmol/l / 5.9%). One miscarriage and one stillbirth were in the placebo group and these women were managed on diet only. This raises the question whether intensive diabetes treatment could have prevented these adverse outcomes. It was difficult to make such a conclusion, since the only case of neonatal death, which was also in the placebo group, was insulin treated. However, since these three adverse cases were among women in the placebo group, one may argue that fish oils may have helped to optimise the pregnancy outcome, despite the result not being significant.

Of the 15 women who had a low-birth-weight infant, approximately half were treated with diet only with the remaining combined total treated with medication (**Table 6.5**). When reference is made to **Table 6.4** (foetal / neonatal outcomes), 15 women who had fish oils had a pre-term birth with 13 moderately pre-mature. That result would indicate that fish oils had no positive effect on prolonging the pregnancy and reducing the risk of premature delivery.

Also, although not significant, there was a higher incidence of preterm births among women who were managed on 'diet only' compared to those who received pharmacotherapy. A higher number of women treated with insulin therapy and on diet only had a caesarean section delivery, but this was not significant. Therefore, the decision for delivery by caesarean section, likewise an instrumental delivery, was not determined by whether or not medication was used for the antenatal management of women's diabetes. This would suggest that individualised plans of care were developed, and the mode of delivery was a derivative of those plans except in cases where there were failed vaginal deliveries and inductions leading to either an instrumental or caesarean section delivery. Likewise, as similar number of subjects in the active and placebo groups had normal,

instrumental and caesarean section deliveries, individualised plans of care appeared to be at the fore front of any clinical decision making.

6.8 Conclusion

Empirical data has shown enhanced maternal DHA status after fish oil supplementation in women with GDM and some benefits of maternal nutrition with omega-3 fatty acid on foetal growth and development and maternal health.

The results from this study have indicated that gestational supplementation with fish oils in women with GDM is not associated with improved maternal and foetal health and outcomes. Supplementation with fish oils had no impact on induction and caesarean section rates, reasons for induction, prolonging pregnancy and reduction in pre-term birth, macrosomia, IUGR, hypertensive disorders of pregnancy (pre-eclapmsia and eclampsia) and postpartum glycaemic control. Further studies are needed to explore other possible benefits of gestational supplementation with fish oils in this high risk group and/or whether a higher dose regimen would be beneficial.

Although oral supplementation with omega-3 fatty acid had no impact on the pregnancy outcomes of women with GDM, it would be useful to explore whether fish oil supplementation had any impact on the pregnancy health and outcomes of non-diabetic women and women with T2 DM. This will be explored in the next chapter (7).

Chapter 7:

The beneficial effects of omega 3 fatty acids on maternal and foetal health and birth outcomes of women diagnosed with and without Type 2 diabetes mellitus

7.1 Chapter overview

In this chapter, I have explored the beneficial effects of omega-3 fatty acids on maternal and foetal health and birth outcomes of women diagnosed with and without T2 DM.

Empirical data has shown that pregnancy outcomes of women with T2 DM are worse compared to non-diabetic women. Maternal nutrition high with fish oils is believed to promote better pregnancy health and outcomes in mothers and their babies. Foetal demand for AA and DHA in pregnancy is high. Previous evidence suggest that T2 DM affect the function of delta-5 and delta-6 which are enzymes necessary for the synthesis of AA and DHA but this can be corrected by insulin therapy. Recent sub-study data has shown that DHA rectified the impairment of red cell membrane lipids in pregnant T2 diabetic women and their neonates. It was worth exploring whether that improved DHA status had any impact on maternal and foetal outcomes.

7.2 Introduction

Diabetes is one of the most common medical disorders in pregnancy of which T2 DM is the second most common type after gestational diabetes mellitus (GDM) (WHO, 2018). Newham had a population of nearing 340,000 (NCCG, 2017a) of which 8.5% has diabetes which is higher than the London average (6.51%) and the UK national average (6.8%) (Diabetes UK, 2019). This prevalence impacts on the number of women who present in pregnancy with the condition within the borough.

A pregnancy when complicated with T2 DM is considered ‘high risk’ and caring for these women pose huge challenges for clinicians. Consequently, NICE (2015) has recommended

a multidisciplinary approach when caring for this group of women from antenatal and throughout to the postnatal period, to reduce the morbidity and mortality associated with pregnancy and diabetes.

As explained in the preceding chapter, diabetes whatever the type involves some degree of insulin resistance. When type 2 diabetes is present, the degree of insulin resistance increases considerably. Insulin resistance can be modulated by DHA (Shin et al, 1995) which is usually challenged in pregnancy, in particular women with DM. Like T1 DM, T2 DM impairs the activity and delta-5 and detal-6; enzymes responsible for the synthesis of AA and DHA (El Boustani et al, 1989 & Brenner, 2000). Also, to promote optimal pregnancy outcomes for women with overt diabetes and their babies good metabolic control prior to and throughout pregnancy is critical. Lifestyle factors of exercise and healthy eating can achieve good diabetes control and when these factors fail to achieve good control, an adjunctive therapy with medication would be the next option. New management strategies are continually being explored to optimise the pregnancy outcomes of women with T2 DM through continuous glucose monitoring to achieve euglycaemia (Buhary et al, 2016) and supplementation with EFAs to normalise lipids levels (Montori, et al 2000). A recent sub-study has shown that supplementation with DHA is beneficial in rectifying maternal and foetal cell membranes DHA anomaly in women with Type 2 diabetes and may subsequently have a positive impact on pregnancy outcomes (Min et al, 2016) and offers hope that that modification may have an impact on the pregnancy outcomes of women with T2 DM.

7.3 Aims

The aims are to investigate the:

Effects of maternal supplementation with arachidonic and docosahexaenoic acids on maternal health and foetal wellbeing during pregnancy and on pregnancy (maternal and foetal) outcomes of women diagnosed with Type 2 diabetes mellitus (T2 DM) and without diabetes.

7.4 Subjects and Methods

This was a placebo-controlled, randomised nutritional trial conducted at Newham University Hospital. Eligible pregnant women diagnosed with T2 DM and ages 17 to 45 were recruited from the hospital's SADC (previously discussed) up to 17 weeks gestation and randomly allocated either omega-3 fatty acids or placebo, taken from the time of recruitment up until delivery. Allocation of omega-3 fatty acids or placebo was of the same duration for their matching comparisons who were healthy controls (women without diabetes) and within the same age groups. Women without diabetes were recruited from the hospital's maternity booking centre where women first presented for history taking when pregnancy was confirmed and routine antenatal clinics.

Demographic, socio-cultural, economic and clinical data were collected using a questionnaire (*appendix 3.7*). Data was collected on pregnancy complications (eg. hypertensive disorders and pregnancy loss), diabetes management and maternal and foetal outcomes (eg. prematurity, post-maturity, macrosomia and low birth weight, neonatal admission to special care baby unit). Women were also asked about their and their babies health and wellbeing, supplement use which included how, when, quantity taken, side

effects, storage of supplements and women's decision on whether or not they wanted to continue on the study. Please refer to chapter 3 for further information.

7.5 Statistical analysis

Data on age, parity and BMI are presented as mean ± standard deviation (df), median (range) and n (%) as number of occurrences with percentages, where appropriate. Pearson's Crosstabulation Chi square test was used to test demographical and clinical characteristics with the study groups which received placebo or active (fish oils) supplements. The Chi square test was also used to evaluate the similarities and differences in maternal and foetal outcomes. The One-way ANOVA test was used to test the equality of variance between birth weight and Apgar scores at 1, 5 and 10 minutes among women with and without T2 DM and supplemented with or without fish oils. Statistical significance equated to $\mathbf{p < 0.05}$. The IBM SPSS Statistics version 25 was used to conduct all analyses.

7.6 Results

7.6.1 Baseline demographic and clinical characteristics

7.6.1.1 *Subjects recruited*

Maternal characteristics of subjects are provided in ***Tables 7.1 & 7.2*** and ***Figure 7.1***. The women studied (T2 diabetics and non-diabetics) had similar ethnic profile. Subjects were predominantly between ages 21– 40 (n = 162; 88.1%) with a mean age of 31 (33.30 / 34.92 and 28.33 / 29.25) for women with T2 DM and healthy controls), respectively (**p < .000**). The majority were of Asian descent (90; 49.2%) followed by Afro-Caribbeans (61; 33.3%) then Whites (32; 17.5%) (**p < .066**), with an average BMI of 28.56 kg/m^2 ranging between 26.53 kg/m^2 – 30.80 kg/m^2 and a distribution of 36.6% (65) and 37.1% (37) being either overweight and obese respectively and the remaining 23.6% (42) of normal weight (**p < .002**). Most women (145; 78.8%) were English speaking (**p < .012**) and had an average of 1 - 2 children (121; 76.2%) with over a quarter (54; 29.6%) having had no previous child (**p < .006**) (***Tables 7.1 & 7.2***).

Of the subjects recruited (n = 184), randomised were women diagnosed with Type 2 diabetes mellitus (T2 DM) (n = 96) and non-diabetics (n = 88) who were supplemented with either fish oils (n = 47 / n = 40) or placebo (n = 49 / n = 48), respectively. Three women who developed GDM (from the control group) continued on the study. Thirty-nine women were withdrawn from the study, 8 moved out of the area while 1 was lost to follow-up; 1 had a medical termination of pregnancy (MTOP) and 21 miscarried accounting for 30 (active) / 34 (placebo) T2 DMs and 24 (active) / 31 (placebo) completing the study. Two babies were stillborn from women who had T2 DM and in the placebo group (***Figure 7.1***).

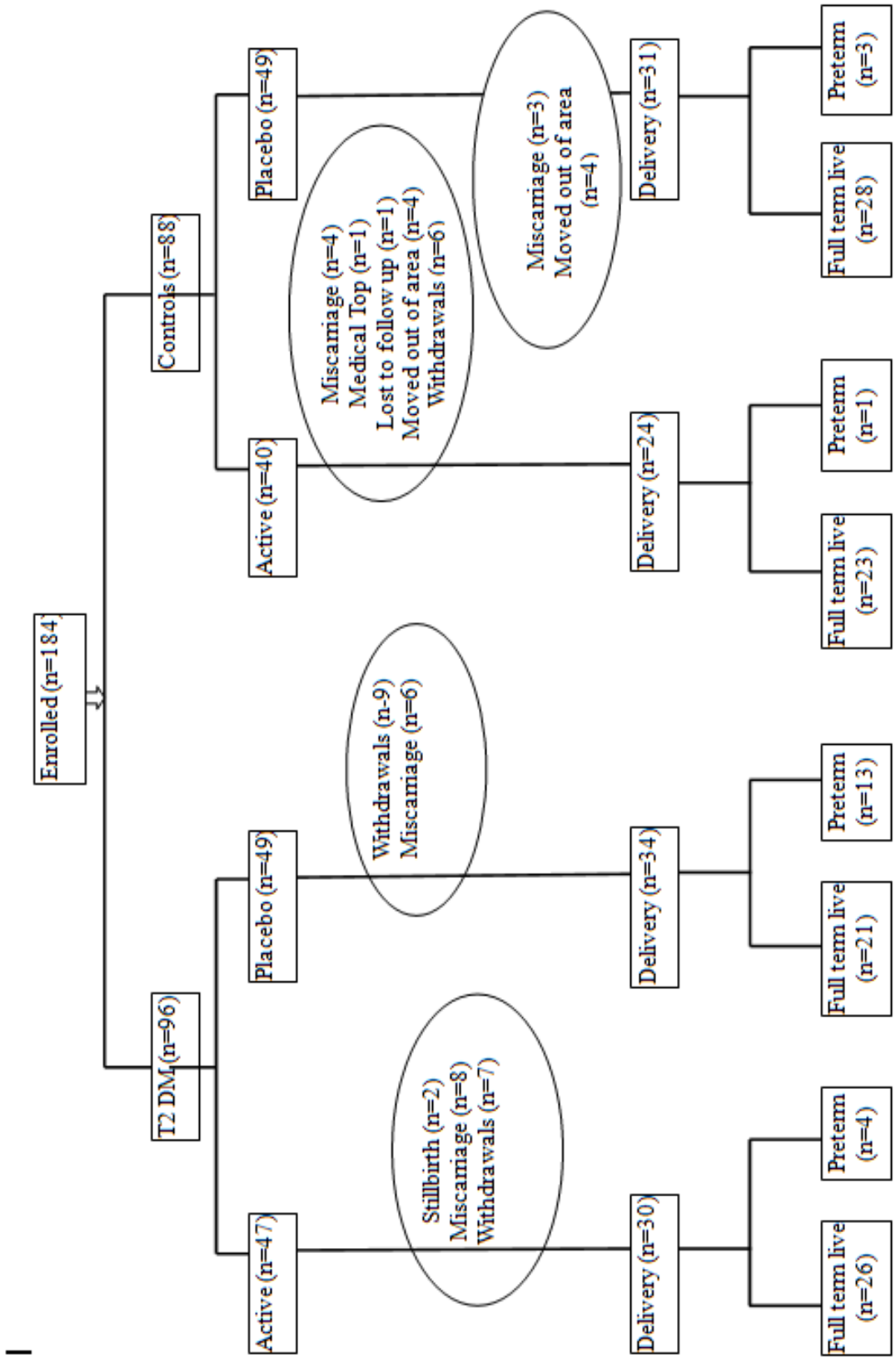


Figure 7.1: Flow chart of subjects: T2 diabetics and non-diabetics

7.6.1.2 Chronic medical and pregnancy complications

Nearing forty percent (38.6%) of subjects started the study with a history of chronic medical complications with the majority being women with T2 DM as demonstrated in ***Table 7.1***. Chronic medical problems noted in the active and placebo groups in women with T2 DM and healthy controls were 27 (69.2%) / 7 (25%) and 32 (76.2%) / 5 (12.8) (**p < .000**), respectively. Pregnancy complications (maternal and foetal/neonatal) also developed during the index pregnancy in active and placebo groups with a higher incidence among T2 DMs compared to healthy controls (**p < .029**). Pregnancy complications were intrauterine growth retardation (IUGR) on ultrasound scan (USS) 1 (3.1%) / 3 (8.8%), big baby on USS 2 (6.3%) / 3 (8.8%), hypertensive disorders 5 (15.6%) / 7 (20.6%) and presumed foetal compromise 3 (9.4%) / 1 (2.9%) in the fish oils and placebo groups among T2 DMs, respectively. Among healthy controls in the placebo group were IUGR on USS 2 (6.5%), mal-presentation 1 (3.2%) and presumed foetal compromise 1 (3.2%) while the latter was 1 (4.2%) and hypertensive disorders 1 (4.2%) in the healthy active group. Other pregnancy complications which included cholestasis, anaemia, antepartum haemorrhage etc (see footnote on *Table 7.1*) also developed among active T2 DMs and controls (n = 10, 31.3%) / 5 (20.8%) and the placebo groups 12 (35.3%) / 11 (35.5%) (**p<.826**) (***Table 7.1***).

Table 7.1: Demographic and clinical characteristics of subjects

Study groups	**Type 2 DM**		**Non-diabetics (Healthy Controls)**		
Intervention	**Fish oils**	**Placebo**	**Fish oils**	**Placebo**	**P value {Standard deviation (df)}**
No. of Subjects (n)	47	49	40	48	
Age, (years) n (%) Overall: Mean 31.59	mean 33.30; minimum 20 - maximum 44	mean 34.92; minimum 25 - maximum 45	mean 28.33; minimum 17 - maximum 42	mean 29.25; minimum 17 - maximum 43	**.000 (9)**
≤ 21	1 (2.1)	0 (0.0)	5 (12.5)	3 (6.3)	
21 - 30	11 (23.4)	12 (24.5)	20.(50.0)	27 (56.3)	
31 - 40	33 (70.2)	29 (59.2)	14 (35.0)	16 (33.3)	
≥ 40	2 (4.3)	8 (16.3)	1 (2.5)	2 (4.2)	
Ethnicity, n (%)					**.066 (6)**
All Whites	6 (12.8)	7 (14.3)	11 (28.2)	8 (16.7)	
Afro-Caribbeans	17 (36.2)	10 (20.4)	15 (38.5)	19 (39.6)	
Asians	24 (51.1)	32 (65.3)	13 (33.3)	21 (43.8)	
Language, n (%)					**.012 (3)**
English	38 (80.9)	31 (63.3)	33 (82.5)	43 (89.6)	
Non-English	9 (19.1)	18 (36.7)	7 (17.5)	5 (10.4)	
Parity, n (%) Overall: Mean 1.45	mean 1.67, minimum 0 - maximum 6	mean 1.68, minimum 0 - maximum 7	mean .98; minimum 0 - maximum 8	mean 1.02; minimum 0 - maximum 5	**.006 (9)**
No previous child	11 (23.9)	8 (16.3)	16 (40.0)	19 (39.6)	
1 child	11 (23.9)	12 (24.5)	17 (42.5)	15 (31.3)	
2-4 children	22 (47.8)	25 (51.0)	6 (15.0)	13 (27.1)	
≥ 5 children	2 (4.3)	4 (8.2)	1 (2.5)	1 (2.1)	
Body mass index (BMI) (kg/m2), n (%) Overall: Mean 28.56	mean 30.80; minimum 20 - maximum 44	mean 29.92; minimum 15 - maximum 43	mean 26.53; minimum 18 - maximum 46	mean 26.73; minimum 18 - maximum 37	**.002 (9)**
Underweight (<18.5)	0 (0.0)	1 (2.1)	2 (5.1)	2 (4.3)	
Normal weight (18.5-24.9)	7 (15.9)	6 (12.5)	17 (43.6)	12 (25.5)	
Over weight (25.0-29.9)	13 (29.5)	19 (39.6)	10 (25.6)	23 (48.9)	
Obese (≥30)	24 (54.5)	22 (45.8)	10 (25.6)	10 (21.3)	
Chronic medical problems, n (%)	**39**	**42**	**30**	**39**	**.000 (3)**
Yes	27 (69.2)	32 (76.2)	7 (25.0)	5 (12.8)	
No	12 (30.8)	10 (23.8)	21 (75.0)	34 (87.2)	
Pregnancy complications, n (%)	**32**	**34**	**24**	**31**	**.826 (6)**
None	10 (31.3)	8(23.5)	17 (70.8)	16 (51.6)	
IUGR by scan	1 (3.1)	3 (8.8)	0 (0.0)	2 (6.5)	
Big baby by scan	2 (6.3)	3 (8.8)	0 (0.0)	0 (0.0)	
Malpresentation	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)	
Stillbirth	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	
PIH, Pre-eclampsia or Eclampsia	5 (15.6)	7 (20.6)	1 (4.2)	0 (0.0)	
¤ Presumed foetal compromise	3 (9.4)	1 (2.9)	1 (4.2)	1 (3.2)	
✤Other pregnancy complications	10 (31.3)	12 (35.3)	5 (20.8)	11 (35.5)	

¤ Presumed foetal compromise: suspicious cardiotocograph, spontaneous rupture of membranes, premature rupture of membranes, prolonged premature rupture of membranes, meconium-stained liquor and reduced amniotic fluid index. ✤Other pregnancy complications: cholestasis, anaemia, ante-partum haemorrhage, postpartum haemorrhage, thrombocytopenia, non-alcoholic fatty liver & unstable blood sugars

7.6.1.3 Diabetes management and control at recruitment and pre-delivery

Of the women who had T2 DM and supplemented with fish oils and placebo, diabetes management at recruitment was 5 (14.3%) / 3 (7.7%) diet only, 17 (48.6%) / 16 (41.0%) oral medication, 1 (2.9%) / 3 (7.7%) insulin treated while 12 (34.3%) / 17 (43.6%) had combination therapy (oral medication and insulin) respectively (**p < .535**). The management regimen pre-delivery was oral 3 (8.3%) / 1 (2.6%) diet only, 14 (38.9%) / 9 (23.1%) oral medication, 7 (19.4%) / 11 (28.2%) insulin treated while 12 (33.3%) / 18 (46.2%) had combination therapy (oral medication and insulin) respectively 36.6% / 23.9%, 19.5% / 26.1% insulin and 34.1% / 47.8% combination therapy, in the active and placebo groups, respectively (**p < .255**) (***Table 7.3***).

Among the active group at recruitment, mean HBA1c performed at approximately 9 weeks was 7.3% Diabetes Control and Complications Trial (DCCT) / 56.86 mmol/l International Federation of Clinical Chemistry (IFCC) compared to 6.1% (DCCT) / 44.0 mmol/l (IFCC) at a mean gestational age of 30 weeks prior to delivery. For those who received placebo, mean gestational age at recruitment was 10 weeks and 33 weeks at delivery with HBA1c of 7.4% (DCCT) / 58.5 mmol/l (IFCC) and 6.5% (DCCT) / 47.4 mmol/l (IFCC, respectively (***Table 7.3***).

Table 7.2: Diabetes management and glycaemic control of women with T2 DM

	T2 DM			**P value (df)**
Diabetes management		**Fish oils**	**Placebo**	
At recruitment**, n (%)**	74	35 (47.3)	39 (52.7)	**.535 (3)**
Diet only	8	5 (14.3)	3 (7.7%)	
Diet & Oral medication	33	17 (48.6%)	16 (41.0%)	
Diet & Insulin	4	1 (2.9%)	3 (7.7%)	
Combination therapy	29	12 (34.3%)	17 (43.6%)	
Pre-delivery, n (%)	**75**	36 (48%)	39 (52%)	**.255 (3)**
Diet only	4	3 (8.3)	1 (2.6%)	
Diet & Oral medication	23	14 (38.9%)	9 (23.1%)	
Diet & Insulin	18	7 (19.4%)	11 (28.2%)	
Combination therapy	30	12 (33.3%)	18 (46.2%)	
Active		**DCCT (%) (df) (minimum / maximum)**	**IFCC (mmol/l) (df) (minimum / maximum)**	
HBA1c (at recruitment), n, (mmol/l) mean (df)	29	7.3, df .1.4 (5.3-10.9)	56.86, df 15.8 (34-96)	
HBA1c (at recruitment) (mmol/l) mean, df (gestational weeks - range)		9, df 2.6 (5-15)		
HBA1c (pre-delivery) n, (mmol/l)	19	6.1, df 1.1 (4.9 – 10.1)	44.0, df 11.8 (30.0 – 87.0)	
HBA1c (pre-delivery) (mmol/l) mean, df – (gestational weeks, range)		30, df 5.2 (20 – 38)		
Placebo		**DCCT (%) (df) (minimum / maximum)**	**IFCC (mmol/l) (df) (minimum / maximum)**	
HBA1c (at recruitment) n, (mmol/l) mean (df)	33	7.4, df 1.59 (5.5 – 11.0)	58.5, df 17.6 (37 - 97)	
HBA1c (at recruitment) (mmol/l) mean, df (gestational weeks - range)		9.7, df 3.4 (4-16)		
HBA1c (pre-delivery) n, (mmol/l), mean, (df)	25	6.5, df .81 (5.2 - 8.6)	47.4, df 9.03 (33 - 72)	
HBA1c (pre-delivery) (mmol/l) mean, df – (gestational weeks, range)		33, df 3.06 (28 - 37)		

HBA1C – glycated haemoglobin (A1c) DCCT – Diabetes Control and Complications trial – units measured in (%)

IFCC – International Federation of Clinical Chemistry – units measured in mmol/l

7.6.2 Pregnancy outcomes

7.6.2.1 Maternal outcomes

Pregnancy outcome data is provided in **table 7.3**. Compared to women with T2 DM and non-diabetics who were supplemented with fish oils and those who received placebo, spontaneous onset of labour was 13 (41.9%) vs 20 (83.3%) and 15 (42.9%) vs 23 (74.2%), rate of induction 10 (32.3%) vs 2 (8.3%) and 8 (22.9%) vs 4 (12.9%) and caesarean section before the onset of labour 8 (25.8%) vs 2 (8.3%) and 12 (34.3%) vs 4 (12.9%), respectively (**p < .007**).

Sixty-four women (52.9%) had a vaginal delivery, 4 (3.3%) were assisted deliveries and an overall caesarean section rate of 53 (43.8%) of which 37 (69.8%) had T2 DM (n = 16, 43.2% active / n = 21, 56.8% placebo) and 16 (30.2%) were healthy controls (n = 6, 37.5% active / n = 10, 62.5% placebo) (**p < .060**). Approximately 50% caesarean section was classified as emergencies. Of all women induced, 36% had an emergency caesarean section while the remaining 64% had a vaginal delivery. Diabetes was the main reason for induction (**p < .095**) (***Table 7.3***).

Table 7.3: Pregnancy outcomes - maternal

Study groups	**Type 2 diabetes**		**Non-diabetics (Healthy controls)**		
Maternal outcomes	**Fish oils**	**Placebo**	**Fish oils**	**Placebo**	**P value {Standard deviation (df)}**
No. of Subjects (n)	**36**	**42**	**29**	**41**	
Onset of labour, n (%)	**31**	**35**	**24**	**31**	**.007 (6)**
Spontaneous	13 (41.9)	15 (42.9)	20 (83.3)	23 (74.2)	
Induced	10 (32.3)	8 (22.9)	2 (8.3)	4 (12.9)	
Elective Caesarean	8 (25.8)	12(34.3)	2 (8.3)	4 (12.9)	
Induction of labour (IOL), n (%)	**32**	**34**	**24**	**30**	**.129 (3)**
Yes	10 (31.3)	8 (23.5)	2(8.3)	4 (13.3)	
No	22 (68.7)	26 (76.5)	22.(91.7)	26 (86.7)	
Indications for IOL, n (%)	**10**	**8**	**2**	**4**	**.095 (12)**
Postdates	0 (0.0)	0 (0.0	1 (50.0)	1 (25.0)	
Premature / Prolonged Rupture of membranes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Diabetes related	5 (50.0)	4 (50.0)	0 (0.0)	0 (0.0)	
Hypertension, PIH, Pre-eclampsia or Eclampsia	2 (20.0)	1 (12.5)	1 (50.0)	0 (0.0)	
Foetal Reasons	1 (20.0)	2 (25.0)	0 (0.0)	3 (75.0)	
✤Other Reasons	2 (20.0)	1 (12.5)	0 (0.0)	0 (0.0)	
Mode of delivery, n (%)	**31**	**35**	**24**	**31**	**.060 (6)**
Vaginal (normal)	14 (45.2)	13 (37.1)	17 (70.8)	20 (64.5)	
Assisted (ventouse / forceps)	1 (13.2)	1 (2.9)	1 (4.2)	1 (3.2)	
Caesarean section (CS)	16 (60.0)	21 (61.9)	6 (25.0)	10 (32.3)	

✤Other pregnancy complications: cholestasis, anaemia, ante-partum haemorrhage, postpartum haemorrhage, thrombocytopenia, non-alcoholic fatty liver & unstable blood sugars

7.6.2.2 *Foetuses / Neonates outcomes*

The clinical outcome data of the babies are outlined in **table 7.4**. Among fish oils and placebo supplemented T2 diabetics and non-diabetics, preterm birth was 4 & 13 and 1 & 4, respectively. Miscarriages were 8 and 6 in the active and placebo groups among T2 DMs and 3 in each of the supplemented non-diabetics. Stillborn (n = 2) was among subjects with T2 DM and received fish oils (**p < .011**). Two (2) babies were very preterm and 2 were moderately preterm in the active T2 DM group compared to 1 very preterm and 12 moderately preterm who received placebo within that same group. In the control group, 1 baby vs 3 babies were moderately preterm in the active and placebo groups, respectively (**p < .005**).

Compared to women with T2 DM and healthy controls who were supplemented with fish oils and those who received placebo, low birth weight was 5 vs 3 and 5 vs 6, respectively (**p < .932**) and admission to special care baby unit 4 vs 0 and 8 vs 1, respectively (**p < .017**). The reasons for admission to SCBU were varied and can be seen in table 6.4 (**p < .678**).

7.6.2.2.1 Birth weight & Apgar scores

An analysis of variance has shown that the effect of fish oils on birth weight was not significant, F (3, 143) = 1.16, **p < 0.258**. Apgar scores at 1 minute, 5 minutes and 10 minutes, the effect of fish oils were F (3, 143) = 0.37 **p < .262**, F (3, 69.4) = 0.538, **p < 0.015**, F (3, 71.4) = 1.001, **p < 0.001**, respectively.

Table 7.4: Pregnancy outcomes - foetal/neonatal

Study groups	Type 2 diabetes		Non-diabetics (Healthy controls)		
Foetal / Neonatal Outcomes	**Fish oils**	**Placebo**	**Fish oils**	**Placebo**	**P value {Standard deviation (df)}**
No. of Subjects (n) (%)					
1a. Birth maturity (weeks) (n)	**40**	**41**	**28**	**33**	**.012 (6)**
Full term (≥37)	26 (65.0)	22 (53.7)	23 (82.1)	26 (78.8)	
Preterm (<37)	4(10.0)	13 (31.7)	1 (3.6)	4 (12.1)	
*Other	10 (25.0)	6 (14.6)	4 (14.3)	3 (9.1)	
1b. Birth maturity (weeks) (n) (%)	**31**	**35**	**24**	**31**	**.005 (9)**
Extremely Preterm (<28)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Very Preterm (28-31)	2 (6.5)	1 (2.9)	0 (0.0)	0 (0.0)	
Moderate Preterm (32-36)	2(6.5)	12(34.3)	1 (4.2)	3 (9.7)	
Term (37-40)	27 (87.1)	22 (62.9)	21 (87.5)	25 (80.6)	
Post-maturity (≥41)	0 (0.0)	0 (0.0)	2 (8.3)	3 (9.7)	
2. Birth Outcome (n) (%)	**40**	**41**	**28**	**34**	**.011 (12)**
Full Term live	26 (65.0)	22 (53.7)	23 (82.1)	28 (82.4)	
Preterm live	4 (10.0)	13 (31.7)	1 (3.6)	3 (8.8)	
Stillbirth/IUD	2 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Neonatal Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Miscarried	8 (20.0)	6 (14.6)	3 (10.7)	3 (8.8)	
Medical termination of pregnancy (MTOP)	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)	
Birth Weight, n (%)	**31**	**34**	**24**	32	**.932 (3)**
Low birth weight (≤2499grams)	5 (16.1)	5 (14.7)	3 (12.5)	6 (18.8)	
Normal birth weight (2500 -4449grams)	26 (83.9)	25 (85.3)	21 (87.5)	26 (81.3)	
3. Admission to Special Care Baby Unit (SCBU) (n) (%)	**31**	**35**	**23**	**32**	**.017 (3)**
Yes	4 (12.9)	8 (22.9)	0 (3.6)	1 (3.1)	
No	27 (87.1)	27 (77.1)	23 (100.0)	31 (96.9)	
4. Reasons for admission to SCBU (n) (%)	**4**	**8**	**1**	**13**	**.678 (8)**
Hypoglycaemia	1 (25.0)	1 (12.5)	0 (0.0)	1 (100.0)	
Respiratory Distress Syndrome	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	
Prematurity	3 (75.0)	4 (50.0)	1(100.0)	0 (0.0)	
Poor feeding/ Jaundice	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	
Suspected Infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Abnormality	0 (0.0)	1(12.5)	0 (0.0)	0 (0.0)	

* Other = stillbirths, miscarriages, termination of pregnancies and neonatal deaths

7.6.3 Glycaemic control and pregnancy outcomes

Pregnancy outcome for women based on diabetes management are presented in **Table 7.5.** Among women who delivered preterm, treatment was 3 oral medication, 5 insulin and 9 combination therapy; stillbirths 2 & neonatal deaths 2 insulin therapy; miscarriages 1, 4 & 6 diet only, oral medication and combination therapy, respectively (**p < .274**); low birth weight 2, 3 & 5 oral medication, insulin and combination therapy, respectively (**p < .645**). Caesarean section deliveries were 1, 8, 11 & 15 oral medication, insulin & combination therapy, respectively. Assisted deliveries 1 oral medication and 1 combination therapy (**p = .546**).

Table 7.5 Diabetes management and pregnancy outcomes

	Diabetes Management				
Pregnancy outcomes	**Diet only**	**Diet and Oral Medication**	**Diet and Insulin**	**Combination therapy**	**P value {Standard deviation (df)}**
Gestational ages at birth, n (%)	**4**	**23**	**18**	**30**	**.274 (9)**
Full term birth	3 (75.0)	16 (69.6)	9 (50.0)	15 (50.0)	
Preterm birth	0 (0.0)	3 (13.0)	5 (27.8)	9 (30.0)	
Stillbirth	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)	
Neonatal death	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)	
Miscarriage	1 (25.0)	4 (17.4)	0 (0.0)	6 (20.0)	
Birth Weight	**3**	**19**	**15**	**23**	**.645 (3)**
Low birth weight (≤2499grams)	0 (0.0)	2 (10.5)	3 (20.0)	5 (21.7)	
Normal birth weight (2500 - 4449grams)	3 (100.0)	17 (89.5)	12 (80.0)	18 (78.3)	
Macrosomia (≥4500grams)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Mode of delivery	**3**	**19**	**15**	**24**	**.546 (6)**
Vaginal	2 (66.7)	10 (52.6)	4 (26.7)	8 (33.3)	
Instrumental	0 (0.0)	1(5.3)	0 (0.0)	1 (4.2)	
Caesarean	1 (33.3)	8 (42.1)	11 (73.3)	15 (62.5)	

7.7 Discussion

7.7.1 *Demographic and clinical characteristics of subjects*

Approximately 70% non-diabetic first time mothers versus 40% of T2 diabetics participated in this phase of the study. The excitement and enthusiasm which comes with being pregnant for the first time, and the need to do what was best for baby, may have accounted for that difference in the level of engagement between the two groups. There was an increasing trend among women with T2 DM, whereby, levels of engagement increased with increased parity. Assuming that some, if not all of those women had previously endured the experience of being pregnant with diabetes, there was possibly a need to reduce likely complications associated with a diabetic pregnancy. The knowledge gained from that experience and/or previous possible bad experiences and/or adverse outcomes related to diabetes in pregnancy may have influenced those women's decision to participate in the study, leading to the increasing levels of engagement with parity among that group.

Also, women were predominantly of Asian descent, followed by Afro-Caribbeans then Whites with the majority being able to speak English across the groups. Non-English speakers were mainly Asians. The diversity noted within this study was reflective of the borough of Newham which has a high prevalence of T2 DM. The DECODA study has shown that the prevalence of diabetes is highest among Asians, intermediate in Japanese and Chinese and lower in Europeans (Nyamdorj et al, 2010).

For over two decades, it was reported that Asians develop DM with lower BMI (Yoon, et al, 2006) at approximately 23 kg/m^2 (Ko et al, 1998). Since then, this was confirmed in a meta-analysis conducted by (Deurenberg et al, 1998) and in a RCT by He et al (2001) and adiposity was a huge factor. This observation has led to the International Association for

the Study of Obesity (IASO) and the International Obesity task force (IOTF) to redefine overweight and obesity as BMI ≥23 kg/m^2 and ≥25 kg/m^2, respectively in Asians (WHO/IASO/IOTF, 2002). In this study which was predominantly of Asians, the mean BMI was 29 kg/m^2. This raises huge questions about the health of the pregnant population within Newham and sets a potential mammoth but vital task for stakeholders, particularly as the majority of women were either obese or overweight and this was significant.

Being obese or overweight has a socio-economic link and is a determinant of health and well being (Psaltopoulou et al, 2017). They are also associated with hyperlipidaemia (Broom, 2006) and many adverse conditions like hypertension (Greenstein & Wood, 2011). Therefore, it was not surprising that compared to non-diabetics, approximately five-fold women with T2 DM started their pregnancy with chronic medical problems and this was highly significant. Previous studies have shown the correlation between T2 DM and chronic medical complications. The longer the duration of living with the T2 DM, the higher the likelihood of developing micro- and macro-vascular complications (Meeking, 2011). Therefore, the duration of disease could have contributed to some women with T2 DM having started their pregnancy with several co-morbidities and this impacted on the high incidence of deliveries by planned caesarean section among women with T2 DM (77%).

The epidemiological trend of Asians being the more dominant ethnic group with overt diabetes is well documented. Contributory factors are urbanisation and socio-economic growth (Ramachadran et al, 2012), the tendency of Asians to be more averse to exercise and living a more sedentary lifestyle (Nayamdorj et al, 2010). Also, compared to other ethnic groups, it is postulated that Asians have a strong genetic predisposition for diabetes with lower threshold for environmental risk factors resulting in them developing the condition at a younger age with lower thresholds (Ramachadran et al, 2012). The impact of

physical inactivity and fatty foods intake can lead to obesity which is a precursor for development of T2 DM (Boffetta et al, 2011) and its high prevalence among Asians. Subsequently, the incidence of the disease state among Asians and its impact on pregnancy and maternal and foetal outcomes can be profound. Also, some Asians associate 'eating in pregnancy' with providing the mother and baby with the strength they need to thrive well and 'exercise in pregnancy' as damaging for the mother and baby (Greenhalgh et al, 2015). These cultural notions go against the lifestyle advice given to pregnant women with diabetes on healthy eating and exercise to achieve euglycemia and reduce the potential risks associated with the condition on maternal and foetal outcomes (NICE, 2015).

7.7.2 Pregnancy outcomes

7.7.2.1 Maternal outcomes

7.7.2.1.1 Onset of labour

Compared to women with T2 DM, most non-diabetic women went into spontaneous labour. This was significant. A higher percentage of those women had fish oils compared to those who received placebo whereas the distribution was similar in both groups for women with T2 DM. In non-diabetic women, a 2-fold increased number of women spontaneously went into labour compared to women with T2 DM who also received fish oils. Local and national (NICE, 2015) guidelines on the management of women with T2 DM would have warranted that women were delivered at approximately 38 weeks gestation to promote a positive outcome for mother and baby. This would have reduced the number of women within this group going into spontaneous labour. Conversely, as the non-diabetics were in better health, having started their pregnancies with less chronic

medical conditions than women with T2 DM and this was significant, there was a higher likelihood of non-diabetics being 'left' to spontaneously go into labour.

The adverse outcomes associated with T2 DM have driven clinicians to employ various clinical management strategies to optimise the wellbeing of mother and baby. Measures taken include increased foetal surveillance and induction of labour at various gestational ages (Berger & Melamed, 2014). In the UK, the rate of IOL varies between maternity units (NMPA Project Team, 2018) but approximately one-third of all pregnancies were induced in 2018 (NHS Digital, 2018) for medical reasons, post-maturity, pregnancy pathologies and multiple pregnancies (Royal College of Midwives, 2019). In this study, the overall induction rate was one-fifth (20%) with thrice the number of women with T2 DM being induced compared to non-diabetics. The majority of T2 diabetics induced had fish oils and was above 2-fold higher than in the placebo group; but this was not significant. Again, that disparity would have been policy and health related as described earlier on the potential reasons for increased spontaneous onset of labour among the non-diabetic group.

Although not significant, diabetes related issues were the main reasons for women being induced. To promote optimal maternal and foetal outcomes, women with T2 DM were induced and delivered between 37-38 weeks in keeping with local and national guidelines (NICE, 2008 & 2015). This is suggestive that regardless of whether or not women with T2 DM were supplemented with omega 3 & omega 6, the decision for induction was made purely for clinical reasons. As no woman within this group (T2 diabetics) delivered beyond 40 gestational weeks, it is difficult to conclude whether omega 3 & omega 6 had any effect on prolonged gestational age, particularly as diabetes management in the active and placebo groups was insignificant at recruitment and pre-delivery. This was substantiated by the fact that diabetes related issues were the main reason given for women with T2 DM being induced, whether or not they received supplementation with omega 3 & omega 6.

Foetal reason was the next highest indicator for IOL and was more common among both placebo groups. This suggested that foetal wellbeing as opposed to diabetic or non-diabetic status appeared to be the key decision making indicator.

Despite the pregnancies of women with T2 DM being considered 'high risk', women whose pregnancies were uneventful and diet-controlled, were at the lower end of the spectrum of the 'high risk' trajectory and were sometimes given the opportunity to go into labour naturally before planning for IOL after 38 weeks gestation. Any delay could have contributed to the overall total number of women having delivered at term within this group. The increased risk of stillbirths (Weissgerber & Mudd, 2015), macrosomia (Jardim et al, 1997Visser & de Valk, 2015), IUGR (Sibai et al, 2005) are among some of the morbidities and mortality associated with pregnancies complicated with diabetic pregnancies. The clinicians' desire to prevent these complications from occurring could have constituted to those foetal reasons; all of which were evaluated within this study.

Among non-diabetics, five (2 fish oils & 3 placebo) women delivered beyond 40 weeks gestation. This is reflective of normal practice where women with low-risk pregnancies are usually given every opportunity to go into labour naturally and where this did not occur, IOL was offered for post-maturity. Yet, the optimal timing of offering IOL in this group remains unclear and this is compounded by the findings of a Cochrane database of systematic review which demonstrated that there was no clear difference in neonatal outcomes of women induced prior to and after 41 weeks gestation (Middleton et al, 2018). This evidence can set precedence for future care planning for women with uneventlful pregnancies.

Among non-diabetics, there was a slightly increased number of women who delivered beyond 40 weeks gestation in the placebo group than in the fish oil group. Consequently, it

may be concluded that fish oils had no effect on prolonging the pregnancy, but this needs further investigation as the sample size was small. Compared to non-diabetics, women with T2 diabetes received more intensive management, including pharmacotherapy, and subsequently, were more than three times more likely to be induced; although not significant. The higher rate of IOL among women with T2 DM, the higher the likelihood of an emergency C/S due to failed IOL.

7.7.2.1.2 Mode of delivery

Mode of delivery distribution was vaginal deliveries (53%), caesarean section (44%) and assisted delivery (3%). The incidence of normal vaginal delivery among women who were non-diabetics and had uneventful pregnancies were 58% compared to 42% among the T2 diabetics, and this was nearing significance. Among T2 diabetics, the distribution was similar in active & placebo groups, and therefore led to the conclusion that spontaneous vaginal delivery occurred regardless of women's diabetic status and whether or not they received active supplements.

Forty-four per cent (44%) of women were delivered by CS with seventy per cent (70%) having had T2 DM. Within that group and non-diabetics, the rate of caesarean section was lower among women who received fish oils and this was nearing significance. This would suggest that fish oil supplementation may have had a positive impact on maternal and foetal health and may have contributed to reducing of the caesarean section rate within these groups but further research is needed in this area.

Elective C/S deliveries were also reduced among women who received fish oils in both groups, indicating some beneficial effect, and this was significant. The difference was 2-fold among non-diabetics and 1.5-fold among T2 diabetics. Elective C/S was approximately 3 times more common among women with pre-existing T2 DM compared

to women without diabetes. The aetiology of the disease coupled with local and national guidance on the management of T2 DM in pregnancy, could be possible reasons for this difference.

The complications of a diabetic pregnancy are multi-factorial impacting on a higher rate of caesarean section deliveries among women with T2 DM compared to non-diabetic women. That rate could be further compounded with co-morbidities associated with pre-existing diabetes was the case in this study, particularly as a significantly high number of women with T2 DM presented at booking with chronic medical problems and this was highly significant. Some women also developed pregnancy complications with a higher incidence among the placebo groups, but mainly among Type 2's, although not significant. In view of this, one may conclude that most complications prior to and developed within pregnancy were associated with the aetiology of the disease (T2 DM) and could have impacted on the high CS rate among women with T2 DM.

Also, increased maternal age has elevated risks for pregnancy complications and adverse maternal outcomes (Luke & Brown, 2007), and could have also been a contributory factor as most women with T2 DM (75%) were aged 31 and above. Women without diabetes were mainly below this age group (63%), and significantly, were approximately 5 times less likely to present at booking with chronic medical problems and 1.5 times less likely to develop maternal and foetal complications, although not significant. As most women without diabetes had a normal delivery and were in the placebo group, active supplementation had no effect on mode of delivery within this group. Conversely, an increased number of women with T2 DM and in the placebo group had a CS delivery and although the level was nearing significance, it is difficult to say whether or not EFAs had any impact on mode of delivery in general.

7.7.2.1.3 Prolonged pregnancy

Previous evidence has revealed that compared to women with T2 diabetes who received placebo, women with that disease state who received fish oils delivered at a later gestational age. Within both study groups (non-diabetic and pre-gestational diabetic), 3-fold and 6-fold less women who received active supplements delivered at moderately pre-mature, respectively. That result would suggest possible benefit of fish oils in reducing preterm delivery, particularly as the rate was significant.

Overall, more women who received the active supplements delivered at term, indicating that fish oils were beneficial in prolonging the pregnancy in both groups. A RCT conducted on primagravidas who were supplemented in early pregnancy (17-19 weeks) until post delivery (3 months) showed a likely correlation between DHA concentration and gestational length from supplementation with cod liver and corn oils, without any proven benefits or harm (Helland et al, 2001). Findings from a multicentre RCT pregnancy study were similar. Prolonged pregnancy in fish consumers (low - middle) after fish oils supplementation and dietary fish consumption was found (Olsen et al, 2007). The profile of those subjects bears similar resemblance to Newham's population which is predominantly from the lower social class and may not afford a daily balanced diet. Women of Bangladeshi origin tend to consume more fish than other ethnic groups and could have started pregnancy with higher levels of membranes fatty acids composition which could have impacted on maternal and foetal outcomes. But, baseline data taken by Min et al, (2006) did not see any difference in fatty acids level between Caucasians & other ethnic groups. This could be because they eat fish which are less oily and low in fatty acid, or because Bangladeshi women of 2nd and 3rd generation are highly likely to be born

in the UK and may have modified their diet to the Western diet and do not consume a diet rich in fish as their 1st generation parents.

7.7.2.1.4 Demographic and clinical characteristics

Most recruits (79%) were either overweight (37%) or obese (42%) and this was highly significant. Forty-four per cent had pre-existing diabetes with 41% and 59% being overweight and obese, respectfully. Similar trends were noted in published data from Public Health England (2014) which has shown that 90% of individuals with T2 DM were either overweight or obese. Also, 40% were from the most deprived areas (like Newham) where people from the ethnic minority groups live and tend to develop DM with lower BMIs compared to White Europeans. Comparatively, there was the same distribution among the non-diabetic women except for an increased number of women who received placebo and were overweight, and that increase was above two-fold.

As most study subjects were either overweight or obese and have T2 DM, perceived benefits of active supplements may not have been achieved because women with diabetes have a greater incapacity of synthesizing DHA (Ghebremeskel et al, 1998 & 2004). A previous study by Min et al (2004) has shown that obesity may adversely affect the red blood cell membranes AA & DHA levels of GDMs (with similar characteristics like T2 diabetics) and the effects of pre-gestational BMI insulin insensitivity is well documented. Subsequently, these factors combined may have adversely impacted on maternal outcomes where there was no difference in onset of labour, rate of induction and mode of delivery between women who received fish oils compared to those who received placebo and within those groups. Also, except for preterm birth, no significant foetal/neonatal difference was found between women who received fish oils and those who did not, and

the effects of pre-gestational BMI insensitivity may have been an influential factor. But, more recent related data has shown that a daily dose of 600mgs DHA rectifies the impairment of red cell membranes in women with T2 DM and their offspring and alters foetal body composition (Min et al, 2016). This begs the question whether a higher dose of active supplement was needed to have a positive impact on pregnancy outcomes?

Obesity (Gutaj et al, 2013; Conway, 2011; Lashen et al, 2004) and T2 DM (de Valk, et al, 2006) are associated with an increased risk of spontaneous abortion, and combined, those risk factors could have contributed to the incidence of miscarriage (n=20; 14%). Most miscarriages occur in the first trimester, as was the case in this study, with a significantly higher incidence among T2 diabetics compared to healthy controls. As there was an equal distribution of miscarriages in the active and placebo groups among healthy women and more common among women with T2 DM who received active supplements, fish oils had no effect on whether or not women miscarried.

Of all preterm births (n=21, 15%), above eighty percent had T2 DM. This was highly significant. There was a six-fold increase of babies that were moderately preterm. Also, there was a marked difference between the active and the placebo groups. When compared to women with and without T2 DM, there was a 3-fold increase of prematurity in the placebo groups. This significant increased would indicate that fish oils were beneficial in reducing pre-term deliveries, and possibly prolonging pregnancy, particularly among T2 diabetics where the majority delivered at term. Conversely, a RCT conducted on high-risk pregnancies showed that supplementation reduced the recurrence risk of preterm birth, although not preterm delivery (Olsen et al, 2000). Preterm babies are believed to have little fat stores and are more susceptible to reduction in AA and DHA (Min & Crawford, 2004).

Pregnant local women had an average of 2-4 children and usually in quick succession. Previous evidence has shown that women with short durations between pregnancies may also be starting with depleted stores of fatty acids. Likewise, quick successions of pregnancies can contribute to low birth weight and preterm births (Rawlings et al, 1995). Consequently, the placental supply of fatty acids available for transportation to the foetus could have been affected, impacting adversely on the maternal and foetal outcomes, despite the higher concentrate of LCPUFAs in a singleton pregnancy compared to multiple pregnancies (Ziejdner et al, 1997). As all recruits had singleton pregnancies, they all should have had an adequate supply of LCPUFAs which would have been boosted in those who had taken additional oral active supplements. But, with the population profile being overweight/obesity; some of which had pre-existing DM, most women would have started pregnancy with depleted stores of essential fatty acids and added supplementation may have contributed to rectifying the depleted stores of LCPUFAs and meeting the ongoing demand for the foetus, but to what extent?

7.7.2.2 Foetal and Neonatal Outcomes

7.7.2.2.1 Birth weight & Apgar scores

An analysis of variance has shown that the effect of fish oils on birth weight and Apgar scores at 1 minute was not significant, unlike Apgar scores at 5 and 10 minutes, where the effect of fish oils was significant. However, as most Apgar scores at 5 and 10 minutes usually fall between normal parameters, one must be cautious to link those values to EFAs consumption.

7.7.2.2.2 Low birth weight

The incidence of low-birth-weight infants was similar among T2 diabetic women who received fish oils and placebo. A Cochrane Database of Systematic Reviews has shown that control of blood sugar levels in people with T2 DM was not affected by fish oils supplementation (Hartweg et al, 2009) and could be the possible explanation for this similarity. Additionally, a systematic review which examined the effects of fish oil supplementation in women with GDM has shown no beneficial effects in the prevention or treatment of diabetes (Ostadrahimi et al, 2016).

Non-diabetic women who received placebo were twice more likely to have a low-birth-weight infant, but this was not significant. Overall, there was no significant difference between & within the active and placebo groups, which indicated that fish oils supplementation in pregnancy was not associated with the prevention of low birth weight infants. Similar findings were found in a systematic review conducted by Saconne et al (2016) unlike a similar and more recent review conducted Middleton et al (2018) which showed that fewer babies are likely to have low birth weight among women who received fish oils.

Previous reported evidence supports the view that fish oils supplementation with 1.62g of eicosapentaenoic acid (AA) and 1.8g of DHA had no positive impact on pregnancy outcome (Onuwude et al, 1995). But, could the lack of benefits be associated with the dose strength of supplements used? Onuwude et al's study was a double-blind placebo controlled randomised trial of fish oils in pregnancies complicated with intrauterine growth retardation and pregnancy induced hypertension which makes comparisons difficult. Considering that half of the women recruited into this study started with medical and/or

obstetric complications, findings from that study may be considered inapplicable. Nevertheless, as a higher strength supplement was used for that study, the morbidity of the Newham population comes into question as presumed benefits may have been obliterated. Various doses and types of fish oils have been used in pregnancy outcome studies. This lack of uniformity makes it difficult to assess the efficacy of fish oils use on maternal and foetal health. A review has shown that uncertainty still exists on the correct dose of omega-3 and omega-6 fatty acids required for use in pregnancy and the correct ratio of omega-3 to omega-6 and possible contraindications when used in combination with other drugs, foods and other supplements (Gogus & Smith, 2010). Complications developed in the index pregnancy and the medical and previous obstetric history with which women present can also affect an accurate assessment on pregnancy health and outcomes. Low levels of AA & DHA were shown to be associated with low birth weight and gestational age (Leaf et al, 1992). To reduce the morbidity; a higher dose of omega-3 fatty acid supplement may need to be considered.

7.7.2.2.3 Admission to SCBU

Most babies were born in good condition, regardless of the health status and whether or not women were supplemented with fish oils. However, compared to women without diabetes, babies born to women with pre-existing diabetes (T2 DM) were 12 times more likely to be admitted to SCBU with the incidence twice increased among those who received placebo. These findings were not significant but were similar to the norm whereby the admission rate of babies born to diabetic mothers is higher than that of mothers whose pregnancies are uncomplicated with diabetes. The main reasons for admission were prematurity followed by hypoglycaemia, and this is commonplace. Consequently, it is difficult to

correlate taking of fish oils with improved wellbeing of those infants and reduced likelihood of admission to SCBU.

7.7.3 Diabetes management and pregnancy outcomes

Management of diabetes in women with T2 DM who received fish oils was mainly oral medication and combination therapy compared to more intensive treatment of insulin and combination therapy in those who received placebo. To obtain optimum diabetes control, aggressive treatment is required to reduce the morbidity and mortality associated with diabetes in pregnancy (Gorig et al, 2018 & Billionnett et al, 2012). Pregnancy is for a shortened period in which good control is critical to optimise the wellbeing maternal and foetal. This would explain why treatment intensified during pregnancy compared to when women were in their early stages of pregnancy.

The average HBA1c results at recruitment and pre-delivery among women who received fish oils were slightly better than for women who received placebo. A possible explanation could be that oral intake of fish oils may have had some impact on glycaemic control, even if it was not to a significant level. But, one needs to be cautious as overall, there was a higher use of combination therapy for diabetes management among women who received placebo compared to women who received fish oils. These results have demonstrated that women in the active group had better glycaemic control which may have been associated with their intake of omega-3 and omega-6 fatty acids, although that difference was not significant. Additionally, since there is a level of inaccuracy in HBA1c results in pregnancy (Little & Rohlfing, 2013); it is difficult to establish any correlation.

The average gestational age at recruitment among women who received fish oils and the placebo group was 9 weeks and 10 weeks, respectively. This raises the question, whether

that week difference in recruitment (although small), resulted in earlier specialist involvement and diabetes management which contributed to better diabetes control and possibly the need for less intensive therapy.

Women who received pharmacotherapy for diabetes control had poorer outcomes compared to those who did not. For example, compared to women on 'diet only', miscarriages were 4-fold and 6-fold more likely in women who received oral medication and combination therapy, respectively. Women managed on 'diet only' were few. One could conclude that those women were possibly newly diagnosed with borderline diabetes and therefore had good control or that they were strongly motivated to manage their condition. Conversely, the use of pharmacotherapy may be indicative of the aetiology of the disease, years of diagnosis and change in regimen.

The incidence of miscarriage was higher among women who received combination therapy than the other treatment groups, combined. That result contravenes the evidence which recommends intensive treatment to achieve optimal glycaemic control and reduce the incidence of miscarriages (CEMACH, 2007). But, since one in five pregnancies in the UK end in a miscarriage (Miscarriage Association UK, 2021) and the incidence is higher among women with T2 DM (CEMACH, 2007), having a definitive conclusion on the causal effect of miscarriages is difficult.

The impact of the disease (T2 DM) on individuals and individuals' response to intensive treatment may have varied, despite their ethnic grouping. Previous studies have shown that Asians have a lower threshold of developing diabetes (Nyamdorj et al, 2010). Similarly, their response to medication may also vary and combined, these factors could have contributed to the increased incidence of miscarriages among women who received

combination therapy, particularly as most subjects recruited were Asians. The effects of being overweight and obese on the prevention of optimal insulin absorption (Hassam & James, 2005) could have been another factor. Also, as individuals with T2 DM and GDM share similar metabolic pathways (Ben Slama, 1997) and obesity was found to have adverse effects on red cell membrane AA and DHA in GDMs, this could be another possible explanation.

Preterm births and low birth weight (≤2499 grams) were more likely, the more intensive the treatment regimen. One can assume that the more complicated or high risk the pregnancy, the more intensive the treatment regimen and therefore the more likely risk of preterm delivery and low-birth weight infant. Stillbirths and neonatal deaths were only common among those who received insulin therapy. This raises the question whether those poor outcomes would have occurred if women received the highest form of treatment (combination therapy)?

Most women had operative deliveries which increased the more intense the treatment regimen; but this was not significant. Vaginal deliveries were more common among those who were on oral medication. Oral medication use is generally the second line of treatment regime after management on 'diet only'. Having not required insulin treatment or combination therapy would suggest that those women had adequate glycaemic control on tablets which meant that many could have gone into spontaneous labour and had vaginal deliveries having had a plan for delivery at a later stage compared to women on more intensive treatment regimen.

7.8 Conclusion

The findings of this phase indicated that fish oils supplementation reduced the number of babies born preterm, neonates admitted to SCBU and caesarean section deliveries but had no impact on the reduction of stillbirths, neonatal deaths, miscarriages, hypertensive disorder in pregnancy, and glycaemic control. Uncertainty still remains on the effect of fish oils on prolonging gestational age and reducing the IOL rate. Further research is needed to explore any additional benefits on pre-existing diabetes including whether supplements should be consumed from the pre-conceptual period and throughout pregnancy to have increased benefits.

The final chapter (8) follows. It has summarised the main findings of this thesis and the unique contribution this thesis has made. The strengths and limitations of each phase of the study, the implications of the findings and areas for future investigations will be highlighted.

Chapter 8:

Overview, summary, future research and conclusion

8.1 Introduction

In this concluding chapter, I will provide an overview of the general thesis. I will reflect on my experience of conducting the study and having completed the study, I will revisit the study aims, objectives and hypotheses to establish whether or not they were achieved. A summary of the findings of each chapter will also be provided with explanation on new knowledge derived from the study. Strengths and limitations will be discussed and areas for future investigation will be highlighted.

8.2 Reflection

It was very cathartic, having reflected on my journey from the start and throughout to the completion of this thesis. Reflection on my experience was two-fold. It was one of self-reflection and more importantly, it was one of critical evaluation of whether or not my initial aims, objectives and hypotheses were supported or annulled with the data presented in each phase of this study.

With English as my first language and having studied at Masters Level, I believed that I had a satisfactory level of academic persuasion to pursue this doctorate. Yet, with limited research experience, I was at times conflicted, but the support and guidance of my supervisors were invaluable.

Having reflected on the actual study, I am amazed at my overall achievements. But, when I examined each phase of the study more closely, and the data presented, it is noticeable that although some things were done well, there were some limitations which may have impacted of the findings and these need to be considered when interpreting the results.

Given the time, money and opportunity again to undertake this project, there were some things that could have been approached and done differently. Likewise, there were other areas which could have been further explored, and combined, these are described below after providing a brief overview of the study to add context to the issues raised.

8.3 Study overview

Pregnancy is usually a time of happiness, but it is fraught with many challenges which if addressed appropriately and effectively, can optimise the well-being of mother and baby, their pregnancy outcomes, as well as the long-term health of mothers and their offspring. Diabetes, which is a metabolic disorder, present significant complex challenges to care providers. However, previous studies have shown that despite the likely morbidity and mortality associated with the condition, pregnancy experience and outcomes can be positive for both mother and baby, should an individualised and multidisciplinary approach to care, be adopted.

Nutrition plays a critical role in the effective management of diabetes care. All pregnant women are advised to have a balanced diet which includes foods high in omega 3 fatty acids [arachodonic acids (AA) and docosahexaeonic acids (DHA)] which are needed for incorporation into the lipids of proliferating membranes from conception and throughout pregnancy. Hence, the recommendation by the Food Standards Agency for pregnant women to have two portions of oily fish weekly. Oily fishes are high in DHA which is essential for baby's brain and visual development. Foods rich in AA are necessary for baby's growth and development.

In women whose pregnancies are complicated with type 2 or gestational diabetes mellitus, insulin resistance of varying degrees is present. Experimental studies have shown that diabetes impairs the activity of delta-6 and delta-5 which are enzymes necessary for the synthesis of AA & DHA. Placental transfer of DHA from mother to foetus becomes affected and AA and DHA are significantly reduced in the red blood cells of women with GDM and T2 DM, and in the plasma and red blood cells of their children, which when combined may impact on pregnancies and pregnancy outcomes.

The UK is becoming increasingly more diverse. Each ethnic group brings its own peculiarities and service providers need to acknowledge, respect and embrace this notion, when caring for all pregnant women in their care, because this in turn can foster positive levels of engagement with HCPs and subsequently reduce morbidities associated with diabetes in pregnancy and lack of engagement. Ethnic minorities from deprived areas like Newham can present with complex health issues in pregnancy which can provide substantially rich empirical data for the provision of quality evidence-based care.

Previous chapters of this thesis have highlighted the impact on maternal and foetal outcomes of women with GDM and T2 DM due to lack of engagement with HCPs, inadequate maternal nutrition lacking in AA and DHA and inadequate screening of pregnant women at risk of GDM. The main findings within this thesis and the implications of these findings are reported below. The strengths, limitations and areas for future research are also highlighted.

8.4 Summary

8.4.1 Phase 1(chapter 4): Client engagement with HCPs and its impact on pregnancy outcomes

This phase evaluated the main factors which facilitated or hindered women's engagement with HCPs. Demographic and socio-economic factors play a key part in the decision-making process, which varied among and between ethnic groups, religion and one's ability to speak English. Regardless, the overarching reason given for positive engagement with HCPs was the likely benefits to the baby while having no research interest was the main reason for lack of engagement.

Inclusion of Non-English-speaking women provided a true representation of the local population which is highly diverse. The provision of the PIS in the 5 most dominant (non-English) locally spoken languages may have engendered recruitment of a larger cohort but this needs further investigation. Regardless, English speaking women who were Asian Muslims and given adequate time to make a decision with the help of their social network (husbands and/or family members) had positive levels of engagement. Home and/or hospital appointments provided women with choice and the opportunity for family engagement and may have helped with positive engagement but needs to be explored further. Also, singleton non-Asian Christians were more likely to engage but their decision on whether or not to engage was made more promptly.

Women with a positive level of engagement <24 weeks gestation developed less pregnancy complications but a slightly higher number of women within this group had hypertensive disorders (PIH, pre-eclampsia or eclampsia) and had poorer birth outcomes, in that, they

suffered more pregnancy loss (stillbirth, miscarry or neonatal death) compared to non-engaged women. Babies of women who engaged early with HCPs were twice less likely to develop macrosomia but more likely to be born pre-maturely and of low birth weight. From this data, one can conclude that further work is needed to ascertain whether these disparities in outcomes were associated with positive engagement with HCPs or lack of it, or due to socio-economic and environmental factors. Overall, data on client engagement with HCPs is limited, particularly in the UK, and there is a need for more robust data to be better able to establish the factors which impede or enhance client engagement and its impact on maternal and foetal outcomes.

Also, some women who engaged were pre-existing diabetics (T2 DM) and previous GDMs who were perhaps knowledgeable on diabetes and its potential risks in pregnancy and may have felt motivated to engage to reduce the morbidity/mortality associated with the condition. Subsequently, the engagement process may have become self-selective and those who needed to engage were those who were less likely to do so, and this could have impacted of the findings.

8.4.2 Phase 2 (chapter 5): Culture-specific screening guidelines for women at risk of GDM

Current guidance from NICE is that women with a history of GDM must be tested as early as possible and, if the result is negative, re-tested along with women with other risk factors between 24-28 weeks of gestation. This recommendation was evaluated within this phase to establish the appropriateness of NICE guidance when caring for women with other risk factors which included family history of diabetes, body mass index (BMI) ≥30 kg/m^2, history of previous GDM and macrosomic babies (birth weight ≥4kg). Having a family

history of diabetes and a body mass index (BMI) ≥30 kg/m^2, were strong indicators for early detection of GDM and were more common as risk factors for screening than women having had previous GDM. These finding would suggest that in communities like Newham which are genetically susceptible to T2 DM, early screening should be offered to pregnant women with a family history of diabetes and those with BMI ≥30. Therefore, NICE guidance would be inappropriate when caring for women with similar disposition. Lack of universal agreement on who and when to screen continue to pose a huge challenge but the strength of these findings should not be ignored, particularly as diagnosis of GDM was made following the use of WHO criteria of 75mgs of glucose load which allows for comparisons with similar studies.

This chapter also discussed whether there was any difference in pregnancy outcome in women who were diagnosed with GDM before 24 weeks of pregnancy. Findings within this phase were similar to adequate available data on previous studies which have shown that the maternal and foetal outcomes are poorer the later the diagnosis of GDM. Therefore, early screening and detection of GDM is critical to reduce the morbidity associated with the condition.

8.4.3 Phase 3 (chapter 6): Impact of fish oil in pregnant women with GDM

Maternal nutrition contributes significantly to maternal and foetal wellbeing during pregnancy and beyond. Nutrition therapy is also an integral strategy in the prevention and treatment of GDM. Pregnant women with GDM are believed to have reduced levels of plasma fatty acid composition resulting in depleted levels for her and her baby's health needs. This phase examined whether supplementation with EFAs (omega 3 & omega 6) had any beneficial effects on maternal and foetal health and pregnancy outcomes of

women diagnosed with GDM. Maternal and foetal health and outcomes were similar in those who received active supplements and placebo. Supplementation with fish oils had no impact on induction and caesarean section rates, prolonging pregnancy and the reduction of pre-term birth, macrosomia, IUGR, hypertensive disorders of pregnancy and postpartum glycaemic control. There was a possible reduction in the incidence of stillbirths, miscarriages and neonatal deaths, but further research is needed to provide empirical evidence in these areas.

From these findings, a daily dose of supplementation with two capsules containing 600mg DHA and 200mg AA showed no marked effect on maternal and neonatal outcomes despite previous sub-set data having shown that in women whose pregnancies were complicated with GDM, daily dose of DHA 600mgs enhanced maternal DHA status but not that of their offspring. Also, previous studies suggest that the transfer of DHA from mother to foetus may be impaired in women with GDM and that DHA modulates insulin resistance which is a characteristic of GDM. Regardless, having an increased daily dose of AA & DHA to rectify fatty acid status in infants of mothers with GDM should be considered to enhance the immediate and long-term potential benefits of these fatty acids in vascular and neurological development and function of the offspring, as shown in previous studies.

Also, overwhelmingly, the evidence has shown that the pregnancy outcomes of women with GDM are poorer than those without diabetes and optimising blood glucose levels can be highly beneficial. It would therefore be invaluable to further explore whether an increased dose of AA & DHA would be imperative to improve insulin sensitivity, and subsequently promote euglycaemia leading to better pregnancy outcomes.

Many large-scale studies were used to support this phase but one of the main limitations was that the pregnancies of women studied were predominantly not complicated with

diabetes. Furthermore, there were marked differences in the socio-economic and demographic profile of subjects studied and therefore the comparisons of the findings were restrictive. Homogeneous comparisons were also inhibited because previous studies used lower and varying doses of DHA. Also, the sample size within this phase was relatively small, but data generated would have provided stronger effects of the intervention if that data was compared with healthy controls, that is, women without GDM. Data derived from this group was excluded from the analysis to enhance the integrity of the findings, due to the low response rate.

Compliance was sometimes difficult to monitor. Medication bottles were not always returned on follow-up visits for counting; making it difficult to have a comprehensive log of the number of supplements taken and this aspect needs to be considered when interpreting the results. Also, dietary logs (food diaries) were excluded from the analysis due to low return rates and of those returned, most were incomplete, and the quality of the data was sub-standard. Data obtained from the food diaries would have provided a comprehensive record of individualised baseline EFAs (omega-3 & omega-6) status and established the difference in EFAs intake from dietary foods and supplementation and that data considered when analysing the outcome data.

8.4.4 Phase 4: Impact of fish oil in pregnant women with T2 DM

Previous studies have reported altered membrane fatty acid composition being a feature of T2 DM and red cell membrane phospholipids anomaly in women with T2 DM and their neonates, characterised by a significant reduction in DHA levels. However, previous sub-set data has shown that a daily dose of DHA 600mgs enhanced maternal and foetal DHA

status in women whose pregnancies were complicated with T2 DM, indicating a possible improvement in maternal and foetal outcomes.

This phase examined whether supplementation with fish oils improved the maternal and foetal health and pregnancy outcomes of women with T2 DM. The findings have revealed that fish oil supplementation had a positive impact on birth maturity and reduced pre-term births. Fewer neonates were admitted to SCBU among women with T2 DM, and had elective caesarean sections. The overall caesarean section rate was also reduced. Fish oils supplementation had no impact on reducing the rate of induction and birth weight. Glycaemic control was also not impacted by fish oils supplementation.

Based on these findings, fish oils consumption should be encouraged to reduce the incidence of preterm birth, neonates' admission to SCBU and caesarean section deliveries. Omega-3 fatty acids are inexpensive and are available on the high streets. All high-risk women, particularly those with pre-existing diabetes may benefit from fish oils consumption as part of their pre-conceptual care but more empirical studies conducted in this area. Also, further studies are required to evaluate the impact of fish oils supplementation in pregnancy on maternal and foetal outcomes.

8.5 Future investigations

When I first started this project, I knew what the scope of my thesis was but the more that I explored the evidence, the more aware I became that there were wider issues that needed to be explored. As a practicing midwife, my duty of care is to mothers and their babies and my scope includes caring for them up to 28 days post-delivery. But, since I work in an area (Newham) which has a predominantly young population, it is commonplace to see women returning, usually within a short duration, with future pregnancies.

It is well documented that women with T2 DM and GDM have poorer pregnancy outcomes compared to non-diabetic women. Therefore, it is critical to ensure that women adequately engage with HCPs prior to and early when pregnancy is confirmed, respectively, for them to get optimal care which will positively impact on their pregnancy health and outcomes, and the future health of them and their babies. Additionally, having had GDM women are at risk of developing the condition in subsequent pregnancies and this justifies the need for early contact with HCPS for adequate and timely screening and management of those with a positive diagnosis. As demonstrated within this study, having a raised BMI $\geq$30 kg/m^2 and family history of DM are strong indicators of developing GDM in future pregnancies and these factors should be considered when screening at-risk women in areas with a similar demographic profile like Newham, which is highly diverse and deprived. Areas of interest which need future exploration to enhance the phases of this study are highlighted hereunder.

The long-term effects of diabetes are well documented and various theories exist on foetal programming and the disease risks of babies in their adult life. Therefore, it would be useful to gather data not only during pregnancy and the immediate post-delivery period but

beyond. Further epidemiological studies would be beneficial to follow up the children of women with GDM and T2 DM after supplementation with AA & DHA. Previous longitudinal studies have demonstrated that LCPUFAs insufficiency is linked to impairment in infants' growth and development, vision and neurological development. Other studies have reported that the offspring of diabetic mothers have cognitive impairment, are obese and develop T2 DM. These findings could establish whether early years' intervention in children's neurological development would be necessary to reduce learning difficulties and/or prevent long term morbidity.

Women with GDM and T2 DM are characterised by some form of insulin resistance which impair their ability to adequately meet their foetal demands for AA & DHA which are necessary for foetal growth and development including their neurological and visual wellbeing. Oral supplementation of these fatty acids (AA & DHA) is believed to rectify these depleted levels. In this study, a daily dose of 600mg DHA and 200mg AA supplementation from as early as the first trimester until delivery, had some positive impact on the pregnancy outcomes (reduction of premature births and prolonging pregnancies) of women with T2 DM but not women with a diagnosis of GDM**.** It would therefore be invaluable to further explore whether insulin resistance and red cell membrane phospholipids can be rectified and/or enhanced by an increased dose of EFAs (AA & DHA) and subsequently promote euglycaemia leading to better pregnancy outcomes.

I believe that the number of women diagnosed with GDM within Newham could be higher than in some areas. At present only women who are high risk of developing GDM are screened but there may be women who develop GDM who are not high risk. Over the

years, I have come across women who had no notable risk factors but developed the condition, but they were only screened for GDM when they became unwell, usually during the 3rd trimester. Data from screening women who are not at high risk of developing GDM for the condition, over a period of a year will provide a more comprehensive overview of women who are at risk of developing GDM, locally, nationally and possibly worldwide and set precedence for further studies.

Also, it would be useful to establish the percentage of women who had GDM and subsequently developed T2 DM within a five-year period because previous studies have shown that within 5-10 years and in some cases even earlier, some women developed T2 DM. This information would be critical for future preventative work, care planning and allocation of resources. Huge cost savings could be made considering the high likelihood of T2 DM in later life after GDM diagnosis and since diabetes costs the NHS millions on a daily basis.

It will be useful to evaluate women's knowledge of GDM before and after attending the education session to establish whether or not their knowledge improved and how that may have impacted on diabetes control and pregnancy outcome, while paying particular attention to the English- and non-English speaking women. This data would establish whether the sessions are 'fit for purpose' and provided equity across ethnic groups. Also, it would have been useful to assess any new learning and whether that new knowledge empowered women to adopt lifestyle changes to optimise their glycaemic control and have influenced their decision on whether or not to engage with the services available to them. Comparing the pregnancy outcomes of previously and newly diagnosed GDMs to establish whether the former with their previous knowledge felt more motivated to engage and whether that had any impact on pregnancy health and outcomes, is another area for study which will provide substantial data on whether or not teaching should be streamlined

differently or not, when the diagnosis of GDM is confirmed. It will also establish the level of input that is required from HCPs. Also, some women may have been 'functional illiterates' who were unable to adequately process the information provided in the education session and subsequently unable to engage effectively and responsibly. Evaluating this in the context of blood glucose control and pregnancy outcomes would provide invaluable information on the structure of the education session in the future.

Having a record of the type and frequency of exercise in which women engaged, the number of dietetic encounters and support they received from the antenatal period and throughout to delivery and evaluating whether those lifestyle factors contributed to women's knowledge and understanding about diabetes, influenced their levels of engagement with HCPs and positively impacted on glycaemic control, maternal and foetal wellbeing and pregnancy outcomes are areas for future study. Healthy eating and exercise are the cornerstone for optimum diabetes control and management, and acquisition of that data would help with the provision of more targeted individualised care to a multi-ethnic clientele; some of which are usually not amenable to making lifestyle changes due to cultural and socio-economic reasons.

Although some factors have been identified for lack of engagement among local women, data on women's level of education, experience of domestic violence, role as carers and occupancy rates per number of rooms in their housing accommodation would have been useful to assess those social factors on engagement, through further work. Also, it would have been useful to evaluate the number of encounters that were made with subjects before they engaged with HCPs to help with budgeting and when conducting research within this population profile.

Data collection on women's previous experiences on service access and availability from their birth countries would be useful to establish whether there was any correlation with those factors and engagement in this country. This information could be matched with women's previous experiences using the health service, concerns and expectations to help in supporting women to access available services and make choices that were amenable to them. Previous negative experiences of health care and services of one's country of origin can dictate how one engages with new services and service providers. Also, women's experiences of all services, including health, since arriving in the UK may have contributed to their willingness to engage or not and future study in this area would be critical for future promotional work on client engagement.

Since completion of this study, emerging new evidence was found in an observational study conducted by Murphy (2020). The management of pregnancy diabetes before, during and after COVID-19 was explored. Conclusions from that study were that as HCPs we need to find new ways of supporting pregnancy women in managing their diabetes. Positive feedback was received on video consultation and patients' experiences of requiring face to face visits were improved.

The results of this study are most fitting for Phase 1 of this study which explored the factors which influenced positive client engagement with HCPs. Women need flexibility in the choices made available to them to do what is right for their babies. One thing that I would have done differently was the offer of video consultation, in addition to the choice of home visit and hospital consultation. This additional choice may facilitate increased levels of engagement which would have had a more positive impact on client the RCTs in Phases 3 and 4.

8.6 Conclusion

The programme of research in this study would make a unique contribution to bridging the gap in existing knowledge. There are no well designed pregnancy outcome studies on fatty acids supplementation in pregnancies complicated with type 2 and gestational diabetes mellitus. This study would help in filling that gap.

The findings of this study have demonstrated that NICE current guidelines on screening for the early detection of GDM are inappropriate for use in communities like Newham with a high disposition of DM. Family history of diabetes and BMI $\geq$30kg/m^2 are strong indicators for early detection of GDM. In communities like Newham which are genetically susceptible to T2 DM, women with these risk factors, as well as a previous history of GDM, should be screened early.

Further explored were the impact of supplementation with AA & DHA in women with GDM and T2 DM on pregnancy outcomes and factors which influence engagement with HCPs among these high-risk groups and the subsequent impact of their decision on maternal and foetal outcomes. Social, cultural and religious factors are critical to decision making. Women need time, flexibility in care delivery and appropriate and adequate information in language they understand to engage effectively. Stakeholders would be better able to prioritise services for early management interventions to reduce any associated risks to mother and baby.

Also, this study has demonstrated that supplementation with fish oils in T2 diabetics improved maternal and foetal outcomes in prolonging pregnancies, reducing preterm births, caesarean section deliveries and admission to SCBU. Having clarity in these area can foster changes in the local maternity diabetes services and help HCPs to improve the nutritional advice provided to pregnant women to rectify maternal and foetal fatty acids status, in particular women with pre-existing diabetes and possibly those with GDM.

For reasons of accountability, HCPs need to take a broad culturally sensitive view when dealing with all pregnant women but particularly, non-Whites, who for the greater part are socio-economically deprived, marginalised, and more susceptible to developing T2 DM and GDM and have poorer pregnancy outcomes. Each ethnic group has its own nuances and stakeholders and service providers need to acknowledge, respect and positively embrace this notion. A start would be to refrain from grouping all non-Whites under the umbrella of 'BAME', to achieve truly individualised woman-centred care and reduce inequalities in health which is not a historic problem.

Finally, the findings of this study should be interpreted as the first step towards future research on maternal and foetal outcomes of the local pregnancy diabetes service. Parameter used within this study can be used for future work on GDM screening, promotion of positive client engagement and enhancement of nutritional status and pregnancy outcome measures for all women whose pregnancies are complicated with DM.

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10.0 Appendices

Appendix 1.1

Publications

Min Y, Djahanbakhch O, **Hutchinson J**, Eram S, Bhullar AS, Namugere I,Ghebremeskel K (2016) Efficacy of docosahexaenoic acid-enriched formula to enhance maternal and foetal blood docosahexaenoic acid levels: Randomized double-blinded placebo-controlled trial of pregnant women with gestational diabetes mellitus. Clin Nutr 35(3):608-614.

Min Y, Bhullar A, **Hutchinson J**, Namugere I, Djahanbakhch O and Ghebremeskel K (2016) Platelet fatty acid composition of pregnant women with type 2 diabetes in early gestation. 12th Congress of the International Society for the Study of Fatty Acids and Lipids, Stellenbosch, South Africa (September 5-9).

Min, Y. Djahanbakhch, O. **Hutchinson, J.** Bhullar, A.S. Raveendran, M. Hallot, A. Eram, S. Namugere, I. Nateghian, S & Ghebremeskel, K (2014) Effects of docosahexaenoic acid-enriched fish oil supplemention in pregnancy with Type 2 diabetes on membrane fatty acids and fetal body composition – double-blinded randomises placebo-controlled trial. Diabetic Medicine 10.1111/dme.12524

Appendix 3.1

Newham University Hospital NHS
NHS Trust

LETTER OF INVITATION TO PARTICIPANT

Date: 15 May 2006

Dear Participant,

You are being invited to take part in a research study entitled ***"Dietary fish oil supplementation to improve maternal and foetal nutritional status in diabetic pregnancy".*** Previous researches have shown that babies born to mothers with established diabetes (whether it's type 1 or type 2 diabetes) or gestational diabetes (that is diabetes developed during pregnancy but resolved after delivery) are at greater risk of becoming obese, insulin resistant and subsequently developing type 2 diabetes. Also some study suggested that children born to mothers with diabetes are associated with learning difficulties.

We have shown that diabetic women and their newborn babies have lower blood levels of long chain omega 6 and omega 3 fatty acids. These are fatty acids found in various food but they have different dietary source. For example long-chain omega 6 fatty acid (it is called arachidonic acid or briefly AA) mainly found in meat, poultry, or egg whereas omega 3 fatty acid (it is called docosahexaenoic acid or briefly DHA) are mainly present in fish, fish oil or seafood. Why are they important? Because these nutrients are vital nutrients for the brain, retina and blood vessels and human body need them to function properly such as fighting for infection, lowering blood cholesterol.

The purpose of this study is to investigate if supplementation with omega 3 and omega 6 fatty acids in pregnant women with diabetes improves the nutritional status of mothers and babies.

The following information sheet will explain details of the study. Please take time to read the leaflet and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

Professor Ovrang Djahanbakhch
Principal Investigator

Website: www.newhamuniversityhospital.nhs.uk **Minicom:** 020 7363 8790
Chairman: Michael Smith **Chief Executive:** Kathy Watkins

be taken about baby including:
- weight and length
- head, shoulder, mid-arm and abdominal circumference
- body fat
- any abnormality.

• **After delivery,** you will be called at one, six and 24 months by the research midwife and information will be taken on:-
- type of baby's feed
- baby's general health
- an assessment of your baby's development will also be done at 24 months.

Will the medication harm my baby?

These nutrients are usually found in food it is therefore unlikely that they may harm your baby. By using the tablets in this study, we should have better information on whether or not they have any impact on your baby's health.

Are there any side effects?

We are not aware of any side effects of either the fish oil tablet or the placebo. However, if you notice anything unusual having started taking the tablets, stop taking them and contact the research midwife immediately.

Also, if you avoid eating fish for personal (eg. you are vegetarian or vegan) or religious reasons or you are allergic to fish or sunflower oil please inform the research midwife as you may wish not to take part in the study.

How long will the study take?

This study will last approximately three years but your involvement will be for two years after delivery to follow up your baby.

Confidentiality

All the information collected on you will be kept strictly confidential. Information about you which leaves the hospital will have any identifying information removed. We recommend that both your GP and Obstetrician be informed about your participation. If you are happy, we will write to them.

Contact Details

If you wish to find out more about the study please contact:-

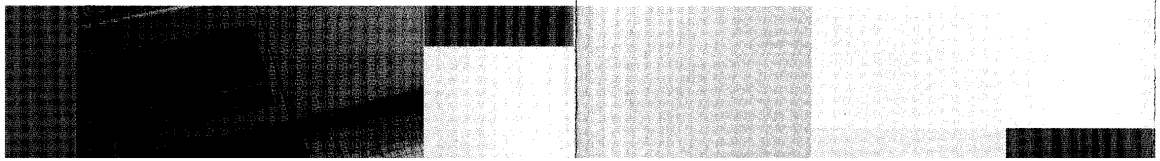
Joanne Hutchinson (Research Midwife) on 07824 825 279

Professor Ovrang Djahanbakhch (Project Director) on 020 7363 8069.

This research project is conducted by the Institute of Brain Chemistry and Human Nutrition and Newham University Hospital NHS Trust.

www.newhamuniversityhospital.nhs.uk

Author: Joanne Hutchinson
Date of Publication: October 2007
Review Date: October 2008



Newham University Hospital NHS
NHS Trust

FOSIP Study

Fish Oils Supplementation in Pregnancy

Can taking supplements of omega-3 and omega-6 acids during pregnancy improve your and your baby's health?

The text of this leaflet is available in large print. If you want this please phone 020 7363 8960 and we will get you a copy.

IBCHN
Institute of Brain Chemistry and Human Nutrition

Patients First!

What is the aim of the study?

The aim of this study is to see if taking supplements of omega-3 and omega-6 acids during pregnancy can improve your and your baby's health.

Previous research suggests that if you are diabetic, develop diabetes during pregnancy or have insufficient amounts of certain nutrients when pregnant, your child may have a higher risk of becoming overweight and is more likely to develop diabetes and high blood pressure in adulthood. A previous study showed that diabetic women and their newborn babies have lower levels of omega-3 and omega-6 fatty acids found in various foods including fish and eggs.

Why have I been chosen?

1. You have diabetes (either Type 1, Type 2 or gestational diabetes – diabetes developed during pregnancy).

2. Your pregnancy is free of diabetes. You are chosen as a 'Control' that is, a healthy woman without diabetes.

Do I have to take part?

No, and whatever you decide this will not affect your care in any way. You can also withdraw from the study at any time.

What are the benefits?

We hope that both treatments will help you. However, this cannot be guaranteed. The information we get from this study may help us to better treat future patients with diabetes and their children.

What will happen to me if I decide to take part?

You will be:-

- Given more detailed information about the study.
- Offered the opportunity to ask any questions, and if you still want to take part.
- The research midwife will take information on your medical/ family and previous pregnancy history and your diet. A four day food diary will be given to you to complete and return to the midwife (recording three days during the week and one day on the weekend).

Then you will be asked to:-

- Sign two consent forms – one for you and one for your baby.
- Take one tablet twice a day, which will be either the fish oil tablet or placebo.

You will not know which of these tablets you will be receiving. You will be asked to take the tablets from the time of agreeing to take part in the study until your baby is born. The fish oil tablet contains active nutrients of omega-3 and omega-6, extracted from tuna fish oil. The placebo tablet looks the same but contains nutrients extracted from sunflower oil.

Additionally we will have to monitor your health but the tests you will have depends on which group you are in:-

1. If you have **Type 1 or Type 2 diabetes,** bloods will be taken before 15 weeks of pregnancy, between 28 and 32 weeks of pregnancy and at delivery.

2. If you are in the **'control group'**, bloods will be taken before 15 weeks of pregnancy and at delivery. We will also test how well your body controls blood sugar between 28 and 32 weeks of pregnancy. That test is called an 'oral glucose tolerance test', which involves taking blood from you after overnight fasting and at two hours after taking 75g of glucose (sugar). When you are pregnant the levels of blood sugar and insulin (hormone that turns glucose into energy) both increase. This is a natural way for your body to cope during pregnancy but can cause some women to develop gestational diabetes, especially during the latter part of pregnancy.

3. If you have **gestational diabetes,** bloods will be taken when the diagnosis is made, at delivery and an oral glucose tolerance test performed six weeks after your baby is born.

Also, whatever group you belong to:-

- **Between 34 and 38 weeks** of pregnancy an ultrasound scan will be done to assess your baby's health.
- **At delivery,** cord bloods and a sample of placenta will be taken and information will

If you would like this leaflet to be explained in your language, please call our Bilingual Health Advocacy Service on 020 7363 8132/8396.

যার মধ্যে অর্ন্তগত শিশুর:

-ওজন ও উচ্চতা
-মাথা, কাঁধ, বাহু ও পেটের পরিধি
-শরীরের চর্বি
-কোন অস্বাভাবিকতা

শিশুর জন্মের পর, ১ম, ৬ষ্ঠ ও ২৪তম মাসে রিসার্চ মিডওয়াইফ (গবেষক ধাত্রী) আপনাকে ডাকবে যে সব বিষয়ে তথ্য সংগ্রহ করা হবে তা হচ্ছে:-

— শিশুর খাদ্যের নমুনা
— শিশুর সাধারন স্বাস্থ্য
— ২৪তম মাসে আপনার শিশুর সার্বিক উন্নয়নের (ডেভেলপমেন্ট) পরিমাপ (এসেসমেন্ট) করা হবে।

এই ওষুধে কী আমার শিশুর ক্ষতি হবে?

এসব পুষ্টিসমূহ সাধারণত খাবারেই পাওয়া যায়, এ কারনে এসব থেকে আপনার শিশুর ক্ষতির সম্ভবনা না হওয়াই স্বাভাবিক। এসব ওষুধ আপনার শিশুর স্বাস্থ্যের উপর কোন প্রভাব ফেলে কী না, এই ষ্টাডির মাধ্যমে আমরা এ ব্যাপারে আরো ভালো করে তথ্য সংগ্রহ করতে পারবো।

এর কী কোন পার্শ্বপ্রতিক্রিয়া আছে?

আমাদের জানামতে মাছের তেলের ট্যাবলেট বা প্লাসিবো'র কোন পার্শ্বপ্রতিক্রিয়া (সাইড এফেক্ট) নেই। তবুও, ওষুধ নেয়া শুরু করার পর আপনি যদি কোন অস্বাভাবিকতা লক্ষ্য করেন, তবে ওষুধ নেয়া বন্ধ করে রিসার্চ মিডওয়াইফের সাথে অবিলম্বে যোগাযোগ করুন।

এছাড়া আপনি যদি ব্যক্তিগত কারনে (যেমন আপনি যদি নিরামিষাশী হন) বা ধর্মীয় কারনে মাছ না খান অথবা মাছ বা সূর্যমূখী
ফুলের তেলে যদি আপনার এলার্জী থাকে তবে অনুগ্রহ করে রিসার্চ মিডওয়াইফকে জানান কেননা হয়তো একারনে আপনি এই ষ্টাডি বা পর্যেষনায় অংশগ্রহন করতে না চাইতে পারেন।

এই ষ্টাডি বা পর্যেষনায় কত দিন লাগবে?

এই ষ্টাডি বা পর্যেষনা চলবে তিন বছর কিন্তু আপনাকে এর সাথে জড়িত থাকতে হবে দুই বছর শিশুর জন্মের পর ফলো আপের (পূর্বক্ত নির্দেশ অনুসরন) জন্য।

গোপনীয়তা

আপনার উপর সংগ্রহ করা সকল তথ্য পরিপূর্ন গোপনীয়তার সাথে সংরক্ষন করা হবে। আপনার সম্পর্কে যে সকল তথ্য হাসপাতালের
বাইরে যাবে তার থেকে সনাক্ত করা যায় এমন সকল তথ্য সরিয়ে ফেলা হবে। আপনার চিকিৎসক (জিপি) এবং অবষ্টিক্ট্রিশিয়ান (ধাত্রীবিদ্যাবিশারদ) উভয়কে এই ষ্টাডিতে আপনার অংশগ্রহনের ব্যাপারে জানানোর জন্য পরামর্শ দেয়া হচ্ছে। আপনার আপত্তি না থাকলে আমরা তাদের লিখিতভাবে জানাতে চাই।

কনটাক্ট ডিটেল (যোগাযোগের আনুপঙ্খিক তথ্য)

আপনি যদি এই ষ্টাডি বা পর্যেষনা সম্পর্কে আরো কিছু জানতে চান তবে অনুগ্রহ করে যোগাযোগ করুন:-

Joanne Hutchinson (জোয়ান হাচিনসন, রিসার্চ মিডওয়াইফ)
কে 07824 825 279 নম্বরে

প্রফেসর Ovrang Djahanbakhch (অভরাং জাহানবাখচ, প্রজেক্ট ডিরেক্টর)'কে 020 7363 8069 নম্বরে

এই রিসার্চ প্রজেক্টটি Institute of Brain Chemistry ও Human Nutrition এবং Newham University Hospital NHS Trust দ্বারা পরিচালিত।

www.newhamuniversityhospital.nhs.uk
Author: Joanne Hutchinson
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Newham University Hospital NHS
NHS Trust

FOSIP Study

Fish Oils Supplementation in Pregnancy
(গর্ভাবস্থায় মাছের তেলের সংযোজন)

গর্ভবতী অবস্থায় ওমেগা-৩ ও ওমেগা-৬ এসিডের সাপ্লিমেন্ট গ্রহনে আপনার এবং আপনার শিশুর স্বাস্থ্যের কী উন্নতি হতে পারে?

এই প্রচারপত্রের মুদ্রণ লার্জ প্রিন্টে (বড় অক্ষরে ছাপা) পাওয়া যায়। আপনি যদি এটি চান তবে অনুগ্রহ করে ফোন করুন 020 7363 8960 নম্বরে এবং আমরা আপনার জন্য এক কপির ব্যবস্থা করবো।

Institute of Brain Chemistry
and Human Nutrition

Bengali

Appendix 3.3

এই ষ্টাডি বা পর্যেবনার উদ্দেশ্য কী?

এই ষ্টাডি বা পর্যেবনার উদ্দেশ্য হচ্ছে দেখা যে গর্ভবতী অবস্থায় ওমেগা-৩ ও ওমেগা-৬ এসিডের সাপ্লিমেন্ট (অতিরিক্ত সম্পূরক হিসেবে যা নেয়া হয়) গ্রহনে আপনার এবং আপনার শিশুর স্বাস্থ্যের কোন উন্নতি হয় কি না।

পূর্ববর্তী গবেষনা থেকে জানা যায় যে, আপনি যদি ডায়াবেটিক (বহুমূত্র রোগী) হন, গর্ভবতী অবস্থায় ডায়াবিটিসে আক্রান্ত হন অথবা গর্ভবতী থাকাকালীন কিছু বিশেষ পুষ্টির অভাব ঘটে, তবে আপনার সন্তানের ওজন অতিরিক্ত হবার অধিক সম্ভাবনা থাকে এবং প্রাপ্তবয়স্ক অবস্থায় তার উচ্চ রক্তচাপ ও ডায়াবিটিসে আক্রান্ত হওয়ার সম্ভাবনা বেশী থাকে। পূর্বেকার একটি পর্যেবনা থেকে দেখা যায় যে ডায়াবেটিক মহিলারা এবং তাদের সদ্যজাত শিশুদের মধ্যে ওমেগা-৩ ও ওমেগা-৬ ফ্যাটি এসিড, যা মাছ ও ডিম সহ নানা খাবারে পাওয়া যায়, কম পরিমানে থাকে।

আমাকে কেন মনোনীত করা হয়েছে?

১.আপনার ডায়াবিটিস রোগ আছে (হয় টাইপ ১, টাইপ ২ অথবা গ্যাসটেশনাল ডায়াবিটিস- ডায়াবিটিস যা গর্ভবতী অবস্থায় মহিলাদের মধ্যে দেখা যায়)।

২.গর্ভবতী অবস্থায় আপনি ডায়াবিটিস মুক্ত। আপনাকে মনোনীত করা হয়েছে "কন্ট্রোল"(নিয়ন্ত্রন), যার মানে হচ্ছে আপনি একজন ডায়াবিটিস মুক্ত সুস্থ্য মহিলা, হিসেবে।

আমাকে কী অংশগ্রহন করতেই হবে?

না, আপনি যাই মনস্থির করুন এর ফলে আপনার সেবা বা চিকিৎসার উপর কোন প্রভাব পরবে না। এছাড়াও আপনি যে কোন সময় এই ষ্টাডি থেকে সরে যেতে পারেন।

এর সুবিধাগুলো কী?

আমরা আশা করছি যে উভয় চিকিৎসাই আপনাকে সাহায্য করবে। তবে নিশ্চিতভাবে কিছু বলা যায় না। এই স্টাডি থেকে আমরা যে সকল তথ্য পাব তা ভবিষ্যতের ডায়াবিটিস রুগী ও তাদের সন্তানদের আরো ভালো চিকিৎসা লাভে সাহায্য করবে।

কী হবে আমি যদি অংশগ্রহন করতে রাজী হই?

আপনাকে :-

• এই ষ্টাডি সম্পর্কে আরো বিস্তারিত তথ্য দেয়া হবে।
• যে কোন প্রশ্ন করার সুযোগ দেয়া হবে, এবং এর পরেও যদি আপনি অংশগ্রহনে রাজী থাকেন
• গবেষক ধাত্রী (রিসার্চ মিডওয়াইফ) আপনার মেডিকাল/পারিবারিক ও পূর্বেকার গর্ভাবস্থা এবং আপনার খাদ্যাভাসের উপর তথ্য সংগ্রহ করবে। একটি চার দিনের ফুড ডায়েরী (খাদ্য তালিকা) আপনাকে দেয়া হবে পূর্ণ করার জন্য এবং তা মিডওয়াইফ বা ধাত্রীকে (উইকডে বা সপ্তাহ চলাকালীন তিনদিন ও উইক এন্ড বা সপ্তাহ শেষের একদিনের খাদ্য তালিকা লিপীবদ্ধ করে) ফেরৎ দিতে হবে।

এরপর আপনাকে বলা হবে :-

• দুটি সম্মতির ফর্মে সই করতে - একটি আপনার এবং একটি আপনার শিশুর জন্য।
• একটি ট্যাবলেট দিনে দু'বার করে নিতে হবে, যার একটি হবে মাছের তেলের ট্যাবলেট আর অন্যটি হবে প্লাসিবো (এটি রোগ নিরাময়ের ওষুধ নয়, রুগীর মানসিক শান্তির জন্য ওষুধের নামে প্রদত্ত অন্য কিছু ; ওষুধকল্প)।

আপনি জানবেন না যে কোন ট্যাবলেট আপনি নিচ্ছেন। এই ষ্টাডিতে অংশগ্রহন করতে রাজী হওয়ার পর থেকে আপনার শিশুর জন্ম পর্যন্ত আপনাকে ট্যাবলেটগুলো নিতে বলা হবে। মাছের তেলের ট্যাবলেট'এ রয়েছে ওমেগা-৩ ও ওমেগা-৬ এর সক্রিয় পুষ্টিকর পদার্থসমূহ, যা টুনা মাছের তেল থেকে নেয়া হয়েছে। প্লাসিবো ট্যাবলেটগুলো দেখতে একইরকম কিন্তু এতে আছে সূর্যমুখী ফুলের তেল থেকে নিষ্ক্রিত পুষ্টিকর পদার্থসমূহ।

এরসঙ্গে, আমাদেরকে আপনার স্বাস্থের উপর নজর রাখতে হবে

কিন্তু কী কী পরীক্ষা আপনাকে করাতে হবে তা নির্ভর করে আপনি কোন গ্রুপের তার উপর:-

১.যদি আপনার **টাইপ১ বা টাইপ২ ডায়াবিটিস** থাকে, গর্ভাবস্থার
১৫ সপ্তাহের আগে, ২৮ থেকে ৩২ সপ্তাহের মধ্যে এবং সন্তান প্রসবের সময়ে আপনার কাছ থেকে রক্ত নেয়া হবে।

২.আপনি যদি "কন্ট্রোল গ্রুপে" থাকেন, রক্ত নেয়া হবে ১৫ সপ্তাহের আগে এবং সন্তান প্রসবের সময়। গর্ভাবস্থার ২৮ থেকে
৩২ সপ্তাহের মধ্যে আমরা আরো পরীক্ষা করে দেখবো যে আপনার শরীর কত ভালোভাবে রক্তে চিনির পরিমান নিয়ন্ত্রন করে। এই পরীক্ষাকে বলা হয় "ওরাল গ্লুকোজ টলারেন্স টেষ্ট", যার জন্য রক্ত নিতে হয় সারা রাত অভুক্ত থাকার পর এবং ৭৫ গ্রাম গ্লুকোজ (চিনি) নেয়ার দুই ঘন্টা পর। গর্ভাবস্থায় রক্তে চিনি ও ইনসুলিন (হরমোন যা গ্লুকোজকে শক্তিতে পরিণত করে)'এর পরিমান বেড়ে যায়। এই প্রাক্রিতিক প্রক্রিয়ার মাধ্যমে আপনার শরীর গর্ভাবস্থায় নিজেকে মানিয়ে নেয় কিন্তু কিছু মহিলারা এর ফলে গ্যাসটেশনাল ডায়াবিটিস (যা গর্ভবতী অবস্থায় হয়)'এ আক্রান্ত হয়, বিশেষ করে গর্ভাবস্থার পরের দিকে।

৩.আপনি যদি **গ্যাসটেশনাল ডায়াবিটিসে** ভুগেন, তবে রোগ নির্ণয়ের সময় ও সন্তান প্রসবের সময় আপনার রক্ত নেয়া হবে এবং সন্তান জন্মের ছয় সপ্তাহ পর ওরাল গ্লুকোজ টলারেন্স টেষ্ট
করা হবে। তদুপরি, যে গ্রুপেই আপনি থাকুন না কেন:-

• **গর্ভাবস্থার ৩৪ থেকে ৩৮ সপ্তাহের মধ্যে** একটি আলট্রা সাউন্ড স্ক্যান করা হবে আপনার শিশুর স্বাস্থের অবস্থা নির্ণয়ের জন্য।
• **শিশুর জন্মের সময়ে** নাড়ীর রক্ত ও গর্ভফুলের নমুনা নেয়া হবে এবং শিশুর উপর নানা তথ্য সংগ্রহ করা হবে

Appendix 3.4

Institute of Brain Chemistry and Human Nutrition
London Metropolitan University
166-222 Holloway Road, London N7 8DB
Website: www.north.londonmet.ac.uk/ibchn
Tel: +44 020 7133 2446

Translating & Interpretation Service
4th Floor, Crown House
Cambridge Road, Barking
Essex IG11 8HJ

Order Form

- Order No: K040772
- Date: 11th October 2007
- Order Reference: Translation (in 5 languages) of Information Sheets, Consent Forms, and Dietary Assessment for Diabetic Study at the Newham General Hospital
- Contact Person: Joanne Hutchinson
  Newham University Hospital

  Tel: 07824 825279
  Email: Joanne.Hutchinson@newhamhealth.nhs.uk
- Invoice to: Professor Michael Crawford
  Institute of Brain Chemistry and Human Nutrition
  London Metropolitan University
  North Campus, 166-220 Holloway Road
  London N7 8DB

Appendix 3.5

INFORMATION SHEET FOR PARTICIPANTS

Title of Project	Dietary fish oil supplementation to improve maternal and foetal nutritional status in diabetic pregnancy	
Principal Investigator	Professor Ovrang Djahanbakhch	
Other Investigators	Professor Michael Crawford, Professor Kebreab Ghebremeskel, Dr Yoeju Min, Ms Joanne Hutchinson	
Ethics Committee		
Version No. 2006-1		**Date** 15 May 2006
Contact Person	Professor Ovrang Djahanbakhch *or* Ms Joanne Hutchinson	
Contact Tel. No.		

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

1. What is the purpose of the study?

Evidence from animal and human studies reveals that unfavourable intrauterine environment may programme the foetus to chronic diseases such as type 2 diabetes and high blood pressure in adulthood. Indeed, maternal diabetes during pregnancy is a strong risk factor of obesity, insulin resistance, type 2 diabetes, and mental deficit in the offspring. We have shown that diabetic women and their newborn babies have lower blood levels of omega-6 and omega-3 fatty acids. These nutrients are vital nutrients for the brain, retina and blood vessels. There is evidence that insulin resistance, obesity, type 2 diabetes and impaired brain function are associated with low level of omega-3 fatty acids in blood. In addition, it has been shown that the omega-6 fatty acid (arachidonic acid) prevents maternal diabetes-induced birth defects in animals. The purpose of the proposed study is to investigate if the low level of blood omega-3 and omega-6 fatty acids in pregnant diabetic women and their babies, at birth, found in our previous investigations could be improved by maternal supplementation during pregnancy.

2. Why have I been chosen?

You are chosen because you have either established diabetes (type 1 or type 2) or are diagnosed with gestational diabetes. Even though you don't have diabetes you are chosen as controls which means you will act as an healthy group and will be tested how effective the fish oil improves your essential fatty acids status compared with those of diabetic women.

3. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

4. What will happen to me if I take part?

Sometimes because we do not know which way of supplement patients is best, we need to make comparisons. People will be put into groups and then compared. The groups are selected by a computer which has no information about the individual – i.e. by chance. Patients in each group then have a different supplement and these are compared. This is also a blind study which means neither you nor your doctor will know in which treatment group you are (although, if your doctor needs to find out he/she can do so).

Your chance of getting the study supplement or placebo will be a one in four. A placebo is a dummy supplement such as a pill which looks like the real thing but is not. It contains no active ingredient.

5. What do I have to do?

We will need to take 2 capsules a day until delivery.

6. What is the treatment or procedure that is being tested?

We will measure your blood lipid and fatty acids at the time of recruitment and during 3rd trimester and after delivery. Also we are going to test how effective your body regulates blood glucose by measuring blood glucose and insulin. For this test you need to come to the clinic in the morning after overnight fast.

7. What are the side effects of any treatment received when taking part?

We are not aware of any side effects of either treatment or placebo.

8. What are the possible disadvantages and risks of taking part?

There are no known disadvantages and risks by taking these capsules. They are already widely available at the chemist, health shops, and supermarket.

9. What are the possible benefits of taking part?

We hope that both treatments will help you. However, this cannot be guaranteed. The information we get from this study may help us to treat future patients with diabetes and their children better.

10. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you

about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form. Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

11. What happens when the research study stops?

Even though the research study stops for any reason all the clinical information and samples will be stored until decision is being made by the research committee. This will not affect any of your routine care.

12. What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

13. Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

14. What will happen to the results of the research study?

The results of the research study will be presented to you and hospital staff. They will be also presented at the national or international scientific meetings and published in journals.

15.Who is organising and funding the research?

The research is organised by the Newham General Hospital and the Institute of Brain Chemistry and Human Nutrition, London Metropolitan University, and funded by the European Union, Foyle Foundation, Mother and Child Foundation.

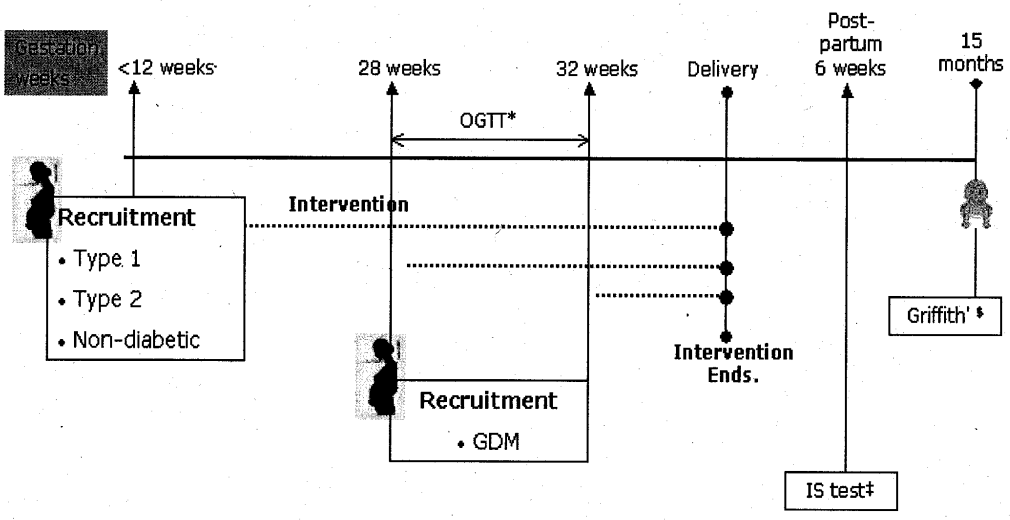
13. Who has reviewed the study?

The Research Ethics Committee (name) reviewed the study.

14. Contact for Further Information

If you wish to find out more about the study please contact Professor Ovrang Djahanbakhch *or* Ms Joanne Hutchson (midwife) at xxxxxxx

Research Plan



OGTT*; Oral Glucose Tolerance Test, All non-diabetic women recruited during 1st trimester will be screened for gestational diabetes.

GDM = Gestational diabetes

IS test‡; Women with GDM, supplemented/unsupplemented, will undergo insulin sensitivity (IS) test at 6 weeks postpartum.

Griffith's Developmental test will be conducted at 15 months of age.

You will be given a copy of the information sheet and a signed consent form to keep.

Appendix 3.6

Newham University Hospital NHS
NHS Trust

Centre Number	
Study Number	
Patient Identification Number for this trial	

CONSENT FORM

Title of Project	Dietary fish oil supplementation to improve maternal and foetal nutritional status in diabetic pregnancy
Principal Investigator	Professor Ovrang Djahanbakhch
Other Investigators	Professor Michael Crawford, Professor Kebreab Ghebremeskel, Dr Yoeju Min, Ms Joanne Hutchinson

	Please tick box
1. I confirm that I have read and understand the information sheet dated (version 2006-1) for the above study and have had the opportunity to ask questions.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from [company name] or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
4. I agree to take part in the above study.	

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Website: www.newhamuniversityhospital.nhs.uk **Minicom:** 020 7363 8790
Chairman: Michael Smith **Chief Executive:** Kathy Watkins

Appendix 3.7

DEMOGRAPHIC & CLINICAL RECORDS

Hospital Reference No.:..... Name:.....

Datr of 1st Booking: ... (dd) ..... (mm) ..... (yyyy) Date of Enrolment: ..... (dd) .... (mm) ..... (yyyy)

Name of Consultant: .....

Status: Normal ☐ Type 1 ☐ Typa 2 ☐ GDM ☐ Supplement Type: A ☐ B ☐

Address:.....

Contact Tel: .....

DOB: ..... (dd) ..... (mm) ..... (yyyy) Age .....

Racial Origin: ..... Partners Racial Origin: .....

Marital Status: Single ☐ Married ☐ Living with partner ☐

Smoking: Self: YES ☐ NO ☐ Ex-smoker ☐ Partner: YES ☐ NO ☐ Ex-smoker ☐

If YES how many cigarettes per day: Self ..... Partner .....

Education: Self: GCSE ☐ A Level ☐ Higher education ☐ Non ☐

Partner: GCSE ☐ A Level ☐ Higher education ☐ Non ☐

Occupation: Self: ..... Partner: .....

Was this pregnancy planned? YES ☐ NO ☐

Contraception: Combined pill ☐ Progestogen-only pill ☐ Contraceptive injections ☐

Male & female condoms ☐ Contraceptive implant ☐ Contraceptive patch ☐

Diaphragm & caps ☐ Intrauterine device ☐ Natural Family Planning ☐

None ☐

Type 1 Diabetes: Maternal father ☐ Maternal mother ☐ Maternal siblings ☐

Paternal father ☐ Paternal mother ☐ Paternal siblings ☐

Type 1 Diabetes: Maternal father ☐ Maternal mother ☐ Maternal siblings ☐

Paternal father ☐ Paternal mother ☐ Paternal siblings ☐

Version 1: 12.09.07 Created by Dr. Y. Min Approved by Professor O. Djahanbakhch

PREVIOUS PREGNANCY

Pre-pregnancy weight: .....(kg) Height: ..... (m) Body mass index (Wt./H) .....

Number of previous pregnancies: ..... Parity: .....

Offspring: -

Date	Gestation age (weeks)	Gender	Birthweight (gram)	Complications?

Complications: -	YES	NO		YES	NO
Pregnancy induced hypertension	☐	☐	Low birthweight.	☐	☐
Preeclampsia	☐	☐	Small for gestation age	☐	☐
Gestational diabetes	☐	☐	Preterm Delivery	☐	☐
Postnatal depression	☐	☐	Miscarriage	☐	☐
Other	.....				
DRUG HISTORY	YES	NO		YES	NO
Alcohol abuse	☐	☐	Antacid	☐	☐
Recreational drug abuse	☐	☐	Antibiotics	☐	☐
Hard drug abuse	☐	☐	Antidepressant	☐	☐
Diuretics	☐	☐	Analgesics	☐	☐
Antihypertensive agents	☐	☐	Steroids	☐	☐
DIET HISTORY	YES	NO		YES	NO
Anorexia Nervosa	☐	☐	Fad diet	☐	☐
Excessive food intake	☐	☐	Vegetarian	☐	☐
Bulima	☐	☐	Vegan	☐	☐

Version 1: 12.09.07 Created by Dr. Y. Min Approved by Professor O. Djahanbakhch

Other .....

MANAGEMENT OF PREGESTATIONAL DIABETES (This section is for pregestational Type 1 & Type 2 diabetes)

Type 1 diabetes ☐ Type 1 diabetes ☐

Diagnosed in ..... (yyyy) at .....(years old)

Treatment: Diet only ☐ Hypoglycaemic drug ☐ Insulin ☐

If you are on Hypoglycaemic drug: Type of drug..... Dose per day .....

If you are on Insulin: Type of Insulin ..... Dose per day .....

Diabetes related Complications. Nephropathy ☐ Retinopathy ☐ Vasculopathy ☐

GLUCOSE TOLERANCE TEST

Date: ..... (dd) ..... (mm) ..... (yyyy) Gestation weeks: ..... (wks) ..... (d)

Random Plasma Glucose	Glucose Plasma	Glucose at 0 min	HbA	Fructosamine

Version 1: 12.09.07 Created by Dr. Y. Min Approved by Professor O. Djahanbakhch

BIOCHEMICAL AND CLINICAL ASSESMENT

	1ST Trimester (< 15 weeks)	3rd Trimester (28-32 weeks)	Post delivery
Date (dd/mm/yy)			
Gestation week			
Weight (kg)			
Blood pressure (Systolic/Diastolic)			
Haemoglobin			
Random glucose (%)			
HbA1c (%)			
Fructosamine at 1st visit			
Insulin type			
Insulin dose			
Hypoglycaemic agent type			
Hypoglycaemic agent dose			
Minor Hypoglycaemic episode			
Major Hypoglycaemic episode			
Major Hypoglycaemic episode			
Major Hypoglycaemic episode			
Urinary protein			
Anaemia			

PREGNANCY OUTCOME

Date: ..... (dd) ..... (mm) ..... (yyyy) Gestation weeks: ..... (wks) ..... (d)

Delivery mode: Spontaneous ☐ Induction ☐ Episiotomy ☐ Forceps ☐

Vacuum extraction ☐ Elective Caesarean ☐ Emergency Caesarean ☐

Reason for Elective/Emergency Caesarean Section

.....

NEONTATE'S RECORD

Hospital Reference No: ..... Name: .....

Gender: Male ☐ Female ☐

Preterm (<37gestation weeks) ☐ Small for gestational age ☐ Low birth weight(<2500g) ☐

Very low birth weight (<1500g) ☐ Hypoglycaemia ☐ Macrosomia ☐

Respiratory distress syndrome ☐ Shoulder Dystocia ☐ Intrauterine growth restriction ☐

Congenial Malformation ☐ .....

Placental weight .....(gram) Observation.....

APGAR score at 10 min .....

	Measurement	Centile
Birth weight (gram)		
Length (cm)		
Head circumference (cm)		
Shoulder circumference (cm)		
Mid arm circumference (cm)		
Abdominal circumference (cm)		
Fat mass		

Version 1: 12.09.07 Created by Dr. Y. Min Approved by Professor O. Djahanbakhch

Appendix 3.8

FOSIP QUESTIONNAIRE Participant UIN: _ _ _ _ _ _ _ _ _

Please tick as appropriate: Gestational age: EDD by scan:

Date 1st meeting: Support:

Follow-up meeting: Support:

Reason engaged:.....

Reason declined:.....

Study group: GDM: ☐ Type DM: ☐ Healthy control: ☐

AN OGTT result: 0min.....120mins..... **PN** OGTT result: 0min.....120mins.....

DOB: ..... **Religion:**..... **Country of birth:**.....

Housing: Owner Private Rent Council Temp Living with relatives

Patient's occupation..... **Partner's occupation**.....

Smoking status: Never smoked ☐ Smoker ☐ Ex-smoker ☐

Ethnicity: All Whites ☐ Afro-Caribbean ☐ Asians ☐

Language:.....**Health Advocate**: .....

Gravida: **Parity:**

Height (cm):..... **Weight (kgs):**.....**BMI (kg/m2):**.....

Chronic medical problems: Yes ☐ No ☐

If yes, record:.....

Pregnancy complications: None ☐ Maternal ☐ Foetal/Neonatal ☐

IUGR by scan ☐ Big baby by scan ☐ Congenital abnormality ☐

Malpresentation ☐ PIH, Pre-eclampsia or Eclampsia ☐

Presumed foetal compromise ☐ Other ☐

Diabetes management: On recruitment ☐ Pre-delivery ☐

HBA1c: On recruitment ☐ Pre-delivery ☐

Pregnancy maternal outcomes: Date of delivery …… Time:……hrs

Onset of labour: Spontaneous ☐ Induced ☐ Elective caesarean ☐

Induction of labour: Yes ☐ No ☐

Indications for IOL: Postdates ☐ Diabetes related ☐

Premature /Prolonged Rupture of membranes ☐

Hypertension, PIH, Pre-eclampsia or Eclampsia ☐

Foetal Reasons ☐ Other ☐

Mode of delivery: Vaginal ☐ Instrumental ☐ Caesarean section ☐

Reason for assisted delivery / caesarean: ……

Birth maturity (weeks): Extremely Preterm (<28) ☐ Very Preterm (28-31) ☐

Moderate Preterm (32-36) ☐ Term (37-40) ☐ Post-maturity (≥41) ☐

Birth outcome: Full term birth ☐ Preterm birth ☐ Stillbirth ☐

Neonatal death ☐ Miscarriage ☐

Birth Weight : ……grams **Apgar:** 1min…… 5mins…… 10mins……

Admission to SCBU: Yes ☐ No ☐

Reasons for admission to SCBU:

Hypoglycaemia ☐ Respiratory Distress Syndrome ☐

Prematurity ☐ Poor feeding/Jaundice ☐

Abnormality ☐ Suspected Infection ☐

Comments:……

Appendix 3.9

East London & The City HA Local Research Ethics Committee 3
1st Floor, Aneurin Bevan House
81-91 Commercial Road
London
E1 1RD

Telephone: 020 7655 6822
Facsimile: 020 7655 6855

29 August 2006

Professor Ovrang Djahanbakhch
Director of Women and Child health
Newham General Hospital
Glen Road
London
E13 8SL

Dear Professor Djahanbakhch

Full title of study: **Dietary fish oil supplementation to improve maternal and foetal status in diabetic pregnancy**

REC reference number: **06/Q0605/89**

The Research Ethics Committee reviewed the above application at the meeting held on 17 August 2006.

Documents reviewed

The documents reviewed at the meeting were:

Document	Version	Date
Application	1	25 July 2006
Investigator CV	1	25 July 2006
Protocol	1	27 July 2006
Covering Letter	1	25 July 2006
Compensation Arrangements	1	08 June 2006
Letter of invitation to participant	1	15 May 2006
Participant Information Sheet	1	15 May 2006
Participant Information Sheet: For GPs	1	15 May 2006
Participant Consent Form	1	15 May 2006
Checklist	1	25 July 2006
SL3 Invalid letter	1	12 July 2006

Provisional opinion

The Committee would be content to give a favourable ethical opinion of the research, subject to receiving a complete response to the request for further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to a meeting of the Sub-Committee of the REC

Further information or clarification required

The Committee thought the Patient Information Sheet/Protocol were not well written and agreed a provisional opinion subject to receipt of further information or clarification as follows:

When submitting your response to the Committee, please send revised documentation where appropriate underlining or otherwise highlighting the changes you have made and giving revised version numbers and dates

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 27 December 2006.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

06/Q0605/89	Please quote this number on all correspondence

Yours sincerely

Dr David Ingram
Chair

Email: lesley.perry@nelondon.nhs.uk

Copy to: European Commission
DG RTD-D2 SDME 3/24, Brussels
[R&D Department for NHS care organisation at lead site]

Appendix 3.10

Newham University Hospital NHS
NHS Trust

Professor Djahanbakhch
Women's & Family Health
NUHT

Research & Development Office,
C/o Academic Centre,
NEWHAM GENERAL HOSPITAL
Glen Road, Plaistow,
E13 8SL.

Tel: 0207 363 8923 / 9266 Direct Line
Fax 020 7363 9463 external (3463 internal)
Email joanne.morris@newhamhealth.nhs.uk
Yvonne.nicholas@newhamhealth.nhs.uk
shanti.vijayaraghavan@newhamhealth.nhs.uk
Dr Shanti Vijayaraghavan, Director of Research & Development (R&D).
Dr Joanne Morris, R&D Manager.
Mrs Yvonne Nicholas, R&D Co-ordinator

26th April 2007

Dear Ovrang,

Re: **Dietary fish oil supplementation to improve maternal and foetal nutritional status in diabetic pregnancy.** Sponsor: European Union Framework Programme 6.

Thank you for providing us with information concerning the above study. This letter is to confirm that the Trust has approved the study and, is providing indemnity to cover the involvement of Newham University Hospital NHS Trust staff. The approval is provided on the understanding that the **'European Commission' has agreed to act as sponsor**, as set out in the Research Governance Framework and has ensured adequate overall indemnity and monitoring arrangements. In addition, as the lead investigator for the study at Newham, you must ensure adherence to the ethically approved study protocol and responsibilities outlined in the 'Research Governance Framework for Health and Social Care', 2nd Edition, DH April 2005 (please see the attached summary of responsibilities; full document available from: http://www.dh.gov.uk/PolicyAndGuidance/ResearchAndDevelopment/ResearchAndDevelopmentAZ/ResearchGovernance/fs/en)

Please inform us if your project is amended and you need to re-submit it to the ethics committee **and when the project terminates**. This is necessary to ensure that your approval and indemnity are valid and also helps the office to maintain up to date records. Should any untoward events or incidents occur then it is essential that you immediately contact the Trust Risk Management Team (020 7363 8507 / 8417) and the R & D Office at Newham. We would also ask that you keep us informed of any publications or final reports that are produced as a result of the research.

Please do not hesitate to contact either Dr. Joanne Morris (R&D Manager) on 020 7363 8923 or myself on 020 7363 8001 if you have any further questions.

With best wishes for the study,

Dr Shanti Vijayaraghavan,
Director of R&D

Cc Professor Michael Crawford, Institute of Brain Chemistry and Human Nutrition.
Jane Ely, Director of Women's and Family Health, Diane Jones, Head of Midwifery,
Dr Essam Elmahdi, Clinical Fellow, Obs & Gynae, NUHT.

Notice of Substantial Amendment (non-CTIMPs)	1	24 July 2008
Covering Letter		01 August 2008

Membership of the Committee

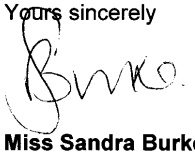
The members of the Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

06/Q0605/89:	**Please quote this number on all correspondence**

Yours sincerely



Miss Sandra Burke
Committee Co-ordinator

E-mail: sandra.burke@thpct.nhs.uk

Enclosures — List of names and professions of members who were present at the meeting and those who submitted written comments

Copy to: — Dr Joanne Morris, Newham University Hospital NHS Trust

Appendix 3.11

Newham University Hospital NHS
NHS Trust

Professor Djahanbakhch
Women's & Family Health
NUHT

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C/o Academic Centre,
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Dr Shanti Vijayaraghavan, Director of Research & Development (R&D).
Dr Joanne Morris, R&D Manager.
Mrs Yvonne Nicholas, R&D Co-ordinator

26th April 2007

Dear Ovrang,

Re: **Dietary fish oil supplementation to improve maternal and foetal nutritional status in diabetic pregnancy.** Sponsor: European Union Framework Programme 6.

Thank you for providing us with information concerning the above study. This letter is to confirm that the Trust has approved the study and, is providing indemnity to cover the involvement of Newham University Hospital NHS Trust staff. The approval is provided on the understanding that the **'European Commission' has agreed to act as sponsor**, as set out in the Research Governance Framework and has ensured adequate overall indemnity and monitoring arrangements. In addition, as the lead investigator for the study at Newham, you must ensure adherence to the ethically approved study protocol and responsibilities outlined in the 'Research Governance Framework for Health and Social Care', 2nd Edition, DH April 2005 (please see the attached summary of responsibilities; full document available from: http://www.dh.gov.uk/PolicyAndGuidance/ResearchAndDevelopment/ResearchAndDevelopmentAZ/ResearchGovernance/fs/en)

Please inform us if your project is amended and you need to re-submit it to the ethics committee **and when the project terminates**. This is necessary to ensure that your approval and indemnity are valid and also helps the office to maintain up to date records. Should any untoward events or incidents occur then it is essential that you immediately contact the Trust Risk Management Team (020 7363 8507 / 8417) and the R & D Office at Newham. We would also ask that you keep us informed of any publications or final reports that are produced as a result of the research.

Please do not hesitate to contact either Dr. Joanne Morris (R&D Manager) on 020 7363 8923 or myself on 020 7363 8001 if you have any further questions.

With best wishes for the study,

Dr Shanti Vijayaraghavan,
Director of R&D

Cc Professor Michael Crawford, Institute of Brain Chemistry and Human Nutrition.
Jane Ely, Director of Women's and Family Health, Diane Jones, Head of Midwifery,
Dr Essam Elmahdi, Clinical Fellow, Obs & Gynae, NUHT.

Appendix 3.12

Newham University Hospital NHS
NHS Trust

DISPENSING OF SUPPLEMENTS PROTOCOL

The Fish Oils Supplementation in Pregnancy (FOSIP) Study

This study is to investigate whether dietary fatty acids (Omega 3 and Omega 6) supplementation during pregnancy improves maternal and neonatal membrane fatty acids status. **Inclusion criteria:** women with Type 1 DM, Type 2 DM and Gestational diabetes (GDM) **and healthy controls.**

Principal Investigator: Professor Djahanbakhch

Dispensing Procedure:

Supplements needs to be dispensed as follows:-

(a) Any woman who has **gestational diabetes** needs to be given up to **bottles x 3 of supplements** with the same code (only 3 bottles available for this group).
(b) Any woman who has **Type 1 and Type 2 diabetes** or from the **'control group'** needs to be given up to **bottles x 7 of supplements** with the same code (7 bottles available for these groups).

1. Prescription needs to be written on the 'pink outpatient's prescription form' and 'FOSIP study' and 'patient's recruitment number' are to be clearly written at the top of the form.
2. Depending on the group that the patient is in, that is, Type 1 diabetes, Control group etc., select the correct bottle of supplements.
3. After selecting the bottles of supplement needed, affix Newham University Hospital NHS Trust pharmacy sticker.
4. Then write on patient's name, D.O.B., study number and date of issue.
5. Complete and sign the 'dispensing of medication record sheet'.
6. File the original copy of the prescription form in the woman's buff folder and the duplicate in the patient's study file.

Appendix 3.13

Patient information

Healthy Eating for Diabetes and Pregnancy

Nutrition and Dietetics Department

Notes:

Name:

Date:

Dietitian:

Contact Number:

Hospital site:

What Causes Diabetes in Pregnancy?

- Diabetes is a condition where the body is not making enough insulin or the body is less responsive to insulin. Insulin is a hormone that helps to keep **blood glucose (often called blood sugar**) at normal levels.

- When your body cannot make enough insulin your blood glucose levels can rise. As your baby develops and grows, the amount of insulin your body needs increases.

- If your blood glucose levels stay high this may cause problems for you and your baby.

- Following the Diabetes and Pregnancy Healthy Diet and lifestyle advice can help keep your blood glucose within the normal range.

- This diet sheet is designed for people who have pre-existing diabetes and those who develop diabetes during pregnancy. Diabetes developed in pregnancy is called gestational diabetes.

- Gestational diabetes is a type of diabetes which affects pregnant women, usually in their second or third trimester. This generally goes away after giving birth. However, there is an increased risk of developing type 2 diabetes later in life. Maintaining a healthy lifestyle is therefore important to reduce this risk.

An Introduction to Carbohydrates

Which Foods and Drinks Affect Blood Glucose Levels?

All **carbohydrates** affect your blood glucose levels. When you eat these foods, your body digests and breaks them down into glucose that is then released into your bloodstream to be used for energy. Carbohydrates are present in a number of foods and drinks:

- **Starchy foods** such as rice, pasta, noodles, bread, oats, breakfast cereals, starchy vegetables such as potatoes, yam, cassava or plantain, and all food made with flour or grains such as chapattis, rotis and parathas.

- **Sugar or foods and drinks containing sugar** such as sweets, cakes, chocolates, biscuits, fizzy drinks, ice-cream and desserts.

- **Fruit** contains a natural sugar called fructose.

- **Milk & Dairy foods** contain a natural sugar called lactose.

It is important to eat a variety of food groups to make sure you and your baby are getting the vitamins, minerals and nutrients you both need.

The Eatwell Guide, on page 4, shows the proportions of each food group the general population needs for a balanced diet. Your carbohydrate intake may need to be altered during your pregnancy to manage your blood glucose levels as too much carbohydrate can lead to high blood glucose levels.

It is not safe to over-restrict carbohydrate intake in pregnancy as this can cause problems to your baby. Your dietitian can assist you with your portion sizes. If your blood glucose levels rise whilst you are eating the recommended amount of carbohydrates, this is a sign that you need some extra treatment to help your diabetes.

Eatwell Guide
Use the Eatwell Guide to help you get a balance of healthier and more sustainable food. It shows how much of what you eat overall should come from each food group.
Check the label on packaged foods
Each serving (150g) contains
Typical values (as sold) per 100g: 697kJ/ 167kcal
of an adult's reference intake
Choose foods lower in fat, salt and sugars
Eat at least 5 portions of a variety of fruit and vegetables a day
Fruit and vegetables
Choose wholegrain or higher fibre versions with less added fat, salt and sugar
Potatoes, bread, rice, pasta and other starchy carbohydrates
Potatoes
Bagels
Rice
Spaghetti
Eat more beans and pulses, 2 portions of sustainably sourced fish per week, one of which is oily, Eat less red and processed meat
Choose lower fat and lower sugar options
Choose unsaturated oils and use in small amounts
Oils & spreads
Water, lower fat milk, sugar-free drinks including tea and coffee all count.
Limit fruit juice and smoothies to a total of 150ml a day.
Eat less often and in small amounts
Per day 2000kcal 2500kcal = ALL FOOD + ALL DRINKS
© Crown copyright 2016
Source: Public Health England in association with the Welsh Government, Food Standards Scotland and the Food Standards Agency in Northern Ireland

Meals and Snacks

- Eat three regular meals per day, with snacks if hungry. Each meal should be spread throughout the day and should contain a similar amount of starchy foods.
- Eat plenty of vegetables.
- Fruits will affect your blood glucose levels but also provide a variety of vitamins, minerals, and fibre that are important for you and your baby's health. It is therefore important to include fruit in your diet. To limit fruit's affect on your blood glucose, spread your fruit intake across the day and have only one portion of fruit at a time.

Snack Ideas

Snacks can be taken if you are hungry. They can be taken **2 hours** after meals, up to **3 times a day** between meals.

Snacks that <u>will</u> affect blood glucose	*Snacks that <u>will not</u> affect blood glucose*
• One piece of fruit • One digestive biscuit • Two rich tea biscuits/ crackers/oatcakes • One slice of bread/ toast with two teaspoons natural peanut butter/Marmite™/low fat cheese • One small pot of low fat natural or 'diet' yoghurt • One handful of cherry tomatoes • 20g non-sweet popcorn • 30g Bombay mix • One glass of milk • One medium pakora/samosa • One small (3 - 4inches) corn on the cob	• Vegetable sticks, e.g. carrots, cucumber, peppers • Avocado • Houmous • Cream cheese • One hard boiled egg • One small handful of nuts/seeds • One or two thin slices of cheese, preferably low fat • 100g cottage cheese • Olives • Gherkins • Cooked meat, e.g. chicken pieces • Sugar-free jelly

½ pitta bread
2-3 tablespoons rice (basmati/easy cook/brown), pasta, couscous, noodles or mashed potato
2 new potatoes or half a baked potato
½ inch slice of yam or cassava
⅓ of a large plantain or green banana
1 egg size piece of Fufu or maize-meal
2-3 crispbreads or crackers
3 tablespoons of breakfast cereal
1 Weetabix™ or Shredded Wheat™
½ sachet of instant oats or 3 tablespoons of uncooked oats
1 corn on the cob / 3 tablespoons tinned corn kernels

Breakfast cereals
Best Cereal Choices:
Weetabix™, Shredded Wheat™, Plain Porridge (non –sweet), All Bran™, Bran Flakes™

Cereals to Avoid:
Rice Krispies™, Cornflakes™, Frosties™, Crunchy Nut™, Coco Pops™, Honey Loops™ , Cheerios™ (plain), or any sugar or honey coated cereals

cucumber, radishes
3 heaped tablespoons of cooked vegetables, e.g. sprouts, carrots, spinach, broccoli, pumpkin, cabbage
2 broccoli/cauliflower spears

Fruit
2-3 portions per day*
Examples of 1 portion:
*Only eat one portion of fruit at a time and spread portions out across the day

1 medium apple, pear or orange
2 small plums, apricots, or kiwis
1 small or half a large banana
Half a mango or grapefruit
5cm slice of melon
1 slice of pineapple
1 heaped tablespoon dried fruit
1 handful of strawberries, cherries or grapes
Limit fruit juice to maximum of 125ml per day

3 tablespoons of dhal, beans or lentils
2 eggs
4 tablespoons of soya/tofu/vegetable bas meat alternative
1 tablespoon of nuts

Milk and dairy products
2 - 3 portions per day
Examples of 1 portion:
1 glass (200ml) milk – semi skimmed or skimmed cows milk/ calcium fortified soy almond, or rice milk
1 small pot low fat natural or 'diet' yoghu (120 – 150g)
2 thin slices / 1 small matchbox size piec fat cheese (40 – 45g)
2 tablespoons of cottage cheese

Foods to Avoid or Limit

- Foods and drinks high in fat and sugar offer little nutritional value and can lead to excess weight gain.
- Foods high in sugar may cause your blood glucose to rise quickly.
- Try to limit salt in your food, as taking too much salt can increase your blood pressure.

Ways to limit added sugars

- Avoid adding sugar or honey to food and drinks such as tea and coffee.
- If you do not like drinks without sugar, try an artificial sweetener such as **Canderel**™ **or Splenda**™, or a plant-based sweetener such as **Stevia**. When used in small amounts, they have no significant effect on your blood glucose levels.
- Avoid ordinary squash and fizzy drinks – use 'diet' or 'no added sugar' varieties or choose water or low fat milk instead.
- Avoid chocolate, sweets, and sweet desserts.
- Have plain biscuits (e.g. digestive or rich tea) or savoury crackers instead of chocolate or cream varieties.

Ways to limit foods high in fat

- Spread butter and margarine thinly
- Avoid deep fried foods, crisps, pastries
- Remove fat or skin on meat and chicken
- Limit the fat or oil used in cooking

Drinks high in caffeine

High caffeine consumption has been linked to low birth weight babies. Try to have less than 200mg caffeine per day.
Caffeine content of common drinks:

- 1 cup of tea - 75mg
- 330ml can of cola - 40mg
- 1 mug of filter coffee - 140mg
- 1 mug of instant coffee - 100mg
- 250ml can energy drink - 80mg
- 50g bar plain chocolate - 50mg

Weight Gain in Pregnancy

The amount of weight a woman will gain during pregnancy can vary. Only some weight gain is due to increased body fat. The baby, placenta, amniotic fluid, and increases in maternal blood and fluid volume all contribute.

The amount of safe weight gain in pregnancy varies according to your body mass index at the start of your pregnancy. Your doctors and midwives will advise you on safe weight targets in pregnancy.

Physical Activity and Exercise

Physical activity can be helpful in managing blood glucose levels and keeping your diabetes under control.

Regular physical activity increases the amount of glucose used by your muscles for energy, so it usually lowers blood glucose levels. It can also help reduce the amount of insulin you need by helping your body use insulin more efficiently.

The general advice for adults is to do 150 minutes of moderate-intensity physical activity each week. For example, going for a 20 – 30 minute walk every day can help to lower your blood glucose levels. If you were regularly active before your pregnancy, continue your pre-pregnancy activity but please discuss this with your midwife.

Foods to Avoid in Pregnancy

Some foods need to be avoided during pregnancy due to the risk of harm to yourself and your baby. You should avoid:

Mould ripened and blue veined cheeses	For example Brie, Camembert, Stilton and Danish Blue.
Liver and liver products	All foods containing liver including liver pate and liver sausage.
Pate or terrine	Including meat, fish, and vegetarian pate or terrine.
Raw or undercooked meat	Make sure it is not pink and there is no trace of blood.
Raw or partially cooked eggs	Make sure the yolk and white are solid and avoid any dishes containing raw egg.
Except for British Lion Code Eggs	**Provided eggs are produced under the British Lion Code,** they are considered very low risk and safe to eat raw or partially cooked
Unpasteurised milk or cheese	Including cheeses made with unpasteurised milk from cow, sheep or goats sources.
Raw shellfish and some types of fish	Avoid shark, swordfish and marlin completely.
Limit intake of oily fish	Eat no more than 2 portions per week of oily fish such as, mackerel, pilchards or salmon. These fish contain high levels of mercury. Limit your intake of tuna to 2 steaks or 4 medium size cans a week.

Note: you can eat peanuts during pregnancy unless you have a nut allergy

Preparing Foods

- Wash your hands before preparing food and wash your hands, surfaces and utensils after preparing raw meat.
- Wash fruit, vegetables and salads to remove all traces of soil.

- Keep leftovers covered in the fridge and use within two days.
- Heat ready meals and leftovers until they are piping hot.
- Check the 'use by' and 'best before' dates on foods and store as advised on the label.

Vitamins and Minerals in Pregnancy

- **Folic Acid** is important during pregnancy to reduce the risk of neural tube defects. Women with pre-existing diabetes and gestational diabetes should take a **5mg folic acid** supplement every day before conception and for the first 12 weeks of pregnancy.

- **Vitamin D** helps to absorb calcium which we need for healthy bones and teeth, and also maintains a healthy immune system. All pregnant and breastfeeding women should take a supplement of **10µg Vitamin D or 400 IU's** or **prenatal vitamins** containing **10µg/d** to maintain adequate vitamin D stores during pregnancy and breastfeeding. Examples include **Healthy Start Vitamins** or **Pregnacare** (both contain 10µg/d vitamin D)

- **Iron** has many important roles in the body. Not getting enough iron can make you tired and lead to anaemia. Red meat, sardines, kidney and eggs are good sources of iron. Dark green leafy vegetables, beans, lentils, nuts such as almonds or pistachio, and dried fruit also contain iron.

- **Calcium** is important for healthy bones and teeth. Dairy products and fish with edible bones, such as sardines, are the best sources of calcium in the diet. Alternative sources of calcium include calcium-enriched milk alternatives, such as unsweetened soya/nut/oat milk.

If you are concerned about your intake of these vitamins and minerals, speak to your doctor.

Large print and other languages

This information can be made available in alternative formats, such as easy read or large print, and may be available in alternative languages, upon request. For more information, speak to your clinical team.

এই তথ্যগুলো সহজে পড়া যায় অথবা বৃহৎ প্রিন্টের মত বিকল্প ফরম্যাটে পাওয়া যাবে, এবং অনুরোধে অন্য ভাষায়ও পাওয়া যেতে পারে। আরো তথ্যের জন্য আপনার ক্লিনিক্যাল টিমের সাথে কথা বলুন।

Na żądanie te informacje mogą zostać udostępnione w innych formatach, takich jak zapis większą czcionką lub łatwą do czytania, a także w innych językach. Aby uzyskać więcej informacji, porozmawiaj ze swoim zespołem specjalistów.

Macluumaadkaan waxaa loo heli karaa qaab kale, sida ugu akhrinta ugu fudud, ama far waa weyn, waxana laga yabaa in lagu heli luuqaado Kale, haddii la codsado. Wixii macluumaad dheeraad ah, kala hadal kooxda xarunta caafimaadka.

Bu bilgi, kolay okunurluk veya büyük baskılar gibi alternatif biçimlerde sunulabilir, ve talep üzerine Alternatif Dillerde sunulabilir. Daha fazla bilgi için klinik ekibinizle irtibata geçin.

مہیں پڑھنے کے لیے آسان، بڑا پرنٹ یا دیگر متبادل زبانوں میں بھی دستیاب ہو سکتی ہیں۔ مزید معلومات کے لیے، اپنی کلینکل ٹیم سے بات کریں۔

Tell us what you think