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Imperial College London

PROTOCOL

EFFECT OF FIBRE SUPPLEMENTS ON GESTATIONAL DIABETES

The use of soluble fibre for the prevention of gestational diabetes among high-risk women. A pilot study.

Main Sponsor	Imperial College London
Funders	Department of Investigative Medicine, Imperial College

Protocol authorised by

Professor Gary Frost,

Professor of Nutrition and Dietetics,

Department of Investigative Medicine,

Hammersmith Hospital Campus, Imperial College,

6th Floor, Commonwealth Building,

Du Cane Road, London,

W12 0NN

Professor Anne Dornhorst,

Professor of Endocrinology and Diabetes,

Department of Investigative Medicine,

Hammersmith Hospital Campus, Imperial College,

6th Floor, Commonwealth Building,

Du Cane Road, London,

W12 0NN

Dr. Lilian Mendoza Mathison,

Clinical Research Physician,

Department of Investigative Medicine,

Hammersmith Hospital Campus, Imperial College,

6th Floor, Commonwealth Building,

Du Cane Road, London,

W12 0NN

Effect of Fibre Supplements on Gestational Diabetes

Long title

The use of soluble fibre for the prevention of gestational diabetes among high-risk women. A pilot study

Study Management Group

Chief Investigator	Professor Gary Frost
Co-investigators	Professor Anne Dornhorst, Dr. Lilian Mendoza Mathison
Study Management	

Sponsor

Imperial College is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance Manager at:

Room 215

Level 2, Medical School Building

Norfolk Place

London

W2 1PG

http://www.imperial.ac.uk/joint-research-compliance-office/

Clinical Queries

Clinical queries should be directed to Gary Frost who will direct the query to the appropriate person.

PROBLEMS RELATED TO THIS TRIAL SHOULD BE REFERRED TO PROFESSOR GARY FROST

g.frost@imperial.ac.uk

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1. GLOSSARY OF ABBREVIATIONS

GDM	**Gestational diabetes mellitus**
BMI	**Body mass index**
GI	**Glycaemic index**
T2DM	**Type 2 diabetes mellitus**
OGTT	**Oral glucose tolerance test**
FPG	**Fasting plasma glucose**
IS	**Insulin sensitivity**
UCPCR	**Urinary C-peptide creatinine ratio**
PCOS	**Polycystic ovarian syndrome**
GAD	**Glutamic Acid Decarboxylase**

2. KEYWORDS

Gestational diabetes mellitus
Risk factors
Diet
Soluble fibre
Insulin sensitivity
Insulin secretion
Insulin treatment

1. STUDY SUMMARY

TITLE The use of soluble fibre for the prevention of gestational diabetes among high-risk women. A pilot study.

AIMS The primary aim of this study is to evaluate the effect of a soluble fibre supplement in the development of gestational diabetes in women at high-risk. The secondary aim will to evaluate the effect of the soluble fibre supplement on glycaemic control in high-risk women who develop gestational diabetes in early pregnancy.

DESIGN We plan to conduct a randomised single-blinded controlled study to evaluate the effect of the consumption of soluble fibre, from early to mid-pregnancy, on the incidence of gestational diabetes, insulin sensitivity, insulin secretion and metabolic control in GDM diagnosed participants.

POPULATION We will be studying women with diagnosis of gestational diabetes in previous pregnancies, (considered as high-risk) aged >18 years.

ELIGIBILITY Women over 18 years old with a history of gestational diabetes in previous pregnancies will be eligible to apply to this study. After first assessment, eligible women will be split according to their glycaemic status in women with and without early gestational diabetes.

TREATMENT Participants in the treatment arms will be taking 5 gr of Guar gum fibre supplement with meals three times a day (total daily 15 g). Participants in the placebo arms will be taking 5 gr of Cellulose three times a day (total daily dose 15 g).

DURATION Participants will be involved for 12 weeks.

OUTCOME MEASURES

<u>In women with normal glucose tolerance at first assessment:</u>

Primary outcome: Gestational diabetes (yes/no) at 28 weeks gestation.

Secondary outcomes: Insulin sensitivity and insulin secretion at 28 weeks gestation.

<u>In women with early gestational diabetes (diagnosed at first assessment):</u>

Primary outcome: Glycaemic control assessed the need of insulin treatment (yes/no)

Secondary outcomes: In women requiring insulin treatment: days-to-insulin and total daily insulin dose.

INTRODUCTION

GESTATIONAL DIABETES

Gestational diabetes (GDM), currently define as diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes (1), has been associated with an increased risk macrosomia and other perinatal complications as well as a higher risk for offspring to develop obesity and type 2 diabetes later in life (2). As for the mothers, women with GDM have a significantly increased risk of developing T2DM in the following years (3). According to the 2015 NICE guidelines for diabetes in pregnancy, approximately 5% of the women given birth in the UK each year have either pre-existing or gestational diabetes. Gestational diabetes accounts for most of the cases of diabetes during pregnancy (87.5%) (4) and its prevalence seems to be on the rise. Previous GDM is a well-established risk factor for developing GDM in subsequent pregnancies, with a recurrence rate of over 40% (5,6). It has been described that women with a history of GDM within the previous 5 years have poorer beta cell compensation and show a faster decline in insulin sensitivity compared to their counterparts without GDM (7). In the UK women with previous GDM should be offered early testing in new pregnancies, either by continuous glucose monitoring or by an oral glucose tolerance test (OGTT) before 16 weeks gestation (4).

GLYCAEMIC INDEX AND HIGH-FIBRE DIET

Glycaemic index is a measure of the impact of carbohydrate-containing foods on post-prandial glycaemic excursions. Both epidemiological and clinical trial evidence supports the beneficial effects of low glycaemic index (GI) diets on glucose homeostasis. Diets that are constructed of low glycaemic index foods with a high dietary fibre content may provide additional metabolic benefits than low glycaemic index diets with a low fibre content. Soluble viscous (gel forming) fibres such as Guar gum, have shown to improve glycaemic control. The consumption of Guar gum before meals has shown to lower postprandial glycaemia in both healthy and diabetic subjects (5-7). As for the long term effects, the consumption of Guar gum supplement showed a decreased in fasting plasma glucose, HbA1c, fasting plasma insulin and HOMA-IR in subjects with metabolic syndrome after 6 months (8) and in patients with type 2 diabetes, 15 gr of Guar gum supplement consumed daily for 48 weeks showed an improvement in postprandial glucose, long-term glycaemic control and C-peptide response after a test meal (9).

The beneficial effects of Guar gum on glycaemic control can possibly be explained through various mechanisms. Firstly, the impact on glycaemic control over the first two hours after consumption of food that possibly relates to the impact of soluble viscous fibres on delaying gastric emptying and slowing the digestion of carbohydrate in the small intestine. There is an additional benefit as Guar gum is fermented by the colonic microbiota to short-chain fatty acids which are recently been shown to have important benefits on beta-cell function presumably by stimulating the production of GLP1 (10).

THE ROLE OF HIGH-FIBRE DIETS IN THE PREVENTION AND TREATMENT OF GESTATIONAL DIABETES

In pregnancy, a high dietary fibre intake has been associated with a lower risk of GDM (11), and in healthy pregnant women, a low GI diet has been associated with lower birth weight and a lower

percentage of large for gestational age newborns (12). As for women who develop GDM, high-fibre diets have been associated with an improvement in perinatal outcomes such as macrosomia (12–14) and risk of C-section (13). In this group of women, high-fibre diets have also to significantly reduce the need to commence insulin treatment (13–15). Despite the documented benefits of a high-fibre diet, as women progress through pregnancy there are often changes in food perception and acceptability which makes compliance to specific diets often difficult. A dietary supplement that can be consumed with meals could be an attractive alternative for complying with the recommended dietary fibre requirements. In pregnancy, Guar gum has shown to reduce postprandial glycaemia after an OGTT (16) and in one study, long term consumption of 10 gr a day showed to decrease both fasting and postprandial glycaemia (17). Therefore, it could be considered in the treatment of women with gestational or who are at high risk of developing the condition.

5. RANDOMISED CONTROLLED STUDY

Aim: To evaluate the effect of a soluble fibre supplement in glucose metabolism in pregnant women at high risk of developing gestational diabetes.

Study methodology: 12 week randomised, placebo-controlled, single-blinded study.

Intervention: Women will first be categorised according to their glycaemic status into two groups: GDM and glucose tolerant women. Afterwards, each group will be randomised into two groups and given either

1) Fibre supplement (Guar gum)

2) Placebo (Cellulose)

The participants will take the dietary supplement three times a day for 12 weeks. They will receive regular antenatal control according to NICE guidelines recommendations. Compliance will be addressed by weekly phone calls.

Number of volunteers: The number of participants will be arbitrarily define as no data of this type of intervention exists in this cohort. 40 participants will be recruited. Previous studies, outside pregnancy, have observed metabolic effects in samples of 15-40 subjects.

Recruitment: Women will be recruited in the antenatal clinic at Queen Charlotte and Chelsea's Hospital. An information sheet will be provided to eligible women in the first antenatal visit to explain the purposes of the study. Women who decide to take part will be asked to sign a consent form.

Randomisation: Initially women will be categorised according to glycaemic status in two cohorts: **Glucose tolerant** and **Early gestational diabetes (GDM)** cohort. Each of the two cohorts will then be independently randomised to either intervention or standard care using the sealed envelope website. Guar gum (intervention) and cellulose (placebo) will be provided in identical packed sachets.

STUDY OUTCOME MEASURES

PRIMARY OUTCOME MEASURES

- Glucose values at 0 and 120 minutes during an OGTT performed at 28 weeks in the glucose tolerant group.
- Glycaemic control assessed by need of insulin treatment (yes/no), days to insulin treatment and total insulin dose.

SECONDARY OUTCOME MEASURES

Assessing insulin sensitivity and insulin secretion at 28 weeks of pregnancy in the glucose tolerant cohort of women through validated indices using glucose and insulin (or C-peptide) values derived from the OGTT.

- Insulin sensitivity will be assessed using the Matsuda formula (18).
- Insulin secretion will be assessed by second-void fasting UCPCR as described by McDonald et al (19).

In the gestational diabetes cohort, where a second OGTT will not be performed, parameters of insulin resistance (HOMA_IR index) and secretion could be assessed using urinary C-peptide obtained from a fasting second-void urine sample at 28 weeks gestation, as described by Oram (20), although these measurements have not been validated in pregnancy.

6. ASSESSMENT AND FOLLOW UP

Women will be assess by the researchers at four different visits. At the first antenatal visit, the general care team will mentioned the study, if the patient consents, she will then be approached by the researchers to explain the study protocol. At the second visit, when the OGTT is performed, women who decided to take part in the study will sign the consent from. At the next antenatal visit where results from the OGTT are explained, women included will be randomised. The last research visit will take place at 28 weeks gestation. Additionally, they will be contacted weekly, by telephone to assess compliance and confirm willingness to participate in the study. All participating women will continue to attend routine follow up by the Obstetrics team at the antenatal clinic. Women diagnosed with GDM in early pregnancy will continue their routine care under the Obstetric team at Queen Charlotte's Hospital. We will be collecting information regarding treatment from the notes taken at this follow-up visits.

1st visit (≤16 weeks gestation)

Women with a previous history of GDM will be considered at high risk of recurrence and will be referred to the antenatal clinic before 16 weeks of pregnancy. At this first visit, the direct care team will inform them about the study and ask them if they are willing to speak with a member of the research team. If they agree, a research team member will explain the protocol and invite them to participate in the study. An information sheet will be provided and women will have time to consider if they are willing to participate and inform the research team at their next antenatal visit.

2nd visit

Women who decide to participate will inform the research team when they attend their second antenatal visit, when an OGTT is to be performed. In this visit, women willing to participate will be asked to sign a consent form.

As part of the standard pregnancy care, these women will be booked for GDM early screening. The following investigations will be performed as part of their usual NHS care:

- Blood tests: full blood count, renal function. GAD antibodies can be requested in women in whom type 1 diabetes is suspected.
- Urine sample to test for proteinuria, glycosuria, leucocytes and nitrates.
- Women willing to participate in the study will be additionally requested to provide a second urine sample after the 120 min during the OGTT. When bloods are taken will also request HbA1c as part of the study's investigations.
- An OGTT to test for early GDM will be performed as part of routine care. During the OGTT blood samples are taken at 0 and 120 minutes. Additionally to glucose, which is normally measure during the OGTT, for study purposes we will request serum C-peptide at these time points.

Baseline insulin sensitivity and insulin secretion will be estimated through validated indices using serum glucose, insulin (or C-peptide) and urinary C-peptide.

After the participants have agreed to take part in the study and consent has been signed, data regarding anthropometrics, demographics and medical history will be collected. This information will be obtained by reviewing the participant's medical notes.

Anthropometric measurements will be recorded at the first antenatal routine visit, including: pre-pregnancy weight, weight at first visit and height. BMI will be calculated with this data.

Demographics, personal and medical history will be extracted from medical records, including: maternal age, ethnicity, education, smoking during pregnancy, medical history (hypertension, PCOS, other relevant condition), obstetric history (parity, stillbirth, macrosomia, pre-eclampsia).

3rd visit (Randomisation)

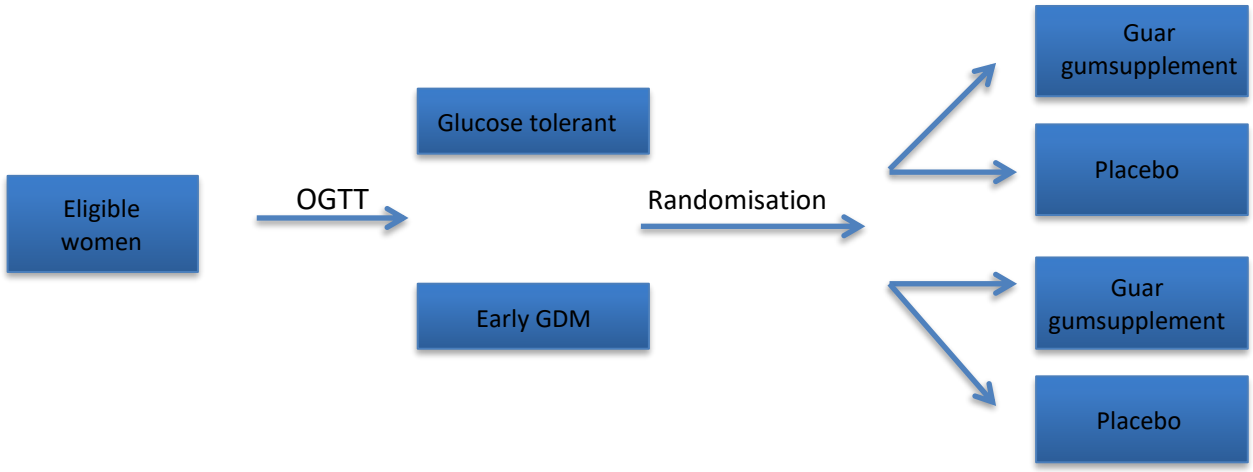
After obtaining the results from the OGTT, women will be categorised by their glycaemic status and divided into two independent cohorts:

- Women diagnosed with gestational diabetes (according to NICE guidelines 2015 diagnostic criteria): **early GDM** cohort
- Women with normal glucose tolerance or impaired glucose tolerance but not fulfilling GDM criteria: **Glucose tolerant** cohort.

Women from each cohort will be randomised into two groups after the results of the OGTT are obtained:

- Intervention group: Guar gum fibre supplement
- Placebo group: Cellulose supplement

Women will the fibre supplement 3 times a day (with each main meal) until the 28th week of pregnancy when they will be re-evaluated.



4rd visit (28th weeks gestation)

Glycaemic status will be assessed at 28 weeks gestation in the two cohorts of women participating in the study:

- Women from the **Glucose tolerant cohort** will undergo a second OGTT. Blood and urine samples will be collected at 0 and 120 minutes. Glycaemic status will then be assessed with the endpoint being the diagnosis of GDM (yes/no). Insulin sensitivity and insulin secretion will be estimated using the same parameters as in the first visit. As part of the study, women will be weight to calculate BMI and gestational weight gain at 28 weeks gestation. The research team will have their last face to face visit with the participant to discontinue the intervention and answer any potential questions about the study.

- In women in the **Early GDM cohort**, glycaemic control will be assessed by the need of insulin treatment (yes/no) and in those requiring insulin the days-to-treatment (insulin) and total insulin dose will be recorded. Data will be obtained by reviewing medical records. As part of the study, women will be weight to calculate BMI and gestational weight gain at 28 weeks gestation. The research team will have their last face to face visit with the participant to discontinue the intervention and answer any potential questions about the study.

PROCEDURES

Women will be advised to fast for 10 hours the night before the oral glucose tolerance test. They will also be advised no to restrict carbohydrate ingestion the three days prior to the OGTT. At the antenatal clinic, blood samples will be collected at baseline (0 min) and at 120 min after the administration of an oral load of 75 g of glucose.

In the baseline sample other parameters will also be determined. Creatinine and HbA1c will measure in all participants and GAD antibodies will be requested in women in whom type 1 diabetes is suspected.

Serum insulin and C-peptide will be collected at 0 and 120 min during the OGTT.

Women will be advised to void their first urine before attending the antenatal clinic. Second-void fasting urine sample will be collected at 0 min during the OGTT. A second urine sample will be collected at 120 min. Urinary C-peptide will measure in these samples will be transfer to boric acid containers, the alliquoted into 1 ml cryotubes ans stored at -80 ºC until analysis. Serum creatinine will be collected at baseline (0 min) and measure in the central lab. The urinary C-peptide creatinine ratio (UCPCR) will be calculated using these data.

ASSESSMENTS

(i) Gestational diabetes

Gestational diabetes will be diagnosed if fasting plasma glucose >5.6 mmol/L and/or 120 min plasma glucose >7.8 mmol/L after the glucose load administered in the OGTT. Women with fasting plasma glucose <5.6 mmol/L and 120 min plasma glucose <7.8 mmol/L will be classified as "Glucose tolerant".

(ii) Insulin sensitivity

Insulin sensitivity will be assessed using the Matsuda index as originally described (18) (Equation 1) and using two modified Matsuda equations in which insulin is substitute by either serum or urinary C-peptide (21,22) (Equations 2 and 3).

Equation 1.

ISOGTT= 10,000 / √ {[FPG x fasting insulin] x [mean glucose x mean insulin during OGTT]}

Equation 2.

ISOGTTC-pep=500,000/√{[FPGxFsC-pep] x [mean glucose x mean sC-pep during the OGTT]}

Equation 3.

ISOGTT-UCPCR=500,000/√{[FPG×FUCPCR $_{pmol/mmol}$] x [mean glucose x mean UCPCR during the OGTT]}

* FPG= fasting plasma glucose. FsC= fasting serum C-peptide. FUCPCR= fasting urinary C-peptide creatinine ratio.

(iii) Insulin secretion

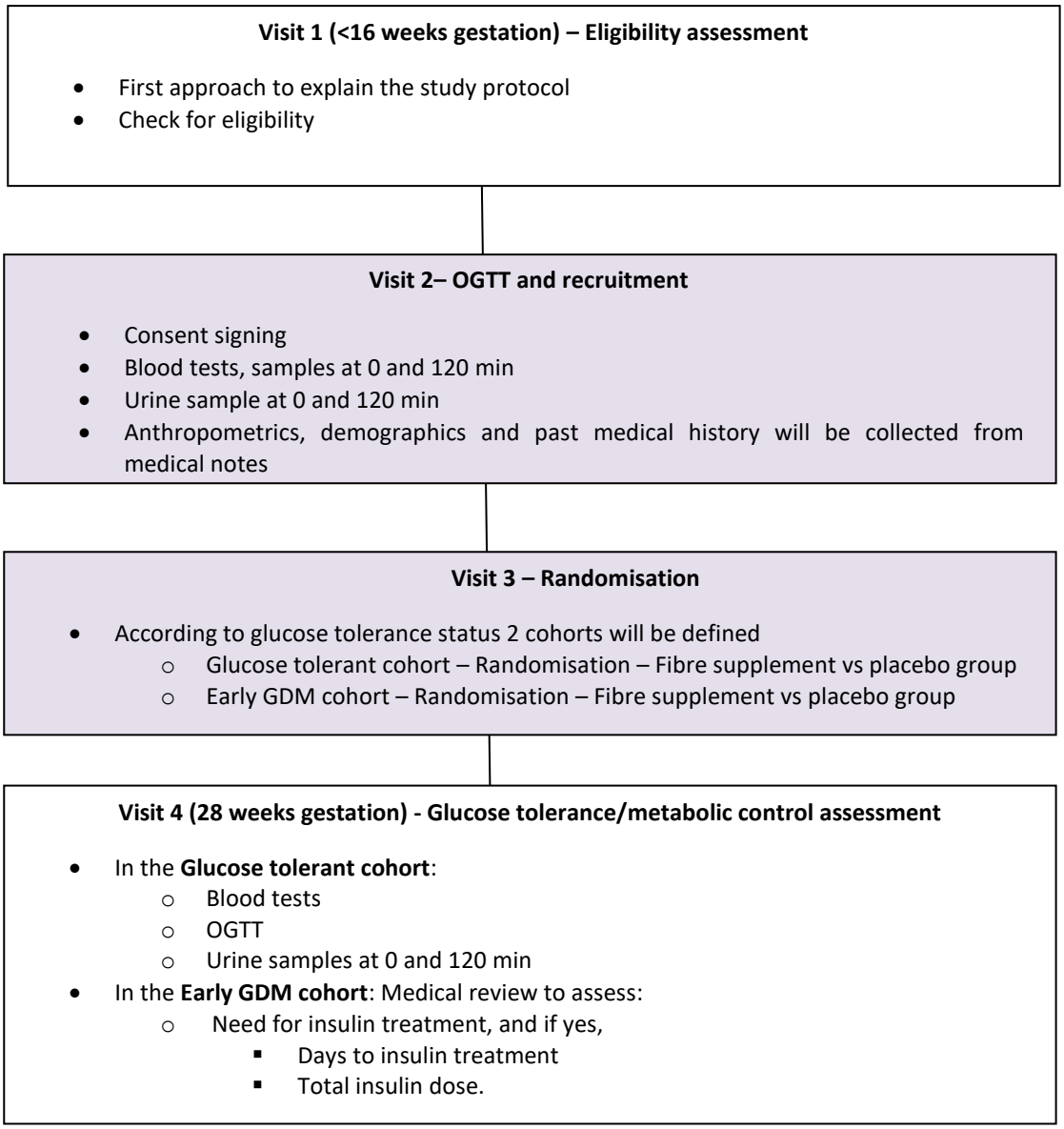
Insulin secretion will be estimated by the UCPCR obtained using the fasting second-void urine sample, as it is strongly correlated with serum insulin, serum C-peptide (19) and 24-h urinary C-peptide (20).

Insulin response will be estimated using the UCPCR calculated with 120 min post-OGTT urine sample, as it is strongly correlated with the C-peptide and insulin area under the curve (19).

(iv) Need of insulin treatment, Days to insulin treatment and Total insulin dose

Medical records of women in the Early GDM cohort will be review in order to determine the need of insulin treatment (yes/no) at 28 weeks gestation. In women requiring insulin treatment at any time during follow up, days-to-insulin treatment, calculated from randomisation day to the day insulin treatment is prescribed, and total insulin dose, calculated as the total dose of insulin international units (IU) divided by weight in Kg (insulin UI/Kg), will be recorded

Timeline for randomised controlled study



7. PARTICIPANT ENTRY

PRE-RANDOMISATION EVALUATIONS

Women will be evaluated by the mid-wife at the first visit in the antenatal clinic. An OGTT will be book to test for early GDM in women with previous GDM considered at high risk of recurrence. Personal and medical history will be recorded. When women attend for the OGTT, blood and urine samples will be collected at 0 and 120 minutes.

INCLUSION CRITERIA

- Women with a history of GDM in previous pregnancies
- Age ≥ 18 years
- Singleton pregnancy
- ≤ 16 weeks gestation

EXCLUSION CRITERIA

- Women unable or unwilling to give consent
- Pre-gestational diabetes or use of anti-diabetic medication in the first visit
- Significant chronic medical conditions (cardiovascular, liver or kidney disease)
- Women participating in other medical trial
- Women who have undergone bariatric surgery
- Women with milk allergy/intolerance
- Women unable to speak/understand English

WITHDRAWAL CRITERIA

Participants will be free to withdraw at any time and are not required to give a reason.

8. ADVERSE EVENTS

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): Any untoward and unexpected medical occurrence that: results in death, is life- threatening, requires hospitalisation, results in persistent or significant disability or incapacity or a congenital abnormality or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

Non serious AEs

All such events, whether expected or not, should be recorded.

Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse, death and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs. All SAEs should be reported to the sponsor.

All SAEs should be reported to the Bromley Research Ethics Committee where in the opinion of the Chief Investigator the event was:

'Related', i.e. resulted from the administration of any of the research procedures; and

'Unexpected', i.e. an event that is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies.

Local investigators should report any SAEs as required by their Local Research Ethics Committee and/ or Research and Development Office.

9. STATISTICS AND DATA ANALYSIS

Data handling and analysis will be carried out by SPSS version 20.0 version.

No power calculation to decide sample size will be used. The number of participants has been arbitrarily defined, as it is a pilot study. We aim to recruit 40 women.

Before randomisation, women will be categorised according to their glycaemic status in two cohorts: Glucose tolerant and GDM. Each of these two cohorts will be randomly allocated into the

intervention (soluble fibre supplement) and control (placebo) group. Randomisation will be by sealed envelopes. Participants but not researchers will be blinded as to the type of intervention prescribed.

Differences between group en each cohort will be assessed using Student t test or Mann-Whitney U test for numeric variables depending on distribution; X^2 will be used for categorical variables.

In the Glucose tolerant women cohort:

For the primary outcome, GDM (yes/no), logistic regression analysis will be performed.

For the secondary outcomes, insulin sensitivity and insulin secretion, linear regression analysis will be performed.

In the early GDM cohort:

For the primary outcome, need for insulin treatment (yes/no), logistic regression analysis will be performed. Additionally days-to-treatment analysis will be performed for those participants starting insulin therapy during follow up.

10. REGULATORY ISSUES

ETHICS APPROVAL

The study has obtained approval from the Bromley Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. After consent is obtained, a letter will be sent to the

participant's GP to inform that she will be taking part in the study. Personal data will only be stored in Trust's files. A specific study code will be used to store anonymised data at Imperial College's Department of Investigative Medicine. Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period. Blood samples will be handled by NHS Trust regular procedures. Urine samples, collected for research purposes will be stored at Imperial College's Department of Medicine until the study is concluded. After analysis, samples will be disposed in accordance with the Human Tissue Authority's Code of Practice.

INDEMNITY

Imperial College holds negligent harm and non- negligent harm insurance policies which apply to this study.

SPONSOR

Imperial College London will act as the main sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

FUNDING

The Department of Investigative Medicine, Imperial College, will be funding this study.

AUDITS AND INSPECTIONS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

GUAR GUM FIBRE SOURCING

Sachets containing 5 gr of partially hydrolised Guar gum fibre will be sourced by Nestle. The product will be stored at room temperature at Imperial College's Department of Medicine.

PLACEBO (CELLULOSE) SOURCING

Cellulose will be sourced by Nestle. The product will be stored at room temperature at Imperial College's Department of Medicine.

11. STUDY MANAGEMENT

The day to day management of the study will be co-ordinated through Dr. Lilian Mendoza Mathison.

12. PUBLICATION POLICY

The findings of the research will be published in an open-access, peer-reviewed journal. In addition we will be collaborating with patient groups and professional groups such as the Society for Endocrinology to disseminate the findings via multiple media channels such as patient association publications, print and broadcast media.

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