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**STUDY PROTOCOL**

**Title: DiGest: Dietary Intervention in Gestational Diabetes**

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**Table of Contents**

**Abstract…………………………………………………………………………………………………………………………………….4**

[1.0 Rationale 5](#_Toc386620945)

[1.1 Background 5](#_Toc386620946)

[1.2 Study Purpose & Objectives 8](#_Toc386620946)

[1.3 Study Hypotheses 8](#_Toc386620946)

[2.0 Study Design 9](#_Toc386620947)

[2.1 Recruitment 9](#_Toc386620948)

[2.2 Inclusion Criteria 9](#_Toc386620949)

[2.3 Exclusion Criteria 10](#_Toc386620950)

[2.4 Withdrawal Criteria .10](#_Toc386620951)

2.5 Intervention & Control ……………………………………………………………………………………………………11

2.6 Outcomes/ Endpoints………………………………………………………………………………………………………13

2.7 Planned Secondary Analyses……………………………………………………………………………………………13

2.8 Study Chronology…………..…………………..……………………………………………………………………………18

2.9 Safety………………………………………………………………………………………………………………………………22

2.10 Milestones………………………………………………………………………………………………………………………..23

2.10 Targets…………………………………………………………………………………………………………………………… 23

3.0 Data Analysis …………………………………………………………………………………………………………………24

3.1 Planned analyses..…………………………………………………………………………………………………..………..24

[3.2 Sample size calculation](#_Toc386620953) …25

[3.3 Recruitment feasibility……………………………………………………………………………………………………..](#_Toc386620953)27

[4.0 Data Handling](#_Toc386620954) 27

[4.1 Protection of Participant Identifiable Information 27](#_Toc386620955)

[4.2 Access to Source Data](#_Toc386620956) 28

[4.3 Storage of data after the study 29](#_Toc386620957)

[5.0 Quality Control & Assurance 29](#_Toc386620958)

[5.1 Laboratory Analysis](#_Toc386620959) 29

[5.2 Record Keeping](#_Toc386620960) 29

[6.0 Ethical Issues 30](#_Toc386620961)

[7.0 Study Funding 3](#_Toc386620962)1

[8.0 Insurance 31](#_Toc386620963)

[9.0 Publication Policy 31](#_Toc386620964)

[10.0 References](#_Toc386620965) 32

**11.0 Appendix 1 & 2 ……………………………………………………… …………………………………………………….34**

**Synopsis of the Study**

**Title: DiGest: Dietary Intervention in Gestational Diabetes**

**Design: Multicentre, prospective, randomised double-blind controlled trial**

**Participants: Women with gestational diabetes**

**Intervention: Standard vs reduced calorie diet, delivered directly to the participant in a dietbox**

**Outcomes: Maternal weight change, 28-36 weeks. Neonatal birth weight standardised for gestational age and sex.**

**Planned sample size: 500 women**

**Treatment duration: From diagnosis of GDM to delivery (maximum16 weeks)**

**Abstract : DiGest: Dietary Intervention in Gestational Diabetes**

# Gestational diabetes affects 35,000 pregnancies annually in the UK, causing adverse outcomes to mother and child, such as large-for-gestational age (LGA) and difficult deliveries. Obesity and excessive gestational weight gain are risk factors for gestational diabetes. However, it is unclear if weight gain remains important in women after diagnosis (28 weeks). National guidelines give no calorie or weight targets to guide management.

# Observational data suggests that women who avoid excessive weight gain during pregnancy, particularly after a diagnosis of gestational diabetes, had improved pregnancy outcomes, needed less medical intervention during labour and gave birth to infants with a healthier birthweight and had lower rates of large-for-gestational- age (LGA). Women with a reduced weight gain after diagnosis also had better postnatal glucose tolerance. This raises the exciting possibility that an 8-10 week intervention in late pregnancy could improve pregnancy outcomes and also reduce maternal diabetes risk long-term.

# This study is a multicentre, prospective, randomised, controlled, double-blind trial to assess the effects of a reduced calorie diet in late pregnancy in women with gestational diabetes. Overweight or obese women with gestational diabetes will be randomised to receive diet boxes containing 1200kcal (reduced calorie) or 2000kcal/day (control) containing all meals from 30 weeks to delivery. Food diaries, continuous glucose monitoring, Bluetooth scales and questionnaires will measure compliance, glucose control, weight changes and quality of life. Women will receive standard antenatal GDM care including regular ultrasound scans and treatment (insulin and/or metformin) as needed. The study will assess if an 8-10 week intervention can reduce maternal weight gain (primary maternal endpoint) and infant standardised birthweight (primary neonatal endpoint). Secondary endpoints include delivery modality, maternal treatment requirements, maternal and neonatal complications and maternal antenatal and postnatal glucose concentrations. The DiGest study is expected to take 4 years with results anticipated in 2022.

# 1.0 Rationale

1.1 Background

Gestational diabetes (GDM) is a common and serious pregnancy-related condition which increases the risk of adverse outcomes for both mother and child and identifies women at risk of type 2 diabetes in later life(1, 2). GDM is usually diagnosed at 24-28 weeks’ gestation and is associated with pre-pregnancy overweight and obesity and excessive gestational weight gain(3, 4). Although excessive gestational weight gain in early pregnancy (0-28 weeks) is well-established as a risk factor for GDM(4), the role of weight control in women after the diagnosis of GDM, from 28 weeks to delivery, is unclear.

Gestational weight gain is a normal part of a healthy pregnancy, but excessive weight gain can contribute to poor outcomes for both mother and child. Excessive gestational weight gain is currently defined using the Institute of Medicine guidelines (2009) based upon a woman’s pre-pregnancy body mass index (BMI)(5). Normal weight, overweight and obese women are advised to gain 11.4-15.9kg, 6.8-11.4kg and 5.0-9.1kg respectively(5). Unfortunately, many pregnant women exceed these targets and have excessive weight gain(6). It is also unclear if these targets are suitable for women with GDM, who are already at higher risk of adverse pregnancy outcomes compared to non-diabetic women(1) and who may benefit from more rigorous targets(7). The guidelines of the National Institute of Health and Care Excellence (NICE) for diabetes in pregnancy highlight the importance of pre-pregnancy and post-partum weight control in women with GDM, but do not mention the importance of controlling gestational weight gain (8), perhaps because targets for weight gain in women with GDM remain unclear. There is therefore limited evidence to guide clinical practice in this area.

Although the optimal level of gestational weight gain is unclear, excessive weight gain has been associated with multiple adverse outcomes. In the general obstetric population (predominantly non-diabetic), excessive gestational weight gain has been associated with hypertensive disorders in pregnancy(9), large-for-gestational age(10), macrosomia(11), depression(12), and may also be linked to infant death(13). In later life, women with excessive gestational weight gain during pregnancy are at increased risk of type 2 diabetes and cardiometabolic disease(14), perhaps because the weight gained in pregnancy is not completely lost after the birth (15). Offspring of women with excessive gestational weight gain have increased body weight, increased fat mass and increased blood pressure in childhood raising concerns about obesity and diabetes risk in later life(16-18).

Women with GDM, pre-pregnancy overweight or obesity may benefit from controlled gestational weight gain in later pregnancy in terms of improving both short and longer term health outcomes. Theoretically, control of gestational weight gain may improve infant birth weight and impact upon postpartum weight retention and future cardiometabolic risk. However, few studies have ever assessed pregnancy outcomes following moderate calorie restriction in women with GDM. It is also unclear how this might be achieved in a practical way, either in real life or in a controlled clinical trial environment.

Attempts to define clear targets for gestational weight gain in women with GDM have been hindered by two concerns: firstly that calorie restriction in pregnancy may be harmful, and secondly, that intervening after 28 weeks is too late. Data from the Dutch Famine Winter cohort have demonstrated that women exposed to severe calorie restriction during pregnancy (<500-800 kcal/day) have infants of lower birth weight who are at higher risk of small-for-gestational-age (SGA) and intrauterine growth restriction (IUGR)(19). However, in clinical and research populations with more modest calorie restriction, there has been no evidence of harmful effects. For example, women with hyperemesis give birth to infants with acceptable birth weights(20). Studies of modest calorie restriction in GDM have demonstrated no adverse effects(21, 22) with SGA rates remaining below those expected for the population(21, 22). There is no evidence of adverse outcomes in moderate calorie restriction in pregnant women with obesity, overweight or GDM. A recent study demonstrated that a reduced calorie diet in pregnant women with GDM is acceptable to patients and associated with good quality of life(23).

Controlling gestational weight gain after 28 weeks gives only a short time for intervention, but previous work has suggested that this still can have beneficial effects upon pregnancy outcomes(22). Overall, gestational weight gain may have an impact upon women’s weight 15 years after the pregnancy(15). There are several studies which support the potential benefits of controlling gestational weight gain after a diagnosis of GDM, and which address the issues of safety and timescales. I have recently completed a retrospective study of 547 women with GDM who gave birth at the Rosie Hospital in Cambridge between October 2014 and March 2017 (Aiken et al., Accepted. See Appendix 1). Overall total gestational weight gain (0-36 weeks) was associated with increased rates of LGA (adjusted odds ratio, aOR 1.08 per kg gained; 95% CI 1.03 to 1.12; p<0.001), Caesarean section (aOR 1.06; 95% CI 1.02 to 1.09; p<0.001), and reduced rates of vaginal deliveries (aOR 0.95; 95% CI 0.92 to 0.98; p<0.001). In addition, I discovered that ‘late’ gestational weight gain (28-36 weeks; n=144) was also associated with multiple adverse pregnancy outcomes, including large for gestational age (LGA; adjusted OR 1.17 95% CI 1.01 to 1.37; p<0.05), instrumental delivery (aOR 1.18 95% CI 1.04 to 1.34; p<0.05) and increased maternal doses of insulatard (long-acting insulin; aOR 1.42 95% CI 0.65 to 2.20; p<0.001). Late GWG was also associated with postpartum glucose homeostasis with a positive association with 2-hour OGTT glucose concentration on the postpartum OGTT (OR 0.12 95% CI 0.01 to 0.22; p<0.05) raising the possibility that controlling GWG for a short 8-10 week period could lead to longer-term beneficial effects upon glucose tolerance and diabetes incidence.

Hodson and colleagues assessed the effects of a low calorie diet in 16 women with GDM upon liver triacylglycerol content(23). Women were recruited at 21-34 weeks’ gestation and followed a 4 week diet supplying 1200 kcal/day (50% carbohydrate, 25% protein, 25% fat). Data for demographic characteristics, method of delivery and other pregnancy outcomes were assessed in comparison to patients with GDM from the maternity database matched for age, body mass index, ethnicity and parity. Women in the intervention group had magnetic resonance imaging of the liver before and after the diet. There was evidence of reduced liver triacylglycerol content after the diet and women also appeared to require less insulin treatment that the comparator group. The diet was well tolerated and women lost a mean of 0.4 ± 0.4 kg per week during the 4 week intervention. The study was not randomised and did not aim primarily to assess pregnancy outcomes, but there was no evidence of adverse outcomes in the intervention group(23). Hodson’s study also demonstrates that calorie restriction in pregnancy is achievable in women with GDM and was well tolerated. The study used a research dietician to give one-to-one support to each participant using a meal plan. Although this was very successful, this methodology placed a high burden on participants and required substantial staff time.

For a clinical trial, I propose to use an alternative, novel methodology to provide a double blind, controlled nutritional intervention using dietboxes. These boxes have become very popular commercially for weight loss and contain all an individual’s meals for the week delivered to their home or workplace. Meals are nutritionally balanced, healthy and appetising and require only minimal time and effort to cook at home. As participants can be randomised to receive a reduced calorie or standard calorie diet box, this overcomes many of the challenges faced in controlling and blinding nutritional studies in free-living volunteers.

This study therefore has real potential to change NHS care for GDM in the next 5-8 years and to improve maternal and neonatal outcomes with no additional NHS expenditure. In fact, there may be cost savings to the NHS, with reduced Caesarean section rates and reduced insulin doses. Women and babies will also benefit: fewer Caesarean sections, reduced instrumental deliveries, faster recovery after birth and reduced interventions – healthier mothers and healthier babies.

## 1.2 Study Purpose, Aims & Objectives

***Purpose of the study***

The purpose of the current study is to evaluate the effect of a reduced calorie diet upon gestational weight gain, maternal and neonatal outcomes in comparison to a standard pregnancy diet in women with GDM. Women diagnosed with GDM will be randomised to receive either 1200kcal/day (reduced calorie diet) or 2000 kcal/day (standard pregnancy diet) using a novel nutritional intervention (dietboxes).

***Aim***

1: To assess the biomedical and psychosocial effects of a reduced calorie diet in late pregnancy (28-36 weeks+) upon maternal and neonatal outcomes in pregnancies affected by gestational diabetes

***Objectives***

1: To assess if a reduced calorie diet in late pregnancy (28 weeks+) can reduce maternal weight gain in women with gestational diabetes

2: To assess if a reduced calorie diet in late pregnancy (28 weeks+) can affect infant birthweight in pregnancies affected by gestational diabetes.

3: To assess if a reduced calorie diet in late pregnancy (28 weeks+) can improve maternal glycaemia (using biochemical measures such as HbA1c and continuous glucose monitoring metrics including average glucose, time in target, time above target, time below target, measures of glucose variability)

4: To assess if a reduced calorie diet in late pregnancy (28 weeks+) can affect maternal treatment requirements in women with gestational diabetes at 36 weeks (metformin and insulin).

5: To assess if a reduced calorie diet in late pregnancy (28 weeks+) can affect maternal and neonatal complications and delivery modality in pregnancies affected by gestational diabetes.

6: To assess if a reduced calorie diet in late pregnancy (28 weeks+) can improve maternal weight and glucose tolerance 6 weeks postpartum in women after gestational diabetes.

7: To assess the safety, tolerability and quality of life aspects of following a reduced calorie diet in late pregnancy (28 weeks+) in women with gestational diabetes

**1.3 Study Hypothesis**

Compared to women taking a standard calorie diet after a diagnosis of gestational diabetes (28-36 weeks of pregnancy):

* Women who have a reduced calorie diet after a diagnosis of gestational diabetes will have reduced weight gain between 28 and 36 weeks of pregnancy
* Women who have a reduced calorie diet after a diagnosis of gestational diabetes will give birth to babies with a significantly lower standardised birthweight
* Women who have a reduced calorie diet after a diagnosis of gestational diabetes will have lower rates of caesarean section and higher rates of normal delivery
* Women who have a reduced calorie diet after a diagnosis of gestational diabetes will have better glucose concentrations during pregnancy and will need less medication to control their gestational diabetes
* Women who have a reduced calorie diet after a diagnosis of gestational diabetes will have reduced weight and lower glucose concentrations postpartum at 6 weeks.
* Women who have a reduced calorie diet after a diagnosis of gestational diabetes will have good quality of life throughout the intervention, comparable to those in the standard calorie control group.

# 2.0 Study Design

## 2.1 Recruitment

## Women will be recruited following a diagnosis of GDM and randomised to intervention or control group. Women will be recruited by research midwives, nurses or by their physician/obstetrician. For training purposes, students in healthcare disciplines (e.g. medicine, biomedical science, nursing, midwifery) may also occasionally recruit patients under appropriate supervision.

## Overweight or obese women who have been referred for an antenatal OGTT between 19-30 weeks of pregnancy will be sent an invitation for the study. Those women who test positive for gestational diabetes according to the NICE guidelines(8) will then be approached again to assess interest in the study. Study documentation will be provided in advance and women who wish to participate will be offered a date to come in and discuss the study and sign the consent forms.

## Throughout the study, participants will receive standard NHS educational sessions and will have standard NHS care, as described in the NICE guidelines(8). Recruitment will be stratified for centre.

## 2.2 Inclusion criteria

## Inclusion criteria are as follows:

## Women with GDM diagnosed at 20 to 30+6 weeks’ gestation using a standard clinical 75g OGTT in accordance with the guidelines of the National Institute of Health and Care Excellence (NICE)(8).

* The NICE criteria state that the diagnosis of gestational diabetes will be made with one or more glucose concentrations during the OGTT of:
  + >5.6 mmol/l in the fasting state
  + >7.8 mmol/l 2 hours after 75g glucose(24).

## Overweight or obese (BMI >25 kg/m2) at time of OGTT.

* A ultrasound-confirmed viable singleton pregnancy
* Planned antenatal care at the same centre or a different study centre throughout their pregnancy (ie: not planning to move away from the region before delivery).

## Exclusion criteria:

## Women will be excluded if any of the following criteria apply:

* Evidence of multiple pregnancy on ultrasound
* Evidence of severe congenital anomaly on ultrasound
* Patient planning to terminate the pregnancy for any reason
* Significant pre-pregnancy diseases or comorbidities which increase risk in pregnancy, for example renal failure, severe liver disease, transplantation, cardiac failure, psychiatric conditions requiring in-patient admission (<1 year).
* Significant complications in the current pregnancy, such as threatened preterm labour, severe anaemia (Hb<8g/dl) or intra-uterine growth restriction (IUGR)
* Previous diagnosis of diabetes outside of pregnancy
* HbA1c at baseline of >48 mmol/mol.
* Medications at the time of the OGTT which may interfere with the results of the OGTT (for example, steroids, immunosuppressants, certain antipsychotics)
* Estimated fetal weight <10th percentile at diagnosis of GDM
* Maternal requirement for a highly specialised diet (e.g. vegan)
* Maternal severe food allergy, for example, a nut allergy causing anaphylaxis
* Weight loss of >5% pre-pregnancy weight during pregnancy, prior to 28 weeks.

**2.4 Withdrawal criteria:**

Women may stop the intervention at any time, according to personal choice. Women who choose to stop the intervention will be encouraged to continue to participate in the study, by attending the 32 and 36 week and postnatal visits.

Women may choose also to withdraw completely from the study at any time. If a participant withdraws consent for ongoing involvement in the study, we will ask for consent to use identifiable data or tissue already collected. Pregnancy outcome data will still be collected, in order to obtain thorough safety information and reporting of adverse events. We will stop collecting and/or remove participant’s data, or tissue already collected from the study at maternal request.

In the event that a participant loses the capacity to consent, the intervention would stop and the participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. Information about pregnancy outcomes will be collected. Information about adverse events will be recorded. We will stop collecting and/or remove participant’s data from the study at maternal request.

**2.5 Intervention & Control:**

Women will be randomised to receive a weekly diet box containing all meals and will be blinded to the overall calorie content (1200kcal/day for intervention group and 2000kcal/day for control group). The dietbox will commence at 1-2 weeks post enrolment and will continue until delivery of the infant. The clinical care team and research team will also be blinded. Women will be told that the study is to compare two different diets to identify which is most suitable for women with GDM. Participants will be warned that there could be initial hunger and weight loss associated with either diet.

The intervention group will receive a 1200kcal box (40% carbohydrate, 25% protein, 35% fat) which will be designed to be nutritionally balanced and low in glycaemic index, low in saturated fat, high in vegetables and protein and suitable for use in pregnancy (no shellfish, uncooked eggs, etc). Women will be asked to eat only items in the dietbox, which will include a range of snacking options in case of hunger. Food will be provided for the following mealtimes:

* Breakfast
* Mid-morning snack
* Lunch
* Mid-afternoon snack
* Dinner

The content of the meals will be developed in collaboration between clinicians, dieticians, nutritionists and a chef. A range of options will be available and women will be able to choose which meals they want each week. In order to ensure that the diets are acceptable to all women, focus groups will be conducted with women from different ethnic and socioeconomic backgrounds.

Examples of the food which will be provided are as follows:

Breakfast:

* Boiled egg and spinach pot
* Scrambled eggs and flaked salmon
* Berries and low-fat yogurt
* Pinhead oatmeal with cinnamon & pecans
* Ham & salami platter with olives
* Cheese, celery and oatcakes
* Dhal and wholemeal pitta fingers

Lunch

* Falafel, hummous and salad
* Harira (Moroccan chickpea & lamb soup)
* Broccoli and cheese soup with breadsticks
* Carrot and coriander soup with pitta bread
* Butterbean and basil dip with vegetable crudites
* Danish-style open sandwich with ham and salad
* Bean chilli with salad
* Cheese and wholemeal crackers
* Herby mushroom bruschetta
* Flaked salmon salad with herb croutons
* Stuffed red or green peppers

Dinner

* Salmon with new potatoes and vegetables
* Low-fat burger with sweet potato wedges
* Steak with mushrooms, red peppers and basmati rice
* Fish with potato wedges and salad
* Chickpea & tomato curry with naan bread
* Thai green curry with chicken and basmati rice
* Chunky minestrone soup
* Roast chicken with olives, herbs and new potatoes
* Fish parcels with oriental vegetables
* Chicken tikka masala and basmati rice
* Sausages and baked potato with onion gravy
* Bolognaise sauce with pasta
* Caponata sauce with aubergine and pasta
* Mushroom stroganoff with basmati rice
* Spiced chicken skewers with vegetables and rice
* Baked sweet potato and rocket with a chilli sauce
* Butternut squash with a herby-breadcrumb crust

Snacks

* Nuts
* Banana
* Apple
* Berry pot with yogurt
* Sugar free jelly with blueberries
* Vegetable crudites with butterbean dip, sour cream and chive dip or hummous
* Digestive biscuits
* Very dark chocolate (~85%)
* Beetroot brownie bites
* Low-sugar flapjack bites.

One of the risks of this intervention is that control women, understanding the importance of weight control in GDM, will work on their own to minimise late gestational weight gain. To overcome this, women in the control group will receive a dietbox containing 2000 kcal/day (also 40% carbohydrate, 25% protein, 35% fat).

The design of the intervention and control boxes is fundamental to the success of this study and to women’s compliance. It is envisaged that the meals supplied will be tasty and appetising and there will be a range of options to allow for a variety of dietary requirements, dietary preferences and ethnic/cultural specifications. Focus groups will be used to ensure the dietboxes are suitable for all women.

Although this is a labour-intensive intervention, it allows a randomised, doubled blinded, fully controlled study design, which is essential to answer the study question in a scientifically valid way. In addition, the use of pre-prepared meals prevents bias as all women receive similar food regardless of educational level, cooking ability, income and kitchen facilities. It also allows control of portion size which is often under-reported in dietary studies.

**Adherence to the intervention/ control dietbox**

The best way of optimising adherence to the dietbox is to ensure that women enjoy the intervention. A system of ordering will be used to give women choice over which individual meals they wish to eat. This system can also be used to get feedback from participants about whether or not they enjoyed the meals from the previous box. A range of healthy snack options will be available to limit consumption of unsuitable foods (high sugar/ high fat).

Unfortunately there is a very limited evidence base for assessing adherence in dietary intervention studies and we have reviewed our plans based on methods most commonly used in other medical or healthcare interventions (for example, ‘Medicines Adherence: Involving Patients in Decisions About Prescribed Medicines and Supporting Adherence’ available at <https://www.ncbi.nlm.nih.gov/books/NBK55447/>, accessed 9/7/2018). However, the literature does emphasise the importance of a non-judgmental attitude and open communication between participant and researcher in order to gain this information in the most helpful way.

Adherence in this study will be assessed using the following methods:

1: The food diary has been updated to include a question asking specifically about adherence. Data from adherence studies for medication has found diaries to be helpful.

2: Participants will receive weekly telephone contact from the research team who will ask specific questions about adherence. The research team will use this information to identify any issues which are resulting in poor adherence, for example, issues with delivery or storage of food, or food preferences.

3: We will also introduce some structured interviews during visits 2 and/or 3 to specifically address adherence (see appendix 3). We will ask participants about:

* Why and when they eat foods not in the dietbox
* What food they choose to eat when eating non-dietbox foods
* What factors are associated with choosing to eat non-dietbox foods? For example, does it happen more often when the participant is tired, stressed, or anxious?
* Particular struggles they have when trying to adhere
* Particular barriers to adherence, for example, eating out, family events, work environment
* Support of family, friends and colleagues and whether this helps adherence

4: Participants’ use of the online food ordering system will provide data about any gaps in ordering the food.

5: Continuous glucose monitoring data will be linked to the food diaries and will identify periods when an undeclared food was likely to have been eaten. Combining information from continuous glucose data and food diaries will give some corroborative indication of self-reported adherence.

## 2.6 Primary Outcomes/ Endpoints

## The aim of the study is to investigate the effects of a reduced calorie diet in late pregnancy upon maternal and neonatal outcomes in pregnancies affected by gestational diabetes. As there are two populations involved in the study – maternal and neonatal populations – there are two primary endpoints.

## The primary outcome for neonatal health is standardised birthweight (birthweight standardised for neonatal sex and gestational age using customised centiles).

## The primary outcome for the maternal population is weight change between study enrolment and 36 weeks of gestation.

**2.7 Planned Secondary Analyses**

Neonatal secondary outcomes:

* Large for gestational age (using local, national and international centiles and customised centiles)
* Small for gestational age (using local, national and international centiles and customised centiles)
* Cord blood C-peptide
* Cord blood glucose
* Amniotic fluid glucose
* Neonatal anthropometry (length, weight, abdominal circumference, head circumference, skinfold thickness, mid upper arm circumference)
* Neonatal body composition (Peapod device)
* Neonatal hypoglycaemia (defined as a low blood glucose requiring intravenous dextrose)
* Neonatal admission to the neonatal intensive care unit (NICU)
* Neonatal feeding type on discharge from hospital
* Neonatal nasogastric feeding
* Duration of neonatal admission
* Neonatal jaundice requiring phototherapy
* Preterm delivery
* Estimated gestational age at birth
* Apgar scores

Maternal secondary outcomes:

* Maternal weight and related measurements at 32 and 36 weeks and postpartum
  + Maternal weight
  + Maternal weight change (baseline to 32 weeks and 32 to 36 weeks)
  + Maternal BMI
  + Maternal weight change (grams per week)
  + Velocity of maternal weight change ( baseline to 32, 36 weeks and postpartum, and between each timepoint)
  + Maternal body composition at 6 weeks postpartum
* Maternal glycaemia on biochemical measurement (HbA1c and other biochemical measures of glycaemia) at 32 and 36 weeks and postpartum
* Maternal glycaemia on continuous glucose monitoring at 32 and 36 weeks
  + Time in target (4.0 – 7.8 mmol/l)
  + Time below target (<4.0 mmol/l)
  + Time below target (<3.5 mmol/l)
  + Time below target (<2.5 mmol/l)
  + Time above target (>7.8 mmol/l)
  + Area under the curve
    - Area under the curve for blood sugars >7.8 mmol/l
    - Area under the curve for blood sugars >6.7 mmol/l
    - Area under the curve for blood sugars <3.5 mmol/L
    - Area under the curve for blood sugars <2.8 mmol/L
  + Incidence of hypoglycaemic events
    - Mild-moderate episodes of hypoglycaemia <3.5mmol/l (mild) and <2.8 mmol/l (moderate) from data for area under the curve <3.5 mmol/l (mild) and <2.8 mmol/l (moderate) and duration of 20 minutes
    - Nocturnal hypoglycaemia: glucose <3.5 mmol/l (mild) and <2.8 mmol/l (moderate) between 23.00-07.00 hours
  + Time in hypoglycaemic range (<4 mmol/l; <2.5 mmol/l)
  + Peak & nadir blood glucose
  + Mean blood glucose
  + Mean nocturnal blood glucose
  + Mean postprandial blood glucose for 1, 2 & 4 hours after breakfast, lunch and dinner
  + Standard deviation of blood glucose
  + Coefficient of variation of glucose measurements
  + Mean amplitude of glycemic excursions (MAGE),
* Ultrasound measurements at baseline, 32 and 36 weeks, measured in absolute values and as a percentile and where relevant, as a categorical variable (<2.5th, <10th, >90th and >97.5th percentile)
  + Abdominal circumference (AC)
  + Estimated fetal weight (EFW)
  + Head circumference (HC)
  + HC/AC ratio
  + Umbilical artery flow studies
  + Velocity of change of AC, HC, HC/AC and EFW
  + Amniotic fluid index
* Cardiovascular variables at 32 and 36 weeks, and postpartum:
  + Blood pressure
  + Mean arterial pressure
  + Heart rate
  + Cardiac output
* Biochemical analysis of maternal blood at 32 and 36 weeks and 6 weeks postpartum:
  + Lipids including triglycerides
  + Insulin
  + Glucose
  + C-peptide
  + Liver function tests
  + Bile acids
  + C reactive protein (including highly sensitive analyses)
  + Metabolomics
  + Nutritional markers
* Indices of insulin production or beta cell function
  + HOMA-IR and HOMA-B scores at 32 and 36 weeks and postpartum.
  + Matsuda scores (postpartum)
  + Stumvoll index
* Maternal complications of pregnancy:
  + Pre-eclampsia
  + Polyhydramnios
  + Oligohydramnios
  + Threatened preterm labour
  + Antepartum haemorrhage
  + Postpartum haemorrhage
  + Cholestasis
  + Abnormal liver function tests in pregnancy
  + Infections
  + Maternal antenatal admissions
  + Pelvic girdle dysfunction
  + Carpal tunnel syndrome
  + Reduced fetal movements
  + Duration of maternal admission at delivery
* Course of gestational diabetes
  + Insulin required (type, dose, time of initiation)
  + Metformin required (dose, time of initiation)
  + Other medication required for glucose control
* Delivery modality
  + Delivery type
  + Timing of labour
  + Duration of labour
  + Induction of labour
  + Pharmacological treatment during induction, labour and delivery
  + Caesarean section rate
    - Elective vs emergency Caesarean sections
    - First vs repeat Caesarean sections
* Maternal quality of life at 36 weeks and postpartum
  + Maternal mobility
  + Maternal self-care
  + Maternal usual activities
  + Maternal pain/discomfort
  + Maternal anxiety and depression
  + Maternal global health rating
  + Changes in quality of life measurements (baseline, 36 weeks and 6 weeks postpartum)
* Maternal eating behaviour (baseline and postpartum)
  + Maternal hunger
  + Maternal emotional eating
  + Maternal uncontrolled eating
  + Maternal restraint
* Food diary analysis at 32 and 36 weeks and 6 weeks postpartum:
  + Reported total calorie input
  + Intake of carbohydrate, protein and fat (g and % of total)
  + Glycaemic index of carbohydrate
  + Saturated vs monounsaturated vs polyunsaturated fat
  + Number of portions of fruit and vegetables eaten per day.
  + Dietary adherence – number, calorie content and nature of non-dietbox foods eaten at 32 and 36 weeks.
  + Timing of non-adherence to dietboxes
  + Effects of non-adherence upon CGM measures of glycaemic control (including all the CGM measurements above)
  + Consistency between reported food intake and CGM glucose concentrations
* Postpartum measurements
  + Postpartum OGTT glucose concentrations and area under the curve
  + Postpartum maternal anthropometry (height, weight, waist circumference, hip circumference, skinfold thickness, mid upper arm circumference)
  + Postpartum fat mass and fat free mass
* Infant feeding choices at 6 weeks postpartum
* Infant feeding behaviour

Additional safety-related analyses:

* Small for gestational age (SGA) and intrauterine growth restriction (IUGR)
* Adverse pregnancy outcomes
  + Stillbirth
  + Neonatal death
  + Major congenital anomaly

Secondary endpoints have been chosen to assess other outcomes of interest, including birth weight, maternal glycaemia, delivery modality and late GWG. Postpartum effects of the intervention will also be assessed at the postpartum visit (6-8 weeks after delivery) including postpartum 2-hour OGTT glucose, lipid profiles and postpartum weight.

A number of safety analyses will also be performed to assess any quantitative difference in effects in adverse pregnancy outcomes. Further qualitative analyses will be used to look at the proportion of women requiring pharmacological treatment for GDM, choice of treatments, dose of treatments and the effect of GWG in early pregnancy at modulating the effect of the intervention in late pregnancy.

Where numbers are sufficient, regression analyses may be performed to look at the impact of pre-pregnancy weight, social deprivation, mental health, physical activity, patterns of glycaemia (eg: fasting vs postprandial hyperglycaemia; nocturnal vs daytime), diagnostic criteria (NICE vs IADPSG) and infant gender upon study outcomes and intervention effect, especially with respect to weight change, LGA rates or adherence to the intervention.

## 2.8 Study Chronology

## The protocol is summarised in figure 1. It is anticipated that women will be seen every 2-4 weeks in the GDM clinic as part of their standard antenatal care. Where possible, research visits will be timed to coincide with clinic visits to reduce inconvenience to the participants.

## Recruitment: At the time of referral for an OGTT, obese and overweight women will receive an introductory flyer about the study. Following the diagnosis of GDM, women will be given a participant information leaflet and an opportunity to discuss study participation with their friends, family and the research team. Women who wish to participate in the study will give written informed consent and will be randomised before 30+6 weeks.

## Study visits: Study visits will occur at enrolment at 32 weeks and 36 weeks during pregnancy and 6 weeks postpartum. The timeline for each participant is as follows:

## Study Visit 1: (approximately 2 hours).

## The participant will have a further detailed explanation of the study, and the opportunity to ask any further questions about the study design or interventions. Patients who agree to participate will then give written informed consent and will be enrolled into the study. At visit 1, the following procedures will be performed:

* Consent form signed
* Baseline weight, height and anthropometry
* Blood pressure
* Fasting blood tests for glucose, insulin, c-peptide, lipids and full blood count and HbA1c. Blood will also be taken and stored for metabolomics, lipidomics and genetic testing.
* Case report form will be completed, including information on pre-pregnancy weight, recent weight changes, normal dietary preferences, dietary requirements, medical and obstetric history.
* 2 weeks’ masked continuous glucose monitoring will commence with detailed explanation to the participant. A wearable activity monitor will be worn at the same time.
* 3 day food diary will commence (25)
* Participants will be given a Bluetooth set of scales on loan
* Questionnaires will be completed:
  + Quality of Life (EuroQuol EQ5D)
  + Eating behaviour (three factor eating questionnaire; TFEQ-18)
* Women’s dietary preferences will be discussed and the first dietbox will be ordered for delivery to the participant’s home
* Women will be randomised to receive either the 1200 or 2000 kcal dietbox.
* The first dietbox will be delivered 1-2 weeks after visit 1, to allow at least 7 days of baseline continuous glucose monitoring to be obtained.

Monitoring period:

Participants will be in weekly telephone contact with the study team. Participants will weigh themselves regularly using the Bluetooth scales and the information will be assessed by the study team. The study team will also enquire about satisfaction with the dietboxes and adherence and will identify any issues which might arise. Participants will also attend their standard antenatal GDM appointments and will follow local hospital policies for monitoring. At their clinic appointments, participants will have:

* Regular weight checks
* Regular ultrasound scans for growth
* Urinalysis

If concerns are identified during the monitoring period, further study visits will be arranged by the research team. This might occur in the following circumstances:

* Crossing down percentiles on ultrasound assessment of estimated fetal weight to around 10th percentile
* Participant has concerns about excessive hunger or other aspects of the diet
* Participant or clinical team identify concerns about weight changes (+/- 5% weight change from pre-pregnancy weight)

Study Visit 2: 32 weeks’ gestation (45 minutes)

The aim of this visit is to assess weight and to identify any issues with the dietboxes or food delivery. The following procedures will be performed at the 32 week visit:

* Weight, and blood pressure
* 2 weeks’ masked continuous glucose monitoring with activity monitoring will commence
* 3-day food diary will commence to allow detailed assessment of the continuous glucose monitoring data
* Questionnaires will be completed:
  + Satisfaction with the dietbox

The participant will also be given the participant information leaflets about placental biopsy, cord blood collection, infant anthropometry examination and infant body composition assessment using the Peapod.

Study Visit 3: 36 weeks’ gestation (45 minutes)

The aim of this visit is to collect information on glycaemia and weight at the end of the intervention period, but before labour has commenced. The study team will discuss with the participant the possibility of taking cord blood, amniotic fluid and placental tissue after labour, should appropriate facilities and staff be present at the time. Infant examination for anthropometry and body composition will also be discussed. These investigations are voluntary and a consent form will be signed at 36 weeks if the participant is willing to have these performed.

The following procedures will be performed at the 36 week visit:

* Weight, anthropometry and blood pressure
* Fasting blood tests for glucose, insulin, c-peptide, lipids, full blood count and HbA1c. Blood will also be taken and stored for metabolomics, lipidomic and genetic testing.
* 2 weeks’ masked continuous glucose monitoring will commence with activity monitoring
* 3 day food diary will commence
* Questionnaires will be completed:
  + Satisfaction with the dietbox
  + Quality of Life (EuroQuol EQ5D)
  + Breastfeeding opinions and intentions

If any concerns are raised at the 36 week visit, for example, about infant growth, or if abnormalities are identified on the blood testing (for example anaemia) a further blood sample may be taken at 38 weeks to allow action to be taken before delivery.

Delivery

Delivery modality and timing will be determined by local protocols in line with NICE guidance. Where possible, participants will be visited by the study team during their admission to allow the following procedures to be performed:

* Sampling of placental tissue
* Sampling of cord blood, cord tissue and amniotic fluid
* Measurement of neonatal anthropometry
* Measurement of neonatal body composition using a Peapod device.

These procedures may not be available at all study sites.

Study Visit 4: 6 Weeks’ Postpartum (2 hours)

## Participants will return at 6 weeks’ postpartum for the last study visit. This visit will replace participants’ standard postnatal glucose testing visit. The following procedures will be performed:

## Weight and anthropometry

## Oral glucose tolerance test (OGTT) with blood testing in the fasting and postprandial state (0, 1 and 2 hours). Blood will be tested for HbA1c, lipids, fasting and postprandial glucose, insulin and c-peptide. Aliquots of blood will be stored for later metabolomic or genetic testing.

## DXA scan for maternal body composition. This procedure may not be available at all study sites.

* Urinalysis; a urine sample will be stored for future batch analysis, for example, for microalbuminuria or metabolomic testing.
* Questionnaires will be completed:
  + Quality of Life (EuroQuol EQ5D)
  + Eating behaviour (three factor eating questionnaire; TFEQ-18)
  + Infant feeding choice will be documented.
* Infant anthropometry will be performed, subject to specific written consent.
* Continuous glucose monitoring and activity monitoring will also be performed at this visit.

## Figure 1: Summary of protocol

## 

**2.9 Safety**

## In this study, the intervention will provide a complete diet which is tailored to women with gestational diabetes and which will meet women’s nutritional requirements throughout pregnancy. Women will be randomised to receive a reduced calorie diet or a standard calorie diet. However, for many women, this diet will be superior to their normal diet. This may be particularly the case for women with lower socioeconomic status, for whom the standard GDM diet can be difficult to achieve within the income available.

Relatively few studies have assessed the effects of a reduced calorie diet in pregnancy but have found moderate energy restriction to be safe in pregnancy. However, in situations of extreme energy restriction, such as might occur during famine, concerns have been raised about fetal growth. Fetal growth will be carefully monitored during the study using ultrasound. Furthermore, the use of Bluetooth scales will also facilitate the early identification of any women who lose unexpectedly large amounts of weight. All adverse events will be documented.

## The intervention will be stopped in the following circumstances:

## If there are signs of severe IUGR (<3rd percentile using customised centiles).

## A further visit will be arranged and the intervention may be stopped in the following circumstances:

## If the participant has gained or lost 10% of pre-pregnancy body weight since randomisation

## If the estimated fetal weight on ultrasound has fallen to the 10th percentile since the intervention commenced.

## If the estimated fetal weight on ultrasound falls by 20 percentiles since the intervention commences and is then below the 10th percentile (i.e. looks small for gestational age).

## In the event that a participant stops the intervention, they will be encouraged to continue to be part of the study and will continue study visits if they are willing. These participants will form part of the final analysis on an intention to treat basis. Participants can withdraw from the study at any time according to personal choice and reasons for withdrawal will be noted.

## A data safety monitoring group (DSMB) and trial steering committee (TSC) have been formed prior to the start of the study. The DSMB will review outcomes after 125 (25%) of participants have delivered their baby, and again at 250 (50%) and 375 (75%). Interim analyses will be performed and reported to the DSMB including rates of severe IUGR, adverse pregnancy outcomes (stillbirth, neonatal death and major congenital malformation) and to identify causes for participant withdrawal.

## 2.10 Milestones

## Start date: 1/9/2018

## Duration: 54 months

End date: 28/2/2023.

## 0 to 12 months: Regulatory approvals, writing study documentation, recruitment of research midwife, design of meals, arranging logistics of meal preparation & delivery

## 12-36 months: Recruitment of women at 4 NHS sites, study visits, database of outcome measures

40 months: Last visit of the last patient.

40-54 months: Analysis and reporting.

## 2.11 Targets:

## 6 months: Regulatory approvals in place.

## 12months: Meal design and delivery logistics in place

12-13 months: Recruitment commenced.

## 36 months: Recruitment completed.

## 40 months: All visits completed for all participants.

40 months: Database completed in preparation for analysis

## 54 months: Report written.

# 3.0 Data Analysis

This is a randomised controlled trial of a nutritional intervention to identify if control of late gestational weight gain (GWG; 28 weeks to term) using a reduced calorie diet can improve maternal and neonatal outcomes in gestational diabetes. The planned analyses for this study have been assessed by Prof Vern Farewell, medical statistician in the MRC Biostatistics Unit. It was also externally peer reviewed with independent statistical input at the Diabetes UK research committee.

**3.1 Planned analyses**

A fundamental requirement for this study is to demonstrate a difference between total energy intake corrected for energy expenditure between control and intervention groups. It is anticipated that this will translate into a difference in late GWG between groups.

Women will be recruited following an abnormal oral glucose tolerance test (OGTT) and those who consent will be randomised to either a 1200kcal or 2000kcal dietary intervention. Randomisation will be stratified according to recruiting centre. Randomisation will be performed by a researcher who is independent of the study team following a process recommended by Prof Farewell. The study will be analysed on an intention to treat (ITT) basis.

The following outcomes will be assessed:

***Neonatal primary outcome***:

* Standardised birth weight (standardised for infant gender and gestational age at delivery)

***Maternal primary outcomes***:

* Maternal weight change (28-36 weeks)

***Secondary outcomes***: see section 2.7 for the full list.

***Additional safety-related analyses:***

* Small for gestational age (SGA) and intrauterine growth restriction (IUGR)
* Adverse pregnancy outcomes
  + Stillbirth
  + Neonatal death
  + Major congenital anomaly

An intention to treat analysis of the primary neonatal outcome will be based on linear regression with adjustment for the stratification variable of study centre through a fixed effects model. Maternal weight change will be examined in a comparable manner. In addition, an analysis of maternal weight change will also be undertaken with weight at study entry as an explanatory variable. The potential role of other explanatory variables such as pre-pregnancy BMI or information from the questionnaires will also be investigated. Secondary outcomes will also be examined through regression analyses (linear or logistic) appropriate for the type of outcome being considered. A further secondary analysis will be performed to assess if any results are altered if early GWG is included in regression models. A number of safety analyses will also be performed to assess any quantitative difference in effects. Rates of SGA/IUGR, stillbirth, neonatal hypoglycaemia and admission to the neonatal intensive care

The sample size takes into account a 20% withdrawal rate. Consent will be taken to collect and analyse outcomes for women who withdraw from the study, to allow assessment of reasons for withdrawal and their bearing upon outcomes.

A per protocol analysis will also be performed in participants with >80% compliance to the intervention and at least 4 weeks’ exposure to the intervention. Data will be used in a qualitative way to assess predictors for withdrawal or poor compliance.

**3.2 Sample size calculation**

Retrospective data assessing the effect of late GWG upon pregnancy outcomes has been used to inform the sample size calculation (Aiken et al. Submitted to press. Appendix 1). Further details on the data used to generate sample size calculations are given in table 1. The following sample size examples are based upon alpha 0.05 and power 0.9.

In the retrospective study, women had a standard deviation of 2kg for late GWG and <3kg for total GWG. Allowing for a standard deviation of 3kg and a 1kg difference between groups, 190 women per group will be required to give 90% power for the primary maternal endpoint.

The neonatal primary endpoint will be standardised birthweight. Recruitment of 175 women per group will give 90% power for identification of a 0.3 sd difference in standardised birthweight. As the standard deviation for birthweight was 508g, this broadly equates to a difference in birthweight of 150g.

A study size of 500 participants will provide sufficient statistical power and will allow for a 20-25% withdrawal rate. This sample size will also gives sufficient power to detect secondary outcomes:

* To identify an increase in LGA (OR 2.25 at 80% power)
* To identify a difference in maternal glycaemia
  + To identify a 2 mmol/mol difference in maternal HbA1c at 36 weeks at 90% power
  + To identify a 0.3 mmol/l difference in mean glucose measured using continuous glucose monitoring
  + To identify a 8% difference in time in target (3.5-7.8mmol/L) on continuous glucose monitoring (This difference of more than 100 minutes per day in target range is associated with clinically relevant differences in neonatal outcomes)(26).
  + To identify a 0.7 mmol/l difference in maternal postnatal 2-hour OGTT glucose.
* To identify a 15% difference in caesarean section rates
* To identify a 0.7 mmol/l difference in postnatal post-load glucose concentrations.

Table 1: Sample size and statistical power.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Expected Values** | | | | **Expected difference**  **C vs T** | **n required per group** | | **Data Source** |
|  | **C mean** | **C sd** | **T mean** | **T sd** | **90% power** | **80% power** |
| **Primary Maternal Endpoint** |  |  |  |  |  |  |  |  |
| Weight change (28-36 weeks) | 4 | 3 | 3 | 3 | 1 kg | 190 | 142 | Comparing first to third terile for late GWG, Aiken et al . Standard deviation 4.75 overall, 3.7 removing single outlier. However, tertiles which kept weight broadly stable had sds of 0.92 and 1.45. |
| **Primary Neonatal Endpoint** |  |  |  |  |  |  |  |  |
| Birth weight z score | 0.3 | 1 | 0 | 1 | 0.3 sd | 175 |  | Aiken et al., sd overall 508g. 0.3 sd broadly equates to 150g difference between groups |
| Birth weight | 3320 | 508 | 3170 |  | 150g difference | 234 | 175 |  |
| **Secondary Neonatal outcomes** |  |  |  |  |  |  |  |  |
| LGA | 16% |  | 8% |  | Expected OR 2.25 | 263 | 197 | 6% and 16% in Aiken et al., |
| **Secondary Maternal Outcomes** |  |  |  |  |  |  |  |  |
| Maternal glycaemia - HbA1c | 36 | 5.6 | 34 | 5.6 | 2 mmol/mol | 165 | 124 | CUH data shows HbA1c average 36 mmol/mol at diagnosis of GDM. |
| Maternal glycaemic – CGM  Average blood glucose | 6.3 | 1 | 6 | 1 | 0.3 mmol/l | 234 | 175 | Yogev et al - normal wt non-diabetic pregnancy women mean 6.1mmol/l sd 0.9. Conceptt 6.7 sd 0.9. But Yu et al 2014 in GDM - mean 5.7 mmol/l sd 0.5-0.7 at 32 weeks. Limited data in GDM, see Cypryk et al., 2006. |
| time in target % | 88% |  | 96% |  | 8% difference | 237 | 177 | 68 +/- 13 from Conceptt in T1DM with CGM at 34 weeks. Yu used targets 3.3-7.8mmol/l: 95% time in target |
| time above 7.8 mmol/l % | 6% |  | 18% |  | 12% difference | 149 | 112 | 27 (IQR 19-37) from Conceptt in T1DM with CGM at 34 weeks (Feig et al). 60 minutes per day, (IQR 0-111) = 4.2% |
| Caesarean section | 50% |  | 35% |  | 15% difference | 224 | 167 | Aiken et al showed 33 vs 50% in overweight women. |
| Postpartum 2hr glucose | 6 | 2.23 | 5.3 | 2.23 | 0.7 mmol/l difference | 214 | 160 | Aiken et al GWG |

## 3.3 Recruitment feasibility

Patients with a recent diagnosis of gestational diabetes will be recruited from Peterborough City Hospital (PCH), Hinchingbrooke hospital, Huntingdon (HH), Norfolk & Norwich University Hospital (NNUH) and Addenbrooke’s Hospital, Cambridge (ADH). Annual rates of GDM diagnosis are between 200-400 women at each site.

In order to complete recruitment in a 24 month period, each site will aim to recruit 5 women per month. This requires a 15-20% recruitment rate. Discussions with the patient-public involvement panel have suggested that the study is likely to be acceptable to many women and that the possibility of having 8-10 weeks of free high-quality food would be a great incentive.

Recruitment will be reviewed monthly in order to assess if this target is likely to be met. If there is concern that recruitment rates are below this figure, additional local sites will be approached and asked to participate. 3-4 local sites have been identified which could join the study if recruitment is suboptimal.

A range of planned measures will be taken to support and maintain recruitment, including particular measures to engage potential participants on social media and through publicity in the hospitals. Previous studies have found advertising on hospital research or antenatal ultrasound noticeboards to be extremely helpful.

The staff at the study centres will be supported by the study team and will be updated with regular newsletters and recruitment competitions. Staff at the study centres will be invited to attend regular face-to-face meetings to discuss study progress and to identify any issues at an early stage. Regular visits from the core study team to the study centres will encourage open lines of communication and will promote engagement.

# 4.0 Data Handling

## 4.1 Protection of Participant Identifiable Information

Potential participants will be identified following referral for an OGTT. Women will be invited to participate by a member of their clinical care team and will be given the opportunity to discuss the study with a member of the study team, such as a research nurse or midwife. These members of the study team will also be directly involved in clinical care of women during pregnancy, and these individuals will have full access to patient data and electronic databases for clinical reasons. If the patient wishes to participate in the study, they will be asked if they are willing for any electronic data held on hospital databases (such as glucose results on the laboratory system, or pregnancy information on the obstetric databases) to be used for the purposes of the research study.

After consent is given the following people will have access to patient identifiable information who will all have honorary or substantive NHS contracts or research passports:

* The local member of the study team who recruited the patient at the local study centre
* The chief investigator
* The lead research nurse/ midwife
* The database administrator or research coordinator
* The randomisation team who will assign intervention/control diets and inform the meal preparation team.
* The chef and meal preparation team who will have access to participants’ names and addresses only and limited information about their food preferences or allergies.

After consent is given, all members of the study team will have access to anonymised information about the participants, using an ID code. The lead nurse/midwife and the chief investigator will hold the key to the ID code. Although the database administrator/study coordinator will predominantly deal with non-identifiable data, they will be occasionally required to answer the telephone to participants who have queries or concerns.

Demographic information, questionnaire results and any laboratory results already performed for the participant will be passed to the study team in this anonymised form for interpretation & analysis.

*General points about data collection:*

All data held electronically will be stored on a computer with password protection. All computers used during this study will be password protected and will be in buildings with secured access to card holders only, such as the WTCRF (Wellcome Trust Clinical Research Facility) or IMS (Wellcome Trust – Medical Research Council Institute of Metabolic Science) in Cambridge or the Department of Chemistry, Peterborough City Hospital. Data collection sheets in paper form which may include participants' personal details and contact details will be stored in secure filing cabinets in buildings with controlled access limited to security card holders only. Encrypted memory sticks will be used to transfer data between computers but not for longer-term data storage. Local policies for ensuring confidentiality will be used.

## 4.2 Access to Source Data

The following people will have access to source data:

* The local member of the study team who recruited the patient at the local study centre
* The chief investigator
* The lead research nurse/ midwife
* The database administrator or research coordinator
* Any representatives of the sponsor or members of local or national regulatory bodies who request to view the data for the purposes of quality assurance or safety monitoring.
* Healthcare professionals involved in the participant’s clinical care during or after pregnancy can request access to source data where this is required for safety monitoring for the women or her baby. This might include for example, sharing the results of a mental health assessment with a participant’s GP or CPN to allow appropriate care to be arranged.

Data analysis will take place within the Department of Clinical Biochemistry, WTCRF and IMS at Addenbrooke's Hospital, Cambridge. Analysis will be undertaken by the investigators named in this application. The final database will be anonymised for analysis.

## 4.3 Storage of data after the study

Research data will be stored for 15 years. Personal identifiable data will be stored for 12 months after the end of the study, unless ethical approval has been given for its use in future studies. The data will be stored on password-protected computers within secure areas. Backup stores are provided by the University of Cambridge Clinical School IT Support Service and a CD backup is held in a firesafe. Paper records will be held in secure filing cabinets within buildings or areas accessed using a security badge only.

Storage arrangements for data fall under European legislation (see GDPR PIL v1 30/5/2018 for more details).

# 5.0 Quality Control & Assurance

## 5.1 Laboratory Analysis

Laboratory analysis for the majority of tests will be carried out in the department of clinical biochemistry and the core biochemical assay laboratory in Addenbrooke’s Hospital and Peterborough City Hospital. These are clinical diagnostic laboratories which hold CPA accreditation.

## 5.2 Record Keeping

Participant-identifiable information will be kept for 12 months after the end of the study. The research data will be kept for 15 years.

# 6.0 Ethical Issues

This proposal involves providing a dietary intervention to pregnant women with gestational diabetes. The main ethical concern is that the dietary intervention (in either treatment or intervention group) is associated with adverse events affecting mother or infant, particularly fetal growth and development and for this reason active weight loss during pregnancy is not generally recommended (8). However, a recent Cochrane review evaluating dietary interventions for women with gestational diabetes (27) included three studies assessing the effects of energy-restricted diets (1200-1600 kcal/day) and although there were no significant differences in maternal or neonatal outcomes between the groups, neither was there any difference in adverse outcomes, suggesting that moderate energy restriction is safe.

We are doing this study because we believe that moderate energy restriction is safe, but also because it may be extremely beneficial to mothers and babies. The women who will be recruited for this study are overweight or obese and have already developed at least one weight-related disorder (gestational diabetes). Observational data from our institution (appendix 1) shows clear evidence of benefit to women and infants from restriction of pregnancy related weight gain with much improved pregnancy outcomes. As women with gestational diabetes are at high risk of type 2 diabetes and cardiovascular disease in later life, there is also a strong possibility that a weight-related intervention could improve their future health and create a healthier environment for the whole family.

Although medical science suggests that control of pregnancy related weight gain can improve outcomes, much of the informal advice given to women in pregnancy today is inappropriate for today’s population, with growing rates of overweight and obesity. Women are still sometimes told to ‘eat for two’ even though this is often quite detrimental. We anticipate that there may be resistance among women and their family members about restricting calories during pregnancy due to concerns about fetal growth.

To manage these ostensible risks, we have adopted the following strategy:

* The intervention will be designed to be nutritionally appropriate for pregnant women, and in line with best available evidence for the dietary management of women with gestational diabetes
* The dietary intervention will avoid known teratogens and foods with a risk of *Listeria* contamination
* The dietary intervention tests calorie amounts which have been successfully given to pregnant women with gestational diabetes in the past.
* There will be regular telephone and face-to-face contact between the participants and the study team to identify any concerns with fetal growth at an early stage.
* Ultrasound report will be assessed to identify any growth concerns. Protocols have been written to allow the study team and clinical staff to identify any issues and to guide in immediate management
* Partners and family members will be encouraged to attend study visits and to participate in the ongoing support and encouragement of the participant

Although some women will have concerns about restricting calories, this study offers the opportunity for many women to gain access to a more nutritious diet than they would otherwise have during pregnancy. Current dietary management of gestational diabetes is complex and controversial. Many women are given different advice and struggle to follow it under the constraints of a limited budget, limited time and limited energy in late pregnancy.

A further potential ethical issue involves blood testing. As with all blood testing, there is a small chance that unexpected abnormalities may be identified. This might include a new diagnosis of hypothyroidism or of high cholesterol. If this situation occurred, we would discuss the results with the patient and arrange follow-up testing if needed. If new diagnoses such as hypothyroidism are confirmed which need prompt treatment, we would arrange appropriate treatment with clinicians from the relevant specialty. Although this raises ethical issues, the study gives the opportunity for important conditions to be diagnosed which should benefit women’s future health.

# 7.0 Study Funding

This study is funded by Diabetes UK as part of an intermediate clinical fellowship to Claire Meek (Diabetes UK Harry Keen Intermediate Clinical Fellowship, 17/0005712). Funding for consumables including laboratory testing for markers of glycaemic control has been obtained from the European Foundation for the Study of Diabetes (EFSD/Sanofi Pilot Research Grant Programme).

# 8.0 Insurance

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

# 9.0 Publication Policy

It is intended that the results of the study will be published in the peer reviewed scientific literature and communicated to participants, lay audiences and the wider public through conventional and social media.

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**Appendix 1: Observational data from Cambridge Universities NHS Foundation Trust gestational diabetes clinic. This unpublished data has been submitted to press and remains confidential. The abstract and table (A1) have been included and further details are available by request.**

**Abstract**:

**Objective:**

Excessive gestational weight gain (GWG) increases risk of gestational diabetes mellitus (GDM) but it remains unclear whether weight control after GDM diagnosis improves outcomes. We assessed whether (i) total GWG during pregnancy (0-36 weeks), (ii) early GWG (0-28 weeks; before GDM diagnosis), or (iii) late GWG (28-36 weeks; after diagnosis) are associated with maternal-fetal outcomes.

**Methods:**

546 women with GDM who delivered viable singleton infants at a single UK obstetric centre (October 2014 - March 2017) were included in this retrospective observational study.

**Results:**

Higher total GWG was associated with Caesarean section (n=376; OR 1.05; CI 1.02-1.08, p<0.001) and large-for-gestational-age (LGA; OR 1.08; CI 1.03-1.12, p<0.001). Higher late GWG (28-36 weeks; n= 144) was associated with LGA (OR 1.17; CI 1.01-1.37, p<0.05), instrumental deliveries (OR 1.26; CI 1.03-1.55, p<0.01), higher total daily insulin doses (36w; Beta Coeff 4.37; 1.92-6.82; p<0.001), and higher postpartum 2-hr OGTT concentrations (Beta Coeff 0.12; CI 0.01-0.22, p<0.05). Women who avoided substantial weight gain after GDM diagnosis had 0.7mmol/l lower postnatal 2-hour glucose and needed half the amount of insulin/day at 36 weeks compared to women with substantial weight gain after diagnosis. There were no significant associations between early GWG (0-28 weeks) and pregnancy outcomes.

**Conclusions:**

These findings suggest that controlling GWG should be a priority following GDM diagnosis to optimise pregnancy outcomes and improve maternal postnatal glucose homeostasis. The period after diagnosis of GDM (often 28 weeks gestation) is not too late to offer lifestyle advice or intervention to improve weight management and pregnancy outcomes.

**Table A1: The effect of total gestational weight gain, early gestational weight gain and late gestational weight gain on pregnancy outcomes and treatment requirements in women with GDM. OR (95% CI) for categorical outcomes and beta coefficient (95% CI) for linear outcomes.** gestational weight gain **categories were analysed as a percentage change from pre-pregnancy/baseline weight and odds ratios/beta coefficients have been adjusted for antenatal fasting glucose (OGTT T0), parity & pre-pregnancy BMI except where otherwise indicated (see a and b below). GWG: gestational weight gain; OGTT: oral glucose tolerance test; VBAC: vaginal birth after Caesarean.**

|  |  |  |  |
| --- | --- | --- | --- |
| Outcomes | Total GWG (0-36w)  n=376 | Early GWG (0-28w)  n=129 | Late GWG (28-36w)  n=144 |
| CATEGORICAL VARIABLES (LOGISTIC REGRESSION) | ODDS RATIO (95% CI) | ODDS RATIO (95% CI) | ODDS RATIO (95% CI) |
| Large for gestational age | 1.08 (1.03 to 1.12)\*\*\* | 1.05 (0.94 to 1.16) | 1.17 (1.01 to 1.37)\* |
| Small for gestational age | 0.93 (0.87 to 0.99)\* | 0.89 (0.79 to 1.01) | 1.03 (0.88 to 1.20) |
| Vaginal delivery (including VBAC) | 0.94 (0.91 to 0.97)\*\*\*a | 0.97 (0.91 to 1.03)a | 0.97 (0.87 to 1.08)a |
| Caesarean delivery | 1.05 (1.02 to 1.08)\*\*a | 1.06 (1.00 to 1.12)a | 0.91 (0.80 to 1.02)a |
| Instrumental delivery | 1.01 (0.97 to 1.05) a | 0.95 (0.88 to 1.03)a | 1.26 (1.03 to 1.55)\*\*a |
| Dietary management only at 36 weeks | 1.00 (0.97 to 1.03) | 1.00 (0.94 to 1.07) | 1.03 (0.91 to 1.15) |
| On Metformin at 36 weeks | 0.98 (0.95 to 1.02) | 0.98 (0.93 to 1.04) | 0.95 (0.85 to 1.06) |
| On Insulin at 36 weeks | 1.01 (0.98 to 1.05) | 1.02 (0.96 to 1.09) | 1.01 (0.90 to 1.13) |
|  |  |  |  |
| CONTINUOUS VARIABLES (LINEAR REGRESSION) | BETA COEFFICIENT (95% CI) | BETA COEFFICIENT (95% CI) | BETA COEFFICIENT (95% CI) |
| Birthweight z score | 0.02 (0.01 to 0.04)\*\*\* | 0.02 (-0.01 to 0.04) | 0.04 (<0.01 to 0.08) |
| Postpartum fasting glucose | <0.01 (-0.01 to <0.01) | -0.01 (-0.02 to 0.01) | 0.03 (<0.01 to 0.07)\* |
| Postpartum 2-hour OGTT glucose | 0.01 (-0.01 to 0.03) b | -0.02 (-0.07 to 0.04) b | 0.12 (<0.01 to 0.22)\* b |
| Total daily insulin dose (36w) | 0.52 (0.01 to 1.03)\* | 1.20 (-0.19 to 2.60) | 4.37 (1.92 to 6.82)\*\*\* |
| Total insulatard dose (36w) | 0.13 (-0.08 to 0.34) | 0.21 (-0.25 to 0.67) | 1.42 (0.62 to 2.21)\*\*\* |
| Total novorapid dose (36w) | 0.38 (-0.17 to 0.92) | 0.81 (-0.63 to 2.25) | 3.03 (0.07 to 6.00)\* |

1. Delivery mode analyses adjusted for antenatal fasting glucose (OGTT T0), pre-pregnancy BMI, parity & birthweight z score.
2. Postpartum 2-hour OGTT glucose concentration adjusted for antenatal 2-hour OGTT glucose, pre-pregnancy BMI & parity.

\* p<0.05 \*\* p<0.01 \*\*\*p<0.001

Appendix 2:  **DiGest Health Professionals Substudy**

As this is a new method, it seems appropriate to have opportunity to assess how well the intervention is tolerated by women with gestational diabetes and other people.

Prior to commencement of the study, we would like to send dietboxes to healthcare professionals and researchers involved in the study (n=20) to:

1: identify any problems with ordering, delivery and storage of food

2: Gain an understanding of challenges women with GDM may face prior to the commencement of recruitment

3: Assess subjectively what factors may be associated with adherence and non-adherence in a non-GDM population.

We would like to collect information from healthcare providers about their experiences of the dietboxes and to identify barriers to adherence at an early stage.

Healthcare providers and researchers will be asked to:

1: Read the HCP PIL and sign the HCP consent form if they would like to take part in this substudy assessing the methodology

2: Complete questionnaires on quality of life and eating behaviour

3: Order food and receive the dietbox, commenting on any issues regarding delivery or storage. Participants will be asked to adhere to dietbox foods for 1 week, and to avoid supplementing their diet with other foods.

4: Structured interviews will be performed in order to assess aids and barriers to adherence.

5: Participants will be asked to give very limited health data (height and weight will be measured).

The results will be used to identify any issues prior to recruitment of women with GDM.

Appendix 3:

**DiGest Qualitative Substudy.**

# Purpose

The novel dietbox methodology overcomes many of the methodological challenges of controlling and blinding in dietary studies. Providing all meals in a pre-prepared format may also facilitate adherence to dietary restriction by reducing participant burden. However, this may not be easy for people to incorporate into their existing routines, particularly where people also prepare meals for other family members.

The current qualitative substudy aims to explore patients’ experiences of participating in the Diet box study. This will enable us to evaluate the extent to which the intervention was implemented as intended and to identify how the intervention supports behavioural change (or not). This study will also examine the personal and contextual factors that influence adherence to the intervention and its incorporation into participants’ everyday lives.

# Aims

**2.1** **Objectives**

To evaluate the extent to which the diet box intervention was implemented as intended

To identify the contextual factors and causal mechanisms associated with variation in outcome

To identify the barriers and facilitators to participants adhering to the diet and incorporating this into their everyday lives.

**2.2 Outcome**

Identify ways in which the diet box intervention can be adapted and refined to maximise effective implementation

Inform the future development of interventions to support women with gestational diabetes to make dietary changes

# 3 Data Collection

For the pilot study, 20 health professionals will take part in the study as participants. Their responses to the interview will be used to refine both the intervention delivery and the interview schedule. For the main study, participants (N~20) will be purposively sampled to represent both intervention arms (low calorie, standard) and a range of demographic characteristics including household size. Potential participants will be identified by the study coordinator using participant characteristics recorded as part of the study.

Shortly before their 2nd study visit, participants will be sent a letter inviting them to take part in the interview. Along with the invitation letter, they will be sent a participant information sheet and a consent form to review. A member of the research team will call the participant about 1 week after mailing the letter and will ask them if they would like to take part. If the participant is willing, they will arrange a mutually convenient time and place to conduct the interview.

Before an interview begins, the interviewer will review the participant information sheet with the participant and will receive informed consent. This will include consent to audio-record the interview

A trained member of the research team will conduct semi-structured interviews with participants from both intervention arms. The interview schedule has been developed by the research team and will be refined during the piloting stage. Where possible, interviews will be conducted face-to-face in a private room. However, telephone interviews will be offered as appropriate to ensure that we are able to capture a broad demographic. Interviews will be audio recorded and transcribed verbatim by an experienced external agency. When transcripts are returned to the research team they will be checked for accuracy and uploaded into NVivo software for data management and analysis.

**Data Analysis**

Transcripts will be analysed thematically using a framework analysis. Initial open codes will be generated based on line by line scrutiny. Higher order analytic categories will be generated by recursively moving between consideration of transcripts and more general themes and explanatory theory. A subset of transcripts will be dual coded by a second member of the research team. Inconsistencies between coders will be resolved through discussion.

Analysis of the extent to which the intervention was implemented as planned will be guided by the MRC guidance on the process evaluation of complex interventions, which examines the context in which the intervention was delivered, the processes by which the intervention was achieved, and the potential causal mechanisms. Understanding of the facilitators and barriers of intervention adherence will be guided by the COM-B model of behaviour change which examines capability, opportunity, and motivation for behaviour change.