

# REduction in the incidence of GEstational DIAbetes mellitus (GDM) with MEDDiet /Lifestyle

<b>Submission date</b> 27/09/2013	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered
<b>Registration date</b> 04/12/2013	<b>Overall study status</b> Completed	<input checked="" type="checkbox"/> Protocol
<b>Last Edited</b> 31/03/2020	<b>Condition category</b> Nutritional, Metabolic, Endocrine	<input type="checkbox"/> Statistical analysis plan
		<input checked="" type="checkbox"/> Results
		<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

### Background and study aims

Gestational Diabetes Mellitus (GDM) is condition that entails a worse prognosis of the gestation, increasing maternal and neonatal morbidity. Some of the immediate adverse outcomes of GDM are increased risk of preeclampsia, pregnancy induced hypertension, prematurity, C-section, and newborns with macrosomia, large for gestational age (LGA) and small for gestational age (SGA). The management of this disease with nutritional and/or pharmacological therapy, when nutrition alone isn't enough seems to lower the incidence of some of these complications. However, appropriate GDM treatment is not yet clear. Several studies have evaluated the effect of different approaches to treat GDM (nutritional, insulin or metformin) on the improvement of maternal and neonatal prognosis. However, studies have not the assessed the effect of treatment of GDM on maternal and pregnancy outcomes compared to those of women with normal glucose tolerance (NGT). The Mediterranean Diet (MedDiet) is characteristically a low-glycemic-index diet. The adherence to this type of diet has proven to improve the anti-inflammatory profile, insulin sensitivity, glucose control and gestational weight gain. Recent results from the St. Carlos Gestational GDM prevention study associated the adherence to this diet with a 30% decrease of GDM incidence (study registry number ISRCTN84389045). This is a post-hoc analysis of this study. The aim is to assess and compare clinical and anthropometric parameters, and maternal and neonatal outcomes of women treated for GDM with women with NGT that followed usual antenatal care.

Added 26/01/2018:

Maternal nutrition can impact placental and fetal growth, and can affect the health of the mother and offspring in both the short- and long-term. It is unknown what is the ideal macronutrient distribution of a diet to be followed during pregnancy that can promote maternofoetal wellbeing. In addition, the available evidence on the effect of maternal diet in pregnancy outcomes mostly originates from observational studies. Thus, randomized controlled trials are needed. General nutritional guidelines provided in clinical practice recommend reducing the intake of fats, with aims to reduce excessive gestational weight gain; however, data on effective dietary interventions are inconclusive. Recent results from the St. Carlos Gestational GDM prevention study associated the adherence to a Mediterranean diet with an

enhanced consumption of extra-virgin olive oil and nuts with a 30% decrease of GDM incidence (study registry number ISRCTN84389045). This is a post-hoc analysis of this study. The aim will be to assess and compare incidence of composite maternofetal outcomes and clinical and anthropometric parameters of normoglycemic women who followed a MedDiet with enhanced consumption of extra-virgin olive oil and nuts versus women who followed standard pregnancy care guidelines, where total fat consumption is limited.

**Who can participate?**

Pregnant women above 18 year old, with normal fasting glucose values in the first gestational assessment.

**What does the study involve?**

Participating women will be randomly allocated to one of two groups: a Med Diet group (free olive oil and nuts plus personalized dietary advice) or a Control group (standard treatment with recommendations to cut down on all types of fat and training program).

**What are the possible benefits and risks of participating?**

Not provided at time of registration

**Where is the study run from?**

Hospital Clínico San Carlos, Madrid (Spain)

**When is study starting and how long is it expected to run for?**

From January 2014 to December 2015

**Who is funding the study?**

Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Spain.

**Who is the main contact?**

Professor Alfonso Luis Calle-Pascual  
acallepascual@hormail.com

## **Contact information**

**Type(s)**

Scientific

**Contact name**

Prof Alfonso Luis Calle-Pascual

**Contact details**

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## **Additional identifiers**

**EudraCT/CTIS number**

**IRAS number**

**ClinicalTrials.gov number**

**Secondary identifying numbers**

01092013HCSC

## **Study information**

### **Scientific Title**

Reduction in the incidence of gestational diabetes mellitus (GDM) with MedDiet/Lifestyle and its impact on genetic and epigenetic pattern expression in pregnant women and their offspring

### **Acronym**

RE-GE-DIA-MED

### **Study objectives**

Added 26/01/2018:

Follow up study:

The hypothesis is that following nutritional recommendations based on a Mediterranean diet, enhanced with extra-virgin olive oil and nuts consumption, as compared to recommendations that limit fat intake, will reduce the incidence of composite maternofoetal outcomes in normoglycemic women.

Current study hypothesis as of 30/08/2017:

The hypothesis is that a MedDiet-based nutritional therapy in GDM treatment can achieve Near-Normoglycemia, making the glycemic control of women with GDM comparable to those of women with NGT.

Previous study hypothesis:

In this project we have hypothesized that a lifestyle intervention based on the Mediterranean Diet (MedDiet) and physical activity/exercise, beginning after 1st gestational visit [8-12 gestational weeks (GWs)] and throughout the pregnancy, will reduce the incidence of gestational diabetes mellitus (GDM) in women with normal fasting plasma glucose (FPG).

### **Ethics approval required**

Old ethics approval format

### **Ethics approval(s)**

St Carlos Hospital Ethics Committee, 22/07/2013

### **Study design**

Single centre clinic-based prospective randomized interventional study with two parallel groups

### **Primary study design**

Interventional

### **Secondary study design**

Randomised controlled trial

### **Study setting(s)**

GP practice

### **Study type(s)**

Prevention

### **Participant information sheet**

Not available in web format, please use the contact details below to request a patient information sheet

### **Health condition(s) or problem(s) studied**

Gestational Diabetes Mellitus

### **Interventions**

Eligible women will be randomly assigned to one of two groups:

1. Control group: Women are assigned to standard treatment with recommendations to reduce all types of fat from both animal and vegetable sources including nuts and olive oil, and a training program. This prudent diet recommendation represents a contribution of total fat less than 30% of the total energy intake, and carbohydrate intake of more than 50%. Women will be followed up by the Obstetric Department

2. MedDiet group: Women receive free virgin olive oil (1 litre/week) and mixed nuts (150 g /week) and the training program. Dietitians will give personalized dietary advice to participants with instructions regarding use of olive oil for cooking and dressing, increased consumption of fruit, vegetables, legumes, fish and avoidance of red or processed meat, butter, cream, fast food, sweets, pastries, and sugar-sweetened beverages. This intervention diet is comprised of an intake of approximately 35-40% of the total fat (predominantly unsaturated fatty acids) and 40-45% of the low glycemic index carbohydrates, maintaining a protein intake of 20%, similar to the control diet. Nutrition interventions are aimed to achieve a lifestyle score >10 based on Diabetes Nutrition and Complications Trial (DNCT) previously reported. Women will be followed up by the Endocrinology Department.

Added 30/08/2017:

To diagnose GDM a single 2-h 75-g oral glucose tolerance test was performed, applying IADPSG criteria. One impaired value above the thresholds was enough to diagnose GDM: fasting glucose  $\geq 92$ mg/dL, 1-hour glucose  $\geq 180$ mg/dL and 2-hours glucose  $\geq 153$ mg/dL. Women diagnosed with GDM were followed-up at the Pregnancy and Diabetes Unit and the Obstetrics Department. GDM was treated with diet alone or in combination with insulin therapy, when diet alone was incapable of controlling glucose excursions. Nutritional treatment of GDM was based on a Mediterranean diet, with recommendations very similar to the ones provided to the Intervention group. Women were also insisted on using extra virgin olive oil (EVOO) as their main cooking fat source and nuts as their snacks. Both should be included regularly in their diet: a minimum of 40 ml/day of EVOO and 4 times/ week of nuts (serving size 25-30g). The main objective of GDM treatment is to reach glycemic goals. To register glycemic control, women were told to perform a six-point daily glycemic profile (fasting/preprandial and 1-h postprandial glycemia). Basal insulin was initiated when glucose monitoring indicated that >50% of fasting or preprandial values were >95 mg/dL and bolus insulin when >50% 1-h postprandial levels were >140 mg/dL (bolus insulin). Insulin requirements were adjusted weekly. The protocol of GDM management is specified in detail in Additional Files. For this post hoc analysis, women were allocated to one of two groups: With GDM or without GDM. For ethical reasons, following GDM diagnosis, all women

were provided with the same treatment, regardless of belonging to the control or intervention group.

## **Intervention Type**

Other

## **Phase**

Not Applicable

## **Primary outcome measure**

To define the prevention of GDM (evaluated at 24-28 GWs with HAPO criteria) after the lifestyle intervention based on MedDiet and physical activity/exercise, as compared to standard treatment, in women with normal FPG at the 1st gestational visit (8-12 GWs).

Added 26/01/2018:

The primary outcome will be to compare the incidence of composite maternofetal outcomes in normoglycemic women who followed two different nutritional recommendations guidelines based on a MedDiet with an enhanced consumption of extra virgin olive oil and nuts versus guidelines provided in regular clinical practice that limit fat consumption. Composite maternofetal outcomes assessed were emergency c-section, perineal trauma, pregnancy induced hypertension, preeclampsia, prematurity, large-for-gestational-age, and small-for-gestational-age.

Added 30/08/2017:

Follow up study:

To evaluate normoglycemia (HbA1c and glycemia levels) and gestational weight gain in both groups of women.

## **Secondary outcome measures**

1. To define the parameters of gestation length, fetal development, delivery characteristics such as cesarean delivery and instrumental vaginal birth, placental weight, and newborn data such as newborn weight, Apgar test values, and cord blood pH. Timepoint: at delivery, Visit 4.
2. To define functional genetic risk of developing GDM focusing on obese and non-obese pregnant women. Method and timepoint: HumanOmniExpress Infinium Illumina Exome v1.0, which allows the genotyping of approximately 950,000 markers in total sample. Of these, 700,000 are included in the common variants HumanOmniExpress Infinium (MAF > 5%) and 250,000 variants are included in the Human Exon Exome BeadChip. Eight samples can be hybridized per chip. Measured at Visit 0.
3. To investigate the effects of MedDiet and scheduled physical exercise/activity on inflammatory biomarkers in pregnant women. Method and timepoint: adiponectin, leptin, insulin and proinsulin will be determined by radioimmunoassay (Linco SA). hsCRP, sCD40L and Lp-PLA2 will be determined by specific ELISA kits. Visit 0-6.
4. To investigate the effects of MedDiet and scheduled physical exercise/activity on epigenetic mechanisms (DNA methylation and miRNA expression) in pregnant women and their offspring. If confirmed, it would represent a novel epigenetic mechanism for regulation of gene expression in the offspring (method and timepoint: we will perform a genome-wide DNA methylation analysis with the Illumina HumanMethylation450 BeadChip, following the Illumina Infinium HD Methylation protocol, using DNA obtained from whole blood. Quantitative methylation-specific PCR assay [qMSP]: validation of the most significant loci. Quantitative MSP will be performed with a 7500 Real-Time PCR System (Applied Biosystems). The primers will be designed using the MethPrimer website. Visit 0-2-4-6.

5. To investigate whether the MedDiet and scheduled physical exercise/activity alters the composition of the gut microbial flora both in the women and their offspring (method and timepoint: fecal collection and bacterial DNA quantification: DNA of microbial flora contained in the stool samples will be isolated using the PSP Spin Stool DNA PLUS Kit (Invitex Biotechnology and Biodesign). Visit 0-2-4-6.
6. To evaluate the impact of all of these parameters on the health of newborns in the first year of life
7. To estimate changes in HbA1c, insulin, HOMA, lipid profile, body weight, blood pressure, adherence to changes in lifestyle estimated by Med Score and urinary hydroxytyrosol levels and plasma alpha-linolenic acid levels (to confirm compliance in the group receiving MedDiet (extra-virgin olive oil and mixed nuts). Timepoint: Visit 0-2-4-6
8. To estimate the conversion rate to abnormal glucose tolerance (type 2 diabetes mellitus, IFG and IGT) of women with prior gestational diabetes mellitus (GDM) between 6 and 12 weeks after delivery. Method: oral glucose tolerance test (OGTT) measured at Visit 5.

Added 26/01/2018:

Follow up study:

1. To compare clinical parameters (glucose, Insulin, HOMA-IR and blood pressure).
2. To compare maternal dietary and physical activity habits throughout pregnancy
3. To compare body weight and weight gain.

Added 30/08/2017:

Follow up study:

1. To compare clinical and anthropometric parameters (insulin, HOMA-IR, lipid profile, blood pressure...) of women with and without GDM
2. Gestational and maternal outcomes: To define rates of urinary tract infections (UTI), perineal trauma, preeclampsia, pregnancy-induced hypertension, albuminuria, type of delivery (vaginal, instrumental and C-sections)
3. Infant outcomes: prematurity, shoulder dystocia, newborns weight LGA and SGA, admission to Neonatal Intensive Care Unit (NICU), Hypoglycemia, Respiratory distress and Hiperbilirubinemia.

**Overall study start date**

01/11/2013

**Completion date**

31/12/2015

## Eligibility

**Key inclusion criteria**

1. Women aged over 18
2. With normal fasting glucose values (< 92 mg/dl) in the 1st gestational assessment (8-12 GWs)
3. Who sign the informed consent

Added 30/08/2017: 4. Having attended GDM screening at 24-28 gestational weeks

Added 26/01/2018: 5. Who did not develop GDM

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Female

**Target number of participants**

1000

**Total final enrolment**

697

**Key exclusion criteria**

1. Women with fasting glucose levels >92 mg/dl in the 1st gestational assessment (8-12 GWs)
  2. Multiple pregnancy
  3. Nut allergy or any other medical condition
  4. Ongoing medication
  5. Significant disability that would prevent the participant from complying with trial consent, treatment and follow-up procedures or potentially jeopardize her medical care
- Added 26/01/2018: 6. GDM diagnosis

**Date of first enrolment**

01/01/2015

**Date of final enrolment**

31/12/2015

**Locations****Countries of recruitment**

Spain

**Study participating centre**

Endocrinology and Nutrition Department

Madrid

Spain

28040

**Sponsor information****Organisation**

The Health Research Institute at the Hospital Clinico San Carlos (Spain)

**Sponsor details**

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**Sponsor type**

Research organisation

**ROR**

<https://ror.org/04d0ybj29>

## **Funder(s)**

**Funder type**

Research organisation

**Funder Name**

Institute for Health Research San Carlos (Instituto de Investigacion Sanitaria San Carlos)(IdISSC)  
(Spain)

**Funder Name**

Foundation for Biomedical Research - Hospital Clinico San Carlos (Fundacion Para La  
Investigacion Biomedica - Hospital Clinico San Carlos) (Spain)

## **Results and Publications**

**Publication and dissemination plan**

Planned publication in a high-impact peer reviewed journal by the end of 2017 (November-December) beginning of 2018 (January-February). Although we are not sure at what exact point this will be, the intended date is to have published it by 31/12/2017. Protocol has been provided.

**Intention to publish date**

31/12/2017

**Individual participant data (IPD) sharing plan**

Datasets will be available upon request from Dr. Alfonso Calle Luis Pascual at endmet.hcsc@salud.madrid.org or alfonsoaluis.calle@salud.madrid.org. The data will be archived in a repository and become available when requested, for a period of 10 years. The type of data that



will be provided are both the database and statistical analyses. Data will be provided once permission is granted, upon request. All the analyses performed will be available at the repository. Consent forms were obtained from participants. However, the participation was anonymous.

## IPD sharing plan summary

Available on request

### Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Protocol file</a>				No	No
<a href="#">Results article</a>	results	19/10/2017	24/01/2019	Yes	No
<a href="#">Results article</a>	results	01/10/2019	31/03/2020	Yes	No