Universitat de Girona
Facultat de Medicina

Salut/ Trueta Hospital de Girona

FINAL DEGREE PROJECT

# PREDICTING ADVERSE MATERNAL OBSTETRIC OUTCOMES IN PREGESTATIONAL DIABETES MELLITUS WITH ULTRASOUND, METABOLIC, AND MATERNAL DEMOGRAPHIC FACTORS

## A PROSPECTIVE COHORT STUDY

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*Throughout the work, reference is made to pregnant women. However, our study will consider all individuals with the capacity for gestation.*

*To Dra. Alexandra Bonmatí, my sincerest appreciation for your support in this project from the very beginning. Your commitment and dedication of time to bring it to fulfillment have been invaluable. I am deeply grateful for your patience and devoted effort. Also, thank you for introducing me to the beautiful world of obstetrics.*

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*And to all of you, for taking a moment to read what I have elaborated with such effort and care.*
*To everyone, thank you!*

## ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| **AAWT** | Anterior Abdominal Wall Thickness |
| **AC** | Abdominal Circumference |
| **ACOG** | American College of Obstetricians and Gynecology |
| **AD** | Abdominal Diameter |
| **ADA** | American Diabetes Association |
| **AFI** | Amniotic Fluid Index |
| **BMI** | Body Mass Index |
| **BPD** | Biparietal Diameter |
| **CEIC** | Comité d'Ètica i Investigació Clínica |
| **CGM** | Continuous Glucose Monitor |
| **CI** | Co-Investigator |
| **CPD** | Cephalopelvic Disproportion |
| **CRL** | Crown-Rump length |
| **CS** | Cesarean Section |
| **D** | Data Manager |
| **DM** | Diabetes Mellitus |
| **EBCOG** | European Board and College of Obstetrics and Gynaecologists |
| **EFW** | Estimated Fetal Weight |
| **EPPH** | Early Postpartum Hemorrhage |
| **FIOL** | Failed Induction of Labor |
| **FL** | Femur Length |
| **GDM** | Gestational Diabetes Mellitus |
| **GW** | Gestational Weeks |
| **HC** | Head Circumference |
| **HCM** | Hypertrophic Cardiomyopathy |
| **HCP** | Health Care Professionals |
| **HUAV** | Hospital Universitari Arnau de Vilanova |

| | |
|---|---|
| **HUJT** | Hospital Universitari Josep Trueta |
| **IOM** | Institute Of Medicine |
| **IUGR** | Intrauterine Growth Restriction |
| **LGA** | Large for Gestational Age |
| **MODY** | Maturity-Onset Diabetes of the Young |
| **OAD** | Oral Antidiabetic Drugs |
| **OASI** | Obstetric and Anal Sphincter Injury |
| **OFD** | Occipito-Frontal Diameter |
| **OGTT** | Oral Glucose Tolerance Test |
| **OVD** | Operative Vaginal Delivery |
| **P** | Percentile |
| **PC** | Project Coordinator |
| **PGDM** | Pregestational Diabetes Mellitus |
| **PI** | Principal Investigator |
| **SEEN** | Sociedad Española de Endocrinología y Nutrición |
| **SEGO** | Sociedad Española de Ginecología y Obstetricia |
| **SFC** | Suspected Fetal Compromise |
| **SS** | Statistical Specialist |
| **TAR** | Time Above Range |
| **TBR** | Time Below Range |
| **TIR** | Time In Range |
| **US** | Ultrasound |
| **WHO** | World Health Organization |

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## 1. ABSTRACT

**BACKGROUND:** Diabetes mellitus is a chronic disease that affects millions of individuals worldwide. Increasingly, it impacts women of reproductive age, posing additional challenges in many pregnancies and deliveries. Pregestational diabetes mellitus (PGDM) complicates approximately 1% of all pregnancies, representing a risk for both the mother and the fetus. Especially in cases of poor glycemic control, PGDM has been associated with congenital malformations, stillbirth, hypertensive disorders, macrosomia, and adverse obstetric events during vaginal delivery that include emergency cesarean sections, obstetric anal and sphincter injuries, postpartum hemorrhage, and even maternal death. A significant challenge in these pregnancies is the occurrence of macrosomic fetuses that present a particular body fat distribution, which can increase the risk of such obstetric complications. Therefore, the estimated fetal weight of a fetus is used to take different decisions regarding the type and timing of delivery. However, it has been observed that calculating this measure through ultrasound can be inaccurate, especially in fetuses of diabetic mothers. Consequently, it is relevant to investigate potential factors associated with maternal complications during childbirth which can help consider alternative delivery options and make well-informed decisions accordingly.

**OBJECTIVE:** the main objective is to identify ultrasound, metabolic, and maternal factors that are associated with adverse maternal obstetric outcomes in women with PGDM.

**DESIGN AND SETTING:** the study is designed as a multicenter observational prospective cohort. It will be carried out in the three main hospitals of the provinces of Girona, Lleida, and Tarragona.

**PARTICIPANTS AND METHODS:** a total of 220 participants will be recruited for the study during the first ultrasound visit, including patients with known preexisting diabetes and those who obtained a positive screening result for PGDM during the first-trimester blood test. Patients with a clear indication for an elective cesarean section at the beginning or end of the pregnancy will be excluded. Patients will be followed throughout the course of pregnancy, collecting all necessary and relevant data until the moment of birth, where possible maternal complications during labor will also be documented.

**KEYWORDS:** diabetes mellitus, pregestational diabetes mellitus, macrosomia, estimated fetal weight, maternal obstetric outcomes, labor, safety, vaginal delivery, cesarean section

# 2. INTRODUCTION

## 2.1 DIABETES MELLITUS

### 2.1.2 Definition and classification

Diabetes mellitus (DM) is a group of metabolic disorders that leads to the onset of **hyperglycemia** associated with alterations in the metabolism of carbohydrates, proteins, and fats. These alterations result from defects in insulin secretion, insulin action, or both. Chronic hyperglycemia typical of DM is linked to long-term damage, dysfunction, or failure of various organs. Several pathogenic processes are involved in the development of diabetes, ranging from the autoimmune destruction of beta cells to peripheral resistance to insulin action (1).

DM can be classified as (1,2):

- **DM type 1:** caused by the destruction of pancreatic beta cells, leading to an absolute **insulin deficiency**. It can be autoimmune or idiopathic, representing 5 to 10% of the total cases of DM in the Western world.
- **DM type 2:** represents the **most common** form of diabetes (90 – 95%). The risk of its development increases with factors such as age, obesity, and sedentarism. It results from a combination of insulin resistance and insufficient compensatory insulin secretion, with a possible predominance of either, although both conditions are necessary.
- **Gestational DM:** it is defined as diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation.
- **Other specific types:** include genetic effects on beta cell function such as maturity-onset diabetes of the young (MODY), genetic defects in insulin action, exocrine pancreatic disease, endocrine disorders, drug or chemical-induced diabetes, infections, uncommon forms of autoimmune diabetes, genetic syndromes…

## 2.2 DIABETES MELLITUS DURING PREGNANCY

### 2.2.1 Epidemiology

The prevalence of DM is on the rise globally. Around 529 million people worldwide suffer from DM, representing 9.3% of the total adult population, and it is expected that the number of cases will increase to 1.31 billion, a 51% rise, by the year 2050 (3). At the same time, DM is considered the **most commonly observed metabolic disorder** associated with pregnancy. Approximately 1% of all pregnant women suffer from pregestational diabetes mellitus (PGDM), and up to 12%, depending on the diagnostic strategy employed and the studied population, will present gestational diabetes

mellitus (GDM) during their pregnancy (4,5). In Spain, the prevalence of GDM is estimated to be 9%, which could increase in the future due to the progressive rise of risk factors (6). Among women experiencing diabetes during pregnancy, around 87.5% have GDM, 7.5% are identified with DM type 1, and the remaining 5% with DM type 2. The prevalence of PGDM has increased in recent years as well as the incidence of GDM due to higher obesity rates in the general population and a greater number of pregnancies in elderly women (5).

### 2.2.2 Classification

#### 2.2.2.1 Gestational Diabetes Mellitus

Traditionally, GDM has been defined as any degree of glucose intolerance beginning or detected during pregnancy. However, this definition is considered to be imprecise as the population is currently facing an obesity and type 2 DM epidemic. Therefore, some cases of GDM diagnosed early (during the first trimester of pregnancy) are actually patients previously undiagnosed of DM2. For this reason, the American Diabetes Association (ADA) proposes the concept of GDM as diabetes diagnosed during the **second or third trimester of pregnancy** in individuals who did not have frank diabetes before gestation (2,7). GDM appears as a consequence of insufficient pancreatic response and failure to achieve an adequate compensatory reaction (7,8). These deficiencies may progress after pregnancy, elevating the risk for these patients to develop overt type 2 DM, and thereby increasing the probability of experiencing preexisting DM in future pregnancies (9).

According to the Protocol for Pregnancy Monitoring in Catalonia, the diagnostic procedure for GDM (Annex 1) includes a **screening** carried with the **O'Sullivan test** (determines the postprandial blood glucose levels after the ingestion of 50g of glucose), ideally during the second trimester. In the presence of a positive screening test, an oral glucose tolerance test (OGTT) should be carried out to confirm the diagnosis. The presence of any diagnostic criteria for DM (mentioned in Table 1) confirms the diagnosis of PGDM and excludes the need to run an OGTT (10).

#### 2.2.2.2 Pregestational Diabetes Mellitus

##### 1) Concept

PGDM includes any diabetes diagnosed **before the onset of pregnancy**. DM is recognized as a significant risk factor for both maternal and fetal health. Consequently, a pregnancy complicated by DM is considered a **high-risk gestation** that will need multidisciplinary management and meticulous planning throughout gestation to minimize potential adverse outcomes (5,11).

## 2) Screening and diagnosis of pregestational diabetes mellitus

Currently, there is no widely accepted and standardized screening for **type 1 DM;** it is only considered in the context of clinical trials that have not yet been extended to clinical practice. Therefore, diagnosis of this type of diabetes typically relies on the presence of **clinical symptoms** such as polyuria, polydipsia, or weight loss together with **elevated blood glucose levels** *(Table 2)*, demonstrated through an analysis with altered fasting plasma glucose levels or through an impaired OGTT (12,13). On the other hand, **type 2 DM** may have a silent and asymptomatic clinic course with short and long-term complications related. Therefore, **screening** is accepted and aims to initiate early treatment and surveillance to reduce complications (13,14). The screening can be carried out using either fasting plasma glucose values, a 2-hour plasma glucose value during a 75g OGTT, or the determination of HbA1c. The "Sociedad Española de Endocrinología y Nutrición" (SEEN), based on the ADA recommendations, suggests a list of criteria for ruling out the screening of type 2 DM in asymptomatic patients (Table 1) (2).

*Table 1. Criteria for screening for diabetes mellitus type 2 or prediabetes in asymptomatic adults (2)*

BMI: Body Mass Index; HDL: High-Density Lipoprotein; GDM: Gestational Diabetes Mellitus; HIV: Human Immunodeficiency Virus

| **Screening of diabetes mellitus type 2 or prediabetes** |
|---|
| 1. Adults with **overweight** or **obesity** (BMI ≥ 25 kg/m$^2$ or ≥ 23 kg/m$^2$ in Asian individuals) who have one or more of the following risk factors:<br>- First-degree relative with diabetes mellitus<br>- High-risk origin (African American, Latino, Native American, Asian or Pacific Islander)<br>- History of cardiovascular disease<br>- Hypertension (≥ 130/80 mmHg or on therapy for hypertension)<br>- HDL cholesterol level of 35 mg/dL and/or triglyceride level > 250mg/dL<br>- Individuals with polycystic ovary syndrome<br>- Physical inactivity<br>- Other clinical conditions associated with insulin resistance (severe obesity, acanthosis nigricans) |
| 2. Adults with **prediabetes** (HbA1c ≥ 5.7%, impaired fasting glucose or OGTT) should be tested yearly |
| 3. Individuals diagnosed with **GDM** should have lifelong testing at least **every 3 years** |
| 4. For the rest of the patients, screening should begin at the **age of 35** |
| 5. If the results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status |
| 6. People with **HIV**, exposure to **high-risk medicines,** or with a history of **pancreatitis** |

The **diagnosis of diabetes** will be established using values of HbA1c or plasma glucose levels at different moments during an **OGTT,** or based on a random value of blood glucose levels along with associated symptoms (Table 2).

*Table 2. Diagnostic criteria of diabetes mellitus and prediabetes (2)*

OGTT: Oral Glucose Tolerance Test

| | PREDIABETES | DIABETES |
|---|---|---|
| **Fasting plasma glucose levels** | 100 – 125 mg/dL | >126mg/dL |
| **Glucose at 2 hours after OGTT** | 140 – 199mg/dL | ≥ 200mg/dL |
| **Clinical symptoms of diabetes and random blood glucose levels** | | ≥ 200mg/dL |
| **HbA1c** | 5.7 - 6.4% | ≥ 6.5% |

* In the absence of hyperglycemic symptoms, the diagnosis requires **two** abnormal results in the same test or **two** different tests.

The prevailing epidemic of obesity and type 2 DM has led to an increased incidence of diabetes in individuals of reproductive age. Consequently, there has been an increase in the occurrence of **undiagnosed DM during the early stages of pregnancy.** Ideally, undetected DM should be identified prior to pregnancy in individuals with risk factors or within high-risk populations to facilitate accurate preconception counseling. But in situations where women with risk factors have not undergone screening before pregnancy, **early screening during the first trimeste**r (before 24 gestational weeks) is recommended to exclude previously undiagnosed DM and implement appropriate management of the situation (2,15).

The screening will be performed by determining the **fasting blood glucose levels** if the pregnant woman presents more than one of the following risk factors (11):

- Obesity (BMI > 27,5 kg/m$^2$ in women of Asian origin or BMI ≥ 30 for the rest of women)
- Personal history of GDM or adverse obstetric history, such as **macrosomia** (fetal weight > 4,000 - 4,500g) or **large for gestational age** (LGA) fetuses (percentile > 90)
- Family history of DM in first-degree relatives
- Fetal demise without explanation or congenital malformation in previous pregnancies

The management will differ depending on the results obtained:

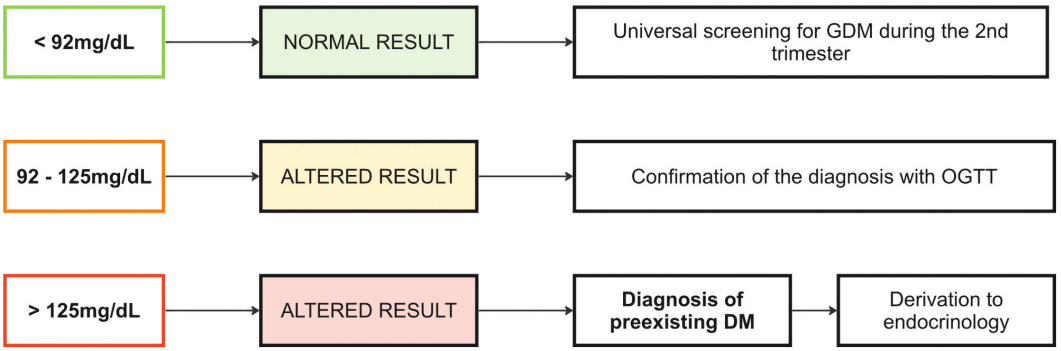


*Figure 1. Results and management of screening for diabetes mellitus in pregnant women with risk factors (10)*

GDM: Gestational Diabetes Mellitus; OGTT: Oral Glucose Tolerance Test; DM: Diabetes Mellitus

### 3) Preconception counseling

According to different endocrinology and obstetrics societies such as the American College of Obstetricians and Gynecology (ACOG), Sociedad Española de Ginecología y Obstetricia (SEGO), and ADA, it is essential to inform and properly educate all individuals diagnosed with DM during their childbearing age about the importance of maintaining optimal glycemic control **(HbAc1 ≤ 6.5%**), especially during the periconceptional and organogenesis period (first 10 weeks of gestation) to minimize the complications associated. In **very high-risk situations** (HbA1c levels > 10%, severe nephropathy, ischemic cardiopathy, severe proliferative retinopathy with poor visual prognosis, or severe autonomic neuropathy*)*, healthcare professionals may advise against pregnancy until there is better control of the clinical condition. Another of the main objectives of preconception counseling will consist of **adjusting the dietary treatment and the insulin therapy regimen**. It will be essential to discontinue unsafe insulins during pregnancy and preferably withdraw oral antidiabetic drugs (OAD). Additionally, it is recommended to initiate periconceptional supplementation with iodine and folic acid to prevent neurological defects and neural tube development abnormalities, respectively (5,16,17). The **objectives of the diabetic** control will be the same as during pregnancy (Table 3).

*Table 3: Preconceptional objective values in diabetes mellitus (11)*

BMI: Body Mass Index

| | |
|---|---|
| BMI | **< 30 kg/m$^2$** |
| HbA1c | **≤ 6.5%** |
| Basal glycemia | **70 - 95mg/dL** |
| 1-hour postprandial blood glucose levels | **90 - 140mg/dL** |
| 2-hour postprandial blood glucose levels | **90 - 120mg/dL** |
| Absence of hypoglycemia and ketonuria | |

## 4) Gestational monitoring and follow-up

The patient's follow-up will be conducted together by **obstetrics** and **endocrinology services**. The figure below (Figure 2) summarizes the main obstetric monitoring for PGDM patients. This framework may be altered or slightly modified depending on the patient's control.

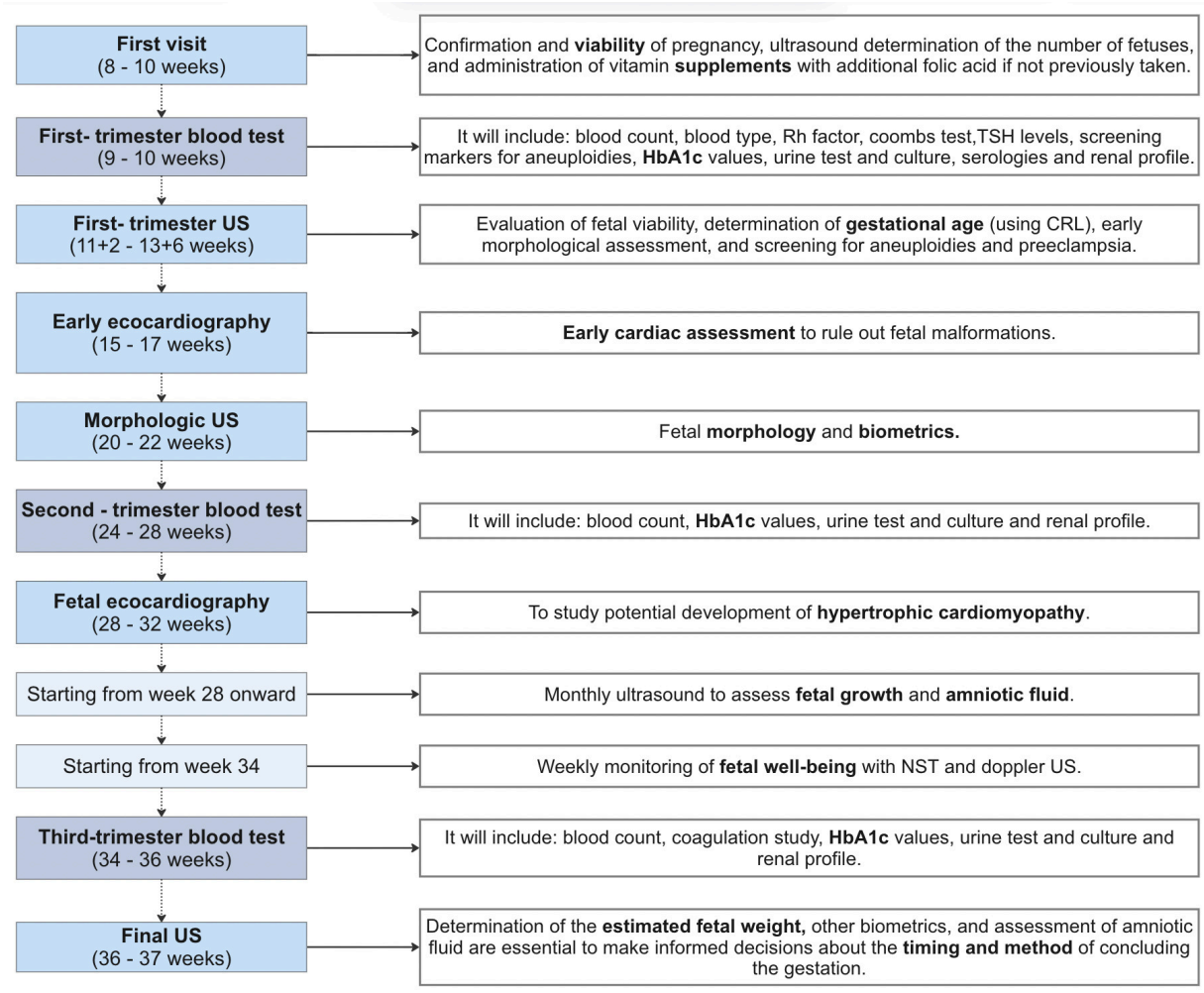


*Figure 2. Gestational control in pregnancies complicated by diabetes mellitus (11)*

US: Ultra Sound; CRL: Crown- Rump Lenght; NST: Non-Stressing Test

**HbA1c** levels are assessed, at a minimum, in each trimester-specific analysis during pregnancy (Annex 2). This value reflects the average glycemia over the past three months, serving as an available tool for diabetes management and providing continuity of care (2).

### 5) Treatment

The management of PGDM during pregnancy involves a combination of **diet**, **exercise,** and **medical therapy** to achieve optimal glucose control. Gestation induces alterations in carbohydrate metabolism as a result of physiological insulin resistance induced by placental hormones. Consequently, maintaining effective diabetes management is essential, and it requires daily glucose level assessments and adjustments to address evolving needs (16,18).

#### Exercise and diet recommendations

Evidence suggests that there is no ideal distribution of calories and macronutrients, so diet should be individualized and adapted taking into account the patient's pregestational weight, gestational needs, as well as personal and cultural preferences. It is important to emphasize that the goal is to achieve a **healthy and balanced personalized diet** rather than focusing on the value of nutrients individually (19,20).

Key ideas that should be considered and promoted (especially in DM type 2) include (20):

- Eat nonstarchy vegetables. Nonstarchy vegetables are those that contain low amounts of carbohydrates (carrots, broccoli, onions, salad greens, tomato, eggplant, etc).
- Reduce overall carbohydrate intake
- Minimize added sugars and refined grains intake
- Choose whole foods over processed products

Regarding **physical activity,** the ADA recommends that patients engage in 150 minutes or more of moderate to vigorous physical exercise per week (16). This exercise should be distributed over three days a week, with no more than two consecutive days without moving. Active exercise has not only been proven to improve blood glucose levels but also to reduce cardiovascular risk factors, contribute to weight loss, and improve overall well-being (21).

#### Medical treatment

As for the pharmacological treatment, the recommendations followed will be the same as during the preconception stage.

- **Insulin therapy:** insulin remains the standard of care for DM type 1 and 2 during pregnancy. It is necessary to consider the increase in insulin sensitivity and therefore the lower requirements that occur during the end of the first trimester as well as the rise in insulin resistance during the second and the third trimesters. All these specifications should be taken into account to adjust the medical treatment according to the patient's needs (18,22). The main types of insulin used during pregnancy are summarized in Table 4:

*Table 4. Types of insulin used during pregnancy, adapted from (8,18)*

NPH: Neutral Protamine Hagedorn

| Type | | Onset of action | Duration | Use |
|---|---|---|---|---|
| **Analogues of ultra-rapid-acting insulin** | Lispro | 1 - 15min | 4 - 6h | Administered before meals (preferred) |
| | Aspart | | | |
| **Rapid-acting insulin** | Recombinant human insulin | 30 - 60 min | 6 - 10h | Administered before meals |
| **Long-acting or basal insulin** | NPH insulin | 1- 3 h | 13 - 18h | Maintain euglycemia between meals |
| | Detemir | | 18 - 26h | |
| | Glargine | 1 - 2 h | 24h | |

Guidelines mainly recommend the use of **human insulin** during gestation. However, since the majority of type 1 DM cases are managed with recombinant insulin, it is not advised to alter the basal treatment. Recombinant insulins are also considered safe during pregnancy, and a change in the type of insulin used could result in undesirable metabolic imbalances (5,18).

Insulin can be administered either in basal-bolus or through continuous infusion (16):

- **Basal bolus:** administration of long-acting insulin in 1 or 2 daily injections to maintain basal insulin levels, along with fast-acting or ultra-fast-acting (preferred) insulin before each meal to control postprandial insulin peak.
- **Continuous subcutaneous insulin infusion:** administering fast-acting or ultrafast-acting insulin through a pump connected to a catheter in the subcutaneous tissue.

- **Non-insulin pharmacological treatment:** in general, OAD should be avoided during pregnancy as they cross the placental barrier and their long-term effects on the fetus are still unknown (16). However, oral agents may have advantages over insulin due to their

lower cost, easier administration, easier storage, and better acceptance (23). Many studies (24–26) have shown similar efficiency between insulin and **Metformin** in treating type 2 diabetes during pregnancy. A randomized double-blinded international study known as the MiTY trial conducted in 2020 compared the use of Metformin vs placebo together with insulin, concluding that along with the reduction in maternal weight gain and insulin dosage, the use of metformin also improved glycemic control, lower adiposity and infant size measures leading to decreased number of large infants (27).

Also, the use of **Glyburide** has been studied for treating this population, concluding that its efficiency is similar to insulin in terms of glycemic control but that has not been able to prove an improvement in obstetric outcomes. Furthermore, as with Metformin, there is a lack of studies that adequately assess long-term safety in offspring (23).

Therefore, individuals with type 2 DM who effectively manage their condition and glucose levels using OAD should be advised to switch to insulin therapy when becoming pregnant, as insulin is the first line of recommended treatment. However, for those who decline insulin or whom their obstetricians believe will be unable to properly administer it, Metformin (and more rarely, Glyburide) could be a reasonable second-line alternative if the patient is correctly informed about the limitations of long-term safety data (16,18).

### 6) Glucose monitoring: analytical assessment and blood glucose targets

The objective of metabolic control during pregnancy is to maintain **normoglycemia,** attempting to achieve glucose levels similar to those of non-diabetic pregnant individuals. Glucose monitoring can be conducted using preferably and whenever possible **FLASH sensors** or a **continuous glucose monitor** (CGM). The FLASH methodology uses a sensor to measure glucose levels in the interstitial fluid. Following this, a real-time glucose level may be obtained by scanning the sensor to the reading device (28). CGM technology is slightly more advanced and consists of a sensor inserted underneath the skin, a transmitter, and a monitor. It provides continuous data by measuring the glucose concentration in interstitial fluid and sending the values via the transmitter to the monitor (which can be a smartphone ) providing real-time and retrospective data. Technology with sensors allows for better glycemic control (29). For patients who do not wear sensors, it is recommended to perform **at least** 3 preprandial and postprandial capillary glucose measurements and 1 nocturnal determination per day. For those patients with continuous glucose monitoring using FLASH or real-time sensors, they should consider the **time in range** (TIR), the **time below range**

(TBR), and the **time above range** (TAR) within which the glucose levels should ideally reside (5). The objectives for metabolic control are documented in Table 5.

*Table 5. Objective metabolic values for pregestational diabetes mellitus, adapted from (5)*

TBR: Time Below Range; TIR: Time In Range; TAR: Time Above Range

| | HbA1c | Basal Glycemia | Postprandial at 1 hour | Postprandial at 2 hours |
|---|---|---|---|---|
| **Objective** | < 6.5% | 70 - 95 mg/dL | 100 - 140mg/dL | 90 - 120mg/dL |
| | **TBR (< 54 mg/dL)** | **TBR (< 63 mg/dL)** | **TIR (63 - 140 mg/dL)** | **TAR (> 140 mg/dL)** |
| **DM1** | < 1% of the lectures | < 5% | > 70% | < 25% |
| **DM2** | TIR should be higher in patients higher than in patients with type 1 DM, without being able to specify optimal values | | | |

In these patients, it will also be important to work towards maintaining the absence of ketonuria and hypoglycemia during the entire pregnancy (5).

## 7) Complications of pregestational diabetes mellitus

PGDM involves increased risks for both the mother and the fetus (30). These risks are primarily associated with **inadequate glycemic control,** emphasizing the importance of maintaining optimal glucose levels from the periconceptional stage and continuing throughout the entire gestation. Consequently, for these patients, it will be important to receive correct counseling and plan the gestation accordingly under the guidance of the endocrinology and gynecology team (16). (See preconception counseling).

### Diabetic embryopathy

Maternal preexisting DM is a well-known risk factor for **specific birth defects** and **congenital malformations**, mainly associated with high blood sugar levels during the period of fetal organogenesis (Table 6). Congenital malformations are the main cause of morbidity and mortality in children of diabetic mothers and it is considered to be a risk 2 to 9 times higher compared to the general population. The most frequent abnormalities include: cardiac alterations (tetralogy of Fallot, transposition of great vessels, ventricular septal defects...), holoprosencephaly, sacral agenesis syndrome, longitudinal limb defects, cleft lip, cleft palate, and urinary defects (30,31).

*Table 6. Risk of congenital malformations depending on HbA1c levels during pregnancy (32)*

| HbA1c (%) | < 7.1 | 7.2 - 9.1 | 9.2 -11.1 | > 11.2 |
|---|---|---|---|---|
| RISK (%) | 1-2 | 14 | 23 | 25 |

## Diabetic fetopathy

Diabetic fetopathy is associated with chronic fetal hyperinsulinemia resulting from maternal hyperglycemia (Figure 3).

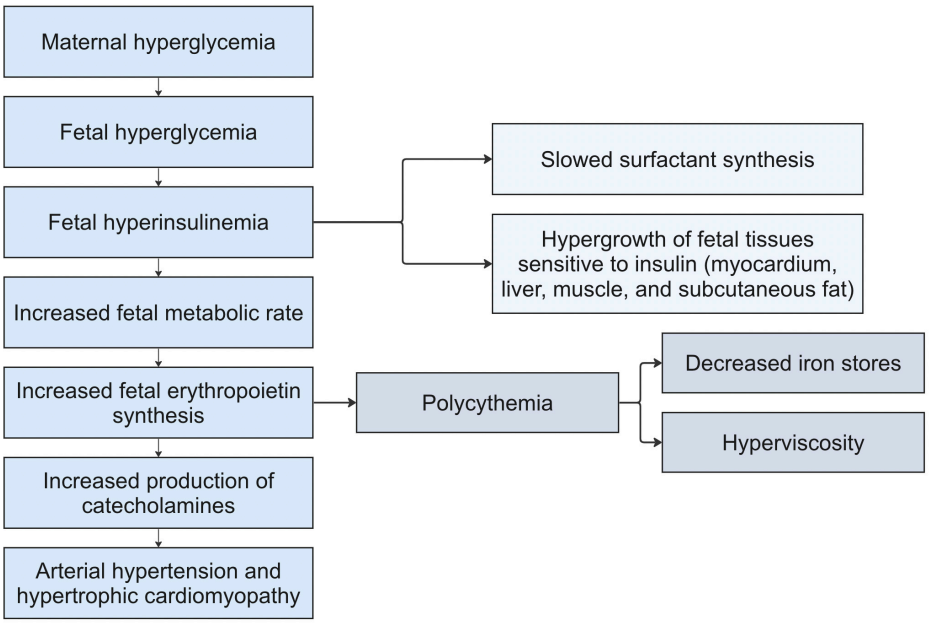


*Figure 3. Pathophysiology of diabetic fetopathy (5)*

The main effects include (32,33):

- **Macrosomia or LGA fetuses**: it is one of the most frequent fetal complications and it is mainly related to poor glycemic control, obesity, inappropriate weight gain of the mother during pregnancy, and previous history of a child with macrosomia. It can become evident as early as 26 - 28 gestational weeks (GW). (See section Excessive Fetal Growth Related to maternal hyperglycemia)
- **Polyhydramnios**: described as an abnormal increase in the amniotic fluid volume. Generally, it complicates approximately up to 1% of pregnancies. However, its prevalence can rise to 18% in high-risk groups, particularly among those with maternal DM and especially in cases with poor glycemic control (34). The most probable mechanism is attributed to increased fetal diuresis resulting from fetal hyperglycemia. Due to overexpansion of the uterus, polyhydramnios is considered a risk factor for preterm labor,

premature rupture of membranes, abnormal fetal presentation, umbilical cord prolapse, hypertensive disorders of pregnancy, and postpartum hemorrhage. The determination of the amniotic fluid volume and the identification of polyhydramnios is performed through fetal ultrasound (US) (35).

- **Overgrowth of fetal tissues sensitive to insulin** such as the myocardium, liver, muscle, and subcutaneous fat.
- **Hypertension and hypertrophic cardiomyopathy (HCM):** PGDM can have structural and functional effects on the fetal heart. In addition to congenital anomalies that may occur in early gestation, it can also lead to HCM in later stages. HCM is a condition in which the cardiac muscle and interventricular septum become abnormally thick in the absence of abnormal loading conditions or systematic disease. Normally it is asymptomatic in the fetus but it can cause systolic and diastolic dysfunction in the neonates' heart (36).
- **Reduced surfactant synthesis:** physiological levels of insulin play a role as a stimulatory hormone in surfactant synthesis, but on the contrary, high insulin levels, as well as hyperglycemia, can inhibit surfactant and protein synthesis. The reduced surfactant synthesis can lead to respiratory distress syndrome in the newborn (37).
- **Stillbirth /perinatal death:** the SEGO defines stillbirth as the death of a fetus that weighs more than **500g** and/or is more than **22 GW** in age, exhibiting no signs of life, characterized by the absence of breathing, heartbeats, pulsation of the umbilical cord, or distinct movement of voluntary muscles. The definitive diagnosis relies on confirming the **absence** of fetal cardiac activity through US examination. In pregnancies where the fetus has deceased, opting for an inducted vaginal delivery is the preferred approach to conclude gestation (38). In the context of PGDM, stillbirth can be caused by an increase in oxygen consumption produced by hyperglycemia and hyperinsulinemia, leading to fetal hypoxia and subsequent death. It can occur in up to **10%** of pregnancies, particularly when associated with poor glycemic control or the presence of multiple risk factors, such as PGDM and obesity (38,39).

### Effects on the newborn

The offspring of a diabetic mother is a high-risk neonate exposed to the development of various neonatal complications (5,11):

- **Hypoglycemia**: is the most frequent complication and it is defined as neonatal blood glucose levels < 30mg/dL during the first 72 hours after birth. It is caused secondary to hyperinsulinemia which produces a decrease in gluconeogenesis and an increase in peripheral glucose uptake. Clinical manifestations include paleness, cyanosis, sweating, apnea, hypotonia, tremors, and coma (32,40).
- **Hypocalcemia and hypomagnesemia:** hypomagnesemia is caused due to magnesium loss in the mother because of the DM, causing functional hypoparathyroidism which leads to neonatal hypocalcemia (41).
- **Macrosomia or LGA and different body fat distribution**: the classic characteristic phenotype of an infant of a diabetic mother can differ from that of non-diabetic infants (see section excessive fetal growth related to maternal hyperglycemia). As a consequence of macrosomia, perinatal asphyxia and injuries during childbirth (clavicle and humerus fractures, brachial or facial paralysis, cephalohematoma, subdural hemorrhage...) are more frequent.
- **Intrauterine growth restriction (IUGR)**: associated with placental vasculopathy and/or preeclampsia.
- **Prematurity:** prematurity can occur spontaneously or be induced by healthcare professionals' decision to end the gestation due to medical or fetal reasons. It can be observed in up to 36% of pregnancies complicated by PGDM.
- **Polycythemia:** it is defined as a hematocrit > 65% in the neonatal period. It is caused due to accelerated erythropoiesis and extramedular focus of erythropoiesis. It can lead to thrombotic complications, the most frequent being venous renal thrombosis.
- **Hyperbilirubinemia:** is defined as levels of indirect bilirubin > 4mg/dL in umbilical cord blood. This may be associated with polycythemia and ineffective erythropoiesis, leading to high red blood cell turnover and immaturity of bilirubin conjugation and liver excretion (42).

Moreover, the offspring of diabetic mothers may experience **long-term effects**, including a heightened risk of developing type 2 DM in adulthood, hypertension, and neurological deficits (32).

## Maternal and obstetric complications

There is considerable heterogeneity in studies addressing the incidence of maternal obstetric complications in pregnant women with PGDM. Nevertheless, overall, it has been observed that maternal hyperglycemia leads to an increase in (33,43):

- **Hypertensive disorders of pregnancy** such as preeclampsia. It is more common in individuals with long-lasting diabetes and pregnant women with angiopathy.
- **Urinary infections and vaginal candidiasis:** evidence suggests that pregnant women with asymptomatic bacteriuria are more likely to develop symptomatic urinary tract infections when associated with PGDM, compared to those without DM. Also, diabetes induces changes in the vaginal microbiota, facilitating the development of candidiasis (44).
- **Birth injuries and labor complications:** they occur primarily due to **fetal macrosomia**, which can lead to shoulder dystocia and consequently result in brachial plexus injury, humeral fracture, or perinatal asphyxia of the newborn. This is attributed not only to macrosomia but also to the distribution of their body fat (see section excessive fetal growth related to maternal hyperglycemia) (45,46). Other related labor complications include instrumental delivery and cephalopelvic disproportion, also mainly associated with macrosomic fetuses.
- **Induction of labor and elective and emergency cesarian section (CS):** in many clinical contexts, pregnant women with PGDM frequently experience induction of labor before their expected due date to try to prevent perinatal complications. However, part of these result in emergency CS. The rate of emergency CS in pregnancies complicated by diabetes is 3-4 times higher when compared to pregnancies in individuals without diabetes (47)**.**
- **Early Postpartum hemorrhage (EPPH):** maternal blood loss during delivery has been related to **atonic uterus** due to prolonged use of oxytocin, high parity, and general anesthesia; **over-distended uterus** mainly due to polyhydramnios and macrosomia; **genital tract trauma** such as vaginal and perianal lacerations; **retained placental tissue** or abnormalities of coagulation due to preeclampsia, infections, etc. (48).
- **Maternal mortality rates:** poor glycemic control and underlying nephropathy may exacerbate maternal mortality rates.
- **Prenatal and postpartum hospital admission:** due to the combination of all the possible complications mentioned previously.

### 8) Timing and mode of birth

Throughout gestation, it is important to progressively discuss with the patient the expected mode and approximate time of delivery based on her progress. Although the ideal scenario is **natural vaginal childbirth**, there are cases where methods to conclude gestation, such as labor induction and scheduled CS, may be necessary before spontaneous labor.

The main objective of **labor induction** is to prevent potential fetal and maternal complications that may arise towards the end of pregnancy. However, it must be considered that labor induction may also pose certain risks, including induction failure that could lead to an emergency CS or an operative delivery. **Elective cesarean section** is indicated in cases of estimated fetal weight (EFW) exceeding 4,500g or a history of shoulder dystocia. The CS aims to reduce the risk of birth trauma. However, patients should receive counseling regarding the limited predictive accuracy of ultrasound estimates of fetal weight and the associated risks and benefits of cesarean delivery. The final decision will be discussed and agreed upon collaboratively with the patient and the obstetric and endocrinology teams, taking into account the mentioned recommendations.

In both methods, determining the ideal timing must be carefully evaluated. This assessment involves finding a balance between the risk of keeping the fetus in utero, with its associated fetal mortality and morbidity, against the potential complications associated with preterm birth. Therefore, it is recommended that pregnancies with good metabolic control and adequate monitoring of fetal well-being conclude gestation starting from 38 + 6 GW. Indication of labor induction due to the risk of macrosomia will be between weeks 37 and 38 + 6 GW, individualizing each case. In cases of suboptimal glycemic control, severe fetal and maternal complications, or no guarantee of adequate obstetric diabetological monitoring, end of gestation will be individually assessed between 36 + 0 and 38 + 6 GW, although efforts will be made to avoid a preterm delivery (Table 7). Expectant management beyond 40 weeks is not recommended (5,11,18).

*Table 7. Timing of the end of pregnancy in pregestational diabetes mellitus (5,11)*

| Good metabolic control and appropriate monitoring of fetal well-being | Risk of macrosomia or bad glycemic control | Suboptimal glycemic control or severe fetal and maternal complications |
|---|---|---|
| Pregnancy progression until **38 + 6 weeks,** moment at which the end of gestation will be recommended | End of gestation will be individually evaluated starting between 37 + 0 and 38 + 6 GW | The end of gestation will be individually assessed between 36 + 0 and 38 + 6 GW, although efforts will be made to avoid preterm delivery |

** In the event of a fetal well-being loss, the end of gestation will be immediate.

## 2.3 EXCESSIVE FETAL GROWTH RELATED TO MATERNAL HYPERGLYCEMIA

### 2.3.1 Concept and Epidemiology

Two terms define excessive fetal growth (49):

- **Fetal macrosomia**: birth weight > 4,000g - 4,500g regardless of gestational age.
- **Large for gestational age:** birth weight ≥ 90th percentile for a given gestational age.

About 15 to 45% of the newborns of diabetic mothers can suffer from macrosomia, which is three times higher compared to non-diabetic pregnancies (50). Macrosomic fetuses in diabetic pregnancies develop a unique pattern of overgrowth, involving the central deposition of subcutaneous fat in the abdominal and interscapular areas. They have larger shoulder and extremity circumferences, a decreased head-to-shoulder ratio, significantly higher body fat, and higher upper extremity skinfolds (Figure 4) (51). Because fetal head size does not increase but shoulder and abdominal circumference can be augmented, there is more risk of **Erb's palsy**, **shoulder dystocia,** and **brachial plexus trauma**. Therefore, macrosomia is associated with excessive rates of neonatal morbidity (50).

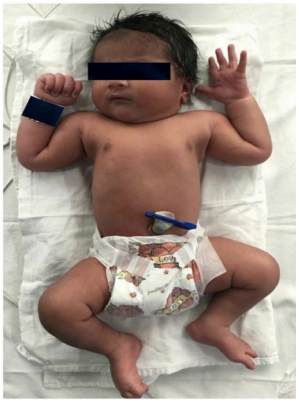

*Figure 4. Macrosomic newborn with broad shoulders (52)*

### 2.3.2 Pathophysiology of macrosomia

The modified Pedersen's hypothesis suggests that maternal hyperglycemia induces fetal hyperinsulinemia, increasing glucose use and resulting in elevated fetal adipose tissue. When maternal glycemic control is impaired and the maternal serum glucose level is high, glucose passes through the placenta. However, maternal-derived or exogenously-administered insulin does not cross the placenta. Consequently, the fetal pancreas responds to hyperglycemia during the second trimester and autonomously secretes insulin, independent of glucose stimulation. The combination of hyperglycemia and hyperinsulinemia leads to an increase in the fat protein stores of the fetus, leading to fetal macrosomia (50).

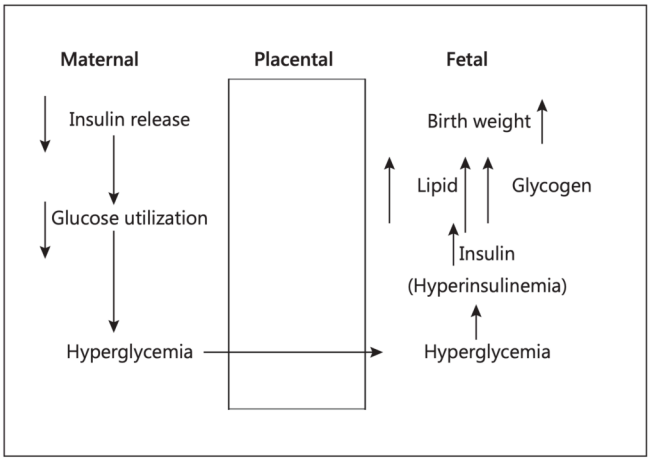


*Figure 5. Results of maternal hyperglycemia modified according to Pedersen's hypothesis (50)*

### 2.3.3 Macrosomia-related complications

#### Maternal complications

The main maternal complications related to macrosomia are summarized in Table 8.

*Table 8. Maternal complications related to excessive fetal growth (50,53)*

CS: Cesarean section

| | |
|---|---|
| **Risk of prolonged 1st** (cervical effacement, gradual dilatation, and onset of regular contractions) **and 2nd stages of labor** (active pushing and movement of the fetus through the birth canal) | |
| **Operative vaginal delivery** | Using forceps, vacuum, or spatulas. |
| **Unplanned or emergency CS** | Due to failure to progress or failed instrumental delivery, suspected fetal compromise, or cephalopelvic disproportion. |
| **Laceration and tear of vaginal tissue or perineal tear** | |
| **Uterine atony and postpartum hemorrhage** | If the uterus fails to contract after placental delivery, it can lead to postpartum hemorrhage. |

#### Fetal complications

The main fetal complications related to macrosomia are summarized in Table 9.

*Table 9. Fetal complications related to excessive fetal growth (50,53)*

| | |
|---|---|
| **Premature Birth** | Due to early induction of labor and/or premature rupture of the membranes. |
| **Shoulder dystocia** | is defined as a vaginal delivery that requires additional obstetric maneuvers to deliver the fetus after the delivery of the head and failure to gentle traction (54). It is the most serious complication associated with macrosomic infants. Generally, |

| | |
|---|---|
| | the incidence of low-risk vaginal delivery is very low (0.2 - 3%). However, it is essential to consider that this risk increases exponentially when infants weigh more than 4,500g, with the risk of shoulder dystocia reaching up to 20 -50% (55,56). (See Complications during delivery, shoulder dystocia) |
| **Hypoxic ischemic encephalopathy** | Results from inadequate blood flow and oxygen delivery to the brain, causing focal or diffuse brain injury. Neuroimaging modalities such as US, computed tomography, and magnetic resonance imaging are used to identify and characterize the accurate location and severity of the brain injury (57). |
| **Neonatal jaundice** | Macrosomic neonates have a higher oxygen demand causing increased erythropoiesis and, ultimately, polycythemia. Therefore, when these cells break down, bilirubin increases resulting in neonatal jaundice. |

### 2.3.4 Management of macrosomic fetuses

The ACOG and the SEGO recommend scheduling **elective CS** for fetuses suspected to weigh more than 5,000g in non-diabetic patients or at least **4,500g** in women with DM (5,49). Prophylactic CS or early induction of labor could reduce the inevitable increase in fetal size with advancing gestational age, therefore reducing maternal and fetal morbidity and mortality (58). The cutoff point is lower in diabetic patients, as this disease has been shown to alter the fetal pattern of overgrowth and consequently elevate the risk of these types of complications (59). Nevertheless, the estimation of fetal weight by US is imprecise, and frequently, the suspected weight of macrosomic fetuses is overestimated resulting in decisions based on this evidence being questionable. In general, fetal weight prediction in diabetic pregnancies is challenging, and pregnant women with suspected macrosomia should be provided individualized counseling (60,61).

## 2.4 CHILDBIRTH

Childbirth is defined as the period from the onset of regular uterine contractions until the expulsion of the placenta. The process by which this normally occurs is called labor (62).

### 2.4.1 Eutocic delivery

The World Health Organization (WHO) defines normal birth as “spontaneous in onset, low-risk at the start of labor and remaining so throughout labor and delivery. The infant is born spontaneously in the vertex position between 37 and 42 completed weeks of pregnancy. After birth, mother and infant are in good condition” (63).

### 2.4.1 Dystocic delivery

Dystocia is defined as an abnormality in the progression of labor. Identifying the risk of dystocia is essential as it is related to operative vaginal delivery, cesarean sections, and postpartum hemorrhage (64).

### 2.4.2 Complications during delivery

- **Perianal or vaginal tears:** obstetric lacerations are a common complication of vaginal delivery, affecting as many as 79% of natural births (65). These can be classified into (Table 10):

*Table 10. Classification of obstetric perianal lacerations (65)*

| DEGREE | DESCRIPTION |
|---|---|
| **1st-degree lacerations** | Involve only the perianal skin without extending into the musculature |
| **2nd-degree lacerations** | Involve the perianal muscles without affecting the anal sphincter complex |
| **3rd-degree lacerations** | Lacerations involving anal sphincter injury. Divided into:<br>a. Less than 50% external anal sphincter involvement<br>b. More than 50% of external anal sphincter involvement<br>c. External and internal anal sphincter involvement |
| **4rth-degree lacerations** | Lacerations involving the anal sphincter complex and the rectal epithelium |

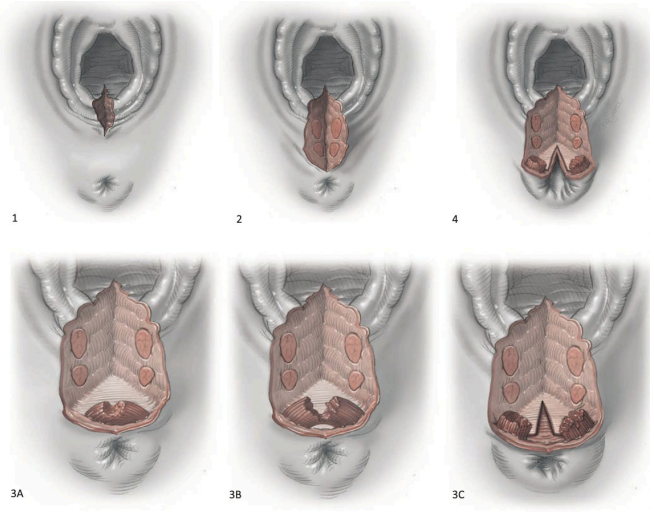


*Figure 6. Classification of perianal lacerations (62)*

**Obstetric anal sphincter injuries (OASI)** are known as severe perianal lacerations which extend into or through the anal sphincter complex. This definition includes the 3rd and 4th-degree lacerations mentioned in the table above (Table 10). They are less common in general, but they are more frequently associated with complications such as elevated risk of

pelvic floor injury, fecal and urinary incontinence, pain, and sexual dysfunction. These symptoms may persist or emerge many years after childbirth (65).

- **Early postpartum hemorrhage:** the ACOG defines EPPH as a minimum of 1,000mL of total blood loss or bleeding concurrent with signs and symptoms of hypovolemia within 24 hours after the delivery of the fetus or intrapartum loss (48).
- **Maternal peripartum infection:** the WHO defines maternal peripartum infection as " a bacterial infection of the genital tract or surrounding tissues occurring at any time between the onset of rupture of membranes or labor and the 42nd day postpartum" (66).
- **Shoulder dystocia:** it is defined as the cessation of spontaneous delivery due to the anterior shoulder impaction against the pubic symphysis, or more rarely, the posterior shoulder against the sacral promontory. This situation requires special maneuvers to disengage the shoulders after the failure of applying traction to the fetal head downward. It occurs as a complication in 0.2 - 3% of vaginal deliveries, varying according to the adopted definition, the specific patient population, and the recording method used (67).

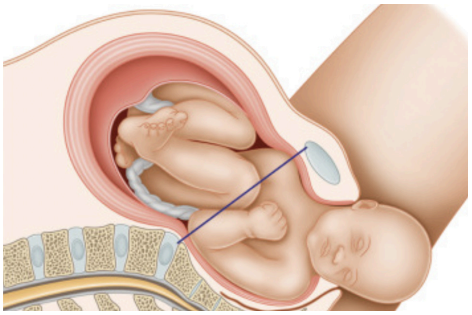

*Figure 7. Anterior shoulder dystocia (68)*

There are various situations related to shoulder dystocia (Table 11):

*Table 11. Risk factors associated with shoulder dystocia, adapted from (67,69)*

| Antepartum risk factors | Intrapartum risk factors |
|---|---|
| · **Fetal macrosomia or history of macrosomia**<br>· **Maternal PGDM and GDM**<br>· History of previous shoulder dystocia<br>· Obesity (BMI > 30kg/m$^2$)<br>· Excessive weight gain<br>· Prolonged pregnancy (> 41 weeks)<br>· Advanced maternal age<br>· Multiparity<br>· Non - gynaecoid pelvis<br>· Male gender | ·Prolonged dilatation and expulsion phase<br>· Labor induction with oxytocin<br>· Instrumental delivery<br>· Precipitous labor<br>· Use of epidural anesthesia |

- **Fetal macrosomia** is a factor strongly associated with shoulder dystocia. The risk increases proportionally with fetal weight (67).
- The **history of shoulder dystocia** is a significant and well-known independent risk factor of spontaneous vaginal deliveries with an incidence of recurrent shoulder dystocia ranging between 1.3 and 25% (70,71).
- **Maternal DM**: a German study concluded that shoulder dystocia is present in 1.8% of pregnancies with GDM and 4.4% with PGDM (72).
- **Instrumental delivery**, particularly the use of vacuum extraction, has been associated with an increased risk of shoulder dystocia. Therefore, in the presence of a combination of risk factors for shoulder dystocia, caution should be taken in considering instrumental delivery for fetal extraction (73).

Shoulder dystocia is considered an unpredictable obstetric emergency that places the pregnant woman and the fetus at risk of injury (Table 12).

*Table 12. Complications of shoulder dystocia (54)*

| COMPLICATIONS OF SHOULDER DYSTOCIA | |
|---|---|
| **Maternal** | **Neonatal** |
| · Lacerations of the bladder, urethra, vagina, anal sphincter or rectum<br>· Lateral femoral cutaneous neuropathy<br>· Postpartum hemorrhage<br>· Symphyseal separation<br>· Uterine rupture | · Fetal death<br>· Fetal hypoxic-ischemic encephalopathy<br>· Fracture of the clavicle or humerus<br>· Neurologic complications: brachial plexus injury, diaphragmatic paralysis, facial nerve injuries, horner syndrome |

### 2.4.3 Delivery interventions

- **Cesarean section:** is defined as the birth of a fetus by a laparotomy (incision of the abdomen wall) and posterior hysterotomy (incision in the lower part of the uterus). Like other types of surgery, it can be scheduled or urgent, depending on the indication. **Scheduled CS** is recommended when this procedure is expected to provide better maternal or fetal outcomes than vaginal delivery. Some accepted indications include abnormal placentation, maternal infections involving the birth canal, maternal severe cardiac or pulmonary disease, placenta previa, malpresentation, macrosomia, and prior neonatal birth trauma (74). **Emergency CS** is performed in the presence of concerning indications and situations where maternal and/or

fetal physiology is unstable. Generally, it involves more risks for the mother and the fetus compared to elective CS. The main causes of emergency cesarean section include (74):

- **Cephalopelvic disproportion (CPD):** it occurs when there is a mismatch between the size and/or the shape of the fetal head and the size and/or shape of the maternal pelvis, resulting in labor failure to progress.
- **Suspected fetal compromise (SFC):** fetal distress can occur during the antenatal or intrapartum period and manifests with severe fetal hypoxia requiring immediate intrauterine resuscitation and cesarean delivery. Clinical suspicion may arise from a reported loss of fetal movements by the mother, meconium-stained amniotic fluid (brown or green), a non-reassuring pattern on tocographic recording, or other biochemical signs such as fetal metabolic acidosis.
- **Failed induction of labor (FIOL):** induction might be considered failed if the methods used do not result in a vaginal delivery after 24 hours or more. In such cases, an emergency C - section might be necessary.

- **Operative vaginal delivery (OVD):** birth accomplished with assistance from forceps, spatulas, or vacuum-cup, applied to the fetal head and generating traction. OVD carries an increased risk for certain morbidity in both the mother (perianal or vaginal lacerations, puerperal infection, and pelvic floor disorders) and the fetus (cephalohematoma, subgaleal hemorrhage, retinal hemorrhage, clavicular fracture or neonatal jaundice) (62).
- **Episiotomy:** is an incision made in the tissue between the vaginal opening and the anus (perineum) during the childbirth. The procedure is performed to make the vaginal opening larger for childbirth in specific necessary cases (75).
- **Induction of labor:** the objective is to achieve a vaginal delivery by prompting uterine contractions before the spontaneous onset of labor. It is considered a therapeutic option when the advantages of speeding up delivery outweigh the risks of prolonging the pregnancy. The potential benefits of labor induction need to be evaluated concerning the possible risks associated with this procedure, like failure of induction which can result in an emergency CS, uterine hyperstimulation, cord prolapse, infection, meconium aspiration, increased risk of uterine rupture… (76).

## 2.5 OBSTETRIC ULTRASOUND

### 2.5.1 Fetal biometrics

- **Crown-Rump length (CRL):** it represents the measurement of the embryo or the fetus from the top of its head to the bottom of its torso (excluding the yolk sack and the extremities). It is particularly significant during the first trimester US as it is used to accurately date the gestation and measure the fetus or the embryo until it reaches 84 mm (77).

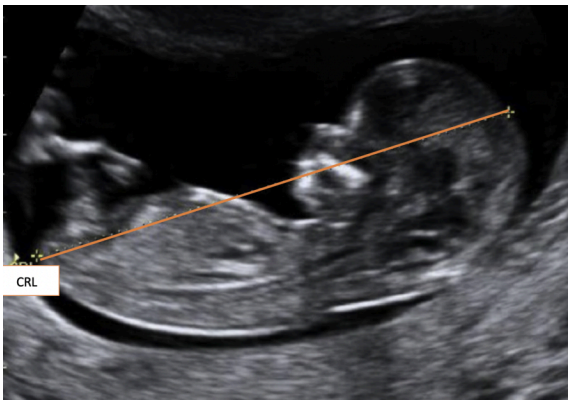


*Figure 8: CRL measurement by ultrasound (77)*

- **Biparietal diameter (BPD):** it is obtained by measuring the maximum diameter between the parietal eminences in a fetal skull. It needs to meet the following requirements: transverse plane of the fetal skull at the thalami level, the tilt angle of 90 º from the fetus's head midline, midline equidistant from the distal and proximal skull parts, visualization of the cavum septum pellucidum located in the anterior third of the midline and symmetric visualization of the two anterior horns of the lateral ventricles (78).

- **Occipitofrontal diameter (OFD):** measured in the same plane as the BDP, with a line drawn from the frontal region's center of the skull to the center of the occipital region.

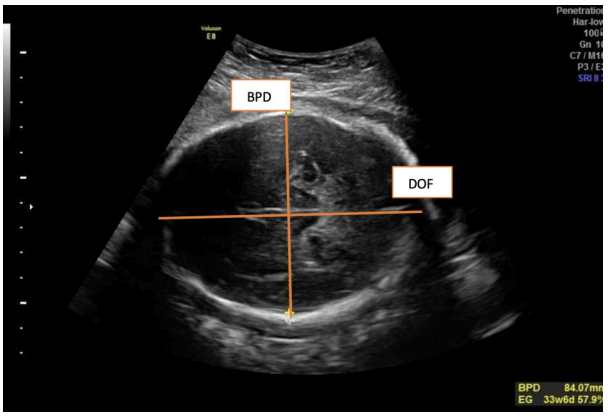


*Figure 9: BPD and DOF measurements by ultrasound (78)*

- **Head circumference (HC):** it is measured in the same plane as the BPD. The US calipers are placed in the cranial external borders trying to adjust them according to their perimeter (78).

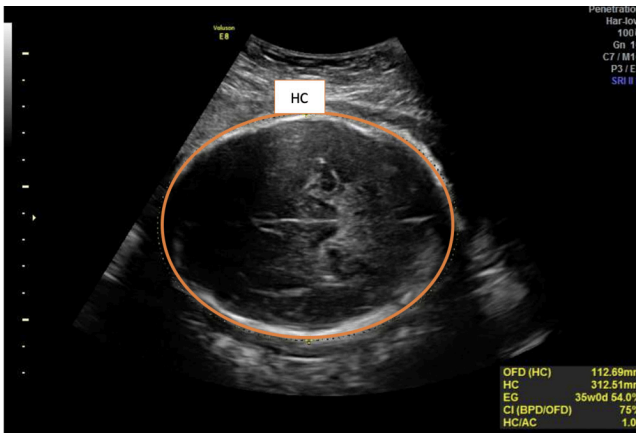


*Figure 10: HC measurement by ultrasound (78)*

- **Abdominal circumference (AC):** measured using an US ellipse in an axial plane of the fetal abdomen. It should be performed at a level where the vertebral column, the descendent aorta, the intrabdominal umbilical vein, and the gastric chamber are visible. It is considered the most important element in measuring the estimated fetal weight but, at the same time, the most challenging to correctly obtain (78).

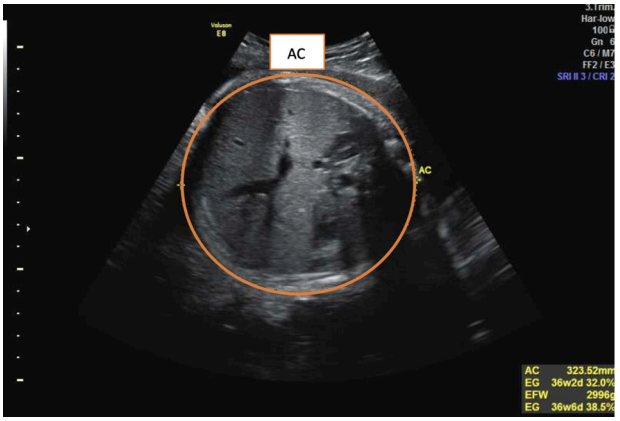


*Figure 11: AC measurement by ultrasound (78)*

- **Anterior abdominal wall thickness (AAWT):** This is measured by assessing the echogenic area located 2 to 3 cm lateral to the umbilical cord insertion in the standard plane for the AC. This measurement provides additional information on excessive adiposity accumulation and may contribute to the prediction of LGA infants (79).

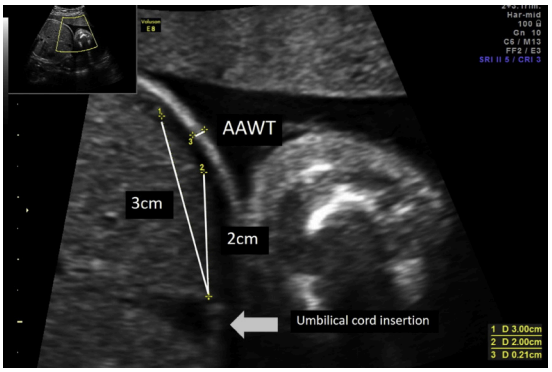


*Figure 12: Measurement of the anterior abdominal wall thickness (79)*

- **Femur length (FL):** it requires aligning the longitudinal axis of the bone with the transducer. Only the bone portions of the proximal femur diaphysis and metaphysis will be measured, the epiphyseal cartilage will be excluded from the measurement to avoid errors (78).

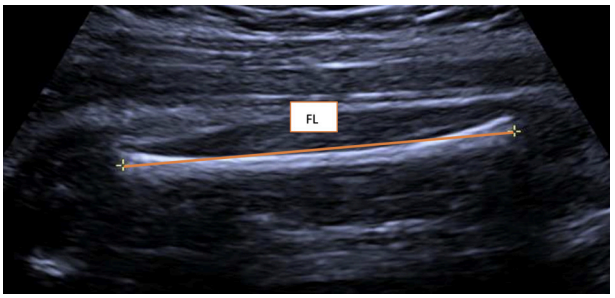


*Figure 13: FL measurement by ultrasound (78)*

Once the fetal biometrics are obtained, it is necessary to verify their correlation with the gestational age to confirm a proportional fetal development.

### 2.5.2 Fetal weight estimation

Fetal growth and screening for potential macrosomia are assessed using the **Hadlock formula** which calculates EFW from various biometric ultrasound measurements (BPD, HC, AC, and FL) (80). Estimated fetal weight by US is an important tool used for determining the optimal timing and method of delivery. However, this method may still lack precision and produce errors, especially in larger fetuses (49). Some studies have attempted to find a specific formula for predicting macrosomia in diabetic patients, although these have not yet been contemplated in routine clinical practice (81,81).

### 2.5.3 Assessment of the amniotic fluid

The assessment of amniotic fluid volume involves a subjective evaluation and semi-quantitative measurement, performed only in cases of suspected anomalies. This measurement is typically based on either the maximum vertical column or the amniotic fluid index (AFI) (78).

- **Maximum vertical column of fluid**, free from fetal parts or the umbilical cord. The results obtained can be classified into:
    - Vertical column of 2-10 cm: normal from 24 GW
    - < 2 cm: oligohydramnios (low amount of amniotic fluid)
    - > 10 cm: polyhydramnios (excess of amniotic fluid)
- The **AFI** involves the addition of the anteroposterior diameters of the largest empty fluid pocket (with no umbilical cord or fetal parts) in the four quadrants that divide the maternal abdomen (82). According to the values obtained, it can be classified as:
    - AFI 5 - 25: normal amniotic fluid
    - AFI < 5: oligohydramnios
    - AFI > 25: polyhydramnios

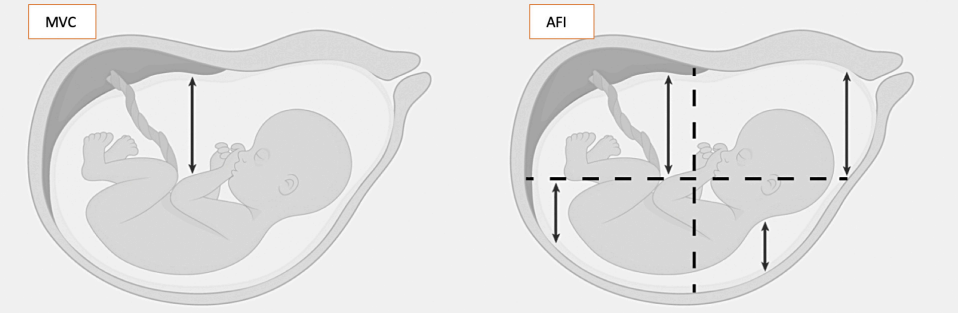


*Figure 14: Assessment of amniotic fluid by ultrasound (83)*

## 3. JUSTIFICATION

Diabetes mellitus is a chronic health condition with a major impact on the lives and well-being of individuals, families, and communities worldwide. With an estimated 529 million people living with diabetes in 2021, this number is projected to increase to 1.31 billion cases by 2050, reflecting a 51% rise. This increase is mainly due to the growing prevalence of type 2 DM associated with rising obesity and sedentary lifestyles (3).

This escalating prevalence of diabetes extends to pregnancy, where **complications for both the mother and the newborn** can not go unnoticed. Pregnancies complicated by preexisting DM are associated with congenital malformations, macrosomic fetuses with distinct growth patterns, stillbirth, hypertensive disorders of pregnancy, and **adverse obstetric events** during delivery that include emergency cesarean sections, OASI, postpartum hemorrhage, and even maternal death (16). Nevertheless, there is a lack of studies determining the incidence of such adverse maternal obstetric events in patients with PGDM.

A significant concern for fetuses of diabetic mothers is the potential occurrence of **macrosomia** or **LGA,** which may imply a higher risk of complications such as shoulder dystocia or OASI, especially in cases of inadequate glycemic control (45,49,53). Therefore, in such pregnancies, opting for **elective cesarean delivery** seems to be the preferred approach for fetuses with ultrasound-estimated fetal weight above **4,500g**, according to the SEGO and ACOG (5,49,84). Furthermore, it is worth noting that, in addition to elective cesarean sections recommended for macrosomia, many women with PGDM are scheduled for **labor induction** before 40 GW to mitigate the increase in fetal size with advancing gestational age and the rising risk of stillbirth (18). Recent unpublished data from the obstetric service at Hospital Universitari Josep Trueta reveal that maternal DM is the third leading cause of labor induction in the hospital. Nevertheless, a significant proportion of these inductions may **result in failure,** leading to emergency cesarean sections.

In these cases, the planned approach of delivery is often based on EFW. The objective of estimating fetal weight is to obtain information to facilitate safe vaginal delivery with minimum complications (85). Unfortunately, the prediction of birth weight is **imprecise** by ultrasonography (61). The Hadlock formula is used in general obstetric populations to estimate fetal weight through US examination. However, it has a mean absolute percent error of 13% in large fetuses, possibly because the formula may not be the most suitable for this type of fetus, which can have a different body fat distribution (61,86). A study concluded that approximately 50% of infants born to diabetic mothers delivered by scheduled cesarean section for sonographic estimated fetal weight > 4,250g

had in reality a birth weight of < 4,000g. This suggests that this group of patients may also experience certain iatrogenic deliveries (87).

These observations suggest that the utility of ultrasonography for obtaining estimated weights and therefore proposing elective cesarean sections based on this outcome is limited (88).

Therefore, **recognizing the challenges** in accurately predicting birth weight and the elevated number of patients undergoing induction, our research aims to **identify the ultrasound, metabolic, and maternal demographic factors that predict adverse obstetric outcomes** during vaginal delivery in women with PGDM. Our hypothesis suggests that the existence of specific factors will contribute to predicting a heightened risk of undesirable obstetric outcomes in this population.

By providing clearer and more accurate information, we seek to facilitate **better decision-making** regarding the necessity and **type of proposed delivery.** This approach is the first step to accurately select patients who would benefit from a **safe vaginal delivery** (induced or naturally), and alternatively, thoughtfully propose elective cesarean sections for patients at very high risk of adverse obstetric maternal outcomes, considering numerous factors beyond only the EFW. The goal is to potentially decrease the rate of maternal obstetric complications, thereby impacting the health of the mother and the newborn in the short and long term. Furthermore, our study aims to enhance the care of pregnant women with diabetes who are at high risk of complications during vaginal delivery, promoting their active participation in decision-making and ensuring comprehensive understanding throughout the entire pregnancy.

In conclusion, the current limitations in predicting EFW with US and the frequent inductions experienced by these patients, highlight the need to explore additional factors that may assist in predictions and guide appropriate decisions regarding labor management in pregnant women with DM. Our study aims to provide useful information to help make better decisions in these situations.

# 4. HYPOTHESIS

## 4.1 MAIN HYPOTHESIS

Fetal ultrasound, metabolic, and maternal demographic factors will allow us to predict adverse maternal obstetric outcomes during delivery in women with pregestational diabetes mellitus.

## 4.2 SECONDARY HYPOTHESIS

1. Ultrasound, metabolic, and maternal demographic factors will allow us to predict the occurrence of **shoulder dystocia** in women with PGDM.

2. Ultrasound, metabolic, and maternal demographic factors will allow us to predict the occurrence of **stillbirth** in women with PGDM.

3. Ultrasound, metabolic, and maternal demographic factors will allow us to predict the risk of **emergency cesarean sections** in women with PGDM.

# 5. OBJECTIVES

The proposed project has the following objectives:

## 5.1 MAIN OBJECTIVE

To identify fetal ultrasound, metabolic, and maternal demographic factors that are associated with **adverse maternal obstetric outcomes** during delivery in women with PGDM.

## 5.2 SECONDARY OBJECTIVES

1. To identify the ultrasound, metabolic, and maternal demographic factors that are associated with **shoulder dystocia** in women with PGDM.

2. To recognize the ultrasound, metabolic, and maternal demographic factors that are associated with **stillbirth** in women with PGDM.

3. To determine the ultrasound, metabolic, and maternal demographic factors that are associated with **emergency cesarean sections** in women with PGDM.

4. To estimate the **incidence** of adverse maternal obstetric outcomes in women with PGDM.

# 6. SUBJECTS AND METHODS

## 6.1 STUDY DESIGN

The project is designed as a **multicenter observational prospective cohort study.**

The cohort will be established according to the predefined selection criteria and will be followed during the course of the pregnancy until the moment of delivery. Study variables will be evaluated at the beginning of the study and periodically throughout gestation, as well as during the moment of delivery and up to one week after.

### 6.1.1 Study setting

The study will involve the simultaneous participation of **three tertiary-level hospitals** located in the provinces of Tarragona, Girona, and Lleida. These hospitals are Hospital Universitari Joan XXIII in Tarragona, Hospital Universitari Arnau de Vilanova (HUAV) in Lleida, and Hospital Universitari Josep Trueta (HUJT) in Girona. The last mentioned hospital will be assigned as the reference and coordinating center of the study. A designated researcher from each hospital will serve as the representative and coordinator of the center, ensuring effective communication and coordination among the other participating centers.

These hospitals have been chosen because they share a similarity in their patient populations, specifically in terms of demographics and delivery rates (see Table 13). As tertiary-level facilities, they serve as the primary centers for managing all diabetic patients in the region throughout pregnancy, providing a centralized approach from the start of gestation and through childbirth. This ensures effective patient management and a representative sample for our study.

## 6.2 STUDY POPULATION

The study population will consist of **pregnant individuals with pregestational diabetes mellitus** (type 1, 2, MODY, or other types) and those **diagnosed with preexisting diabetes during gestation** through screening. This screening, conducted in the first trimester of pregnancy for patients with high-risk factors, aims to identify potential previously undiagnosed overt DM.

To accurately define our study population, participants must adhere to the inclusion and exclusion criteria:

### 6.3.1 Inclusion criteria

- Singleton pregnancy
- Adequate level of awareness and ability to collaborate through the process
- Individuals over 18 years old
- Individuals diagnosed with PGDM (type 1, 2, or others) or with a positive screening for DM during the first trimester of pregnancy
- Pregnancy follow-up and expected delivery at HUJT, HUAV, or Hospital Universitari Joan XXIII

### 6.3.2 Exclusion criteria

The main exclusion criterion for our study will be the indication for a **scheduled cesarean section** unrelated to maternal hyperglycemia. This information is subject to change, and decisions regarding the time and type of delivery can be made until close to the time of birth.

Therefore, to define the study cohort, the exclusion criteria will be divided into two steps:

1. **Exclusion criteria during the moment of the study recruitment:**
    - Indication of an elective cesarean section from the beginning of pregnancy, which includes:
        - Two or more previous cesarean sections
        - History of uterine rupture
        - History of myomectomy
        - Maternal medical pathology discouraging vaginal delivery: severe cardiac disease or high risk of stroke.
2. **Exclusion criteria at the last scheduled ultrasound (36 - 37 GW):** in general, the second moment of exclusion will take place during the last ultrasound before delivery. If a patient

presents any of the following indications, a CS will be scheduled in the new fest days, and therefore, the patient will not be able to continue our study. Although it is estimated that a few patients will be excluded at the last moment, this will be taken into account when calculating the required number of participants for the study. Therefore, the second exclusion criteria include:

- Indication of cesarean section previous to birth:
    - Breech, transverse, or oblique fetus presentation
    - Placenta previa
    - Vasa Previa
    - IUGR type III or IV
    - Maternal infection: extensive condyloma affecting the birth canal, HIV - positive patients with > 1.000 copies at or near labor or with active lesions of genital herpes
    - Fetal malformation with an indication for elective cesarean section

### 6.3.3 Withdrawal criteria

Efforts should be made to ensure the completion of the study for every patient, taking into account both safety considerations and individual patient preferences. Patients who start the follow-up process should continue to track their progression unless there is a valid reason for discontinuation. Factors justifying the removal of a patient from the study follow-up comprise:

- **Request of the patient to withdraw** from the study at any time for personal reasons, without any implication on the follow-up of her pregnancy.
- If a patient experiences a **severe adverse event or an unexpected medical condition** during the study that is **unrelated to the research** procedures but makes participation unsafe.
- **Spontaneous abortion,** which is the pregnancy loss before 20 weeks of gestation.
- **Loss to follow-up:** if a participant, despite attempts at telephone contact with the patient or a designated contact person, does not attend the scheduled visit. Conscientious efforts will be made to encourage continued follow-up. Additionally, it includes situations where the participants opt for pregnancy follow-ups or delivery at a hospital not included in our study.
- Patients with **pregnancy complications** to the extent that they are advised to seek alternative medical care outside of the study.

## 6.4 SAMPLING

### 6.4.1 Sample size

Based on the limited published studies addressing the epidemiology of maternal obstetric complications during childbirth in women with PGDM, the estimated incidence of experiencing any of these adverse outcomes can range from 2.2% to 28.1% (89,90). Due to the heterogeneity of the studies and the absence of obstetric outcomes reported in a composite similar to the one studied in our work, and given that the presence of a single complication will be considered a positive adverse obstetric outcome, we have chosen the highest incidence as a reference point, which is the presence of emergency cesarean section in women with PGDM at 28.1%. With this information and considering that there will be a certain degree of overlap between outcomes, we estimate the incidence to be **30%.**

In a bilateral sample, accepting an alpha risk of 0.05 and a power of 0.8 in a two-tailed test, **220 subjects** are required to detect a statistically significant relative risk equal to or greater than 1.5. The estimated incidence rate in the non-exposed group is 0.3, and a dropout rate of 20% has been anticipated which also takes into account the estimated percentage of patients excluded during the last US scheduled visit.

### 6.4.2 Sample collection and recruitment

A **non-probabilistic consecutive** method of recruitment will be followed in this study. Patients meeting the inclusion criteria and without any of the exclusion criteria will be informed about the study objectives. Those expressing interest will have the opportunity to voluntarily participate and will be provided with an information document (Annex 5) along with the informed consent form (Annex 6). Participation will be confirmed when patients sign the informed consent.

The patients will be recruited in the three hospitals participating in the study and the estimated time of recruitment will be **1 year and 6 months.**

Considering that all diabetic patients in a province will give birth at their third-level reference hospital, the approximate number of deliveries in each of them has been collected (Table 13). Adding the three provinces together, it is estimated that there will be a total of 15,000 deliveries per year. Taking into account that the approximate percentage of PGDM is 1% of all pregnancies, it is estimated that the recruitment of 220 patients in the participating hospitals will be completed in 1.5 years.

*Table 13: Number of deliveries per province and reference hospital for women with pregestational diabetes mellitus (91)*

| **Province** | **Total births attended** (2022) | **Reference Hospital for PGDM women** |
|---|---|---|
| Girona | 5,876 | Hospital Universitari Josep Trueta |
| Lleida | 3,188 | Hospital Universitari Arnau de Vilanova |
| Tarragona | 5,925 | Hospital Universitari Joan XXIII |

For individuals with known PGDM, **the invitation to participate in the study** will take place during their scheduled first visit to the **high-risk obstetric unit**, typically around 8 - 10 GW. Additionally, our study will include **patients diagnosed with unknown preexisting diabetes during gestation**. These individuals will be identified through diabetes screening conducted during the first-trimester blood test (9 - 10 GW) in pregnant women with high-risk factors. The proposal for participating in the study for these patients will take place after the screening confirms the presence of previously undiagnosed PGDM.

In conclusion, there will be two closely related instances in which patients will be invited to participate in our study (Figure 15).

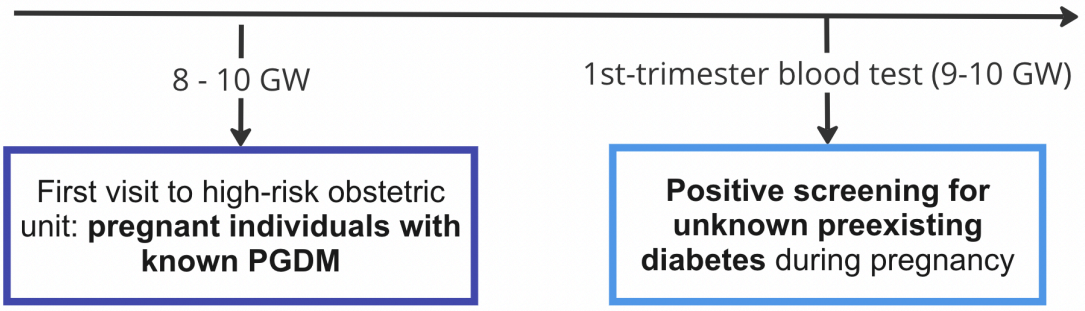


*Figure 15: Proposal process for patient participation in our study*

**The definitive recruitment** will occur uniformly for all eligible patients during their **first ultrasound visit** (between 11+2 and 13+6 GW). Participants meeting exclusion criteria at the time of recruitment will be excluded from the study. Additionally, during the last scheduled ultrasound (36 - 37 GW), participants with a clear indication for an elective cesarean section, unrelated to the variables under study, will be excluded.

## 6.5 VARIABLES AND MEASUREMENTS

### 6.5.1 Dependent variable

The main **dependent variable** under investigation is the **presence of adverse obstetric maternal outcomes** during vaginal delivery. This variable is characterized as a **composite outcome**, which is a combined measure that includes multiple individual outcomes. Each individual outcome will be designated either as 'present' or 'absent'. Consequently, the presence of adverse obstetric outcomes will be treated as a **composite dichotomous nominal qualitative variable**, labeled as 'yes' if any of the following complications are present or 'no' if none of the specified complications occur. Therefore, the presence of adverse obstetric maternal outcomes contemplates:

- Emergency cesarean section: surgical procedure performed when there exists an immediate threat to the life of the fetus and/or woman. In the context of pregnant individuals with DM, this situation can occur due to CPD, SFC, or FIOL. It will be documented at the moment the patient enters the operating room to undergo an unscheduled CS.
- Obstetric anal sphincter injuries: it includes exclusively 3rd and 4th-degree perianal tears which can lead to significant maternal morbidity including fecal or gas incontinence, pain, and sexual dysfunction. If present, they will be documented at the time of delivery.
- Early postpartum hemorrhage: defined as a minimum of 1,000mL of blood loss or blood loss concurrent with signs and symptoms of hypovolemia (Annex 3) after vaginal delivery (48). It will be measured at **1 hour postpartum**, and if there is continued bleeding, for up to 2 hours postpartum. In cases of clinically suspected EPPH, the visual estimation of blood (Annex 4) can be quantified to estimate the bleeding present in surgical dressings, sheets, and puddles. This approach offers a fast and simple method for detecting bleeding, although the most accurate method involves using **calibrated blood collection bags** along with measuring **blood losses by weight**. To achieve this, if the weight of the compresses, gauzes and underpads during delivery is known, it can be subtracted from the total weight once soaked in blood, using the conversion 1g = 1mL (92).

  Therefore, the presence of EPPH will be considered positive if the estimated weight of the material used exceeds 1,000g or directly if the patient exhibits symptoms of hypovolemia along with estimated visual blood loss.
- Maternal death: caused as a result of major complications arising from childbirth. The consideration will extend to death during childbirth and up to one week afterward.

The **secondary dependent variables** that will answer the secondary objectives include:

- Shoulder dystocia: it occurs when the descent of the fetus's anterior shoulder is obstructed by the mother's symphysis pubis, but it can also result from the impaction of the posterior shoulder of the fetus on the sacral promontory. It requires additional obstetric maneuvers to facilitate fetal expulsion after the head has emerged (54). It should be suspected in the following situations:
    1. Failure to deliver the fetal shoulders using only gentle downward traction
    2. Requirement of additional delivery maneuvers to successfully deliver the newborn
    3. Documented head-to-body interval of greater than 1 minute

  The definitive diagnosis of shoulder dystocia will be determined at the time of delivery by the care provider, who could be the obstetrician or a midwife. This diagnosis will be treated as a dichotomous nominal qualitative variable, documented as present or absent.
- Stillbirth: this variable records fetal death during pregnancy in fetuses weighing more than 500g or those that are more than 22 GW old, according to the SEGO definition (38). The definitive diagnosis will be made through the absence of cardiac activity on ultrasound and will be documented at the time of discovery. It will be treated as a dichotomous nominal qualitative variable, labeled as present or absent.
- Emergency cesarean section: due to CPD, SFC, or FIOL. It will be documented at the moment the patient enters the operating room to undergo an unscheduled CS and treated as a dichotomous nominal qualitative variable, labeled as present or absent.
- Number of cases of adverse maternal obstetric outcomes: discrete quantitative variable presented as absolute frequencies. It will also be documented during vaginal delivery.

*Table 14: Summary of the Dependent Variables*

OASI: Obstetric and Anal Sphincter Injury; CS: Cesarean Section; EPPH: Early Postpartum Hemorrhage

| VARIABLE | | | TYPE OF DATA | CATEGORIES |
|---|---|---|---|---|
| **MAIN DEPENDENT VARIABLE** | **Presence of adverse obstetric maternal outcomes** (Yes/ No) | Emergency CS | Dichotomous nominal qualitative | Present or Absent |
| | | OASI | | |
| | | EPPH | | |
| | | Maternal death | | |
| **SECONDARY DEPENDENT VARIABLES** | **Shoulder dystocia** | | Dichotomous nominal qualitative | Present or Absent |
| | **Stillbirth** | | | Present or Absent |
| | **Emergency CS** | | | Present or Absent |
| | **Number of cases of adverse obstetric maternal outcomes** | | Discrete quantitative | - |

## 6. 5.2 Independent variables

- Third-trimester ultrasound biometrics: main biometric measurements will be obtained as part of standard practice during the **third-trimester abdominal ultrasound** (conducted at 34 - 36 GW). These biometric measurements include (See section Fetal Biometrics):
  - **Biparietal diameter:** measured by the maximum diameter of the parietal eminences in a transverse section of the skull.
  - **Occipitofrontal diameter**: measured in the same plane as the BDP, with a line drawn from the frontal region's center of the skull to the center of the occipital region.
  - **Head circumference:** measured by placing the US calipers on the outer margins of the head trying to adjust them to its perimeter.
  - **Abdominal circumference:** measured using an US ellipse in an axial plane of the fetal abdomen.
  - **Anterior abdominal wall thickness**: measured by assessing the echogenic area located 2 to 3 cm lateral to the umbilical cord insertion in the standard plane for the AC.
  - **Femur length:** calculated by aligning the US transducer with the longitudinal axis of the bone and measuring the bone portions of the femur diaphysis and metaphysis (excluding the epiphyseal cartilage).

All of the previously listed ultrasound biometrics will be treated as individual quantitative variables and expressed in millimeters. Each measurement will then be introduced into a **digital calculato**r that generates an estimated percentile using **local population-based curves**. These curves result from birthweight databases at the population level, providing estimations for gestational age and fetal weight. While digital calculators developed in our context are often used to assign percentiles based on gestational age, this study opted to use the **WHO's online calculator** for comprehensive determination and result standardization (93). This choice is motivated by the fact that certain individual biometrics cannot be computed using the digital calculators commonly employed in our hospitals. Subsequently, each parameter will be finally treated as an ordinal qualitative variable and categorized according to a percentile calculated using the online fetal growth calculator**:**

- < 10 percentile
- 11- 90 percentile
- > 90 percentile

- **Combination of sonographic measurements:** these combinations will be determined through simple calculations using biometrics obtained or derived from measurements taken in routine US third-trimester clinical practice. Given the distinct body fat distribution that fetuses of diabetic mothers can display, some biometric relationships have been identified as posing an elevated risk of shoulder dystocia and therefore will be taken into account in our study. These include:
  - **Abdominal diameter (AD) - Biparietal Diameter:** this measure will be obtained by subtracting the AD from the BPD. The AD is a biometric measurement that is not routinely performed but can be easily calculated in the same ultrasound plane as the abdominal circumference. This process involves drawing a transverse line between the edges of the abdominal circumference, thereby obtaining a value in millimeters. An article found that when the value of the subtraction is > 26 mm, the risk of shoulder dystocia is significant (46). Therefore, we will treat this variable as a dichotomous ordinal qualitative variable, classified into:
    - ≥ 26 mm
    - < 26 mm
  - **Femur length / Abdominal Circumference:** this ratio is obtained by dividing the ultrasound measurement of FL in millimeters by the value of AC also expressed in millimeters. A study observed that this relationship was significantly associated with

shoulder dystocia at the value of 0.208 (94). Hence, we will categorize this measurement as a dichotomous ordinal qualitative variable grouped into:

- ≥ 0.208
- < 0.208

- **Estimated fetal weight:** this variable will be collected and recorded during the **final US** before delivery. In most cases, this US will be conducted during weeks 36 - 37; however, if not available, the EFW obtained in the patient's most recent ultrasound will be used. The EFW is determined by applying the Hadlock formula to the BPD, HC, AC, and FL measurements (80). This formula is used in daily clinical practice with all patients and is, in fact, integrated into our hospital ultrasound machines, which automatically calculate the EFW once the necessary biometric measurements are obtained. This variable will be treated as an ordinal qualitative variable, divided into the following categories:
  - < 3,000g
  - 3,000 - 3,500g
  - 3,501g - 4000g
  - 4,001 - 4,500g
  - 4,501 - 5,000g
  - > 5,000g

- Other ultrasound and fetal characteristics:
  - **Amniotic fluid volume:** it will be obtained during the **third-trimester ultrasound**, and measured by calculating the maximum liquid column (free of fetal parts or umbilical cord) in a vertical direction. It will be treated as an ordinal qualitative variable divided into three categories:
    - < 2 cm: oligohydramnios
    - 2-10 cm: normal from 24 GW onward
    - > 10 cm: polyhydramnios
  - **Interval between the last ultrasound and delivery** (days): this will be considered a continuous quantitative variable, represented as the average number of days with a deviation. It will be documented on the day the pregnant woman is admitted for delivery.

- **Gestational age at birth:** it is an ordinal qualitative variable that will be classified once the newborn is born into:
    - Preterm: < 37 GW
    - Early term: 37 - 38+ 6 GW
    - Full term: 39 - 40 + 6 GW
    - Late term: > 41 GW

- Metabolic characteristics of the mother:
    - **Type of preexisting diabetes:** this variable will be recorded during the baseline visit and it will be treated as a polytomous nominal qualitative variable divided into:
        - Type 1 DM
        - Type 2 DM
        - MODY
        - Other types of DM
    - **HbA1c levels:** HbA1c will be measured and recorded during the 1st, 2nd, and 3rd-trimester blood analysis. It will be considered as an ordinal qualitative variable, stratified according to the level of glycemic control:
        - HbA1c ≤ 6.5%: Good control
        - HbA1c 6.6 - 8%: Suboptimal control
        - HbA1c 8.1 - 10%: Poor control
        - HbA1c > 10%: Very poor control
    - **Type of treatment:** polytomous nominal qualitative variable, recorded during the final visit as treatment requirements may vary through pregnancy. It will be classified into:
        - Diet and exercise
        - Diet and exercise + Metformin
        - Diet and exercise + Insulin
    - **Duration of diabetes:** this variable will be categorized as an ordinal qualitative variable, representing the time in **years** since the onset of DM. It will be documented during the first visit and classified into the following categories:
        - DM diagnosed during pregnancy through first-trimester screening
        - Duration of < 5 years since pregnancy
        - Duration of 5 - 10 years since pregnancy
        - Duration of > 10 years since pregnancy

- Maternal demographic and other factors: all the following variables will be documented during the initial visit, either through a clinical interview or by reviewing the medical history. The only exception is the variable "weight gain during pregnancy", which will be assessed and documented during the last scheduled visit. The main maternal factors studied are:
  - **Age:** it is a quantitative variable measured in years and categorized as an ordinal qualitative variable in the following intervals:
    - < 25 years old
    - 25 - 35 years old
    - 36 - 40 years old
    - > 40 years old
  - **Origin:** it will be treated as a polytomous nominal qualitative variable and divided into
    - Caucasian
    - Sub-Saharan
    - Asian
    - North African
    - Latino American
    - Others
  - **Parity:** treated as a dichotomous nominal qualitative variable divided into:
    - Nulliparous: 0 previous births
    - Multiparous: ≥1 previous birth
  - **Previous cesarean sections:** It will be treated as a dichotomous nominal qualitative variable. Classified into:
    - Yes
    - No
  - **Maternal body mass index (BMI) at conception:** it will be calculated using the following formula BMI = weight/height$^2$, expressed in Kg/m$^2$. It will be treated as an ordinal qualitative variable:
    - < 18.5 kg/m$^2$: underweight
    - 18.5 - 24.9 kg/m$^2$: normal weight
    - 25 - 29.9 kg/m$^2$ : overweight
    - 30 - 34.9 kg/m$^2$: obese
    - ≥ 35: extremely obese

- **Weight gain during pregnancy:** it will be considered an ordinal qualitative variable and categorized into three different groups based on the Institute of Medicine (IOM) recommendations regarding weight gain during pregnancy in relation to the starting body mass index:

*Table 15. IOM recommendations for total weight gain during pregnancy (95)*

| **Pregnancy BMI** | **Recommended Total Weight Gain** (kg) |
|---|---|
| Underweight (<18.5kg/$m^2$) | 12.5 - 18 |
| Normal weight (18.5 - 24.9 kg/$m^2$) | 11.5 - 16 |
| Overweight (25.0 - 29.9 kg/$m^2$) | 7 - 11.5 |
| Obese (≥ 30.0 kg/$m^2$) | 5 - 9 |

*Calculations assume a 0.5 -2 kg weight gain in the first trimester

The three designated categories are:

- Below IOM recommendations
- Within IOM recommendations
- Above IOM recommendations

- **Follow-up and delivery hospital:** it will be treated as a polytomous nominal qualitative variable and classified, according to the reference hospital of the women, into:
  - Hospital Universitari Josep Trueta (HUJT)
  - Hospital Universitari Arnau de Vilanova (HUAV)
  - Hospital Universitari Joan XXIII

*Table 16. Summary of the Independent Variables*

P: Percentile; IUGR: Intrauterine Growth Restriction; SGA: Small for Gestational Age; LGA: Large for Gestational Age; IOM: Insitute of Medicine; HUJT: Hospital Universitari Josep Trueta; HUAV: Hospital Universitari Arnau de Vilanova; AD: Abdominal Diameter; BPD: Biparietal Diameter; FL: Femur Lenght; AC: Abdominal Circumference

| | VARIABLE | | TYPE OF DATA | CATEGORIES OR VALUES |
|---|---|---|---|---|
| INDEPENDENT VARIABLES | **3rd-trimester ultrasound biometrics** | | | |
| | Biparietal diameter | | Ordinal qualitative variable | < 10p / 10 - 90p / > 90p |
| | Head circumference | | | |
| | Occipito-frontal diameter | | | |
| | Abdominal circumference | | | |
| | Anterior abdominal wall thickness | | | |
| | Femur length | | | |
| | Combination of sonographic measurements | AD - BPD | Dichotomous ordinal qualitative variable | ≥ 26 mm / < 26 mm |
| | | FL/AC | | ≥ 0.208 / < 0.208 |
| | Estimated fetal weight | | Ordinal qualitative variable | < 3,000g / 3,000 - 3,500g / 3,501g - 4,000g / 4,0001 - 4,500g / 4,501 - 5,000g / > 5,000g |
| | **Other ultrasound and fetal characteristics** | | | |
| | Amniotic fluid | | Ordinal qualitative variable | < 2cm (oligohydramnios) / 2-10cm (normal from 24 GW onward) / > 10cm (polyhydramnios) |
| | Interval between last ultrasound and delivery | | Continous quantitative variable | - |
| | Gestational age at birth | | Ordinal qualitative variable | Peterm (< 37 GW) / Early term (37 - 38+ 6 GW) Full term (39 - 40 + 6 GW) / Late term (> 41 GW) |
| | **Metabolic characteristics of the mother** | | | |
| | Type of diabetes | | Polytomous nominal qualitative variable | Type 1 DM / Type 2 DM / MODY / Other types of DM |

| | | | |
|---|---|---|---|
| | Glycemic control (during the 1st, 2nd and 3rd trimester) | Ordinal qualitative variable | HbA1c ≤ 6.5% (Good control) / HbA1c 6.6 - 8% (Suboptimal control) / HbA1c 8.1 - 10% (Poor control) / HbA1c > 10% (Very poor control) |
| | Type of treatment | Polytomous nominal qualitative variable | Diet and exercise / Diet and exercise + Metformin / Diet and exercise + Insulin |
| | Duration of diabetes | Ordinal qualitative variable | Diagnosed during pregnancy / < 5 years since pregnancy / 5 - 10 years since pregnancy / > 10 years since pregnancy |
| | **Maternal demographic and other factors** | | |
| | Age | Ordinal qualitative variable | < 25 years old / 25 - 35 years old / 35 - 40 years old / > 40 years old |
| | Origin | Polytomous nominal qualitative variable | Caucasian / Sub-Saharan / Asian / North African / Latino American / Others |
| | Parity | Dichotomous nominal qualitative variable | Nulliparous (0 previous births) / Multiparous (≥1 previous birth) |
| | Previous cesarean sections | Dichotomous nominal qualitative variable | Yes / No |
| | Weight gain during pregnancy | Ordinal qualitative variable | Below IOM recommendations / Within IOM recommendations / Above IOM recommendations |
| | Maternal BMI at conception | Ordinal qualitative variable | < 18.5 (underweight) / 18.5 - 24.9 (normal weight) / 25 - 29.9 (overweight) / 30 - 34.9 (obese) / ≥ 35 (extremely obese) |
| | Follow up and delivery hospital | Polytomous nominal qualitative variable | HUJT / HUAV / Hospital Universitari Joan XXIII |

## 6.6 DATA COLLECTION

As this is a prospective study, and all the variables included in our research are **systematically collected** in any PGDM pregnancy, a significant portion of the data will be registered and documented by healthcare professionals in the clinical history of both the mother and the newborn as the study progresses. Another small portion of the data will be collected through clinical interviews and a review of the medical history during the baseline visit.

Professionals at the participating hospitals will receive **training** specifically focused on how to record the information to prevent any confusion or errors in this regard. This training aims to ensure uniform and correct data entry in the patient's medical records.

Before starting the study, each participating center will be assigned a co-investigator and one of their principal functions will be to collect all the relevant participant data and transfer it to an **online database**, the "Redcap", which will permit the subsequent analysis of results. The data manager will be responsible for overseeing data quality and ensuring its consistency to avoid any type of errors. Additionally, he/she will handle the anonymization process by coding the name and personal information of each participant using an identification number.

Patients previously diagnosed with DM type 1, 2, MODY, or others and with suspected pregnancy, will be scheduled for an initial visit at the high-risk obstetric unit between 8 - 10 GW. This visit will include a US to confirm pregnancy, assess viability, and determine the gestational age. Eligible patients will be informed about the possibility of participating in the study during this visit.

Also, patients without a known history of diabetes but with high-risk criteria will undergo early screening during the first-trimester blood analysis to exclude previously undiagnosed DM. Patients with a positive screening will also be proposed to participate in the study (following the same criteria as the previous group) during the confirmation visit. All of them will receive an information document (Annex 5) providing all the necessary details about the study and its objectives.

Subsequently, during the **first-trimester ultrasound** appointment, a thorough review of the information document will be conducted. Within this session, aside from the routine US, a designated portion of the visit will be reserved to offer the patients the opportunity to address any doubts they may have regarding the study. If the patient agrees to participate, they will be provided with the informed consent form (Annex 6) for her to sign, allowing entry into the study. Furthermore, during this visit, the obstetrician will gather the necessary information about the

patient's medical history and first-trimester laboratory results. A detailed clinical interview will be conducted to collect essential data related to the study variables.

The patients in the study will be followed throughout their pregnancy, collecting all the necessary information for the study until the moment of birth.

At the immediate moment of delivery and within the following 24 hours, patients will be assessed and any potential maternal complications during this period will be documented.

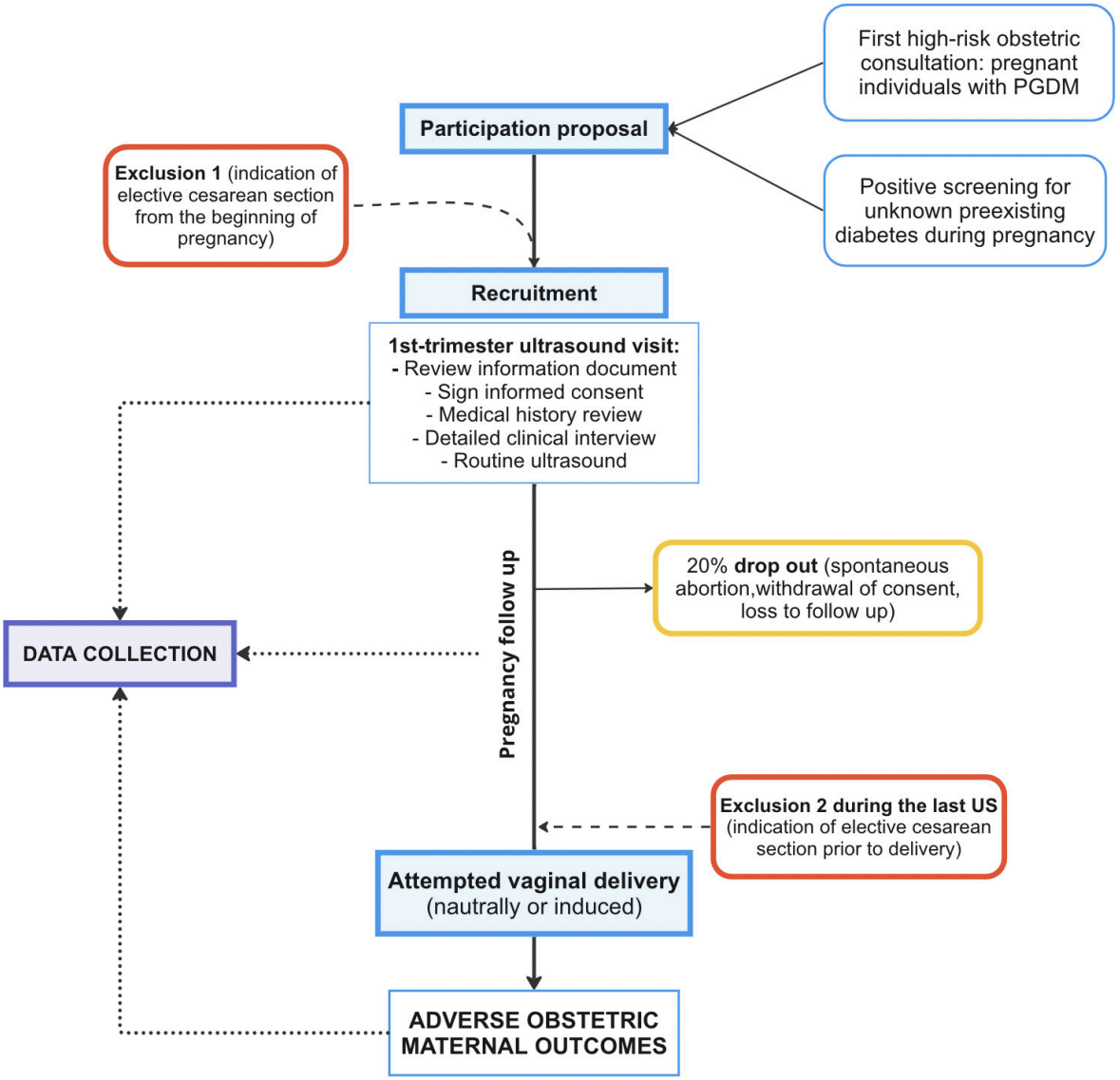


*Figure 16. Study methodology summary*

## 7. STATISTICAL ANALYSIS

The statistical analysis will be conducted by the contracted statistical analyst, using the Statistical Package for Social Science (SPSS) software version 29.0.1.

We will consider a p-value < 0.05 as statistically significant, with a defined confidence interval of 95% for all analyses.

### 7.1 Descriptive analysis

Statistical summaries of **quantitative variables** will be presented using means with standard deviation for precision for continuous variables or those with a symmetrical distribution; medians with interquartile ranges for discrete variables or those continuous with an asymmetrical distribution. For **qualitative variables**, proportions will be calculated.

The incidence of adverse maternal obstetric outcomes will be estimated with a **crude rate** (number of cases during the study period divided by the population studied).

### 7.2 Bivariate inference

In the bivariate inference, we will compare the group of patients who have experienced the outcome (adverse maternal obstetric outcome during delivery) with those who have not.

The **Student's t-test** will be used to compare the means between these two groups of quantitative continuous variables with a symmetrical distribution and **Mann-Whitney's U test** for the medians of discrete or continuous variables with an asymmetrical distribution.

The **Chi-Square** or **Fisher's exact test** will be used to compare the proportions of qualitative categorical variables.

### 7.3 Multivariate analysis

To assess the association and identify a potential independent effect among the ultrasound, metabolic and maternal demographic factors, and adverse maternal obstetric outcomes, a **logistic regression** will be employed. The independent and the dependent variables will be adjusted to avoid possible confounding. This way, we will determine which variables are independently associated with the outcome and the magnitude of their association.

To standardize the age-specific incidence rate with the population, a **Poisson regression** will be employed.

## 8. ETHICAL AND LEGAL CONSIDERATIONS

Principal investigators and co-investigators will commit to conducting the study in strict adherence to human rights and ethical principles outlined in the World Medical Association Declaration of Helskiny, specifically in the "Ethical Principles for Medical Research Involving Human Subjects" last revised in October 2013.

Furthermore, this study adheres to the Principles of Biomedical Ethics as proposed by Beauchamp and Childress, commonly known as the four fundamental ethical principles:

- **Autonomy:** all patients will be provided with an **informative document** (Annex 5) detailing the study's objectives and execution plan, presented clearly and transparently to enable them to comprehend and interpret it accurately. Additionally, they will be given a document to sign their **informed consent** (Annex 6) regarding the study, indicating their willingness to participate after correctly understanding all the provided information and the study procedures, with the assurance that they can withdraw at any time from the study plan without consequences (Annex 7). The voluntary decision of patients to participate or not in the study will be respected, without coercion, following the *"Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica".*
- **Justice:** the study will adhere to the principle of justice by ensuring an equitable distribution of well-being benefits. All pregnant individuals who meet the inclusion criteria and none of the exclusion criteria shall enter the study, avoiding any type of discrimination in access to health resources or against any group of individuals.
- **Beneficence:** this study will act for the benefit of women to offer them a potential improvement in their experience with pregnancy and childbirth. Adherence to the ethical principle of beneficence will be ensured by committing to provide all enrolled women with quality resources and healthcare professionals who follow evidence-based practices. The study aims to improve obstetric outcomes for patients and potentially impact the health of both women and their offspring.
- **Non-maleficence:** given the observational nature of the study, no harm will be caused to the patients, thereby respecting the principle of non-maleficence.

The research protocol will be subjected to evaluation by the "Comitè Ètic d'Investigació Clínica (CEIC)" of Hospital Universitari Josep Trueta and the other participating hospitals. In case of any

objections or concerns, necessary modifications will be made, taking into account their observations. The study will initiate only upon obtaining their approval.

All the personal data collected from the patients included in the study will be **private** and **confidential**, guaranteed following the "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los Derechos Digitales" and "the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural people with regards to the processing of personal data and on the free movement of such data". To ensure confidentiality, each patient will be assigned a unique identification number, which will be recorded in the database for analyzing information anonymously. This pseudonymization process will be conducted by external personnel, different from the investigators, to maintain privacy.
Furthermore, the team is committed to collecting only relevant data, ensuring that it remains exclusively available to the research team and solely for the purpose of the study.

Investigators of this study declare there are no conflicts of interest and authors affirm that the main goal of this research is to develop knowledge to improve human health and quality of life. Additionally, all results will be published with complete transparency, including unexpected or unfavorable data.

# 9. WORK PLAN AND CHRONOGRAM

## 9.1 PARTICIPATING CENTERS

The three third-level participating centers in the study are as follows: Hospital Universitari Josep Trueta in Girona, Hospital Universitari Joan XXIII in Tarragona, and Hospital Universitari Arnau de Vilanova in Lleida.

## 9.2 RESEARCH TEAM MEMBERS

The research team involved in the study will include:

- **Principal Investigator (PI)**: individual leading the study and responsible for the protocol development, result organization, formulation of conclusions, publication, and management of global communication with participating centers.
- **Project coordinator (PC)**: who will serve as the individual responsible for the project supervision and ensuring the proper development and adherence to the protocol.
- **Co-investigators (CI):** in each participating center, there will be one investigator responsible for coordinating and supervising their team. The co-investigators will also be tasked with transferring data from the medical records of their respective hospitals to the database. All co-investigators involved in the study will meet every six months with the principal investigator and the project coordinator to ensure the proper development of the study.
- **Health care professionals (HCP):** including obstetricians, endocrinologists and midwives. They will be in charge of monitoring and following up on diabetes and pregnancy, as well as facilitating childbirth for women participating in our study. They will also document all the relevant information in the patient's medical history.
- **Data manager (D):** will be responsible for establishing the database, supervising the collected data, and overseeing the anonymization process.
- **Statistical specialist (SS):** will conduct the statistical analysis of the study.

## 9.3 STUDY STAGES

The chronological sequence will be as follows:

**STAGE 0: ELABORATION OF THE PROTOCOL AND STUDY DESIGN** (November 2023 - February 2024), led by the principal investigator and the project coordinator.

- **First meeting** (November 2023, concluded): in the first meeting, the principal investigator (Laura López) and the project coordinator (Dra. Alexandra Bonmatí) met to agree on developing this study. The main objectives, methodology, and hypothesis of the protocol

were defined. During the meeting, the subsequent steps for conducting the study were also established and agreed upon.

- **Literature review and protocol elaboration** (November 2023 - January 2024, concluded): Over these months, an extensive literature review on the main clinical practice guidelines related to PGDM was conducted, in addition to reviewing the latest articles published on the topic. This effort was made to gather the essential information for developing a study protocol based on current scientific evidence.
- **Contact with participating hospitals** (February 2024): the principal investigator will reach the proposed participating centers and provide them with a copy of the protocol for thorough review.
- **Creation of the database** (February 2024): the data manager will create a database to ensure proper data collection for the study.

**STAGE 1: ETHICAL EVALUATION OF THE PROTOCOL** (February - April 2024), led by the principal investigator and the *Comitè Ètic d'Investigació Clínica* (CEIC).

Before initiating the study, the protocol will need to be reviewed and approved by the Ethics Committee of Clinical Investigation, the CEIC, of the HUJT. At the same time, the protocol will be submitted to the Ethical Committee of the other participating centers. Relevant changes to the protocol will be made if necessary during this period. The duration of this stage may vary based on the time required for the project approval by the CEIC.

**STAGE 2: COORDINATION** (May - June 2024), led by all the team.

- **Research team meeting and selection of co-investigators** (May 2024): it will have the objective of bringing together the members of the research team to discuss and identify the key health professionals who will actively contribute to the study. Also, each hospital's research team will meet and choose a co-investigator who will be responsible for communication and coordination with the other participating centers throughout the study. This session plays an important role in detailed planning, facilitating communication, and creating a cohesive environment to achieve successful collaboration among the team members. Any questions that may arise will be addressed by the principal investigators and the project coordinator. Continuous communication via telephone or email with all the members will be proposed to ensure uniformity throughout the entire project.

- **Training sessions** (May - June 2024)**:** medical professionals in the Obstetrics and Gynaecology department of each participating hospital will receive short training on how to collect all the data properly to avoid any possible errors.

**STAGE 3: DATA COLLECTION AND FOLLOW-UP** (June 2024 -June 2026) led by the healthcare professionals, co-investigators, and the data manager.

- **Patient recruitment** (June 2024 - December 2025)**:** patients will be recruited using a consecutive non-probabilistic sampling method. Participants will have to meet the inclusion criteria and any of the exclusion criteria. Also, they are required to sign the informed consent paper (Annex 6). Recruitment will continue until the desired number of participants, which is 220, is achieved. It is estimated that this process will take 1.5 years.
- **Patients' follow-up** (June 2024 - June 2026)**:** participants will be followed throughout the entire pregnancy and until the moment of delivery. Emphasis will be placed on attending scheduled visits and telephone contact will be maintained with participants to ensure they do not discontinue their involvement in the study. Once the woman has given birth, data related to the delivery and potential complications arising up to 24 hours afterward will be collected.
- **Data collection** (June 2024 - June 2026): all this information will be documented in the clinical history of both the mother and the newborn. Professionals from the referral hospitals will receive training on what information to record and how to record it. Subsequently, co-investigators at each hospital will enter the recorded data into the "RedCap" platform. The data manager will be responsible for overseeing and anonymizing the entered information.

Additionally, during this stage, the principal investigator and the project coordinator will meet up periodically to ensure the correct progress of the study.

**STAGE 4: STATISTICAL ANALYSIS AND INTERPRETATION** (June - August 2026), led by the statistical specialist, the principal investigator, and the project coordinator.

- **Statistical analysis** (June - August 2026): once all the necessary data is gathered and recorded, a contracted statistician will conduct the statistical analysis through descriptive, bivariate, and multivariate analysis.
- **Data interpretation** (August 2026): the final data interpretation will be conducted by the principal investigator and the project coordinator, together with the help and advice of the

statistician. This will allow a comprehensive discussion of the study and the formulation of coherent and relevant conclusions.

**STAGE 5: FINAL ARTICLE ELABORATION AND PUBLICATION OF THE RESULTS** (August 2026 - December 2026), led by the principal investigator and project coordinator.

- **Article elaboration and revision** (August - October 2026): the principal investigator, with the collaboration of the project coordinator, will be responsible for writing a paper summarizing the main findings obtained during the study and their relevance.
- **Publication of the study and congresses** (October - December 2026)**:** the final paper and the main conclusions will be presented to the *Sociedad Española de Ginecología y Obstetricia (SEGO)* and the *European Board and College of Obstetrics and Gynaecologists (EBCOG).* Furthermore, the publication of the results in the "Revista Científica de la Sociedad Española de Ginecología y Obstetricia" will be proposed. Additionally, there will be a proposal to present and disseminate the obtained results at national and international congresses.

## 9.4 CHRONOGRAM

| STAGE AND TASKS | STAFF | 2023 | | 2024 | | | | | | | | | | | | 2025 | | | | | | | | | | | | 2026 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | D | J | F | M | A | M | J | J | A | S | O | N | D | J | F | M | A | M | J | J | A | S | O | N | D | J | F | M | A | M | J | J | A | S | O | N | D |
| **STAGE 0 - ELABORATION OF THE PROTOCOL AND STUDY DESIGN** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| First meeting | PC, PI | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Literature review + protocol elaboration | PI | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Contact with participating hospitals | PI | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **STAGE 1 - ETHICAL EVALUATION** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ethical evaluation and approval | CEIC, PI | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **STAGE 2 - COORDINATION** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Research team meeting | PC, PI, HCP, CI | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Training sessions | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **STAGE 3 - DATA COLLECTION AND FOLLOW - UP** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Patient recruitment | HCP | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Patient's follow up | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Data collection | CI, D | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **STAGE 4 - STATISTICAL ANALYSIS AND INTERPRETATION** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Statistical analysis | SS | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Data interpretation | SS, PC, PI | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **STAGE 5 - FINAL ARTICLE ELABORATION** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Article elaboration and revision | PC, PI | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Publication of the Study and congresses | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

# 10. BUDGET

## 10.1 NOT INCLUDED COSTS

- **Staff:** the personnel participating in the study will not receive financial compensation as investigation is considered part of their job and professional experience. This aims to avoid any economic incentive in the study's execution. It includes the principal investigator, the project coordinator, the co-investigators, and all the healthcare professionals involved.
- **Available materials:** the centers where the study will take place have all the necessary materials for its proper execution. All the tests, ultrasounds, and procedures performed in the study are considered routine clinical practice for this type of pregnancy.
- **Travel expenses:** all the meetings between the principal investigator, the project coordinator, and the co-investigators will be held telematic via videoconference. Therefore, no travel expenses are expected.

## 10.2 INCLUDED COSTS

### 10.2.1 Personal expenses

- **Training sessions on data collection:** the personnel involved in the study will require training sessions on how to properly record all the data in the medical history of the patients to avoid differences and standardize the results.

### 10.2.2 Subcontracted services

- **Data Manager:** a data manager will be hired to create the database, oversee the entered information, and anonymize the process. The approximate salary will be 40€ per hour and with an estimated 100 hours of work, the total cost will be 4,000€.
- **Statistical specialist:** a professional statistician will be hired to conduct the statistical analysis of the study and perform the corresponding data analysis. The approximate salary will be 40 € per hour, and it is expected that the work will take around 60 hours, resulting in a total cost of 2,000€.

### 10.3 Material expenses

- **Printing costs:** This will cover expenses related to the printing of necessary documents and materials. It includes the informative document (approximately 3 pages) and the informed consent (1 page). That is a total of 4 pages per patient, so for 220 patients it will amount to

approximately 880 pages. Also, the printing of 10 copies of the protocol will be taken into account, and considering that it will be approximately 80 pages, it will result in an additional 800 pages printed. The printing cost will be 0.05€/page, so the total expenses will be around 85€.

### 10.2.4 Divulgation expenses

- **Publication fees:** fees associated with publishing the study results in scientific journals will be expected to cost around 1,500€.
- **Linguistic correction:** before publishing the article, it will undergo linguistic proofreading to ensure accuracy and eliminate possible errors. A linguistic corrector will be hired for this purpose, with a budget of 400€ for their service.
- **National and international congresses** to disseminate the study results, the findings will be presented at Gynecology and Obstetrics national and international congresses. The estimated budget for Congress participation includes registration and provisions for travel, accommodation, and meals. Anticipated costs are expected to be around 700€ for the national congress and 2,000€ for the international congress. These expenses will be considered for both the principal investigator and the project coordinator.

*Table 17: Budget details of the study*

| EXPENSES | | NUMBER OF UNITS | COST PER UNIT | SUBTOTAL |
|---|---|---|---|---|
| **Personal expenses** | | | | |
| **Training sessions on data collection** | | 10 hours | 35€ | 350 € |
| **Subcontracted services** | | | | |
| **Data manager and database creation** | | 100 hours | 40 € | 4,000 € |
| **Statistical specialist** | | 60 hours | 40€ | 2,400 € |
| **Material expenses** | | | | |
| **Printing costs** | Informative document and consent for each patient | 4 pages x 220 patients = 880 pages | 0.05 € | 84 € |
| | Protocol | 80 pages x 10 copies= 800 pages | | |
| **Divulgation expenses** | | | | |
| **Publication fees and open access** | | 1 article | 1,500 € | 1,500 € |
| **Linguistic correction** | | 1 article | 400 € | 400 € |
| **National congress** | | 2 attendants | 700 € | 1,400€ |
| **International congress** | | 2 attendants | 2000€ | 4,000€ |
| **TOTAL COST:** 14.134€ | | | | |

## 11. LIMITATIONS AND STRENGTHS

### LIMITATIONS

Prospective cohort studies have high value in assessing the association between different exposures and an outcome over time. However, they also come with certain limitations.

In the context of our study, the main limitations we can encounter include:

- **Selection Bias**: the non-probabilistic consecutive sampling method in our study may lead to selected participants who are not entirely representative of the broader population of women with PGDM, potentially limiting the generalization of the identified associations. This type of sampling could lead to the following situation: individuals who prioritize their health and adopt healthier lifestyle habits, potentially with fewer comorbidities, might be more inclined to have their pregnancy followed up and to participate in our study. Meanwhile, those who have poorer lifestyle habits and exhibit a higher prevalence of comorbidities may be less inclined to participate or show up to the obstetric unit. To attempt to minimize this limitation, we will work to make the selection criteria as representative as possible of the population. Also, we will adjust all the independent variables that could act as potential confounders.
- **Confounding bias:** given the study's observational nature, the occurrence of confounding bias is anticipated. To minimize potential confusion, a multivariate analysis will be conducted, stratified by all independent variables that could potentially act as confounders with one another.
- **Loss to follow-up:** although measures will be implemented to prevent losses during the study follow-up, such as periodic email reminders and phone calls in case of missing a scheduled visit, there may still be a smaller proportion of patients who discontinue follow-up at our centers or choose to withdraw from the study. Nevertheless, anticipating this event, the percentage of patients that could experience loss to follow-up has been taken into account when calculating the required sample size.
- **Measurement errors**: one of the main challenges of this study is obtaining accurate measurements and fetal biometrics through US, which requires specific techniques and training. Variations in results may occur between different observers or even within the same observer over time, and these measurement errors could be amplified in a multicenter study such as ours. Inaccuracies in these measurements could result in misclassifying important factors in our study. To mitigate this, professionals will be

instructed to repeat measurements three or four times to ensure precision. Additionally, physicians performing the US will be specialized obstetricians, adequately trained in taking these measurements. Moreover, in the multivariate model section of the statistical analysis, we will adjust for the variable "follow-up and delivery hospital". This adjustment will consider the possible variability between hospitals, reinforcing the reliability of our statistical analysis.

- **Unknown incidence of adverse maternal obstetric outcomes:** a potential limitation of our study is that the exact incidence of adverse maternal obstetric outcomes (either as a composite or individually) during delivery in women with PGDM is unknown or highly heterogeneous in our population. Therefore, the sample calculation has been based on an estimated incidence that could be either overestimated or underestimated. For this reason, one of the secondary objectives of our study will be to determine the incidence of these adverse events in our population.

## STRENGTHS

Concerning the main strengths of this study,

- **Study design:** the prospective nature of the study allows for the collection of data in real-time, providing a more accurate representation of the exposure and outcomes. Moreover, using a cohort design allows for the examination of the association between exposures (ultrasound, metabolic, and maternal demographic factors) and outcomes. Furthermore, our study has a very reasonable cost and low execution difficulty. As an observational study, its safety is ensured as it will not involve interventions beyond routine clinical practice.
- **Clinical relevance:** the increasing prevalence of diabetes is considered to affect women of reproductive age. Investigating potential associations between various factors and the occurrence of adverse maternal outcomes is clinically relevant. This research can provide valuable information for healthcare professionals involved in the care of these patients, potentially leading to improved risk assessment and management strategies.
- **Low loss to follow-up**: although, as mentioned, we acknowledge that due to the design of our study we may lose patients during follow-up, we believe this number will be minimal. This is because PGDM patients are recommended for monitoring and delivery at our centers, given that these pregnancies are considered high-risk, and included hospitals in our study are competent tertiary-level facilities specialized in managing such pregnancies.

## 12. CLINICAL AND HEALTHCARE IMPACT

Diabetes mellitus is a chronic condition associated with numerous health problems and clinical vulnerabilities that raise concerns within the entire scientific community due to its implications and the increasing prevalence observed in recent years, with the prediction that this trend will continue in the future. Furthermore, when diabetic patients become pregnant, their condition becomes a risk not only for themselves but also for their future descendants.

The childbirth process inherently involves certain risks, and these are heightened and extended in patients with preexisting diabetes mellitus. These complications not only have a major impact during delivery but can also lead to situations of morbidity for both the mother and the fetus in the future. Such circumstances can be particularly concerning and stressful for women. Therefore, our study is relevant not only for advancing medical knowledge but also for improving the safety of women in such a delicate and overwhelming experience.

In current clinical practice, significant decisions regarding the type and timing of delivery are made primarily relying on a combination of US measurements, ultimately resulting in the calculation of an estimated fetal weight. However, these measurements and calculations have been shown to be imprecise, particularly in macrosomic fetuses, as seen in a significant proportion of diabetic mothers. Consequently, it is considered that diabetic patients may have an elevated risk of iatrogenic delivery. Therefore, there is an urgent need to identify which risk factors other than estimated fetal weight could predict adverse maternal outcomes during delivery in these patients.

Given all these considerations, analyzing the association between these factors and adverse outcomes could represent a significant step in solidifying informed decisions, thereby helping obstetricians determine the optimal timing and mode of delivery. Thus, if our hypothesis were accepted, our work could not only potentially exert a direct impact on decision-making processes but also assist patients in understanding their risks and actively involving them in the decisions made. This would contribute to an increasingly personalized approach to medicine and clinical practice, to treat patients by taking into account all their factors and risks, rather than only focusing on diseases. Moreover, in the future, these results may prompt reconsideration of clinical practices to improve maternal obstetric outcomes.

## 13. FEASIBILITY

The present study will involve the participation of three tertiary hospitals that serve as reference centers for the management and delivery of pregnant individuals with DM across the province. These hospitals are fully equipped with essential materials and advanced ultrasound technology, facilitating the accurate obtention of some of our designated variables. Each hospital disposes of a well-equipped delivery room, ensuring optimal care for our patients.

Moreover, our project will involve the participation of an expert and skilled multidisciplinary team of healthcare professionals, including obstetricians, midwives, and endocrinologists with experience in managing this patient population. Additionally, several team members have been part of similar studies before. To ensure the precision of our analysis, we subcontracted the expertise of a statistician and a data manager.

We have estimated the involvement of 220 individuals in our study. Considering the childbirth rates within our participating centers, we anticipate reaching the necessary number of participants within one year and a half, which we consider reasonable.

Given the observational nature of our study, we estimate a minimum and feasible cost of implementation. Importantly, our study design prioritizes the safety and well-being of participating patients, with no alterations to their routine clinical practices during the research. Furthermore, the study topic involves the potential for making changes to the usual clinical practice to enhance the management of this type of patient, encouraging strong interest and engagement from our participants.

In conclusion, we consider the feasibility of this study due to its cost-effectiveness, reasonable duration, well-equipped facilities of our hospitals, a trained and experienced responsible team, and the security of the participants involved.

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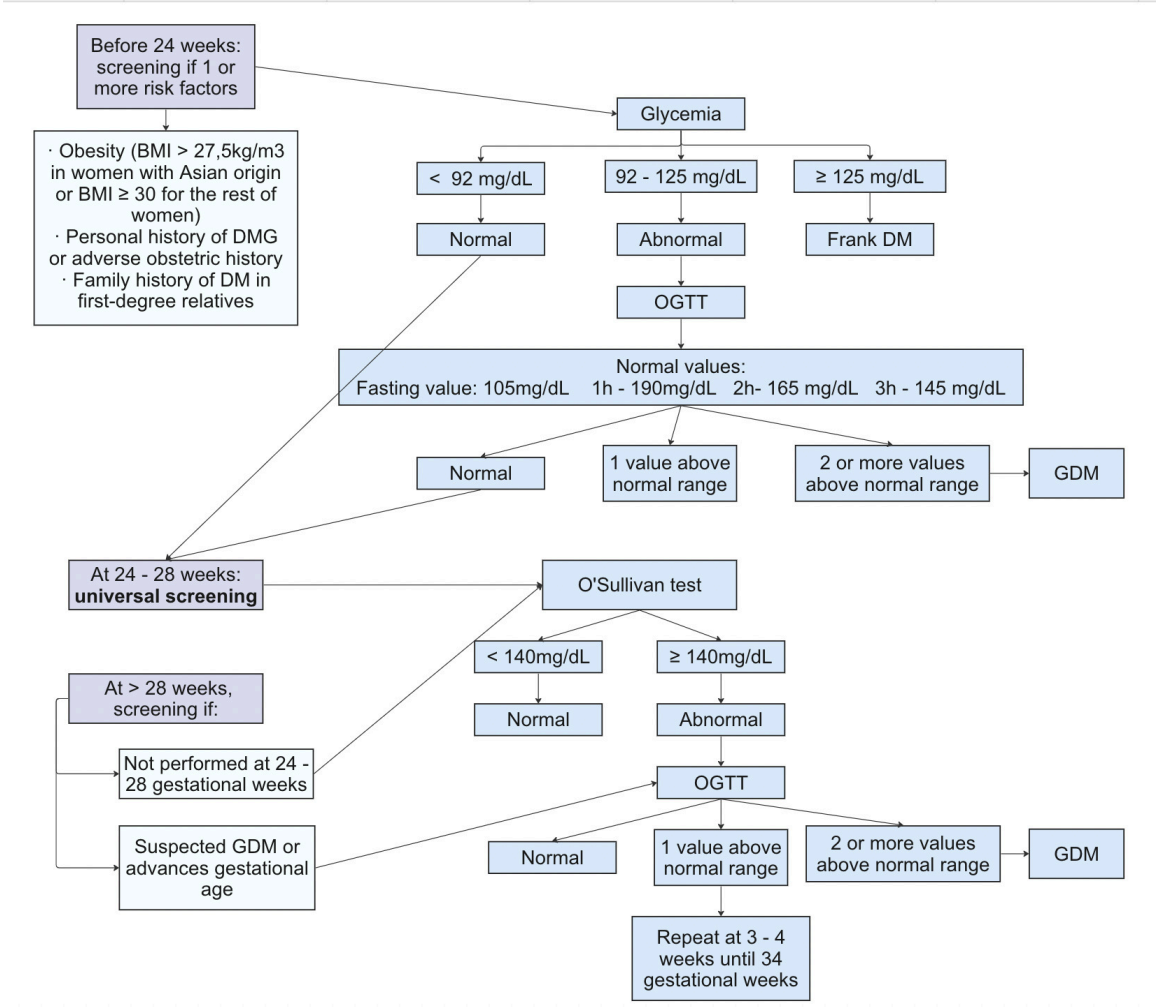
# 15. ANNEXES

## 15.1 ANNEX 1- Pregestational diabetes mellitus and gestational diabetes mellitus screening (10)




## 15.2 ANNEX 2 - Recommended analytical determinations during PGDM follow-up, adapted (11)

| Analytical parameter | 1st-trimester | 2nd-trimester | 3rd trimester |
|---|---|---|---|
| **Blood group and Rh** | + | | |
| **Indirect Coombs test** | + | + if Rh- | + if Rh- |
| **Syphilis and HIV serology** | + | | + If absent or the population at risk |
| **Hepatitis B serology** | + | | + If absent or the population at risk |
| **Rubella serology** | + | | |
| **Blood count** | + | + | + |
| **HbA1c** (assess individual cases) | + | + | + |
| **Urine test** | + | + | + |
| **Urine culture** | + | + | + |
| **Vaginal and rectal SGB culture** | | | + |

## 15.3 ANNEX 3 - Signs and symptoms in hemorrhagic shock (92)

| **Volume loss** | **Systolic blood pressure** (mmHg) | **Signs and symptoms** | **Degree of shock** |
|---|---|---|---|
| 10 - 15% | Normal | Palpitations, tinnitus, and tachycardia (> 110 bpm) | Compensated |
| 15 - 25% | Slightly decreased (80 - 85) | Weakness, sweating, and tachycardia ( > 110 bpm) | Mild |
| 25 - 35% | 70 - 80 | Restlessness, paleness, and oliguria | Moderate |
| 35 - 45% | 50 - 70 | Syncope, dyspnea, and anuria | Severe |

## 15.4 ANNEX 4 - Pictogram for quantifying blood loss (96)

| Surface area coverage | 25% | 50% | 75% | 100% | 100% with dripping |
|---|---|---|---|---|---|
| | 90 ml | 180 ml | 260 ml | 350 ml | |
| Under buttock Drape 15 in x 14 in |  |  |  |  | |
| dry | 2.5 ml | 5 ml | 7.5 ml | 10 ml | |
| 8 ply 4-in x 4-in Gauze sponge |  |  |  |  | |
| dry | 2.5 ml | 5 ml | 7.5 ml | 10 ml | |
| 8 ply 4-in x 4-in Gauze sponge |  |  |  |  | |
| wet | 10 ml | 20 ml | 30 ml | 40 ml | 60 ml |
| dry | 12.5 ml | 25 ml | 37.5 ml | 50 ml | 80 ml |
| 6 ply 6-in x 18-in Laparotomy sponge |  |  |  |  |  |
| wet | 25 ml | 50 ml | 75 ml | 100 ml | 130 ml |
| dry | 32.5 ml | 65 ml | 97.5 ml | 130 ml | 160 ml |
| 6 ply 18-in x 18-in Laparotomy sponge |  |  |  |  |  |

## 15.5 ANNEX 5 - Informative document

**FULL D'INFORMACIÓ A LA PARTICIPANT**

**NOM DE L'ESTUDI:** Predicting adverse maternal obstetric outcomes in pregestational diabetes mellitus with ultrasound, metabolic and maternal demographic factors

**INVESTIGADORA PRINCIPAL:** Laura López de Moragas

**CO- INVESTIGADORA:** Dra. Alexandra Bonmatí Santané

**CENTRE DE REFERÈNCIA:** Hospital Universitari Doctor Josep Trueta

Ens dirigim a vostè per informar-la sobre un estudi que s'està duent a terme al servei de Ginecologia i Obstetrícia, en el qual la convidem a participar. Aquest estudi ha estat aprovat pel Comitè d'Ètica i Investigació Clínica de l'Hospital Universitari Doctor Josep Trueta, conforme amb la legislació vigent i els principis postulats en la declaració de Hèlsinki.

Volem que rebi tota la informació necessària perquè pugui avaluar si desitja o no participar-hi, de forma totalment lliure i voluntària. Abans de confirmar la participació, es prega que llegeixi aquest full informatiu detingudament i faci totes les preguntes que li puguin sorgir per tal de poder aclarir-les.

**Descripció i objectiu de l'estudi**

El present estudi té com a objectiu principal avaluar quins factors ecogràfics, del control de la diabetis o demogràfics de la mare es podrien relacionar amb una possible complicació materna durant el moment del part de tipus vaginal, i per tant ajudar-nos a preveure-les.

Actualment, la principal indicació de programar una cesària abans del moment part en mares diabètiques és si el pes estimat del nadó (calculat a través de diferents mesures del fetus en l'ecografia de seguiment de l'embaràs) supera els 4.500g. Així i tot, coneixem que l'eina per a fer aquest càlcul pot arribar a ser imprecisa i tenir dificultats en el càlcul quan el nadó s'espera que sigui més gran del normal o distribueixi de manera diferent el seu greix corporal, com sol passar en fills de mares diabètiques. Aquest fet és força comú en aquest tipus d'embarassos, motiu pel qual considerem rellevant buscar possibles relacions entre diferents factors (no només el pes calculat a través de l'ecografia) que ens puguin ajudar a preveure l'aparició de possibles complicacions durant el part i que ens permetin prendre millors decisions en quant a l'elecció i decisió consensuada del tipus de part. Així doncs, aquest estudi permetria obtenir evidència científica i aconseguir un millor enteniment dels riscos que suposaria un part vaginal per aquest tipus de pacients.

**Procediments de l'estudi**

L'estudi es realitzarà en el seu hospital de referència i tindrà la duració del seu embaràs. És important entendre que es tracta d'un estudi observacional i que, per tant, no es durà a terme cap intervenció addicional i el maneig hospitalari no serà diferent del d'una pacient que no participi en l'estudi. Per tal de poder desenvolupar l'estudi, es recopilarà informació de la història mèdica, del curs de l'embaràs i del moment del part.

**Beneficis i riscs associats a la participació**

L'estudi està enfocat a proporcionar un benefici general a les pacients amb diabetis mellitus durant la gestació, ja que el sol fet de quedar-se embarassada suposa un risc tant per la mare com pel nadó. S'espera obtenir resultats que puguin beneficiar a aquestes pacients i els seus descendents en un futur. Amb la seva participació en aquest estudi no obtindrà cap benefici directe, però ajudarà a ampliar el coneixement científic sobre la diabetis i la seva relació amb l'embaràs, i poder contribuir així a optimitzar el seguiment i resultats de futures embarassades.

En tractar-se d'un estudi observacional i no modificar la seva pràctica clínica habitual, no s'exposa a cap risc afegit participant en aquest estudi.

**Centres participants i duració de l'estudi**

En aquest estudi hi participaran un total de 3 centres, localitzats a les províncies catalanes de Girona, Lleida i Tarragona. Així doncs, es comptarà amb la participació dels hospitals de tercer nivell següents: Hospital Universitari Josep Trueta (Girona), Hospital Universitari Arnau de Vilanova (Lleida) i Hospital Universitari Joan XXIII (Tarragona). L'estudi està previst que tingui una duració de 2 anys.

**Participació voluntària**

És important que entengui que la participació és completament voluntària i que la seva decisió no influirà en la seva atenció mèdica. A més, podrà canviar la seva decisió respecte la participació en qualsevol moment, revocant el consentiment informant, sense necessitat de justificar-se i sense que es produeixi cap alteració amb el seu metge ni cap prejudici en la seva atenció sanitària.

Les pacients rebreu tota la informació necessària i haureu de donar el vostre consentiment informat que li facilitarem per a participar. Abans de decidir si vol formar part de l'estudi, té dret de demanar segones opinions a altres professionals si així ho desitja.

**Compensació econòmica**

L'equip d'investigació responsable d'aquest estudi no obtindrà cap mena de benefici econòmic procedent d'aquest estudi. De la mateixa manera, la participació és totalment voluntària i, per tant, no rebrà cap remuneració pel fet de participar-hi. Tampoc li comportarà cap cost econòmic addicional a la pràctica clínica habitual.

**Confidencialitat i protecció de dades**

La informació obtinguda durant l'estudi serà totalment confidencial, recollida i analitzada anònimament, d'acord amb la Llei Orgànica de Protecció de Dades de Caràcter Personal i Garantia de Drets Digitals (3/2018) i del Reglament 2016/679 del Parlament i Consell Europeu. Per a garantir la màxima confidencialitat, a l'inici de l'estudi se li assignarà un codi numèric mitjançant el qual s'identificaran les seves dades i informació personal, garantint que no pugui ser reconeguda en cap moment. L'accés a les dades de caràcter personal quedarà restringit a l'equip d'investigadors amb finalitats científiques. Les dades que es recullin amb motiu d'aquest estudi, entre els quals es trobaran dades personals i de salut, seran processades i analitzades amb la finalitat d'avaluar-les científicament. Vostè podrà exercitar en qualsevol moment els seus drets d'accés, rectificació, cancel·lació i oposició dirigint-se al metge/essa que l'atén en aquest estudi el qual no haurà de posar en coneixement del promotor. Així mateix, els resultats de l'estudi poden ser comunicats a les autoritats sanitàries i eventualment a la comunitat científica a través de congressos i publicacions, però sempre de manera anònima i sense que la seva identitat sigui revelada en cap moment.

**Preguntes/Informació**

En cas de qüestions o necessitat d'aclarir qualsevol tema relacionat amb l'estudi, no dubti a posar-se en contacte amb l'equip investigador que queda a la seva disposició pel que calgui. Se li proporcionarà un document amb les dades de contacte corresponents.

Moltes gràcies per la seva col·laboració

| | |
|---|---|
| Signatura de la pacient | Signatura de l'investigador/a |
| Nom: | Nom: |
| Data: | Data: |

## 15.6 ANNEX 6 - Informed consent

**FULL DE CONSENTIMENT INFORMAT A LA PACIENT**

**NOM DE L'ESTUDI:**

Jo,_____, amb document d'identificació personal (DNI/NIE) _____ declaro que:

- ☐ He rebut una còpia i he llegit el full d'informació a la participant sobre l'estudi que se m'ha entregat.
- ☐ He pogut plantejar tots els dubtes relacionats amb l'estudi que m'han sorgit, i aquests s'han aclarit.
- ☐ He estat informada de les implicacions i objectius de l'estudi.
- ☐ Entenc que es respectarà la confidencialitat de les meves dades.
- ☐ Entenc que la meva participació a l'estudi és voluntària i no remunerada
- ☐ Entenc que puc revocar el consentiment a la participació quan vulgui, sense necessitat de justificació i sense que això repercuteixi en la meva assistència mèdica
- ☐ Autoritzo que les meves dades i la meva història clínica pugui ser utilitzada per l'equip investigador per a fins relacionats amb l'estudi

Conforme l'establert a L.O 3/2018, de 5 de desembre, de *Protección de Datos Personales y Garantía de los Derechos Digitales,* declaro haver estat informada:

- ☐ Que existeix un fitxer o tractament de dades de caràcter personal, de per què es recullen aquestes dades, i dels destinataris de la informació
- ☐ Que pot accedir, rectificar, oposar-se i cancel·lar-la dirigint-se per escrit al titular del fitxer de les dades

Vull rebre informació via telefònica o per correu electrònic dels meus resultats.

Contacte: _____

Número de telèfon: _____

Adreça de correu electrònic: _____

Per tot això, **ATORGO EL MEU CONSENTIMENT** per a participar en aquest estudi i estic d'acord que la informació obtinguda pugui ser utilitzada en investigacions futures.

Signatura de la pacient

Nom:

Data:

Signatura de l'investigador/a

Nom:

Data:

A _____ , _____ de 20 ___

## **15.7 ANNEX 7 -** Withdrawn consent

**FULL DE REVOCACIÓ DEL CONSENTIMENT**

Jo,_____, amb document d'identificació personal (DNI/NIE) _____ revoco el consentiment prèviament signat de participar en l'estudi anteriorment especificat.

Signatura de la pacient

Nom:

Data:

Signatura de l'investigador/a

Nom:

Data:

A _____ , _____ de 20 ___