Research Article

The Influence of Gestational Diabetes Mellitus Diagnosis Trimester on Maternal-Fetal Outcomes

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ABSTRACT

Gestational Diabetes Mellitus (GDM) is defined as a carbohydrate intolerance that results in hyperglycemia of varying severity with onset or first recognition during pregnancy. It is known that this intolerance, which can appear from the early stage to the end of pregnancy, can cause several maternal-fetal complications during pregnancy, delivery and postpartum.

Our objective was to compare maternal-fetal outcomes according to whether the diagnosis of gestational diabetes mellitus was made in the first or second trimester of pregnancy. For this purpose, a retrospective study was conducted with a consecutive sample of 194 pregnant women followed in the gestational diabetes mellitus appointment at Hospital da Senhora da Oliveira -Guimarães.

This analysis showed that there are statistically significant associations between gestational diabetes mellitus diagnosis trimester and the variables obesity and maternal comorbidities. On the other hand, no differences with statistical meaning were found regarding maternal age or used therapy when comparing cases of diagnosis made in the first and second trimesters. Regarding maternal-fetal outcomes, there are no significant associations between the different variables (preeclampsia, onset of labor, oxytocic acceleration, type of delivery, labor instrumentation, prematurity, newborn hospitalization time, macrosomia, hyperbilirubinemia, hypoglycemia and the postpartum reclassification of glycemic status) with the diagnosis trimester.

We conclude that the trimester in which gestational diabetes mellitus is diagnosed is not a preponderant factor for maternal-fetal outcomes. This study also showed that a BMI<30 kg per m^2 appears to be an independent factor, protective against the diagnosis in the first trimester. Other studies addressing this issue will be necessary to validate these results.

Keywords: Gestational Diabetes Mellitus; Diagnosis; Maternal-fetal Outcomes; Trimester

INTRODUCTION

During pregnancy there is a progressive increase in insulin resistance. To compensate for this resistance, pancreatic β-cells increase their insulin secretion. Thus, low variations of glucose levels during gestation are guaranteed [1].

Gestational Diabetes Mellitus (GDM) is defined as a carbohydrate intolerance that results in hyperglycemia of varying severity with onset or first recognition during pregnancy [2]. This intolerance is caused by the insufficiency of endogenous insulin to meet the needs of the tissues [1]. As glucose is able to pass the placental barrier, the maternal hyperglycemia affects the fetal blood glucose.

Thus, the fetal pancreas, in an attempt to counterbalance the maternal hyperglycemia, increases the release of insulin, culminating in hyperinsulinemia. This is the mechanism that causes the main complications associated with GDM in the fetus/newborn: macrosomia (which appears to be related to the fact that fetal insulin acts as growth factor in utero), shoulder dystocia, respiratory distress syndrome (RDS) in the newborn, perinatal hypoglycemia, hyperbilirubinemia and hypocalcemia [3].

This pathology also has maternal implications, being the most relevant and frequent the preeclampsia and the increase in cesarean rates (the latter is not due to a direct relation, but to other complications of GDM such as macrosomia) [4,5].

These complications can be minimized or prevented by controlling maternal blood glucose. Therefore, currently in Portugal, all pregnant women are screened for GDM in the first and second trimesters. At the first prenatal visit, fasting plasma glucose levels are collected and, if negative, a re-evaluation is performed between 24-28 weeks of gestation with an oral glucose tolerance test (OGTT) with 75 grams of glucose [2].

Glycemic self-monitoring and nutritional therapy is essential in the treatment of GDM throughout all the pregnancy. The dietary plan must be personalized and elaborated by a nutritionist. Pharmacological therapy should be initiated when glycemic targets are not reached after the institution of non-pharmacological measures and at any time during pregnancy. Studies have demonstrated its safety and efficacy in pregnancy [2,6-8].

It is known that pregnant women with GDM have a higher risk of developing type 2 diabetes mellitus, intermediate hyperglycemia or metabolic syndrome, so a postpartum reclassification of glycemic status is performed [2,9,10]. It seems intuitive to think that the longer the time of maternal-fetal exposure to hyperglycemia, the more repercussions there will be. Thus, the main purpose of this study is to verify if there are, in fact, significant differences in maternal-fetal outcomes depending on whether the diagnosis of the GDM was made in the first or second trimester of pregnancy.

OBJECTIVE

Our aim was to compare the maternal-fetal outcomes according to whether the diagnosis of GDM was done in the first or second trimester of pregnancy.

METHODS

A retrospective cohort was conducted with a consecutive sample of 194 pregnant women, followed in the gestational diabetes mellitus appointment at Hospital da Senhora da Oliveira-Guimarães, with the first visit performed between January and December 2018.

The exclusion criteria were: multiple gestation, incorrect diagnosis, non-cephalic presentation and delivery in another institution. The application of the exclusion criteria to the initial sample of 194 pregnant women led to a final sample of 155 pregnant women with GDM (N=155). In some of the variables analyzed, occasional cases were excluded due to the lack of punctual data. Only valid cases for the analysis in question are presented.

Collected variables included trimester of diagnosis, maternal age, body mass index (BMI), maternal co-morbidities, therapy used for metabolic control, preeclampsia, delivery route, labor characteristics (onset, oxytocic acceleration, instrumentation and gestational age), postpartum reclassification of glycemic status, APGAR Score at 1st, 5th and 10th minute, hospitalization time, weight and eventual intercurrences of the newborn.

In this sample, the average age was 33.7 years with a standard deviation (SD) of 4.9 years, with ages ranging from 18 to 43 years. The mean BMI was 26.7 kg/m² with a SD of 6.1 kg/m². Forty-eight (31.0%) were diagnosed in the first trimester and 107(70.0%) in the second trimester. Table 1 illustrates the different variables analyzed regarding the diagnostic trimester of the GDM.

The measure of association between the diagnostic trimester of GDM and each variable was analyzed through Odds Ratio (OR), with 95% Confidence Intervals (CI), considering the existence of statistically significant differences for values of $p \leq 0.05$. Univariate and multivariate conditional logistic regression models were constructed. In order to verify the relations presented in this study, the Pearson's Chi-Squared Test or the Fisher's Exact Test, were used for all categorical variables. The continuous variable (newborn hospitalization time) was analyzed using the Student's T-test for independent samples. Statistical analysis was performed using IBM SPSS Statistics, version 24.0.

Our analysis looked retrospectively at outcomes for a cohort of patients, all data analysed were collected as part of routine diagnosis and treatment and their anonymity was guaranteed. Patients were diagnosed and treated according to national guidelines and agreements. All exams and the recording of the variables included in our analysis were essential for confirming diagnosis and classifying patients.

RESULTS

Two groups were formed according to maternal age. One group included women aged ≤ 35 years and the other group included women aged >35 years, since this is the limit from which a pregnancy is defined as being off advanced age [11-13]. No statistically significant association was found for the variables maternal age and the diagnostic trimester of GDM (OR=0.74, CI 95%=0.37 to 1.49, p>0.05). The sample was also fractionated into two sets for BMI, <30 kg/m² and ≥ 30 kg/m² (obese and non-obese pregnant women). An association with statistical significance was found between these two variables (OR=0.26, CI 95%=0.12 to 0.56, $p \leq 0.05$).

Pregnant women with BMI <30 are more likely to be diagnosed only in the second trimester of pregnancy. The same was observed for the variable maternal comorbidities (OR=0.35, CI 95%=0.16 to 0.79, $p \leq 0.05$). Pregnant women without previous comorbidities are more likely to be diagnosed with GDM only in the second trimester of pregnancy. As far as the results of the maternal-fetal outcomes, no difference in statistic significance was found between preeclampsia and the trimester of GDM diagnosis (OR=1.72, CI 95%=0.37 to 7.99, p>0.05).

The association between the therapy (dietetic or pharmacological) used to obtain metabolic control and the diagnostic trimester of GDM was not statistically significant (OR=0.50, CI 95%=0.24 to 1.02, p>0.05) as well as the positivity of the postpartum reclassification of glycemic status (OR=0.59, CI 95%=0.13 to 2.67, p>0.05).

No statistically significant result was found in the association between the diagnostic trimester of GDM and each of the follow variables: labor onset (OR=0.76, CI 95%=0.38 to 1.53, p>0.05), oxytocic acceleration (OR=0.87, CI 95%=0.44 to 1.75, p>0.05), route of delivery (OR=1.2, CI 95%=0.6 to 2.5, p>0.05) and instrumentation of labor (OR=0.5 CI 95%=0.2 to 1.6, p>0.05).

Relatively to fetal macrosomia (weight>4000 g) [4], no statistically significant association was found between this variable and the GDM diagnosis trimester (OR=1.80, CI 95%=0.20 to 16.59, p>0.05). The same was observed for prematurity (OR=3.68, CI 95%=0.99 to 13.70, p>0.05), perinatal hypoglycemia, (OR=1.83, CI 95%=0.20 to 16.78, p>0.05) and hyperbilirubinemia (OR=0.78, CI 95%=0.37 to 1.62, p>0.05). The association between the newborn hospitalization time and the diagnosis of GDM in the first (M=4.35, SD=8.41) or second trimester (M=2.84, SD=1.07) is not statistically significant t (151)=1.83, p>0.05.

Table 1: Trimester of GDM diagnosis analysis by determinant.

Determinants		First Trimester Diagnosis	Second Trimester Diagnosis	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Maternal age	≤ 35 years	58.3% (n=28)	65.4 % (n=70)	OR=0.74 (0.37-1.49) p>0.05	-
	> 35 years	41.7% (n=20)	34.6% (n=37)		
BMI	<30 kg/m²	56.3% (n=27)	83% (n=88)	OR=0.26 (0.12-0.56) p ≤ 0.05	ORa=0.32 (0.14-0.71) p ≤ 0.05
	≥ 30 kg/m²	43.8% (n=21)	17% (n=18)		
Maternal comorbidities	Yes	33.3% (n=16)	15.0% (n=16)	OR=0.35 (0.16-0.79) p ≤ 0.05	ORa=0.46 (0.19-1.1) p>0.05
	No	66.7% (n=32)	85% (n=91)		
Preeclampsia	Yes	6.3% (n=3)	3.7% (n=4)	OR=1.72 (0.37-7.99) p>0.05	-
	No	93.8% (n=45)	96.3% (n=103)		
Therapy	Dietetic	58.3% (n=28)	73.8% (n=79)	OR=0.50 (0.24-1.02) p>0.05	-
	Pharmacological	41.7% (n=20)	26.2% (n=28)		
Postpartum reclassification of glycemic status	Positive	10.3% (n=3)	6.4% (n=5)	OR=0.59 (0.13-2.67) p>0.05	-
	Negative	89.7% (n=26)	93.6% (n=73)		
Onset of labour	Induced	48.9% (n=22)	42.1% (n=45)	OR=0.76 (0.38-1.53) p>0.05	-
	Spontaneous	51.1% (n=23)	57.4% (n=62)		
Oxytocic acceleration	Yes	42.6% (n=20)	39.3% (n=42)	OR=0.87 (0.44-1.75) p>0.05	-
	No	57.4% (n=27)	60.7% (n=65)		
Route of delivery	Vaginal	70.2% (n=33)	66% (n=70)	OR=1.2 (0.6-2.5) p>0.05	-
	Cesarean	29.8% (n=14)	34% (n=36)		
Instrumentation of labour	Eutocic	72.7% (n=24)	84.3% (n=59)	OR=0.5 (0.2-1.6) p>0.05	-
	Instrumented	27.3% (n=9)	15.7% (n=11)		
Prematurity	Yes	12.5% (n=6)	3.7% (n=4)	OR=3.68 (0.99-13.70) p>0.05	-
	No	87.5% (n=42)	96.3% (n=103)		
Macrosomia	Yes	2.1% (n=1)	3.8% (n=4)	OR=1.80 (0.20-16.59) p>0.05	-
	No	97.9% (n=47)	96.2% (n=102)		
Perinatal hypoglycemia	Yes	2.1% (n=1)	3.7% (n=4)	OR=1.83 (0.20-16.78) p>0.05	-
	No	97.9% (n=46)	96.3% (n=103)		
Hyperbilirubinemia	Yes	33.3% (n=16)	28% (n=30)	OR=0.78 (0.37-1.62) p>0.05	-
	No	66.7% (n=32)	72% (n=77)		
Newborn Hospitalization time (Days)	-	Mean=4.35	Mean=2.84	t(151)=1.83, p>0.05	-

The logistic regression model was performed for the two variables that presented a statistical significance association with the diagnostic trimester of the GDM (multivariate regression). The BMI (Adjusted OR=0.32 CI 95%=0.14 to 0.71, p ≤ 0.05) remained independently associated with the trimester of diagnosis (**Table 1**).

DISCUSSION

It has been demonstrated that maternal age is a risk factor for the development of GDM [14]. However, in this analysis, this association was not verified. Although not significant, it was noticed that pregnant women diagnosed in the second trimester tended to be younger.

It is well documented in the literature that obesity is also one of the risk factors for the development of GDM [15]. This is in line with what was found in this sample. It has been proven that this factor, as well as other related maternal comorbidities (including chronic hypertension and hypothyroidism), increases the likelihood of developing GDM as early as the first trimester of pregnancy. Thus, this study additionally emphasizes the importance of maintaining a healthy lifestyle and the prevention of these risk factors.

In Portugal, pharmacological therapy is initiated when it is no longer possible to optimize metabolic control by non-pharmacological measures [2]. In this analysis, no significant association was found

between the type of therapy used and the GDM trimester of diagnosis. However, although it has no statistical significance, there is a strong tendency for pregnant women diagnosed in the first trimester to require a higher degree of pharmacological therapy.

Regarding maternal complications, studies indicate that GDM is a risk factor for the development of preeclampsia and for cesarean delivery [4]. However, in this study, no statistical significance association was found between these variables and the trimester of diagnosis. The same was observed for the characteristics of labor (onset, oxytocic acceleration and instrumentation) that appear not to be influenced by this factor.

In this sample, no correlation was found between the trimester in which the diagnosis is made and the postpartum reclassification of glycemic status.

Analyzing the incidence of the different fetal complications influenced by this pathology (macrosomia, fetal hypoglycemia, hyperbilirubinemia) as referred above [3,4], in this sample there was no particular association of these and the diagnosis trimester of the GDM. The same was observed regarding the prematurity status. However, although not statistically significant, there is a tendency to have a longer hospital stay in the newborns of mothers diagnosed with GDM in the first trimester.

Although variables such as shoulder dystocia and RDS in the newborn have been collected and are also possible complications of the GDM, they were not analyzed since no cases were found in the period contemplated by this study. The APGAR score was also not analyzed because there were no newborns with values indicative of suffering (Apgar ≤ 7).

It should be noted that it would be important to obtain a larger sample with more adverse maternal-fetal outcomes already described as inherent to the GDM to verify the associations presented. An analysis with a larger number of cases could present variations in the results, namely in the variables in which a greater tendency for a positive correlation was noticed.

To sum up, in this sample, the trimester in which GDM was diagnosed is not a preponderant factor in maternal-fetal outcomes. It is known that this is pathology with several associated risks and one could think that by increasing the exposure time to the same the impact could be bigger, having more adverse results. However, this was not observed for the mother or the newborn, proving that the time factor, in this sample, does not have a major influence. This can be attributed to the good metabolic control to which these pregnant women are subjected after the diagnosis. Thus, it is understood that the onset of the disease in the first trimester does not necessarily translate into an increase in the time of exposure to variations in glycaemia.

CONCLUSION

This theme was subject to recent reviews, with also recent changes in diagnostic values [16,17]. Thus it is perceived that it is a current theme, still not totally clarified. In this study a BMI <30 kg/m^2 appears to be an independent factor, protective against the diagnosis in the first trimester. Other studies that address this issue will be necessary to validate these results.

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