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Artigo Original

Gestational Diabetes Recurrence: Differences between First and Second Pregnancy

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A B S T R A C T

Introduction: Women with gestational diabetes (GD) have increased risk of GD in subsequent pregnancies (30%-50%), glucose intolerance and type 2 diabetes mellitus. Risk factors for GD recurrence are obesity, multiparity, advanced maternal age, early onset GD, need of insulin treatment, macrosomia and weight gain between pregnancies.
The aim of this study is to compare the first and second pregnancy with GD in the same woman.
Material and Methods: This was a retrospective observational study comparing women who had GD twice, followed in our hospital, between 2012 and 2019. Our sample included 2 groups (first pregnancy with GD – G1, second pregnancy with GD – G2), each with 30 pregnancies. We considered literary qualifications, age, parity, pre-conception body mass index (BMI), weight increase between and during each pregnancy, gestational age at diagnosis and at delivery, HbA1c, maternal, fetal and neonatal complications, therapy required, mode of delivery, birth weight, macrosomia and results of reclassification test 6 to 8 weeks after delivery. We used Kolmogorov-Smirnov, McNemar, Wilcoxon and paired T tests for statistical analysis and $p<0.05$ was considered for statistical significance.
Results: The mean age was 30±5 and 33±5 years, in the first and second pregnancies. In G2, 40% had an initial BMI≥30 kg/m^2 vs 33% in G1. Women had a significant average increase of 3.8 kg on the initial weight between pregnancies. The diagnosis of GD was slightly earlier in G2 ($p=0.4313$). G2 required more pharmacological treatment 66.7% *vs* 43.3%, with higher need for combined therapy ($p<0.05$). HbA1c on the 3rd trimester was higher in G2 ($p<0.05$). Gestational age at delivery was similar between groups. Vaginal delivery was the most frequent mode of delivery in both pregnancies. Median birth weight was higher in G2 ($p<0.05$) Reclassification test was normal in 92% *vs* 60% of G1 *vs* G2 ($p=0.1336$).
Conclusion: GD recurrence seems metabolically more challenging, which associated with higher incidence of maternal obesity and advanced maternal age can explain the findings of our study.

Palavras-chave:
Diabetes Gestacional;
Gravidez;
Recorrência.

Diabetes Gestacional Recorrente:Diferenças entre a Primeira e a Segunda Gravidez

R E S U M O

Introdução: Mulheres com diabetes gestacional (DG) têm risco aumentado de DG nas gravidezes subsequentes (30%-50%), de intolerância à glicose e de diabetes mellitus tipo 2. Factores de risco para recorrência da DG são obesidade, multiparidade, idade materna avançada, DG com início precoce, necessidade de insulina, macrossomia e aumento de peso entre gravidezes.
O objectivo deste estudo é comparar a primeira e segunda gravidez com DG na mesma mulher.
Material e métodos: Realizou-se um estudo observacional retrospectivo, comparando as grávidas com DG em 2 gravidezes, vigiadas no nosso hospital, entre 2012 e 2019. A amostra incluiu 2 grupos

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(primeira gravidez com DG –G1; segunda gravidez com GD –G2), cada um com 30 gravidezes. Foram analisadas habilitações literárias, idade, paridade, índice de massa corporal (IMC), aumento de peso entre e durante as gravidezes, idade gestacional (IG) no diagnóstico e parto, HbA1c, complicações maternas, fetais e neonatais, terapêutica, via de parto, peso do recém-nascido (RN), macrossomia e resultados da prova de reclassificação. A análise estatística foi feita com os testes de Kolmogorov-Smirnov, McNemar, Wilcoxon e T-student para amostras emparelhadas. Foi considerado estatisticamente significativo $p<0,05$.

Resultados: As idades médias foram 30 e 33±5 anos (G1 ***vs*** G2). Em G2, 40% tinham IMC≥30 kg/m^2, *vs* 33% em G1. Verificou-se um aumento médio significativo de 3,8 kg no peso inicial entre gravidezes. O diagnóstico de DG foi mais precoce em G2 ($p=0,4313$). Houve maior necessidade de terapêutica farmacológica em G2 66,7% *vs* 43,3%, com maior recurso à terapêutica combinada ($p<0,05$). HbA1c no 3º trimestre foi mais elevada em G2 ($p<0,05$). A Idade gestacional no parto foi semelhante entre grupos e a via vaginal foi a mais frequente. O peso médio ao nascer foi maior em G2 ($p<0,05$). A prova de reclassificação foi normal em 92% *vs* 60% (G1 vs G2, $p=0,1336$).

Conclusão: A recorrência de DG parece metabolicamente mais desafiante, o que associado à maior incidência de obesidade e idade materna mais avançada pode explicar os resultados.

Introduction

Gestational diabetes (GD) is a carbohydrate intolerance that is diagnosed for the first time in pregnancy.[1] It´s incidence varies worldwide, according to the population studied. In Portugal, the estimated prevalence is 8.8%, increasing for 17.7% in women >40 years old.[2,3] It is associated with increased maternal and neonatal complications, which can be reduced with an adequate metabolic control.[4,5] Furthermore, these women have higher risk of having GD in subsequent pregnancies, glucose intolerance and type 2 diabetes mellitus in the future. The recurrence rate is different within the literature (30%-50%), according to the criteria used for diagnosis and the ethnicity of the population included.[6-10]

Risk factors for recurrence are obesity, multiparity, advanced maternal age, early onset GD, need of insulin treatment, macrosomia and weight gain between pregnancies.[6,11,12,13,14,15]

The reclassification test is essential to the post-partum reevaluation of these women. According to the literature, only 2/3 of women will do the test. It's expected that 2% have diabetes mellitus and 11% have impaired glucose metabolism.[1,10,13,16,]

The purpose of this study is to characterize and compare the first and second pregnancy with GD in the same woman.

Material and Methods

Retrospective observational study comparing women who had gestational diabetes twice, both pregnancies followed in the obstetric unit of our hospital, between 2012 and 2019. Our sample included 2 groups (1st pregnancy with GD – G1, 2nd pregnancy with GD – G2), each with 30 singleton pregnancies. The diagnosis of GD was made by a fasting glucose value ≥92 mg/dL in the first or second trimester or by glucose values ≥180 mg/dL or ≥153 mg/dL 1 and 2h after 75 g glucose tolerance test, in the 2nd trimester. We considered literary qualifications, maternal age, parity, pre-conception body mass index (BMI), weight increased between and during each pregnancy, gestational age at diagnosis and at delivery, therapy required, HbA1c, hypertensive disorders, abortion, fetal death, hydramnios, neonatal infections and need for intensive care unit care, hyperbilirubinemia, respiratory distress syndrome, congenital anomalies, hypoglycemia, birth trauma, mode of delivery, birth weight, macrosomia (≥4 kg), large for gestational age and small for gestational age fetus and results of reclassification with fasting and 75 g 2 hours oral glucose tolerance test, 6 to 8 weeks after pregnancy.[1,16]

We defined obesity has BMI ≥30 kg/m^2, according to the definition of the World Health Organization (WHO).[17]

Weight gain during pregnancy was classified according to Institute of Medicine 2009 recommendation.[18]

Hydramnios was considered when the ultrasound assessment in the 2nd or 3rd trimester of amniotic fluid index was ≥25 cm or when the deepest pocket was ≥8 cm.[19]

Hypertension in pregnancy is defined has a systolic blood pressure ≥140 mg/dL or diastolic blood pressure ≥90 mmHg in two measures 4 hours apart, according to o the American College of Obstetrics and Gynecologists (ACOG).[16] Also, on ACOG, preeclampsia is defined has hypertension in pregnancy or systolic blood pressure ≥160 mg/dL or diastolic blood pressure ≥110 mmHg in two measures minutes apart and one of the following[20]:

- Proteinuria ≥ 300 mg per 24 hour urine collection (or this amount extrapolated from a timed collection), protein/creatinine ratio of 0.3 mg/dL or more or dipstick reading of 2+ (used only if other quantitative methods not available);
- Thrombocytopenia: platelet count less than 100,000 mg/dL;
- Renal insufficiency: serum creatinine concentration >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease;
- Impaired liver function: elevated blood concentrations of liver transaminases to twice normal;
- Severe persistent right upper quadrant or epigastric pain and not accounted for by alternative diagnoses;
- Pulmonary edema;
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms.

The reclassification test was classified into four categories, according to WHO: Diabetes mellitus if the fasting value ≥126 mg/dL or the 2 hour value is ≥200 mg/dL, twice, impaired fasting glucose if the fasting value is ≥110 mg/dL and <126 mg/dL, impaired glucose tolerance if the 2 hour value is ≥140 mg/dL and <200 mg/dL, normal if the first value is <110 mg/dL and the 2h value is <140 mg/dL.[21,22] Impaired glucose tolerance and impaired fasting glucose are considered as pre-diabetes, by the American Diabetes Association, which corresponds to glycated hemoglobin levels between 5.7%-6.4%. Although there is no HbA1c cut-off established for pregnancy, since values below 5.7% are associated with good metabolic control in general population and the HbA1c levels tend to be lower in pregnancy, we considered the 5.7% cut-off to access metabolic control.[16]

Hadlock curves were used to classify fetus in large for gestational age (birth weight ≥90th centile), small for gestational age (birth weight ≤10th centile) and appropriate for gestational age

(birth weight <90th>10th centile). Macrosomia was defined has newborn weight ≥4000 g.[23]

We used Kolmogorov-Smirnov test to access the normal distribution of continuous data. McNemar, Wilcoxon and paired T tests were used for statistical analysis and $p<0.05$ was considered for statistical significance.

The study was conducted in accordance with the amended Declaration of Helsinki There was no use of experimental or new protocols. Being a retrospective observational and non-interventional study where anonymity is granted, informed consent was considered not to be a requirement. The article was submitted to the Hospital's Ethics for Health Comitee ("*Comissão de Ética para a Saúde do Hospital Beatriz Ângelo*", presided by Maria João Heitor) evaluation and it was approved on the 6th of November of 2020 (approval number 3400/2020).

Results

Our sample included 30 women and 60 pregnancies (Table 1).

First degree family history of diabetes mellitus was present in 66.7% (n=20) of cases.

Table 1. Comparison between the two groups

	1st pregnancy (G1)	2nd pregnancy (G2)	*p* value
Nr of women	30		-
Nr of pregnancies	30	30	-
Mean age	30±5	33±5	-
Initial BMI≥30 kg/m²	33% (n=10)	40% (n=12)	*ns*
Weight increase in pregnancy			
– Excessive	26% (n=7)	26% (n=7)	*ns*
– Normal	37% (n=10)	30% (n=8)	*ns*
– Insufficient	37% (n=10)	44% (n=12)	*ns*
Mean gestational age of diagnosis of GD	20w+6d	19w+4d	*ns*
Average HbA1c in 3rd T	5.28%	5.63%	0.01
Abortions/Fetal deaths	0	0	-
Hypertensive disorders	23% (n=7)	23% (n=7)	*ns*
Hydramnios	13% (n=4)	0	*ns*
Gestational age at delivery	38w+6d	38w+6d	*ns*
Vaginal delivery	66.7% (n=20)	57.1% (n=16)	*ns*
Mean birth weight	3235 ±429 g	3450 ±353 g	0.03299
Macrosomia	0	7.1% (n=2)	*ns*
Reclassification test done	86.7% (n=26)	73.3% (n=22)	*ns*
Abnormal reclassification test	7.7% (n=2)	27.2% (n=6)	*ns*

nr – number, ns – not significant, BMI – body mass index, w- weeks, d – days, 3rd T – third trimester, g - grams

In what regards literary habilitations, 53.3% (n=16) had concluded high school or college. The interval between the first and second pregnancy was on average 3 years and 4 months.

Although there was no difference in the incidence of obesity (BMI≥30 kg/m²) between groups (Table 1), women had an average increase of 3.8 kg on the initial weight between pregnancies ($p=0.00443$). There were no differences between weight increase during 1st and 2nd pregnancies, comparing both groups ($p=0.3787$) (Table 1).

The mean gestational age of diagnosis of GD was at 20w+6d in G1 and at 19w+4d in G2, ($p=0.4313$).

Pharmacological treatment (Table 2) was required in 43.3% of cases in G1 *vs* 66.7% in G2 ($p=0.0704$).

Table 2. Need for pharmacological treatment and metabolic evaluation

	1st pregnancy (G1)	2nd pregnancy (G2)	*p* value
Pharmacological treatment	43.3% (n=13)	66.7% (n=20)	*ns*
Metformin monotherapy	17% (n=5)	27% (n=8)	*ns*
Insulin monotherapy	7% (n=2)	3% (n=1)	*ns*
Metformin + Insulin	10% (n=3)	37% (n=11)	0.0133
HbA1c ≥5.7%	24% (n=5)	33% (n=7)	*ns*

ns – not significant

Table 3. Analysis of LGA cases

	1st pregnancy (G1)		2nd pregnancy (G2)		*p* value
SGA	3 (10.7%)		1 (3.6%)		*ns*
AGA	25 (89.2%)		24 (85.6%)		*ns*
LGA	0		3 (10.7%)		*ns*
	IMC class*	**Weight gain****	**Treatment**	**3rd T HbA1c**	**Comorbidities**
	Obese	Adequate	M+I	5.3%	Polycystic kidney
	Normal weight	Insufficient	Diet	5.1%	None
	Obese	Insufficient	M+I	6.3%	None

SGA – small for gestational age, AGA - appropriate for gestational age, LGA - large for gestational age, ns – not significant M – metformin; I – insulin; 3rd T – third trimester; * Mother's IMC class; ** weight gain during pregnancy

Although there was higher need for pharmacological treatment in the second pregnancy, only the combined therapy (metformin + insulin) reached statistical significance (p 0.0133) (Table 2).

In those who did metformin in both pregnancies:

- Mean gestational age of metformin beginning was 24w+1d in G1 *vs* 23w+4d in G2 ($p=0.79176$);
- Average dose at the end of the pregnancy was 1200±400 mg in G1 *vs* 1500±387 mg in G2 ($p=0.14015$).

We evaluated the HbA1c only in the 3rd trimester, due to insufficient data in the 1st and 2nd trimesters. HbA1c on the 3rd trimester was higher in G2 ($p<0.05$). (Table 1).

There were no abortions, neither fetal deaths.

There was no difference on hypertensive disorders incidence (both 23%, $p=0.6831$). Chronic hypertension had higher prevalence in the 2nd pregnancy (18.5% *vs* 6.7%), although with no statistical significance ($p=0.2482$).

Hydramnios was more frequent in the 1st pregnancy (13% in G1 *vs* 0% in G2), ($p=0.1129$).

Gestational age at delivery was 38w+6d in both pregnancies ($p=0.93624$).

There were two preterm deliveries, both in the 1st pregnancy, both at 34 weeks, ($p=0.4795$). One spontaneous preterm labor and one induced after prelabor rupture of membranes.

Vaginal delivery was the most frequent mode of delivery in both pregnancies (G1 66.7% and G2 57.1%), ($p=0.6831$).

C-section incidence was higher in G2, where 41.7% of which (5 out of 12) were due to previous uterine surgery.

Mean birth weight was 3235 ±429 g in G1 *vs* 3450 ±353 g in G2 ($p=0.03299$).

The macrosomia rate was 7.1% in the 2nd pregnancy and 0% in the 1st pregnancy (p=0.2287).

Large for gestational age (LGA) cases are described in Table 4. Its incidence was 10.7% in the 2nd pregnancy and 0 in the 1st pregnancy (p=0.2482).

Table 4. Neonatal data

	1st pregnancy (G1)	2nd pregnancy (G2)	*p* value
HBRB w/ phototherapy	3 (10%)	2 (7.1%)	-
RDS	2 (6.7%)	1 (3.6%)	-
Infection	2 (6.7%)	0	-
ICU	4 (13.3%)	1 (3.6%)	-
Congenital anomalies	2 (7.1%)	2 (7.1%)	-
Hypoglycemia	1 (3.3%)	0	-
Birth trauma	0	0	-

HBRB – hyperbilirubinemia, RDS – respiratory distress syndrome, ICU - intensive care unit

Neonatal morbidity was higher in the 1st pregnancy (9 *vs* 4 affected newborns – 30% in G1 *vs* 14.3% in G2, p=0.2278). Some of the affected newborns had more than one condition (Table 4).

The preterm newborns, described earlier, did not have any complication.

There were 4 cases of congenital anomalies, 2 in each group: 1 epispadia and 1 preauricular pit in G1, 1 polycystic kidney and 1 mild hydronephrosis in G2. The 3 cases of respiratory distress syndrome (RDS), 2 in G1 and 1 in G2, are described in Table 5.

In the 1st group 86.7% did the reclassification test *versus* 73.3% in G2 (p=0.2888).

Table 5. Analysis of RDS cases

	Treatment	3rd T HbA1c	GA at delivery	Birth weight	Delivery mode	C-section cause	ICU
G1	Diet	5.1%	40w	3720g	Normal	-	Yes
	Diet	unknown	37w	1715g	C-section	Fetal distress	Yes
G2	Metformin + Insulin	5.3%	37w	4150g	C-section	Macrosomia	Yes

3rd T – 3 third trimester, GA – gestational age, w – weeks, RDS – respiratory distress syndrome, ICU - intensive care unit

The reclassification was normal in 92.3% *vs* 72.8% of women (G1 *vs* G2), (p=0.1336), (Table 6).

Table 6. Reclassification test results

	1st pregnancy (G1)	2nd pregnancy (G2)	*p* value
DM	0% (n=0)	5% (n=1)	*ns*
IFG	5% (n=1)	10% (n=2)	*ns*
IGT	5% (n=1)	20% (n=4)	*ns*

DM – diabetes mellitus, IFG – impaired fasting glucose, IGT – impaired glucose tolerance, ns – not significant

Discussion

Women with familiar history of diabetes in first-degree relatives are at greater risk to develop gestational diabetes. In our study, 66.7% of women had familial antecedents, which was higher than in the literature (13%-52%).[9,12,23]

Although not statistically significant, the diagnosis was earlier and there was higher need for pharmacological treatment in the 2nd pregnancy, particularly combined therapy. These may translate a harder metabolic control in recurrent gestational diabetes and higher prevalence of obesity. The higher value of glycated hemoglobin in G2 may also support this hypothesis.

Gestational age of delivery was similar in both groups and vaginal mode was the most frequent. The c-sections due to prior uterine surgery, can justify in part the higher rate in the 2nd pregnancy.

Birth weight was higher in the 2nd pregnancy, in agreement to what was expected.[4,5,7] Macrosomia and LGA incidences were also higher in G2, despite they did not have statistical significance. In the LGA newborns, 75% of the mothers were obese. Unfortunately, the data is too small to make assessments.

The first pregnancy had more neonatal complications, what we would not expect, according to the metabolic control. However, we shall highlight that it was not statistically significant and that none of the congenital anomalies found is often associated with gestational diabetes and were probably incidental findings.

The reclassification test is crucial in the follow-up of these women. As so, we must reinforce its importance in order to achieve better adherence rates. Nevertheless, our rates of compliance were higher than the ones described in the literature.[9]

After the second pregnancy, there were more diabetic and especially pre-diabetic states, in agreement with the presupposition, although not statistically significant.[1,9, 16,10,11]

There are few studies comparing outcomes of recurrent GD in the same women and our study has a great limitation: a short sample. It is necessary to do studies with larger samples in this matter, in order to get more consistent conclusions.

Conclusion

GD recurrence seems to be metabolically more challenging. This fact, added to the greater morbidity associated with older age, can explain the findings of these study.

It is of great importance that women with GD understand its consequences in short and long-term and implement measures to lose weight and to have healthier habits, in order to improve the outcomes.

Contributorship statement / Declaração de contribuição:

MG: Conceptualization, Methodology, investigation, data curation, writing original draft, and final approval.
NA: Conceptualization, methodology, supervision, review and final approval.
JR, CR, AF, FC, BA, NP: Review and final approval.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.
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Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).
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