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Gestational Diabetes: How Heavy is Obesity?

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A B S T R A C T

Introduction: Both obesity and gestational diabetes (GD) are independent risk factors for several pregnancy complications and neonatal adverse outcomes. With a growing incidence of metabolic syndrome, there is an increasing number of pregnant women with GD and obesity simultaneously. The objective of this study was to compare obstetric and perinatal outcomes between two groups of pregnant women with GD – Group 1 (G1) with normal body mass index (BMI) – 18.5-24.9 kg/m^2 – and Group 2 (G2) with obesity – BMI ≥30 kg/m^2.
Methods: It was a retrospective, comparative study between both groups (G1, n=284; G2, n=235). Inclusion criteria were: unifetal pregnancies with GD with surveillance in our institution between 2012-2018, excluding incomplete files. From this group we selected women with normal BMI and with obesity. The analysed parameters were demographic data, first-degree diabetes family history, previous GD and previous fetal macrosomia, gestational age at diagnosis of diabetes, weight gain during pregnancy, maternal, fetal and neonatal complications, metabolic control and therapy required, delivery and reclassification test. In the statistical analyses (p<0.05 as level of significance) we used the Chi-Square, Fisher, Kolmogorov-Smirnov and T-test.
Results: G2 had more 1st degree diabetes family history, previous GD and previous fetal macrosomia (46% *vs* 31%, 16% *vs* 6%, 11% *vs* 4%, p<0.05). In G2 diagnosis of GD was earlier (p<0.05), excessive weight gain was higher (36% *vs* 13%, p<0.05), metabolic control was harder to achieve, needing pharmacological treatment in 53% *vs* 24% in G1, p<0.05. Chronic hypertension was more common in G2, but without statistical significance regarding preeclampsia. Gestational age at delivery was similar but G2 had more cesarean (37% *vs* 23%, p<0.05). G1 was associated with low birth weight (10% *vs* 5%, p<0.05), while G2 offspring had more macrosomia (8% *vs* 1%, p<0.05), neonatal hypoglycemia and respiratory distress syndrome, but admission to neonatal care unit was similar between groups. No differences were found in post-partum reclassification oral glucose tolerance test (OGTT).
Discussion and Conclusion: This study corroborates the burden of obesity as an additional risk factor in pregnant women with GD as it increases the risk of complications, fetal macrosomia and neonatal morbidities, with impaired metabolic control. Closer surveillance of these pregnancies should be reinforced, so that we can prevent maternal and neonatal adverse outcomes.

Palavras-chave:
Complicações na Gravidez;
Diabetes Gestacional;
Obesidade.

Diabetes Gestacional: Qual o Peso da Obesidade?

R E S U M O

Introdução: Tanto a obesidade como a diabetes gestacional (DG) são fatores de risco independentes para várias complicações da gravidez e desfechos neonatais adversos. Com o aumento da incidência de síndrome metabólica, o número de grávidas que apresentam simultaneamente DG e obesidade é crescente. O objetivo deste estudo foi comparar os resultados obstétricos e perinatais entre dois grupos de grávidas com DG – grupo 1 (G1) com índice de massa corporal (IMC) normal (18,5-24,9 kg/m^2) e grupo 2 (G2) com obesidade (IMC ≥ 30 kg/m^2).

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Métodos: Tratou-se de um estudo retrospetivo e comparativo entre os dois grupos (G1, n=284; G2, n=235). Foram critérios de inclusão gestações unifetais, com vigilância na instituição entre 2012-2018, excluindo-se processos incompletos. As variáveis estudadas foram: dados demográficos, antecedentes de diabetes em familiares de primeiro grau, DG prévia, macrossomia fetal anterior, idade gestacional no diagnóstico de diabetes, aumento ponderal durante a gravidez, complicações maternas, fetais e neonatais, controlo metabólico e terapêutica instituída, dados do parto e prova de tolerância à glicose oral (PTGO) de reclassificação.
Na análise estatística comparativa (p<0,05 como nível de significância) utilizaram-se os testes qui-quadrado, Fisher, Kolmogorov-Smirnov e Teste-t.
Resultados: No G2 verificou-se maior incidência de antecedentes familiares de diabetes, antecedentes de DG e macrossomia anterior (46% *vs* 31%, 16% *vs* 6%, 11% *vs* 4%, p<0,05). No G2 verificou-se uma tendência de diagnóstico mais precoce da DG (p<0,05), o aumento ponderal excessivo foi superior (36% *vs* 13%, p<0,05) e o controlo metabólico mais difícil de atingir, com maior necessidade de instituição terapêutica farmacológica (53% *vs* 24% no G1, p<0,05). A hipertensão crónica foi mais comum no G2, sem diferenças estatisticamente significativas no desenvolvimento de pré-eclâmpsia.
A idade gestacional no parto foi semelhante entre grupos, mas o G2 apresentou maiores taxas de cesariana (37% *vs* 23%, p<0,05).
O IMC normal associou-se com maior frequência a baixo peso ao nascimento (10% *vs* 5%, p<0,05), enquanto a obesidade se associou a macrossomia (8% *vs* 1%, p<0,05). O G2 apresentou uma taxa superior de hipoglicemia neonatal e síndrome de dificuldade respiratória, sem diferenças na necessidade de internamento em unidade de cuidados neonatais. A prova de reclassificação revelou-se maioritariamente normal nos dois grupos, sem diferenças significativas.
Discussão e Conclusão: Este estudo corrobora a importância da obesidade como fator de risco acrescido nas grávidas com DG, tanto para complicações da gravidez como para maior dificuldade no controlo metabólico, maior risco de macrossomia fetal e de algumas complicações neonatais. Assim, reforça-se a necessidade de uma vigilância hospitalar adequada destas grávidas para prevenir desfechos neonatais adversos.

Introduction

Both obesity and gestational diabetes (GD) are independent risk factors for several pregnancy complications and neonatal adverse outcomes,[1-4] and their prevalence are increasing worldwide.[1]

The incidence of GD in obese women is higher than in the general obstetric population and the risk of GD increases with maternal BMI.[1]

Pregnancy, itself, is a condition of decreased insulin sensitivity and increased insulin response in women with normal glucose tolerance,[5] but in obese women there is an increase in insulin resistance by a mechanism that may involve higher plasma levels of triglycerides and non-esterified fatty acids and lower plasma levels of adiponectin, that predispose to GD.[1] Since they have subclinical decreased insulin sensitivity and β-cell dysfunction, the metabolic stress of pregnancy predisposes them to the manifestation of GD.[5]

Several studies reported that obese women with GD had a higher incidence of cesarean section, induced labor, gestational hypertension, preeclampsia, macrosomia, large for gestational age (LGA) newborns and maternal morbidity.[2-7] In one study the rate of preterm delivery was also increased in this group.[4] Not only obesity increases the risks associated with GD, but also the existence of an excessive gestational weight gain appears to enhance them.[2]

On the other hand, obesity without GD revealed to be an isolated risk factor for macrosomia, caesarean delivery, labor induction, low APGAR score and admission to neonatal intensive care unit and GD seemed to increase these risks.[4]

In contrast, the study of Hildén K *et al* (2019) revealed no interaction effect between GD and BMI for severe perinatal outcomes such as malformations, perinatal mortality, stillbirth, prematurity, low APGAR score, fetal distress or Erb's palsy.[8]

The HAPO study showed that maternal obesity was independently associated with fetal hyperinsulinemia[9] and other studies revealed that the long-term sequelae related to an abnormal in utero metabolic environment are also increased in these children.[5]

Even though obesity has a significant impact on the complications associated with GD, these complications can be minored, at least in part, by optimized glycemic control during pregnancy.[1,6]

In one study, GD was diagnosed earlier in overweight and obese women and the median fasting glucose values were superior in that groups.[3] Glucose intolerance associated with GD usually resolves postpartum, however, obese women with GD have twice the risk of subsequent type 2 diabetes compared with non-obese.[1]

In obese, proper diet and counselling prior to gestation and higher medical intervention during pregnancy are required to prevent macrosomia and LGA and to reduce maternal complications.[3]

The objective of this retrospective comparative study was to understand the impact of obesity in our population of pregnant women with GD. For that purpose, we compared obstetric and perinatal outcomes, as well as differences in the post-partum OGTT between two groups of pregnant women with GD – Group 1 (G1) with normal BMI and Group 2 (G2) with obesity.

Methods

Retrospective, comparative study between two groups (G1, n=284; G2, n=235). Inclusion criteria were: unifetal pregnancies with GD with surveillance in our institution between 2012 and 2018 (N=874), who have delivered in our hospital (62 excluded), obtaining a sample of 812 pregnancies. Diagnosis of GD was made by a fasting plasma glucose value ≥92 mg/dL on the first, second or third trimester or by glucose values ≥180 mg/dL or ≥153 mg/dL 1 hours and 2 hours after 75 g OGTT between 24 and 28 weeks of gestation.

From the main group we then selected pregnant women with normal BMI (G1) – n=284 and with obesity (G2) – n=235.The analyzed parameters were demographic data (age, country of origin), family and obstetric history, gestational age at diagnosis of diabetes, weight gain during pregnancy, maternal, fetal and neonatal complications, metabolic control (with HbA1c in 3rd trimester) and therapy required, mode of delivery, birth weight and results of reclassification OGTT.

Weight gain during pregnancy was classified according to Insti-

tute of Medicine 2009 recommendation[10]:

- Prepregnancy underweight (BMI <18.5 kg/m²) – recommended weight gain of 12.5-18 kg
- Prepregnancy normal weight (BMI 18.5-24.9 kg/m²) – recommended weight gain of 11.5-16 kg
- Prepregnancy overweight (BMI 25-29.9 kg/m²) – recommended weight gain of 7-11.5 kg
- Prepregnancy obese (BMI ≥30 kg/m²) – recommended weight gain of 5-9 kg

Polyhydramnios was defined as an amniotic fluid index ≥25 cm or when the deepest pocket was ≥8 cm, according to Fetal Medicine Barcelona.[11]

Hypertension in pregnancy, as defined by American College of Obstetrics and Gynecologists (ACOG),[12] was considered when women had systolic blood pressure ≥140 mg/dL and/or diastolic blood pressure ≥90 mmHg in two measures 4 hours apart; preeclampsia was defined as 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:

- 300 mg or more of proteinuria per 24 hour urine collection (or this amount extrapolated from a timed collection), protein/creatinine ratio of 0.3 mg/g or more or dipstick reading of 2+ (used only if other quantitative methods not available);
- Thrombocytopenia: Platelet count less than 100000/μL;
- 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[13]: diabetes mellitus if the fasting value ≥126 mg/dL or the 2 hour value on a 75g OGTT ≥200 mg/dL, impaired fasting glucose if the fasting value is 110-125, impaired glucose tolerance if the 2 hour value is 140-199 mg/dL, normal if the first value is <110 mg/dL and the 2h value is <140 mg/dL. Fenton and Portuguese curves were used to access birth weight. Fetus were classified as large for gestational age (LGA - birth weight ≥90th centile), small for gestational age (SGA - birth weight ≤10th centile) and appropriate for gestational age (AGA - birth weight <90th and >10th centile)[14,15]. Macrosomia was defined as newborn weight ≥4000 g.

To evaluate metabolic control we used the HbA1c cut-off of 5.7%, as it is diagnostic of prediabetes according to ADA[16] and considering HbA1c values tend to be lower in pregnant compared with nonpregnant women.[17]

In the statistical analyses (p<0.05 as level of significance) we used the Chi-Square test or the Fisher exact test to examine association between two categorical variables, Kolmogorov-Smirnov test of normality, and T-test to compare the numerical variables..

The study was conducted in accordance with the amended Declaration of Helsinki as revised in 2013 and approved by the local institutional ethics committee – *"Comissão de Ética para a Saúde do HBA"* – on the 6th of November of 2020 (approval number 3399/2020).

Results

The mean maternal age was similar between groups (G1 33±5.7 y.o. *vs* G2 33±5.5 y.o.).

Obese women (G2) had more first-degree diabetes family history, previous GD and previous fetal macrosomia (46% *vs* 31%, 16% *vs* 6%, 11% *vs* 4%, p<0.05).

In G2, diagnosis of GD was earlier (G1 21.8±8w *vs* G2 19.3±8.4w, p<0.05) – 44% in 1st trimester *vs* 29% in G1, 48% in 2nd trimester *vs* 57% in G1 and 8% in 3rd trimester *vs* 14% in G1, and excessive weight gain was higher (36% *vs* 13%, p<0.05), as we can see in Fig. 1.

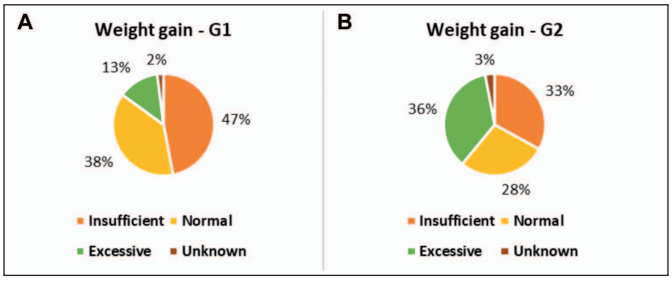

Figure 1. Weight gain in G1 (A) and G2 (B)

In obese pregnant women with GD, metabolic control was harder to achieve (Table 1). Although the mean HbA1c didn't show a significant difference between groups, G2 had higher rates of women with HbA1c≥5.7% in 3rd trimester. G2 had also a higher need for pharmacological treatment (53% *vs* 24% in G1) and combined therapy (metformin plus insulin), and those medications were started earlier, p<0.05.

Table 1. Differences in metabolic control and maternal-fetal complications

	G1	G2	*p* value
3rd Trimester HbA1c ≥5.7%	12.3%	25%	p<0.001
Mean HbA1c	5.2 ± 0.4%	5.5 ± 1.1%	NS
Need pharmacological treatment	24%	53%	p<0.001
Medication starting week	29 ± 6.7 w	26 ± 7.6 w	p<0.05
Needing insulin	8%	21.2%	p<0.001
Needing metformin	17.6%	46.4%	p<0.001
Insulin + metformin	2%	14.4%	p<0.001
Average daily dose of insulin	20 ± 25 U	26 ± 18 U	NS
Average daily dose of metformin	1254 ± 584 mg	1243 ± 599 mg	NS
Chronic hypertension	2.8%	21.3%	p<0.001
Gestational hypertension	2.8%	6%	NS
Preeclampsia	1%	3.4%	NS
Polyhydramnios	2.5%	1.7%	NS

Chronic hypertension was more common in G2, but no statistically significant differences in gestational hypertension or preeclampsia were found.

We found that gestational age at delivery was similar but G2 had higher cesarean rate, as well as higher rates of programmed delivery (induced labor or elective cesarean) and more macrosomia (all p<0.001). The average birth weight was higher in G2, while G1 was associated with higher rates of low birth weight newborns. Also, with both curves used we found higher rates of large for gestational age (LGA) newborns in G2 and of small for gestational age (SGA) newborns in G1 (p<0.05). While low birth weight was significantly associated with insufficient weight gain in normal BMI

mothers (p<0.01), the inverse was not verified in the obese group, where there were no statistical differences in weight gain in mothers with macrosomic newborns. The delivery and birth weight data are summarized in Table 2.

Table 2. Differences in delivery and birth weight between groups

	G1	G2	*p* value
Spontaneous labor	46%	26%	p<0.001
Inducted labor/elective cesarean	54%	74%	p<0.001
Gestational age at delivery	39 ± 1.2 w	39 ± 1.2 w	NS
Prematurity	4.9%	4.3%	NS
Vaginal delivery	77%	63%	p<0.001
Cesarean	23%	37%	p<0.001
Average birth weight	3 125 ± 468 g	3 329 ± 502 g	p<0.001
<2 500 g	10%	4.7%	p<0.05
≥4 000 g	1.4%	7.7%	p<0.001
Appropriate for gestational age			
Portuguese curves	80%	76%	p<0.001
Fenton curves	82%	84%	p<0.001
Large for gestational age			
Portuguese curves	5%	19%	p<0.001
Fenton curves	1%	8%	p<0.001
Small for gestational age			
Portuguese curves	15%	5%	p<0.001
Fenton curves	17%	8%	p<0.001
APGAR score <7 at 5th min	1%	1.7%	NS

APGAR scores were similar between groups. Regarding neonatal complications, G2 had more neonatal hypoglycemia and respiratory distress syndrome (p<0.05), but the rate of admissions to neonatal care unit was not significantly different between groups, despite it was slightly higher in G2 (9% *vs* 5.7%) (Table 3). The

Table 3. Neonatal morbidity

	G1	G2	*p* value
Admission to neonatal unit	5.7%	9%	NS
Neonatal hypoglycemia	0.4%	2.7%	p<0.05
Hyperbilirubinemia	5.8%	6.8%	NS
Respiratory distress syndrome	0.4%	3.6%	p<0.05
Neonatal sepsis	1.1%	3.6%	NS
Birth trauma	0.4%	0.5%	NS
Hypoxic encephalopathy	0%	0.5%	NS
Birth malformation	2%	0.5%	NS

main reasons of admission to neonatal care in G1 neonates were prematurity, neonatal sepsis and low birth weight, while in G2 the main reasons were neonatal sepsis, respiratory distress syndrome and hypoglycemia (Fig. 2).

There were no fetal or neonatal deaths in both groups and only one early pregnancy loss at 7 weeks of gestation occurred in G2.

No differences were found in reclassification OGTT, as shown in Table 4.

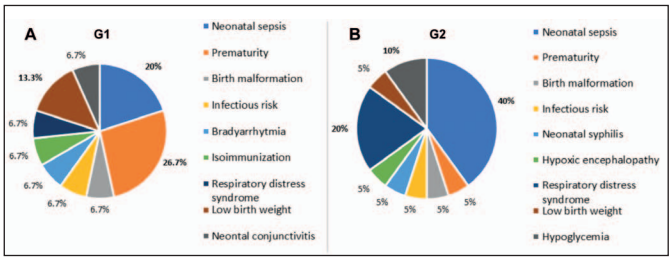

Figure 2. Main reasons for admission to neonatal care unit in G1 (A) and G2 (B)

Table 4. Post-partum reclassification with OGTT

	G1	G2	*p* value
Normal	76%	71%	NS
Impaired fasting glucose	0.7%	1.7%	NS
Impaired glucose tolerance	4.9%	6.3%	NS
Diabetes	0.4%	0%	NS
Lost to follow-up	18%	21%	-

Discussion and Conclusion

The results of this study corroborate the importance of obesity as an additional risk factor in pregnant women with GD.

We identified that obese women had more 1st degree diabetes history, previous GD and previous fetal macrosomia and the diagnosis of GD was earlier, which is in line with previous studies[3] and probably results from the fact that in obese women there is a status of insulin resistance.

In our study excessive weight gain was higher in obese women, which is in line with previous studies.[3] This reinforces the need of recognition by the women of the potential risks that overweight have in their pregnancies and in their own health and the need for a more intensive intervention in this group of women, with a multidisciplinary approach with the obstetrician, the nutritionist and the endocrinologist.

As expected, metabolic control was harder to achieve in obese women, as shown by the values of HbA1c in 3rd trimester and the higher need for pharmacological treatment and combined therapy with insulin plus metformin.

Chronic hypertension was more common in obese women, but no differences in gestational hypertension and preeclampsia, which contraries previous studies that showed a higher risk of preeclampsia in these women.[2-5,18] This can be justified by the current practice in our institution - screening of preeclampsia risk in 1st trimester applied to all pregnant women and starting low dose aspirin when indicated, to prevent early onset preeclampsia. Another hypothesis is that the increased metformin therapy in group 2 has protected those women from developing preeclampsia, as suggested by recent experimental studies in which metformin administration in early pregnancy decreased the rate of preeclampsia by a reduction in the production of antiangiogenic factors and improvement of endothelial dysfunction, probably through an effect on mitochondria.[19]

Gestational age at delivery was similar between groups but obese women had more cesarean and higher rates of induced labor, corroborating previous literature.[2,3,5]

As expected from previous studies,[2-4] obese women had more macrosomic newborns, with higher rates of LGA newborns in both weight classification curves we used.

Obesity was associated with neonatal hypoglycemia, in accordance with the HAPO study that revealed that maternal obesity was independently associated with fetal hyperinsulinemia.[9] In our study

respiratory distress syndrome was also more common in obesity group, but rates of admission to neonatal care unit were not statistically different between groups, despite it was slightly higher in G2. This contrasts with a previous study that showed that obesity without GD was a risk factor for treatment at neonatal unit and GD seemed to increase that risk in all BMI categories.[4]

Our study corroborates that of Hildén K *et al* (2019) that revealed no interaction effect between GD and obesity for newborn malformations, perinatal mortality, stillbirth, prematurity or birth trauma.[8]

It is known that obese women with a history of GD have twice the risk of subsequent type 2 diabetes compared with non-obese women.[1] Despite that, no differences were found in reclassification OGTT at 6-8 weeks post-partum between groups in our study. However, we must be aware that probably only a long-term follow-up would correctly identify those who will develop type 2 diabetes later in life, namely the ones with an unhealthy lifestyle and abnormal (higher) BMI.

With this study we can conclude that there is a need of a closer surveillance of these diabetic obese pregnant women, so that we can prevent maternal and neonatal adverse outcomes. Efforts should be made to reduce overweight and obesity prior to conception and to reduce excessive weight gain in obese women with GD.

The main limitation of this study is the fact that it was conducted in a single hospital, with a relatively small sample. However, this might end up being beneficial as a result of more standardized interventions by the reduced number of obstetricians involved in the surveillance of these pregnancies. The small sample size could be supplanted with the use of national data. Although, in that case, the outcomes would not be so comparable since surveillance and interventions in different institutions are not standardized.

Another limitation to our study is the fact that it did not include the overweight women with gestational diabetes. Although obesity is a disease with a continuous development spectrum, that includes the overweight, the authors considered that women with slight excess weight are not comparable to obese women in terms of cardiovascular risk. For that reason, since the number of overweight women is higher than the obese women group, the authors considered that it's inclusion in the study would skew the results. However, this study may lead to the development of a new prospective study to assess the impact of overweight in pregnancies complicated with GD.

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 de 2013 da Associação Médica Mundial.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Protection of Human and Animal Subjects: The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.
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