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Gestational Diabetes Treatment and its Impact on Pregnancy and Neonatal Complications

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A B S T R A C T

Introduction: The incidence of gestational diabetes (GD) has been increasing, mostly due to better diagnostic tools and recent diagnostic criteria, allowing early screening. This study aims to evaluate the impact of GD therapeutics on the occurrence of cesarean sections and pregnancy and neonatal complications.
Methods: This is a cohort study of GD pregnant women followed-up in various Portuguese hospitals and maternities, diagnosed between 2014 and 2018. Our sample was 15 089 pregnant women, divided in four groups, based on the therapeutics used to treat GD: diet and exercise, insulin, oral hypoglycemic drug (OHD) and insulin+OHD.
Results: The insulin group showed higher risk of caesarean section, neonatal hypoglycemia, neonatal hyperbilirubinemia and large for gestational age (LGA) newborns. Regarding the OHD group, there was higher probability for hydramnios and trauma at delivery and lesser risk for low birth weight and small for gestational age newborns (SGA). Lastly, the OHD+insulin group exhibited more likelihood to maternal and neonatal morbidity, like neonatal hypoglycemia, hyperbilirubinemia, trauma at delivery, and LGA newborns.
Conclusion: The simultaneous administration of insulin and OHD was more likely associated with pregnancy and neonatal complications. However, this group already had pre-conception characteristics that predisposed to complications (more advanced maternal age, higher previous BMI, familial history of diabetes, previous GD and/or macrosomia) and worse therapeutic adherence leading to a badly controlled glycemic profile. Therefore, these complications may be the result of the presence of previous characteristics and a glycemic profile that is difficult to control, rather than the use of insulin and OHD, *per se*.

Palavras-chave:
Complicações na Gravidez;
Diabetes Gestacional/tratamento farmacológico;
Resultado da Gravidez.

Tratamento da Diabetes Gestacional e o seu Impacto nas Complicações Obstétricas e Neonatais

R E S U M O

Introdução: A incidência da diabetes gestacional (DG) tem vindo a aumentar devido à melhoria da capacidade diagnóstica e à utilização de novos critérios de diagnóstico, possibilitando rastrear mais precocemente. Este estudo visa averiguar o impacto da terapêutica da DG quanto à ocorrência de complicações obstétricas e neonatais.
Material e Métodos: Estudo coorte de uma população de grávidas DG seguidas em hospitais e maternidades portuguesas, diagnosticadas entre 2014 e 2018. A amostra obtida foi de 15 089 grávidas, dividida em 4 grupos de terapêutica para controlo glicémico: dieta e exercício, insulina, antidiabéti-

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cos orais (ADO) e ADO+insulina.

Resultados: O tratamento com insulina apresentou maior risco de cesariana, hipoglicemia e hiperbilirrubinemia neonatais e nascituros grandes para idade gestacional. Quanto ao grupo sob ADO demonstrou maior probabilidade de hidrâmnios e trauma no parto e menor risco de nascituros com baixo peso à nascença e leves para idade gestacional. O grupo com uso concomitante de ADO e insulina exibiu maior risco de morbilidades materna e neonatal, nomeadamente hipoglicemia, hiperbilirrubinemia neonatal, trauma no parto e recém-nascidos grandes para idade gestacional.

Conclusão: A co-utilização de insulina+ADO esteve associada a maior probabilidade de complicações. No entanto, este grupo já apresentava características pré-concepção que predispunham para complicações e um comportamento insuficiente durante a gestação com perfis glicémicos mais difíceis de controlar. Estas complicações podem ser resultado da presença de características prévias e um perfil glicémico de difícil controlo, mais do que da utilização de insulina e ADO, *per se*.

Introduction

Gestational diabetes (GD) is a metabolic alteration that occurs during pregnancy and is due to placental diabetogenic hormones that induce insulin resistance and pancreatic insufficiency.[1,2] When uncontrolled, this condition may lead to complications to the mother and to the fetus.[1-5]

The prevalence of GD has been increasing. It might be due to the new screening recommendations indicated by the conjoint effort of Portuguese national health department and International Association of Diabetes and Pregnancy Study Groups, since 2011, as well as the increased incidence of obesity in women at reproductive age.[6-8] According to these criteria, the diagnosis of GD is made through fasting glucose ≥92 mg/dL or by OGTT performed between the weeks of 24 and 28 (0' ≥ 92 mg/dL and/or 60' ≥ 180 mg/dL and/or 120' ≥ 153 mg/dL).[7,9]

GD has been associated to macrosomia, neonatal metabolic changes, neonatal hyperbilirubinemia, and disproportional growth, among other neonatal complications.[1,10-12] It also affects the course of pregnancy, sometimes causing the development of gestational hypertension, preeclampsia, hydramnios or even other maternal morbidities and mortality.[6,10-13]

In the majority of cases, it is possible to control GD by non-pharmacological means such as lifestyle intervention and adapted healthy diet.[1,14] As for the rest, it is necessary to use pharmacological therapy: oral hypoglycemic drugs (OHD) or insulin, isolated or in association.[14-17]

In our study, we aim to analyze the impact of the therapeutics used during pregnancy to reach glycemic control as for the occurrence of cesarean sections and maternal and neonatal complications.

Material and Methods

1. Study Design

This is a retrospective cohort study based on data from the National Registry of GD under the responsibility of Diabetes and Pregnancy Study Group initiated by the Portuguese Society of Diabetes and in which some maternities and hospitals of Portugal are represented, in digital format, as Microsoft Excel®. The data on the registry was acquired on interviews with the participants and from clinical reports on digital files.

The data comprised a total of 17 959 pregnant women followed-up from January 2014 to December 2018 (five years).

We excluded underaged participants (under 18 years-old), pregnant women with previous or de novo diabetes mellitus (fasting glucose or OGTT at 0' ≥ 126 mg/dL or occasional glycemia/OGTT at 60' or 120' ≥ 200 mg/dL), missing values (no information) regarding treatment used to control GD and multifetal pregnancies. We included the data of 15 089 pregnant women (18 years-old and over, GD women with hospital follow-up between 2014 and 2018, within hospital establishments taking part in the national registry record) and their newborns (Fig. 1).

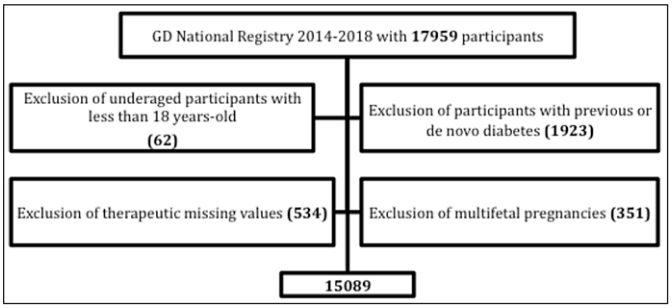


Figure 1. Flowchart of selection course for the final sample.

We considered the following maternal variables: maternal age, first-degree familial history of diabetes, previous macrosomia or GD, weight and height with estimated BMI, BMI categories following WHO guidelines, final gestational weight gain (GWG – difference between weight at delivery or at last appointment and pregestational weight), GWG groups according to the Institute of Medicine (IOM) guidelines, third trimester HbA1c (%), and treatment used for GD (lifestyle intervention and diet *vs* insulin *vs* OHD *vs* insulin + OHD).

According to the World Health Organization (WHO), the body mass index (BMI) categories are underweight (< 18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25 – 29.9 kg/m^2) and obesity (≥ 30 kg/m^2).

GWG was grouped into adequate (A), insufficient (I) and excessive (E), within each BMI category, being considered adequate if between 12.5 – 18 kg for underweight, 11.5 – 16 kg for normal BMI, 7 – 11.5 kg for overweight and 5 – 9 kg for obese. It was considered insufficient or excessive when the presented values would be lower or higher, respectively, than the indicated range for each category.

Regarding the variables related to the delivery or the newborn, we analyzed the occurrence of dystocic delivery, specially, cesarean section, newborn weight and assortment by the Fenton and Portuguese growth charts (adequate, small or large for gestational age) depending on the percentile (P) of the newborn (small for gestational age < P10; large for gestational age > P90).

2. Study Groups

The data from the 15 089 mothers and their newborns were divided according to the therapy used to treat GD: control group

with lifestyle intervention and diet, insulin group, OHD group and OHD + insulin group.

Surveillance of glycemic control during pregnancy was done by self-vigilance, with at least four measurements of capillary glycemia per day. The defined targets were fasting glucose ≤ 95 mg/dL and post-prandial glucose ≤ 140 mg/dL (one hour after the beginning of the three main daily meals). When the targets were reached, the therapeutic approach was maintained until the end of pregnancy.

3. Neonatal and Obstetric Outcomes

The sample was divided into four groups regarding its treatment for GD and each was characterized by the variables mentioned above, with means and standard deviations or total number and frequency.

For obstetric outcomes, we analyzed maternal morbidity as primary outcome and secondary outcomes: abortion, fetal death, gestational hypertension (gHT; systolic BP > 140 mmHg or diastolic BP > 90 mmHg after 20 weeks of gestation and without proteinuria), preeclampsia (hypertension associated with proteinuria after week 20), hydramnios (amniotic liquid excess) and cesarean section.

As for neonatal outcomes, we investigated the occurrence of neonatal mortality and morbidity, the latter being a composite for macrosomia (birthweight ≥ 4000 g), low birthweight (< 2500 g), large for gestational age (LGA), small for gestational age (SGA) according to Fenton and Portuguese growth charts, premature (delivery with < 37 weeks of gestation), neonatal hypoglycemia (< 40 mg/dL within the first 48 hours of life), neonatal hyperbilirubinemia (> 18 mg/dL), respiratory distress syndrome (RDS), admission to neonatal intensive care unit (NICU), congenital abnormalities and trauma at delivery.

4. Statistical Analysis

The statistical analysis was done by Statistical Package for Social Sciences (SPSS) software, for Windows, 25.0 version. Continuous variables were characterized by means and SD whilst the qualitative variables were defined by total number and frequency. Considering our sample size, we checked histograms, symmetry, and kurtosis to assess normal distribution of continuous variables. To verify the variables relationship, we used the Kruskal-Wallis test in case of a continuous variable without normal distribution and categorical variable (non-parametric test) and χ^2 or Fisher's exact test for the comparison of categorical variables. We used binomial and multinomial logistic regression to calculate the odds ratio (OR) and verify the influence of the different treatment modes on the maternal and neonatal outcomes, adjusting in order to reduce the confounding effect of the variables. We established 95% confidence interval (CI) and considered statistically significant for p values < 0.05.

Adjustment was made through backward likelihood ratio method in binomial logistic regression and backward stepwise method in multinomial logistic regression for automatic selection of pre-selected covariates. Therefore, our outcomes were adjusted to maternal age, pregestational BMI, HbA1c, first-degree familial history of diabetes and number of weeks between diagnosis and first hospital appointment.

Results

As expected, most of the participants (nr = 9015) were able to control their glycemic values with diet and exercise or other lifestyle changes, leaving 40.3% (nr = 6074) requiring pharmacological therapy in order to control GD: 23.8% (nr = 3596) with insulin, 11% (nr = 1660) with OHD and 5.4% (nr = 818) with the association of OHD and insulin (Table 1).[1,11,14]

In our sample, 42.7% (nr = 6437) of pregnant women had first-degree familial history of diabetes, 12.4% (nr = 1877) had previous GD and 4.9% (nr = 737) previous macrosomia. Comparing the groups of pregnant women controlled with lifestyle intervention and those who needed pharmacological therapy, we observed a higher incidence of familial history of diabetes, previous GD and macrosomia in the second group, with statistical evidence (Table 1).[14,17-19]

The mothers that needed insulin and/or OHD therapy were older than the ones in the lifestyle intervention group (mean > 33.9 *vs* 32.8, p value<0.001).[17] They also exhibited a superior

Table 1. Sample characteristics of mothers and their newborns (nr = 15 089)

Characteristics	Diet and exercise nr= 9015 (59.7%)	Pharmacological treatment nr= 6074 (40.3%)∝	Insulin nr= 3596 (23.8%)	Oral hypoglycemic drug (OHD) nr= 1660 (11.0%)	Insulin + OHD nr= 818 (5.4%)	*p* value
Maternal age (years-old), mean ± SD	32.8 ± 5.3	34.0 ± 5.1	34.0 ± 5.1	33.9 ± 5.2	34.4 ± 5.2	**<0.001**
BMI (kg/m2), mean ± SD	26.0 ± 5.4	28.7 ± 6.2	28.1 ± 6.0	29.1 ± 6.2	31.0 ± 6.6	
Underweight, nr (%)	227 (2.5%)	62 (1.0%)	48 (1.3%)	9 (0.5%)	5 (0.6%)	
Normal, nr (%)	4152 (46.1%)	1779 (29.3%)	1191 (33.1%)	441 (26.6%)	147 (18.0%)	**<0.001**
Overweight, nr (%)	2528 (28.0%)	1840 (30.3%)	1073 (29.8%)	544 (32.8%)	223 (27.3%)	
Obesity, nr (%)	1754 (19.5%)	2181 (35.9%)	1174 (32.6%)	593 (35.7%)	414 (50.6%)	
1st degree familial history of diabetes, nr (%)	3532 (39.2%)	2905 (47.8%)	1723 (47.9%)	764 (46.0%)	418 (51.1%)	**<0.001**
Previous GD, nr (%)	871 (9.7%)	1006 (16.6%)	587 (16.3%)	249 (15.0%)	170 (20.8%)	**<0.001**
Previous macrosomia, nr (%)	344 (3.8%)	393 (6.5%)	231 (6.4%)	107 (6.4%)	55 (6.7%)	**<0.001**
GWG (kg), mean ± SD	11.1 ± 5.8	9.8 ± 5.9	9.6 ± 6.0	10.1 ± 5.7	9.6 ± 6.1	
Adequate, nr (%)	2578 (28.6%)	1708 (28.1%)	1024 (28.5%)	466 (28.1%)	218 (26.7%)	**<0.001**
Insufficient, nr (%)	3121 (34.6%)	2082 (34.3%)	1248 (34.7%)	558 (33.6%)	276 (33.7%)	
Excessive, nr (%)	2214 (24.6%)	1629 (26.8%)	903 (25.1%)	482 (29.0%)	244 (29.8%)	
HbA1c, mean ± SD	5.2 ± 0.4	5.3 ± 0.4	5.3 ± 0.4	5.3 ± 0.4	5.4 ± 0.4	**<0.001**
Newborn birthweight (g), Mean ± SD	3157.3 ± 501.0	3205.5 ± 493.4	3184.2 ± 496.1	3222.0 ± 477.9	3265.9 ± 507.0	**<0.001**

BMI: body mass index; GD: gestational diabetes; GWG: gestational weight gain; HbA1c: glycosylated hemoglobin; nr: number; OHD: oral hypoglycemic drug; SD: standard deviation.

∝ types of pharmacological treatment: insulin, OHD or association of OHD and insulin.

previous BMI (insulin 28.1 kg/m², OHD 29.1 kg/m² and OHD + insulin 31.0 kg/m² *vs* diet 26.0 kg/m²), and more than half of the patients in the group medicated with OHD + insulin were in the obese range (50.6%, nr = 414; Table 1).[11,14,17,20-23]

As for the GWG, the lifestyle intervention group presented a higher mean in comparison with the other groups (Table 1).[14,24] On the other hand, HbA1c value of the non-pharmacological group was the lowest of the four groups (diet 5.2%, insulin 5.3%, OHD 5.3% and OHD + insulin 5.4%).[14]

Regarding the newborn weight, it was lower in the group of pregnant women controlled with lifestyle intervention (diet 3157.3 g, insulin 3184.2 g, OHD 3222 g and OHD + insulin 3265.9 g; Table 1).[25]

When analyzing the implications of GD treatment on obstetric complications, it was possible to observe an association with statistical significance, in which mothers that required pharmacological therapy had higher risk of maternal morbidity (Table 2).[20,25] This statistical relationship was explored (supplementary Table 1) and, afterwards, was adjusted for maternal age, previous BMI, and third trimester HbA1c because these were the factors that demonstrated significant association in most of the pregnancy complications (Table 3).

There was a higher percentage of maternal complications within the group that needed concomitant use of OHD and insulin (23.8%; nr = 195; Table 2). We examined the associated risk to each of the therapy modes and compared to lifestyle intervention, in the development of complications.

Only the risk of cesarean section had statistical significance in the insulin group, with 17% more probability than the lifestyle intervention group, after adjustment (aOR 1.17; CI 95% 1.05-1.31; *p* value = 0.006) (supplementary Fig. 1; Table 3). The OHD group had 60% higher risk of hydramnios (aOR 1.60; CI 95% 1.07-2.39; *p* value = 0.023), whilst the other complications did not have statistical significance (supplementary Fig. 2; Table 3). As for the OHD and insulin group, only global maternal morbidity showed a 27% higher probability of occurring when compared to diet and exercise, with statistical significance (aOR 1.27; CI 95% 1.01-1.60; *p* value = 0.042) (Table 3).[20]

Overall, neonatal complications were more frequent within the pharmacological groups, especially the OHD and insulin association group, apart from low birthweight and SGA (Table 4). While various complications had statistical significance before adjustment (supplementary Table 2), only few retained significance after adjustment to maternal age, pregestational BMI, third trimester HbA1c, and first-degree familial history of diabetes (Table 5).[17]

In the insulin group, there was a higher probability of hypoglycemia (aOR 1.51; CI 95% 1.18-1.93; *p* value = 0.001) and hyperbilirubinemia (aOR 1.24; CI 95% 1.05-1.46; *p* value = 0.011) in the newborn by 51% and 24%, respectively, as well as an increase of 63% of LGA babies via Fenton charts (aOR 1.63; CI 95% 1.25-2.13; *p* value <0.001) and 25% via Portuguese charts (aOR 1.25; CI 95% 1.05-1.47; *p* value = 0.010) (supplementary Fig. 3, Table 5).[1,16,25]

Regarding the OHD group, only trauma at delivery was more likely to occur, with an increase of 76% over the lifestyle intervention group (aOR 1.76; CI 95% 1.12-2.76; *p* value = 0.014) and lower probability of low birthweight (aOR 0.57; CI 95% 0.41-0.81; *p* value = 0.001) and SGA (aOR 0.59; CI 95% 0.46-0.76; *p* value <0.001 Fenton charts; aOR 0.67; CI 95% 0.51-0.87; *p* value = 0.003 Portuguese charts) newborns (supplementary Fig. 4, Table 5).[25]

Table 2. Association between GD treatment and the development of obstetric complications

Obstetric complications	Diet and exercise nr= 9015	Pharmacological treatment nr= 6074 ∝	Insulin nr= 3596	Oral hypoglycemic drug (OHD) nr= 1660	Insulin + OHD nr= 818	*p* value
Maternal morbidity, nr (%)	1303 (14.5%)	1020 (16.8%)	542 (15.1%)	283 (17.0%)	195 (23.8%)	**<0.001**
Abortion, nr (%)	72 (0.8%)	25 (0.4%)	13 (0.4%)	9 (0.5%)	3 (0.4%)	**0.002**
Fetal death, nr (%)	28 (0.3%)	15 (0.2%)	7 (0.2%)	3 (0.2%)	5 (0.6%)	**<0.001**
gHT, nr (%)	348 (3.9%)	268 (4.4%)	139 (3.9%)	77 (4.6%)	52 (6.4%)	**<0.001**
Preeclampsia, nr (%)	225 (2.5%)	198 (3.3%)	111 (3.1%)	53 (3.2%)	34 (4.2%)	**0.038**
Hydramnios, nr (%)	158 (1.8%)	172 (2.8%)	90 (2.5%)	54 (3.3%)	28 (3.4%)	**<0.001**
Cesarean section, nr (%)	2705 (30.0%)	2152 (35.4%)	1259 (35.0%)	574 (34.6%)	319 (39.0%)	**<0.001**

GD: gestational diabetes; gHT: gestational hypertension; nr: number; OHD: oral hypoglycemic drug;.
∝ types of pharmacological treatment: insulin, OHD or association of OHD and insulin.

Table 3. Adjusted correlation between GD therapy and the development of pregnancy complications.

Obstetric complications	Diet and exercise aOR (CI 95%)	Pharmacological treatment ∝ aOR (CI 95%)	*p* value	Insulin aOR (CI 95%)	*p* value	Oral hypoglycemic drug (OHD) aOR (CI 95%)	*p* value	Insulin + OHD aOR (CI 95%)	*p* value
Maternal morbidity	1.00	0.95 (0.84-1.08)	0.421	0.90 (0.78-1.04)	0.154	0.92 (0.75-1.12)	0.383	1.27 (1.01-1.60)	**0.042**
Abortions	1.00	1.10 (0.36-3.41)	0.869	0.93 (0.23-3.66)	0.912	1.43 (0.29-7.12)	0.661	1.27 (0.15-11.13)	0.827
gHT	1.00	0.92 (0.73-1.15)	0.457	0.83 (0.64-1.08)	0.171	0.96 (0.69-1.34)	0.828	1.10 (0.73-1.64)	0.655
Preeclampsia	1.00	1.08 (0.82-1.44)	0.584	1.14 (0.83-1.57)	0.415	0.92 (0.59-1.43)	0.706	1.14 (0.69-1.89)	0.599
Hydramnios	1.00	1.41 (1.06-1.89)	**0.018**	1.34 (0.97-1.86)	0.078	1.60 (1.07-2.39)	**0.023**	1.61 (0.98-2.66)	0.062
Cesarean section	1.00	1.10 (1.00-1.22)	0.053	1.17 (1.05-1.31)	**0.006**	0.98 (0.84-1.14)	0.766	1.05 (0.86-1.29)	0.637

aOR: adjusted odds ratio; CI 95%: confidence intervals at 95%; GD: gestational diabetes; gHT: gestational hypertension; OHD: oral hypoglycemic drug.

∝ types of pharmacological treatment: insulin, OHD or association of OHD and insulin.

Adjusted for maternal age, pregestational BMI and HbA1c.

Table 4. Association between GD treatment and the development of obstetric complications.

Neonatal complications	Diet and exercise nr= 9015	Pharmacological treatment nr= 6074 ∝	Insulin nr= 3596	Oral hypoglycemic drug (OHD) nr= 1660	Insulin + OHD nr= 818	*p* value
Neonatal mortality, nr (%)	15 (0.2%)	13 (0.2%)	8 (0.2%)	3 (0.2%)	2 (0.2%)	**<0.001**
Neonatal morbidity, nr (%)	1541 (17.1%)	1217 (20.0%)	703 (19.5%)	321 (19.3%)	193 (23.6%)	**<0.001**
Hypoglycemia, nr (%)	317 (3.5%)	313 (5.2%)	181 (5.0%)	82 (4.9%)	50 (6.1%)	**<0.001**
Hyperbilirubinemia, nr (%)	893 (9.9%)	737 (12.1%)	418 (11.6%)	186 (11.2%)	133 (16.3%)	**<0.001**
RDS, nr (%)	274 (3.0%)	186 (3.1%)	104 (2.9%)	53 (3.2%)	29 (3.5%)	**<0.001**
Admission to NICU, nr (%)	640 (7.1%)	410 (6.8%)	233 (6.5%)	119 (7.2%)	58 (7.1%)	**<0.001**
Prematurity, nr (%)	641 (7.1%)	419 (6.9%)	256 (7.1%)	99 (6.0%)	64 (7.8%)	0.283
Macrosomia, nr (%)	310 (3.4%)	269 (4.4%)	159 (4.4%)	63 (3.8%)	47 (5.7%)	**<0.001**
Low birthweight, nr (%)	728 (8.1%)	389 (6.4%)	256 (7.1%)	83 (5.0%)	50 (6.1%)	
Fenton charts, nr (%)						
LGA	265 (2.9%)	340 (5.6%)	199 (5.5%)	77 (4.6%)	64 (7.8%)	**<0.001**
SGA	1171 (13.0%)	573 (9.4%)	374 (10.4%)	130 (7.8%)	69 (8.4%)	
Portuguese charts, nr (%)						
LGA	806 (8.9%)	819 (13.5%)	459 (12.8%)	216 (13.0%)	144 (17.6%)	**<0.001**
SGA	990 (11.0%)	507 (8.3%)	333 (9.3%)	114 (6.9%)	60 (7.3%)	
Congenital abnormalities, nr (%)	338 (3.7%)	224 (3.7%)	126 (3.5%)	55 (3.3%)	43 (5.3%)	**<0.001**
Trauma at delivery, nr (%)	122 (1.4%)	104 (1.7%)	46 (1.3%)	40 (2.4%)	18 (2.2%)	**0.004**

GD: gestational diabetes; LGA: large for gestational age; OHD: oral hypoglycemic drug; NICU: neonatal intensive care unit; nr: number; RDS: respiratory distress syndrome; SGA: small for gestational age.

∝ types of pharmacological treatment: insulin, OHD or association of OHD and insulin.

Table 5. Adjusted correlation between GD therapy and the development of neonatal complications.

Neonatal complications	Diet and exercise aOR (CI 95%)	Pharmacological treatment ∝ aOR (CI 95%)	*p* value	Insulin aOR (CI 95%)	*p* value	Oral hypoglycemic drug (OHD) aOR (CI 95%)	*p* value	Insulin + OHD aOR (CI 95%)	*p* value
Neonatal mortality	1.00	1.25 (0.42-3.73)	0.691	1.49 (0.46-4.83)	0.509	0.68 (0.08-5.65)	0.719	1.27 (0.14-11.14)	0.831
Neonatal morbidity	1.00	1.14 (1.02-1.28)	**0.025**	1.14 (0.999-1.30)	0.052	1.02 (0.85-1.22)	0.869	1.46 (1.17-1.82)	**0.001**
Hypoglycemia	1.00	1.41 (1.13-1.76)	**0.003**	1.51 (1.18-1.93)	**0.001**	1.06 (0.74-1.52)	0.756	1.74 (1.18-2.59)	**0.006**
Hyperbilirubinemia	1.00	1.28 (1.11-1.47)	**<0.001**	1.24 (1.05-1.46)	**0.011**	1.15 (0.92-1.43)	0.212	1.73 (1.33-2.24)	**<0.001**
RDS	1.00	0.82 (0.63-1.06)	0.133	0.87 (0.64-1.18)	0.365	0.73 (0.47-1.12)	0.152	0.88 (0.52-1.48)	0.619
Admission to NICU	1.00	0.92 (0.77-1.10)	0.357	1.02 (0.83-1.25)	0.854	0.82 (0.62-1.09)	0.176	0.77 (0.53-1.13)	0.180
Macrosomia	1.00	0.98 (0.78-1.24)	0.881	1.09 (0.84-1.43)	0.525	0.83 (0.57-1.21)	0.321	1.05 (0.69-1.60)	0.825
Low birthweight	1.00	0.80 (0.67-0.96)	**0.017**	0.92 (0.75-1.13)	0.411	0.57 (0.41-0.81)	**0.001**	0.81 (0.545-1.21)	0.307
Fenton charts									
LGA	1.00	1.62 (1.28-2.05)	**<0.001**	1.63 (1.25-2.13)	**<0.001**	1.38 (0.97-1.96)	0.070	1.89 (1.29-2.78)	**0.001**
SGA	1.00	0.79 (0.69-0.91)	**<0.001**	0.88 (0.75-1.03)	0.116	0.59 (0.46-0.76)	**<0.001**	0.83 (0.61-1.15)	0.262
Portuguese charts									
LGA	1.00	1.27 (1.10-1.47)	**0.001**	1.25 (1.05-1.47)	**0.010**	1.24 (0.998-1.54)	0.052	1.58 (1.22-2.05)	<0.001
SGA	1.00	0.86 (0.74-0.995)	**0.043**	0.95 (0.80-1.12)	0.533	0.67 (0.51-0.87)	**0.003**	0.94 (0.67-1.31)	0.704
Prematurity	1.00	0.97 (0.80-1.17)	0.717	1.03 (0.83-1.27)	0.808	0.78 (0.57-1.09)	0.142	1.16 (0.80-1.69)	0.436
Congenital abnormalities	1.00	1.17 (0.92-1.50)	0.211	1.30 (0.99-1.70)	0.062	0.77 (0.50-1.18)	0.226	1.38 (0.88-2.16)	0.157
Trauma at delivery	1.00	1.25 (0.89-1.75)	0.204	0.93 (0.60-1.43)	0.724	1.76 (1.12-2.76)	**0.014**	2.13 (1.23-3.68)	**0.007**

aOR: adjusted odds ratio; CI 95%: confidence intervals at 95%; GD: gestational diabetes; LGA: large for gestational age; OHD: oral hypoglycemic drug; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome; SGA: small for gestational age.

∝ types of pharmacological treatment: insulin, OHD or association of OHD and insulin.

Adjusted for maternal age, pregestational BMI, HbA1c, weeks between diagnosis and first hospital appointment and first-degree familial history of diabetes.

Lastly, there was a higher risk, of about 46%, for neonatal morbidity (aOR 1.46; CI 95% 1.17-1.82; *p* value = 0.001), particularly neonatal hypoglycemia (aOR 1.74; CI 95% 1.18-2.59; *p* value = 0.006) and hyperbilirubinemia (aOR 1.73; CI 95% 1.33-2.24; *p* value <0.001) within the group with OHD and insulin. In this group there was also 113% higher odds of developing trauma at delivery (aOR 2.13; CI 95% 1.23-3.68; *p* value = 0.007) and higher probability of mothers giving birth to LGA newborns (aOR 1.89; CI 95% 1.29-2.78; *p* value = 0.001 Fenton charts and aOR 1.58; CI 95% 1.22-2.05; *p* value < 0.001 Portuguese charts) (supplementary Fig. 5, Table 5).[1,16,25]

Supplementary Table 1. Crude correlation between Gestational Diabetes treatment and the development of pregnancy complications.

Obstetric complications	Diet and exercise OR (CI 95%)	Pharmacological treatment ∝ OR (CI 95%)	*p* value	Insulin OR (CI 95%)	*p* value	Oral hypoglycemic drug (OHD) OR (CI 95%)	*p* value	Insulin + OHD OR (CI 95%)	*p* value
Maternal morbidity	1.00	1.21 (1.10-1.32)	**<0.001**	1.06 (0.95-1.18)	0.341	1.23 (1.07-1.42)	**0.005**	1.92 (1.61-2.28)	**<0.001**
Abortions	1.00	0.52 (0.33-0.81)	**0.004**	0.45 (0.25-0.82)	**0.009**	0.68 (0.34-1.35)	0.269	0.46 (0.14-1.45)	0.184
Fetal death	1.00	0.81 (0.43-1.51)	0.498	0.64 (0.28-1.47)	0.292	0.58 (0.18-1.91)	0.372	1.97 (0.76-5.11)	0.164
gHT	1.00	1.18 (0.998-1.38)	0.053	1.02 (0.83-1.25)	0.861	1.22 (0.95-1.57)	0.121	1.82 (1.35-2.46)	**<0.001**
Preeclampsia	1.00	1.32 (1.09-1.60)	**0.005**	1.25 (0.99-1.57)	0.060	1.28 (0.95-1.74)	0.107	1.68 (1.17-2.43)	**0.005**
Hydramnios	1.00	1.64 (1.32.2.04)	**<0.001**	1.45 (1.11-1.88)	**0.006**	1.88 (1.38-2.58)	**<0.001**	1.97 (1.31-2.97)	**0.001**
Caesarean section	1.00	1.27 (1.18-1.37)	**<0.001**	1.24 (1.14-1.36)	**<0.001**	1.24 (1.10-1.39)	**<0.001**	1.49 (1.27-1.74)	**<0.001**

CI 95%: confidence intervals at 95%; gHT: gestational hypertension;

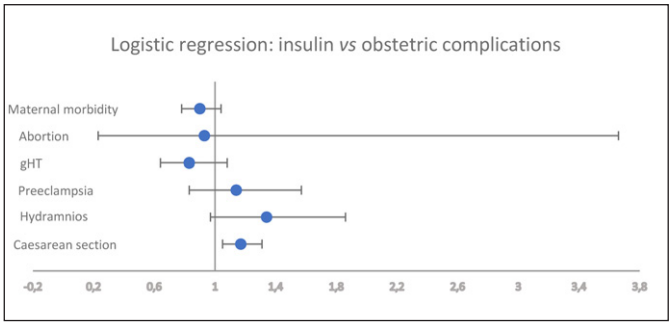
∝ types of pharmacological treatment: insulin, oral hypoglycemic drug (OHD) or association of OHD and insulin.

Supplementary Table 2. Crude correlation between GD treatment and the development of neonatal complications.

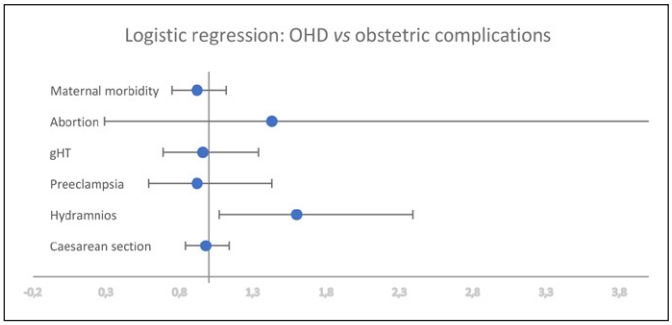
Neonatal complications	Diet and exercise OR (CI 95%)	Pharmacological treatment ∝ OR (CI 95%)	*p* value	Insulin OR (CI 95%)	*p* value	Oral hypoglycemic drug (OHD) OR (CI 95%)	*p* value	Insulin + OHD OR (CI 95%)	*p* value
Neonatal mortality	1.00	1.32 (0.63-2.78)	0.463	1.40 (0.59-3.31)	0.440	1.08 (0.31-3.72)	0.909	1.49 (0.34-6.52)	0.598
Neonatal morbidity	1.00	1.23 (1.13-1.34)	**<0.001**	1.21 (1.09-1.33)	**<0.001**	1.16 (1.01-1.33)	0.030	1.51 (1.27-1.79)	**<0.001**
Hypoglycaemia	1.00	1.54 (1.32-1.81)	**<0.001**	1.55 (1.28-1.87)	**<0.001**	1.41 (1.10-1.80)	**0.007**	1.82 (1.34-2.48)	**<0.001**
Hyperbilirubinemia	1.00	1.30 (1.17-1.44)	**<0.001**	1.26 (1.12-1.43)	**<0.001**	1.13 (0.96-1.34)	0.153	1.80 (1.48-2.20)	**<0.001**
RDS	1.00	1.04 (0.86-1.25)	0.720	0.998 (0.79-1.26)	0.989	1.04 (0.77-1.40)	0.818	1.19 (0.81-1.76)	0.377
Admission to NICU	1.00	0.97 (0.86-1.11)	0.667	0.95 (0.81-1.11)	0.530	0.996 (0.81-1.22)	0.973	1.01 (0.76-1.34)	0.942
Macrosomia	1.00	1.28 (1.08-1.51)	**0.004**	1.29 (1.06-1.56)	**0.012**	1.07 (0.81-1.41)	0.628	1.68 (1.22-2.30)	**0.001**
Low birthweight	1.00	0.79 (0.69-0.89)	**<0.001**	0.88 (0.76-1.02)	0.096	0.60 (0.48-0.76)	**<0.001**	0.76 (0.57-1.02)	0.069
Fenton charts									
LGA	1.00	1.88 (1.59-2.22)	**<0.001**	1.87 (1.55-2.26)	**<0.001**	1.51 (1.17-1.96)	**0.002**	2.68 (2.02-3.57)	**<0.001**
SGA	1.00	0.72 (0.64-0.80)	**<0.001**	0.80 (0.70-0.90)	**<0.001**	0.58 (0.48-0.70)	**<0.001**	0.65 (0.51-0.85)	**0.001**
Portuguese charts									
LGA	1.00	1.54 (1.39-1.71)	**<0.001**	1.46 (1.29-1.65)	**<0.001**	1.46 (1.24-1.71)	**<0.001**	2.12 (1.74-2.58)	**<0.001**
SGA	1.00	0.78 (0.69-0.87)	**<0.001**	0.86 (0.76-0.99)	**0.029**	0.63 (0.51-0.77)	**<0.001**	0.72 (0.55-0.95)	**0.018**
Prematurity	1.00	0.97 (0.85-1.10)	0.617	1.00 (0.86-1.16)	0.986	0.83 (0.67-1.03)	0.091	1.11 (0.85-1.45)	0.449
Congenital abnormalities	1.00	1.03 (0.87-1.23)	0.727	1.03 (0.83-1.26)	0.813	0.86 (0.64-1.14)	0.293	1.43 (1.03-1.98)	**0.032**
Trauma at delivery	1.00	1.33 (1.02-1.73)	**0.035**	1.02 (0.73-1.44)	0.903	1.78 (1.24-2.56)	**0.002**	1.67 (1.01-2.75)	**0.045**

CI 95%: confidence intervals at 95%; GD: gestational diabetes; LGA: large for gestational age; NICU: neonatal intensive care unit; OHD: oral hypoglycemic drug; OR: odds ratio; RDS: respiratory distress syndrome; SGA: small for gestational age.

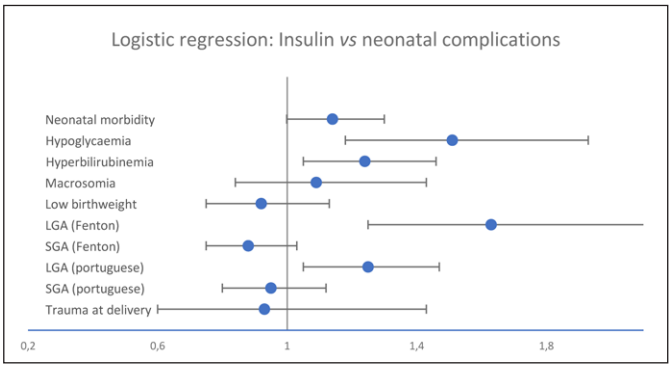
∝ types of pharmacological treatment: insulin, oral hypoglycemic drug (OHD) or association of OHD and insulin.



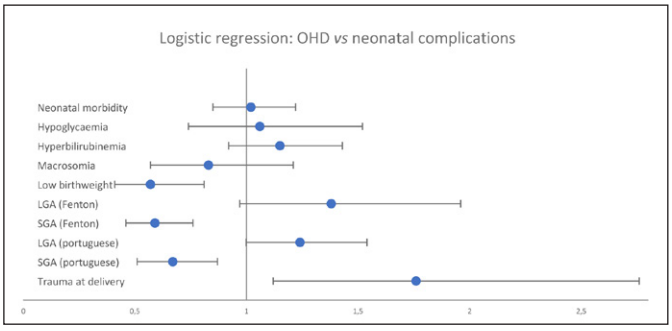
Supplementary Figure 1. Logistic regression of insulin therapy in the development of obstetric complications.



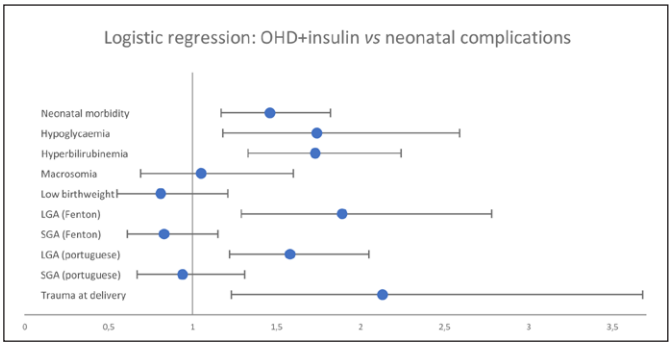
Supplementary Figure 2. Logistic regression of OHD in the development of maternal complications.



Supplementary Figure 3. Logistic regression of insulin in the development of neonatal complications.



Supplementary Figure 4. Logistic regression of OHD in the development of neonatal complications.



Supplementary Figure 5. Logistic regression of OHD+insulin in the development of neonatal complications.

Discussion

GD therapy differs from patient to patient and is conditioned by many pregestational risk factors, being that its administration might have an impact in the development of maternal and neonatal complications.

Only a few pregnancy complications showed statistically significant differences within the different therapeutic groups, such as maternal morbidity, hydramnios and cesarean section,[20] when unadjusted. After adjustment to maternal age, pregestational BMI and third trimester HbA1c, some lost the association evidence, demonstrating the presence of confounding variables. Nonetheless, it was possible to verify that the need for pharmacological treatment, in particular insulin and OHD association, was connected to an increased probability of obstetric complications,[1] although not statistically significant, which shows the need for a bigger sample to reach statistical evidence.

As for neonatal complications, those also ceased to have statistical significance after adjustment to maternal age, pregestational BMI, third trimester HbA1c, and family history of diabetes, demonstrating confounding. However, the use of medical therapy for GD may be related to increased occurrence of complications, particularly for the ones with simultaneous use of OHD and insulin, whose glycemic profile is much more difficult to control and with higher risk for neonatal hypoglycemia, hyperbilirubinemia and LGA newborns which leads to trauma during delivery.[1,16,20,25] Additionally, this particular group demonstrated a synergistic effect on the risk that either OHD or insulin alone were associated with.

Despite that, it is important to take into account the fact that mothers that required medical treatment, had previous pregestational characteristics which predisposed to complications, like advanced maternal age, superior pregestational BMI, history of familial diabetes, previous GD and macrosomia.[1,26-29] They also featured glycemic profiles that were more difficult to control, greater third trimester HbA1c values, requiring pharmacological treatment.[14] Therefore, the simultaneous use of OHD and insulin may not be directly related to complications *per se*, but it might reflect the difficulty to control glycemic profile that favors the development of complications.[14,16,28]

This study presented various limitations. The national registry of GD is a database fulfilled by health professionals that previously volunteered to take part in the registration. This results in lack of total national representation because many peripheral hospitals are not represented and those, who miss the deadlines and do not deliver the patients data, may also be out of the registry. Consequently, this results in selection by participation bias. Moreover, some filling criteria are sometimes subjective, leading to lack of uniformity, high variability, and many missing data, causing an information bias due to variability of the observer and interviewer.

At last, there is also another bias of information due to measuring error, memory, and social desirability when the information is the result of self-report recollection.

Although there are many significant biases, some may be reduced through training and establishing action protocols for the information acquisition and filling methods. Additionally, prospective studies may also avoid some of these limitations.

Conclusion

It is essential for pregnant women, after being diagnosed with GD, to have precocious and regular hospital appointments, allowing the institution of lifestyle intervention strategies and pharmacological therapy as soon as possible, in order to rapidly reach glycemic control.

In this retrospective study, in some pregnant women with the need for pharmacological therapy a stricter surveillance, with more frequent appointments and immediate and adequate therapeutic adjustments, might have lacked.

Equally, we should take into account the importance of pregestational risk factors, like advanced maternal age, high pregestational BMI, history of familial diabetes, previous GD and/or macrosomia, that affects the gestational course and augment the probability of future pharmacological requirements, sometimes more than one medical therapy and therefore increasing the risk for maternal and neonatal complications.

In conclusion, it is crucial to provide frequent hospital appointments as well as preconception follow-up to pregnant women so to avoid complications.

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Contributorship Statement / Declaração de Contribuição:

JCX: Contributed to conception and design, acquisition of data, analysis and interpretation of data, drafting and revising the article and giving the final approval of the version to be published.
AC: Contributed to conception and design, acquisition of data, revising the article and providing the final approval of the version to be published.

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 pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.
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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 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).
Provenance and Peer Review: Not commissioned; externally peer reviewed.
Data Availability Statement: The data that support the findings of this study are available from the Diabetes and Pregnancy Study Group initiated by the Portuguese Society of Diabetes, but restrictions apply to the availability of these data, that is not publicly accessible. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable.

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