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Clinical Predictors of Neonatal Morbidity in a Prospective Cohort of Mothers with Gestational Diabetes

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Abstract

Introduction

Gestational diabetes mellitus poses significant risks for maternal and neonatal health, highlighting the need for metabolic control and specialized follow-up during pregnancy. The aim of this study was to assess the short-term outcomes from neonates born to mothers with gestational diabetes mellitus. It was also investigating the relation between metabolic control during pregnancy and neonatal complications.

Material and methods

A prospective observational study was undertaken at a level III natal care centre from June to December of 2023, including 212 dyads of mothers with gestational diabetes mellitus and newborns. Maternal data included age, parity, weight before the current pregnancy, risk factors for gestational diabetes mellitus, gestational age at diagnosis and weight gain during pregnancy. Neonatal data included mode of delivery, gestational age, birth weight, need for resuscitation, Apgar score, metabolic complications, trauma lesions, congenital anomalies, neonatal sepsis, admission to the Neonatal Intensive Care Unit and mortality.

Results

Advanced maternal age (41%), multiparity (52.4%), excess weight and obesity before pregnancy (59.4%), history of gestational diabetes mellitus (26.1%) or multiple risk factors for gestational diabetes mellitus (62.3%) were common. Gestational weigh gain was excessive in 34.2% of the sample and in 48.1% of obese women. Most women did not experience pregnancy-related complications (84.9%) and hypertension was the most frequently recorded complication (6.1%). C-section was the mode of delivery in 35.4% and 7.5% experienced preterm birth. Foetal macrosomia occurred in 8.5%, congenital malformations in 10.4% and metabolic complication in 21.2% (9% hypoglycaemia). Macrosomia (p=0.041) and hyperbilirubinemia treated with phototherapy (p=0.013) were more frequent in newborns born to mothers with two or more risk factors for gestational diabetes mellitus. Macrosomia was also more frequent in women with excessive gestational weight gain (p=0.045).

Conclusion

Risk factors for gestational diabetes mellitus and excessive weight gain during pregnancy appear to be significant factors in determining obstetric and neonatal morbidity.

Keywords

Gestational diabetes mellitus, newborn, hypoglycaemia, morbidity, disease management

Resumo

Introdução

A diabetes gestacional apresenta riscos significativos para a saúde materna e neonatal, reforçando a necessidade do controlo metabólico e seguimento especializado durante a gravidez. O objetivo deste estudo foi analisar os *outcomes* a curto-prazo nos recém-nascidos de mães com diabetes gestacional e investigar a relação entre o controlo metabólico durante a gravidez e complicações neonatais.

Materiais e métodos

Foi realizado um estudo prospetivo num hospital de nível III entre junho e dezembro de 2023, que inclui 212 díades de mães com diabetes gestacional e respetivos recém-nascidos. As variáveis maternas incluíram a idade, paridade, peso antes da gravidez, fatores de risco para a diabetes gestacional, idade gestacional no momento do diagnóstico e ganho ponderal durante a gravidez. As variáveis neonatais incluíram o tipo de parto, idade gestacional, peso ao nascimento, necessidade de ressuscitação, índice de Apgar, complicações metabólicas, lesões traumáticas, anomalias congénitas, sépsis neonatal e internamento na Unidade de Cuidados Intensivos Neonatais e mortalidade.

Resultados

A idade materna avançada (41%), multiparidade (52,4%), excesso de peso e obesidade antes da gravidez (59,4%), antecedente de diabetes gestacional (26,1%) e múltiplos fatores de risco para diabetes gestacional (62,3%) foram frequentes. O ganho ponderal durante a gravidez foi excessivo em 34,2% da amostra e em 48,1% das mulheres obesas.

A maioria das mulheres não sofreu complicações relacionadas com a gravidez (84,9%) e a hipertensão arterial foi a complicação mais frequente (6,1%). A cesariana foi o tipo de parto em 35,4% e 7,5% foram partos pré-termo. A macrossomia fetal ocorreu em 8,5%, malformações congénitas em 10,4% e complicações metabólicas em 21,2% (hipoglicemia em 9%). Os partos instrumentados (p=0,035), a macrossomia (p=0.041) e a hiperbilirrubinemia tratada com fototerapia (p=0,013) foram mais frequentes em recém-nascidos com mães com dois ou mais fatores de risco para diabetes gestacional. A macrossomia também foi mais frequente em recém-nascidos cujas mães tiveram um ganho ponderal excessivo na gravidez (p=0,045).

Conclusão

Os fatores de risco para diabetes gestacional e o ganho ponderal excessivo na gravidez parecem ser importantes fatores a condicionar morbilidade obstétrica e neonatal.

Palavras-Chave

Diabetes gestacional, recém-nascido, hipoglicemia, morbilidade

Introduction

Gestational Diabetes Mellitus (GDM) is characterized by glucose intolerance first recognized during pregnancy, typically in the second or third trimester. In most cases, it regresses after delivery (1). It affects approximately 15-17% of pregnancies worldwide (2,3) and the prevalence has been steadily increasing due to various factors including changes in lifestyle, advanced maternal age, and obesity (2,4–8). However, the prevalence varies depending on the diagnostic criteria used and the population studied (5). In Portugal, it is estimated that about 7.5 % of pregnant women are diagnosed with GDM (9).

The condition arises due to a combination of insulin resistance and inadequate insulin secretion to compensate for increased metabolic demands during pregnancy (5). A state of maternal hyperglycaemia is established, leading to foetal hyperglycaemia with hyperinsulinism, which are responsible for most neonatal co-morbidities (6).

GDM poses significant risks not only to maternal health but also to foetal well-being, with potential adverse outcomes extending to the neonatal period. Many studies demonstrated that GDM increases the risk of maternal complications, including preeclampsia, pregnancy-induced hypertension, preterm delivery, and caesarean section (2,10). Also, neonates born to mothers with GDM are at an increased risk of various co-morbidities, including macrosomia, neonatal hypoglycaemia, respiratory distress syndrome, congenital anomalies, and others (2,11,12). Macrosomia, defined as birth weight equal or above 4000 g (13), is a well-documented complication of GDM and is associated with an increased risk of birth trauma and caesarean delivery (2,12,13). Neonatal hypoglycaemia, resulting from foetal hyperinsulinemia in response to maternal hyperglycaemia, is a common and potentially life-threatening complication that requires prompt recognition and management. Additionally, respiratory distress syndrome, caused by delayed foetal lung maturation, and congenital anomalies, such as cardiac defects, are also observed at higher rates in neonates born to mothers with GDM (2,12,14).

All pregnant women diagnosed with GDM in primary care are referred to hospital-level Obstetrics consultation. It is widely recognized that an adequate glycaemic control is associated with a reduction in complication rates during pregnancy and in the neonatal period (3,12,15). The initial treatment includes lifestyle changes such as diet and physical exercise, which seems to be sufficient for the achievement of metabolic control in 70-85 % of GDM cases (14,16). If glycaemic control is not achieved, it may be necessary to initiate oral antidiabetic drugs or insulin (14,16).

Identifying risk factors and clinical parameters associated with perinatal adverse outcomes is essential for prevention and risk assessment, to guide clinical management during pregnancy and neonatal period. The aim of the study aims was to evaluate the short-term outcomes from neonates born to mothers with GDM and to analyse the association between maternal

characteristics and metabolic control during pregnancy with obstetric and neonatal complications.

Methods

Study Design

This was a prospective cohort study from a population of mothers with the diagnosis of GDM and newborn dyads, conducted in a tertiary hospital (compiling two maternity buildings) during seven months (June-December 2023).

Setting and relevant context

Gestational Diabetes was diagnosed according to the national recommendations (17): fasting plasma glucose in the first prenatal visit ≥ 92 mg/dL (first phase) or after 75-g oral glucose tolerance test (OGTT) when one of following values were met: 1) fasting plasma glucose ≥ 92 mg/dL, 2) 1-hour plasma glucose ≥ 180 mg/dL, 3) 2-hour plasma glucose ≥ 153 mg/dL (second phase, at 24-28 weeks gestation). The surveillance of patients with GDM is performed by a multidisciplinary team including obstetricians, endocrinologists, nutritionists, and nurses specialized in maternal care. Initial therapeutic approach includes lifestyle modification (dietary modifications and physical exercise). Pharmacologic interventions (insulin or oral antidiabetic medication) are started when target glucose levels (fasting glucose ≤ 95 mg/dL and 1-hour postprandial ≤ 140 mg/dL) cannot be consistently achieved (16).

In this neonatal tertiary centre, which includes two maternity wards and two neonatal intensive care service (UCINs), occurs a total of 4930 annual births, with a c-section rate of 25.6 % (2023). Preterm birth occurred in 9.5% of births (2023). Criteria for admission to the NICU are prematurity <34 weeks and birth weight <2400g as well as other conditions in need for intensive care support. The follow-up of pregnant women diagnosed with GDM is done in a specific appointment by obstetricians.

Currently, the diagnose of GDM is based on the national recommendations in force since 2011 (17) and the beginning of insulin therapy is also based in a national consensus of 2017 (16).

Population

All women diagnosed with GDM (and their respective newborns) were recruited after delivery and invited to participate in the study.

After birth, all women with an established diagnosis of GDM and their respective newborns admitted to one of the maternity wards were flagged for inclusion in the study.

The exclusion criteria were multiple pregnancy and the lack of monitoring since the first trimester or incomplete monitoring of the pregnancy.

Data collection and outcomes measures

Clinical maternal characteristics included were age, parity, overweigh or obesity before pregnancy, previous history of GDM, macrosomia, recurrent pregnancy loss, previous foetal malformation, in-uterine foetal death (IUFD), and family history of diabetes, GA at diagnosis of GDM, diagnosis with fasting blood glucose level or with OGTT. The variables studied in relation to metabolic control were gestational weight gain (GWG) and therapy (non-pharmacological and pharmacological). Obstetric complications included were pregnancy complications such as hypertension, pre-eclampsia (PEC), cholestasis, urinary tract infection, and threatened preterm labour and pre-term birth and C-section delivery.

The following definitions were used:

- Gestational hypertension: corresponds to systolic blood pressure greater than or equal to 140 mmHg or diastolic blood pressure greater than or equal to 90 mmHg on two separate measurements at least 4 hours apart after 20 weeks of gestation, without proteinuria or target organ damage diagnosed (18).
- Overweight: corresponds to a body mass index (BMI) above 25 kg/m^2 and below 29.9 kg/m^2 (19).
- Obesity: body mass index greater than 30 kg/m^2 (19).
- Gestational weight gain (GWG): weight gain since conception until the delivery (19,20).
    - In agreement with Direção Geral da Saúde, the optimal weight gain during pregnancy according to the BMI before pregnancy is:
        - BMI < 18.5 kg/m^2: 12.5-18 Kg
        - BMI between 18.5-24.9 kg/m^2: 11.5-16 Kg
        - BMI between 25-24.9 kg/m^2: 7-11.5 Kg
        - BMI between ≥ 30,0 kg/m^2: 5-9 Kg (21).
    - It was considered insufficient GWG when the minimum weight gain was not achieved.
    - It was considered excessive GWG when there was a superior weight gain than the maximum recommended.
- Preeclampsia: arterial hypertension associated with proteinuria (18).
- Preterm birth: birth before 37 weeks of gestation.
- Recurrent pregnancy loss: two or more failed pregnancies documented by ultrasound (22).

The risk factors considered for GDM were maternal age above than 35 years, multiparity, prior diagnosis of GDM, overweight, obesity, prior newborn with macrosomia, recurrent pregnancy loss, prior IUFD and family history of diabetes on a first degree relative. Combined risk factors for GDM were considered when three or more of these were present.

Physical exercise (PE) was considered when any form of planned physical activity (example: walking for more than thirty minutes, swimming, and Pilates classes) was performed.
Combined maternal morbidity was defined as the presence of two or more maternal complications during pregnancy.
General clinical neonatal characteristics included sex and birth weight. Neonatal morbidity studied was: macrosomia, large (LGA) and small for GA (SGA), Apgar score under seven at the fifth minute, resuscitation at birth (positive pressure ventilation, endotracheal tube with or without chest compressions), metabolic complications (hypoglycaemia and hyperbilirubinemia treated with phototherapy), trauma lesions (soft tissue trauma, clavicle fracture, brachial plexus injury, cranial fracture, subgaleae haemorrhage and other intra-cranial complications), hypoxic-ischemic encephalopathy, congenital anomalies (*minor* and *major*), neonatal sepsis, admission to the Neonatal Intensive Care Unit (NICU) and mortality. The following definitions were used:

- Appropriate for gestational age newborn (AGA): birth weight between the 10th and 90th percentile for gestational age; LGA: birth weight above the 90th percentile for gestational age; SGA: birth weight below the 10th percentile for gestational age (23).
- Macrosomia: newborn weight more or equal to 4000g (13).
- Polycythaemia: peripheral venous haematocrit greater than 65%, according to the national consensus of the Portuguese Neonatology Society (24).
- Hypoglycaemia: glycaemia below 50 mg/dL in the first 48h of life and below 60mg/dl after that period, according to the Pediatric Endocrine Association (PES) 2015 recommendations (25); since the definition of hypoglycaemia is not consensual and treatment thresholds vary according to different societies, this definition facilitated data collection and standardization between both maternities, as the protocols used for neonatal hypoglycaemia have differences.
- Hyperbilirubinemia and criteria for phototherapy: according to the American Academy of Pediatrics (AAP) 2022 guidelines “Clinical Practice Guideline Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation” (26).
- Brachial plexus injury: flaccid paresis of an arm at birth, with the passive range of motion being greater than the active range of motion (27).
- Intracranial haemorrhage: brain imaging, including transfontanelar ultrasound or magnetic resonance.
- Hypoxic ischaemic encephalopathy: according to the criteria in the national consensus of the Portuguese Neonatology Society 2022 (28).

- Congenital malformation (CM) or birth defects: alterations in the structure and function of the organ systems of a newborn that occurs during pregnancy and is identified before, at, or later after birth (29).
- Neonatal death: deaths among live births during the first 28 completed days of life, according to the World Health Organization.

For combined neonatal morbidity it was considered three or more complications.

During the admission period or after discharge, within the first month after delivery, data was collected from the electronic clinical record (SClínico®) and completed with a questionnaire delivered to the mothers (Annex I).

Data analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 26 (SPSS®). Categorical variables were expressed as absolute and relative frequency, while continuous variables were expressed as measures of central tendency and dispersion according to their type of distribution after normality tests and plots were assessed.

To study the association between categorical variables, the chi-square test was applied. In variables with low expected frequency count (<5), Fisher´s exact test was alternatively used. The odds ratio (OR) was also obtained for each verified association, considering a 95% confidence interval. The association between categorical and numerical variables (discrete or continuous), was assessed according to the distribution of the numerical variables, either parametric testing with t-student test for independent samples or non-parametric testing with Mann Whitney-U test. A statistically significant value was assumed when $p<0.05$.

Ethics

This study was submitted for approval by the Ethics Committee of the Unidade Local de Saúde (ULS) de Coimbra according to all necessary requirements of Declaration of Helsinki (OBS.SF.127/2023).

Results

During the study period, a total of 258 women were identified with the diagnosis of gestational diabetes. After exclusion criteria, 255 mothers were eligible to the study and a total of 212 accepted to participate.

From the 212 women in our study, 41.0% (n=87) were over 35 years-old with a mean age of 33.7 years (± 5.8). Most women (52.4%, n=111) were multiparous. Regarding weight before pregnancy, 34.4% (n=73) had excess weight and 25.0% (n=53) were obese. More than a quarter (26.1%, n=29) had previously been diagnosed with GDM and 62.3% (n=132) had been identified with two or more risk factors for GDM (Table 1).

The diagnose of GDM was made through fasting blood glucose in 48.1% (n=102) and by the OGTT in 51.9% (n=110) and the majority were diagnosed in the first and second trimesters (97.2%, n=206)). The median GA at the diagnosis was 24 weeks (IQR: 7.00;25.00). The treatment was diet and PE in 59.9% (n=127), oral antidiabetics in 21.7% (n=46) and insulin therapy in 18.4% (n=39). Regarding PE, 58.0% (n=123) reported doing it during two or more trimesters. The median of cumulative PE per week was 90 minutes (IQR: 0.00;210.00).

GWG was adequate in 27.0% (n=69) of diabetic women, excessive in 34.2% (n=67) and insufficient in 38.8% (n=76) (Table 1). In the group of obese women (BMI>30Kg/m^2), excessive GWG (>10Kg) was higher (48.1%, n=25). The majority (84.9%, n=178) had no pregnancy-related complications and only two women (0.9%) had two or more maternal complications besides GDM (Table 1). Hypertension was the most frequent recorded complication during pregnancy (6.1%, n=13), complicated by PEC in 4.2% (n=9) of the cases. C-section was the mode of delivery in 35.4% (n=75) of the cases. Pre-term birth occurred in 7.5% (n=16).

Regarding the newborn, 54.2% (n=115) were males. The median weigh was 3280g (IQR: 2970-3550) and 8.5% (n=18) were macrosomic. When considering birthweight for GA, there were 5.7% (n=12) LGA and 10.4% (n=22) SGA. Metabolic complications were identified in 21.2% (n=45): hypoglycaemia in 9.0% (n=19) and hyperbilirubinemia treated with phototherapy in 12.3% (n=26). Most hypoglycaemias occurred in AGA newborn (n=17; 89.5%). One macrosomic newborn experienced hypoglycaemia.

The Apgar score was <7 at fifth minute in three cases (1.4%) and resuscitation was needed in 11 (5.2%), ten with positive pressure ventilation and one with endotracheal tube. In 94.8% of the newborns, resuscitation was not required. Regarding *minor* and *major* traumatic injuries, there were 16 (7.5%): 16 (7.5%) cephalohematomas/*caput succedaneum*, six (2.8%) soft tissue trauma, three (1.4%) clavicle fractures, one brachial plexus injury (0.5%) and one (0.5%) posterior parietal fracture. There were six newborns with two or more injuries from birth.

Table 1. Maternal and neonatal morbidity and mortality.

	Variables	**n=212, n (%)**
Maternal	Age > 35 years	87 (41.0)
	Multiparity	111 (52.4)
	Excess weight before pregnancy	73 (34.4)
	Obesity before pregnancy	53 (25.0)
	Prior diagnosis of GDM	29 (26.1)
	Prior neonate with macrosomia	9 (8.1)
	Recurrent pregnancy loss	12 (5.7)
	Prior foetal malformation	8 (7.2)
	Prior in-utero foetal death	3 (2.7)
	Family history of diabetes	63 (29.7)
	Combined risk factors for GDM	132 (62.3)
Pregnancy	GA at diagnosis (w/), median (IQR)	24 (7.0-25.0)
	1st trimester	99 (46.7)
	2nd trimester	107 (50.5)
	3rd trimester	6 (2.8)
	Fasting blood glucose	102 (48.1)
	OGTT	110 (51.9)
	Insulin therapy	39 (18.4)
	PE (min/week), median (IQR)	90 (0.00;210.00)
	No PE during pregnancy	56 (26.4)
	PE during two or more trimesters	123 (58.0)
	Excess GWG (n=196[&])	67 (34.2)
	Excess GWG in obese (n=52)	25 (48.1)
	Insufficient GWG (n=196[&])	76 (38.8)
	Pre-eclampsia	9 (4.2)
	Hypertension	13 (6.1)
	Urinary tract infection	6 (2.8)
	Cholestasis	3 (1.4)
	Threatened preterm labour	3 (1.4)
	Combined maternal morbidity[+]	2 (0.9)
	Forceps or vacuum delivery	41 (19.3)
	C-section	75 (35.4)
	Pre-term birth	16 (7.5)

	Variables	**n=212, n (%)**
Neonatal	Male	115 (54.2)
	Birthweight (g), median, (IQR)	3280 (2970-3550)
	Macrosomia	18 (8.5)
	LGA	12 (5.7)
	SGA	22 (10.4)
	APGAR score < 7 at 5´	3 (1.4)
	Resuscitation (total)	11 (5.2)
	Traumatic injury	16 (7.5)
	Congenital malformations	22 (10.4)
	Metabolic complications (total)	45 (21.2)
	Hyperbilirubinemia with phototherapy	26 (12.3)
	Hypoglycaemia	19 (9.0)
	Neonatal sepsis	1 (0.5)
	NICU admission	13 (6.1)
	Combine neonatal morbidity*	41 (19.3)
	Mortality	0 (0)

[&] Excluded preterm births. [+]Combined maternal morbidity: two or more maternal complications; *Combined neonatal morbidity: three or more neonatal complications. Legend: GA, gestational age; GDM, gestational diabetes mellitus; GWG, gestational weight gain; LGA, large for gestational age; NICU, Neonatal Intensive Care Unit; OGTT, oral glucose tolerance test; PE, physical exercise; PT, phototherapy; SGA, small for gestational age.

Congenital malformations were detected in 10.4% (n=22) newborns: nine (4.2%) newborns with minor cardiovascular malformations, five (2.4%) with urinary tract malformations, four (1.9%) head and neck malformations, two (0.9%) anterior displacement of anus, one (0.5%) with multiple sacral dimples, and one (0.5%) *metatarsus adductus*.

The causes for admission to the NICU (6.1%, n=13) were: prematurity (<34 weeks) and/or birth weight <2400g, without other problems, in 2.8% (n=6), acute respiratory distress syndrome in 1.9% (n=4) and hyperbilirubinemia for intensive phototherapy in 1.4% (n=3). In 19.3% (n=41) of newborns, there were three or more complications (combined neonatal morbidity). There were no neonatal deaths (Table 1).

When assessing maternal characteristics and metabolic control in relation to obstetric complications, combined risk factors for GDM was significantly associated with vacuum or forceps assisted delivery (p=0.035) (Table 2). When assessing neonatal morbidity, macrosomic and LGA newborns were significantly associated with excessive GWG (p=0.045 and p=0.006, respectively), and macrosomia was also higher in women with combined risk factors for GDM (p=0,041). Combined risk factors for GDM were significantly associated with hyperbilirubinemia treated with phototherapy (p=0.013) and excessive GWG was significantly associated with combined neonatal morbidity (p=0.031) (Table 3). None of the other maternal characteristics or metabolic control variables were significantly associated with the studied neonatal morbidity.

Table 2: Maternal characteristics and metabolic control in relation to obstetric complications.

	Obesity before pregnancy n (%)	p[&]	Combined risk factors for GDM n (%)	p[&]	GA at the time of diagnosis of GDM Median (IQR)	p*	Insulin therapy n (%)	p[&]	PE min/week Median (IQR)	p*	Excessive GWG n (%)	p[&]	Insufficient GWG n (%)	p[&]
Combine maternal morbidity														
Yes	11 (34.4%)	0.184	22 (68.8%)	0.320	24.0 (7.0;25.0)	0.864	4 (12.5%)	0.350	120 (45;210)	0.064	9 (36.0%)	0.838	8 (32.0%)	0.895
No	42 (23.3%)		107 (59.4%)		23.0 (7.0;25.0)		35 (19.4%)		90 (0.0;180)		58 (33.9%)		57 (33.3%)	
Vacuum and forceps assisted delivery														
Vacuum and forceps	6 (14.6%)	0.179	19 (46.3%)	**0.035**	24.0 (8.0;25.0)	0.730	3 (7.3%)	0.053	90.0 (0.0;150.0)	0.149	15 (39.5%)	0.162	13 (34.2%)	0.758
Eutocic	24 (25.0%)		63 (65.6%)		12.0 (8.0;25.0)		20 (20.8%)		90.0 (0.0;210.0)		24 (27.0%)		33 (37.1%)	
C-section														
C-section	23 (30.7%)	0.410	47 (62.7%)	0.689	24.0 (7.0:25.0)	0.626	16 (21.3%)	0.937	120 (40;210)	0.406	28 (40.6%)	0.071	19 (27.5%)	0.205
Eutocic	24 (25.0%)		63 (65.6%)		12.0 (8.0;25.0)		20 (20.8%)		90 (0.0;210.0)		24 (27.0%)		33 (37.1%)	
Pre-term birth														
Yes	4 (25,0%)	1.000	8 (50.0%)	0.355	24.0 (7.25;25.0)	0.971	2 (12.5%)	0.527	120 (0.0;210)	0.809	-	-	-	-
No	49 (25,0%)		121 (61.7%)		23.5 (7.0;25.0)		37 (18.9%)		90 (0.0;178)		-		-	

* Mann Whitney-U test for independent samples; [&]Chi-square test; [$]Fisher test. [+]Combined maternal morbidity: two or more maternal complications. Legend: GA, gestational age; GDM, gestational diabetes mellitus; GWG, gestational weight gain; PE, physical exercise.

Table 3. Maternal characteristics and metabolic control in relation to neonatal complications.

	Obesity before pregnancy n (%)	*p*[&]	Combined risk factors for GDM n (%)	*p*[&]	GA at the time of diagnosis of GDM Median (IQR)	*p**	Insulin therapy n (%)	*p*[&]	PE min/week Median (IQR)	*p**	Excessive GWG n (%)	*p*[&]	Insufficient GWG n (%)	*p*[&]
Macrosomia														
Yes	7 (38,9%)	0.155	15 (83.3%)	**0.041**	24,5 (7.00;26.0)	0.366	3 (16.7%)	0.843	65 (0.0;156)	0.125	10 (55.6%)	**0.045**	3 (16.7%)	0.119
No	46 (23,7%)		114 (58.8%)		23,0 (7,0;25,0)		36 (18.6%)		105 (0.0;210)		57 (32.0%)		62 (34.8%)	
LGA														
Yes	7 (36,8%)	0.212	13 (68,4%)	0.478	24,0 (7,0;25,0)	0.948	5 (26,3%)	0.350	90 (0;210)	0.567	10 (66.7%)	**0.006**	3 (20.0%)	0.260
No	46 (23,8%)		116 (60,1%)		24,0 (7,0;25,0)		34 (17,6%)		100 (0;210)		57 (31.5%)		62 (34.3%)	
SGA														
Yes	5 (22,7%)	0.795	11 (50,0%)	0.271	11.5 (7,5;25.0)	0.648	1 (4,5%)	0,077	90.0 (45;289)	0.457	5 (25.0%)	0.361	10 (50.0%)	0.091
No	48 (25,3%)		118 (62,1%)		24.0 (7.0;25.0)		38 (20,0%)		102 (0.0;210)		62 (35.2%)		55 (31.3%)	
APGAR score <7 at 5´														
Yes	0 (0,0%)	0.314[$]	0 (0.0%)	0.059[$]	5,0 (4.0;5.00)	0.160	0 (0.0%)	0.408[$]	105 (0; -.)	0.540	1 (100.0%)	0.164[$]	0 (0.0%)	1.000
No	53 (25,4%)		129 (61.7)		24,0 (7.0; 25.0)		39 (18.7%)		90 (0;210)		66 (33.8%)		65 (33.3%)	
Resuscitation (total)														
Yes	3 (27,3%)	0.858	4 (36.4%)	0.087	12,0 (6.0;24.0)	0.439	4 (36.4%)	0.674	90 (0;280)	0.740	4 (50.0%)	0.336	3 (37.5%)	0.790
No	50 (24,9%)		125 (62.2%)		24.00 (7.0;25.0)		61 (30.3%)		100 (0;210)		63 (33.5%)		62 (33.0%)	
Traumatic injury														
Yes	5 (31.3%)	0.548	10 (62.5%)	0.888	9.0 (6.0;25.0)	0.436	3 (18.8%)	0.970	97,5 (0;210)	0.866	5 (35.7%)	0.900	4 (28.6%)	0.705
No	48 (24.5%)		119 (60.75)		24.00 (7.0;25.0)		36 (18.4%)		95 (0;210)		62 (34.1%)		61 (33.5%)	

Table 3. Maternal characteristics and metabolic control in relation to neonatal complications (contin.)

	Obesity before pregnancy n (%)	$p^{\&}$	Combined risk factors for GDM n (%)	$p^{\&}$	GA at the time of diagnosis of GDM Median (IQR)	p^{*}	Insulin therapy n (%)	$p^{\&}$	PE min/week Median (IQR)	p^{*}	Excessive GWG n (%)	$p^{\&}$	Insufficient GWG n (%)	$p^{\&}$
Congenital malformations														
Yes	6 (27.3%)	0.795	12 (54.5%)	0.522	25.0 (7.0;26.0)	0.328	5 (22.7%)	0.580	120 (45;176)	0.781	5 (31.3%)	0.796	6 (37.5%)	0.701
No	47 (24.7%)		117 (61.6%)		23.0 (7.00;25.00)		34 (17.9%)		90 (0;210)		62 (34.4%)		59 (32.8%)	
Hyperbilirubinemia with phototherapy														
Yes	5 (19.2%)	0.468	10 (38.5%)	**0.013**	16 (8;25)	0.627	4 (15.4%)	0.672	175 (18,75;210)	0.292	4 (26.7%)	0.523	8 (53.3%)	0.084
No	48 (25.8%)		119(64.0%)		24 (7;25)		35 (18.8%)		90 (0;210)		63 (34.8%)		57 (31.5%)	
Hypoglycaemia														
Yes	6 (31.6%)	0.488	14 (73.7%)	0.230	8 (6;25)	0.122	3 (15.8%)	0.759	120(0;180)	0.709	5 (35.7%)	0.900	7 (50.0%)	0.165
No	47 (24.4%)		115 (59.6%)		24 (7,5;25)		36 (18.7%)		90 (0;210)		62 (34.1%)		58 (31.9%)	
NICU admission														
Yes	4 (30.8%)	0.620	6 (46.2%)	0.263	8 (6;24.5)	0.072	2 (15.4%)	0.772	120 (12.5;195)	0.873	1 (25.0%)	0.696	2 (50.0%)	0.470
No	49 (24.6%)		123 (61.8%)		24 (8;25)		37 (18.6%)		90 (0;210)		66 (34.4%)		63 (32.8%)	
Combine neonatal morbidity**														
Yes	13 (31.7%)	0.269	22 (53.7%)	0.294	9,00 (6,00;25,00)	0.107	7 (17.1%)	0.808	120 (12.5;210)	0.446	15 (51.7%)	**0.031**	7 (34.7%)	0.263
No	40 (23.4%)		107 (62.6%)		24,00 (8,00;25,00)		32 (18.7%)		90 (0;210)		52 (31.1%)		58 (34.7%)	

* Mann Whitney-U test for independent samples; $^{\&}$Chi-square test; $^{\$}$Fisher test. **Combined neonatal morbidity: three or more neonatal complications. Legend: GA, gestational age; GDM, gestational diabetes mellitus; GWG, gestational weight gain; LGA, large for gestational age; NICU, Neonatal Intensive Care Unit; PE, physical exercise; SGA, small for gestational age.

Discussion

The findings of this study reinforce the impact of GDM on neonatal outcomes, some already known in literature. As one of the most common medical complications during pregnancy (30), obstetric and neonatal related morbidity is also well-known, namely c-section, preterm birth, macrosomia, neonatal hypoglycaemia, and others (10–12,31). Other additional factors may have independent or additive impact on neonatal morbidity.

Most studies report an increased risk of preterm birth in diabetic pregnant women (32,33). The link between spontaneous preterm birth and GDM is still controversial. In our study, the occurrence of preterm birth (7.5%) closely mirrored a recent study from 2023, which reported a rate of 7.4% (33). However, contrasting with the general data from our Centre in 2023, our study exhibited a lower frequency of preterm birth, registering at 7.5% compared to 8.4%. This difference might be explained by the tertiary nature of our hospital, serving as the primary referral centre for all maternal and foetal pathologies within the Central region of Portugal.

Combined risk factors for GDM were significantly associated with vacuum or forceps assisted delivery (p=0.035), but we found no differences comparing to c-section delivery.

Foetal macrosomia typically impacts 12% of infants born to mothers without GDM, while prevalence rates range from 15% to 45% among neonates born to mothers with GDM (34). In our study, the occurrence of foetal macrosomia was lower, standing at 8.5%. This aligns with findings from a prior study conducted at this Centre, which also reported a lower prevalence of foetal macrosomia at 4.8%. (11). Categorizing newborns according to its intrauterine growth is fundamental, since macrosomic and/or LGA newborns have been associated with peripartum and neonatal morbidity, such as c-section and traumatic lesions. In neonates born to diabetic mothers, macrosomia is characterized by excess body fat, increased muscle mass and organomegaly, without increase in brain size (31). Many factors can influence foetal growth, some are non-modifiable, such as maternal age, parity, gender, and genetic predisposition, and some are modifiable, such as maternal weight/BMI, and can benefit from early identification and intervention. Maternal glycaemia and foetal insulin levels seems to play a major role in the growth of foetal body fat (35). Pre-pregnancy BMI consistently emerges as an independent factor for foetal macrosomia, and it appears to be independent of maternal metabolic control (36–38). In our study, over half of the women had excess weight or obesity, accounting for 59.4%. When compared to the general population of Portuguese women, the obesity rate before pregnancy was lower in our study (25.0% vs 32.1%) (39). Despite this difference, obesity did not show a positive correlation with any of the neonatal morbidity studied. Concerning GWG, 34.2% of women exceeded the recommended, with a higher rate of 48.1% observed among that previous classified as obese. Many studies have highlighted that excessive GWG poses an increased risk of pregnancy-related complications, such as c-section, foetal macrosomia, LGA and low Apgar scores (36,40–42). In our study, excessive

GWG emerged as significant risk factor for macrosomia (p=0.045) and LGA (p=0.006), but no significant differences were found for other neonatal complications. Combined risk factors for GDM, observed in 62.3% of the women in our study, was significantly associated (p=0.041) with foetal macrosomia. Several included risk factors are related to lifestyle-associated conditions, such as overweight, obesity, family history of diabetes on a first degree relative, and some are potentially modifiable.

The purpose of administering insulin therapy in GDM is to effectively regulate blood sugar levels, consequently decreasing the likelihood of neonatal complications such as macrosomia and neonatal hypoglycaemia (35,43). It has been predicted in a previous study that approximately 15-30% of women diagnosed with GDM would necessitate insulin therapy to attain optimal metabolic control (44), a proportion consistent with our findings (18.4% with insulin therapy). Insulin treatment was not associated with neonatal morbidity. Contrary to concerns, several studies have refuted the association between insulin therapy during pregnancy and the risk of congenital malformations (45,46).

Apgar score is a very subjective clinical measure, and mild variations can occur, particularly in small sample sizes. Compared to the data from our Centre in 2023, there was a higher occurrence of an Apgar score <7 at the fifth minute (1.4% vs. 0.2%). Neonatal resuscitation, which involves interventions such as positive pressure ventilation or more advanced resuscitative measures immediately after birth, was required in 5.2%, a rate consistent with those reported for the general neonatal population (47,48).

Traumatic injuries rate was 7.5%, including also *minor* trauma, such as soft tissue trauma a caput succedaneum. We had one case of brachial plexus injury and three cases of claviculae fracture (1.9%), comparing to 0.7% and 0.3% in other studies (10,11).

Global prevalence of congenital malformations differs along countries, but it is assumed globally between 1 and 2.5% (12,49,50). Women with GDM have a 1.18 higher risk of CM (51,52). The increased risk is associated with hyperglycaemia, maternal age, pre- pregnancy BMI, parity, and maternal smoking (51,52). Our study revealed a higher incidence (10.4%), consistent with a previous study in our maternity hospital (10.5%) (11). It is important to notice, once again, that we included also *minor* congenital malformations.

For decades, the connection between macrosomia, hyperinsulinism, and hypoglycaemia has been well-established. Hyperinsulinism in these neonates is transitory but prevents the normal activation of secondary metabolic pathways for the producing glucose and ketone bodies (31). Hypoglycaemia was lower (9.0%) than in other studies (10.4%-27.0%) (12,45,53). The incidence of hypoglycaemia in newborns born from diabetic mothers is difficult to assess due to the different guidelines and protocols used for neonatal hypoglycaemia. Other factors may have biased this difference, namely the absence of records of mild asymptomatic hypoglycaemias and the different protocols used in both maternity hospitals. Furthermore, our

maternity Centre promote skin-to-skin contact, first breastfeed in the first hour of life and rooming-in, which can reduce the risk of hypoglycaemia. Hyperbilirubinemia is another metabolic complication that is more frequent in newborns born from diabetic mothers (31,54). Our rates of hyperbilirubinemia treated with phototherapy was higher (28.9%) in relation to a similar study (8.7%) (54) and combined risk factors for GDM positively associated with his neonatal complication (p=0.013).

We highlight some limitations of this study, including the small sample size from a single neonatal centre. Furthermore, one of the main variables to assess metabolic control in pregnant women with GDM is glycated haemoglobin, which was not possible to obtain in most cases. Also, some variables as physical exercise, number of sessions per week and time per session was self-reported which can lead to biased answers.

Future studies including larger multicentre case-control studies could clarify our conclusions about the impact of GDM on neonatal morbidity.

Despite specialized monitoring of pregnant women with GDM, previous lifestyles and the increasing obesity rates in general population seems to play a significant role in this population and consequently on the newborns. Therefore, to improve maternal and neonatal outcomes in the context of GDM it may be necessary to start by primary prevention.

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1. Annexes

Anex I: Questionnaire for the mother

Clinical predictors of neonatal morbidity in a prospective cohort of mothers with gestational diabetes
Identification code_____ Date of fil the form_____ Paediatrician/Neonatologist _____

Maternal variables

1. Age (years) _____
2. Ethnicity? ____ Caucasian ____ Black _____ Other
3. Height in meters (eg: 1,57m)? _____
4. Weight before pregnancy (eg: 60 Kg)? _____
5. Weight after pregnancy (eg. 70Kg) _____
6. BMI before pregnancy (Kg/m2) _____
7. Did you practice exercise during the pregnancy? ___ Yes ___ No

    7.1 If yes, which trimesters? ___ 1º trimester ___ 2º trimester ___ 3º trimester

    7.2 If yes, how many days a week (ex: 2 days)?_____

    7.3 If yes, how much time per session (ex:30 min)? _____

8. Did you smoke during pregnancy? ___ Yes ___ No

    a. How many cigarettes a day? _____

9. Other personal important medical history? ____Yes ___ No

   a. Specify_____

10. Family history of diabetes (first degree relative)? ____ Yes ___ No

11. Obstetric history

    8.1 Recurrent pregnancy loss ____ Yes ___ No

    8.2 Parity_____ _____

    8.3 Prior newborn with macrosomia (>= 4000g) ___ Yes ____ No

    8.4 Gestational diabetes in a previous pregnancy ____ Yes ___ No

    8.5 Congenital abnormalities in a previous newborn ____ Yes ___ No

    8.6 Prior in-utero fetal death ____ Yes ___ No

12. Comorbidities during the current pregnancy?

    a. Arterial hypertension? ____ Yes ____ No

    b. Pre-eclampsia? ____ Yes ____ No

    c. Urinary tract infections ____ Yes ____ No

    d. Cholestasis ____ Yes ____ No

    e. Others? (specify if applicable) _____

13. Gestational age ate the time of diagnosis of gestational diabetes (ex. 28)? _____

14. Treatment of gestational diabetes?

    ___ Lifestyle (food and physical exercise) ___ Oral antidiabetic ___ Insulin

15. Gestational age ate the time of beginning of insulin? _____