

Perinatal and neonatal outcomes of pregestational diabetes mellitus: a retrospective study

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Abstract

Background

The aim of the study was to evaluate maternal-foetal and neonatal clinical outcomes in a group of patients with pregestational diabetes mellitus (PGDM) such as diabetes mellitus type 1 (DM1), diabetes mellitus type 2 (DM2), and maturity onset diabetes of the young (MODY).

Methods

Overall, 174 pregnant women, nulliparous and multiparous, with single pregnancy were enrolled. The selected patients were divided into two groups: PGDM (42 with DM1, 14 with DM2, and 2 with MODY); 116 patients with a negative pathological history of diabetes mellitus were the control.

Results

We reported an incidence of preterm delivery of 55.2% in the PGDM group, of 59.5% in the DM1 group, and 42.9% in the DM2 group VS. 6% in the controls. Foetal growth disorders, such as intrauterine growth retardation, small for gestational age, and foetal macrosomia were found in 19% and 3.6% in the case and in the control group, respectively. A relationship between DM2 and gestational hypertension was found.

Conclusions

patients with PGDM are at increased risk of perinatal and neonatal complications in comparison with pregnant women without PGDM.

Background

The prevalence of diabetes mellitus in pregnancy is increasing worldwide in parallel with that of obesity. Gestational Diabetes Mellitus (GDM) is diagnosed in the majority of the cases, followed by pre-gestational diabetes (PGDM), such as Diabetes Mellitus type 1 (DM1) and type 2 (DM2) [1].

The Italian region Sardinia has an incidence rate of DM1 equal to 33.4 per 100,000, which is the second highest globally [2]. Pre-gestational diabetes is associated with adverse neonatal outcomes [3].

The incidence of adverse maternal outcomes is high in case of PGDM [4–8]: abortions and low birth weight (< 2,500 grams) were more common, as well as congenital anomalies. Notably, the types and patterns of congenital malformations associated with maternal PGDM are non-random [9], with an increased risk of heart, central nervous system, and skeleton malformations.

The aim of the present study was to evaluate maternal-fetal and neonatal clinical outcomes of a cohort of patients with PGDM (DM1, DM2, and maturity onset diabetes of the young -MODY-) in comparison with those of pregnant individuals without diabetes.

Methods

A retrospective longitudinal study was carried out: patients aged 18 and 44 years were enrolled between January 2016 and August 2020. They were followed-up in a tertiary care Italian hospital.

A formal ethical approval was not needed according to the Italian law on observational studies.

Selected patients were divided into two groups: PGDM and control (negative pathological history of DM and with a negative oral glucose test tolerance -OGTT- performed at 24–28 weeks of gestation) [10–11].

The two groups were homogeneous by age (calculated at the time of delivery), with a ratio of 1: 2.

The criteria for the diagnosis of diabetes included a fasting plasma glucose (FPG) levels ≥ 126 mg/dl (7.0 mmol/l) and 2-h plasma glucose (PG) level ≥ 200 mg/dl (11.1 mmol/l) during an OGTT.

Characteristics of pregnancy and delivery were collected at the hospital admission and at delivery; Neonatal data were retrieved from the admission registries and from the medical records of newborns admitted to the neonatal intensive care unit (NICU). The following data were collected: age, parity, height, pregravidic weight, weight at delivery, last menstruation, comorbidity (cardiovascular diseases, thyroid diseases, multiple sclerosis, and other autoimmune diseases), prenatal screening surveys (e.g., combined test, noninvasive prenatal test, villocentesis, amniocentesis, and fetal echocardiography).

The variables collected for each group of women were summarized in the following categories: pregnancy outcomes, diseases of pregnancy and fetal pathologies, and neonatal outcomes. The following pregnancy outcomes were collected: gestational age at childbirth (GA); hospital stay; mode of delivery (spontaneous vaginal delivery or caesarean section). Diseases of pregnancy and foetal pathologies: Threatened abortion; Threatened preterm birth; Gestational hypertension; Preeclampsia and HELLP syndrome; Placental abruption; Pathology of amniotic fluid (oligohydramnios and polyhydramnios); Premature rupture of membranes (PROM) and preterm rupture of membranes (P-PROM); Macrosomia; Intrauterine growth retardation (IUGR) foetus; Morphological abnormalities diagnosed on ultrasound. Neonatal outcomes: Weight at birth compared to those expected for the gestational age (in percentiles), and then classification within one of the classes of Appropriate for Gestational Age (AGA), Small for Gestational Age (SGA), or Large for Gestational Age (LGA). For this study we used the definition of the Royal College of Obstetricians and Gynaecologists (RCOG) [12] which informs UK clinical practice, based on sonographic estimated fetal weight (EFW) measurement < 10 th percentile to describe a fetus that has not reached its target weight. Patients were divided in three groups for comparison; fetuses with EFW below the 10th percentile for gestational age (SGA), fetuses with EFW > 10 th percentile for gestation (AGA) and fetuses > 90 th percentile for gestation (LGA) according to the Alexander growth standard [13]; Apgar at the first minute; Number of hospitalization days and at which intensity of care (nursery, neonatology or NICU); Recognition of respiratory diseases at birth such as Respiratory Distress Syndrome (RDS), transient tachycardia of the newborn (TTN) or apnea crisis, and if there has been any intubation;

Blood glucose at the third hour; Hypoglycemia status and glucose supplementation; Neonatal jaundice, treated or not with phototherapy; Morphological abnormalities found at birth.

An ad hoc electronic database was created to collect all study variables. Qualitative data are summarized with absolute and relative (percentage) frequencies. Medians and interquartile ranges were used for quantitative variables with a non-parametric distribution. Chi-squared or Fisher exact test was used to compare qualitative variables for individuals with and without diabetes, whereas Mann-Whitney test to compare non-normal quantitative variables. Logistic regression analysis was performed to assess the relationship between pregnancy and fetal characteristics and diabetes. A two-tailed p-value < 0.05 was considered statistically significant. Statistical software STATA version 16 (StataCorp, Texas, USA) was adopted for all statistical analyses.

Results

A total of 58 PGDM patients were recruited, with 42 diagnosed with DM1, 14 with DM2, and 2 with MODY. 116 patients had a negative pathological history of diabetes mellitus (control group)

A higher median (IQR) pre-gestational body weight [61 (55.5-72.5) VS. 57 (50.5-63); p-value: 0.003] and BMI [23.7 (20.8-28) VS. 22 (19.8-24); p-value: 0.005] were found in the PGDM group (Table 1). Furthermore, the prevalence of obesity was significantly higher among the cases (16.7% VS. 2.6%; p-value 0.001).

Similarly, a higher median (IQR) body weight [74 (65-85) VS. 70 (63-75); p-value: 0.01] and BMI [27.9 (25.7-32.2) VS. 26.6 (24.8-28.8); p-value: 0.02] were recorded at the time of delivery.

A history of multiple sclerosis (5.2%) and Hashimoto's thyroiditis (17.2%) was retrieved in patients belonging to the PGDM group.

77.6% of patients in the PGDM group had a good glycemic compensation at the time of delivery.

Pregnancy disorders

No statistically significant difference were found for the following outcomes: threat of miscarriage, abnormal placental insertion and detachment, amniotic fluid disorders.

However, an association between the threat of abortion and DM2 was found.

The frequency of threatened preterm birth in the PGDM group (24.1%) was higher than that in the control group (9.5%; p-value: 0.009). This difference was more striking when the incidence of preterm delivery was evaluated in DM1 patients (26.2%, p-value: 0.02).

Pregnancy-induced hypertension and preeclampsia were reported only in the PGDM group.

Amniotic fluid disorders were only detected in patients with DM1 (12.1%).

Foetal disorders

Foetal growth disorders were more prevalent in the PGDM group (19%; p-value <0.0001). Foetal macrosomia (foetal growth $\geq 95^{\circ}$ percentile) was found in foetuses of diabetic mothers (p-value < 0.0001), the majority of whom in the DM1 group. An intrauterine growth restriction (foetal growth < 5^o percentile) was found more frequently in in the DM2 group (21.4%; p-value: 0.02).

Foetal echocardiography was used to investigate cardiac abnormalities more frequently in the PGDM group (67.4% VS. 17%; p-value <0.0001).

Pregnancy outcomes

CS delivery was more frequently performed in PGDM patients (87.9% VS. 52, 44.8%; p-value <0.0001). This finding was confirmed stratifying by DM (DM1: 90.5%; DM2: 85.7%). CS in emergency was more prevalent in the PGDM group (62.8% VS. 38.5%; p-value: 0.02).

Frequency of preterm deliveries was higher in the PGDM group (55.2% VS. 6.0%; p-value <0.0001).

Neonatal outcomes

The median length of hospital stay was 3 days for the births of the control group VS. 11 days for those of the DM1 group (p-value <0.0001) and 6 for those of the DM 2 group (p-value: 0.0001) (Table 2).

Admission to NICU occurred more frequently in the PGDM group (p-value <0.0001), with 73.8 % of the births of the DM1 group and 50% of those of the DM2 group (p-value <0.0001). Prevalence of respiratory disorders was higher the PGDM group (31%; p-value < 0.0001).

Similarly, RDS occurred more frequently in the PGDM group (29.3% VS. 5.2%; p-value < 0.0001), as well as neonatal hypoglycemia (65.5% VS. 5.2%; p-value <0.0001)

Incidence of neonatal jaundice was significantly higher (74.1%) in the PGDM cohort.

There was a statistically significant difference in birth weight.

Morphological anomalies were detected in 12.1% and 32.8% in the control and PGDM group (p-value: 0.001), respectively.

Discussion

Diabetic patients had a pregravidic body weight higher than that of the patients in the control group and the median pregravidic BMI differed by 1.7 points between cases and controls. In agreement with other studies [3–8], the increase in pre-pregnancy BMI corresponded to a lower weight gain during pregnancy, probably linked to a greater dietary and behavioral control [14]. However, BMI at delivery was significantly higher in diabetic patients; dietary behavioral control was apparently not sufficient to reverse the differences with the control group. No statistically significant differences were found for: threat of miscarriage, abnormal placental insertion and detachment, amniotic fluid disorders. Higher frequency of threatened preterm births was reported in the PGDM group, confirming the findings of Kong L. et al. [15]. This difference was more evident when preterm delivery was considered in patients with PGDM, explained by spontaneous onset, induction occurred to early schedule childbirth, prevention of maternal and/or fetal complications, reduction of perinatal mortality. The most important causes of preterm childbirth in DM1 could be the uterine overdistension due to fetal macrosomia and/or polyhydramnios. Dollberg et al [16] did not associate the high incidence of preterm childbirth with polyhydramnios, but recognized the role played by genitourinary infections and a history of previous preterm deliveries.

Regarding fetal outcomes, fetal macrosomia was found in the group of cases (12.1%).

Diabetic patients delivered more frequently by CS [17], with 90.5% in DM1 patients [17].

No statistically significant differences were found between cases and controls in the use of medical induction of labor with prostaglandins or oxytocin. This is consistent with the fact that diabetic patients are often subjected to elective CS.

LGA infants were more frequently described in DM1 patients [18, 19]. Another large population-based study in Catalonia [20] found a more prevalent LGA in infants of DM1 mothers. However, no relationship was found with the number of macrosomic fetuses, in line with the literature [21]: the error in the estimation of the fetal weight (10%-15%) increases as the gestational age advances, as the fetal weight increases [21].

Morphological abnormalities at birth with diabetes have been documented; in particular congenital heart disease is the outcome most associated with diabetes mellitus [23].

The epidemiology of respiratory disorders at birth seems to partially differ from that of the scientific literature [24–26]. TTN rate was 3.4% in our cohort VS. 10% of other studies. The relationship between RDS and PGDM was confirmed in a recent meta-analysis by Yan Li et al. [27]. The incidence of neonatal hypoglycemia was higher in neonates of DM1 mothers (66.7%) [27, 28, 29]. The percentage of neonatal jaundice in children of diabetic mothers ranged from 8.7–29% [26, 27, 29]. Our study showed a higher incidence (74.1%), even if those requiring phototherapy were less frequent (44.8%).

Strengths And Limitations

Although the retrospective nature of the study and the selection associated to the enrollment in a reference center may hinder the statistical inference of the findings, the present study shows the epidemiological perspective of an Italian region characterized by a highest incidence of diabetes mellitus in the general population. For this reason, it is of paramount importance to early detect patients at risk to immediately implement preventive measures.

Conclusion

Patients with PGDM are at increased risk of perinatal and neonatal complications in comparison with pregnant women without PGDM.

Declarations

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Ethics approval and consent to participate

An ethics approval was not necessary according to the Italian law on observational studies

Conflicts of Interest: The authors report no conflicts of interest.

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Tables

Table 1. Anthropometric characteristics of the patients.

	<i>Controls (n= 116)</i>	<i>PGDM (n=58)</i>	<i>p value</i>
Median (IQR) pregestational weight, kg	57 (50.5-63)	61 (55.5- 72.5)	0.003
Median (IQR) pregestational BMI, kg/m ²	22 (19.8- 24)	23.7 (20.8- 28)	0.005
Normal weight, n (%)	93 (80.2)	25 (52.1)	<0.0001
Under weight, n (%)	7 (6.0)	2 (4.2)	1.00
Overweight, n (%)	14 (12.1)	10 (20.8)	0.15
Obese, n (%)	3 (2.6)	8 (16.7)	0.001
Median (IQR) weight increase, kg	12 (10- 14)	11 (7.5- 14)	ns
Excessive weight increase (>12 kg), n (%)	44 (37.9)	19 (39.6)	ns
Median (IQR) weight at delivery, kg	70 (63-75)	74 (65-85)	0.01
Median (IQR) BMI at delivery, kg/m ²	26.6 (24.8-28.8)	27.9 (25.7-32.2)	0.02
	<i>Controls (n=116)</i>	<i>DM1 (n=42)</i>	<i>p value</i>
Median (IQR) pregestational weight, kg	57 (50.5-63)	60 (55-68)	0.04
Median (IQR) pregestational BMI, kg/m ²	22 (19.8- 24)	23.7 (20.8-25.9)	0.01
Normal weight, n (%)	93 (80.2)	20 (58.8)	0.02
Under weight, n (%)	7 (6.0)	0 (0.0)	ns
Overweight, n (%)	14 (12.1)	8 (23.5)	ns
Obese, n (%)	3 (2.6)	3 (8.8)	ns
Median (IQR) weight increase, kg	12 (10- 14)	11.5 (9-13)	ns
Excessive weight increase (>12 kg), n (%)	44 (37.9)	14 (41.2)	ns
Median (IQR) weight at delivery, kg	70 (63-75)	73 (65-80)	ns
Median (IQR) BMI at delivery, kg/m ²	26.6 (24.8-28.8)	27.8 (25.8-30.1)	ns
	<i>Controls (n=116)</i>	<i>DM2 (n=14)</i>	<i>p value</i>
Median (IQR) pregestational weight, kg	57 (50.5-63.0)	76 (55.5-83.5)	0.009
Median (IQR) pregestational BMI, kg/m ²	22.0 (19.8-24.0)	28.2 (21.2-32.9)	0.03
Normal weight, n (%)	93 (80.2)	3 (25.0)	<0.0001
Under weight, n (%)	7 (6.0)	2 (16.7)	ns
Overweight, n (%)	14 (12.1)	2 (16.7)	ns
Obese, n (%)	3 (2.6)	5 (41.7)	<0.0001
Median (IQR) weight increase, kg	12 (10-14)	11 (6-15.5)	ns
Excessive weight increase (>12 kg), n (%)	44 (37.9)	4 (33.3)	ns
Median (IQR) weight at delivery, kg	70 (63-75)	84.5 (65.0-92.5)	0.02
Median (IQR) BMI at delivery, kg/m ²	26.6 (24.8-28.8)	30.6 (25.1-37.1)	ns

Pregestational diabetes mellitus (PGDM); Diabetes Mellitus type 1 (DM1); Diabetes Mellitus Type 2 (DM2); Normal weight (BMI between 18 and 24.9 kg/m²); under weight (BMI< 18 kg/m²); overweight (BMI between 25 and 29.9 kg/m²); obese (BMI ≥ 30 kg/m²).

Table 2. Neonatal outcomes.

	<i>Controls (n=116)</i>	<i>PGDM (n=58)</i>	<i>p-value</i>
Fetus appropriate for gestational age (AGA) n (%)	96 (82.8)	27 (46.6)	<0.0001
Fetus small for gestational age (SGA) n (%)	12 (10.3)	4 (6.9)	ns
Fetus large for gestational age (LGA) n (%)	8 (6.9)	27 (46.5)	<0.0001
Respiratory disorders n (%)	11 (9.5)	18 (31.0)	<0.0001
RDS (Respiratory Distress Syndrome) n (%)	6 (5.2)	17 (29.3)	<0.0001
TTN (Neonatal transient tachypnea) n (%)	2 (1.7)	2 (3.5)	ns
Neonatal intubation n (%)	4 (3.5)	6 (10.3)	ns
Median (IQR) glycemia at 3° hours,mg/dl	66.5 (60-73.5)	58.5 (37-72)	0.003
Median (IQR) lower glycemia, mg/dl	61.9 (14.2)	40.3 (17.0)	<0.0001
Neonatal hypoglycemia n (%)	6 (5.2)	38 (65.5)	<0.0001
Neonatal jaundice n (%)	29 (25.0)	43 (74.1)	<0.0001
Phototherapy n (%)	14 (12.1)	26 (44.8)	<0.0001
Morphological anomalies n (%)	16 (13.8)	19 (32.8)	0.003
	<i>Controls (n=116)</i>	<i>DM1 (n=42)</i>	<i>p-value</i>
Fetus appropriate for gestational age (AGA) n (%)	96 (82.8)	17 (40.5)	<0.0001
Fetus small for gestational age (SGA) n (%)	12 (10.3)	1 (2.4)	ns
Fetus large for gestational age (LGA) n (%)	8 (6.9)	24 (57.1)	<0.0001
Respiratory disorders n (%)	11 (9.5)	15 (35.7)	<0.0001
RDS (Respiratory Distress Syndrome) n (%)	6 (5.2)	14 (33.3)	<0.0001
TTN (Neonatal transient tachypnea) n (%)	2 (1.7)	2 (4.8)	ns
Neonatal intubation n (%)	4 (3.5)	6 (14.3)	0.02
Median (IQR) glycemia at 3° hours,mg/dl	66.5 (60-63.5)	58 (37-76)	0.02
Median (IQR) lower glycemia, mg/dl	61.9 (14.2)	40.2 (18.1)	<0.0001
Neonatal hypoglycemia n (%)	6 (5.2)	28 (66.7)	<0.0001
Neonatal jaundice n (%)	29 (25.0)	43 (74.1)	<0.0001
Phototherapy n (%)	14 (12.1)	26 (44.8)	<0.0001
Morphological anomalies n (%)	16 (13.8)	16 (38.1)	0.001
	<i>Controls (n=116)</i>	<i>DM2 (n=14)</i>	<i>p-value</i>
Fetus appropriate for gestational age (AGA) n (%)	96 (82.8)	8 (57.1)	0.04
Fetus small for gestational age (SGA) n (%)	12 (10.3)	3 (21.4)	ns
Fetus large for gestational age (LGA) n (%)	8 (6.9)	3 (21.4)	ns
Respiratory disorders n (%)	11 (9.5)	3 (21.4)	ns
RDS (Respiratory Distress Syndrome) n (%)	6 (5.2)	3 (21.4)	ns
TTN (Neonatal transient tachypnea) n (%)	2 (1.7)	0 (0.0)	ns
Neonatal intubation n (%)	4 (3.5)	0 (0.0)	ns
Median (IQR) glycemia at 3° hours,mg/dl	66.5 (60-63.5)	53 (37-67)	0.003
Median (IQR) lower glycemia, mg/dl	61.9 (14.2)	41.1 (13.4)	<0.0001

Neonatal hypoglycemia n (%)	6 (5.2)	9 (64.3)	<0.0001
Neonatal jaundice n (%)	29 (25.0)	9 (64.3)	0.002
Phototherapy n (%)	14 (12.1)	4 (28.6)	ns
Morphological anomalies n (%)	16 (13.8)	2 (14.3)	ns