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Gestational Diabetes Mellitus pregnancy by pregnancy: early, late and nonrecurrent GDM

Chiara Giuliani [a,*], Laura Sciacca [b], Nicolina Di Biase [c], Andrea Tumminia [d], Agostino Milluzzo [b], Antongiulio Faggiano [e], Francesca Romana Amorosi [f], Alessio Convertino [a], Olimpia Bitterman [g], Camilla Festa [h], Angela Napoli [e,i,j]

[a] Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy
[b] Department of Clinical and Experimental Medicine, Endocrinology Section, University of Catania Medical School, Catania, Italy
[c] UOS Diabetologia, San Pietro Hospital, Rome, Italy
[d] Endocrinology Unit, Garibaldi-Nesima Hospital, Catania, Italy
[e] Department of Clinical and Molecular Medicine Sapienza University of Rome, Rome, Italy
[f] School of General Practice, ASL Roma2, Rome, Italy
[g] Diabetes Centre, ASL Viterbo, Viterbo, Italy
[h] Sapienza University of Rome, Rome, Italy
[i] Israelitico Hospital, Rome, Italy
[j] Santa Famiglia CdC, Rome, Italy

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ABSTRACT

Aims: To assess the GDM recurrence rate in a cohort of pregnant women with prior GDM, to compare two consecutive pregnancies complicated by GDM, to compare women with nonrecurrent and recurrent GDM and to stratify the latter in women with early and late recurrent GDM.

Methods: Retrospective study including 113 women with GDM in an index pregnancy (G1), at least a postindex pregnancy (G2) and normal glucose tolerance in between. The GDM recurrence rate was assessed, and maternal and neonatal outcomes and pancreatic beta cell function of the index pregnancy were compared with those of the postindex pregnancy (G1 vs. G2). Women with nonrecurrent GDM were compared with those with recurrent GDM.

Results: The GDM recurrence rate was 83.2% and the minimum prevalence of early recurrent GDM was 43,4%. The pregravid BMI of women with recurrent GDM increased between the two pregnancies (27.3 ± 5.98 vs. 28.1 ± 6.19 kg/m^2, $p < 0.05$). Women with recurrent GDM had a higher prepregnancy BMI than those with nonrecurrent GDM either at the index (27.3 ± 5.98 vs. 23.1 ± 4.78 kg/m^2, $p < 0.05$) or the postindex pregnancy (27 ± 6vs.24 ± 4,4 kg/m^2, $p < 0.05$).

Conclusions: GDM shows a high recurrence rate in our cohort of slightly overweight women, with an early GDM minimum prevalence of 43.4%.

1. Introduction

Gestational diabetes mellitus (GDM) is a common complication in pregnant women defined as "impaired glucose tolerance first detected during pregnancy"[1].

The GDM prevalence is rising worldwide due to an increasing incidence of both obesity and advanced maternal age [2,3].

In 2010, the International Association of the Diabetes and Pregnancy Study Groups recommended a "one-step" screening protocol for GDM using 75-g, 2-h oral glucose tolerance testing at 24–28 weeks of gestation and introduced new diagnostic criteria [4]. These criteria are now recommended by the World Health Organization (WHO) [1] and are widely used in Italy, as suggested by the Ministry of Health [5].

Early detection and initiation of treatment is important because unrecognized and untreated GDM is responsible for an important proportion of maternal and foetal adverse outcomes, including pregnancy-induced hypertension, preeclampsia, urinary tract infections, caesarean delivery, foetal macrosomia, birth trauma, neonatal hypoglycaemia and

* Corresponding author at: Department of Experimental Medicine, Sant'Andrea Hospital, Sapienza University of Rome, via di Grottarossa 1035, 00189 Rome, Italy.
E-mail address: chi.giuliani@uniroma1.it (C. Giuliani).

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future diabetes [6–8].

Gestational diabetes in an index pregnancy increases the risk of recurrent GDM in subsequent pregnancies [9]. The recurrence rate of GDM has been reported to range between 30% and 84% [10–12]. According to these data, Italian guidelines for screening and diagnosis of GDM recommend an earlier 75 g OGTT at the 16th gestational week for all pregnant women with prior GDM [5]. Predictive factors of GDM recurrence include advanced maternal age, multiparity, obesity, weight gain between pregnancies, requirement of insulin therapy and macrosomia during index pregnancy [11]. Although previous studies have reported important data regarding the GDM recurrence rate, there is little evidence about the clinical and metabolic features of GDM in women with prior GDM. Furthermore, despite the evidence of early GDM prevalence ranging between 29 and 42% in a high-risk population [13–16], there are no data about recurrent GDM onset in early or late pregnancy.

Therefore, the aim of the current study was to assess the GDM recurrence rate in a cohort of pregnant women with prior GDM and to compare maternal and neonatal outcomes and pancreatic beta cell function in two consecutive pregnancies complicated by GDM.

The secondary endpoints were to identify the clinical and metabolic features of women with nonrecurrent and recurrent GDM and to stratify the latter in women with early and late recurrent GDM, identifying the main features of these two groups.

2. Subjects, materials and Methods

This was a retrospective, multicentric, observational study that included women attending three Italian Diabetes Centers (Sant'Andrea Hospital of Rome "La Sapienza University", San Pietro Hospital of Rome and Garibaldi-Nesima Hospital of Catania "University of Catania") between 2010 and 2018.

We included 113 women with two consecutive pregnancies—index pregnancy complicated by GDM (G1) and postindex pregnancy (G2)—and normal glucose tolerance in between.

Most of the women attended such diabetes centres only for the postindex pregnancy, so missing data about the index pregnancy were collected, when available, during the first visit of the second pregnancy.

In these patients, the GDM recurrence rate was assessed, and then, maternal and neonatal outcomes and pancreatic beta cell function of the index pregnancy were compared with those of the subsequent pregnancy (G1 vs. G2).

Furthermore, maternal and neonatal outcomes and pancreatic beta cell function of women with nonrecurrent GDM were compared with those of women with recurrent GDM and then with those of women with early and late recurrent GDM.

Women were universally screened in early pregnancy (in the first trimester) to exclude overt diabetes.

A 100 g or 75 g 2-hour OGTT diagnosed GDM. The results were interpreted according to IADPSG criteria [4]. The few cases who were diagnosed by 100 g OGTT were not included in the statistical analysis.

The majority of women brought in vision results of the OGTT performed just before the first visit.

According to Italian recommendations [5], an OGTT should be performed early between 16 and 18 weeks of gestation in high-risk women and between 24 and 28 weeks of gestation in moderate-risk women and high-risk women with a negative early OGTT.

We defined early GDM when diagnosed within the 20th gestational week and late GDM when occurring from the 21st gestational week.

Insulin resistance/sensitivity and secretion indices were obtained by OGTT plasma glucose (PG) and insulin levels (IRI). Insulin resistance was defined by the HOMA-IR, and pancreatic function was defined by the HOMA-B and Disposition Index. HOMA-IR and HOMA-B values were estimated using the HOMA calculator; the disposition index was calculated with the following formula: [(IRI60′-IRI0′)/(PG60′-PG0′]/HOMA-IR.

During the first visit, prepregnancy BMI (kg/m^2) was calculated, and family, physiological, past medical, diabetes and obstetric history were investigated.

Patients were taught to self-monitor their plasma glucose level 4–6 times a day using the same type of glucometer. All data were recorded in a diary kept by the patients at each control visit.

Women were visited at regular intervals (1–2weeks). At each visit, home capillary blood glucose profiles, insulin requirements and adjustments, hypoglycaemic episodes, blood pressure and body weight were recorded. Capillary blood glucose profiles during the previous 1 or 2 weeks were recorded, and mean values ± standard deviation (SD) were calculated by the software.

The following glycaemic targets were considered: fasting glucose < 90 mg/dl (5 mmol/l) and 1 h after meal < 130 mg/dl (7.22 mmol/l).

Medical nutritional treatment (MNT) was the first-line therapy prescribed according to the patients' own preferences (ethnic, cultural, financial, etc.), physical activity level, gestational age and prepregnancy BMI group, with a distribution of carbohydrate intake of 40–50%, 30% lipids, 20% proteins and 28 g/day fibre [17].

When MNT was not sufficient to control postprandial hyperglycaemia, short-acting insulin analogues such as aspart or lispro were injected before meals; when fasting glycaemia was not controlled, basal insulin analogues such as Levemir or glargine was prescribed at bed time.

The adverse pregnancy outcomes studied included caesarean delivery. Maternal composite adverse outcomes included at least one of the following: gestational hypertension (new onset blood pressure > 140/90 mmHg after 20 weeks of gestation), preeclampsia (oedema, proteinuria and hypertension: new onset blood pressure > 140/90 mmHg after 20 weeks of gestation, with coexistence of > 300 mg/day proteinuria and oedema), and HELLP syndrome (haemolysis, elevated liver enzymes and low platelets).

The neonatal outcomes studied included birth weight, ponderal index, and APGAR score at 1 and 5 min. The neonatal composite adverse outcomes included at least one of the following: macrosomia (birthweight > 4000 g), large for gestational age (LGA: birthweight > 90th percentile adjusted for gestational age and gender), small for gestational age (SGA: birthweight < 10th percentile adjusted for gestational age and gender), hypoglycaemia (BGL < 2.6 mmol/L), phototherapy-treated jaundice, respiratory distress syndrome (RDS), and congenital malformations.

Obstetric composite adverse outcomes included one of the following: preterm birth (birth before 37 weeks of gestation), shoulder dystocia and polyhydramnios.

This study was conducted in accordance with the Helsinki Declaration on Medical Research on Humans [18] and with the Good Clinical Practice (GCP) guidelines [19]. Ethics committees to which the participating centres belonged approved the study.

Women gave their written consent for the anonymous use of their clinical data at the first visit, as previously approved by our ethics committee.

2.1. Sample size calculation and statistics

Sample size estimation was based on the most prevalent GDM recurrence. From the international literature, a GDM recurrence rate of approximately 45% [10] was considered. To identify risk factors with a minimum prevalence of 30% in the study population, with a statistical power of 80% and an estimated α error of 0.05, enrolment of at least 82 women with prior GDM was needed.

Sample size analysis was carried out using clincalc.com.

Statistical analyses were performed using IBM SPSS Statistics software version 26.0 (IBM Corp., Armonk, NY).

All data are expressed as the means ± standard deviation (SD) for continuous variables with Gaussian distribution, as median and interquartile range (25th-75th centile) for continuous variables with non-

Gaussian distribution and as a frequency percentage for categorical variables.

Continuous variables were compared by Student's paired or unpaired *t* test and ANOVA as parametric tests and the Wilcoxon rank-sum test or the Mann–Whitney *U* test for paired or unpaired groups, respectively, and the Kruskal–Wallis test for three unmatched groups as nonparametric tests.

Categorical variables were compared by Fisher's exact test or the chi-square test for unpaired groups and the exact symmetry test for paired groups.

Statistical significance was set at $p < 0.05$.

ROC analysis was performed, and the Youden Index was employed to identify a BMI cut-off point associated with GDM recurrence.

3. Results

3.1. Maternal characteristics and GDM recurrence rate

We studied two consecutive pregnancies (G1 and G2) in 113 women who were affected by GDM during the index pregnancy and were normotolerant in between pregnancies.

Among these, 7 of 11 women who had undergone an early OGTT at the first pregnancy were already diagnosed with early GDM at the first pregnancy.

The main general characteristics of all women in the two consecutive pregnancies are shown in Supplementary Table 1.

Ninety-four of 113 women (83,2%) had recurrent GDM in the postindex pregnancy, 49/113 (43,4%) were diagnosed in early pregnancy and 45/113 (39,8%) in late pregnancy, while 19 of 113 (16,8%) were found to be normotolerant (Fig. 1).

It should be noted that only 17 women with late GDM had undergone both early and late OGTTs according to current guidelines [5]; therefore, 43,4% is considered the minimum prevalence of early recurrent GDM, and only these 17 women can be classified as having "really late" recurrent GDM (Fig. 1).

3.2. Longitudinal analysis of the main clinical and metabolic characteristics and outcomes in the index and the postindex pregnancy (G1 vs G2) in women with recurrent GDM (Table 1)

Comparing the two subsequent pregnancies only in women with recurrent GDM, we found that during the postindex pregnancy, maternal age and pregravid BMI were significantly higher; women came earlier to the first visit and showed lower blood glucose levels at 60 min of the OGTT performed between the 24th and 28th gestational weeks.

Finally, a higher rate of women needed insulin therapy in the second pregnancy, during which they recorded lower third trimester capillary glucose levels after breakfast than those recorded during the index pregnancy.

During the second pregnancy, we observed a nonsignificant reduction in neonatal and obstetric composite adverse outcomes and a significant APGAR score 1′ and 5′ improvement.

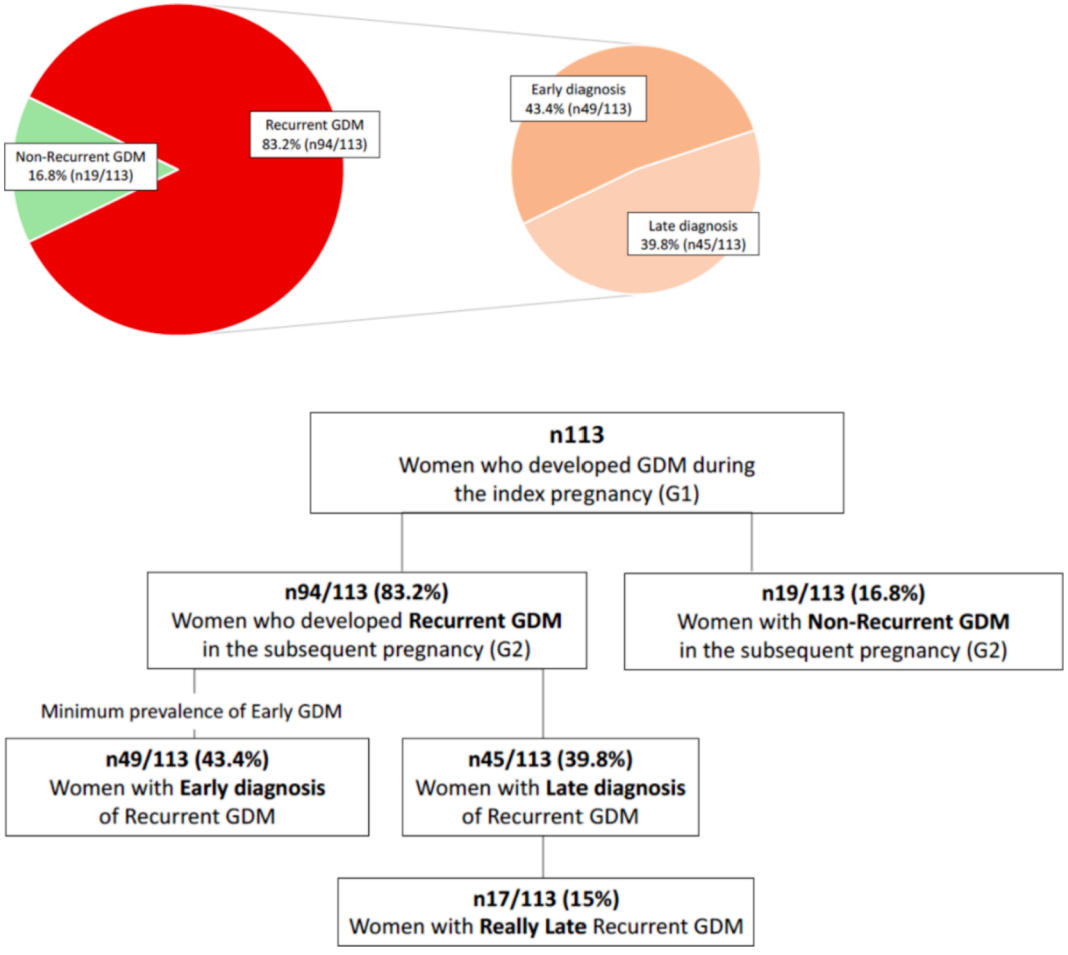

Fig. 1. GDM Recurrence rate and distribution of early, late and "really late" diagnosis of recurrent GDM. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Longitudinal analysis of the main clinical and metabolic characteristics and outcomes in the index and the postindex pregnancy (G1 vs G2) in women with recurrent GDM.

N = 94	G1	G2
Age (yrs)	32.3(4.82)*	36(4.9)*
BMI (kg/m^2, n65)	27.3(5.98)*	28.1(6.19)*
First visit gestational week (g.w.)	27.2(6.3)**	19.6(7.24)**
HbA1c at first visit (%(mmol), n35)	5.3(0.4)	5.3(0.4)
	(34.3(4.2))	(34.5(4.2))
LATE OGTT (n40)		
Gestational week (G.W.)	27.2(3.16)	25.8(2.91)
[1]PG0′	91.3(12.13)	90.5(9.99)
PG60′	193.5(26.75)*	179.9(18.43)*
PG120′	157.1(40.59)	129.1(26.75)
[2]IRI0′ (n11)	9.5(6.5–12.7)	10.6(7–14)
HOMA-IR (n11)	1.8(1.41–1.99)	1.9(1.86–2.21)
HOMA-B (n11)	129.3	127
	(81.6–160)	(114.55–210)
Weight gain (kg, n77)	10(7–13)	10.1(7–12.6)
CAPILLARY GLUCOSE LEVELS AT THIRD TRIMESTER (mg/dl, n38)		
Fasting	83.9(8.42)	84.9(9.86)
1hr-After breakfast	119.3(14)*	113.2(11.55)*
1hr After lunch	115.3(15.27)	117.6(13.41)
1hr After dinner	118.8(15.07)	119.7(13.08)
24 h	107(3.89)	104(5.88)
INSULIN THERAPY (n72)	35(48.6%)*	47(65.3%)*
OUTCOMES		
Neonatal composite adverse outcome (n45)	26(57.7%)	19(42.2%)
Maternal composite adverse outcome (n45)	3(6.7%)	3(6.7%)
Obstetric composite adverse outcome (n48)	5(10.4%)	3(6.3%)
APGAR 1′ (n25)	9(8–9)**	9(9–10)**
APGAR 5′ (n25)	9.5(9–10)*	10(10–10)*

Data are shown as n(%), mean(standard deviation), median(25th-75th centile). Significant differences are marked with * indicating $p < 0.05$, ** $p < 0.001$.
[1] PG: plasma glucose
[2] IRI: plasma insulin.

3.3. Comparison between women with recurrent and nonrecurrent GDM during the index pregnancy (Table 2)

Women with recurrent GDM had a higher prepregnancy BMI and a similar weight gain than those with nonrecurrent GDM either in the index or the postindex pregnancy (G2: BMI 27 ± 6 vs. 24 ± 4,4 kg/m^2, *p* 0,004; weight gain 10(6–12) vs. 10(9,5–13) kg, *p* 0,43). No difference was found in weight change between the two pregnancies (+0,2(-2–5,5) vs. +1(-2–3) kg, *p* 0,84) or in intergravid period length (2(0–4) vs. 3 (2–4) years, *p* 0,4) between the two groups.

The AUC for prepregnancy BMI was 0.68 (95% CI 0.52–0.85) in the index pregnancy and 0.71 (95% CI 0.57–0.84) in the postindex pregnancy, and BMI cut-off points identified by the Youden Index showed sensitivity and specificity that were too low to be considered discriminant.

No difference was found in age or HbA1c values at the first visit.

Similarly, we found no difference in parity, smoking habits, family history of diabetes, ethnicity or insulin therapy rate between the two groups.

In early pregnancy, we could not compare OGTT blood glucose values, insulin values and pancreatic function and insulin resistance indices because only a few women had undergone an early OGTT.

In late pregnancy, no difference was found in OGTT blood glucose values, insulin values, pancreatic function or insulin resistance indices.

Women with recurrent GDM had higher third trimester mean fasting and 24-hour capillary blood glucose levels.

Infants born to women with recurrent GDM showed a higher rate of jaundice, higher birth weight and ponderal index and a lower rate of SGA than those born from women with nonrecurrent GDM.

We found no difference in other maternal, neonatal and obstetric outcomes between the two groups.

Table 2
Comparison between women with recurrent and nonrecurrent GDM during the index pregnancy (G1).

	Non-Recurrent	Recurrent
	n = 19	**n = 94**
Age G1 (yrs)	30.6(4.79)	32.3(4.82)
	n = 14	n = 65
BMI G1 (kg/m^2)	23.1(4.78)*	27.3(5.98)*
Weight gain during pregnancy (kg)	10(7–11.8)	9.5(6.6–13)
Parity	n = 15	n = 68
Primiparous	12(80%)	43(63.24%)
Family history of T2 diabetes	n = 17	n = 82
Yes	10(58.82%)	63(76.83%)
Ethnicity	n = 19	n = 94
Caucasian	18(94.7%)	90(95.75%)
Asian	1(5.3%)	4(4.25%)
Smoking habit	n = 18	n = 83
Yes	3(16.7%)	17(20.5%)
HbA1c at first visit (%(mmol))	n = 7	n = 41
	5.1(0.3)	5.3(0.4)
	(32.1(3.6))	(34.3(4.6))
LATE OGTT	n = 12	n = 48
G.W.	29.1(3.87)	26.9(3.16)
PG0′	85.4(15.47)	92.1(12.31)
PG60′	198.5(27.11)	183.1(28.89)
PG120′	182.3(38.56)	146.7(35.64)
IRI0′	n = 5	n = 15
	10.6(10–13)	9.2(6.84–12.8)
	n = 5	n = 15
HOMA-IR	2.1(1.86–2.66)	1.81(1.40–2.64)
HOMA-B	183.3	149.6
	(161.4–238.5)	(91.6–174.2)
CAPILLARY GLUCOSE LEVELS AT THIRD TRIMESTER (mg/dl)	n = 12	n = 45
Fasting	75.7(8.74)*	83.7(8.4)*
24-hours	96.3(3.98)*	105(9.7)*
Insulin therapy	n = 17	n = 62
Yes	5(31.25%)	33(55%)
OUTCOMES		
Delivery-CS	n = 18	n = 86
	9(50%)	43(50%)
Gestational age at delivery (wk)	n = 18	n = 86
	38.3(1.87)	38.9(1.64)
Birth weight (kg)	n = 18	n = 85
	2951.1(608.49)*	3318(504.01)*
Ponderal Index	n = 10	n = 49
	2.29(2.19–2.51)*	2.87(2.66–3.06)*
Neonatal composite adverse outcomes	n = 18	n = 84
	8(44.4%)	42(50.0%)
SGA	n = 17	n = 84
	6(35.3%)*	11(13.1%)*
Phototherapy treated Jaundice	n = 17	n = 79
	0(0%)*	18(22.8%)*
Maternal composite adverse outcomes	n = 18	n = 84
	3(16.7%)	8(9.5%)
Obstetric composite adverse outcomes	n = 16	n = 74
	3(18.8%)	7(9.5%)

3.4. Comparison between women with nonrecurrent, early and late recurrent GDM during the index pregnancy (Table 3)

During the index pregnancy, women who developed GDM early in the postindex pregnancy showed a higher BMI than women with nonrecurrent GDM and a higher rate of family history of diabetes than women with late GDM.

Women with late recurrent GDM showed a greater need for insulin therapy than women with nonrecurrent GDM.

Women with nonrecurrent GDM showed higher 2-h glucose values at the OGTT than women with early recurrent GDM, also taking into account that the latter group of women had undergone the OGTT approximately 3 weeks before than women with nonrecurrent GDM.

Conversely, fasting capillary blood glucose levels in the third trimester were lower in women with nonrecurrent GDM than in women

Table 3
Comparison between women with nonrecurrent, early and late recurrent GDM during the index pregnancy (G1).

	No GDM	Early	Late
	n = 19	**n = 49**	**n = 17**
Age G1 (yrs)	30.63(4.79)	32.96(4.59)	32.24(4.89)
	n = 14	n = 41	n = 10
First visit g.w.	29.21(4.81)	26.90(6.45)	27.10(8.16)
	n = 18	n = 41	n = 11
BMI G1 (kg/m^2)	23.1(4.78)*	27.56(6.28)*	27.1(7.00)
Weight change during pregnancy (kg)	10.00 (7.00–11.80)	9.50 (5.00–14.80)	9.50 (8.20–11.00)
Parity	n = 15	n = 34	n = 11
Primiparous	12(80.00%)	21(61.76%)	6(54.55%)
Family history of T2 diabetes	n = 17	n = 42	n = 16
Yes	10(58.82%)	37(88.10%)*	9(56.25%)*
Ethnicity	n = 18	n = 42	n = 17
Caucasian	17(94.44%)	42(100.00%)	17(100.00%)
Asian	1(5.56 %)	0(0.00%)	0(0.00%)
Smoking habit	n = 18	n = 42	n = 17
Yes	3(16.67%)	8(19.05%)	2(11.76%)
HbA1c at the first visit (%(mmol/mol))	n = 7 5.1(0.3) (32.08(3.6))	n = 26 5.3(0.5) (34.9(5.2))	n = 9 5.1(0.3) (32.7(3.1))
LATE OGTT	n = 12	n = 28	n = 10
G.W.	29.08(3.87)	26.43(3.36)	27.20(3.26)
PG0′	n = 12 85.42(15.47)	n = 28 93.04(12.32)	n = 10 94.00(13.65)
PG60′	n = 6 198.5(27.11)	n = 17 178.00(30.97)	n = 10 189.50 (19.91)
PG120′	n = 6 182.33(38.56)*	n = 17 137.76(31.06)*	n = 9 160.78 (43.80)
CAPILLARY GLUCOSE LEVELS AT THIRD TRIMESTER (mg/dl)	n = 12	n = 29	n = 10
Fasting	75.70(8.74)* [a]	83.71(8.19)* [a]	85.32(10.20)* [a]
Insulin therapy	n = 16	n = 35	n = 11
Yes	5(31.25%)*	22(62.86%)	10(90.91%)*
OUTCOMES			
Delivery-Cesarean S	n = 18 9(50.00%)	n = 45 20(44.44%)	n = 13 8(61.54%)
Gestational age at delivery (wk)	n = 17 38.28(1.87)	n = 45 38.87(1.38)	n = 12 38.67(2.27)
Birth weight (kg)	n = 18 2951.11 (608.49)*	n = 44 3290.68 (472.71)*	n = 13 3366.92 (509.92)
Neonatal composite adverse outcome	n = 18 8(44.4%)	n = 44 23(52.3%)	n = 12 4(33.3%)
Maternal composite adverse outcome	n = 18 3(16.7%)	n = 44 4(9.1%)	n = 12 2(16.7%)
Obstetric composite adverse outcome	n = 16 3(18.8%)	n = 38 2(5.3%)	n = 12 3(25%)

[a] No GDM vs Early e Late.

with both early and late recurrent GDM.

In the first pregnancy, infants born to women who would develop early GDM in the second pregnancy already showed a higher birth weight than those born to women with nonrecurrent GDM.

3.5. Comparison between women with nonrecurrent, early and late recurrent GDM in the postindex pregnancy (G2) (Table 4)

We did not observe any difference in age, parity, smoking habits, or weight change between the two pregnancies and during the second pregnancy at equal interpregnancy intervals among the three groups.

Women with early recurrent GDM showed a higher rate of family history of diabetes and an earlier GDM diagnosis than women with late GDM and a higher pregravid BMI than women with nonrecurrent GDM. Moreover, their first diabetic visit was earlier than women with late and nonrecurrent GDM.

Table 4
Comparison between women with nonrecurrent, early and late recurrent GDM during the postindex pregnancy (G2).

	No GDM	Early	Late
	n = 19	**n = 49**	**n = 17**
Age G2 (yrs)	33.37(4.98)	36.06(4.45)	35.82(4.63)
	n = 18	n = 48	n = 17
First visit g.w.	22.22(6.85)*[a]	16.56(5.90)*[a]	21.71(9.05)*[a]
BMI G2 (kg/m^2)	23.40(4.52)*	27.77(6.20)*	26.68(6.07)
Weight change during pregnancy (kg)	n = 10 10.05 (9.50–13.00)	n = 30 10.05 (4.20–12.60)	n = 11 10.10 (6.00–12.00)
	n = 15	n = 40	n = 11
Weight change between G1 and G2 (kg)	1(-2–3)	1.25(-0.75–5.5)	−0.5(-4–3)
Weight increase	8(53.33%)	22(55.00%)	4(36.36%)
Weight loss	5(33.33%)	12(30.00%)	6(54.55%)
Intergravidic interval (yrs)	3(2–4)	3(2–4)	3(3–4)
Family history of T2 diabetes	n = 17	n = 42	n = 16
Yes	10(58.82%)	37(88.10%)*	9(56.25%)*
Smoking habit	n = 18	n = 42	n = 17
Yes	3(16.67%)	8(19.05%)	2(11.76%)
HbA1c at the first visit (%(mmol/mol))	n = 8 4.9(0.3) (30.2(3.0))	n = 32 5.3(0.4) (34.9(4.0))	n = 16 5.3(0.6) (33.9(6.5))
GDM diagnosis week (g.w.)	n = 0	n = 46 14.72(4.37)*	n = 15 26.33(1.84)*
EARLY OGTT	n = 6	n = 49	n = 17
G.W.	16.17(2.40)	14.69(4.41)	16.19(2.79)
PG0′	80.67(6.95)**	96.11(10.33)**	81.50(5.21)
	n = 5	n = 32	n = 15
PG60′	134.20(35.02)	153.55(39.20)	143.53(21.19)
PG120′	117.00(26.43)	124.56(31.70)	111.87(21.83)
	n = 2	n = 23	n = 7
IRI0′	7.5(6–9)	9(6–17)	10(6.15–12)
IRI60′	165(38–292)	69(29–120.4)	43(29–119)
IRI120′	191.5(136–247)	65(44–104)	77(25.5–96)
HOMA-IR	1.40(1.13–1.66)	1.98(1.19–3.85)	1.78(0.97–2.27)
HOMA-B	130.09 (98.18–162.00)	101.25 (73.16–163.64)	196.36 (124.62–276.75)
DISPOSITION INDEX	1.47(0.72–2.21)	0.44(0.36–0.51)	0.59(0.15–0.74)
LATE OGTT	n = 19		n = 17
G.W.	25.94(2.21)		26.13(2.39)
PG0′	78.22(6.87)**		90.27(8.15)**
PG60′	149.94(27.78)*		178.20(14.44)*
PG120′	118.31(19.90)		137.73(28.46)
	n = 11		n = 8
IRI0′	4.8(4–14)		8.95(5.5–13.5)
IRI60′	58.3 (36.15–158.2)		77(50.2–117)
IRI120′	47.55 (28.55–131.3)		83(38.5–184)
HOMA-IR	0.84(0.72–2.40)		1.66(0.95–2.72)
HOMA-B	153.82 (82.29–360.00)		178.50 (88.23–262.50)
DISPOSITION INDEX	0.63(0.47–0.79)		0.41(0.28–0.65)
CAPILLARY GLUCOSE LEVELS AT THIRD TRIMESTER(mg/dl)	n = 11	n = 36	n = 16
Fasting	77.49(9.06)*	87.12(10.19)*	84.83(11.87)
After breakfast	108.87(16.11)	112.34(13.57)	116.68(12.96)
After lunch	106.20(21.53)*	118.73(13.03)*	111.89(13.53)
After dinner	105.50(26.42)	117.67(13.46)	113.25(16.93)
24-hours	96.85(17.43)	108.04(10.53)	109.24(15.04)
Insulin therapy	n = 16	n = 35	n = 11
Yes	0(0%)	31(86.11%)	12(75.00%)
OUTCOMES			
Delivery-CS	n = 13 7(53.8%)	n = 24 9(37.5%)	n = 8 5(62.5%)
Gestational age at delivery (wk)	n = 12 38.25(1.28)	n = 24 38.9(1.35)	n = 7 37.29(2.81)
Birth weight (kg)			

(*continued on next page*)

Table 4 (*continued*)

	No GDM	Early	Late
	n = 13	n = 25	n = 8
	3309.4 (401.051)	3355.0(570.5)	3249.4(476.9)
Ponderal Index	n = 6	n = 16	n = 6
	2.57(2.5–2.76)	2.73(2.55–2.9)	2.68(2.36–2.82)
Neonatal composite adverse outcome	n = 13	n = 26	n = 8
	2(15.4%)	11(42.3%)	3(37.5%)
Maternal composite adverse outcome	n = 13	n = 25	n = 9
	1(7.7%)	1(4.0%)	0(0%)
Obstetric adverse outcome	n = 14	n = 21	n = 11
	2(14.3%)	1(4.8%)	2(18.2%)

[a] Early vs No GDM e Late.

Women with early recurrent GDM showed higher fasting plasma glucose levels at the early OGTT than women with late and nonrecurrent GDM as well as higher capillary glucose levels in a fasting state and after lunch at the third trimester than women with nonrecurrent GDM.

Women with late recurrent GDM showed higher fasting and 1-h plasma glucose levels at the OGTT performed in late pregnancy than women with nonrecurrent GDM.

With respect to pancreatic function indices, we did not find any difference in early pregnancy between the three groups or in late pregnancy between women with nonrecurrent and late recurrent GDM.

The great majority of women with both early and late recurrent GDM needed insulin treatment.

We found no significant difference in maternal and neonatal outcomes in the three groups for the second pregnancy.

3.6. Comparison of the OGTT diagnostic points between women with recurrent and nonrecurrent GDM in the first pregnancy (Table 2 Supplementary files)

In the first pregnancy, we found no significant differences in the OGTT diagnostic points between recurrent and nonrecurrent patients. In the first pregnancy, "After load" diagnostic points were more frequently altered in women with nonrecurrent GDM in the second pregnancy (n11/13 = 84.62%).

3.7. Comparison of the OGTT diagnostic points between women with nonrecurrent, early and late recurrent GDM in the first and second pregnancy (Table 3 Supplementary files)

In the first pregnancy, "All" and "Fasting" OGTT points were more frequently diagnostic in women with early recurrent GDM; in contrast, "After load" OGTT points were often diagnostic in women with nonrecurrent and late recurrent GDM.

In the second pregnancy, the diagnostic point "Fasting" was more frequent in women with early recurrent GDM, and the "After load" points were more frequently diagnostic in women with late GDM.

4. Discussion

Our cohort of women was on average over 30 years old and was slightly overweight since the index pregnancy; moreover, women showed a high rate of family history of type 2 diabetes.

These data confirm the role of maternal age, BMI and family history of diabetes as risk factors for gestational diabetes [20].

During the second pregnancy, the first diabetic visit time was significantly earlier, since women with GDM had been advised, at the end of the first gestation, to undergo early testing for GDM by the 16th gestational week according to current Italian guidelines. These guidelines recommend early screening in high-risk women who show at least one of the following characteristics: prior GDM, BMI over 30 kg/m2, and fasting plasma glucose levels ≥ 100 mg/dl (5.6 mmol/l) [5].

In these women, generic recommendations were also delivered on lifestyle to prevent type 2 diabetes after delivery [21].

In our study, a GDM recurrence rate of 83.2% was consistent with the highest recurrence rate reported in two *meta*-analyses (recurrence rate from 30 to 84%). [10,11].

In particular, recent Chinese data [12] show a lower recurrence rate (48,9%), but in a population of different ethnicity.

Interestingly, among women with recurrent GDM, at least 49 had an early diagnosis of GDM during the second pregnancy; thus, in our population, the minimum prevalence of early recurrent GDM was 43.4%.

However, this figure could be underestimated because only 17 women of the remaining 45 with recurrent GDM had respected recommendations and had performed both early and late OGTTs during the postindex pregnancy.

Although there is discrepancy in the early GDM prevalence due to the differing diagnostic criteria used and heterogeneous study population, our rate of 43.4% is consistent with those of other studies reporting an early GDM prevalence of 29–42% in both unselected and high-risk cohorts [13–16].

Notably, early GDM rates have been as high as 62–66% in high-risk populations [22,23].

In 2017, The DALI Core Investigator Group found an early (<20 weeks' gestation) GDM (IADPSG CRITERIA) prevalence of 24% in a cohort of heavily overweight women (inclusion criteria BMI ≥ 29 kg/m2) [24].

The higher prevalence of early GDM found in our cohort could be explained by the fact that all of our women had a history of previous GDM.

The longitudinal comparison of the two subsequent pregnancies in women with recurrent GDM showed a significantly advanced maternal age and an increase in prepregnancy BMI in the second pregnancy.

These results are in line with other studies demonstrating the role of advanced maternal age [11] and increased interpregnancy BMI as risk factors for GDM in subsequent pregnancies [25].

Notwithstanding, a greater proportion of women required insulin therapy in the second pregnancy with a clinical outcome improvement significant for neonatal APGAR scores.

In our cohort of women, in contrast with other studies [26], GDM recurrence was not affected by parity, likely because the majority of our women were primiparous.

In the index pregnancy, women with recurrent GDM showed a higher pregravid BMI than women with nonrecurrent GDM, in agreement with previous studies that observed a positive association between maternal BMI and GDM recurrence [27,12].

Higher fasting and 24-hour capillary blood glucose levels in women with recurrent GDM during the third trimester of the index pregnancy, on equal treatment with nonrecurrent women, could correlate with more severe glucose impairment as well as with a higher rate of neonatal jaundice and a higher ponderal index. The higher rate of neonatal jaundice observed in the index pregnancy of women with recurrent GDM could be explained by a worse glucose impairment, usually responsible for hypoxic status [28].

In the postindex pregnancy, women with recurrent GDM still showed a higher pregestational BMI in comparison with those who did not develop GDM, without a difference in interpregnancy interval and weight change.

Despite the evidence of a higher BMI in women with recurrent GDM, in our study, we could not identify a prepregnancy BMI cut-off point discriminant for GDM recurrence, probably due to the heterogeneity of the population studied, including normoweight, overweight and obese women.

Consistent with other studies [29], we observed that women with early recurrent GDM were more likely to have a family history of diabetes than women with late recurrent GDM, both during the index and the postindex pregnancy. This finding draws attention to the role of a

family history of DM as a risk factor for early GDM and, consequently, as a possible indication for early screening.

Furthermore, our cohort of women with early recurrent GDM had a higher pregravid BMI than women with nonrecurrent GDM, both in the index and the postindex pregnancy, with no difference in interpregnancy weight change.

It should be noted that women with nonrecurrent GDM were normal weight during the index as well as during the postindex pregnancy, whereas women with recurrent GDM were overweight both during the first and second pregnancy.

Although we did not find a significant difference in weight change between the two pregnancies among the three groups, women with early recurrent GDM had gained on average a kilo, whereas late recurrent women had lost on average half a kilo between the two pregnancies. Therefore, we can speculate that in overweight women with prior GDM, interpregnancy weight loss could delay the onset of recurrent GDM [30].

Interestingly, in the postindex pregnancy, women with early recurrent GDM showed higher fasting plasma glucose levels at the early OGTT (with a nonsignificant higher HOMA-IR value) than women with nonrecurrent and late recurrent GDM.

Therefore, considering early dysglycaemia with higher fasting plasma glucose level and the higher BMI with no weight loss between pregnancies in women with early recurrent GDM, this cohort may be characterized by a more insulin-resistant phenotype.

This speculation is supported by a recent study evaluating clinical and pathophysiological characteristics in women with early and late GDM onset. The authors found that women with early GDM showed a higher pregestational BMI related to fasting glucose and were affected by a higher degree of insulin resistance, which retained significance even after accounting for maternal BMI. ß-cell dysfunction was also detectable both in women with early and late GDM, indicating defective compensatory mechanisms emerging in early pregnancy [31].

These findings are in keeping with our results showing that each OGTT time point was more frequently impaired in women with early GDM, while “postload” OGTT time points were more frequently diagnostic in women with late GDM and in women with nonrecurrent GDM when considering the first pregnancy.

In the postindex pregnancy, we did not find early recurrent GDM to be associated with worse pregnancy outcomes than late GDM, in contrast with other studies on early-onset GDM but not on early recurrent GDM [29,31,32]. Notably, the similar second pregnancy outcome among the three groups is likely due to the fact that, during the index pregnancy, women had already experienced GDM and had been advised to follow a healthy lifestyle and to perform an early screening in case of a subsequent pregnancy.

The main study limitation is that this is a multicentric retrospective analysis of a cohort of women followed by “Diabetes and Pregnancy” centres sharing the same diagnostic and therapeutic protocols. Moreover, because approximately one-third of these women were not followed in our centres during the first pregnancy, there were some missing data.

Second, although all the women had received a dietary and healthy lifestyle prescription, we could not fully document physical activity and lifestyle during the pregnancies and in the interpregnancy period.

However, to date, this is the first longitudinal study comparing women’s main clinical and metabolic characteristics and maternal and neonatal outcomes in two consecutive pregnancies complicated by GDM. On the other hand, this is also the first transversal study stratifying women with recurrent GDM into early and late recurrence groups and identifying the main clinical and metabolic features of these two groups.

5. Conclusions

GDM showed a high recurrence rate in our cohort of slightly overweight women, with an early GDM minimum prevalence of 43.4%.

Women with recurrent GDM show a higher prepregnancy BMI than those with nonrecurrent GDM both in the index and the postindex pregnancy, with no difference in interpregnancy weight change and gestational weight gain, as well as time interval between the two pregnancies.

Women with early recurrent GDM showed early dysglycaemia in the second pregnancy and a higher BMI than women with nonrecurrent GDM. These findings suggest that this group of women is characterized by a more insulin-resistant phenotype since the index pregnancy.

However, in our study, early GDM was not associated with worse pregnancy outcomes. This is likely due to the experience of prior GDM and to the education received by women during the index pregnancy about healthy lifestyle and early GDM screening, together with prompt and intensive treatment.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contributors

All authors contributed equally. All authors have approved the final manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.109911.

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