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Gestational diabetes mellitus complicating twin pregnancies

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Abstract

Objective: To compare outcomes of twin pregnancies with and without gestational diabetes mellitus (GDM).
Study design: We compared 105 twin pregnancies with GDM (7.8% of all twin pregnancies) to 315 controls without GDM, matched for gestational age, chorionicity and year of birth.
Results: Pre-gravid obesity appears to predispose women to GDM during twin pregnancy [odds ratio (OR) 3.5; 95% confidence interval (CI) 1.7, 7.0]. Overweight and obese women that subsequently developed GDM during their twin gestation were less likely to conceive spontaneously (OR 0.4; 95% CI 0.3, 0.7). Twins from the GDM group had more respiratory distress syndrome (RDS, OR 2.2; 95% CI 1.3, 3.7) and had a three-fold, but not significantly increased perinatal mortality rate. Birth weight characteristics were similar in both groups.
Conclusion: Twin pregnancies complicated by GDM might be associated with pre-pregnancy maternal obesity and are at increased risk of RDS and non-significant increased risk of perinatal death.

Keywords: Gestational diabetes; obesity; respiratory distress syndrome; twin pregnancy.

Introduction

Gestational diabetes mellitus (GDM) is a relatively common disease. Much information on the clinical significance of GDM in singleton pregnancies but relatively little information exists on the association between gestational diabetes and multiple pregnancy [6]. It has been argued that multiple pregnancies are prone to GDM because of larger placental mass (hyperplacentosis), older age of expecting mothers of multiples, increased weight gain and body mass in twin gestations, and because of exaggerated response to fasting and food [6]. Indeed, Simchen et al. [12] showed that pregnancy in advanced maternal age after ovum donation had, among other complications, 31% of GDM. It also appears that a plurality-dependent frequency of GDM exists whereby GDM was significantly more frequent in triplets compared to (reduced) twins [14]. At the same time, however, conflicting data exist concerning GDM and multiple pregnancies, whereby a similar prevalence of GDM was found in twin and singleton pregnancies, no difference was found in glucose challenge and tolerance tests between twin and singleton pregnancies, and similar insulin requirements were found in twin and singleton pregnancies complicated by GDM [6].

Irrespective of the conflicting views, the increasing numbers of twin pregnancies and births observed in most developed countries increases the number of expecting mothers of twins diagnosed with GDM. Moreover, the few quasi-epidemiological studies describing the prevalence of GDM in twin gestations are quite old and presumably include few multiple pregnancies resulting from iatrogenic conceptions (i.e., after infertility treatment). Also, some bias exists which overlooks changes in management over time. For example, it would be interesting to know how recommendations for excess weight gain during early stages of a multiple pregnancy would influence carbohydrate metabolism [9].

It is also striking that data concerning the effect of GDM on perinatal outcome in multiple pregnancies are very scant. Tchobroutsky et al. [15] reported on a high-frequency of fetal malformations in type I diabetic women with twin pregnancies, however, the small number of cases precluded a final conclusion and are irrelevant for gestational diabetes. Keller et al. [7] compared 13 twin pregnancies complicated with GDM to matched-by-gestational-age twin pregnancies. Within this very small sample size there was a trend of greater likelihoods of respiratory distress syndrome (RDS), hyperbilirubinemia and prolonged neonatal intensive care nursery admission in the diabetic group. More recently, Rauh-Hain et al. [11] compared twin to singleton pregnancies and found that patients with twins had a two-fold increased risk of developing GDM. In terms of neonatal outcome, twins of gestational diabetics had a higher rate of admission to the neonatal intensive care unit, longer hospitalization, and higher risk of RDS.

With these difficulties in mind, we conducted a case-control study to examine the perinatal outcome related to the co-occurrence of GDM and twin gestations.

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Material and methods

During the period January 1, 1999 through September 30, 2010, there were 1346 twin pregnancies followed and delivered after 24 weeks' gestation at the Maternity Dr. Alfredo da Costa, Lisbon, Portugal (a tertiary perinatal center that cares for the Lisbon area, and serves as a referral center for the south of Portugal). This figure represents approximately 2.5% of all deliveries. During this period, information about pregnancy and delivery was registered prospectively on a preset form and subsequently entered into a computerized system. We excluded twin gestations that were delivered only and were not followed at our service.

For this study, we identified twin pregnancies with the diagnosis of GDM, established according to the Carpenter and Coustan criteria [1]. For controls, we matched the remaining twin gestations by gestational age (completed week), chorionicity, and year of delivery. A 3:1 setting was chosen to achieve an 80% power at $P<0.05$ to detect a 10% inter-group difference in being small- or large- for gestational age (SGA and LGA, $>10^{th}$ percentile or $>90^{th}$ percentile, respectively). Gestational age was derived from the last menstrual period that was confirmed by first trimester ultrasound scans and from the day of oocyte retrieval in pregnancies after assisted reproduction. Chorionicity was established by standard ultrasonographic criteria performed by level III ultrasonographers, confirmed by careful examination of the delivered placenta by experienced obstetricians, and double-checked by pathologic examination of the placentas. Cases with pre-gestational diabetes were excluded from the analysis. Treatment was tailored according to blood glucose levels and given as in singleton pregnancies [1]. No elective preterm deliveries are done; however, indicated preterm deliveries were carried out, following corticosteroid treatment, on the basis of maternal and/or fetal conditions. In otherwise normally progressing gestations, we offered, after detailed counseling, elective deliveries at 36–37 completed weeks of gestation.

The following variables were considered in our analysis: maternal age and parity, pre-gravid body mass index (BMI, weight in kg/squared height in cm; BMI 25–30 was considered overweight, BMI > 30 considered obese), mode of conception (spontaneous vs. iatrogenic), maternal complications, such as premature contractions (< 34 weeks of gestation), hypertensive disorders (pre-eclampsia, pregnancy-induced hypertension, and chronic hypertension), preterm rupture of membranes (PTROM) at < 34 weeks of gestation, mode of delivery, gestational age at birth, birth weight, frequency of being SGA and LGA (according to twin birth weight standards [2]), birth weight discordance of 25% (intertwin birth weight difference expressed as percentage of the heavier twin), frequency of Apgar scores < 7 at 5 min, major malformations (excluding stillbirths), early (< 7 days of life) neonatal death, and major neonatal morbidity (RDS diagnosed by clinical signs supported by classical X-ray findings, sepsis, intraventricular hemorrhage, retinopathy of prematurity, hyperbilirubinemia requiring either follow-up or phototherapy). We compared continuous data by using two-tailed Student's *t*-test, and categorical data by two-tailed Fisher's exact test. We used SPSS version 13 (Chicago, IL, USA) and True EPISTAT Software (Math Archives, Round Rock, TX, USA) for statistical analyses. P-values < 0.05 were considered significant. The study has been approved by local institutional review board.

Results

The study group included 105 twin pregnancies with GDM (7.8% of the total number twin births). Table 1 shows the demographic data of twin gestations with GDM compared with 315 twin pregnancies without GDM matched for gestational age (mean 34.9 ± 2.1 weeks; 12.4% at 28–32 weeks, 26.7% at 33–35 weeks, and 60.9% at ≥ 36 weeks) and chorionicity (62.8% dichorionic twins).

Both groups were similar in terms of mean maternal age, frequency of maternal age > 35 years, and parity but mothers of twins with GDM had a significantly greater pre-gravid BMI. As shown in Table 2, the greater pre-gravid BMI was a result of significantly more obese mothers of twins who eventually developed GDM. Although statistically insignificant, one cannot overlook the increased prevalence of hypertensive disorders and cholestasis of pregnancy among study group patients.

We further compared the proportion of pre-gravid normal BMI mothers who conceived spontaneously in both groups. This analysis showed that significantly fewer pre-gravid normal BMI mothers (n = 34, 35.2%) had a spontaneous twin conception and eventually developed GDM compared with matched controls that did not (n = 172, 54.6%; OR 0.4, 95% CI 0.3, 0.7).

Table 3 shows that twins born to mothers with GDM had a significantly increased prevalence of respiratory distress at birth and jaundice. These infants, however, had similar frequencies of major malformations, and similar birth weight characteristics. There was a single fetal death in the GDM group and three fetal deaths in the controls (one case of double death, with both twins having severe malformations), for an uncorrected (for malformation) stillbirth rate of 4.7:1000 twins in both groups. There were four neonatal

Table 1 Demographic data of twin gestations with GDM compared with matched for gestational age and chorionicity non-GDM controls.

	GDM n = 105	Non-GDM n = 315	Statistics
Mean maternal age (years)	31.4 ± 4.8	30.5 ± 5.2	NS
≥ 35 years	30 (28.5)	74 (23.5)	NS
Nulliparas	68 (64.8)	176 (55.9)	NS
Spontaneous pregnancies	70 (66.7)	241 (76.8)	NS
Mean BMI (kg/cm^2)	25.4 ± 5.4	23.4 ± 4.1	P < 0.001
BMI < 25 kg/cm^2 and spontaneous pregnancy	37 (35.2)	172 (54.6)	0.4 (0.3, 0.7)
Cesarean section	76 (72.4)	216 (68.6)	NS

Data presented as mean ± SD or as n (%), statistics are shown as P-values or odds ratio (95% CI).
NS = not significant, GDM = gestational diabetes mellitus.

Table 2 Maternal complications during twin gestations with GDM compared with matched non-GDM controls.

	GDM n = 105	Non-GDM n = 315	Statistics
BMI 25–30 kg/cm^2	31 (29.5)	67 (21.3)	NS
BMI > 30 kg/cm^2	21 (20.0)	21 (6.7)	3.5 (1.7, 7.0)
Hypertensive disorders	29 (27.6)	58 (18.4)	NS
Preterm contractions	49 (46.7)	162 (51.4)	NS
Cholestasis of pregnancy	9 (8.6)	11 (3.5)	NS
PTROM	8 (7.6)	25 (7.9)	NS

Data presented as mean ± SD or as n (%); statistics are shown as P-values or odds ratio (95% CI).
NS = not significant, GDM = gestational diabetes mellitus, PTROM = preterm rupture of membranes.

mortalities: three in the GDM group (one infant with encephaloocele, one due to sepsis in an SGA infant born to a mother who had also pre-eclampsia, and one after PTROM of four weeks duration, born at 30 weeks) and one monochorionic twin in the non-GDM group who had congenital arthrogriposis. The uncorrected (for malformation) neonatal mortality rate was 14/1000 live births in the GDM group and 1.5/1000 in the controls, for an uncorrected perinatal mortality rate of 19/1000 and 6/1000, respectively.

Discussion

This is, to the best of our knowledge, the largest and most carefully matched case-control study on twin pregnancies complicated with GDM. A higher frequency of mothers who were obese before a twin-pregnancy required assisted reproduction and eventually developed GDM. This observation, albeit not surprising, may suggest a common denominator whereby obese women might require more frequent infertility treatment which, in turn, might result in more twin gestations, some of which complicated by GDM. The European Society of Human Reproduction and Embryology (ESHRE) Capri Workshop Group [3] maintained that obesity can affect reproduction through fat cell metabolism, steroids and secretion of proteins such as leptin and adiponectin and through changes induced at the level of important homeostatic factors such as pancreatic secretion of insulin, androgen synthesis by the ovary and sex hormone-binding globulin production by the liver. Hence the link between this obesity-related metabolic condition, infertility status [3, 10] and twin pregnancy is not surprising. It is also noteworthy that the possible association between the current recommendations on weight gain during early twin pregnancies and the potential of developing GDM has not been explored [5]. One may speculate that some borderline overweight women may turn obese due to increased calories intake during early twin pregnancy [4, 13].

Although expecting mothers of twins with GDM seem to fare as well (or as bad) as mothers without GDM, there was a definite trend towards more hypertensive disorders and cholestasis of pregnancy in the former group. It was somewhat unexpected that hypertensive disorders are not more frequent in twin as they are in singleton pregnancies affected by GDM. At this stage, and given the trend towards an increased risk of hypertensive disorders, we cannot exclude a type-II error. We also found an increased risk of respiratory distress in twins born to gestational diabetics and this complication was significant although the groups were *a priori*

Table 3 Fetal/neonatal complications in twin gestations with GDM compared with matched non-GDM controls.

	GDM n = 105	Non-GDM n = 315	Statistics
Mean birth weight (g)	2222 ± 452	2218 ± 432	NS
SGA	18 (8.6)	70 (11.1)	NS
LGA	8 (3.8)	11 (1.7)	NS
Discordant birth weight 25%*	8 (7.6)	33 (10.5)	NS
5-min Apgar score < 7	3 (1.4)	10 (1.6)	NS
Major malformations	7 (3.3)	15 (2.4)	NS
Respiratory distress	30 (14.3)	43 (7.0)	2.2 (1.3, 3.7)
Intraventricular hemorrhage	1	0	
Sepsis	4 (1.9)	7 (1.1)	NS
Retinopathy of prematurity	2	1	
Jaundice	22 (10.5)	12 (1.9)	6.0 (2.7, 13.2)
Fetal death	1 (0.5)	3 (0.5)	NS
Neonatal death	3 (1.4)	1 (0.2)	NS
Perinatal mortality	4 (1.9)	4 (0.6)	NS

*Data calculated per pregnancy.
Data presented as mean ± SD or as n (%), statistics are shown as P-values or odds ratio (95% CI).
NS = not significant, SGA = small for gestational age, LGA = large for gestational age, GDM = gestational diabetes mellitus.

matched by gestational age. Thus, our policy to recommend delivery at 36–37 weeks did not influence the rate of these complications and it seems that neonatal respiratory disorders appear to complicate twin pregnancies with GDM irrespective of gestational age.

The overall perinatal mortality rate in our cohorts suggests a three-fold increased uncorrected perinatal mortality (borderline significance) in the GDM group. However, it appears that most mortalities were related to fatal malformations and hence the corrected for malformation mortality rate seems to be low and similar in both groups.

Our data do not support the observation of Klein et al. [8] that twin pregnancies with insulin requiring gestational diabetes seem to have less birth discordance. However, this may be due to the different categorization of discrepant intertwin birth weight. Because we excluded patients with type I diabetes, we cannot comment on the observation of Tchobroutsky et al. [15] on a high-frequency of fetal malformation, but we could support the results of a small series evaluated by Keller et al. [7] who reported on a trend of greater likelihoods of RDS and hyperbilirubinemia among twins born to mothers with GDM.

Because one of the most significant causes of morbidity of multiple gestations is low birth weight, it was argued [6] that, at least theoretically, a ''hidden'' advantage might exist for twins born to women with GDM because the fetal growth-promoting effect of GDM may counterbalance the inherent growth restricting effect of the limited and overwhelmed uterine milieu in twin gestation. Surprisingly (or not), the data indicate no effect on birth weight parameters, although the frequency of LGA was almost twice higher. The best explanation for our observation is that the growth promoting effect of GDM is balanced by the growth inhibiting effect of the uterine constraints in twin gestations.

This study cannot address the role of adequate glycemic control in changing the outcomes of the mothers and their twins. Nor can this study address potential confounders of birth weight characteristics such as smoking, level of exercise, genetic predisposition for GDM, etc. Because our hospital is a referral center, we could not exclude an undetected bias if the women with GDM were more likely referred to our center for management whereas those without GDM more likely come from uncomplicated population of the Lisbon area.

Regardless, this study provides convincing data supporting the view that GDM is a further complication of an already complicated gestation.

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