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Research letters

Metabolic syndrome and impaired glucose metabolism during early postpartum after twin pregnancies complicated by gestational diabetes mellitus: Is the risk comparable to singleton pregnancies?

Abbreviations:
GMD, gestational diabetes mellitus
T1DM, type 1 diabetes mellitus
T2DM, type 2 diabetes mellitus
CVD, cardiovascular disease
ART, assisted reproductive technology
OGTT, oral glucose tolerance test
AUC-GTT, area under the glucose tolerance test curve
3T-HbA_{1c}, average third-trimester HbA_{1c}
IFG, impaired fasting glucose
IGT, impaired glucose tolerance
HDL-Chigh-density lipoprotein cholesterol ;,
MetSmetabolic syndrome

Introduction

Having a previous history of gestational diabetes mellitus (GDM) or even just mild glucose disturbances during pregnancy are associated with an increased risk of type 2 diabetes mellitus (T2DM) [1] and the metabolic syndrome (MetS) in young women [2–5]. This population is also at high risk for cardiovascular disease (CVD) during long-term follow-up [6,7].

MetS is defined as the co-occurrence of a number of metabolic disorders, including abdominal obesity, glucose disturbances, dyslipidaemia and/or arterial hypertension [8], and is also associated with an incremental risk for the development of T2DM and CVD [9].

During early postpartum, the reported incidence of MetS after a GDM-complicated pregnancy ranges from 10.9% to 15.4% [4]. However, it has an increasing trend over time, rising to 27–45% compared with 0–8% in women not having a GDM pregnancy, at > 10 years after delivery [2,3,7]. Prepregnancy obesity is the main risk factor for a diagnosis of GDM [4,5], and maternal obesity in GDM pregnancies is associated with the detection of MetS during early postpartum [2,4].

Multiple pregnancies are also increasing due to older maternal age at first pregnancy and the availability of assisted reproductive technnology (ART) which, nowadays, accounts for around 2% of all births in Spain [10].

A previous study comparing the incidence of GDM metabolic disturbances in singleton and twin pregnancies over a long-term follow-up found that multiple pregnancy was not an independent risk factor for developing impaired glucose metabolism. Even though women with multiple pregnancies had a lower rate of progression to T2DM at 1.8% vs 17.9% for singleton pregnancies, this difference did not reach statistical significance due to the small sample size [11].

GDM in twin pregnancies has been proposed to be milder and to affect neonatal overgrowth on a lesser degree than in singleton pregnancies [12]. Our present study aimed to determine whether there is any difference in early postpartum risk for MetS or impaired glucose metabolism in women with a previous twin gestation compared with singleton GDM gestation.

Materials and methods

In this observational retrospective study of 186 GDM pregnancies, women were followed throughout their pregnancy, then underwent postpartum examination between January 1991 and December 2015. However, only 62 out of 131 women (48.9%) with previous twin gestations attended the postpartum visit. In addition, 124 women with previous singleton gestations were randomly chosen as controls on a 2:1 ratio, and matched by maternal age and year of delivery, from out of 2883 GDM singleton pregnancies; those with either pregestational or newly diagnosed type 1 diabetes mellitus (T1DM) or T2DM were excluded. An initial postpartum visit was systematically scheduled for all included women with GDM. The study was approved by the relevant hospital ethics committee.

GDM diagnosis was based on the two-step strategy, using National Diabetes Data Group criteria [13]. Women were given information on diet and physical activity during pregnancy, and again during the postpartum visit, by expert nurses (4 h of education divided into two sessions). A standard GDM diet of 25–40 kcal/kg/day, depending on prepregnancy body mass index (BMI) scores and physical activity habits, was followed from the time of GDM diagnosis to delivery. In the absence of contraindications, women were also recommended to walk at a moderate intensity for 1 h daily and to stay physically active after delivery.

GDM severity was measured as fasting glycaemia and area under the oral glucose tolerance test curve (AUC-OGTT). The trapezoidal method — [(fasting glycaemia + 2 • 1-h glycaemia + 2 • 2-h glycaemia + 3-h glycaemia)/2] — was used to calculate the AUC-OGTT. Glycated haemoglobin (HbA_{1c}) was obtained monthly from time of GDM diagnosis until delivery. Third-quartile values were considered threshold values for AUC-OGTT and HbA_{1c}. The average third-trimester HbA_{1c} (3T-HbA_{1c}) was considered the glycaemic control parameter.

Maternal weight gain was calculated as the difference between measured weight at the last pregnancy visit and self-reported prepregnancy weight. Gestational mass-gain ratio referred to the proportion between total weight gain and midpoint range of optimal weight gain for each prepregnancy BMI category

[4,14]. Pregnancy-induced hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg at 20 weeks of gestation, and preeclampsia as the co-occurrence of proteinuria ≥ 30 mg/mmol of creatinine.

Pregestational BMI was recorded, and any weight gain beyond the recommended upper limit of the range (> 16 and > 25 kg for normal-weight, > 11.5 and > 23 kg for overweight, and > 9 and > 19 kg for obese women with singleton and twin gestations, respectively) was considered excessive gestational weight gain [14,15]. Also recorded was the use of ART and maternal smoking habits.

Women who attended the first postpartum visit (when lactation had concluded or, otherwise, at 3 months after delivery) underwent metabolic evaluation, and MetS was defined according to "Harmonizing the Definition of the Metabolic Syndrome" criteria [8]. MetS was diagnosed if at least three of the following five criteria were met: fasting serum glucose ≥ 5.6 mmol/L; waist circumference ≥ 88 cm; plasma triglycerides ≥ 1.7 mmol/L; plasma high-density lipoprotein cholesterol (HDL-C) < 1.3 mmol/L; and systolic and/or diastolic blood pressure ≥ 130 mmHg and/or 85 mmHg, respectively. Glucose tolerance was evaluated postpartum by a 75-g OGTT (fasting glycaemia at 30-min, 1-h and 2-h time points). Impaired glucose metabolism was defined as the presence of impaired fasting glucose (IFG) ≥ 5.6 mmol/L and/or impaired glucose tolerance (IGT) if 2-h glucose was ≥ 7.8 mmol/L).

Pregnancy outcomes were compared using Student's t test for quantitative variables, and the chi-square or Fisher's exact test for categorical variables. Main predictors of MetS and impaired glucose metabolism were obtained by multiple logistic regression analyses. IBM SPSS version-20 software (IBM Corp., Armonk, NY, USA) was used for data analyses, and P values < 0.05 were considered statistically significant.

Results

Prenatal characteristics of the studied women are presented in Table 1. Insulinization rates during pregnancy were 55.3% for singleton vs 38.7% for multiple-pregnancy groups (P = 0.033). There was no difference in 3T-HbA_{1c}: medians (interquartile range, IQR): 5.1% (4.9–5.4%) and 32 mmol/mol (30–36 mmol/mol) for singleton pregnancies vs 5.0% (4.8–5.2%) and 31 mmol/mol (29–33 mmol/mol) for twin pregnancies (P = 0.557).

Postpartum examinations took place [medians (IQR)] at 7 months (4–10 months) for singleton pregnancies vs five months (4–7 months) for twin pregnancies (P = 0.038). Weight retention were 2.1 ± 5.0 kg vs 2.2 ± 4.7 kg (P = 0.906), and natural lactation was reported in 84.1% and 68.8% of singleton and twin pregnancies, respectively (P = 0.039).

Women with previous twin vs singleton pregnancies had a lower rate of impaired glucose metabolism at 22.6% vs 39.5% (P = 0.021) and, for MetS, 5.9% vs 18.4% (P = 0.035), respectively. IFG was found in 12.9% of women with previous twin gestations vs 29.8% with singleton gestations (P = 0.011). IGT rates were 4.8% vs 8.9%, respectively (P = 0.392), and IFG and IGT rates were 4.8% vs 2.4%, respectively (P = 0.402).

Impaired glucose metabolism was diagnosed in 38.1% of women with pregestational BMI scores > 25 kg/m^2 (overweight/obesity) vs 14.6% of women with pregestational scores < 25 kg/m^2 (P = 0.054) in the twin-pregnancy group, and in 50.9% vs 30.4% (P = 0.026), respectively, in the singleton-pregnancy group. MetS was found in 17.6% of women with pregestational BMI > 25 kg/m^2 vs 0% of women with pregestational BMI < 25 kg/m^2 (P = 0.033) in the twin-pregnancy group, and in 32.7% vs 7.8% (P = 0.001), respectively, in the singleton-pregnancy group.

On multivariate analyses (adjusted for multiple pregnancy, maternal age, ART, gestational mass-gain ratio, excessive weight gain, gestational hypertensive disorders, fasting plasma glucose at diagnosis, AUC-OGTT, 3T-HbA_{1c}, smoking habits, family history of diabetes and GDM in a previous gestation), multiple pregnancy did not reduce the risk of developing MetS or impaired glucose metabolism during early postpartum (Fig. 1).

Pregestational BMI was the main risk factor for developing MetS [adjusted odds ratio (AOR): 12.5, 95% confidence interval (CI): 1.69–92.27; P = 0.013]. Fasting glucose at diagnosis (AOR: 1.08, 95% CI: 1.02–1.15; P = 0.008) and 3T-HbA_{1c} (AOR: 22.6, 95% CI: 1.3–390.3; P = 0.032) were the main predictors for a diagnosis of abnormal glucose metabolism.

Discussion

Our present study data suggest a lower incidence of MetS and abnormal glucose metabolism in women with an index GDM twin pregnancy that is comparable to the attributed risk with a normal glucose-tolerant pregnancy [2,3].

However, impaired glucose metabolism and MetS were more frequent among women with pregestational BMI scores > 25 kg/m^2 in both study groups. After adjusting for possible confounders, multiple pregnancy was not associated with a lower risk of abnormal glucose metabolism or MetS during early postpartum. Pregestational BMI was confirmed to be the main risk factor for the development of MetS, while fasting glucose at diagnosis and 3T-HbA1c were for the diagnosis of abnormal glucose metabolism, in agreement to available data in singleton pregnancies [2,4].

Table 1
Population characteristics of singleton and twin pregnancies complicated by gestational diabetes mellitus (GDM).

	Singleton pregnancy (n = 124)	Twin pregnancy (n = 62)	P value
Age (years)	35.5 ± 4.5	35.8 ± 5.4	0.722
Parity (primiparous, %)	44.4	62.9	0.017
Assisted reproductive technology (%)	5.6	72.3	0.000
Pregestational BMI score (kg/m^2)	24.8 ± 4.3	24.0 ± 4.1	0.171
Underweight (%)	2.5	4.8	0.406
Normal weight (%)	54.9	46.8	0.598
Overweight (%)	29.5	25.8	0.598
Obese (%)	12.3	8.1	0.384
Total weight gain (kg)	9.4 ± 4.7	13.4 ± 5.6	0.000
Gestational mass-gain ratio	0.83 ± 0.5	0.67 ± 0.30	0.042
Gestational age at diagnosis (weeks)	21.6 ± 5.3	22.5 ± 4.3	0.235
*Area under the oral glucose tolerance test (mmol/L * min^{-1})*	28.3 ± 2.6	28.7 ± 2.9	0.309
Pregestational hypertension (%)	1.8	0	0.535
Gestational hypertension (%)	5.6	8.2	0.508
Preeclampsia	1.6	3.2	0.602

Data are means ± standard deviation (SD) or %; P < 0.05 is considered statistically significant.

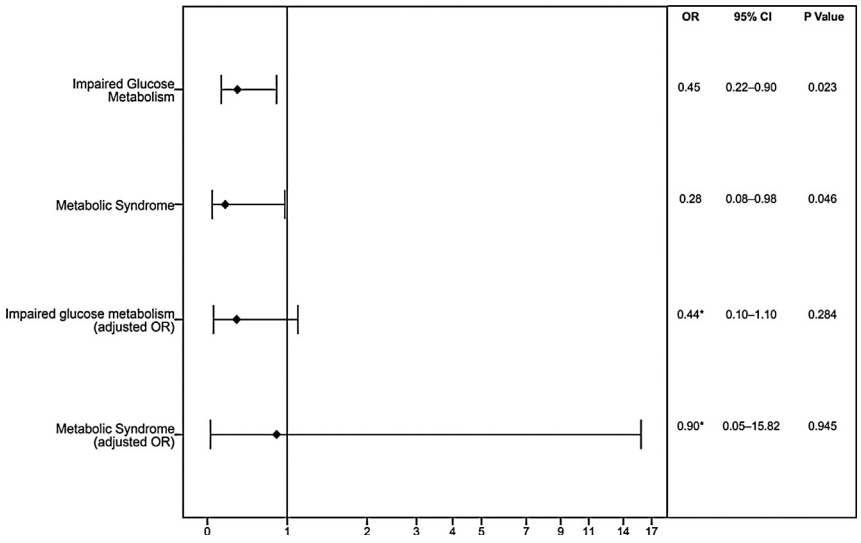

Fig. 1. Graphic display of postpartum impaired glucose metabolism and the metabolic syndrome shows adjusted odds ratio (OR) for multiple pregnancy, maternal age, assisted reproductive technology (ART), gestational mass-gain ratio, excessive weight gain, gestational hypertensive disorders, fasting plasma glucose at diagnosis, area under the curve of the oral glucose tolerance test (AUC-OGTT) at diagnosis, average third-trimester HbA_{1c} (3T-HbA_{1c}), smoking habits, family history of diabetes and gestational diabetes mellitus (GDM) during a previous pregnancy.

In fact, in our study population, all of the women diagnosed with MetS in the twin-pregnancy group were obese. Barquiel et al. [4] previously described prepregnancy BMI and fasting glycaemia as the main predictors of a diagnosis of MetS during early postpartum in Spanish women with singleton pregnancies, and this observation has held true for multiple pregnancies as well. The importance of pregestational obesity in women diagnosed with GDM over long-term follow-up has also been confirmed by several published reports, as well as a recent meta-analysis by Xu et al. [5]. The co-occurrence of both conditions in young women increases the risk of developing MetS by seven times compared with GDM in normal-weight women [3], and up to 26 times compared with normal glucose-tolerant women [2].

In our study population, the incidence of MetS was higher than previously described in the Spanish population, but this difference may have been due to a selection bias in our control group, which was matched by maternal age. In fact, the women included in our study were older than in other series [4,11].

The present report has some limitations. First, it was a retrospective observational study. Second, the proportion lost to follow-up was 51.1% of our GDM twin pregnancies over the study period. However, this rate is comparable to that described in major published series [1], which reported that around 40–60% of women fail to attend postpartum visits.

Postpartum metabolic assessment following a GDM-complicated gestation may be an early opportunity to initiate lifestyle or pharmacological interventions if necessary, which might then prevent or delay the appearance of cardiovascular risk factors such as obesity, dyslipidaemia and diabetes and, therefore, reduce morbidity and mortality. Indeed, according to our present findings, efforts to prevent postpartum metabolic disease should be focused on obese women with GDM and singleton or twin pregnancies, whereas twin pregnancies in women with normal prepregnancy BMI scores should be considered as having low risk.

Conclusion

Our present data suggest a lower incidence of MetS and abnormal glucose metabolism in women with index GDM twin pregnancies vs GDM singleton pregnancies. After adjusting for possible confounders, multiple pregnancy was not associated with a lower risk of either abnormal glucose metabolism or MetS during the early postpartum period.

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Disclosure of interest

The authors declare that they have no competing interest.

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The design of the study, as well as the data analyses, conclusions and interpretation of the data, are the responsibility of the authors.

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Gestational diabetes mellitus and the ghrelin system

Introduction

Gestational diabetes mellitus (GDM) is associated with adverse pregnancy and perinatal outcomes. A variety of serum biomarkers (such as inflammatory cytokines, adipokines and other circulating proteins) have been explored in attempts to identify a reliable predictor in early pregnancy for the subsequent development of GDM, but so far, none has been found [1]. Thus, the pool of biochemical markers requires further exploration.

Ghrelin, a gastrointestinal peptide hormone, is the endogenous ligand for growth hormone secretagogue receptor (GHSR) type 1a. Total serum ghrelin levels are composed of acylated ghrelin (AG) and unacylated ghrelin (UAG). The enzyme ghrelin o-acyltransferase (GOAT) is required for acylation of ghrelin. Ghrelin appears to have a wide range of biological activities and has been implicated in the regulation of glucose homoeostasis [2].

Ghrelin or ghrelin mRNA is expressed in the human ovary, testis and placenta, suggesting a role in fertility and pregnancy [3]. The pathophysiological role of ghrelin in GDM remains unclear, however. It has been reported that ghrelin levels are lower in women with GDM, which may reflect the inhibitory effect of insulin on ghrelin secretion [4]. Other studies have found decreased ghrelin levels in pregnancy irrespective of glucose tolerance [5]. However, to date, most studies measured total ghrelin without differentiating between AG and UAG. Furthermore, single-antibody ghrelin assays recognize either the COOH-terminal (total ghrelin) or acylated NH_2-terminal part of the peptide (AG) and are therefore measuring full-length ghrelin as well as circulating fragments of ghrelin, which have unknown biological activities. Indeed, it has been estimated that 60% of the ghrelin measured using these assays is fragmented [6].

For this reason, the present study has used a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA), which measures full-length AG and UAG. Our hypothesis is that women with GDM have higher degrees of insulin resistance and hyperinsulinaemia and, consequently, lower ghrelin levels than women with normal glucose tolerance (NGT). Thus, the aim of the study was to compare AG and UAG levels, and AG/UAG ratios, between pregnant women with GDM and with NGT.

Methods and materials

Subjects

A total of 19 pregnant women with GDM and 19 women with NGT were enrolled in our study. Women were prospectively recruited from the gynaecology outpatients' clinic at Maasstad Hospital in Rotterdam, Netherlands. Women with a singleton pregnancy and aged $\geq$ 18 years at gestational ages 24–28 weeks and at high risk of GDM, according to the Dutch Society of Obstetrics and Gynaecology [7], were eligible for inclusion. Women were excluded if they met any of the following criteria:

- endocrine disorders such as acromegaly, preexisting type 2 diabetes mellitus or Cushing's syndrome;
- use of glucocorticoid medications;
- inflammatory diseases or active infections;
- and/or a history of gastrointestinal surgery or hormonal treatments before or during pregnancy, including insulin.

All subjects were screened for GDM at 24–28 weeks of gestation by means of a 75-g oral glucose tolerance test (OGTT) and GDM diagnosis was based on International Association of the Diabetes and Pregnancy Study Groups (IADPSG)/World Health Organization (WHO) 2013 diagnostic criteria. Blood samples were drawn during fasting and at 2 h post-glucose load. Patient demographics, such as age, body mass index (BMI; kg/m^2), first trimester glucose (mmol/L) and gestational age at the time of sampling (weeks), were obtained from electronic medical records. All patients gave their written informed consent before inclusion in the study, which was approved by the relevant medical ethics committee.

Materials

Vacutainers (catalogue # 367899, 6-mL K2 EDTA; Becton, Dickinson and Company, Franklin Lakes, NJ, USA) were used, and 4-(2-aminoethyl) benzenesulphonyl fluoride hydrochloride (AEBSF; Pefabloc SC, catalogue # 11429876001) was purchased from Roche Applied Science (Penzberg, Germany). Aliquots of 200 mg/mL stock solutions of AEBSF were prepared with distilled water and stored at −80 °C for a maximum of 3 months. Human AG and UAG were determined by a double-antibody sandwich technique and the enzyme immunoassay (EIA) kits (A05106 and A05119, respectively) were obtained from Bertin Pharma (Montigny-le-Bretonneux, France).