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Original Research

Fetal Sex, Need for Insulin, and Perinatal Outcomes in Gestational Diabetes Mellitus: An Observational Cohort Study

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ABSTRACT

Purpose: This was a prospective observational cohort study that aimed to determine whether fetal sex influences the maternal and fetal outcomes of gestational diabetes mellitus (GDM).

Methods: In this study, 327 European primiparous women were consecutively recruited after diagnosis of GDM. AUC on the oral glucose tolerance test (OGTT), need for insulin therapy, maternal and obstetrical outcomes, and fetal fat mass (by measuring the thickness of the anterior abdominal subcutaneous tissue) were recorded and compared between the two subgroups of female and male fetuses.

Findings: Despite the absence of differences in multiple comparisons of the OGTT, the AUC–OGTT was significantly higher in women carrying a male fetus (22.6 [3.2] mmol/L vs 19.7 [2.8] mmol/L). The abdominal fat thickness appeared to increase with gestational age, with higher growth in male fetuses than in female fetuses. The overall risk of need for insulin therapy was significantly higher in women carrying a male fetus (odds ratio = 1.837). At delivery, birthweight was higher in males than in females only if adjusted for gestational age, similarly for placental weight, otherwise there were no significant differences between the groups in total length of gestation, rates of cesarean delivery, and Apgar scores.

Implications: Overall, our data propose an association between fetal sex and GDM outcomes, suggesting the hypothesis that in maternal–fetal interactions, the fetus can affect maternal glucose metabolism. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮)

Key words: fetal sex, GDM, insulin, OGTT.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a carbohydrate metabolism disorder with onset or first recognition as early as during pregnancy and is the most common type of diabetes affecting pregnancy. The frequency of GDM varies between 3% and 14%, depending on the method used for diagnosis and the study population.[1,2] GDM causes high risks in pregnancy and induces a series of consequences, including macrosomia, fetal abnormalities, high blood pressure, and polyhydramnios.[3] In infants born to mothers with GDM, neonatal respiratory disease syndrome, hypocalcemia, and hypoglycemia can occur after birth, and the perinatal mortality rate is high among these infants. The magnitude of the risk of postpartum diabetes depends on the ethnicity, the duration of follow-up, and the specific criteria for GDM diagnosis. Several studies have shown that 3% to 65% of women with previous GDM develop type 2 diabetes within 5 to 6 years after the pregnancy.[4] Concerning the child, recent studies have reported increased risks for obesity and other metabolic disorders.[5–7] An adequate control of blood glucose levels is the primary goal in managing women with GDM. Nutrition therapy and exercise are the mainstay of treatment for GDM, but if these fail, insulin treatment is needed to reduce glucose levels in order to ensure normal fetal development and better perinatal outcomes.[8] By retrospective analyses of perinatal databases, the presence of a male fetus may be

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associated with an increased incidence of GDM in the mother,[9,10] and the presence of a male fetus is associated with poorer maternal β-cell function.[11]

The aim of this prospective observational cohort study was to determine whether fetal sex influences maternal and fetal outcomes of GDM.

PATIENTS AND METHODS

The study population consisted of European primiparous women consecutively recruited in a prospective observational cohort at Salesi Teaching Hospital (Ancona, Italy) between January 2008 and December 2013 at the time of antepartum screening for GDM. The study was restricted to nonsmoking women with singleton pregnancies who underwent the universal screening by the internal department protocol with oral glucose tolerance test (OGTT) between 24 and 28 weeks' gestation (n = 327). All patients recruited were instructed to fast overnight for at least 8 hours before their testing day and to eat at least 150 g of carbohydrate the day before testing and undergoing the 100-g, 3-hour OGTT. The diagnosis was made according to the Carpenter-Coustan criteria[12] using ≥1 abnormal values. Exclusion criteria were preexisting diabetes mellitus, history of stillbirth, multifetal pregnancy, asthma or chronic hypertension, current use of corticosteroids, known fetal anomaly, or anticipated imminent preterm delivery. After diagnosis of GDM, all patients started a diet into seven servings, with 35 kcal kg-ideal-weight-1 day-1, and 300 kcal/d were added in the third trimester of gestation. Physical activity for 30 minutes per day was recommended. All patients recruited were followed-up until delivery, all were compliant with recommended therapy and physical exercise and no loss to follow-up was registered. By the internal protocol, the decision of starting insulin therapy was made when >50% of blood glucose values were outside the target range in the last week (fasting: 95 mg/dL or 2-hour postprandial: 120 mg/dL [6.7 mmol/L]). A cesarean section was performed for failure of labor induction, dystocia, or non-reassuring fetal heart monitoring.

AUC–OGTT was calculated by trapezoidal rule. Ultrasound examinations were performed at 4-week intervals and the fetal fat mass of the abdomen was determined by measuring the thickness of the anterior abdominal subcutaneous tissue on the same axial image from which the abdominal circumference was obtained.[13]

Maternal and obstetrical outcomes that were assessed included need of insulin, gestational age at delivery, birthweight, need of cesarean delivery, and Apgar score. Weight gain at OGTT screening was quantified as the difference between weight at the OGTT visit and the pre-pregnancy self-reported weight. Maternal characteristics are presented according to the GDM treatment regimens. Continuous data are presented as mean (SD). Categorical data are presented as number and percentage. For continuous data, the differences between the groups were tested using Student's unpaired *t*-test or the Mann-Whitney U test in case of skewed distribution. The analysis of OGTT was performed also with Tukey's honest significant difference test for multiple comparisons. Categorical variables were compared using the χ^2 test and Fisher's exact test.

The protocol of the study was approved by the local Institutional Review Board. Informed consent was obtained from all pregnant women. Women were informed that their ultrasound examination would be prolonged by approximately 10 minutes if they participated in the study. Data were then treated anonymously.

RESULTS

Table I shows the study population of pregnant women, stratified into those carrying a female fetus (n = 157) and those carrying a male fetus (n = 170). There were no significant differences

between the groups with respect to the pre-pregnancy body mass index and weeks' gestation at OGTT. The analysis of blood glucose response to the 100-g OGTT revealed no significant differences at post-hoc Tukey honest significant difference test for multiple comparisons even if the single means were higher in women carrying a male fetus than in those carrying a female (OGTT at 1 hour: 9.25 (1.2) mmol/L vs 8.87 (1.3) mmol/L; $P = 0.006$; OGTT at 2 hours: 8.21 (1.8) mmol/L vs 7.78 (1.6) mmol/L; $P = 0.023$; OGTT at 3 hours: 6.56 (1.6) mmol/L vs 6.21 (1.5) mmol/L; $P = 0.042$). Despite the absence of differences in multiple comparisons, the AUC–OGTT was higher in women carrying a male fetus ($P < 0.001$) (Figure 1). The weight gain in pregnancy up to OGTT was higher in women carrying a male fetus ($P <$