Influence of Gestational Diabetes Mellitus on Weight Discrepancy in Twin Pregnancies

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Objective: To evaluate the influence of gestational diabetes mellitus on weight discrepancy in twin pregnancies. *Methods:* 200 twin pregnancies were included in the study. 157 nondiabetic pregnant women with twin gestations and 43 twin pregnancies with gestational diabetes mellitus (GDM) with viable fetuses born after 24 weeks of gestation were enrolled. Influence of maternal age, body-mass-index at the time of the oral glucose tolerance test, parity, smoking, chorionicity, gestational age at delivery and diagnosis of GDM on weight discrepancy of the twins was evaluated. *Results:* Mean weight discrepancy of all analyzed twin pregnancies was 285 grams (± 231), relative weight discrepancy was 11.3% (± 8.6). Univariate regression analyses showed that GDM, chorionicity and gestational age at delivery were significantly associated with weight discrepancy. In the multivariate model only diagnosis of GDM was significantly associated with weight discrepancy. *Conclusion:* Twin pregnancies with insulin requiring gestational diabetes seem to have less birth weight discrepancy than twin pregnancies with normal glucose tolerance.

Keywords: twin pregnancy, gestational diabetes mellitus, weight discrepancy

Multiple birth rates are increasing in the last decades and contribute disproportionately to perinatal mortality and morbidity (ACOG, 1996). Multiple births account for approximately 3% of all births, 14% of infant deaths and 23% of preterm deliveries before 32 weeks of gestation (ACOG, 2004; Collins, 2007). Rising maternal age and increasing use of fertility treatment are major reasons for this trend (Collins, 2007; Kiely, 1998). Twin pregnancies are at higher risk for several pregnancy complications compared to singletons. Major complications are spontaneous preterm delivery, growth restriction, discordant growth, preeclampsia and preterm rupture of membranes. (Roberts et al., 1990; Spellacy et al., 1990)

Intrauterine growth restriction may be caused by fetal factors like genetic abnormalities, congenital anomalies or infection, by impaired placental function and by maternal factors like reduction in uteroplacental blood flow, uterine malformations, immunologic disorders, diminished caloric intake or smoking (Hendrix & Berghella, 2008; Redline, 2008).

Birthweight discrepancy in twin pregnancies is associated with an increased risk of perinatal mortality and morbidity (Demissie et al., 2002; Hartley et al., 2002). Mechanisms leading to discordant growth are differences in genetic potential, intrauterine crowding, unequal sharing of placental mass, and placental insufficiency (Victoria et al., 2001).

Fetal growth less than the tenth centile is more common among highly discordant twins than nondiscordant twins (Branum & Schoendorf, 2002). Neonatal mortality rates of the smaller twin increase with pronounced weight discrepancy. In twins with 15% to 19% weight discrepancy, the neonatal mortality risk for the smaller twin is 5%, rising to 43% when the discrepancy is 30% or more (Branum & Schoendorf, 2002).

Gestational diabetes mellitus (GDM) is defined as 'glucose intolerance with onset or first recognition during pregnancy' (ADA, 2001; Metzger et al., 2007). GDM complicates about 7% of all pregnancies, it is one of the most common pregnancy complications and the prevalence of GDM is rapidly increasing (Jovanovic, 2001; Persson & Hanson, 1998). GDM is associated with increased risks of adverse perinatal outcomes (HAPO study, 2002; Hawthorne et al., 1994; Jovanovic, 2001; Persson & Hanson, 1998). One of the most common complications in singletons is the higher incidence of birthweight above the 90th percentile (Persson & Hanson, 1998). According to the Pedersen hypothesis maternal hyperglycemia leads to fetal hypergycemia, followed by fetal hypersinulinemia leading to increased fetal growth since insulin plays an important role in the regulation of fetal growth (Acker & Barss, 1995; Pedersen 1952). The

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influence of this maternal metabolic disorder on growth discrepancy in twin pregnancies has not been elucidated so far. Therefore we have evaluated the influence of GDM on weight discrepancy in twin pregnancies at a tertiary care center.

Materials and Methods

This cohort study was conducted at the Department of Obstetrics and Gynecology of the Medical University of Vienna, a tertiary care center serving high-risk pregnancies between 2007 and 2008. The study was approved by the local ethics committee.

Women who underwent an oral glucose tolerance test between 24 and 28 weeks of gestation and were admitted to our department before 28 weeks of gestation were included in the study. In order to exclude women with mild abnormalities in glucose metabolism and to collect data of a homogenous group of GDM only women on insulin therapy were included in the study.

Multiple pregnancies after fetal reduction, twin pregnancies with fetal demise of one fetus and pregnancies with fetal malformations were excluded from the study.

All women had a first trimester scan and an anomaly scan at 20 to 22 weeks of gestation. Patients were monitored on a weekly or two weekly basis, depending on their metabolic situation, fetal biometrical data and chorionicity. Monochorionic twins were screened for signs of twin-to-twin transfusion syndrome, including amniotic fluid discrepancy, visualisation of the bladders and fetal Doppler studies of the umbilical artery and the ductus venosus. To screen for preeclampsia, blood pressure measurements and a urine dipstick was performed at each visit. Preeclampsia was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy (Brown et al., 2001).

This requires two recordings of diastolic blood pressure of > 90 mm Hg at least four hours apart in previously normotensive women, and proteinuria of 300 mg or more in 24 hours, or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available. Gestational age was determined from the menstrual history and, if necessary, corrected from the measurement of the crown-rump length of the bigger twin at the first-trimester ultrasound scan.

For a difference in weight discrepancy of 100 grams between patients with GDM and nondiabetic twin pregnancies, we calculated a sample size of 45 patients with GDM and 135 nondiabetic patients at a p value of .05 and a power of 80%.

Overall 212 patients of Caucasian origin were eligible for the study. Ten patients who developed preeclampsia and two patients with twin-to-twin transfusion syndrome were excluded.

All pregnant women in our study were screened for GDM using an oral glucose tolerance test (OGTT). The OGTT was conducted between 24th–28th weeks of gestation with a standardized 75-gram glucose solution (Glucodrink®, Unipack, Wr. Neustadt, Austria). Blood samples were taken in the fasting state, one hour and two hours after glucose ingestion. The OGTT was evaluated according to the guidelines of the Austrian and German Diabetes Society (Kautzky-Willer et al., 2004). Upper normal limit for fasting, 1-hour, and 2-hour serum glucose levels were 90 mg/dL, 180 mg/dL and 155 mg/dL, respectively. If any of these limits was exceeded, patients were rated as GDM. Women with GDM were referred to the Department of Internal Medicine, Division of Endocrinology and Diabetes, and to dietary counseling and requested to measure their blood glucose levels four times daily. The aim was to achieve blood glucose levels below 90 mg/dL at fasting and 130 mg/dL 1 hour postprandially.

When a patient had five excess values per week in the blood glucose self-assessment, insulin therapy was started. Insulin dose was adapted if these limits were exceeded five times or more within one week.

Birthweight centiles were calculated according to centile charts used for singletons (Gardosi & Francis, 2000; 2007).

Weight discrepancy was calculated by the difference of the absolute birthweights of the twins, divided by the birthweight of the larger twin. The study cohort was evaluated for the relationship between weight discrepancy and maternal age, body-mass-index at the time of the OGTT, parity, smoking, chorionicity, gestational age at delivery and diagnosis of GDM.

Statistical analyses were performed with SPSS software (version 15.0; SPSS, Chicago, IL). Parametric continuous variables are summarized as means (± standard deviation), nonparametric continuous variables as medians (minimum and maximum) and categorical data as percentages. The chi-square test was used for comparisons of inter-twin weight discrepancy in women with GDM and women with normal glucose tolerance. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors of weight discrepancy. Maternal age, body-mass-index, parity, smoking, chorionicity, gestational age at delivery and diagnosis of GDM were entered into the regression models as independent variables. P values of .05 were considered significant.

Results

Patient characteristics are shown in Table 1. Women with GDM did not significantly differ from nondiabetic pregnant women concerning maternal age, body-mass-index, parity, smoking, chorionicity and gestational age at delivery. The high rate of women with GDM may also be caused by the fact that our clinic is a tertiary care centre.

Newborns of diabetic mothers did not significantly differ from newborns of nondiabetic mothers

concerning birthweight below the 10th or above the 90th centile (twin I: 37% vs 49% below the 10th centile and 0% vs. 2% above the 90th centile; twin II: 51% vs 55% below the 10th centile and no birthweights above the 90th centile).

Mean weight discrepancy was 285 gram ± 231 (11.3% ± 8.7) in all patients. Mean weight discrepancy in twins with mothers without GDM was significantly greater compared to twins with mothers with GDM, 304 gram ± 235 (12.0% ± 8.8) and 214 gram ± 200 (8.7% ± 7.6), respectively (p = .02). Fifty per cent (100 out of 200) of all twins had a weight discrepancy of ≥ 10%. Twins with mothers with normal glucose tolerance had significantly more often a weight discrepancy of ≥ 10% than twins with mothers with GDM (56% versus 39%, p = .05). Fetal outcome is shown in Table 2.

Univariate regression analyses showed that chorionicity, gestational age at delivery and diagnosis of GDM were significantly associated with absolute weight discrepancy (coefficient –.15, p = .04; coefficient .15, p = .03; coefficient –.15, p = .03). In the multivariate model only diagnosis of GDM was significantly associated with absolute weight discrepancy (coefficient –.16, p = .02), see Table 3. Evaluating risk factors for relative weight discrepancy, diagnosis of GDM was significantly associated with relative weight

discrepancy (coefficient –.15, p = .03). Additionally, we performed subgroup analyses only for dichorionic twin pregnancies. Univariate regression analyses showed that diagnosis of GDM was significantly associated with absolute and relative weight discrepancy (coefficient –.19, p = .02; coefficient –.16, p = .04).

Discussion

Our data demonstrate that twin pregnancies with normal glucose tolerance show higher weight discrepancy than those with GDM.

In singletons GDM is associated with abnormal fetal weight. Neonates of women with pre-existing diabetes mellitus complicated by vasculopathy are at risk for delivery of low birthweight or small for gestational age (SGA) infants (Haeri et al., 2008). Otherwise, women with GDM are at risk for delivery of infants with birthweights above the 90th percentile (Cheng et al., 2008).

Relations between maternal weight gain during pregnancy and birthweight have been described in women with GDM. Increased weight gain is associated with a higher risk of macrosomia and preterm delivery. On the other hand, there is some evidence that women with GDM and weight gain below the normal range are more likely to remain on diet control but are at risk to have SGA infants (Cheng et al., 2008).

Table 1

Patient Characteristics of Women With Twin Pregnancies With Insulin Requiring Gestational Diabetes Mellitus and Twin Pregnancies With Normal Glucose Tolerance

	All pregnant women (n = 200)	Women with GDM (n = 43)	Women with normal glucose tolerance (n = 157)
Maternal age (years [mean ± SD])	31.8 ± 5.5	32.9 ± 5.1	31.5 ± 5.6
Body-mass-index (kg/m²) [median; range]	24.0; 17.5–46.0	24.9; 18.1–40.0	23.8; 17.5–46.0
Parity [mean ± SD]	1.2 ± 1.1	1.2 ± 0.9	1.3 ± 1.1
Smoking (%,n)	12.5% (25/200)	16.2% (7/43)	11.4% (18/157)
Dichorionic twins (%,n)	78.5% (157/200)	81.4% (35/43)	77.7% (122/157)
Monochorionic twins (%, n)	21.5% (43/200)	18.6% (8/43)	22.3% (35/157)
Gestational age at delivery [mean ± SD]	35.6 ± 2.2	35.6 ± 1.9	35.6 ± 2.3

Note : GDM: gestational diabetes mellitus, SD: standard deviation.

Table 2

Fetal Outcome of the Twin Pregnancies

	All pregnant women (n = 200)	Women with GDM (n = 43)	Women with normal glucose tolerance (n = 157)
Birthweight (gram) [mean ± SD]	2349 ± 497	2370 ± 446	2342 ± 510
Weight discordance (gram) [mean ± SD]	285 ± 231	214 ± 200	304 ± 235
Relative weight discordance [mean ± SD]	11.3% ± 8.7%	8.7% ± 7.6%	12.0% ± 8.8%
Arterial pH value twin I [median; range]	7.27; 7.01–7.41	7.28; 7.13–7.41	7.27; 7.01–7.40
Arterial pH value twin II [median; range]	7.27; 6.98–7.59	7.27; 6.98–7.40	7.27; 6.98–7.59

Note: GDM: gestational diabetes mellitus, SD: standard deviation.

Table 3

Predictors of Weight Discrepancy in Twins

	β	SE (β)	T	P value
Chorionicity	−0.11	36.38	−1.49	0.69
Gestational age at delivery	0.11	7.98	1.51	0.13
Diagnosis of GDM	−0.16	39.27	−2.29	0.02

Due to the decreasing growth rate in twins relative to that of singletons starting from the 30th week of gestation onwards, it is rather unlikely to have fetuses above the 90th centile (regarding biometry charts for singletons) in twin pregnancies with GDM (Alexander et al., 1998). Furthermore, twins are delivered earlier than singletons, and this decreases the rate of growth discrepancy even more.

Limited literature exists concerning the impact of GDM on neonatal outcome in twin pregnancies (Cho et al., 2006). Cho et al. reported that twin pregnancies with well-controlled GDM have a comparable outcome to twin pregnancies with normal glucose tolerance (Cho et al., 2006). In the group of twin pregnancies it is well known that monochorionic twins show a more pronounced weight discrepancy than dichorionic, due to placental vascular anastomoses (Cleary-Goldman & D'Alton, 2008). The observed weight discrepancy in monochorionic twins is of a higher impact on perinatal outcome than in dichorionic twins (Acosta-Rojas et al., 2007).

Assuming that monochorionic twins are at higher risk for intrauterine growth restriction and weight discrepancy, we have performed subgroup analyses that only include dichorionic twins, to evaluate the influence of GDM on weight discrepancy in a homogeneous population. These subgroup analyses of dichorionic twins reveal that women with normal glucose tolerance are at higher risk for weight discrepancy than those with GDM.

The mechanism of the apparent balancing effect of GDM on growth discrepancy is not yet known. In animal models it has been shown that IUGR fetus have a greater beta cell mass compared to normal fetus (Chakravarthy et al., 2008).

One could hypothesize that in twin pregnancies with weight discrepancy, the smaller twin develops hyperinsulinemia due to a stimulation of the pancreatic beta-cells, since insulin plays an important role as a growth factor. As a consequence, the smaller twin may get relatively more glucose from the hyperglycaemic mother compared to the larger co-twin, which could lead to a diminishing weight discrepancy, but this is highly speculative.

In sheep the basal adrenocortical function is delayed in twins compared to singletons (Gardner et al., 2004).

Under basal conditions twins have lower plasma cortisol concentrations, which are known to regulate glucose metabolism. This relative adrenocortical immaturity in twin fetuses may have an influence on the glucose turnover and fetal growth. Furthermore, a study looking at growth factors and their binding proteins in twin pregnancies have shown a compensatory mechanism by increased insulin levels in the smaller twin of discordant fetuses to promote fetal growth (Davidson et al., 2006). Although the endocrine environment is different in twin pregnancies, the exact mechanism of the altered glucose metabolism still remains unclear.

In conclusion, our data support gestational diabetes mellitus as a possible factor influencing weight discrepancy in twins.

Acknowledgments

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