Disproportionate Body Composition and Neonatal Outcome in Offspring of Mothers With and Without Gestational Diabetes Mellitus

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OBJECTIVE—High birth weight is a risk factor for neonatal complications. It is not known if the risk differs with body proportionality. The primary aim of this study was to determine the risk of adverse pregnancy outcome in relation to body proportionality in large-for-gestational-age (LGA) infants stratified by maternal gestational diabetes mellitus (GDM).

RESEARCH DESIGN AND METHODS—Population-based study of all LGA (birth weight [BW] >90th percentile) infants born to women with GDM (n = 1,547) in 1998–2007. The reference group comprised LGA infants (n = 83,493) born to mothers without diabetes. Data were obtained from the Swedish Birth Registry. Infants were categorized as proportionate (P-LGA) if ponderal index (PI) (BW in grams/length in cm^3) was ≤90th percentile and as disproportionate (D-LGA) if PI >90th percentile. The primary outcome was a composite morbidity: Apgar score 0–3 at 5 min, birth trauma, respiratory disorders, hypoglycemia, or hyperbilirubinemia. Logistic regression analysis was used to obtain odds ratios (ORs) for adverse outcomes.

RESULTS—The risk of composite neonatal morbidity was increased in GDM pregnancies versus control subjects but comparable between P- and D-LGA in both groups. D-LGA infants born to mothers without diabetes had significantly increased risk of birth trauma (OR 1.19 [95% CI 1.09–1.30]) and hypoglycemia (1.23 [1.11–1.37]). D-LGA infants in both groups had significantly increased odds of Cesarean section.

CONCLUSIONS—The risk of composite neonatal morbidity is significantly increased in GDM offspring. In pregnancies both with and without GDM, the risk of composite neonatal morbidity is comparable between P- and D-LGA.

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High birth weight (BW), in both diabetic and nondiabetic pregnancies, is associated with increased risk of maternal and perinatal complications as well as long-term adverse health consequences for the offspring (1–10). Gestational diabetes and maternal obesity are well-established risk factors for high BW (11–14). In pregnancies with gestational diabetes mellitus (GDM), reported rates of high-BW infants range between 15 and 62.5% (15–18), corresponding to a several-fold increased risk compared with the general obstetric population (19). Complications associated with high BW include excessive maternal bleeding, prolonged labor, instrumental delivery, Cesarean section, perineal tears, stillbirth, neonatal birth trauma, low Apgar scores, acute respiratory disorders, hypoglycemia, and neonatal death (1–7). Irrespective of BW, GDM offspring face an excess risk of future morbidities (20–23). However, the risk may be even further increased in infants born with fetal macrosomia (24,25).

The definition for high BW is not consistent. Current definitions are based on either absolute BW (>4,000 or 4,500 g) and referred to as fetal macrosomia or BW in relation to gestational age and sex (large for gestational age [LGA], BW >90th or 97.5th percentile). It is unclear which of these definitions best predicts the risk of adverse outcome. None of the current definitions take into account body proportionality, i.e., the relation between the infant's BW and birth length (BL). The ponderal index (PI; i.e., BW in grams/BL in cm^3) is a marker for body proportionality, and at a population level, the PI is a useful estimate of body proportionality when BW and BL are routinely collected. Fetal macrosomia or LGA in infants born to mothers with GDM and/or obesity is characterized by a disproportionate body composition with high BW in relation to BL (26) and increased fat mass (27–29).

The primary aim of this study was to determine the risk of adverse pregnancy outcome in relation to body proportionality in LGA infants (BW >90th percentile) stratified by maternal GDM status. We hypothesized that infants with a disproportionate body composition, most likely as a consequence of fetal hyperinsulinemia, would have an increased risk of perinatal complications compared with those with a proportionate body composition.

RESEARCH DESIGN AND METHODS

—This prospective population-based cohort study was performed using data from the Swedish Medical Birth Registry (MBR) from 1998 to 2007. The MBR includes data on >98% of all pregnancies in Sweden. The registry includes information on maternal demographics and medical and obstetric history. Maternal complications during pregnancy and delivery, as well as neonatal diagnoses are classified according the Swedish version of ICD-10. All diagnoses are made by a physician before hospital discharge, and copies of the records are forwarded to the MBR. The registry is regularly evaluated by the national board of health and has also been evaluated

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by an independent group of researchers. The conclusion from these validations is that the quality of the data is considered to be high (30,31). In Sweden, screening for GDM is universal, including all pregnant women. There are a few local variations, but the principal screening program includes random capillary glucose measured four to six times during pregnancy starting at the first antenatal visit in the first trimester. During the study period, women were selected for oral glucose tolerance test (OGTT) based on repeated random capillary plasma glucose tests ≥9 mmol/L and/or in combination with traditional risk factors, including a first-degree relative with diabetes, prior GDM, obesity, or prior delivery of a macrosomic infant (mean BW greater than +2 SD corrected for gestational age and sex) (32). In 10–15% of the pregnant population, an OGTT is performed based on positive screening criteria. This means that most non-GDM women have not performed an OGTT but do not fulfill the screening criteria for OGTT. A minor part of non-GDM women performed an OGTT with a normal result. In the southern part of Sweden, all pregnant women have been offered a simplified OGTT (omitting fasting blood glucose) as a one-step screening and diagnostic test since 1995 (33). The main diagnostic criteria for GDM applied in Sweden are based on the Diabetes in Pregnancy Study Group recommendation from 1991, i.e., a fasting capillary whole blood glucose ≥6.1 mmol/L (fasting plasma glucose ≥7.0 mmol/L) and/or 2-h capillary whole blood glucose ≥9 mmol/L (plasma glucose ≥10 mmol/L) after 75-g OGTT.

Study cohort

The current study included only LGA infants, defined as infants with a BW >90th percentile in relation to gestational age and sex. The study cohort comprised 1,547 live born singletons to mothers with GDM and 83,493 singletons born to mothers without a diagnosis of diabetes. Women with a diagnosis of GDM were identified by ICD-10 code O24. All the infants in the study cohort were born between 37 and 43 weeks of gestation. In Sweden, all pregnant women are offered an ultrasonic scan performed around the 17th week of gestation, with the primary aim to determine gestational age. More than 95% of pregnant women accept this offer (34). When information on ultrasound was not available, gestational age was estimated from date of last menstrual period. We excluded stillborn infants, infants with major malformations, and infants born at <37 weeks of gestation or with BW ≤90th percentile. In the current study, we used the same limits for data acceptance as in the Swedish Perinatal Quality Registry, i.e., infants with a BW <200 or >9,998 g and a BL <15 or >65 cm. Applying these limits, no records were excluded due to BW but 90 records were excluded due to extreme values on BL. We also excluded records with missing data on BW, BL, gestational age, or sex and records with extreme values on maternal age (<13 or >54 years), weight (<40 and >200 kg), and height (<120 and >200 cm). Pregnancy-induced hypertension (PIH) was defined as a resting blood pressure ≥140/90 after the 20th week of gestation (ICD-10 code O13). Preeclampsia was defined as PIH and proteinuria of ≥0.3 g/day or ≥1+ on a urine dipstick (ICD-10 codes O14.0, O14.1, and O15).

Collection and categorization of infant anthropometry

According to standardized operation of procedures, all infant anthropometrics were measured within 12 h after birth by trained midwifes. BW was registered to the nearest gram on an electronic scale; BL was measured using a standardized measuring board for length. Sex- and gestational age–adjusted reference percentiles for BW, BL, and PI were based on data from singleton infants, without major malformations and born between 28–43 weeks in the same time period to mothers without diabetes (n = 874,620). LGA was defined as BW >90th percentile. Disproportionate body composition (D) was defined as a PI (BW in grams/BL in cm^3) >90th percentile and proportionate (P) as PI ≤90th percentile. LGA infants were classified as proportionate (P-LGA) and disproportionate (D-LGA).

Outcomes

The primary outcome was a composite morbidity variable including any of the following diagnoses: Apgar score 0–3 at 5 min, birth trauma in vaginally delivered infants (Erb palsy ICD-10 code P140; fractured clavicle ICD-10 code P134), acute respiratory disorders (respiratory distress syndrome ICD-10 code P220; transient tachypnea ICD-10 codes P22.1, P22.8, and P22.9; meconium aspiration), and hypoglycemia or hyperbilirubinemia requiring treatment with phototherapy or exchange transfusion. Neonatal hypoglycemia was defined as blood glucose <2.6 mmol/L after 6 h postnatal (ICD-10 code P70.4 B). The secondary outcomes included delivery by Cesarean section, and the diagnoses stated above were analyzed separately.

Statistical analysis

Given the prevalence of neonatal morbidities and of LGA in the offspring of women with GDM (15,18,19) and hypothesizing that 40% of the LGA infants are D-LGA (35), we will need a cohort size of ~339 LGA infants with disproportionate body composition and 776 LGA infants with proportionate body composition to detect a 30% increase in the prevalence of neonatal morbidity (composite outcome) comparing P-LGA and D-LGA infants with 80% power and α = 0.05. Continuous data were summarized by the median and interquartile range, and univariate analyses were performed using the Mann-Whitney U test. Univariate analyses of dichotomous data were performed using the χ^2 test. Odds ratios (ORs) for perinatal complications were estimated using logistic regression with P-LGA infants, born to women without diabetes, as the reference category. In the multivariate model, the estimate for the primary outcome (composite morbidity) was adjusted for maternal country of birth (Nordic yes/no), age, BMI, height, smoking in the first trimester of pregnancy, parity, mode of delivery, PIH, and preeclampsia. Multivariate regression models for the secondary outcomes included covariates significantly associated with the outcome in univariate analysis. As none of the above-stated covariates were significantly associated with three of the secondary outcomes, i.e., birth trauma, Apgar score 0–3 at 5 min, and hypoglycemia, no multivariate models were constructed for these outcomes.

In the multivariate logistic regression, missing indicator variables were used for maternal age, BMI, and height. To disclose any potential differences between P-LGA and D-LGA within the GDM cohort, all regression models were also performed with P-LGA infants born to GDM mothers as the reference category. Likelihood ratio test was used to explore the interaction between maternal GDM, BW category, and the different outcomes.

RESULTS—During the study period, there were 947,096 deliveries in Sweden, of which 0.94% (n = 8,929) were pregnancies to mothers with GDM. The prevalence of LGA among offspring of women with GDM was 26% (n = 1,547) and 10.6% (n = 83,493) in infants born to mothers

without diabetes. Of the LGA infants in the GDM cohort, 44% (n = 694) had a disproportionate body composition, compared with 36% (n = 29,969) in the reference group (P value <0.001).

Compared with women without diabetes, women in the GDM group were more often of non-Nordic origin, older, and multiparous, had a higher prepregnancy BMI, and were more likely to be shorter. Women giving birth to a D-LGA infant had a significantly higher BMI compared with mothers of P-LGA infants (GDM group: BMI 30.5 [D-LGA] vs. 25.0 [P-LGA] kg/m^2; reference group: BMI 25.5 [D-LGA] 24.9 [P-LGA] kg/m^2; P value <0.05). The prevalence of smoking and hypertensive disorders in pregnancy was significantly higher in the GDM cohort (Table 1). The infants born to mothers with GDM were more likely delivered earlier with lower absolute BW compared with the non-GDM group. The incidence of LGA, however, was higher in infants of women with GDM. Furthermore, LGA infants born to mothers with GDM were more likely to be disproportionate with a slightly higher PI compared with the LGA infants born to mothers without diabetes. When BW was compared by body proportionality, BW was highest among infants who were D-LGA and born to mothers with GDM. Infants born to mothers with GDM were also more likely delivered by Cesarean section.

The frequency of the primary and most secondary outcomes was significantly higher in infants born to GDM mothers compared with infants born to mothers without diabetes (Table 2). Within both the GDM and the non-GDM cohorts, there were no significant differences in the occurrence of composite neonatal morbidity between P-LGA and D-LGA infants. D-LGA infants born to mothers with and without GDM were more often delivered by Cesarean section than P-LGA infants. In both GDM and reference groups, the incidence of birth trauma and hypoglycemia was higher in D-LGA compared with P-LGA. However, the difference reached statistical significance only in the reference group.

In comparison with P-LGA infants born to mothers without diabetes, the ORs for the primary and most secondary outcomes were significantly higher in both P-LGA and D-LGA infants born to GDM mothers (Table 3). The increased odds persisted even after adjustment for potential confounders (Table 3). In the non-GDM group, D-LGA was associated with significantly increased odds of Cesarean section, birth trauma, and hypoglycemia. Confining the regression analysis to the GDM cohort, with P-LGA infants as the reference category, D-LGA was associated with significantly increased odds of Cesarean section ($P < 0.001$). There were no significant differences between P-LGA and D-LGA GDM offspring for any of the other outcomes. There was no significant interaction between LGA category and GDM for any of the outcomes (Table 3).

Table 1—*Maternal and infant characteristics*

	GDM (n = 1,547)	Non-GDM (n = 83,493)	P value
Maternal characteristics			
Nordic origin	1,111 (71.8%)	74,857 (89.7%)	<0.001
Primapara	336 (21.7%)	23,161 (27.7%)	<0.001
Age (years)	32 (29–36)	31 (27–34)	<0.001
BMI (kg/m^2)	30.0 (25.7–34.8)	25.1 (22.7–28.5)	<0.001
Overweight/obese: P-LGA	80.6%	57.2%	<0.001
Overweight/obese: D-LGA	85.8%*	61.3%*	<0.001
Height (cm)	166 (162–170)	169 (164–173)	<0.001
Height, P-LGA (cm)	167	168	<0.001
Height, D-LGA (cm)	165*	169*	<0.001
Smoking first trimester	135 (8.7%)	4,631 (5.6%)	<0.001
PIH	33 (2.1%)	671 (0.80%)	<0.001
Preeclampsia	95 (6.1%)	1,899 (2.3%)	<0.001
Infant characteristics			
LGA	1,547 (100%)	83,493 (100%)	
Male	776 (50.2%)	42,907 (51.4%)	0.338
Gestational age (weeks)	39 (38–40)	40 (39–41)	<0.001
BW (g)	4,400 (4,202–4,675)	4,410 (4,200–4,630)	<0.001
PI	3.03 (2.87–3.22)	2.98 (2.82–3.15)	<0.001
P-LGA	873 (56.4%)	53,524 (64.1%)	<0.001
D-LGA	674 (43.6%)	29,969 (35.9%)	<0.001
BW, P-LGA (g)	4,360 (4,180–4,575)	4,385 (4,185–4,590)	<0.001
BL, P-LGA (cm)	53 (53–54)	54 (53–55)	<0.001
BW, D-LGA (g)	4,480 (4,245–4,785)	4,450 (4,230–4,690)	<0.001
BL, D-LGA (cm)	52 (51–53)	52 (51–53)	0.08
Mode of delivery			
Cesarean section	555 (35.9%)	16,940 (20.3%)	<0.001
Ventouse/forceps	89 (5.8%)	5,471 (6.6%)	0.207

Data are n (%) or medians (interquartile range) unless otherwise indicated. BMI: at inscription to antenatal care (first trimester); missing data 16% in GDM and 14% in reference group. *Significant difference between mothers to D-LGA and P-LGA, within GDM and reference group, respectively.

CONCLUSIONS—Forty-four percent of this population-based cohort of LGA GDM offspring had a disproportionate body composition, similar to our previous finding of 46% in LGA newborns of mothers with type 1 diabetes (35). The major finding of this study was that the risk of adverse neonatal outcome did not differ significantly with body proportionality in infants born to mothers with GDM. As expected, neonatal morbidity was significantly more common in both P-LGA and D-LGA GDM offspring than in infants born to mothers without diabetes. The increased odds of complications in GDM offspring remained even after adjustment for differences in maternal characteristics and hypertensive disorders. Another important finding in the current study was that in infants born to mothers without diabetes, a disproportionate body composition was associated with significantly increased odds of birth trauma and hypoglycemia.

The strength with the current study is the large national cohort, including >1,500 LGA infants born to women with GDM and >80,000 LGA infants born to women without diabetes. The large sample size enabled adjustment for several important confounders and also a stratified risk analysis for subgroups of LGA infants. The population-based design limits the risk of selection bias regarding the exposure (GDM) and reference groups. However, in the current

Table 2—*Neonatal outcomes*

	GDM, P-LGA	GDM, D-LGA	*P* value	Non-GDM, P-LGA	Non-GDM, D-LGA	*P* value
Composite morbidity	99 (11.3%)	94 (14.0%)	0.124	3,745 (7.0%)	2,184 (7.3%)	0.117
Apgar 5 <4	7 (0.8%)	5 (0.7%)	0.894	106 (0.2%)	44 (0.2%)	0.094
Cesarean section	277 (31.8%)	278 (41.3%)	<0.001	9,691 (18.1%)	7,249 (24.2%)	<0.001
Birth trauma	35 (6.5%)	22 (6.6%)	0.992	1,315 (3.2%)	792 (3.8%)	<0.001
Respiratory disorders	8 (0.9%)	12 (1.8%)	0.136	774 (1.5%)	421 (1.4%)	0.630
Hypoglycemia	48 (5.5%)	51 (7.6%)	0.099	843 (1.6%)	579 (1.9%)	<0.001
Hyperbilirubinemia	13 (1.5%)	10 (1.5%)	0.993	849 (1.6%)	430 (1.4%)	0.088

Data are *n* (%).

study, the incidence of neonatal complications was quite low, and in spite of the large sample size, statistical power was limited for some of the secondary outcomes and also may have affected the ability to detect statistically significant interaction.

A potential weakness with this study is that the MBR does not contain data on maternal glycemic control. Accordingly, the influence of different degrees of maternal hyperglycemia on the risk of neonatal complications could not be assessed. The incidence of GDM in Sweden is low (0.9%) compared with other countries, reflecting differences in screening strategies, diagnostic criteria, and above all a low rate of type 2 diabetes in the background population. The screening strategies in Sweden do not detect all cases of GDM. There is evidence that with the screening strategies used in most of Sweden, ~50% of cases with GDM (mainly impaired glucose tolerance) are not diagnosed, but the more severe cases and overt diabetes are found by this screening strategy (32). By comparing data from a population study in Sweden where all pregnant women were offered an OGTT (32) with data from the MBR, the rate of undiagnosed GDM in the non-GDM group was estimated to be ~0.7%. This proportion of undiagnosed milder GDM in the background population is low and unlikely to affect the results. If any effect, the differences between the groups in the current study may have been underestimated. We are aware of the potential limitation regarding the measurement of infant length. However, in Sweden, BL is measured according to a standardized procedure using a measure board for length. We consider it unlikely that any potential systematic error of length measurement would differ between infants born to mothers with and without diabetes; i.e., the possible misclassification is nondifferential. It is noteworthy that the number of infants excluded due to extreme BL in the current study was very low (0.01%).

This study is, to our knowledge, the first to analyze the risk of neonatal complications by body proportionality in GDM offspring. A high BW-to-BL ratio was not associated with an increased risk of composite neonatal morbidities in infants born to GDM mothers. This finding

Table 3—*Logistic regression analysis for adverse outcomes stratified by maternal GDM and infant size*

	Reference*	Non-GDM, D-LGA	GDM, P-LGA	GDM, D-LGA	Interaction *P* value
Composite morbidity					
Crude OR	1.0	0.97 (0.93–1.01)	1.52 (1.26–1.83)	1.76 (1.44–2.15)	
Adjusted OR	1.0	1.00 (0.95–1.06)	1.47 (1.18–1.83)	1.75 (1.38–2.21)	0.22
Cesarean section**					
Crude OR	1.0	1.44 (1.39–1.49)	2.11 (1.82–2.43)	3.18 (2.72–3.71)	
Adjusted OR	1.0	1.40 (1.35–1.45)	1.77 (1.53–2.05)	2.59 (2.21–3.04)	0.17
Apgar 5 <4					
Crude OR	1.0	0.74 (0.52–1.05)	4.07 (1.89–8.78)	3.77 (1.53–9.27)	0.13
Birth trauma					
Crude OR	1.0	1.19 (1.09–1.30)	2.10 (1.49–2.97)	2.11 (1.36–3.26)	0.37
Hypoglycemia					
Crude OR	1.0	1.23 (1.11–1.37)	3.64 (2.70–4.90)	5.12 (3.81–6.86)	0.39
Respiratory disorders					
Crude OR	1.0	0.97 (0.86–1.09)	0.63 (0.31–1.27)	1.24 (0.69–2.20)	
Adjusted OR	1.0	0.90 (0.86–1.02)	0.54 (0.27–1.08)	0.96 (0.54–1.70)	0.14
Hyperbilirubinemia					
Crude OR	1.0	0.90 (0.80–1.02)	0.94 (0.54–1.63)	0.93 (0.50–1.75)	
Adjusted OR	1.0	0.88 (0.78–0.99)	0.80 (0.46–1.39)	0.76 (0.41–1.43)	0.75

ORs adjusted for variables associated with outcomes in univariate analysis; for birth trauma, Apgar <4 at 5 min, and hypoglycemia, no significant associations were found with any of the potential confounders and therefore only the crude estimate is reported. *Reference = non-GDM, P-LGA. **Significant difference between P-LGA and D-LGA within GDM cohort.

was unexpected and not in line with our prespecified hypothesis. We speculated that infants with a disproportionate largeness (D-LGA) had been subjected to a more profound fetal hyperinsulinemia compared with infants who are proportionally large (P-LGA). This view is supported by previous studies that have demonstrated an increasing linear relationship between maternal fasting glucose levels and cord blood levels of C-peptide, neonatal fat mass, and fetal macrosomia in pregnancies with mild GDM (36). In this context, it is of interest that the incidence of neonatal hypoglycemia was higher in D-LGA, compared with P-LGA, infants in both cohorts, although the difference reached statistical significance only in the reference group. It cannot be excluded that fetal hyperinsulinemia, which is known to be associated with increased risk of neonatal hypoglycemia, could explain the higher prevalence of hypoglycemia in disproportionally grown infants. It is unclear to what extent the absence of difference in composite neonatal outcome between P- and D-LGA GDM offspring can be attributed to differences in time of GDM diagnosis and treatment. All mothers in the current study received treatment that may well have modified the risk of neonatal complications. Results from two randomized, controlled studies of GDM demonstrate a positive effect of treatment on the infant's size, fat mass at birth, and risk of neonatal complications (18,37).

It is noteworthy that the incidence of D-LGA infants was also high (36%) in the non-GDM population. Studies on pregnant women without diabetes have demonstrated a linear association between maternal glucose values (fasting and 1- and 2-h values from 75-g OGTT at 24–32 weeks of gestation) and cord blood levels of C-peptide, neonatal fat mass, and BW >90th percentile (38). Additional findings of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study also indicate that maternal BMI per se is associated with increased risk of neonatal fat mass and BW >90th percentile, independent of maternal glycemia (12). Accordingly, we found a higher proportion of overweight/obesity in women delivering a D-LGA infant (Table 1) compared with mothers of P-LGA infants. This association was found both in the GDM and non-GDM groups. In contrast to the findings in GDM offspring, D-LGA infants born to mothers without diabetes had increased risk of birth trauma and hypoglycemia. One might speculate that this difference is attributed to the lower rate of Cesarean section in the non-GDM cohort. One might speculate that D-LGA infants were more likely to be delivered by Cesarean section due to a higher absolute BW. However, it is well recognized that methods used for antenatal prediction of fetal macrosomia are considered inaccurate, and the odds of Cesarean section remained significantly increased even after adjusting for differences in absolute BW (data not shown).

In conclusion, the risk of composite neonatal morbidity is significantly increased in GDM offspring compared with infants born to mothers without diabetes. In pregnancies both with and without GDM, the risk of composite neonatal morbidity is comparable between P-LGA and D-LGA. The lack of difference observed between D-LGA and P-LGA may reflect other metabolic effects of GDM independent of neonatal body proportionality.

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M.P. conceived and designed the research, analyzed data, interpreted results, and drafted the manuscript. H.F. and D.P. interpreted results and critically revised the manuscript. U.H. acquired the data, interpreted results, and critically revised the manuscript. D.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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