Accelerated Fetal Growth Prior to Diagnosis of Gestational Diabetes Mellitus: A Prospective Cohort Study of Nulliparous Women

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

To determine whether fetal overgrowth precedes the diagnosis of gestational diabetes mellitus (GDM) and to quantify the interrelationships among fetal overgrowth, GDM, and maternal obesity.

RESEARCH DESIGN AND METHODS

We conducted a prospective cohort study of unselected nulliparous women and performed ultrasonic measurement of the fetal abdominal circumference (AC) and head circumference (HC) at 20 and 28 weeks of gestational age (wkGA). Exposures were diagnosis of GDM ≥28 wkGA and maternal obesity. The risk of AC >90th and HC-to-AC ratio <10th percentile was modeled using log-binomial regression, adjusted for maternal characteristics.

RESULTS

Of 4,069 women, 171 (4.2%) were diagnosed with GDM at ≥28 wkGA. There was no association between fetal biometry at 20 wkGA and subsequent maternal diagnosis of GDM. However, at 28 wkGA, there was an increased risk of AC >90th percentile (adjusted relative risk 2.05 [95% CI 1.37–3.07]) and HC-to-AC ratio <10th percentile (1.97 [1.30–2.99]). Maternal obesity showed similar associations at 28 wkGA (2.04 [1.62–2.56] and 1.46 [1.12–1.90], respectively). The combination of GDM and obesity was associated with an approximately fivefold risk of AC >90th (4.52 [2.98–6.85]) and approximately threefold risk of HC-to-AC ratio <10th percentile (2.80 [1.64–4.78]) at 28 wkGA. Fetal AC >90th percentile at 28 weeks was associated with an approximately fourfold risk of being large for gestational age at birth.

CONCLUSIONS

Diagnosis of GDM is preceded by excessive growth of the fetal AC between 20 and 28 wkGA, and its effects on fetal growth are additive with the effects of maternal obesity.

Gestational diabetes mellitus (GDM) is one of the most common acquired medical disorders of pregnancy (1), and the major complication of GDM is excessive fetal growth. Low- and middle-income countries have a GDM prevalence similar to that in high-income countries, although the prevalence is particularly high in Vietnam, India, Bangladesh, and Sri Lanka (2). Pregnancies affected by GDM carry an increased risk of adverse outcome for the mother and the offspring in the short term (1,3,4), and the

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offspring are at increased risk of childhood obesity in the long term (4). Large-scale randomized controlled trials (RCTs) have confirmed that screening and treatment for GDM are associated with improved short-term outcomes (5,6) but have failed to show reduced rates of childhood obesity (7,8). Current guidelines recommend screening women for GDM between 24 and 28 weeks of gestational age (wkGA) (1,3). In practice, many units screen at approximately 28 wkGA. The aims of the present analysis were *1*) to determine whether the onset of fetal overgrowth among women subsequently diagnosed with GDM preceded the normal time of screening for the condition and *2*) to determine the interrelationships between fetal overgrowth, GDM, and maternal obesity.

RESEARCH DESIGN AND METHODS

Design

The Pregnancy Outcome Prediction study was conducted at the Rosie Hospital, Cambridge, U.K., and has previously been described in detail (9,10). In brief, it was a prospective cohort study of nulliparous women with a viable singleton pregnancy who attended the hospital for their dating ultrasound scan between 14 August 2008 and 31 July 2012. Blood was obtained at the time of recruitment. Further participation in the study involved attending the National Institute for Health Research Cambridge Clinical Research Facility at ~20, ~28, and ~36 wkGA for blood sampling and performance of ultrasound scans. Outcome data were obtained by review of each woman's paper case record by research midwives and by linkage to the hospital's electronic databases. Ethics approval for the study was given by the Cambridgeshire 2 Research Ethics Committee (reference no. 07/H0308/163), and all participants provided written informed consent. The reporting of this study conforms to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

Analysis of Fetal Growth

The conduct and descriptive data of the research ultrasounds have previously been described in detail (9,10). In brief, gestational dating was performed using ultrasound, and 99.5% of these examinations were performed prior to 15 wkGA. The current analysis focuses on the results of fetal biometry at 20 and 28 wkGA. All scans were performed on a Voluson i (GE, Fairfield, CT). The data from the 20 wkGA scan were from the routine anomaly scan offered to all women, and these results were revealed to the women and clinical team. The data from the 28 wkGA scan were fetal biometry performed for the purposes of research, and these results were blinded. The fetal head circumference (HC) and abdominal circumference (AC) were measured using the ellipse function on the machine at the standard anatomical sites (11). We have previously shown that these measurements have low interobserver variability (10). To allow for minor variations in the exact timing of the 20 and 28 wkGA ultrasound scans, all fetal biometry was expressed as gestational age–adjusted SD scores (*z* scores), using the distribution of the measurements within the data set (10). The AC growth velocity was quantified as the difference between the AC *z* score at 28 wkGA and the AC *z* score at 20 wkGA. This approach accounts for nonlinear changes and the increasing variability of biometric measurements by gestational age and makes different measurements from different gestational ages comparable (12,13). *z* scores for HC, AC, and AC growth velocity were categorized into deciles, using the distribution within the study cohort. The highest decile of AC and AC growth velocity and the lowest decile of HC-to-AC ratio were defined as abnormal. Sex- and gestational age–corrected birth weight percentiles and *z* scores were calculated using a population-based U.K. reference (14).

Definitions

Maternal age was defined as age at recruitment. BMI was calculated using each woman's measured height and their measured weight on the day of their booking scan. Maternal obesity was defined as BMI $\geq$30 kg/m^2. Maternal weight gain was defined as the difference in measured weight at the time of the 28 wkGA scan and the booking scan. Maternal ethnicity was defined by self-report in a questionnaire administered at the 20 wkGA scan. Large for gestational age (LGA) was defined as a sex- and gestational age–specific birth weight percentile >90th.

Screening and Diagnosis of GDM

All pregnant women were offered screening at the first antenatal booking visit with a random plasma glucose. Women with random glucose >7.0 mmol/L (>126 mg/dL) were offered a 75-g oral glucose tolerance test (OGTT). Women were screened again at ~28 wkGA, first with a 50-g glucose challenge test (GCT), followed by a 75-g OGTT if the GCT was >7.7 mmol/L (>139 mg/dL), as previously described (15). Screening for GDM was usually performed on the same day as the 28-week ultrasound scan, and GDM diagnosis was made shortly after. Uptake of the GCT was >85% (the exact proportion could not be calculated, as some tests took place in primary care). Between 2008 and 2010, GDM diagnosis was based on diagnostic criteria adapted from the World Health Organization (WHO) (1999) recommendations: fasting, 1-h, and 2-h glucose levels >6.1 (110 mg/dL), 10.0 (180 mg/dL), or 7.8 mmol/L (140 mg/dL), respectively. From 2011 onwards, these were replaced with diagnostic criteria adapted from the International Association of Diabetes and Pregnancy Study Groups' recommendations: fasting, 1-h, and 2-h glucose levels >5.3 (95 mg/dL), 10.0 (180 mg/dL), or 8.5 mmol/L (153 mg/dL), respectively (16). Information on the subsequent treatment of GDM was obtained by individual review of each patient's clinical case record. Treatment was generally informed and monitored by home testing using a glucometer, with fasting and 1-h postprandial measurements made four times per day. All women diagnosed with GDM were offered a postpartum 2-h, 75-g fasting OGTT to exclude any ongoing glycemic dysregulation (impaired fasting hyperglycemia, impaired glucose tolerance, or type 2 diabetes). This allowed us to identify women who also had abnormal glucose tolerance outside pregnancy and, therefore, had nongestational glycemic dysregulation.

Exclusion Criteria

We excluded women who withdrew from the study, who were lost to follow-up, who failed to attend the 20 or 28 wkGA scan, who had preexisting diabetes or had GDM diagnosed prior to 28 wkGA, or had missing data on GDM or BMI. The women with GDM who could not be confirmed to have a normal postpartum

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OGTT were included in the main analysis, and the effect of excluding them was assessed in a sensitivity analysis.

Statistical Analysis

Numerical data were compared using a two-sample Wilcoxon rank sum test, and categorical data were compared using a Pearson χ^2 test with test for trend, as appropriate. The associations between the combination of GDM and obesity and the indicators of abnormal fetal growth were modeled using log-binomial regression to obtain adjusted relative risks. The relative risk of AC in the top decile at 28 wkGA associated with subsequent GDM was estimated in the whole study group and stratified by maternal obesity, the treatment used, and the diagnostic criteria used and confined to women with a normal postpartum OGTT. Nonlinearity was assessed using fractional polynomials, and interactions were tested using the likelihood ratio test. Missing covariate data were imputed using chained equations (17). All analyses were adjusted for the year of the 28 wkGA scan to take into account any temporal changes in the incidence, screening, diagnosis, or treatment of GDM. Analyses were performed with and without adjustment for maternal age, height, ethnicity, weight gain, and BMI, as appropriate. Finally, the relative risk of LGA at birth associated with the indicators of abnormal fetal growth was estimated in the group of women who were obese or had GDM diagnosed at ≥28 wkGA. All analyses used Stata, version 14.0.

RESULTS

Among 4,512 recruited women, a total of 4,305 attended for their 28 wkGA scan. (See Sovio et al. [10] for flow diagram.) Of these, 7 withdrew, 6 failed to attend their 20 wkGA scan, 188 delivered elsewhere, 14 had preexisting diabetes, 17 had GDM diagnosed prior to 28 wkGA, and 7 had missing data on GDM or BMI. A total of 236 (5.5%) of these women had one or more of the exclusion criteria, leaving a study group of 4,069, among whom 171 (4.2%) had a diagnosis of GDM at ≥28 wkGA. Women who subsequently developed GDM were older, were shorter, were more likely to be obese, gained slightly less weight, and were more likely to have induced labor and cesarean delivery (Table 1). Their babies were born slightly smaller but had higher birth weight *z* scores, and a higher proportion of them were LGA.

At 20 wkGA, there were no significant differences in fetal biometry associated with subsequent GDM; however, the risks of AC >90th and HC-to-AC ratio <10th percentile were increased in fetuses of obese mothers (Table 2). At 28 wkGA, subsequent GDM and maternal obesity were each associated with an ~2.0-fold risk of AC >90th and a 1.5- to 2.0-fold risk of HC-to-AC ratio <10th percentile. The effects of obesity and subsequent GDM were additive: the combination was associated with an almost fivefold risk of AC >90th and an almost threefold risk of HC-to-AC ratio <10th percentile at 28 wkGA. Subsequent GDM and maternal obesity were each associated with an increased risk of AC growth velocity >90th percentile, and the combination was associated with an almost threefold risk.

There were no interactions between the two exposures or between either exposure and any of the maternal covariates in their associations with fetal biometry (all $P > 0.05$). Of the 171 women with GDM, 123 (72%) attended for a postpartum 75-g fasting OGTT, and 116 of them had a normal result (fasting glucose <6.1 [110 mg/dL] and 2-h glucose <7.8 mmol/L [140 mg/dL]). The proportion of AC >90th percentile in the 116 women who had a normal postpartum OGTT was similar to the 55 women who could not be confirmed to have a normal postpartum OGTT (19.8 vs. 25.5%, $P = 0.4$). The relative risk of AC >90th percentile associated with subsequent GDM was similar when stratified by maternal obesity, the treatment used, and the diagnostic criteria used and when the analysis was confined to women with a normal postpartum OGTT (Fig. 1). Of the 4,069 women in the cohort, 749 (18.4%) had complete data on the result of the 75-g fasting OGTT. Of the 4,069 women, 194 (4.8%) were deemed to screen positive using the modified WHO (1999) criteria, whereas 142 (3.5%) screened positive using the modified International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria. There were 54 (1.3%) women who were screen positive using the modified WHO criteria but not the modified IADPSG criteria and two (<0.1%) women who were screen positive using the modified IADPSG criteria but not the modified WHO criteria.

Ultrasonic fetal biometry at 28 weeks identified pregnancies at increased risk of an LGA infant at delivery among the 672 women who were obese and/or had a diagnosis of GDM ≥28 wkGA. AC growth velocity >90th percentile was associated with a twofold risk of LGA (adjusted relative risk 1.87 [95% CI 1.05–3.35]), and AC >90th percentile was associated with a fourfold risk of LGA (3.86 [2.37–6.29]).

CONCLUSIONS

We found that excessive fetal growth preceded clinical diagnosis of GDM. At 28 wkGA, the risks of AC >90th and HC-to-AC ratio <10th percentile were doubled. No differences were apparent at the time of the 20 wkGA scan. Moreover, fetuses of women who were subsequently diagnosed with GDM had increased growth velocity of the AC between 20 and 28 wkGA. These data suggest that the onset of fetal growth disorder in GDM predates the usual time of screening. The current observations cannot be explained by misclassification of nongestational glycemic dysregulation as GDM because the results were very similar when confined to women with confirmed normal postpartum glucose tolerance. A slightly different pattern was observed for maternal obesity, as the fetuses of obese women already demonstrated increased risks of AC >90th and HC-to-AC ratio <10th percentile at 20 wkGA. However, obesity was also associated with accelerated growth between 20 and 28 wkGA. Moreover, the effects of obesity and GDM on fetal growth were additive. Consequently, at 28 wkGA, the fetuses of obese women who had a subsequent diagnosis of GDM had an almost fivefold risk of AC >90th and an almost threefold risk of HC-to-AC ratio <10th percentile. Finally, among the population of women with obesity and/or GDM, fetal AC >90th percentile at 28 weeks and increased fetal AC growth velocity between 20 and 28 weeks were associated with an increased risk of macrosomia at delivery.

The U.S. Preventive Services Task Force and the American College of Obstetricians and Gynecologists in the U.S. (1,3) and the National Institute for Health and Care Excellence in the U.K. (18) all recommend that biochemical testing for

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Table 1—Characteristics of the study population (n = 4,069) by GDM

	No GDM (n = 3,898)	GDM (n = 171)	P*
Maternal characteristics			
Age, years	30 (27–33)	32 (28–35)	<0.001
<20	145 (3.7)	2 (1.2)	
20–24.9	524 (13)	17 (9.9)	
25–29.9	1,216 (31)	42 (25)	<0.001
30–34.9	1,445 (37)	64 (37)	
35–39.9	502 (13)	37 (22)	
≥40	66 (1.7)	9 (5.3)	
Age stopped FTE, years	21 (18–23)	21 (18–23)	0.18
<19	1,306 (34)	62 (36)	
19–22	1,352 (35)	56 (33)	0.37
≥23	1,128 (29)	45 (26)	
Missing	112 (2.9)	8 (4.7)	
Height, cm	165 (161–170)	164 (160–167)	0.001
<160	699 (18)	42 (25)	
160–164.9	1,064 (27)	52 (30)	0.003
165–169.9	1,157 (30)	48 (28)	
≥170	978 (25)	29 (17)	
BMI, kg/m^2	24 (22–27)	26 (24–32)	<0.001
<25	2,324 (60)	56 (33)	
25–29.9	1,073 (28)	63 (37)	
30–34.9	366 (9.4)	23 (13)	<0.001
35–39.9	94 (2.4)	20 (12)	
≥40	41 (1.1)	9 (5.3)	
Weight gain between 12 and 28 wkGA scans, kg†	8 (6–10)	7 (5–10)	0.04
Ethnicity			
White	3,625 (93)	154 (90)	
Indian/Pakistani/Bangladeshi	71 (1.8)	6 (3.5)	
African Caribbean/African	22 (0.6)	0 (0.0)	0.33
Far/South East Asian	62 (1.6)	3 (1.8)	
Other/mixed	55 (1.4)	4 (2.3)	
Missing	63 (1.6)	4 (2.3)	
Birth characteristics			
Birth weight, g	3,425 (3,110–3,745)	3,295 (3,015–3,550)	<0.001
Birth weight, z score	−0.16 (−0.73 to 0.40)	0.04 (−0.45 to 0.60)	<0.001
Birth weight, centile			
Small (<10th)	356 (9.1)	7 (4.1)	
Normal (10th–90th)	3,367 (86)	151 (88)	0.004
Large (>90th)	174 (4.5)	13 (7.6)	
Missing	1 (<0.1)	0 (0.0)	
Gestational age, completed weeks	40.4 (39.3–41.1)	38.9 (38.3–39.6)	<0.001
<37	158 (4.1)	7 (4.1)	
37–38	550 (14)	81 (47)	<0.001
39	787 (20)	54 (32)	
40	1,134 (29)	24 (14)	
≥41	1,269 (33)	5 (2.9)	
Fetal sex			
Male	1,952 (50)	90 (53)	0.52
Female	1,945 (50)	81 (47)	
Missing	1 (<0.1)	0 (0.0)	
Induction of labor	1,177 (30)	115 (67)	<0.001
Mode of delivery			
Spontaneous vaginal	1,927 (49)	61 (36)	
Assisted vaginal	915 (23)	43 (25)	
Intrapartum cesarean	674 (17)	33 (19)	<0.001
Prelabor cesarean	373 (9.6)	33 (19)	
Missing	9 (0.2)	1 (0.6)	

Data are expressed as median (interquartile range) or n (%) as appropriate. For fields where there is no category labeled "missing," data were 100% complete. FTE, full-time education. *P values are for difference between groups calculated using the two-sample Wilcoxon rank sum (Mann-Whitney) test for continuous variables and the Pearson χ^2 test for categorical variables, with a trend test as appropriate. The missing category was not included in statistical tests. †The difference in weight gain between the 12 and 28 wkGA scans was tested additionally using linear regression. Without BMI adjustment, the difference in weight gain associated with GDM was −0.6 kg (95% CI −1.1 to −0.1, P = 0.01), and after BMI adjustment it was −0.3 kg (95% CI −0.8 to 0.2, P = 0.20).

GDM take place between 24 and 28 wkGA. Practice differs internationally, and between units within countries, about whether biochemical screening is universal, using a 50-g GCT, or targeted at high-risk women using a 75-g fasting OGTT. We use the former approach, as previously described (15). Whichever method is used, units typically screen women at 28 wkGA. Our data suggest that fetal growth is already abnormal at 28 wkGA in women subsequently diagnosed with GDM. Consequently, our data suggest that screening prior to 28 wkGA may be one approach to improving the short- and long-term outcomes of pregnancies complicated by GDM. The U.S. Preventive Services Task Force has previously observed that there is an absence of evidence regarding the effects of earlier screening (1). Such an approach may be particularly likely to improve outcomes among obese women, as fetal growth was already abnormal by 20 wkGA among these women in the cohort. In fact, the current data indicate that any intervention aimed at reducing the risk of LGA in the infants of obese women may need to be implemented before 20 wkGA. Finally, the offspring of women with GDM are at increased risk of childhood obesity (4), but RCTs have failed to demonstrate that screening and intervention in pregnancy reduce this risk (7,8). The current data suggest a possible explanation, namely, that screening and intervention are taking place when the effects of GDM are already manifested in the fetus. Hence, the current findings indicate that earlier screening and intervention for GDM may result in better short- and long-term outcomes. Testing this hypothesis would be an appropriate focus for future RCTs.

The main strengths of the current study are that it was prospective and that ultrasonic fetal biometry was performed at 20 and 28 wkGA in a large cohort of unselected nulliparous women. Many other studies of fetal growth in both preexisting diabetes and GDM are confined to women who had a diagnosis of diabetes (19,20). It is clearly problematic to define abnormal growth related to diabetes in the absence of data on fetal growth in women without diabetes. Further strengths of the study are that we had detailed clinical information on the individual women. Hence, we were able to analyze the results in

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Table 2—Association among GDM, obesity, and fetal growth indicators

Growth outcomes†	*N**	Exposure: obesity only		Exposure: GDM only		Exposure: GDM and obesity	
		Adjusted for year	Fully adjusted‡	Adjusted for year	Fully adjusted‡	Adjusted for year	Fully adjusted‡
AC at 20 wkGA >90th percentile	4,052	1.55 (1.23–1.96)	1.63 (1.29–2.06)	0.89 (0.49–1.63)	0.93 (0.51–1.70)	1.82 (1.00–3.33)	2.01 (1.10–3.69)
HC:AC at 20 wkGA <10th percentile$	3,994	1.78 (1.41–2.24)	1.80 (1.42–2.27)	1.05 (0.59–1.86)	1.08 (0.61–1.93)	1.78 (0.93–3.39)	1.93 (1.01–3.70)
ACGV 20–28 wkGA >90th percentile	4,048	1.37 (1.06–1.77)	1.40 (1.08–1.81)	1.72 (1.12–2.64)	1.77 (1.15–2.71)	2.55 (1.54–4.25)	2.78 (1.67–4.65)
AC at 28 wkGA >90th percentile	4,065	1.86 (1.48–2.34)	2.04 (1.62–2.56)	2.06 (1.38–3.09)	2.05 (1.37–3.07)	3.89 (2.54–5.95)	4.52 (2.98–6.85)
HC:AC at 28 wkGA <10th percentile$	3,861	1.37 (1.05–1.78)	1.46 (1.12–1.90)	2.07 (1.37–3.14)	1.97 (1.30–2.99)	2.64 (1.54–4.50)	2.80 (1.64–4.78)

Data are associations expressed as relative risks (95% CI), referent to nonobese women with no diagnosis of GDM. *The sample size in the different analyses varies between 3,861 and 4,065, principally due to missing values in biometric head measurements, which are dependent on fetal position. ACGV, AC growth velocity; HC:AC, HC-to-AC ratio. †Growth outcomes were dichotomized as >90th percentile (AC and AC growth velocity) or <10th percentile (HC:AC). The *z* score cutoff points were 1.2721 for AC at 20 wkGA, −1.2320 for HC-to-AC ratio at 20 wkGA, 1.2851 for AC growth velocity at 20–28 wkGA, 1.2851 for AC at 28 wkGA, and −1.2373 for HC-to-AC ratio at 28 wkGA. The mean (SD) gestational ages of the scans were 20.4 (0.5) and 28.3 (0.4) wkGA. ‡Adjusted for the year of the 28 wkGA scan, maternal age, height, ethnicity (Indian/Pakistani/Bangladeshi vs. others), and weight gain. (All maternal characteristics listed in Table 1 were considered as potential confounders.) Multiple imputation was performed using chained equations (m = 10 imputations). Predictive mean matching (k = 10 donors) and logistic regression were used in the imputation of weight gain and ethnicity, respectively. For improvement of the imputation accuracy of the covariates, exposures and outcomes were also included in the imputation model, along with age when the woman stopped full-time education, since this variable was associated with weight gain and ethnicity. $Significantly reduced HC-to-AC ratios were not due to smaller HC.

relation to the treatment used for GDM and in relation to the results of retesting of women in the postpartum period. Moreover, we had detailed information on maternal covariates, such as anthropometry, weight gain, ethnicity, and age. The incidence of GDM in our cohort was consistent with U.K. rates of 3–5% when universal biochemical screening is performed (21). However, the women in the cohort were mostly of white European ancestry. We did not observe any statistically significant interactions between ethnicity and the exposures; however, the numbers were small. The current study recruited women over a 4.5-year period. During this period of time, there were changes in the definition of GDM. In the study cohort, 4.8% of the women were deemed screen positive using the modified WHO (1999) criteria, whereas 3.5% screened positive using the modified IADPSG criteria. There were 54 (1.3%) women who screened positive using the modified WHO (1999) criteria but not the modified IADPSG criteria and two (<0.1%) women who had the opposite discrepancy. However, the results were virtually identical when the association was studied by year of the 28 wkGA scan. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (22) demonstrated a continuum in the risk of LGA in relation to hyperglycemia. The similar findings in relation to AC comparing the modified WHO and the modified IADPSG criteria may reflect the fact that women just below a given threshold are very similar to those who lie just above it. Finally, the use of the 50-g GCT approach is estimated to have a sensitivity of 74% for GDM (23). It follows that some of the women defined as normal in the cohort may have had undiagnosed GDM. Misclassification tends to lead to underestimates of the strength of true associations, and it is possible that the associations would have been even stronger had all women been screened using a fasting 75-g OGTT.

Diagnosis of GDM ≥28 wkGA is preceded by excessive fetal growth between 20 and 28 wkGA. Currently, biochemical testing for GDM typically takes place at ~28 wkGA. As fetal growth is already abnormal at this stage, it is plausible that earlier screening and intervention may result in lower risks of adverse outcomes.

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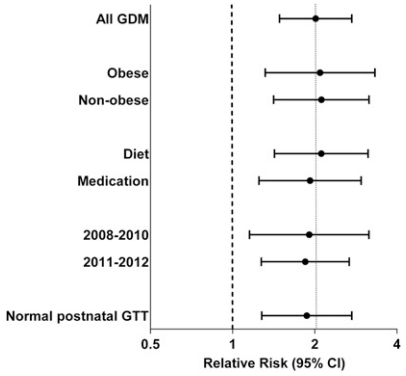

Figure 1—Stratified analysis of the association between GDM and abdominal circumference (AC) >90th percentile at 28 wkGA. Points are adjusted relative risks, and bars are 95% CI. Stratification was by obesity (BMI ≥30 kg/m^2), GDM treatment type (diet only or medication [insulin or metformin]), and year of the 28 wkGA scan (2008–2010 diagnoses were based on a modified version of the 1999 WHO criteria: fasting, 1-h, and 2-h glucose levels >6.1 mmol/L [110 mg/dL], 10.0 mmol/L [180 mg/dL], or 7.8 mmol/L [140 mg/dL], respectively, and 2011–2012 diagnoses were based on the modified IADPSG criteria: thresholds 5.3 mmol/L [95 mg/dL], 10.0 mmol/L [180 mg/dL], or 8.5 mmol/L [153 mg/dL], respectively). One hundred sixteen women had a diagnosis of GDM in the pregnancy, attended for a 75-g fasting OGTT at ~6 weeks postpartum, and had a normal result (fasting glucose <6.1 [110 mg/dL] and a 2-h glucose <7.8 mmol/L [140 mg/dL]). Analyses were adjusted for the year of the 28 wkGA scan, maternal age, height, ethnicity (Indian/Pakistani/Bangladeshi vs. others), weight gain, and BMI, as appropriate (where the analysis was not stratified by the respective variable). GTT, glucose tolerance test.

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Duality of Interest. H.R.M. sits on a scientific advisory board for Medtronic (insulin pump manufacturer). G.C.S.S. receives/has received research support from GE (supply of two diagnostic ultrasound systems used in the current study). Other commercial interests, not directly relevant to the current study, for G.C.S.S. are as follows: support from Roche (supply of equipment and reagents for biomarker studies, ~£600,000 in value) and from GlaxoSmithKline (GSK) (~£200,000) for a project to study effects of retosiban in human myometrium, payment to attend advisory boards by GSK and Roche, and payment for consultant work for GSK. G.C.S.S. is named inventor in a patent submitted by GSK (U.K.) for novel application of an existing GSK compound for the prevention of preterm birth (PCT/EP2014/062602). No other potential conflicts of interest relevant to this article were reported.

Author Contributions. U.S., H.R.M., and G.C.S.S. analyzed and interpreted data, critically revised the manuscript for important intellectual content, and gave final approval of the version to be published. U.S. and G.C.S.S. drafted the manuscript. G.C.S.S. developed the study concept and design. G.C.S.S. 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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References

1. Moyer VA; U.S. Preventive Services Task Force. Screening for gestational diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014; 160:414–420

2. Kanguru L, Bezawada N, Hussein J, Bell J. The burden of diabetes mellitus during pregnancy in low- and middle-income countries: a systematic review. Glob Health Action 2014;7:23987

3. Committee on Practice Bulletins–Obstetrics. Practice Bulletin No. 137: Gestational diabetes mellitus. Obstet Gynecol 2013;122:406–416

4. Hartling L, Dryden DM, Guthrie A, et al. Screening and diagnosing gestational diabetes mellitus. Evid Rep Technol Assess (Full Rep) 2012:1–327

5. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477–2486

6. Landon MB, Spong CY, Thom E, et al.; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009;361:1339–1348

7. Gillman MW, Oakey H, Baghurst PA, Volkmer RE, Robinson JS, Crowther CA. Effect of treatment of gestational diabetes mellitus on obesity in the next generation. Diabetes Care 2010;33: 964–968

8. Landon MB, Rice MM, Varner MW, et al.; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network. Mild gestational diabetes mellitus and long-term child health. Diabetes Care 2015;38:445–452

9. Pasupathy D, Dacey A, Cook E, Charnock-Jones DS, White IR, Smith GC. Study protocol. A prospective cohort study of unselected primiparous women: the pregnancy outcome prediction study. BMC Pregnancy Childbirth 2008;8:51

10. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. Lancet 2015;386:2089–2097

11. Loughna P, Chitty LS, Evans AL, Chudleigh T. Fetal size and dating: charts recommended for clinical obstetric practice. Ultrasound 2009;17: 161–167

12. Altman DG, Chitty LS. Charts of fetal size: 1. Methodology. Br J Obstet Gynaecol 1994;101: 29–34

13. Papageorghiou AT, Ohuma EO, Altman DG, et al.; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet 2014;384: 869–879

14. Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. Arch Dis Child 1995;73:17–24

15. Church D, Halsall D, Meek C, Parker RA, Murphy HR, Simmons D. Random blood glucose measurement at antenatal booking to screen for overt diabetes in pregnancy: a retrospective study. Diabetes Care 2011;34:2217–2219

16. Metzger BE, Gabbe SG, Persson B, et al.; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676–682

17. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;30: 377–399

18. National Collaborating Centre for Women's and Children's Health. *NICE Guideline: Diabetes in Pregnancy*. London, U.K., RCOG Press, 2008

19. Schaefer-Graf UM, Kjos SL, Kilavuz O, et al. Determinants of fetal growth at different periods of pregnancies complicated by gestational diabetes mellitus or impaired glucose tolerance. Diabetes Care 2003;26:193–198

20. Neff KJ, Walsh C, Kinsley B, Daly S. Serial fetal abdominal circumference measurements in predicting normal birth weight in gestational diabetes mellitus. Eur J Obstet Gynecol Reprod Biol 2013;170:106–110

21. Fraser R, Farrell T. Diabetes. In *High Risk Pregnancy: Management Options*. 4th ed. James D, Ed. St. Louis, Elsevier, 2011, p. 795–812

22. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002

23. van Leeuwen M, Louwerse MD, Opmeer BC, et al. Glucose challenge test for detecting gestational diabetes mellitus: a systematic review. BJOG 2012;119:393–401

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