Accelerated fetal growth prior to diagnosis of gestational diabetes mellitus: a prospective cohort study of nulliparous women

Running title: Fetal overgrowth predates GDM diagnosis

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Abstract

Objectives To determine whether fetal overgrowth preceded the diagnosis of GDM, and to quantify the inter-relationships between 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 wkGA. Exposures were diagnosis of GDM ≥28 wkGA and maternal obesity. The risk of AC >90th and HC:AC ratio <10th percentile were modelled using log-binomial regression, adjusted for maternal characteristics.

Results 171 (4.2%) of 4069 women 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 (adjusted relative risk [95% CI]) of AC >90th percentile (2.05 [1.37 to 3.07]) and HC:AC ratio <10th percentile (1.97 [1.30 to 2.99]). Maternal obesity showed similar associations at 28 wkGA (2.04 [1.62 to 2.56] and 1.46 [1.12 to 1.90], respectively). The combination of GDM and obesity was associated with ~5-fold risk of AC >90th (4.52 [2.98 to 6.85]) and a ~3-fold risk of HC:AC ratio <10th percentile (2.80 [1.64 to 4.78]) at 28 wkGA. Fetal AC >90th percentile at 28 weeks was associated with ~4-fold 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 similar prevalence of GDM compared to 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 offspring are at increased risk of childhood obesity in the long term.[4] Large scale randomized controlled trials have confirmed that screening and treatment for GDM is 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 to 28 weeks of gestational age (wkGA).[1;3] In practice, many units screen at around 28 wkGA. The aims of the present analysis were (1) to determine whether the onset of fetal over-growth among women subsequently diagnosed with GDM preceded the normal time of screening for the condition, and (2) to determine the inter-relationships between fetal over-growth, GDM and maternal obesity.

Methods

Design

The Pregnancy Outcome Prediction study was conducted at the Rosie Hospital, Cambridge (UK) and has been previously 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 14/08/2008 and 31/07/2012. Blood was obtained at the time of recruitment. Further participation in the study involved attending the NIHR 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. Ethical approval for the study was given by the Cambridgeshire 2 Research Ethics Committee (reference number 07/H0308/163) and all participants provided written informed consent. The reporting of this study conforms to the STROBE (The Strengthening the Reporting of Observational Studies in Epidemiology) statement.

Analysis of fetal growth

The conduct and descriptive data of the research ultrasounds are described in detail elsewhere.[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, USA). 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 inter-observer 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 standard deviation scores (z scores), using the distribution of the measurements within the dataset.[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 categorised into deciles, using the distribution within the study cohort. The highest decile of AC and AC growth velocity and the lowest decile of HC:AC ratio were defined as abnormal. Sex and gestational age corrected birth weight percentiles and z scores were calculated using a population-based UK reference.[14]

Definitions

Maternal age was defined as age at recruitment. Body mass index (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 ≥30kg/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 >7.0mmol/l (>126mg/dl) were offered a 75g oral glucose tolerance test (OGTT). Women were screened again at ~28 wkGA, firstly with a 50g glucose challenge test (GCT), followed by a 75g OGTT if the GCT was >7.7mmol/l (>139mg/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 that. 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 WHO (1999) recommendations: fasting, 1-hour and 2-hour glucose levels greater than 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-hour and 2-hour glucose levels greater than 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-hour post-prandial measurements made four times per day. All women diagnosed with GDM were offered a post-partum 2 hour, 75g fasting OGTT to exclude any ongoing glycaemic dysregulation (impaired fasting hyperglycaemia, impaired glucose tolerance or type 2 diabetes mellitus). This allowed us to identify women who also had abnormal

glucose tolerance outside pregnancy and, therefore, had non-gestational glycaemic 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 pre-existing 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 post-partum 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 Chi-square test with test for trend, as appropriate. The associations between the combination of GDM and obesity and the indicators of abnormal fetal growth were modelled using log-binomial regression to obtain adjusted relative risks. The relative risk of AC in the top decile at 28wkGA associated with subsequent GDM was estimated in the whole study group and stratified by maternal obesity, the treatment used, the diagnostic criteria employed, and confined to women with a normal post-partum OGTT. Non-linearity 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 and/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 women had pre-existing diabetes, 17 women had GDM diagnosed prior to 28 wkGA and 7 women 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 ≥28 wkGA. Women who subsequently developed GDM were older, shorter, more likely to be obese, gained slightly less weight, and were more likely to have induced labour and caesarean 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: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 approximate 2-fold risk of AC >90th and a 1.5 to 2-fold risk of HC:AC ratio <10th percentile. The effects of obesity and subsequent GDM were additive: the combination was associated with an almost 5-fold risk of AC >90th and an almost 3-fold risk of HC: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 3-fold 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 post-partum 75g fasting OGTT, and 116 of them had a normal result (fasting glucose <6.1 [110 mg/dl] and a 2 hour glucose <7.8 mmol/l [140 mg/dl]). The proportion of AC >90th percentile in the 116 women who had a normal post-partum OGTT was similar to the 55 women who could not be confirmed to have a normal post-partum OGTT (19.8% versus 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, the diagnostic criteria employed, and when the analysis was confined to women with a normal post-partum OGTT (Figure 1). Of the 4,069 women in the cohort, 749 (18.4%) had complete data on the result of the 75g fasting OGTT. 194 (4.8%) of the 4,069 women were deemed screen positive using the modified WHO (1999) criteria whereas 142 (3.5%) screened positive using the modified 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 weeks. AC growth velocity >90th percentile was associated with a 2-fold risk (adjusted relative risk [95% CI]) of LGA (1.87 [1.05 to 3.35]) and AC >90th percentile were associated with a 4-fold risk of LGA (3.86 [2.37 to 6.29]).

Discussion

We found that excessive fetal growth preceded clinical diagnosis of GDM. At 28 wkGA, the risks of AC >90th and HC: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 non-gestational glycaemic 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: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 5-fold risk of AC >90th and an almost 3-fold risk of HC:AC ratio <10th percentile. Finally, among the population of women with obesity and/or GDM, fetal AC >90th 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 & Gynecologists in the US,[1;3] and the National Institute for Health and Care

Excellence in the UK,[18] all recommend that biochemical testing for GDM takes place between 24 and 28 wkGA. Practice differs internationally, and between units within countries, about whether biochemical screening is universal, using a 50g GCT, or targeted at high risk women using a 75g fasting OGTT. We use the former approach, as previously described.[15] Whichever method is employed, 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 reduces this risk.[7;8] The current data suggest a possible explanation, namely, that screening and intervention is 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 randomised controlled trials.

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 pre-existing and gestational diabetes 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 non-diabetic women. Further strengths of the study are that we had detailed clinical information on the individual women. Hence, we were able to analyse the results in relation to the treatment used for GDM, and in relation to the results of re-testing of women in the post-partum 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 UK 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 present 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 HAPO study[22] demonstrated a continuum in the risk of LGA in relation to hyperglycaemia. 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 50g 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 75g OGTT.

Conclusions

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 around 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.

Author Contributions

Study concept and design: Smith. Analysis and interpretation of data: Sovio, Murphy, Smith. Drafting of the manuscript: Sovio, Smith. Critical revision of the manuscript for important intellectual content: Sovio, Murphy, Smith. Final approval of the version to be published: Sovio, Murphy, Smith. Smith is the guarantor.

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None of the authors has a directly relevant competing interest. Two authors have commercial interests in other areas. Murphy sits on a scientific advisory board for Medtronic (insulin pump manufacturer). Smith receives/has received research support from GE (supply of two diagnostic ultrasound systems used in the present study). Other commercial interests, not directly relevant to the present study are: support from Roche (supply of equipment and reagents for biomarker studies, ~£600,000 in value) and from GSK (~£200,000) project to study effects of retosiban in human myometrium). Smith has been paid to attend advisory boards by GSK and

Roche. Smith has acted as a paid consultant to GSK. Smith is named inventor in a patent submitted by GSK (UK), for novel application of an existing GSK compound for the prevention of preterm birth (PCT/EP2014/062602).

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Table 1. Characteristics of the study population by gestational diabetes mellitus (GDM), n=4,069.

Characteristic	No GDM (n=3,898)	GDM (n=171)	P Value*
Maternal characteristics			
Age, years	30 (27 to 33)	32 (28 to 35)	<0.001
<20	145 (3.7)	2 (1.2)	
20 to 24.9	524 (13)	17 (9.9)	
25 to 29.9	1216 (31)	42 (25)	<0.001
30 to 34.9	1445 (37)	64 (37)	
35 to 39.9	502 (13)	37 (22)	
≥40	66 (1.7)	9 (5.3)	
Age stopped FTE, years	21 (18 to 23)	21 (18 to 23)	0.18
<19	1306 (34)	62 (36)	
19 to 22	1352 (35)	56 (33)	0.37
≥23	1128 (29)	45 (26)	
Missing	112 (2.9)	8 (4.7)	
Height, cm	165 (161 to 170)	164 (160 to 167)	0.001
<160	699 (18)	42 (25)	
160 to 164.9	1064 (27)	52 (30)	0.003
165 to 169.9	1157 (30)	48 (28)	
≥170	978 (25)	29 (17)	
BMI, kg/m^2	24 (22 to 27)	26 (24 to 32)	<0.001
<25	2324 (60)	56 (33)	
25 to 29.9	1073 (28)	63 (37)	
30 to 34.9	366 (9.4)	23 (13)	<0.001
35 to 39.9	94 (2.4)	20 (12)	
≥40	41 (1.1)	9 (5.3)	
Weight gain from 12 to 28 wkGA scan, kg†	8 (6 to 10)	7 (5 to 10)	0.04
Ethnicity			
White	3625 (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	3425 (3110 to 3745)	3295 (3015 to 3550)	<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)	3367 (86)	151 (88)	0.004
Large (>90th)	174 (4.5)	13 (7.6)	
Missing	1 (<0.1)	0 (0.0)	
Gestational age,	40.4 (39.3 to 41.1)	38.9 (38.3 to 39.6)	<0.001

completed weeks			
<37	158 (4.1)	7 (4.1)	
37-38	550 (14)	81 (47)	<0.001
39	787 (20)	54 (32)	
40	1134 (29)	24 (14)	
≥41	1269 (33)	5 (2.9)	
Fetal sex			
Male	1952 (50)	90 (53)	0.52
Female	1945 (50)	81 (47)	
Missing	1 (<0.1)	0 (0.0)	
Induction of labour	1177 (30)	115 (67)	<0.001
Mode of delivery			
Spontaneous vaginal	1927 (49)	61 (36)	
Assisted vaginal	915 (23)	43 (25)	
Intrapartum caesarean	674 (17)	33 (19)	<0.001
Pre-labour caesarean	373 (9.6)	33 (19)	
Missing	9 (0.2)	1 (0.6)	

Data are expressed as median (IQR) or n (%) as appropriate.
**P-values are for difference between groups calculated using the two-sample Wilcoxon rank-sum (Mann-Whitney) test for continuous variables and the Pearson Chi-square test for categorical variables, with trend test as appropriate. The missing category was not included in statistical tests.*
†The difference in weight gain from 12 to 28 wkGA scan 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 kg, p=0.01) and after BMI adjustment it was -0.3 kg (95%CI: -0.8 to +0.2 kg, p=0.20).
For fields where there is no category labelled "missing", data were 100% complete.
FTE denotes full time education, BMI denotes body mass index.

Table 2. The association between gestational diabetes mellitus (GDM), obesity and fetal growth indicators.

		Exposure: Obesity only RR (95% CI)*		**Exposure: GDM only** RR (95% CI)*		**Exposure: GDM and obesity** RR (95% CI)*	
Growth outcomes†	*N*	*Adjusted for year*	*Fully adjusted‡*	*Adjusted for year*	*Fully adjusted‡*	*Adjusted for year*	*Fully adjusted‡*
AC at 20 wkGA >90th percentile	4052	1.55 (1.23 to 1.96)	1.63 (1.29 to 2.06)	0.89 (0.49 to 1.63)	0.93 (0.51 to 1.70)	1.82 (1.00 to 3.33)	2.01 (1.10 to 3.69)
HC:AC at 20 wkGA <10th percentile$	3994	1.78 (1.41 to 2.24)	1.80 (1.42 to 2.27)	1.05 (0.59 to 1.86)	1.08 (0.61 to 1.93)	1.78 (0.93 to 3.39)	1.93 (1.01 to 3.70)
ACGV 20-28 wkGA >90th percentile	4048	1.37 (1.06 to 1.77)	1.40 (1.08 to 1.81)	1.72 (1.12 to 2.64)	1.77 (1.15 to 2.71)	2.55 (1.54 to 4.25)	2.78 (1.67 to 4.65)
AC at 28 wkGA >90th percentile	4065	1.86 (1.48 to 2.34)	2.04 (1.62 to 2.56)	2.06 (1.38 to 3.09)	2.05 (1.37 to 3.07)	3.89 (2.54 to 5.95)	4.52 (2.98 to 6.85)
HC:AC at 28 wkGA <10th percentile$	3861	1.37 (1.05 to 1.78)	1.46 (1.12 to 1.90)	2.07 (1.37 to 3.14)	1.97 (1.30 to 2.99)	2.64 (1.54 to 4.50)	2.80 (1.64 to 4.78)

**Associations were expressed as relative risks (RR) with 95% confidence intervals (CI), referent to non-obese women with no diagnosis of GDM.*

†Growth outcomes were dichotomized as >90th percentile (AC and ACGV) or <10th percentile (HC:AC).The z score cut-off points were 1.2721 for AC at 20 wkGA, -1.2320 for HC:AC at 20 wkGA, 1.2851 for ACGV 20-28 wkGA, 1.2851 for AC at 28 wkGA and -1.2373 for HC:AC at 28 wkGA. The mean (SD) gestational age 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 employed in the imputation of weight gain and ethnicity, respectively. To improve 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.

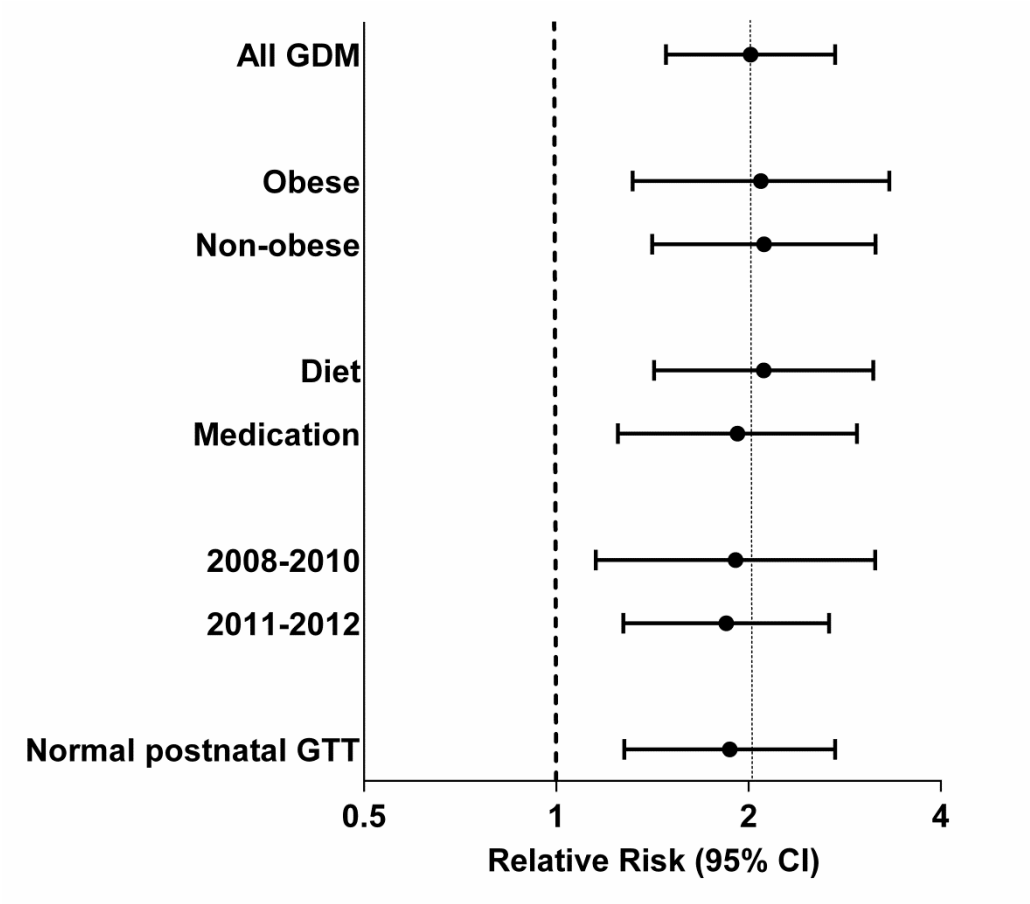
$Significantly reduced HC:AC ratios were not due to smaller HC.

AC denotes abdominal circumference, GV denotes growth velocity, HC denotes head circumference and wkGA denotes weeks of gestational age.

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.

Figure legend

Figure 1. Stratified analysis of the association between gestational diabetes mellitus (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≥30kg/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-hour and 2-hour glucose levels greater than 6.1 [110 mg/dl], 10.0 [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 [95 mg/dl], 10.0 [180 mg/dl] or 8.5 mmol/l [153 mg/dl], respectively). 116 women had a diagnosis of GDM in the pregnancy, attended for a 75g fasting OGTT at ~6 weeks postpartum, and had a normal result (fasting glucose <6.1 [110 mg/dl] and a 2 hour 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).


All GDM
Obese
Non-obese
Diet
Medication
2008-2010
2011-2012
Normal postnatal GTT
0.5
1
2
4
Relative Risk (95% CI)