ATLANTIC-DIP: Raised Maternal Body Mass Index (BMI) Adversely Affects Maternal and Fetal Outcomes in Glucose-Tolerant Women According to International Association of Diabetes and Pregnancy Study Groups (IADPSG) Criteria

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Context: Raised maternal body mass index (BMI) in association with hyperglycemia is associated with adverse pregnancy outcome. The contribution of raised BMI as an independent risk factor for adverse pregnancy outcome is of growing concern and increasing prevalence.

Objective: The aim of this study was to investigate the effects of raised maternal BMI on pregnancy outcome in glucose-tolerant women using the International Association of Diabetes and Pregnancy Study Groups criteria.

Participants and Setting: We studied a cohort of glucose-tolerant, pregnant women (n = 3656) who were attending antenatal obstetric clinics and were recruited to a universal screening program for gestational diabetes under the ATLANTIC-DIP partnership.

Design: We conducted a prospective observational study of pregnancy outcome. Maternal outcomes include glucose, delivery mode, pregnancy-induced hypertension, preeclampsia, antepartum hemorrhage, and postpartum hemorrhage. Fetal outcomes included birthweight, congenital malformation, fetal death, neonatal jaundice, hypoglycemia, and respiratory distress.

Results: Increasing maternal BMI was associated with adverse pregnancy outcomes: higher cesarean section rates, preeclampsia, pregnancy-induced hypertension, increased birth weight, and congenital malformation. The association of glucose with adverse pregnancy outcome was weak and did not interact with raised BMI. A BMI threshold of 28 kg/m^2 was associated with a significant rise in adverse pregnancy outcome.

Conclusions: Raised maternal BMI, within the overweight range, is associated with adverse pregnancy outcomes. These adverse effects of BMI occur independently of maternal glucose. It is apparent that pregnancy unmasks an underlying unhealthy metabolic milieu in obese and overweight women. **(*J Clin Endocrinol Metab* 97: E608–E612, 2012)**

In the United States, obesity has a prevalence of 21% in prepregnant females (1). Maternal obesity is associated with gestational diabetes mellitus (GDM) and adverse pregnancy outcomes, and it carries the highest risk for maternal mortality within the developed world (2–5). Most studies addressing the effects of maternal BMI on pregnancy outcomes include women with GDM (6, 7). Two studies investigating maternal BMI in glucose-toler-

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Abbreviations: CRT, Classification and regression tree; GDM, gestational diabetes mellitus; LGA, large for gestational age; LSCS, lower segment cesarean section by Pfannensteil incision; OGTT, oral glucose tolerance test; PET, preeclamptic toxemia; PIH, pregnancy-induced hypertension.

ant women used World Health Organization (WHO) criteria to diagnose GDM (8, 9). The International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommend reducing the diagnostic glucose threshold for GDM using the 75-g oral glucose tolerance test (OGTT) as follows: fasting, < 5.1 mmol/liter; 1 h, <10.0 mmol/liter; and 2 h, <8.5 mmol/liter (10). Therefore, many "glucose-tolerant" women included in previous studies now satisfy diagnostic criteria for GDM. There are no published data investigating maternal BMI and pregnancy outcome in glucose-tolerant women using the IADPSG criteria.

This study addresses raised maternal BMI in the setting of glucose tolerance within the Atlantic Diabetes in Pregnancy (ATLANTIC-DIP) cohort, using updated IADPSG criteria (10).

Subjects and Methods

Study design

ATLANTIC-DIP is a prospective observational study investigating universal screening for GDM across five antenatal centers in Ireland incorporating a population of 500,000. Data are collected from study entry until 12 wk postpartum.

A representative sample of our obstetric population including euthyroid women with normal glucose tolerance (IADPSG criteria) carrying singleton pregnancies was selected. Recruitment occurred from September 2006 to 2009. Normal glucose tolerance was based on IADPSG recommendations (10, 11). Data were recorded using an optimized digital database, DIAMOND (Hicom, Woking, UK). Research ethics committee approval was obtained from participating centers, and recruitment occurred under informed consent.

Maternal BMI was calculated at booking visit (14–24 wk), and OGTT (75 g) was performed at 24–28 wk. WHO BMI categorization was used: normal, 18.5–25 kg/m^2; overweight, 25–29.9 kg/m^2; obese, >30 kg/m^2 (grade I, 30–34.9 kg/m^2; grade II, 35–39.9 kg/m^2; grade III, >40 kg/m^2).

Maternal outcomes included delivery mode [vaginal (normal *vs.* instrumental), lower segment cesarean section by Pfannensteil incision (LSCS) (elective and emergency)]; pregnancy-induced hypertension (PIH; blood pressure >140/90 mm Hg on at least two occasions more than 6 h apart in women with normal booking blood pressure); preeclamptic toxemia (PET) [hypertension, proteinuria (>300 mg/24 h) onset >20 wk]; antepartum hemorrhage (APH; vaginal bleeding from 24 wk until term); and postpartum hemorrhage (bleeding >500 ml after vaginal delivery, >1000 ml post-LSCS] (8).

Fetal outcomes included birthweight, congenital malformations (ICD-10), shoulder dystocia, neonatal hypoglycemia, jaundice, respiratory distress, miscarriage (death <20 wk gestation), stillbirth (death >24 wk gestation), and neonatal death (within 1 wk of delivery) (8).

Statistical analysis

Maternal BMI was modeled as continuous and categorical variables to explain neonatal/fetal and maternal outcomes. Odds ratios were calculated using backward stepwise logistic regression, adjusted for age, parity, ethnicity, cigarette smoking, and venous glucose (PASW/SPSS 18.0; IBM, Chicago, IL). Covariates were selected based on previous data and using classification and regression tree (CRT) analysis (12, 13). BMI "risk" cutoffs were calculated using CRT (Fig. 1) with growth limits set at 0.05. Hypothesis testing was performed for multigroup comparisons using fixed-effects ANOVA and Tukey's *post hoc* comparison.

Data are expressed as means ± SD, adjusted odds ratios, relative risk, and 95% confidence intervals. Statistical significance is accepted when the 95% confidence interval does not contain 1.0 (regression analyses) or zero (multigroup comparisons). The significance level (α) was <0.05. Statistical assumptions were satisfied.

Results

Demographic factors

A total of 3656 women satisfied inclusion criteria. Mean maternal age was 31 ± 5.3 yr (range, 16–48). A total of 3428 (94%) were Caucasian; 291 (8%) smoked during pregnancy; 1582 (43%) had normal BMI; and 1369 (38%) were overweight. A total of 695 (19%) were obese, 482 (13%) were grade I obese; 168 (5%) were grade II obese, and 55 (1.5%) were grade III obese (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Effect of BMI on venous glucose

Maternal BMI correlated with glucose: fasting [r (1, 3654) = 0.220; P <0.001]; 60-min glucose [r (1, 3654) = 0.212; $P < 0.001$]; and 120-min glucose [r (1, 3654) = 0.149; $P < 0.001$].

Overweight and obese women had higher glucose compared with women with normal BMI: fasting [mean difference: overweight, 0.07 mmol/liter (0.49, 0.93); obese, 0.16 mmol/liter (0.13, 0.19); F (4, 3651) = 42.12; $P <$ 0.001], 60-min glucose [mean difference: overweight, 0.42 mmol/liter (0.32, 052); obese, 0.78 mmol/liter (0.66, 0.91); F (4, 3651) = 42.82; $P < 0.001$], and 120-min glucose [mean difference: overweight, 0.20 mmol/liter (0.13, 0.28); obese, 0.43 mmol/liter (0.34, 0.52); F (4, 3651) = 21.85; $P < 0.001$].

Effect of BMI on maternal blood pressure

Maternal BMI correlated with systolic blood pressure [r (1, 3191) = 0.235; $P < 0.001$] and diastolic blood pressure [r (1, 3187) = 0.166; P (two-tailed) <0.001].

Overweight and obese women had higher systolic blood pressure [mean difference: overweight, 3.24 mm Hg (2.11, 4.37); obese, 7.60 mm Hg (6.21, 8.99); F (4, 3188) = 45.92; $P < 0.001$] and diastolic blood pressure [mean difference: overweight, 1.89 mm Hg (0.92, 2.87); obese, 3.75 mm Hg (2.72, 4.78); F (4, 3184) = 23.86; $P < 0.001$].

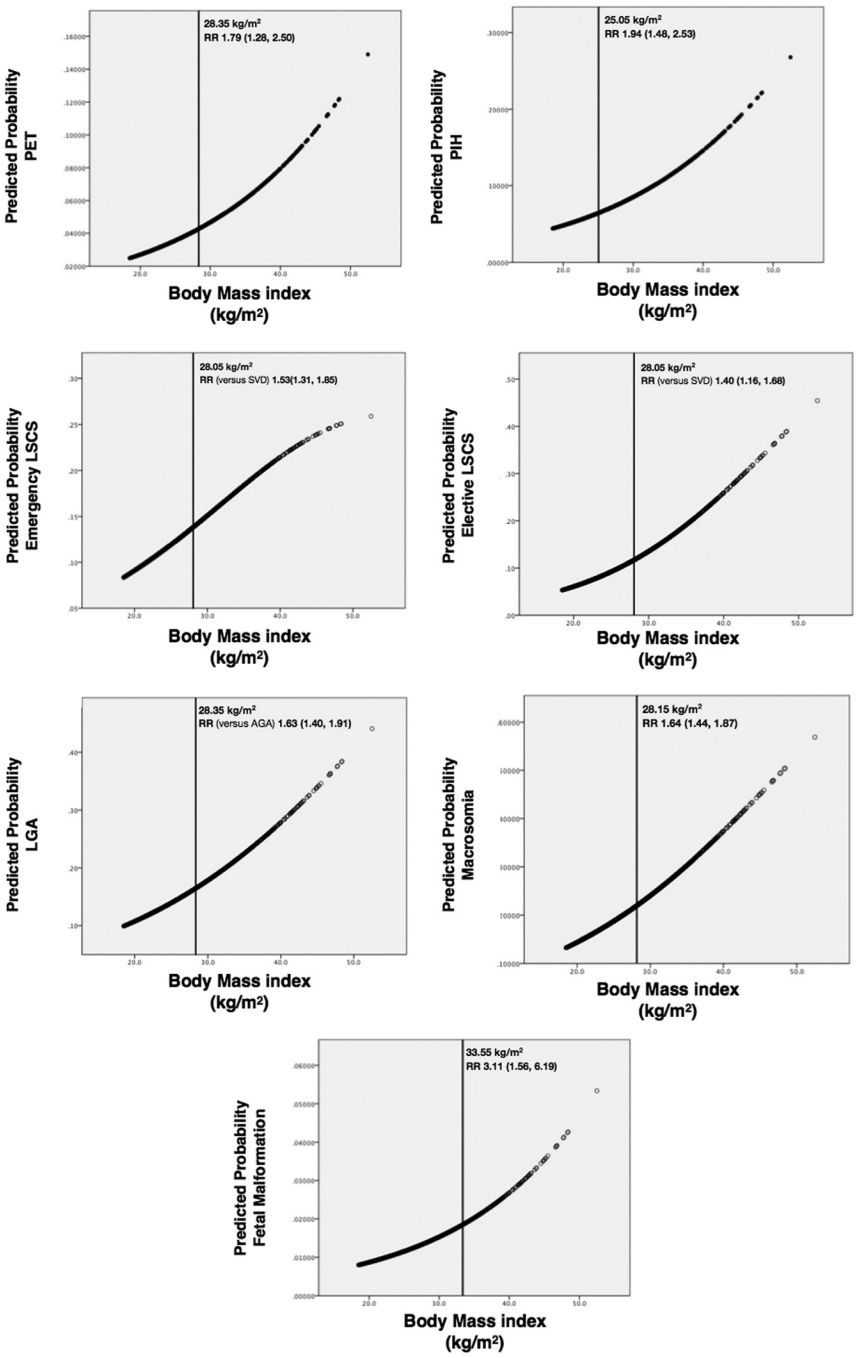

FIG. 1. Fitted logistic regression curves showing predicted probability plotted against BMI (in kg/m^2) for each outcome measure: PET, PIH, emergency LSCS, elective LSCS, LGA birthweight, macrosomia, and congenital malformation 1. The *vertical line* represents the threshold BMI at which risk becomes statistically significant. RR, Relative risk with 95% confidence intervals.

Maternal outcomes

Increasing maternal BMI showed higher odds for LSCS, PIH, and PET. There was no association between maternal BMI, antepartum hemorrhage, and postpartum hemorrhage.

Delivery mode

Elective LSCS was undertaken for 11.5% of overweight mothers and 18.5% of obese mothers, compared with 7.1% of mothers with normal BMI; 13.4% of overweight and 17.4% of obese mothers had emergency LSCS, compared with 10.6% of mothers with normal BMI. Emergency LSCS was most commonly undertaken consequent to failure of induction, labor progression, or instrumentation and fetal distress. Elective LSCS was most commonly undertaken due to abnormal fetal lie or prior history of emergency LSCS. Maternal glucose at 60 min was associated with emergency LSCS, but maternal glucose and elective LSCS were not associated (Table 1).

PIH occurred in 4.8% of normal BMI, 8.3% of overweight, and 17.8% of obese mothers and increased across obesity subcategories from 16.3–24.6% (Table 1).

PET occurred in 2.9% of mothers with normal BMI and in 4.2% of overweight and 6.2% of obese mothers (Table 1).

Fetal/neonatal outcomes

Birthweight correlated with maternal BMI [r (1, 3523) = 0.133; $P < 0.001$] and was higher in infants born to overweight mothers [mean difference, 0.09 kg (0.05, 0.13)] and obese mothers [mean difference, 0.18 kg (0.13, 0.23)] when compared with offspring of women with normal BMI [F (4, 3520) = 13.39; $P < 0.001$].

Twenty-two percent of infants born to obese mothers and 16% born to overweight mothers were large for gestational age (LGA), compared with 12% born to mothers with normal BMI. LGA birthweight was associated with fasting and 60-min glucose (Table 1).

A total of 20.9% of infants born to overweight mothers and 27.3% born to obese mothers were macrosomic, compared with 15% of infants born to mothers with normal BMI. Fasting glucose was associated with macrosomia (Table 1).

Congenital malformation

Two percent of infants born to obese mothers had a congenital malformation compared with 0.8% of infants born to mothers with normal BMI. Maternal glucose had no association. The main congenital malformations were talipes equinovarus, facial defects, and cardiovascular abnormality (Table 1).

TABLE 1. Effect of gestational BMI and glucose on pregnancy outcome

	Maternal outcomes				Fetal/neonatal outcomes		
	Elective LSCS	Emergency LSCS	PET	PIH	LGA	Macrosomia	Malformation
BMI	1.081 (1.052, 1.110)[a]	1.075 (1.044, 1.106)[a]	1.073 (1.034, 1.114)[a]	1.053 (1.017, 1.090)[a]	1.031 (1.007, 1.056)[b]	1.047 (1.025, 1.070)[a]	1.065 (1.003, 1.131)[b]
Normal	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Overweight	1.611 (1.168, 2.223)[a]	1.611 (1.175, 2.209)[a]	1.728 (1.104, 2.706)[a]	2.117 (1.368, 3.276)[a]	1.372 (1.057, 1.780)[b]	1.446 (1.136, 1.842)[a]	1.824 (0.849, 3.916)
Obese	2.659 (1.852, 3.817)[a]	2.476 (1.713, 3.580)[a]	2.660 (1.607, 4.402)[a]	2.220 (1.342, 3.672)[a]	1.456 (1.067, 1.987)[b]	1.725 (1.295, 2.298)[a]	2.446 (1.038, 5.762)[b]
Obese I	2.439 (1.629, 3.650)[a]	2.416 (1.615, 3.615)[a]	2.569 (1.486, 4.442)[a]	2.236 (1.289, 3.878)[a]	1.385 (0.975, 1.967)	1.731 (1.258, 2.383)[a]	2.024 (0.764, 5.364)
Obese II	2.566 (1.439, 4.577)[a]	2.285 (1.196, 4.369)[a]	2.484 (1.053, 5.858)[a]	2.020 (0.889, 4.590)	2.031 (1.249, 3.302)[a]	1.943 (1.212, 3.114)[a]	3.542 (1.063, 11.797)[b]
Obese III	4.893 (2.169, 11.035)[a]	3.920 (1.425, 10.782)[a]	3.793 (1.082, 13.301)[a]	2.203 (0.634, 7.657)	0.956 (0.408, 2.334)	1.396 (0.636, 3.063)	2.922 (0.356, 23.999)
Fasting Glucose	1.400 (0.877, 2.234)	1.069 (0.672, 1.699)	0.812 (0.427, 1.546)	1.220 (0.663, 2.246)	1.526 (1.034, 2.253)[b]	1.817 (1.265, 2.609)[a]	0.903 (0.309, 2.635)
Glucose 60 min	1.035 (0.930, 1.152)	1.159 (1.041, 1.290)[a]	1.157 (0.998, 1.341)	1.049 (0.910, 1.209)	1.129 (1.032, 1.235)[a]	1.065 (0.980, 1.157)	1.095 (0.856, 3.960)
Glucose 120 min	0.956 (0.830, 1.102)	1.094 (0.977, 1.256)	0.922 (0.759, 1.120)	1.160 (0.960, 1.402)	0.954 (0.874, 1.074)	0.968 (0.867, 1.082)	1.064 (0.770, 1.472)

Stepwise logistic regression analysis was adjusted for maternal age, parity, cigarette smoking, and ethnicity. Data are expressed as adjusted odds ratio (95% confidence interval). BMI is expressed as a continuous variable. Normal BMI, 18.5–24.9 kg/m^2; overweight BMI, 25–29.9 kg/m^2; obese BMI, >30 kg/m^2 (obese I, 30–34.9 kg/m^2; obese II, 35–39.9 kg/m^2; obese III, >40 kg/m^2).

[a] $P < 0.01$.

[b] $P < 0.05$.

There was no association between maternal BMI or glucose and neonatal hypoglycemia, jaundice, respiratory distress, neonatal intensive care unit admission, and fetal death.

Figure 1 shows threshold BMI conferring increased risk for adverse outcome. CRT analyses showed greater association for adverse pregnancy outcome in primiparous women.

Discussion

We confirm the findings of previous analyses addressing independent effects of maternal BMI on adverse obstetric outcomes (8, 9) but with the application of stricter criteria for glucose tolerance (10, 11). This is the first large study investigating maternal BMI and pregnancy outcomes in glucose-tolerant mothers using IADPSG criteria.

We show in this cohort that raised maternal BMI has the greatest independent association with the adverse pregnancy outcomes, LSCS (odds doubled per 12 kg/m^2), PIH (odds doubled per 14 kg/m^2), PET, LGA, and macrosomia. We also show an association with congenital malformation (odds doubled per 15 kg/m^2) independent of maternal glucose, suggesting a pathogenesis distinct from hyperglycemia.

ATLANTIC-DIP study 2 showed associations between raised maternal BMI and poor obstetric/neonatal outcome using WHO criteria for GDM (8). We investigate a larger cohort (3656 *vs.* 2329 women) using IADPSG criteria for glucose tolerance and show that the risks for adverse obstetric outcome are similar, highlighting the greater risk conferred by raised maternal BMI over glucose in this cohort. We also show an exponential relationship between BMI and adverse pregnancy outcomes, reaching a threshold for unacceptable risk at 28 kg/m^2. We use "booking BMI," calculated between 14 and 24 wk, as a surrogate indicator for pregestational BMI. Pregnancy-associated weight gain, sufficient to significantly alter BMI, should not have occurred across this gestational period (14, 15). Clinically, our findings highlight the importance of optimizing maternal BMI below 28 kg/m^2 in the pre- and intergestational periods. This may best be achieved at the primary care level.

We do not show significant association for maternal BMI and pregnancy loss. The rate of pregnancy loss was low. However, because this study was carried out in an obstetric setting, we cannot account for early pregnancy loss. Studies of women undergoing fertility treatment suggest that raised maternal BMI may contribute to early pregnancy loss (15).

Although maternal glucose and BMI did not interact in terms of adverse effects, we do not rule out a pathogenic contribution of maternal insulin resistance. When you consider the correlation between maternal BMI, glucose, and blood pressure, our observations suggest that despite apparent glucose tolerance, many women of reproductive age with raised BMI have already developed an adverse metabolic milieu, unmasked during the physiological challenge of pregnancy. The correlation between birthweight, maternal BMI, and glucose further indirectly supports the presence of hyperinsulinemia in this cohort (16). We propose routine universal screening for GDM (17, 18) and are also currently investigating hyperinsulinemia by performing OGTT and calculating homeostasis model of assessment for insulin resistance in women with BMI greater than 28 kg/m^2 at 32–34 wk. Long-term follow-up for the onset of type 2 diabetes mellitus is also merited in these women.

Despite the best care, the odds for developing adverse pregnancy outcomes are greater in women with raised BMI at booking visit (6, 13, 19, 20). Prepregnancy education, planning, and weight optimization are essential to

modern obstetric and prepregnancy care (3–5). Large interventional studies are investigating lifestyle intervention and metformin ("EMPOWaR" Study) in "glucose-tolerant" pregnant women with raised BMI. Finally, we again highlight the obesity epidemic and its adverse consequences in a young female population.

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