Higher Gestational Weight Gain Is Associated With Increasing Offspring Birth Weight Independent of Maternal Glycemic Control in Women With Type 1 Diabetes

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OBJECTIVE

We evaluate the association between gestational weight gain and offspring birth weight in singleton term pregnancies of women with type 1 diabetes.

RESEARCH DESIGN AND METHODS

One hundred fifteen consecutive women referred at <14 weeks were retrospectively classified as underweight (prepregnancy BMI <18.5 kg/m^2; *n* = 1), normal weight (18.5–24.9; *n* = 65), overweight (25.0–29.9; *n* = 39), or obese (≥30.0; *n* = 10). Gestational weight gain was categorized as excessive, appropriate, or insufficient according to the Institute of Medicine recommendations for each BMI class. Women with nephropathy, preeclampsia, and/or preterm delivery were excluded because of restrictive impact on fetal growth and limited time for total weight gain.

RESULTS

HbA_{1c} was comparable at ∼6.6% (49 mmol/mol) at 8 weeks and ∼6.0% (42 mmol/mol) at 36 weeks between women with excessive (*n* = 62), appropriate (*n* = 37), and insufficient (*n* = 16) gestational weight gain. Diabetes duration was comparable, and median prepregnancy BMI was 25.3 (range 18–41) vs. 23.5 (18–31) vs. 22.7 (20–30) kg/m^2 (*P* = 0.05) in the three weight gain groups. Offspring birth weight and birth weight SD score decreased across the groups (3,681 [2,374–4,500] vs. 3,395 [2,910–4,322] vs. 3,295 [2,766–4,340] g [*P* = 0.02] and 1.08 [−1.90 to 3.25] vs. 0.45 [−0.83 to 3.18] vs. −0.02 [−1.51 to 2.96] [*P* = 0.009], respectively). In a multiple linear regression analysis, gestational weight gain (kg) was positively associated with offspring birth weight (g) (β = 19; *P* = 0.02) and birth weight SD score (β = 0.06; *P* = 0.008) when adjusted for prepregnancy BMI, HbA_{1c} at 36 weeks, smoking, parity, and ethnicity.

CONCLUSIONS

Higher gestational weight gain in women with type 1 diabetes was associated with increasing offspring birth weight independent of glycemic control and prepregnancy BMI.

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Pregnancy in women with pregestational diabetes is still associated with adverse perinatal outcomes, with nearly half of the infants born large for gestational age (1–5). This is mainly attributed to the placental transfer of maternal glucose, leading to fetal hyperinsulinemia and accelerated fetal growth (6), and strict maternal glycemic control is therefore a cornerstone in the clinical management of these women (7,8). Poor maternal glycemic control before and during pregnancy has been associated with both restrictive (2) as well as excessive (2,4) fetal growth, and elevated third-trimester HbA_{1c} predicts both increased offspring birth weight (2) and the prevalence of macrosomia (4). The recommendation of frequently performed plasma glucose measurements and the use of insulin analogs (9), insulin pumps (10), and continuous glucose monitoring (11) are recent attempts striving for maternal normoglycemia. However, other nutritional substrates than glucose, such as lipids, probably also contribute to fetal overgrowth in pregnancies of women with diabetes (12,13).

In healthy pregnant women, obesity predisposes to fetal overgrowth (14,15), and the risk increases with rising prepregnancy BMI (16). Excessive gestational weight gain has been identified as yet another emerging risk factor for neonatal overweight (16–18), whereas low gestational weight gain has been shown to be associated with the birth of small-for-gestational-age infants (16). In 2009, the Institute of Medicine (IOM) suggested the following recommendations for BMI-appropriate gestational weight gain: 12.5–18.0 kg for underweight, 11.5–16.0 kg for normal weight, 7.0–11.5 kg for overweight, and 5.0–9.0 kg for obese women (19). Whether these IOM recommendations are applicable in women with pregestational type 1 or type 2 diabetes still remains unclear (20–22). Existing studies on the topic mainly include overweight and obese women with gestational diabetes mellitus or type 2 diabetes and show that excessive gestational weight gain increases the risk of large-for-gestational-age infants and macrosomia (20–23) and is associated with higher rates of cesarean section (21,22), neonatal morbidity (21,23), and gestational hypertension (20). Interestingly, maternal glycemic control was reported to be comparable between women with excessive and nonexcessive gestational weight gain (20,21,23).

Along with increasing prepregnancy BMI (4,24) and persisting high rates of macrosomic offspring despite strict maternal glycemic control (8,11) in women with type 1 diabetes, other potential contributors to fetal overgrowth need to be addressed. Fetal growth restriction, on the contrary, is only rarely seen in women with diabetes without diabetic nephropathy or preeclampsia (25,26).

We hypothesized that excessive gestational weight gain in women with type 1 diabetes confers additional risks and evaluated the association between gestational weight gain and offspring birth weight in these women. We also wished to describe the weekly gestational weight gain resulting in appropriate total gestational weight gain according to the IOM recommendations in women with type 1 diabetes.

RESEARCH DESIGN AND METHODS

This retrospective cohort study included all Danish-speaking women with type 1 diabetes referred to our Center for Pregnant Women with Diabetes, Rigshospitalet, Copenhagen, Denmark, before 14 completed gestational weeks in the period of February 2009 to February 2011, with singleton pregnancies delivered at term (>37 weeks of gestation; $n = 133$). Women with diabetic nephropathy ($n = 3$) and/or the development of preeclampsia ($n = 9$) were excluded due to the well-known possible restrictive impact of these conditions on fetal growth (25,26). Women with preterm deliveries were excluded because of the limited time for total gestational weight gain. Women with severe concomitant disease were also excluded ($n = 3$), and for women with several pregnancies in the study period ($n = 3$), only the first pregnancy was included. In total, 115 women were included. Our population of women originates from a geographically well-defined region of 2.4 million inhabitants with unrestricted referral (11).

Due to the retrospective study design, approval from the Danish National Committee on Biomedical Research Ethics was not required. Information about medications and pregnancy complications was drawn from the hospital maternity records.

Management of Diabetes in Pregnancy

All women followed the routine pregnancy care program for pregestational diabetes with antenatal visits at our clinic typically at 8, 12, 21, 27, and 33 gestational weeks (11). Self-monitored plasma glucose measurements were recommended seven times daily (before and 1.5 h after each main meal and at bedtime), and diet and insulin doses were adjusted by the women themselves every third day and in collaboration with an experienced diabetologist every second week. Treatment goals for self-monitored plasma glucose values were 4.0–6.0 mmol/L preprandially, 4.0–8.0 mmol/L 1.5 h postprandially, and 6.0–8.0 mmol/L prebedtime. For HbA_{1c}, the aim was <5.6% (38 mmol/mol) after 20 gestational weeks (27). HbA_{1c} was measured on a DCA 2000 analyzer (Bayer, Mishawaka, IN) by a latex immunoagglutination inhibition method. Diabetic retinopathy was diagnosed with retinal photos at the first pregnancy visit (28). Mild hypoglycemia was self-reported and defined as events familiar to the patient as hypoglycemia and managed by the patient (29) with available data from early and late pregnancy in 88 (76%) of the women. At ~2-week intervals throughout pregnancy, all women visited our clinic and/or their local diabetes clinic, where HbA_{1c}, blood pressure, weight, and urine dipstick test for protein, nitrites, and leukocytes (30) were registered. Elevated urine albumin excretion at the first pregnancy visit was defined as albumin-to-creatinine ratio ≥30 mg/mmol in two samples of random urine. Later on in pregnancy, a dipstick test positive for protein (>1+) led to analysis of albumin-to-creatinine ratio (30). A dipstick test positive for nitrites or leukocytes led to sterile urine culture, and antibiotic treatment was given when relevant. Obstetrical ultrasound scanning was performed at all five routine visits and when indicated (11). In women with hypertension (≥135/85 mmHg) or urinary albumin excretion >300 g/24 h, antihypertensive treatment was initiated with methyldopa as the primary drug as previously described (26).

At the first pregnancy visit at median 8 (range 6–13) weeks, all women had a 1-h tailored dietitian consultation for individual dietary planning following national guidelines for a diabetes diet

recommending a low glycemic index diet (11). Carbohydrate counting was mainly used in women on insulin pumps (n = 29), and specific recording of dietary data was not performed. According to local guidelines, women with BMI <30 kg/m^2 were advised to gain 10–15 kg in pregnancy, whereas women with BMI >30 kg/m^2 were advised to stay weight neutral in the first half of pregnancy and thereafter to limit the total gestational weight gain to 5 kg (11,23). Moderate physical activity for at least 30 min/day was encouraged (23).

To evaluate social status, the women's professional educational level was graded from 0 (no professional education) to 5 (university level) (31), with available data for 104 (90%) women. Fetal abdominal circumference was assessed by antenatal ultrasound examinations at 36 gestational weeks and was given as an SD score adjusted for gestational age; data were available in 88 (76%) women.

Prepregnancy BMI and Gestational Weight Gain

Prepregnancy BMI was calculated using the self-reported prepregnancy weight and self-reported height, and the women were classified according to World Health Organization standards as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥30.0 kg/m^2). The total gestational weight gain was calculated as the difference between the last weight measured before delivery and the self-reported prepregnancy weight (32). Based on prepregnancy BMI classification and the IOM recommendations on gestational weight gain, the women's weight gain was then categorized as follows: excessive (>18.0, >16.0, >11.5, and >9.0 kg for the different BMI classes, respectively), appropriate (12.5–18.0, 11.5–16.0, 7.0–11.5, and 5.0–9.0 kg), or insufficient (<12.5, <11.5, <7.0, and <5.0 kg) gestational weight gain (19) (Fig. 1).

The weekly gestational weight gain from before pregnancy to the first pregnancy visit was calculated as the difference between the weight measured at the first pregnancy visit and the self-reported prepregnancy weight divided by the number of gestational weeks with days precision. Similarly, the weekly gestational weight gain between in the first and second halves of pregnancy was calculated as the difference between the weight measured at a midpregnancy routine visit (21 [19–24] weeks) and the self-reported prepregnancy weight and the difference between the weight measured at 21 weeks and the last weight measured in pregnancy (36 [34–39] weeks), respectively, divided by the number of weeks of observation with days precision.

Pregnancy Complications and Outcomes

The following parameters were registered: the development of hypertension (blood pressure ≥135/85 mmHg) after 20 weeks of gestation without the presence of proteinuria where antihypertensive treatment was initiated (26), large- and small-for-gestational-age infants (infant birth weight ≥90th or ≤10th percentile adjusted for sex and gestational age [33]), birth weight SD score, severe neonatal hypoglycemia (2-h plasma glucose <2.5 mmol/L treated with intravenous glucose infusion [34]), transient tachypnea of the newborn (continuous positive airway pressure for >60 min required), and neonatal jaundice (phototherapy required). Ponderal index of the infants was calculated as 100 × birth weight (g) / length^3 (cm); data were available in 88 (76%) women.

Statistical Analysis

The three groups were compared by using trend analysis for continuous variables and χ^2 test for categorical variables. To control for confounding, multiple linear regression analysis was applied using total gestational weight gain (kg) as the exposure variable and offspring birth weight (g) and birth weight SD score as the outcome variables. Based on theoretical considerations, five possible confounders were included: prepregnancy BMI (kg/m^2) (2,4,5,15,18,24), HbA_{1c} in late pregnancy (%; at 36 weeks) (2,4), smoking (yes/no) (2,4,18), nulliparity (yes/no) (2,4), and Nordic Caucasian ethnicity (yes/no). Univariate linear regression analysis was performed to examine the following associations: maternal gestational weight gain (kg) versus infant 2-h plasma glucose (mmol/L) and self-reported prepregnancy weight (kg) versus maternal weight measured in our clinic at the first pregnancy visit (kg).

Continuous variables are given as median (range). However, interquartile ranges are used for data on weekly gestational weight gain in Supplementary Fig. 1. Categorical variables are given as numbers (percentage). A P value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics 19.0 (SPSS, Chicago, IL).

RESULTS

The 115 included women were first classified according to prepregnancy BMI as underweight (n = 1), normal weight (n = 65), overweight (n = 39), or obese (n = 10). Thereafter, based on the IOM recommendations on BMI-appropriate gestational weight gain, the women were categorized into three weight gain groups: excessive (n = 62; 54%), appropriate (n = 37; 32%), or insufficient (n = 16; 14%) gestational weight gain (Supplementary Fig. 1; Table 1).

Offspring birth weight decreased across the three weight gain groups: median birth weight was 3,681 (range 2,374–4,500) vs. 3,395 (2,910–4,322) vs. 3,295 (2,766–4,340) g (P = 0.02), and birth weight SD score was 1.08 (−1.90 to 3.25) vs. 0.45 (−0.83 to 3.18) vs. −0.02 (−1.51 to 2.96) (P = 0.009) (Table 2; Fig. 2). Fetal abdominal circumference decreased across the three weight gain groups (P = 0.04), while infant birth length was comparable. Only two infants were born small for gestational age (excessive and insufficient group; P = 0.36).

HbA_{1c} was comparable at ~6.6% (49 mmol/mol) at 8 weeks (P = 0.78) and ~6.0% (42 mmol/mol) at 36 weeks (P = 0.40) between women with excessive, appropriate, and insufficient gestational weight gain (Table 1). Prepregnancy BMI was 25.3 (18–41) vs. 23.5 (18–31) vs. 22.7 (20–30) kg/m^2 (P = 0.05) in the three weight gain groups. The numbers of insulin pump users as well as insulin dosages were comparable regardless of gestational weight gain group (Table 1). The maternal professional education level (P = 0.55) as well as the rate of vaginal deliveries (Table 2) was similar across the weight gain groups.

The total gestational weight gain in the three weight gain groups was 17.7 (10–30), 13.1 (6–16), and 8.5 (−2 to 11) kg (P < 0.001). Already at the first

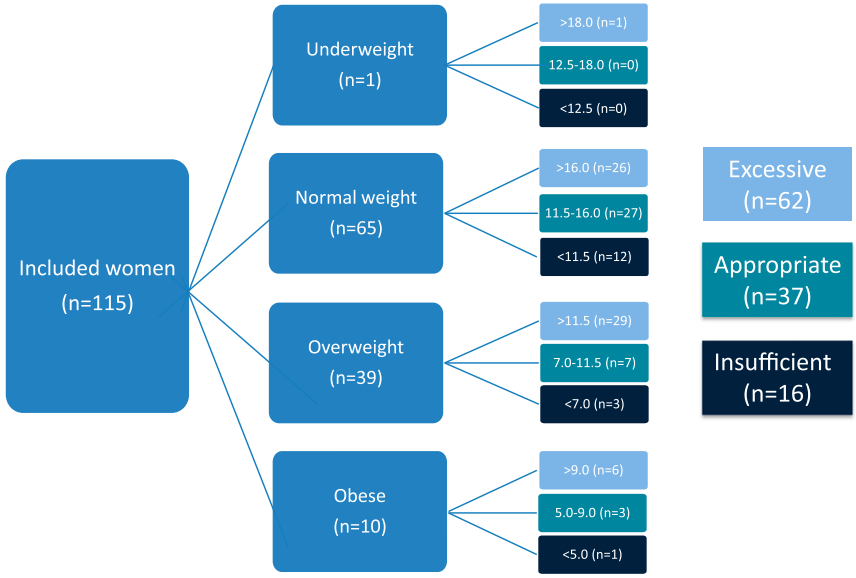

Figure 1—Classification of 115 pregnant women with type 1 diabetes according to prepregnancy BMI (underweight, normal weight, overweight, and obese) and gestational weight gain (excessive, appropriate, and insufficient) according to the IOM recommendations for each BMI class (19).

pregnancy visit at 8 weeks of gestation, the weight gain was higher in women ending up with excessive gestational weight gain compared with women with appropriate and insufficient gestational weight gain (P = 0.003). For all three weight gain groups, the weekly weight gain was higher in late compared with early pregnancy (Table 1). The weekly weight gain between the pregnancy visits at 8, 12, 21, 27, 33, and 36 weeks was 117 (−700 to 1,861), 405 (−738 to 2,925), 513 (78–1,805), 513 (−1,033 to 1,800), and 675 (−633 to 2,200) g/week in the study population as a whole (Supplementary Fig. 1). Among 27 normal-weight women with appropriate weight gain, the weekly weight gain was 350 (159–591) and 464 (250–771) g/week in the first (from 8 to 21 weeks of gestation) and second (from 21 to 36 weeks of gestation) halves of pregnancy. In multiple linear regression analyses, gestational weight gain (kg) was positively associated with both offspring birth weight (g) (R^2 = 0.15; β = 19; P = 0.02) and birth weight SD score (R^2 = 0.16; β = 0.06; P = 0.008) when adjusted for prepregnancy BMI, HbA_{1c} in late pregnancy (at 36 weeks), smoking, parity, and ethnicity. This corresponds to an infant birth weight increase of 95 g per 5 kg maternal gestational weight gain. When categorized according to prepregnancy BMI only, the total gestational weight gain was 21.3 (one woman) vs. 15.2 (5–25) vs. 14.2 (−2 to 30) vs. 11.0 (0–22) kg (P = 0.02) for underweight, normal-weight, overweight, and obese women. The maternal weight at first pregnancy visit was 1.7 (−3.9 to 14.4) kg higher than the self-reported prepregnancy weight, with a strong correlation between the two weights (R^2 = 0.95; $P < 0.0001$).

Admittance to the neonatal intensive care unit, severe neonatal hypoglycemia, transient tachypnea of the newborn, and neonatal jaundice were similar across the three gestational weight gain groups (Table 2). There was no significant correlation between maternal gestational weight gain (kg) and infant 2-h plasma glucose (mmol/L) (R^2 = 0.03; P = 0.08). There were no cases of perinatal death. The development of blood pressure ≥135/85 mmHg after 20 weeks of gestation without the presence of proteinuria occurred in 11 (10%) women, all with excessive gestational weight gain (Table 1; $P < 0.004$). These women were characterized by prepregnancy BMI of 23.9 (20–32) kg/m^2 and weekly gestational weight gain of 366 (0–2,016) g/week from before pregnancy to the first pregnancy visit at 9 weeks, 282 (127–631) g/week from the first pregnancy visit to 21 weeks, and 698 (494–1,050) g/week from 21 weeks until the last pregnancy visit at 36 weeks, and the total gestational weight gain was 20.7 (12–26) kg. HbA_{1c} declined from 7.1% (5.9–8.4) (54 mmol/mol [41–68]) to 6.2% (5.3–6.9) (44 mmol/mol [34–52]) from early to late pregnancy. Offspring birth weight in these 11 infants was 3,146 (2,810–4,100) g, birth weight SD score was 0.36 (−0.73 to 2.64), and none were small for gestational age.

CONCLUSIONS

This study documents the impact of gestational weight gain, independent of maternal glycemic control expressed as HbA_{1c} at 36 weeks and prepregnancy BMI, on offspring birth weight in women with type 1 diabetes. These findings highlight the importance of increased clinical focus on appropriate gestational weight gain along with strict maternal glycemic control in the effort against neonatal overweight in the offspring of these women.

The strong relation between excessive gestational weight gain and fetal overgrowth has also been described in other studies dealing with healthy women (35,36) and women with gestational diabetes mellitus or mainly pregestational type 2 diabetes (20–23). Our study, however, is the first study on a cohort of women with type 1 diabetes alone and where adjustment for the possible impact of maternal glycemic control assessed by HbA_{1c} in late pregnancy has been available. In addition, possible confounders like diabetic

Table 1—Clinical data in 115 women with type 1 diabetes with excessive, appropriate, and insufficient gestational weight gain according to the IOM recommendations

	Excessive (n = 62)	Appropriate (n = 37)	Insufficient (n = 16)	P value
Maternal age, years	29 (21–39)	33 (23–43)	31 (21–39)	0.03
Prepregnancy BMI, kg/m^2	25.3 (18–41)	23.5 (18–31)	22.7 (20–30)	0.05
Duration of diabetes, years	14 (1–37)	14 (1–38)	9 (2–26)	0.36
Smokers	7 (11)	4 (11)	1 (6)	1.00
Insulin pump therapy	14 (23)	9 (24)	6 (38)	0.48
Diabetic retinopathy	28 (48)	13 (37)	4 (25)	0.22
Antihypertensive therapy at referral, n = 104	2 (3)	2 (1)	0 (0)	0.64
Microalbuminuria at 8 weeks	1 (2)	2 (1)	0 (0)	0.41
HbA_{1c}, %, mmol/mol				
8 weeks	6.7 (5.6–8.4), 50 (38–68)	6.5 (5.4–8.3), 48 (36–67)	6.6 (5.6–8.3), 49 (38–67)	0.78
21 weeks	6.0 (4.9–7.7), 42 (30–61)	6.0 (5.2–7.1), 42 (33–54)	6.1 (5.0–7.6), 43 (31–60)	0.51
36 weeks	6.0 (5.1–6.9), 42 (32–52)	6.0 (4.7–7.1), 42 (28–54)	6.3 (5.1–7.0), 45 (32–53)	0.40
Insulin dose, IU/kg/24 h				
8 weeks	0.62 (0.23–1.31)	0.61 (0.20–1.43)	0.57 (0.23–0.91)	0.36
36 weeks	1.09 (0.10–1.88)	0.94 (0.38–2.25)	1.00 (0.30–1.31)	0.30
Mild hypoglycemia, events/week, n = 88				
8 weeks	7 (0–30)	5 (1–14)	5 (0–10)	0.13
36 weeks	5 (0–21)	3 (0–27)	4 (0–10)	0.61
Blood pressure ≥135/85 mmHg after 20 weeks of gestation without proteinuria	11 (18)	0 (0)	0 (0)	0.004
Gestational weight gain				
Total, kg	17.7 (10–30)	13.1 (6–16)	8.5 (−2 to 11)	<0.001
Prepregnancy–8 weeks, g/week	257 (−303 to 2,016)	216 (−335 to 515)	87 (−385 to 463)	0.003
8–21 weeks, g/week	405 (42–818)	293 (−177 to 717)	171 (−692 to 338)	<0.001
21–36 weeks, g/week	640 (271–1,173)	444 (27–771)	350 (−100 to 533)	<0.001

Trend analysis for continuous variables and χ^2 test for categorical variables. Results are given as median (range) or n (%).

nephropathy, preeclampsia, and preterm delivery were eliminated. In Fig. 2, we present a median infant birth weight SD score similar to the background population only in the group of women with insufficient gestational weight gain, while women with appropriate weight gain had infants with a slightly higher SD score. These results may indicate that "appropriate" gestational weight gain in women with type 1 diabetes perhaps should be referred to as gestational weight gain in the lower end of the scale of the IOM 2009 recommendations on appropriate gestational weight gain for healthy women (19). The national Danish recommendation for gestational weight gain in normal-weight healthy women of 10–15 kg is quite similar to the IOM recommendations and was used in the clinical guidance of this present cohort of women with BMI <30 kg/m^2. Obese women, on the other hand, were recommended to limit the total gestational weight gain to 5 kg (11,23,37). Our experience from the current study as well as from studies on women with type 2 diabetes (23,37) suggests that obtaining these restrictive recommendations in obese women with diabetes appears safe and efficient—if obtained—in reducing fetal overgrowth. However, the number of obese women in this study was low. An increasing subset of our women with type 1 diabetes is nowadays overweight but not obese, and in the future, we will change our local recommendations for gestational weight gain in this subset of women to 5–8 kg. Similar to our studies on type 2 diabetes, excessive gestational weight gain in the entire cohort was present already early in pregnancy, indicating the need for patient information already during pregnancy planning and early in pregnancy (23,37).

Additionally, this study is in line with the findings of fetal overgrowth related to excessive maternal weight gain independent of glycemic control assessed by HbA_{1c} presented in previous articles from our center covering women with type 2 diabetes (23,37). The factual numbers of self-reported mild hypoglycemia in early pregnancy were higher in women with excessive gestational weight gain, although the difference across the groups did not reach significance. This supports the clinical impression that frequent hypoglycemic events leading to extra carbohydrate intake may add to the gestational weight gain. Insulin doses were comparable across the groups, so it seems unlikely that higher insulin doses per se could explain the excessive gestational weight gain.

Strengths of our study are the incorporation of a relatively large cohort of consecutively referred women; careful collection of data, including body weight measured several times during pregnancy; and the presentation of possible confounders. The study population represents patients from a geographically well-defined area where four out of five women with type 1 diabetes deliver at term and only 8% of them develop preeclampsia (11). Due to the well-known restrictive impact of nephropathy and preeclampsia on fetal growth (25,26) and the limited time for total

Table 2—Pregnancy outcomes and antenatal ultrasound data in 115 women with type 1 diabetes with excessive, appropriate, and insufficient gestational weight gain according to the IOM recommendations

	Excessive (*n* = 62)	Appropriate (*n* = 37)	Insufficient (*n* = 16)	*P* value
Gestational age at delivery, days	265 (259–278)	267 (259–280)	267 (259–274)	0.13
Vaginal delivery	38 (61)	21 (57)	13 (81)	0.23
Birth weight, g	3,681 (2,374–4,500)	3,395 (2,910–4,322)	3,295 (2,766–4,340)	0.02
Birth weight SD score	1.08 (−1.90 to 3.25)	0.45 (−0.83 to 3.18)	−0.02 (−1.51 to 2.96)	0.009
Birth length, cm, *n* = 88	52 (47–60)	51 (47–55)	51 (49–53)	0.35
Ponderal index, g/cm^3, *n* = 88	2.60 (1.93–3.14)	2.59 (2.27–3.09)	2.50 (2.17–3.09)	0.45
Fetal abdominal circumference at 36 gestational weeks, SD score, *n* = 88	1.54 (−1.05 to 4.15)	1.21 (−1.02 to 3.79)	0.48 (−0.95 to 2.78)	0.04
Large for gestational age	29 (47)	11 (30)	4 (25)	0.12
Small for gestational age	1 (2)	0 (0)	1 (6)	0.36
Admission to neonatal intensive care unit	10 (16)	6 (16)	3 (19)	0.94
Infant 2-h plasma glucose, mmol/L	2.9 (1.3–5.9)	2.5 (0.9–4.9)	2.9 (1.5–3.6)	0.06
Severe neonatal hypoglycemia	3 (5)	4 (11)	1 (7)	0.53
Transient tachypnea of the newborn	7 (11)	3 (8)	1 (6)	0.91
Neonatal jaundice	3 (5)	1 (3)	1 (6)	0.87

Trend analysis for continuous variables and χ^2 test for categorical variables. Results are given as median (range) or *n* (%).

gestational weight gain in women with preterm deliveries, women with these conditions were excluded from the study material.

Based on Scandinavian literature traditions (18,23,32,38) and to enable comparison with other recent studies on the topic (20,21,23), we chose the self-reported prepregnancy body weight as reference for calculations on total gestational weight gain in spite of potential recall bias. Both self-reported prepregnancy weight and maternal weight at the first pregnancy visit in our clinic were reported. A tight correlation between the two weight determinations was documented with an average difference of 1.7 kg. For accurate estimation of the weekly weight gain within pregnancy, the actual measured values at the same scale in the clinic were chosen for those calculations.

Unfortunately, we do not have data available on nutritional factors like lipids or fasting glucose that may influence fetal growth. Two-thirds of the women with type 1 diabetes report nausea or vomiting in early pregnancy (29), but the influence on gestational weight gain remains speculative. The numbers of underweight and obese women in the present material were small, and the findings on these subsets of women need to be confirmed in other studies. Also, our cohort of included women is fairly healthy given the median HbA_{1c} of 6.6% in early pregnancy and the rare occurrence of microalbuminuria and/or antihypertensive therapy at referral. Whether the results are applicable to other cohorts of women with type 1 diabetes who are in less optimal glycemic control or who have more complications from their disease needs to be further explored. Other possible confounders due to the retrospective observational study design cannot be excluded.

Even after exclusion of women with nephropathy and preeclampsia, 11 (10%) previously normotensive women developed blood pressure ≥135/85 mmHg after 20 weeks of gestation and had antihypertensive treatment initiated (26). All of these 11 women gained weight excessively in pregnancy. The diagnostic threshold for hypertension in the normal population is referred to as ≥140/90 mmHg, and the threshold for antihypertensive treatment in pregnant women with diabetes has been suggested to be ≥130/80 mmHg by the American Diabetes Association (39). Higher prevalence of gestational hypertension in women with excessive gestational weight gain has also been observed in obese glucose-tolerant women (18) and in women with gestational diabetes mellitus (20). A recent meta-analysis covering randomized controlled trials on diet and lifestyle interventions in healthy women to restrict gestational weight gain presented reduced risk of hypertensive disorders in pregnancy among women allocated intervention compared with controls (36). These findings of randomized controlled trials support the hypothesis that lifestyle factors leading to excessive gestational weight gain per se may induce an adverse metabolic milieu affecting the vessels and leading to hypertensive changes. We therefore suggest that excessive caloric intake rather than increased extracellular volume in early pregnancy may explain the increased risk of gestational hypertension in our women with excessive gestational weight gain. However, quantification of edema formation is difficult to perform and was not done in this study. Along with other pregnancy products like the fetus and amniotic fluid, as well as increased maternal blood volume and adipose tissue, edema may also contribute to the total gestational weight gain. In very late pregnancy, edema formation probably contributed to a weight gain of almost 700 g/week in the study population as a whole, while the excessive weight gain in women developing gestational hypertension, at least to some extent, seemed to occur already in early pregnancy. Only very few women in this cohort received antihypertensive therapy or had microalbuminuria at first pregnancy visit with similar prevalence across the gestational weight gain groups. It therefore seems unlikely that pregestational hypertensive complications could explain the increased risk of blood pressure ≥135/85 mmHg in late pregnancy. We also know from a

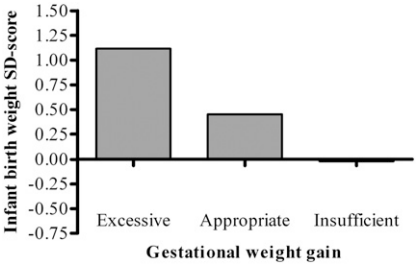

Figure 2—Median infant birth weight SD score in 115 women with type 1 diabetes classified by excessive, appropriate, or insufficient maternal gestational weight gain. Birth weight SD score in the background population is zero (33).

previous study that the risk of fetal growth restriction is low in both women with normal urinary albumin excretion and women with microalbuminuria (25). None of the 11 infants of women with blood pressure ≥135/85 mmHg in late pregnancy were growth restricted, which indicates sufficient placentation and placental function in these women.

In this study, severe neonatal morbidity was comparable across the three gestational weight gain groups. These results oppose the findings of studies on women with type 2 diabetes (21–23), which indicates that other factors, i.e., maternal glycemic control, are of major impact on neonatal morbidity in women with type 1 diabetes. Infant overweight in women with excessive gestational weight gain was also characterized by increased fetal abdominal circumference but comparable infant length when compared with women with appropriate or insufficient gestational weight gain. Increased central adiposity of the infants is therefore likely, but unfortunately, skin folds were not measured. However, infants of women with diabetes born overweight are at increased risk of adult overweight and type 2 diabetes in later life (40). There were only very few small-for-gestational-age infants and no cases of perinatal death.

Obese glucose-tolerant women gaining ≥15 kg in pregnancy as compared with those gaining <5.0 kg had infants weighting approximately 260 g more (18). For women with gestational diabetes mellitus or type 2 diabetes, infant birth weight was ~85 g higher in women with excessive as compared with appropriate gestational weight gain according to the IOM recommendations (19,21). In our previous study on obese women with type 2 diabetes, the difference in infant birth weight of women gaining more versus less than 5.0 kg in pregnancy was 230 g (23). Recently published data from our center on 142 women with type 2 diabetes show that women with excessive gestational weight gain had infants with birth weight ~450 g higher than women with nonexcessive (i.e., insufficient or appropriate) gestational weight gain (37). Whether the impact of gestational weight gain is greater in women with insulin resistance and to what extent lipid metabolism (12,13) may influence fetal overgrowth in pregnancies of women with diabetes need to be further explored.

To conclude, higher gestational weight gain in women with type 1 diabetes was associated with increasing offspring birth weight independent of maternal glycemic control in late pregnancy and prepregnancy BMI. Our findings call for increased focus on gestational weight gain in the clinical care of these women, addressing both strict maternal glycemic control as well as appropriate gestational weight gain control in the effort for improved pregnancy outcome.

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