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Pre-pregnancy body mass index and the risk of adverse outcome in type 1 diabetic pregnancies: a population-based cohort study

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ABSTRACT

Objective: To assess the risk of perinatal complications in overweight and obese women with and without type 1 diabetes (T1DM).

Design: Prospective population-based cohort study.

Setting: This study was based on data from the Swedish Medical Birth Registry from 1998 to 2007.

Participants: 3457 T1DM and 764 498 non-diabetic pregnancies were included. T1DM was identified based on ICD code O24.0. Mothers were categorised according to pre-pregnancy body mass index (BMI: weight in kilograms per height in square metres) as normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9) or obese (BMI ≥30). Only women with singleton pregnancies and with data on BMI were included.

Primary/secondary outcomes: The primary outcome was large for gestational age (LGA: birth weight >90th percentile) infants. Secondary outcomes were major malformations, pre-eclampsia (PE), preterm delivery, perinatal mortality, delivery by Caesarean section and neonatal overweight. Logistic regression analysis was performed with normal weight non-diabetic women as the reference category and also within the diabetic cohort with normal weight type 1 diabetic women as the reference. The ORs were adjusted for ethnicity, maternal age, height, parity, smoking and chronic hypertension.

Results: 35% of women with T1DM were overweight and 18% were obese, as compared with 26% and 11%, respectively, in non-diabetic pregnancies. The incidences of adverse outcome increased with greater BMI category. As compared with non-diabetic normal weight women, the adjusted OR for obese T1DM for LGA was 13.26 (95% CI 11.27 to 15.59), major malformations 4.11 (95% CI 2.99 to 5.65) and PE 14.19 (95% CI 11.50 to 17.50). T1DM was a significant effect modifier of the association between BMI and LGA, major malformations and PE ($p<0.001$).

Conclusion: High pre-pregnancy BMI is an important risk factor for adverse outcome in type 1 diabetic pregnancies. The combined effect of both T1DM and overweight or obesity constitutes the greatest risk. It seems prudent to strive towards normal pre-pregnancy BMI in women with T1DM.

ARTICLE SUMMARY

Article focus

- To assess the risk of obstetric and perinatal complications in overweight and obese women with and without type 1 diabetes (T1DM).

Key messages

- High pre-pregnancy body mass index (BMI) is an important risk factor for adverse outcome in type 1 diabetic pregnancies.
- The combined effect of both T1DM and overweight or obesity constitutes the greatest risk.
- T1DM is a significant effect modifier of the association between BMI and large for gestational age, major malformations and pre-eclampsia ($p<0.001$).

Strengths and limitations of this study

- The present study is to our knowledge, the first to present risk estimates of several obstetric and perinatal complications in women with T1DM, stratified by BMI category and compared with a non-diabetic reference population. The population-based study design, including a very large cohort of T1DM pregnancies, offers a unique possibility to provide solid data on risks associated with high BMI, including comparatively rare outcomes such as perinatal mortality. A potential limitation is that the study design did not allow assessment of the impact of maternal glycaemic control on the association between exposure and outcome.

INTRODUCTION

Body mass index (BMI) has increased among fertile women in many countries, including Sweden.[1] Maternal overweight and obesity are well-known risk factors for adverse pregnancy outcome. High pre-pregnancy BMI has been associated with increased risk for stillbirth, fetal malformations, large for date neonates, neonatal and infant death, pregnancy-induced hypertension and pre-eclampsia (PE), maternal diabetes, delivery

by Caesarean section as well as increased numbers of days spent in hospital for both mother and infant.[2–11] The pathophysiological mechanism behind the increased risk of adverse pregnancy outcome in obese women is not fully understood. Increased insulin resistance and a state of inflammation associated with obesity[12] are likely important contributing factors.

Given the links between overweight, insulin resistance and adverse pregnancy outcome, any additional pregnancy risks in overweight women with diabetes are important to disclose, especially since overweight and obesity are more prevalent among diabetic women than in the general obstetric population.[13] Increased risks of neonatal and maternal morbidity have been reported in overweight and obese women with gestational diabetes.[14–16] In contrast, data are very limited regarding the impact of high maternal BMI on the risk of adverse pregnancy outcome in women with type 1 diabetes (T1DM). An interaction between maternal diabetes, including both pregestational and gestational diabetes, and obesity has been suggested to increase the risk of malformations in the offspring.[17] However, the majority of women in that study had gestational diabetes and no separate analysis was performed in women with T1DM.

The aim of the present study was to analyse the association between maternal overweight and obesity and the risk of fetal and obstetric complications in type 1 diabetic pregnancies, with special reference to the high and increasing incidence of large for gestational age infants.[13] This study includes a large national cohort of more than 3000 type 1 diabetic pregnancies, and the risk of adverse outcome in relation to maternal BMI was also compared with non-diabetic pregnancies. Our hypothesis was that maternal overweight/obesity and maternal T1DM have independent impact on the risk of adverse outcome and that the combination of the two constitutes the greatest risk.

RESEARCH DESIGN, MATERIALS AND METHODS

This population-based cohort study was based on data from the Swedish Medical Birth Registry (MBR). The MBR prospectively collects information on maternal medical history, obstetric and neonatal diagnoses and covers more than 99% of all pregnancies in Sweden. Until 2008, the MBR did only collect data on pregnancies from $28^{0/7}$ weeks of gestation and did not register data on earlier fetal losses or induced abortions. The quality of data in the registry is continuously evaluated by the National Board of Health and the conclusion of the latest extensive validation in 2002 was that quality of data is high.[18] Maternal and neonatal diagnoses were classified according to ICD-10, introduced in Sweden in 1997. ICD-9 codes were also included to ensure that no patients would be missed. All diagnoses were made by a physician before hospital discharge and copies of the records were forwarded to the MBR. Maternal characteristics included in the present study were mother's age, parity, pre-pregnancy weight, height, chronic hypertension, smoking habits and whether the mother was born in one of the Nordic countries (Sweden, Finland, Denmark, Norway or Iceland) or elsewhere. Chronic hypertensive disease ICD-10 I10 or O10.0) was defined as blood pressure above 140/90 mm Hg diagnosed before pregnancy or before 20 weeks of gestation. Maternal height and pre-pregnancy weight were recorded by recall, and BMI was calculated as weight in kilograms divided by the square of the height in metres. Exposure in women with and without T1DM was defined as overweight (BMI $\geq$25–29.9 kg/m^2) or obese (BMI $\geq$30 kg/m^2), and pregnancy outcomes were compared with that of normal weight women (BMI 18.5–24.9 kg/m^2). Women with BMI$<$ 18.5 kg/m^2 (under weight) and records with missing data on BMI were excluded as well as records with extreme values on maternal age ($<$13 or $>$54 years), maternal weight ($<$40 or $>$200 kg) or maternal height ($<$120 or $>$200 cm). We applied the same limits for data acceptance of birth weight and birth length as in the National Perinatal Quality Registry in Sweden: that is, records with birth weight $<$200 or $>$9998 g or birth length $<$15 or $>$65 cm, were excluded.

Study cohort

Infants from singleton pregnancies and born to mothers with T1DM in Sweden between 1998 and 2007 were included, in total n=3457. Type 1 diabetic pregnancies were identified based on ICD-10 code O240 and ICD-9 code 250 for pregestational diabetes.

Non-diabetic cohort

The reference group (n=764 498) included all singleton pregnancies to mothers without a diagnosis of diabetes (based on ICD-10 and -9 codes for T1DM (O240, 250×1/×3), type 2 diabetes (O241) and all codes starting with E11 and E 177-119, 250×0/×2 or gestational diabetes codes (O244 A, B, X, 648.8)) and born in the same time period as the study cohort. Percentiles for birth weight were based on all live born, singleton infants, without major malformations to mothers without a diagnosis of diabetes. Birthweight percentiles were adjusted for sex and gestational age.

Primary outcome

Fetal macrosomia, that is, giving birth to a large for gestational age (LGA) infant, was the primary outcome of this study. LGA was defined as a birth weight $>$90th percentile for sex and gestational age.

Secondary outcomes

Secondary outcomes were major malformations, PE, preterm delivery, perinatal mortality, delivery by Caesarean section (emergency and elective) and neonatal overweight. Major malformations were predefined in the MBR as fatal or potentially life-threatening malformations or if the malformation would likely lead to a serious handicap or major cosmetic defect if not surgically corrected. PE was defined as a blood pressure

above 140/90 mm Hg after 20 weeks of gestation and proteinuria (at least 0.3 g/day or >1+ on a urine dipstick, ICD-10 codes: O14.0, O14.1 and O15/ICD-9 codes: 642.4, 642.5 and 642.6). Preterm birth was defined as delivery before 37 gestational weeks. Perinatal mortality was defined as intrauterine death after $28^{0/7}$ weeks of gestation or death during the first week of postnatal life. Neonatal overweight was defined as birth weight and ponderal index (PI, birth weight in grams per length in cubic centimetres) above the 90th percentile for sex and gestational age.

This study was approved by the Regional Ethical Review Board in Uppsala, Sweden.

Statistical methods

Comparison between groups were made using Kruskal–Wallis test for continuous data and χ^2 test and χ^2 test for trend for binary and categorical data as appropriate. Unconditional logistic regression was used to explore associations between maternal BMI categories and adverse outcomes with normal weight (BMI 18.5–24.9 kg/m^2) women as the reference category as follows: the ORs of adverse outcomes in relation to BMI category were estimated in women with T1DM with (1) normal weight women with T1DM as reference category and (2) normal weight non-diabetic women as reference category. Crude and adjusted ORs were calculated. The following variables were included in the final model for LGA as possible confounders/covariates: Nordic origin (yes/no), maternal age, height, parity, smoking and chronic hypertension. The final regression models for the secondary outcomes included covariates significantly associated with the outcomes in univariate analysis. Missing indicator variables were used for maternal age and height. The likelyhood ratio test was used to explore potential interaction between BMI categories and T1DM for the risk of the adverse outcomes. A p value <0.05 was considered significant. All statistical analyses were performed using STATA 10.1 SE.

RESULTS

Between 1998 and 2007, there were 947 096 deliveries in Sweden, including 4208 (0.4%) deliveries to mothers with T1DM. Of all pregnancies, we excluded 441 records (0.05%) with extreme values on maternal age, maternal weight or height. No records were excluded due to extreme values on birth weight, but 3402 records were missing for this variable. We excluded 90 records (0.01%) due to extreme values on birth length and 14 544 were missing for birth length. In women with T1DM, 652 records (15%) were excluded due to missing data on maternal BMI or BMI <18.5 and 116 (2.8%) due to multiple pregnancies. Seventeen records were identified as both missing for BMI and with multiple pregnancies, thus giving a final study cohort of 3457 infants (1758 male infants, 51%) born to mothers with T1DM. The reference population included 764 498 singleton pregnancies to mothers without a diagnosis of diabetes, excluding 28 018 records from multiple pregnancies and 147 835 records with missing data on maternal BMI or BMI <18.5.

Reference percentiles for birth weight, birth length and PI were formed using records from all non-diabetic pregnancies and excluding stillborn infants (0.31%), infants with major malformations (1.84%) and multiple pregnancies (3.01%).

Maternal and infant characteristics

Mothers with T1DM had a significantly higher median pre-pregnancy BMI (25.1 kg/m^2) compared with the non-diabetic group (23.6 kg/m^2, p<0.001). In the type 1 diabetic cohort, 35% (n=1195) of women were overweight and 18% (n=618) were obese as compared with 26% (n=200 600) and 11% (n=82 331), respectively, in the non-diabetic population. Women with T1DM were also more often of Nordic origin and had a higher prevalence of chronic hypertension and smoking during the first trimester compared with women without diabetes (p value for all comparisons <0.01). Infants to mothers with T1DM were born at a significantly lower median gestational age, and preterm birth was four times as common compared with non-diabetic offspring (p value for all comparisons <0.001). The median birth weight was significantly higher in infants delivered by mothers with T1DM than in the reference group, table 1.

Adverse outcomes in relation to BMI category

Overall, the incidence of all adverse outcomes was significantly higher in women with T1DM, irrespective of BMI category. The incidence of the primary outcome LGA was highest in obese type 1 diabetic women; however, the differences between BMI categories did not reach statistical significance within the diabetes cohort. The incidence of all secondary outcomes was highest in obese women with T1DM, except for perinatal mortality in type 1 diabetic pregnancies with the highest recorded frequency in overweight women. Within the non-diabetic pregnancies, the incidence of all outcomes increased significantly with greater BMI category (χ^2 for trends for all outcomes p<0.001) (table 2).

There was a similar pattern of increasing OR for adverse outcome with greater BMI category in women with and without T1DM. Inclusion of maternal covariates in the regression models did not significantly change these estimates. Relative to a normal weight non-diabetic woman, the adjusted OR for the risk of having a LGA infant in overweight or obese women with T1DM was approximately 13 as compared with approximately 2 in overweight and obese non-diabetic women, table 3. In relation to a normal weight woman without diabetes, obesity in women with T1DM was associated with an adjusted OR for major malformation of 4.11 (95% CI 2.99 to 5.65) as compared with 1.15 (95% CI 1.09 to 1.22) in non-diabetic women with obesity. Compared with a normal weight non-diabetic woman, the adjusted ORs for PE in a woman with T1DM of normal weight was

Table 1 Maternal and infant characteristics, type 1 diabetes and non-diabetic reference population

	Type 1 diabetes, N=3457	Non-diabetic population, N=764 498	p Value*
Maternal characteristics			
Nordic, n (%)	3194 (92)	643 608 (84)	<0.001
Swedish origin, n (%)	3151 (91)	628 534 (82)	<0.001
Maternal age, years (median, IQR)	30 (27–34)	30 (27–33)	<0.001
Smoking first trimester, n (%)	384 (11)	72 766 (10)	0.001
Primipara, n (%)	1559 (45)	337 199 (44)	0.242
BMI, kg/m^2 (median, IQR)	25.1 (23.0–28.4)	23.6 (21.6–26.4)	<0.001
Overweight (BMI ≥25–29.9), n (%)	1195 (35)	200 600 (26)	<0.001
Obese (BMI ≥30), n (%)	618 (18)	82331 (11)	<0.001
Height, cm (median, IQR)	167 (162–170)	167 (162–170)	0.250
Chronic hypertension, n (%)	92 (2.7)	2472 (0.32)	<0.001
Infant characteristics			
Male, n (%)	1758 (51)	393 324 (51)	0.485
Gestational age, weeks (median, IQR)	38 (37–39)	40 (39–41)	<0.001
Preterm delivery, n (%)	741 (21)	35 878 (4.7)	<0.001
Birth weight, g (median, IQR)	3805 (3350–4265)	3575 (3240–3915)	<0.001
Birth length, cm (median, IQR)	51 (49–52)	51 (49–52)	0.576
LGA, BW >90 percentile, n (%)	1694 (49)	81 142 (11)	<0.001
AGA, BW 10–90 percentile, n (%)	1661 (48)	614 784 (80)	<0.001
SGA, BW <10 percentile, n (%)	109 (3.2)	76 214 (10)	<0.001

*χ^2 test, ranksum test.
AGA, appropriate for gestational age; BMI, body mass index; BW, birth weight; LGA, large for gestational age; SGA, small for gestational age.

7.17 (95% CI 6.04 to 8.50) and in combination with overweight 9.91 (95% CI 8.61 to 11.40) and in obese type 1 diabetic women, the adjusted OR was 14.19 (95% CI 11.50 to 17.50). The corresponding estimates for a non-diabetic woman with overweight or obesity were 1.74 (95% CI 1.69 to 1.80) and 3.37 (95% CI 3.25 to 3.49), respectively. The OR for Caesarean section increased with BMI category, both in women with and without T1DM, table 3.

Table 4 shows the OR for adverse outcome in women with T1DM by BMI category with normal weight women with T1DM as the reference category. In obese type 1

Table 2 Perinatal outcomes for pregnant women with or without type 1 diabetes and stratified on pre-pregnancy BMI

	BMI 18.5–24.9	BMI 25–29.9	BMI ≥30	p Value*
LGA infant				
Type 1 diabetes	778 (47)	603 (50)	313 (51)	0.170
Non-diabetic	39 265 (8.2)	26 828 (13)	15 049 (18)	<0.001
Major malformations				
Type 1 diabetes	65 (4.0)	44 (3.7)	41 (6.6)	0.008
Non-diabetic	8186 (1.7)	3736 (1.9)	1610 (2.0)	<0.001
Pre-eclampsia				
Type 1 diabetes	222 (14)	185 (15)	114 (18)	0.012
Non-diabetic	9872 (2.1)	6529 (3.3)	4810 (5.8)	<0.001
Preterm delivery				
Type 1 diabetes	322 (20)	275 (23)	144 (23)	0.041
Non-diabetic	21 714 (4.5)	9464 (4.7)	4700 (5.7)	<0.001
Perinatal mortality				
Type 1 diabetes	14 (0.85)	15 (1.3)	6 (0.97)	0.566
Non-diabetic	1554 (0.32)	948 (0.47)	593 (0.72)	<0.001
Caesarean section				
Type 1 diabetes	748 (46)	639 (53)	362 (59)	<0.001
Non-diabetic	64 131 (13)	34 081 (17)	18 166 (22)	<0.001
Neonatal overweight				
Type 1 diabetes	351 (21)	288 (24)	166 (27)	0.016
Non-diabetic	15 359 (3)	10 430 (5)	6466 (8)	<0.001

Data are presented as numbers (percentages).
*χ^2 test, Kruskal–Wallis test, χ^2 test for trends.
BMI, body mass index; LGA, large for gestational age.

Table 3 Crude and adjusted* ORs (95% CI) for adverse perinatal outcomes in pregnant women with and without T1DM and stratified on pre-pregnancy BMI

	BMI 18.5–24.9	BMI 25–29.9	BMI ≥30	Interaction p-value†
LGA infant				
T1DM				
Crude	10.16 (9.10 to 11.36)	12.40 (11.22 to 13.70)	12.29 (10.50 to 14.40)	<0.001
Adjusted	10.72 (9.56 to 12.01)	13.55 (12.23 to 15.02)	13.26 (11.27 to 15.59)	<0.001
Non-diabetic				
Crude	1.0	1.74 (1.71 to 1.77)	2.52 (2.47 to 2.57)	<0.001
Adjusted	1.0	1.76 (1.73 to 1.79)	2.60 (2.55 to 2.66)	<0.001
Major malformations				
T1DM				
Crude	2.28 (1.71 to 3.04)	2.34 (1.81 to 3.02)	4.11 (2.99 to 5.65)	0.03
Adjusted	2.28 (1.71 to 3.04)	2.34 (1.81 to 3.03)	4.11 (2.99 to 5.65)	0.03
Non-diabetic				
Crude	1.0	1.10 (1.06 to 1.14)	1.15 (1.09 to 1.22)	0.03
Adjusted	1.0	1.10 (1.06 to 1.14)	1.15 (1.09 to 1.22)	0.03
Pre-eclampsia				
T1DM				
Crude	7.12 (6.02 to 8.42)	9.30 (8.11 to 10.67)	11.23 (9.15 to 13.77)	<0.001
Adjusted	7.17 (6.04 to 8.50)	9.91 (8.61 to 11.40)	14.19 (11.50 to 17.50)	<0.001
Non-diabetic				
Crude	1.0	1.61 (1.56 to 1.66)	2.96 (2.86 to 3.07)	<0.001
Adjusted	1.0	1.74 (1.69 to 1.80)	3.37 (3.25 to 3.49)	<0.001
Preterm delivery				
T1DM				
Crude	4.86 (4.22 to 5.60)	6.23 (5.53 to 7.02)	6.39 (5.30 to 7.71)	0.16
Adjusted	4.72 (4.09 to 5.44)	5.98 (5.31 to 6.74)	5.97 (4.94 to 7.21)	0.15
Non-diabetic				
Crude	1.0	1.05 (1.02 to 1.07)	1.28 (1.24 to 1.32)	0.16
Adjusted	1.0	1.04 (1.02 to 1.07)	1.26 (1.22 to 1.30)	0.15
Perinatal mortality				
T1DM				
Crude	2.55 (1.36 to 4.76)	3.93 (2.49 to 6.19)	3.14 (1.40 to 7.04)	0.29
Adjusted	2.46 (1.32 to 4.60)	3.72 (2.36 to 5.89)	2.86 (1.27 to 6.44)	0.31
Non-diabetic				
Crude	1.0	1.47 (1.35 to 1.59)	2.24 (2.04 to 2.46)	0.29
Adjusted	1.0	1.46 (1.35 to 1.59)	2.22 (2.03 to 2.44)	0.31
Caesarean section				
T1DM				
Crude	5.59 (5.00 to 6.25)	7.09 (6.42 to 7.83)	9.44 (8.04 to 11.08)	0.42
Adjusted	5.69 (5.09 to 6.37)	7.12 (6.44 to 7.88)	9.35 (7.95 to 11.00)	0.36
Non-diabetic				
Crude	1.0	1.33 (1.31 to 1.35)	1.84 (1.81 to 1.88)	0.42
Adjusted	1.0	1.34 (1.32 to 1.36)	1.87 (1.83 to 1.90)	0.36
Neonatal overweight				
T1DM				
Crude	8.46 (7.39 to 9.70)	9.93 (8.83 to 11.17)	11.71 (9.79 to 14.00)	<0.001
Adjusted	8.40 (7.32 to 9.64)	9.86 (8.76 to 11.11)	11.29 (9.42 to 13.53)	<0.001
Non-diabetic				
Crude	1.0	1.66 (1.62 to 1.71)	2.59 (2.51 to 2.67)	<0.001
Adjusted	1.0	1.65 (1.61 to 1.69)	2.55 (2.48 to 2.63)	<0.001

Reference group: non-diabetic women with normal pre-pregnancy BMI.
*Adjusted for ethnicity, maternal age, height, parity, smoking first trimester and chronic hypertension.
†Interaction between BMI category and T1DM.
BMI, body mass index; LGA, large for gestational age; T1DM, type 1 diabetes.

diabetic women, the adjusted OR of major malformations (1.77 (95% CI 1.18 to 2.65)) and PE (1.74 (95% CI 1.35 to 2.25)) were significantly increased compared with normal weight type 1 diabetic women. The OR of Caesarean section was significantly increased in both overweight and obese type 1 diabetic women, table 4. The OR for LGA did not differ significantly between the different BMI categories. However, the adjusted OR for delivering a disproportionate LGA infant with neonatal overweight (PI >90th percentile) was significantly

Table 4 Crude and adjusted* ORs; 96% CI for adverse perinatal outcome in pregnant women with T1DM and stratified on BMI

	T1DM		
	BMI 18.5–24.9	BMI 25–29.9	BMI ≥30
LGA infant			
Crude	1.0	1.13 (0.98 to 1.32)	1.14 (0.95 to 1.37)
Adjusted	1.0	1.18 (1.01 to 1.38)	1.21 (1.00 to 1.47)
Major malformations			
Crude	1.0	0.93 (0.63 to 1.37)	1.73 (1.15 to 2.58)
Adjusted	1.0	0.92 (0.62 to 1.36)	1.77 (1.18 to 2.65)
Pre-eclampsia			
Crude	1.0	1.17 (0.95 to 1.45)	1.45 (1.13 to 1.86)
Adjusted	1.0	1.21 (0.98 to 1.50)	1.74 (1.35 to 2.25)
Preterm delivery			
Crude	1.0	1.23 (1.02 to 1.47)	1.25 (1.00 to 1.56)
Adjusted	1.0	1.22 (1.02 to 1.47)	1.25 (1.00 to 1.56)
Perinatal mortality			
Crude	1.0	1.48 (0.71 to 3.08)	1.14 (0.44 to 2.98)
Adjusted	1.0	1.47 (0.70 to 3.03)	1.08 (0.41 to 2.83)
Caesarean section			
Crude	1.0	1.38 (1.19 to 1.60)	1.69 (1.40 to 2.04)
Adjusted	1.0	1.37 (1.18 to 1.60)	1.67 (1.38 to 2.03)
Neonatal overweight			
Crude	1.0	1.17 (0.98 to 1.40)	1.35 (1.09 to 1.67)
Adjusted	1.0	1.19 (0.99 to 1.42)	1.36 (1.09 to 1.69)

Reference group: type 1 diabetic women with normal pre-pregnancy BMI.
*Adjusted for ethnicity, maternal age, height, parity, smoking first trimester and chronic hypertension.
BMI, body mass index; LGA, large for gestational age; T1DM, type 1 diabetes.

increased in obese type 1 diabetic women 1.36 (95% CI 1.09 to 1.69).

DISCUSSION

This study shows that high maternal pre-pregnancy BMI is a very important risk factor for adverse pregnancy outcome in women with and without T1DM. High maternal BMI and T1DM are independent risk factors for maternal and perinatal complications. However, T1DM remains a stronger risk factor for adverse outcome than obesity. The risk of adverse outcome in women with concomitant T1DM and obesity exceeds that of either condition alone, indicating synergism between the two exposures. Obesity in T1DM is associated with significantly increased risk of PE, major malformations, neonatal overweight and Caesarean section as compared with type 1 diabetic women with normal BMI.

The prevalence of overweight and obesity in pregnant women is increasing in Sweden and worldwide,[1 12] and the harmful effects of high maternal BMI on pregnancy outcome are well established in the general obstetric population.[2–11] On the other hand, data on the potential association between high maternal BMI and adverse pregnancy outcome in women with T1DM is scarce.[17 19 20] In a cohort of 46 women with T1DM and nephropathy, maternal overweight was identified as an important risk factor for poor pregnancy outcome.[19] In mixed populations of women with pregestational diabetes, maternal obesity has been associated with pregnancy complications[20] and increased risk of birth defects.[17] These two studies however do not separate women with diabetes type 1 from those with diabetes type 2 and do not include any comparable data from a non-diabetic reference population.

The present study is to our knowledge the first to present risk estimates of obstetric and perinatal complications in a large cohort of women with exclusively T1DM, stratified by BMI category and compared with a non-diabetic reference population. The large sample size enabled risk estimation of rare outcomes such as perinatal mortality and major malformations in relation to subgroups of maternal BMI. The population-based study design provides unanimous risk estimates for overweight and obese women with and without T1DM. The vast majority of our study population is of Nordic origin and 91% were Swedish. The study population is also homogenous with respect to medical care in pregnancy. In Sweden, healthcare is free of charge as well as insulin, test strips for home monitoring of glucose and equipment for insulin administration. The care of pregnant women with T1DM is uniform over the whole country and pregnancy outcome does not differ with geographical area.[13]

Some limitations with the present study should be noted. BMI was calculated from recalled data on pre-pregnancy weight and height. Women tend to underestimate their weight, and it has been demonstrated that this bias increases directly with the degree of overweight.[21] A potential misclassification of women to lower BMI categories would lead to an underestimation of our

findings of increased risks associated with high maternal BMI. The Swedish MBR does not collect data on maternal glycaemic control, duration of diabetes and insulin regimens or data on diet and physical activity. Data on socioeconomic factors are also very limited. Consequently, the impact of socioeconomic factors, diet, physical activity and level of control on the risk of adverse outcome could not be assessed. It is plausible that the achieved level of metabolic control differed between normal weight, overweight and obese type 1 diabetic women. In a study on pregnancies complicated by gestational diabetes, the fasting glucose levels were significantly higher in obese compared with overweight and normal weight women.[14] However, results from the HAPO study confirm that maternal BMI and glycaemia exert independent effects on the risk of adverse pregnancy outcome.[2]

In the present study, obese women with T1DM had significantly increased risks of major malformations and PE as compared with normal weight women with T1DM. This is in line with the finding of an interaction between maternal diabetes and obesity on the risk of adverse outcome in a mixed population of women with different types of diabetes.[17] However, the increased risk of major malformations in relation to BMI in the present analysis should be interpreted with caution as maternal overweight and obesity rend ultrasound assessment of fetal anatomy difficult,[22] and we do not have data on the number of induced abortions due to malformations. Maternal hyperglycaemia in early pregnancy is a well-known risk factor for major malformations and PE.[23] Obesity is associated with increased insulin resistance,[12] and one could speculate that women with obesity had a poorer level of control in early pregnancy than women with normal or slightly elevated BMI. In line with previous studies, we found increased risks of PE and major malformations in obese non-diabetic women.[5 6 10] In the present study, the risks of these complications were also significantly elevated in non-diabetic women with overweight. Obesity is associated with decreased insulin sensitivity, and already slightly elevated levels of fasting glucose, within the upper normal range, are associated with increased risk of PE in women without diabetes.[24] In Sweden, there is no uniform screening for gestational diabetes. It is possible that the increased risk of PE and major malformations in overweight and obese women in the reference group is partly due to undetected cases of impaired glucose tolerance or diabetes. Interestingly, maternal pre-pregnancy BMI has been demonstrated as a stronger predictor of major malformations than severity of gestational diabetes.[25]

In women with T1DM, the incidence of LGA was very high in all weight classes and increased with greater BMI category. However, the OR for an LGA outcome did not differ significantly between BMI categories, as opposed to in non-diabetic women. This is in accordance with findings in two recent studies.[26 27] On the contrary, the risk of delivering a disproportionate, overweight LGA infant (PI >90th percentile) was significantly increased in obese women within the type 1 diabetic cohort. In accordance with the study by Ehrenberg, our findings indicate that maternal overweight is an important risk factor for LGA, but maternal diabetes has an even greater impact.[28] A possible contributing factor to this finding could also be the increasing prevalence of PE with greater BMI category.

This study confirms the observations in non-diabetic pregnancies[2–5] that increasing maternal BMI is associated with increased risk of delivery by Caesarean section also in women with T1DM. The increased incidence of complications such as PE and LGA in these groups most likely contributes to this finding.

The majority of perinatal deaths were stillbirths in all BMI categories and in both women with and without T1DM. The risk of perinatal mortality was independent of BMI category within the type 1 diabetic cohort but increased significantly with higher BMI in the reference group. This finding is in line with previous studies, reporting increased risk of both stillbirth and neonatal mortality in obese non-diabetic women even after adjusting for maternal and perinatal risk factors.[7–9] The lack of a significantly increased risk of perinatal mortality with increasing BMI category within the diabetes cohort indicate that diabetes is a stronger risk factor for perinatal mortality than maternal overweight/obesity.

In the present study, we found an increasing risk of preterm delivery with greater BMI category, both in women with and without T1DM. Results from some earlier studies have shown an increased risk of preterm delivery in obese non-diabetic women,[3 4] while others have reported the opposite association.[2 5]

It is hypothesised that the increased risk of pregnancy complications in overweight and obese women is related to increased maternal fat mass. In the present study, pre-pregnancy BMI was used as a proxy for maternal fat mass as there is a strong correlation (r^2=0.86) between pre-pregnancy BMI and maternal fat mass in women without diabetes.[29] However, BMI does not provide information on the localisation of fat mass. One suggested link between high maternal pre-pregnancy BMI and increased risk of adverse outcome pregnancy is a large visceral fat mass. The visceral fat mass is associated with increased insulin resistance, inflammation and lipotoxicity with potential harmful effects on maternal vascular and placental function and fetal development.[30] Other pathophysiological mechanisms behind the increased risk of adverse pregnancy outcome in overweight/obese mothers are not clear but are most likely complex. Genetic and socioeconomic factors, maternal diet and physical activity are probable contributing factors.

In conclusion, this population-based study on more than 3000 type 1 diabetic pregnancies demonstrates a strong association between maternal pre-pregnancy BMI and elevated risk of adverse pregnancy outcome. T1DM in combination with overweight or obesity constitutes a higher risk than either condition alone.

Striving towards normal pre-pregnancy BMI in women with T1DM could hopefully reduce the risk of adverse outcome.

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