Microalbuminuria, Preeclampsia, and Preterm Delivery in Pregnant Women With Type 1 Diabetes

Results from a nationwide Danish study

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OBJECTIVE — To study the association between microalbuminuria and development of preeclampsia and preterm delivery in pregnant women with type 1 diabetes.

RESEARCH DESIGN AND METHODS — This was a population-based prospective study in 846 normoalbuminuric or microalbuminuric women with type 1 diabetes without antihypertensive treatment in early pregnancy. Data were collected prospectively by one to three caregivers in each center and reported to a central registry.

RESULTS — The prevalence of microalbuminuria in the first trimester was 10%, median diabetes duration was 11 years, and third-trimester A1C was 6.6%. The frequencies of preeclampsia and preterm delivery before 34 weeks in the microalbuminuric group were 40 and 13%, both significantly higher than those in the normoalbuminuric group (12 and 6%, respectively, $P < 0.001$). After adjustments for possible confounders, significant predictors for development of preeclampsia were microalbuminuria (odds ratio 4.0 [95% CI]), nulliparity (3.1 [1.9–5.1]), and third-trimester A1C (1.3 [1.1–1.5] per 1% increase). Delivery before 34 weeks was associated with early microalbuminuria in univariate analyses, but in multivariate analyses A1C was the only significant predictor of this outcome. Preeclampsia was associated with a threefold higher risk of delivery before 34 weeks.

CONCLUSIONS — The presence of microalbuminuria in early pregnancy is associated with a fourfold increased risk of developing preeclampsia. A1C values during pregnancy are highly predictive of both preeclampsia and preterm delivery. Future research with antihypertensive treatment in normotensive, microalbuminuric pregnant women to prevent preeclampsia is proposed.

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Women with type 1 diabetes and their offspring are at increased risk of development of preeclampsia and preterm delivery (1). It is well documented that the presence of diabetic nephropathy is associated with a very high risk of gestational hypertension, preeclampsia, and preterm delivery. The forerunner of diabetic nephropathy is characterized by urinary albumin excretion between 30 and 300 mg/24 h, so-called microalbuminuria (2,3). Whether the presence of microalbuminuria in early pregnancy is also associated with development of preeclampsia has only been investigated in relatively small selected samples (4–9), and some of these include women with type 1, type 2, and gestational diabetes mellitus. In one center a prevalence of preeclampsia of 40% in 26 women with type 1 diabetes and microalbuminuria has been described (9). Others could not find an association between slightly elevated protein excretion early in pregnancy and development of preeclampsia (10).

In Denmark, clinical data on >1,200 pregnancies in women with type 1 diabetes were collected prospectively during 7 years. The current report focuses on the relationship between microalbuminuria present at the first pregnancy visit and the risk of preeclampsia and preterm delivery in patients without preexisting use of antihypertensive medication and/or diabetic nephropathy.

RESEARCH DESIGN AND METHODS

— During 1993–1999 all pregnancies (N = 1,215) in Danish women with type 1 diabetes were reported prospectively to a central registry in the Danish Diabetes Association (11). The patients delivered in eight centers. Pregnancies were registered if the duration was ≥24 weeks, and only the first pregnancy during the study period was included. Of the women, 66 with overt diabetic nephropathy (urine albumin excretion rate [UAER] ≥300 mg/24 h or 200 μg/min) and 30 receiving antihypertensive medical treatment at the first visit were excluded together with those with recurrent pregnancies (n = 225) and twin pregnancies (n = 24) and those with no information on early urinary albumin to-creatinine ratio (n = 24), leaving 846 women for analysis. Hypertension was defined as blood pressure ≥140/90 mmHg. The methods of the data collection were described previously (11). In brief, information on maternal demography, diabetes status, and pregnancy outcome was collected prospectively with status at predefined time points: up to 3

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months before gestation, first trimester, second trimester, third trimester, and after delivery. Data were reported after delivery by one to three caregivers per center. Microalbuminuria in early pregnancy was defined as microalbuminuria before conception and/or during the first trimester (UAER between 30 and 300 mg/24 h or between 20 and 200 μg/min). The clinical practice for instituting antihypertensive treatment in pregnancy was similar in all centers during the study period: blood pressure of ≥140/90 mmHg. All patients gave informed consent, and the local ethics committees approved the study. A subgroup of ~25% of the material from one center was included in a previous report (9).

Preeclampsia was defined as blood pressure ≥140/90 mmHg and proteinuria (2+ on a dipstick) after 20 weeks of gestation and preterm delivery as delivery before 37 completed gestational weeks. Gestational age was based on an ultrasound scan before 20 weeks in the majority of the women; alternatively the date of the last menstrual bleeding was used. For further details of the clinical setting, see Jensen et al. (11).

Statistical analysis was performed with STATA 9.0 (StataCorp, College Station, TX). Data are given as medians (interquartile range), numbers, and percentages. Comparisons were made by the Wilcoxon rank-sum test or the χ^2 test. Risks of preeclampsia and preterm delivery before 34 weeks are given as odds ratio (95% CI). Logistic regression analysis was performed to determine predictors for preeclampsia and preterm delivery: age, BMI, preconceptional daily insulin dose, first- and third-trimester A1C (continuous variables), and nulliparity, proliferative retinopathy, blood pressure ≥140/90 mmHg, and microalbuminuria at first visit/before conception (binary variables). $P < 0.05$ was considered statistically significant. Because the first- and third-trimester A1C values were highly correlated, we only inserted one of them at the time in the multivariate models. Results are given for both models in Tables 2 and 3.

RESULTS — The women in the study were median 28 (interquartile range 25–32) years old and had BMI of 23 (21–25) kg/m^2 and diabetes duration of 11 (5–17) years. Of the women, 509 (60%) were nulliparous and first- and third-trimester A1C values were 7.2 (6.5–8.0)% and 6.6 (6.1–7.4)%, respectively. Birth weight and gestational age of the offspring were 3,625 (3,145–4,030) g and 260 (252–266) days, respectively.

Of the women, 93 (10%) had microalbuminuria in early pregnancy, and they were characterized by longer duration of diabetes, lower parity, higher BMI, higher prevalences of proliferative retinopathy, untreated hypertension at conception, and higher A1C (Table 1). Of the women with microalbuminuria, 41% (34 of 84) developed preeclampsia vs. 12% (97 of 762) of the women with normal UAER ($P < 0.001$). Hypertension during the second trimester was seen in 13% (11 of 84) of the microalbuminuric women vs. 1.5% (11 of 762) in the normoalbuminuric group.

BMI, high blood pressure at conception, diabetes duration, and daily insulin dose at conception were significantly associated with preeclampsia in the univariate analyses but not in the multivariate analysis (Table 2). A1C values during the

Table 1—*Maternal and fetal characteristics in 846 normoalbuminuric and microalbuminuric women with type 1 diabetes*

	Normoalbuminuria	Microalbuminuria	*P*
n	762	84	
Age (years)	28 (25–32)	27 (24–31)	0.34
BMI (kg/m^2)	23 (21–25)	24 (22–26)	0.002
Duration of diabetes (years)	10 (4–17)	15 (10–20)	<0.001
Nulliparity	452 (59)	57 (68)	0.12
Prepregnancy insulin dose (IU/day)	44 (32–54)	47 (40–58)	<0.001
Blood pressure ≥140/90 mmHg at first visit	5 (1)	3 (4)	<0.001
Proliferative retinopathy	25 (3)	9 (11)	<0.001
First-trimester A1C (%)	7.1 (6.4–8.0)	7.6 (6.8–8.5)	0.007
Third-trimester A1C (%)	6.6 (6.0–7.3)	6.8 (6.2–7.5)	0.14
Hypertension during second trimester*	11 (1.5)	11 (13)	<0.001
Preeclampsia	92 (12)	34 (41)	<0.001
Gestational age (days)	260 (252–266)	260 (250–266)	0.2
Gestational age <34 weeks	45 (6)	11 (13)	0.02
Gestational age <37 weeks	284 (37)	30 (36)	0.78
Birth weight (g)	3,650 (3,162–4,060)	3,335 (2,900–3,650)	<0.001
Large-for-gestational-age infant	483 (63)	42 (50)	0.02

Data are medians (interquartile range) or *n* (%). *Blood pressure ≥140/90 mmHg.

Table 2—*Predictors of preeclampsia in women with type 1 diabetes: univariate and multivariate logistic regression analyses*

	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (years)	1.0 (0.9–1.0)	0.07	—	—
BMI (kg/m^2)	1.1 (1.0–1.1)	0.003	1.04 (1.0–1.1)	0.17
Duration of diabetes (years)	1.03 (1.01–1.05)	0.003	1.01 (1.0–1.04)	0.21
Nulliparity	2.6 (1.7–4.1)	<0.001	3.1 (1.9–5.3)	<0.001
Prepregnancy insulin dose (IU/day)	1.02 (1.01–1.03)	<0.001	1.01 (1.00–1.03)	0.14
Blood pressure ≥140/90 mmHg at first visit	5.8 (1.4–23.6)	0.011	1.0 (1.0–1.02)	0.91
Proliferative retinopathy	1.9 (0.9–4.4)	0.30	—	—
First-trimester A1C (%)*	1.2 (1.0–1.3)	0.016	—	—
Third-trimester A1C (%)	1.2 (1.1–1.4)	0.008	1.3 (1.1–1.5)	0.010
Microalbuminuria	5.0 (3.0–8.1)	<0.001	4.0 (2.2–7.2)	<0.001

*First-trimester A1C was not a significant predictor in a separate multivariate model without third-trimester A1C (OR 1.2 [95% CI 0.9–1.4], $P = 0.07$). ORs of microalbuminuria, nulliparity, and prepregnancy insulin dose did not change significantly in this model.

Table 3—*Predictors of delivery before gestational week 34 in women with type 1 diabetes: univariate and multivariate logistic regression analyses*

	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Prepregnancy insulin dose (IU/day)	1.01 (1.00–1.03)	0.045	1.01 (0.99–1.03)	0.32
First-trimester A1C (%)*	1.3 (1.1–1.5)	0.010		
Third-trimester A1C (%)	1.5 (1.1–1.9)	0.003	1.6 (1.2–2.0)	0.003
Microalbuminuria	2.4 (1.2–4.8)	0.015	1.6 (0.6–4.0)	0.34

*First-trimester A1C was a significant predictor in a separate multivariate model without third-trimester A1C (OR 1.3 [95% CI 1.1–1.6], $P = 0.004$).

first and third trimesters were both positively related to the rate of preeclampsia. Because these values correlated strongly, we inserted only one A1C value at the time in the multivariate models. Independent predictors of preeclampsia were early microalbuminuria (odds ratio [OR] 4.0 [95% CI 2.2–7.2]), nulliparity (3.1 [1.9–5.3]), and third-trimester A1C (1.3 [1.1–1.5] increase per 1%).

Neonatal outcomes in the normoalbuminuric versus microalbuminuric group were hypoglycemia (intravenous glucose) 28 vs. 30% ($P = 0.61$), perinatal mortality 3 vs. 5% ($P = 0.26$), respiratory distress 17 vs. 19% ($P = 0.65$), and jaundice (phototherapy) 15 vs. 17% ($P = 0.76$).

The rates of preterm delivery before 37 weeks were equal in the two groups (37 vs. 36%). Preterm delivery before 34 weeks was seen in 11% (13 of 84) of the women with microalbuminuria and in 6% (45 of 746) of the women with normoalbuminuria. First- and third-trimester A1C, microalbuminuria, and preconceptional insulin dose were significant predictors for preterm delivery before 34 weeks in univariate analyses, whereas only A1C remained significant in the multivariate analyses (Table 3). Of the very preterm deliveries, 34% (19 of 56) were complicated by preeclampsia vs. 13% (107 of 790) among deliveries after 34 weeks (OR 3.3 [95% CI 1.8–5.9], $P < 0.001$). Hypertension during the second trimester was seen in 16% (9 of 55) and 2% (13 of 780), respectively (very preterm vs. others) (2.3 [1.7–3.1], $P < 0.001$).

CONCLUSIONS — Our study confirms that both microalbuminuria in early pregnancy and poor glycemic control throughout pregnancy are strongly associated with development of preeclampsia in women with type 1 diabetes. Thus, the risk of preeclampsia was fourfold higher in women with microalbuminuria compared with that in normoalbuminuric women.

Strengths and weaknesses of the study and relation to other studies

To our knowledge, this is the largest prospective national population-based study of unselected pregnant women with type 1 diabetes with detailed information on glycemic control and microangiopathic complications in early pregnancy. The large sample size and homogeneity of the population give a good estimate of the incidence of preeclampsia in pregnant women with type 1 diabetes. For comparison, the rate of preeclampsia in the background population was 2.6% (11).

Of the women with microalbuminuria, 25% were also included in the study of Ekbom et al. (9), but the majority of the remaining 75% of women with microalbuminuria came from seven other centers without any special focus on microalbuminuria. Thus, the bias of this study is considered to be relatively small because the overall incidence of preeclampsia was the same. Furthermore, the clinical practice for instituting antihypertensive treatment in pregnancy was similar in all centers during the study period. Another weakness of our study was that eight different centers contributed to the register. It could be argued that a number of women may have type 2 diabetes, as no data were recorded on C-peptide or islet cell immune markers. However, women entering the study were all judged to have type 1 diabetes by their caregivers and were receiving insulin treatment before conception, the majority were of normal weight, and the mean diabetes duration was 11 years. During the study period, both severe childhood obesity and type 2 diabetes among young women were uncommon in Caucasian Danish women.

It is well known that the presence of diabetic nephropathy leads to an even higher rate of preeclampsia (1,9) and that antihypertensive treatment reduces urinary albumin excretion and thereby confounds the data (12,13). Women with diabetic nephropathy and women receiving antihypertensive treatment without any signs of diabetic nephropathy were therefore excluded. Measurements of urinary albumin excretion in women with diabetes are now generally preferred among diabetologists, whereas measurements of small amounts of protein are not widely used. Incidental detection of small amounts of protein in the urine is frequently seen. In addition, urinary albumin excretion does not change during normal pregnancy, whereas an increase in protein excretion can be demonstrated (1). This fact may explain why a study using urinary protein excretion could not demonstrate that a slightly increased level was associated with increased risk of preeclampsia (10).

Meaning of the study

The study highlights a significant clinical problem and calls for improved clinical practice in this group of patients. Our finding of an association between metabolic control and development of preeclampsia is in accordance with previous findings from Scandinavia (14,15). Both high levels of A1C early in pregnancy and a suboptimal decrease in A1C during pregnancy are associated with development of preeclampsia (16). A decrease in A1C of at least 0.5% during pregnancy and an upper normal limit of 5.6% in late pregnancy have been described in the normal population of pregnant women (17). Strict metabolic control aiming for A1C near the upper normal limit in pregnancy of women with a high risk of development of preeclampsia thus seems justified.

In nonpregnant normotensive patients with type 1 diabetes and microalbuminuria, antihypertensive treatment with an ACE inhibitor improves the long-term prognosis by postponing the progression to overt nephropathy (18). Furthermore, data suggest that treatment with an ACE inhibitor before pregnancy has beneficial effects on maternal renal function during pregnancy and overall pregnancy outcome (12). However, in pregnancy, exposure to ACE inhibitors and angiotensin II receptor blockers has been associated

with fetal complications including congenital malformations (19,20). Thus, treatment with ACE inhibitors or angiotensin receptor blockers should be discontinued before conception or as soon as pregnancy is suspected and replaced by alternative antihypertensive drugs with careful monitoring of blood pressure and UAER. In the present study, other antihypertensive agents were initiated only if blood pressure exceeded 140/90 mmHg. This situation often occurred at the time when preeclampsia was diagnosed in these women, and the majority of the women in this study were therefore not treated with antihypertensive medication until preeclampsia actually developed. The beneficial effect of antihypertensive treatment based on methyldopa or labetalol in normotensive women with microalbuminuria has been suggested (13,21). Applying intensive antihypertensive treatment from the early phase of pregnancy in woman with microalbuminuria seems to reduce the risk of preeclampsia leading to preterm delivery (21). Our data on microalbuminuria and second-trimester hypertension might indicate that a rise in blood pressure was preceded by microalbuminuria. On the other hand, data were not collected with this purpose, and we cannot draw firm conclusions on this point.

We found a higher frequency of preterm delivery before 34 weeks in the microalbuminuric group. After adjustment for confounders, early microalbuminuria was not a significant predictor whereas both first- and third-trimester A1C remained highly predictive. A possible explanation is the association between microalbuminuria and glycemic control, thus indicating that the relationship with preterm delivery of the former may have been underestimated. Another issue is the small number at risk, which may lead to type 2 error. As expected, preeclampsia was associated with delivery before 34 weeks. Our dataset cannot provide more details concerning this association, but it is likely that the presence of preeclampsia led to indicated preterm delivery. Preeclampsia, pregnancy-induced hypertension, and preterm delivery might be part of the same disease complex: both second-trimester hypertension and preeclampsia were highly associated with very preterm delivery. However, adding these components to the multivariate model did not markedly change the strength of other predictors. These associations should be investigated prospectively with data collection focusing on the precise onset of the rise in blood pressure and/or UACR and more clinical details on the preterm delivery.

In contrast to our previous study (9), we did not identify microalbuminuria as a significant predictor of preterm delivery before 37 weeks. This result may be explained by a less precise recording of microalbuminuria in the present study or the fact that women with antihypertensive treatment or overt nephropathy were excluded from our analysis. Another possibility is that almost 50% of the women delivered preterm, partly due to routine procedures followed at that time. Still, preterm delivery before week 34 might have a more profound adverse effect on the infant than preterm delivery before 37 weeks and is therefore clinically relevant.

Unanswered questions and proposals for future research

The results of this study underline the need for identification and treatment of women with microalbuminuria and poor glycemic control in early pregnancy. So far, the primary focus has been on glycemic control, but observational studies indicate that more aggressive antihypertensive treatment in normotensive, microalbuminuric women with type 1 diabetes may reduce the risk of development of preeclampsia with no apparent adverse effect on pregnancy outcome (13,21). These findings should be confirmed in large-scale prospective randomized studies.

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