

**Microalbuminuria, preeclampsia and preterm delivery in pregnant women with type 1 diabetes - results from a nation-wide Danish study.**

Running title: Predictors of preeclampsia in type 1 diabetes

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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:* Population-based prospective study in 846 normo- or microalbuminuric women with type 1 diabetes without antihypertensive treatment in early pregnancy. Data were collected prospectively by 1-3 caregivers in each center and reported to a central registry.

*Results:* The prevalence of microalbuminuria in the first trimester was 10%, median diabetes duration 11 years and 3<sup>rd</sup> trimester HbA1c 6.6 %. The frequency of preeclampsia and preterm delivery before 34 weeks in the microalbuminuric group was 40% and 13%, both significantly higher than in the normoalbuminuric group where the figures were 12% and 6% respectively ( $p < 0.001$ ). After adjustments for possible confounders, significant predictors for development of preeclampsia were: Microalbuminuria 4.0 (2.2-7.2) (odds ratio, 95% confidence interval), nulliparity 3.1 (1.9-5.1) and 3<sup>rd</sup> trimester HbA1c 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 HbA1c was the only significant predictor of this outcome. Preeclampsia was associated with a threefold higher risk of delivery before 34 weeks.

*Conclusions:* Presence of microalbuminuria in early pregnancy is associated with a four-fold increased risk of developing preeclampsia. HbA1c 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.

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 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/24h – so called microalbuminuria (2, 3). Whether presence of microalbuminuria in early pregnancy is also associated with development of preeclampsia is only investigated in relatively small selected samples (4-9) and some of these include both 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 more than 1200 pregnancies in women with type 1 diabetes were prospectively collected during 7 years. The current report focuses on the relationship between microalbuminuria present at first pregnancy visit and the risk of preeclampsia and preterm delivery in patients without preexisting antihypertensive medication and/or diabetic nephropathy.

## **RESEARCH DESIGN AND METHODS**

During 1993-99 all pregnancies (N=1215) in Danish women with type 1 diabetes were prospectively reported 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 or more and only the first pregnancy during the study period

was included. Sixty-six women with overt diabetic nephropathy (Urine Albumin Excretion Rate (UAER)  $\geq$  300 mg/24 hours or 200  $\mu$ g/min) and 30 women with antihypertensive medical treatment at first visit were excluded together with recurrent pregnancies (n=225), twin pregnancies (n=24) and pregnancies with no information of early UACR (n=24) leaving 846 pregnancies for analysis. Hypertension was defined as blood pressure  $>$  140/90 mmHg. The methods of the data collection are described in (11). In brief, information of maternal demography, diabetes status and pregnancy outcome was collected prospectively with status at predefined time-points: up to 3 months prior to gestation, 1<sup>st</sup> trimester, 2<sup>nd</sup> trimester, 3<sup>rd</sup> trimester and after delivery. Data were reported after delivery by 1-3 caregivers per center. Microalbuminuria in early pregnancy was defined as microalbuminuria prior to conception and/or during 1<sup>st</sup> trimester (UAER between 30 and 300 mg/24h or between 20 and 200  $\mu$ g/min). The clinical practice for instituting antihypertensive treatment in pregnancy was similar in all centers during the study period: Blood pressure of 140/90 or higher. All patients gave informed consent, and the local ethic committees approved the study. A subgroup of about 25% of the material from one center was included in (9).

Preeclampsia was defined as blood pressure  $\geq$  140/90 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 last menstrual bleeding was used. For further details of the clinical setting please see (11).

Statistics were performed with STATA 9.0 (Stata Corporation, College Station, Texas). Data are given as median and

interquartile range, numbers and %. Comparisons were made by Wilcoxon Rank Sum test or Chi<sup>2</sup>-test. Risks of preeclampsia and preterm delivery before 34 weeks are given as odds ratio and 95% confidence intervals. Logistic regression analysis was performed to determine predictors for preeclampsia and preterm delivery: Age, body mass index (BMI), preconceptional daily insulin dose, 1<sup>st</sup> and 3<sup>rd</sup> trimester HbA1c (continuous variables) and nulliparity, proliferative retinopathy, blood pressure  $\geq$  140/90 and microalbuminuria at first visit/prior to conception (binary variables). P-values  $<$  0.05 were considered statistically significant. As 1<sup>st</sup> and 3<sup>rd</sup> trimester HbA1c values were highly correlated we only inserted one of them at the time in the multivariate models. Results are given for both models in table 2 and 3.

## **RESULTS**

The women in the study were 28 (25-32) years old, had BMI of 23 (21-25) kg/m<sup>2</sup> and diabetes duration of 11 (5-17) years (median and interquartile range). Fivehundred-and-nine women (60%) were nulliparous and 1<sup>st</sup> and 3<sup>rd</sup> trimester HbA1c were 7.2 (6.5-8.0) % and 6.6 (6.1-7.4) % respectively. Birth weight and gestational age of the offspring were 3625 (3145-4030) g and 260 (252-266) days.

Ninety-three women (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 HbA1c (table 1). Forty-one percent (34/84) of the women with microalbuminuria developed preeclampsia versus 12 % (97/762) of the women with normal UAER ( $p <$  0.001). Hypertension during 2<sup>nd</sup> trimester was seen in 13% (11/84) of the microalbuminuric women versus 1.5% (11/762) 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). HbA1c values during 1<sup>st</sup> and 3<sup>rd</sup> trimester were both positively related to the rate of preeclampsia. Because these values correlated strongly we inserted only one HbA1c value at the time in the multivariate models. Independent predictors of preeclampsia were: early microalbuminuria (OR (95% CI): 4.0, (2.2-7.2)), nulliparity (3.1 (1.9-5.3)) and 3<sup>rd</sup> trimester HbA1c (1.3 (1.1-1.5) increase per %).

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

The rate of preterm delivery before 37 weeks were equal in the two groups (37% vs. 36%). Preterm delivery before 34 weeks was seen in 13 % (13/84) of the women with microalbuminuria and in 6% (45/746) of the women with normoalbuminuria. First and 3<sup>rd</sup> trimester HbA1c, microalbuminuria and preconceptional insulin dose were significant predictors for preterm delivery before 34 weeks in univariate analyses, whereas only HbA1c remained significant in the multivariate analyses (table 3). Thirty-four percent (19/56) of the very preterm deliveries were complicated by preeclampsia versus 13% (107/790) among deliveries after 34 weeks i.e. OR (95% CI) of 3.3 (1.8-5.9);  $p <$  0.001. Hypertension during 2<sup>nd</sup> trimester was seen in 16% (9/55) and 2% (13/780) respectively (very preterm versus others) with OR (95% CI) of 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 to normoalbuminuric women.

Strengths and weaknesses of the study and in 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 gives 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).

Twenty-five percent of the women with microalbuminuria were also included in this study of Ekblom et al (9), but the vast majority of the remaining 75% women with microalbuminuria came from 7 other centers without any special focus on microalbuminuria. Thus, the bias of this is considered to be relatively small, as 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 8 different centers contributed to the register. It could be argued that a number of women might 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 as having type 1 diabetes by their caregivers and on insulin treatment before conception, the majority was 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 presence of diabetic nephropathy leads to an even higher rate of preeclampsia (1, 9) and that antihypertensive treatment reduces the urinary albumin excretion and thereby confound the data (12, 13). Women with diabetic nephropathy and women on 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 while measurements of small amount of protein is not widely used. Incidental detection of small amounts of protein in the urine is frequently found. In addition, urinary *albumin* excretion does not change during normal pregnancy while an increase in *protein* excretion can be demonstrated (1). This might 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 call 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 HbA1c early in pregnancy and suboptimal decrease in HbA1c during pregnancy are associated with development of preeclampsia (16). A decrease in HbA1c 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). A strict metabolic control aiming for HbA1c near the upper normal limit in pregnancy of women with high risk of development of preeclampsia seems thus justified.

In non-pregnant 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 ACE inhibitor prior to pregnancy has beneficial effects on maternal renal function during pregnancy and overall pregnancy outcome (12). However, in pregnancy exposure to ACE inhibitors and angiotensin 2 receptor blockers (ARB) have been associated with fetal complications including congenital malformations (19, 20). Thus treatment with ACE-inhibitors or ARB's should be discontinued before conception or as soon as pregnancy is suspected and replaced by alternative antihypertensive drugs under careful monitoring of blood pressure and UAER. In the present study other antihypertensive agents were only initiated if blood pressure exceeded 140/90. This often occurred at the time where 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. Beneficial effect of antihypertensive treatment based on methyldopa or labetalol treatment in normotensive women with microalbuminuria has been suggested (13, 21). Applying intensive antihypertensive treatment from 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 2<sup>nd</sup> 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 do not find that we can 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 1<sup>st</sup> and 3<sup>rd</sup> trimester HbA1c remained highly predictive. A possible explanation could be associations between microalbuminuria and glycemic

control thus underestimating the relationship with preterm delivery of the former. 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 data set can not answer 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 2<sup>nd</sup> 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 rise in blood pressure and/or UACR and more clinical details on the preterm delivery.

In contrast to our previous paper (9) we did not identify microalbuminuria as a significant predictor of preterm delivery before 37 weeks. This might 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 the 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 the glycemic control but observational studies indicate that more aggressive antihypertensive treatment in normotensive, microalbuminuric women with type 1 diabetes might reduce the

risk of developing 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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Table 1. Maternal and fetal characteristics in 846 normo- and microalbuminuric women with type 1 diabetes.

	Normo- albuminuria n=762	Micro-albuminuria n=84	p-value
Age (yrs)	28 (25-32)	27 (24-31)	0.34
BMI (kg/m <sup>2</sup> )	23 (21-25)	24 (22-26)	0.002
Duration of diabetes (yrs)	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 $\geq$ 140/90 at first visit	5 (1)	3 (4)	<0.001
Proliferative retinopathy	25 (3)	9 (11)	<0.001
1 <sup>st</sup> trimester HbA1c (%)	7.1 (6.4-8.0)	7.6 (6.8-8.5)	0.007
3 <sup>rd</sup> trimester HbA1c (%)	6.6 (6.0-7.3)	6.8 (6.2-7.5)	0.14
Hypertension <sup>†</sup> during 2 <sup>nd</sup> 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)	3650 (3162-4060)	3335 (2900-3650)	<0.001
Large for gestational age infant	483 (63)	42 (50)	0.02

\* Median and interquartile range or n (%).<sup>†</sup> Blood pressure  $\geq$  140/90

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-value	OR (95% CI)	p-value
Age (yrs)	1.0 (0.9-1.0)	0.07	-	-
BMI (kg/m <sup>2</sup> )	1.1 (1.0-1.1)	0.003	1.04 (1.0-1.1)	0.17
Duration of diabetes (yrs)	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 $\geq$ 140/90 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	-	-
1 <sup>st</sup> trimester HbA1c* (%)	1.2 (1.0-1.3)	0.016		
3 <sup>rd</sup> trimester HbA1c (%)	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

\* 1<sup>st</sup> trimester HbA1c was not a significant predictor in a separate multivariate model without 3<sup>rd</sup> trimester HbA1c (OR (95% CI); p-value): 1.2 (0.9-1.4); p=0.07. OR 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-value	OR (95% CI)	p-value
Prepregnancy insulin dose (IU/day)	1.01 (1.00-1.03)	0.045	1.01 (0.99-1.03)	0.32
1 <sup>st</sup> trimester HbA1c* (%)	1.3 (1.1-1.5)	0.010		
3 <sup>rd</sup> trimester HbA1c (%)	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

\* 1<sup>st</sup> trimester HbA1c was a significant predictor in a separate multivariate model without 3<sup>rd</sup> trimester HbA1c (OR (95% CI); p-value): 1.3 (1.1-1.6); p=0.004.