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

Results from a nationwide Danish study

DORTE M. JENSEN, PHD1
PETER DAMM, DMSC2
PER OVESEN, DMSC3
LARS MØLSTED-PEDERSEN, DMSC4
HENNING BECK-NIELSEN, DMSC1
JES G. WESTERGAARD, DMSC3
MARGRETHE MOELLER, MD5
ELISABETH R. MATHIESEN, DMSC2

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 pre-eclampsia and preterm delivery before 34 weeks in the microalbuminuric group were 40 and 3, 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 normoalbuminuric, microalbuminuric pregnant women to prevent preeclampsia is proposed.

© 2010 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/licenses/by-nc-nd/3.0/ for details.

From the 1Department of Endocrinology, Odense University Hospital, University of Southern Denmark, Odense, Denmark; the 2Department of Endocrinology and Obstetrics, Center for Pregnant Women with Diabetes, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; the 3Department of Obstetrics and Gynecology, Aarhus University Hospital, Skejby, Denmark; the 4Department of Obstetrics and Gynecology, Copenhagen County Hospital, University of Copenhagen, Copenhagen, Denmark; the 5Department of Obstetrics and Gynecology, Odense University Hospital, Odense, Denmark; and the 6Department of Obstetrics and Gynecology, Aalborg University Hospital, Aalborg, Denmark.

Corresponding author: Dorte M. Jensen, dortemj@dadmelt.dk.
Received 3 July 2009 and accepted 11 October 2009. Published ahead of print at http://care.diabetesjournals.org on 21 October 2009. DOI: 10.2337/dc09-1219

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
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 χ² test. Risks of preeclampsia and preterm delivery before 34 weeks were 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/m² 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 (3,162–4,060) g and 260 (250–266) 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/m²) | 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 (1.3) | <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/m²) | 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.
Predictors of preeclampsia in type 1 diabetes

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

| Predictor                          | 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).

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 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 women 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.

Acknowledgments — The study was funded by the Danish Diabetes Association.

No potential conflicts of interest relevant to this article were reported.

Data collection was performed by the authors and the following individuals: Joachim Klebe, Niels Hahnenmann, Hans Gjessing, Jens Kragh Mostrup, K.H. Frandsen, Edna Stage, Anders Thomsen, Thea Lousen, Kresten Rubbeck Petersen, Bjarnar Ovlsen, Jan Kvetny, and Hedvig Poulsen. The central data registration was performed by Susanne Jørgensen, Danish Diabetes Association. Information on A1C values in different centers was collected by Anders Klitgaard. The original registry working group also included Anders Friland, Joachim Klebe, and Carl Erik Mogensen.

References

1. Kitzmiller JL, Block JM, Brown FM, Catalano PM, Conway DL, Coustan DR, Gunderson EP, Herman WH, Hoffman LD, Inturrisi M, Jovanovic LB, Kjos SI, Knopp RH, Montoro MN, Ogata ES, Paramothy P, Reader DM, Rosenbl M, Thomas AM, Kirkman MS. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. Diabetes Care 2008;31:1060–1079

2. Mogensen CE, Keane WF, Bennett PH, Jerums G, Parving HH, Passa P, Steffes MW, Striker GE, Viberti GC. Prevention of diabetic renal disease with special reference to microalbuminuria. Lancet 1995;346:1080–1084

3. Mathiesen ER. Prevention of diabetic nephropathy. Microalbuminuria and perspectives for intervention in insulin-dependent diabetes. Dan Med Bull 1993;40:273–285

4. Biesenbach G, Zazgornik J, Stoger H, Grafinger P, Hulmann R, Kaiser W, Janko O, Stuby U. Abnormal increases in urinary albumin excretion during pregnancy in IDDM women with pre-existing microalbuminuria. Diabetologia 1994;37:905–910

5. Schröder W, Heyl W, Hill-Grashoff F, Rath W. Clinical value of detecting microalbuminuria as a risk factor for pregnancy-induced hypertension in insulin-treated diabetic pregnancies. Eur J Obstet Gynecol Reprod Biol 2000;91:155–160

6. Latuszus FF, Rasmussen OW, Lousen T, Klebe TM, Klebe JG. Ambulatory blood pressure as predictor of preeclampsia in diabetic pregnancies with respect to urinary albumin excretion rate and glycemic regulation. Acta Obstet Gynecol Scand 2001;80:1096–1103

7. Cundy T, Slef F, Gamble G, Neale L. Hypertensive disorders of pregnancy in women with type 1 and type 2 diabetes. Diabet Med 2002;19:482–489

8. Ekborn P, Damm P, Nøgaard K, Clausen P, Feldt-Rasmussen U, Feldt-Rasmussen B, Nielsen LH, Melsted-Pedersen L, Mathiesen ER. Urinary albumin excretion and 24-hour blood pressure as predictors of pre-eclampsia in type I diabetes. Diabetologa 2000;43:927–931

9. Ekborn P, Damm P, Feldt-Rasmussen B, Feldt-Rasmussen U, Mølvig J, Mathiesen ER. Pregnancy outcome in type 1 diabetic women with microalbuminuria. Diabetes Care 2001;24:1739–1744

10. How HY, Sibai B, Lindheimer M, Caritis S, Hauth J, Klebanoff M, Macpherson C, Van Dorsten P, Miodownik M, Landon M, Paul R, Meis P, Thurnau G, Dombrowski M, Roberts J. Is early-pregnancy proteinuria associated with an increased rate of pre-eclampsia in women with pregestational diabetes mellitus? Am J Obstet Gynecol 2004;190:775–778

11. Jensen DM, Damm P, Moelsted-Pedersen L, Ovesen P, Westergaard JG, Moeller M, Beck-Nielsen H. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. Diabetes Care 2004;27:2819–2823
12. Hod M, van Dijk DJ, Karp M, Weintraub N, Rabinerison D, Bar J, Peled Y, Erman A, Boner G, Ovadia J. Diabetic nephropathy and pregnancy: the effect of ACE inhibitors prior to pregnancy on fetomaternal outcome. Nephrol Dial Transplant 1995; 10:2328–2333

13. Nielsen LR, Müller C, Damm P, Mathiesen ER. Reduced prevalence of early preterm delivery in women with type 1 diabetes and microalbuminuria: possible effect of early antihypertensive treatment during pregnancy. Diabet Med 2006;23:426–431

14. Hiilesmaa V, Suhonen L, Teramo K. Glycaemic control is associated with pre-eclampsia but not with pregnancy-induced hypertension in women with type 1 diabetes mellitus. Diabetologia 2000;43:1534–1539

15. Hanson U, Persson B. Epidemiology of pregnancy-induced hypertension and preeclampsia in type 1 (insulin-dependent) diabetic pregnancies in Sweden. Acta Obstet Gynecol Scand 1998;77: 620–624

16. Suhonen L, Hiilesmaa V, Kaaja R, Teramo K. Detection of pregnancies with high risk of fetal macrosomia among women with gestational diabetes mellitus. Acta Obstet Gynecol Scand 2008; 87:940–945

17. Nielsen LR, Ekbom P, Damm P, Glümer C, Frandsen MM, Jensen DM, Mathiesen ER. HbA1c levels are significantly lower in early and late pregnancy. Diabetes Care 2004;27:1200–1201

18. Mathiesen ER, Hommel E, Hansen HP, Smidt UM, Parving HH. Randomised controlled trial of long term efficacy of captopril on preservation of kidney function in normotensive patients with insulin dependent diabetes and microalbuminuria. BMJ 1999;319:24–25

19. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, Hall K, Ray WA. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 2006;354:2443–2451

20. Alwan S, Polifka JE, Friedman JM. Angiotensin II receptor antagonist treatment during pregnancy. Birth Defects Res A Clin Mol Teratol 2005;73:123–130

21. Nielsen LR, Damm P, Mathiesen ER. Improved pregnancy outcome in type 1 diabetic women with microalbuminuria. Diabetic nephropathy: effect of intensified antihypertensive therapy? Diabetes Care 2009;32:38–44

22. Ekbom P, Damm P, Feldt-Rasmussen B, Feldt-Rasmussen U, Jensen DM, Mathiesen ER. Elevated third-trimester haemoglobin A1c predicts preterm delivery in type 1 diabetes. J Diabetes Complications 2008;22: 297–302