Improved Pregnancy Outcome in Type 1 Diabetic Women With Microalbuminuria or Diabetic Nephropathy

Effect of intensified antihypertensive therapy?

LENE RINGHOLM NIELSEN, MD, PHD[1,2]
PETER DAMM, MD, DMSC[1,3]
ELISABETH R. MATHIESEN, MD, DMSC[1,2]

OBJECTIVE — To describe pregnancy outcome in type 1 diabetic women with normoalbuminuria, microalbuminuria, or diabetic nephropathy after implementation of an intensified antihypertensive therapeutic strategy.

RESEARCH DESIGN AND METHODS — Prospective study of 117 pregnant women with type 1 diabetes. Antihypertensive therapy, mainly methyldopa, was given to obtain blood pressure <135/85 mmHg and urinary albumin excretion <300 mg/24 h. Blood pressure and A1C were recorded during pregnancy. The pregnancy outcome was compared with recently published studies of pregnant women with microalbuminuria or diabetic nephropathy.

RESULTS — Antihypertensive therapy was given in 14 of 100 women with normoalbuminuria, 5 of 10 women with microalbuminuria, and all 7 women with diabetic nephropathy. Mean systolic blood pressure during pregnancy was 120 mmHg (range 101–147), 122 mmHg (116–135), and 135 mmHg (111–145) in women with normoalbuminuria, microalbuminuria, and diabetic nephropathy, respectively ($P = 0.0095$). No differences in mean diastolic blood pressure or A1C were detected between the groups. No women with microalbuminuria developed preeclampsia. The frequency of preterm delivery was 20% in women with normoalbuminuria and microalbuminuria in contrast to 71% in women with diabetic nephropathy ($P < 0.01$) where the median gestational age was 258 days (220–260). Compared with previous studies using less stringent antihypertensive therapeutic strategy and less strict metabolic control, gestational age was longer and birth weight was larger in our study.

CONCLUSIONS — With intensified antihypertensive therapy and strict metabolic control, comparable pregnancy outcome was seen in type 1 diabetic women with microalbuminuria and normoalbuminuria. Although less severe than in previous studies, diabetic nephropathy was associated with more adverse pregnancy outcome.

Diabetes Care 32:38–44, 2009

Type 1 diabetic women with microalbuminuria or diabetic nephropathy are at particular risk of poor pregnancy outcome (1–6). Diabetic nephropathy is associated with a high risk of gestational hypertension, preeclampsia, and preterm delivery (1–4,6). Likewise, preeclampsia and preterm delivery occur more frequently in type 1 diabetic women with microalbuminuria (3,5).

Outside pregnancy, the importance of antihypertensive therapy with ACE inhibition to reduce the risk of renal complications is well documented in both type 1 diabetic patients with microalbuminuria (7) and diabetic nephropathy (8). To prevent development of hypertension and proteinuria, ACE inhibition has been documented to be effective even in normotensive diabetic women with microalbuminuria (7). However, ACE inhibition in early pregnancy has been associated with congenital malformations (9), while use late in pregnancy may cause fetal renal failure (10). ACE inhibition therefore should be discontinued before conception or as soon as pregnancy is confirmed (9). In diabetic women with microalbuminuria or diabetic nephropathy, the effect of antihypertensive therapy in relation to development and progression of hypertension and proteinuria during pregnancy seems promising when using antihypertensive drugs considered safe during pregnancy. However, this is only sparsely investigated (1,3,5).

A retrospective study suggested that early intervention with antihypertensive therapy reduces the risk of preterm delivery in type 1 diabetic women with diabetic nephropathy (1).

Previously, we found an association between early onset of antihypertensive therapy in pregnant type 1 diabetic women with microalbuminuria and a reduced prevalence of preterm delivery, probably due to a reduced prevalence of preeclampsia (5). Methyldopa was first-choice therapy based on reports of stable utero-placental blood flow, fetal hemodynamics (11,12), and long-term follow-up (13). Given that the prevalence of preterm delivery and preeclampsia was still high (5), we speculated that pregnant type 1 diabetic women with microalbuminuria or diabetic nephropathy would benefit from further intensified antihypertensive therapy in early pregnancy. Therefore, in 2004, we intensified our treatment strategy in early pregnancy in type 1 diabetic women with microalbuminuria or diabetic nephropathy.

In this study, we describe the pregnancy outcome in type 1 diabetic women according to their degree of albuminuria after the implementation of an intensified antihypertensive therapeutic strategy.

From the [1]Center for Pregnant Women with Diabetes, Rigshospitalet, Faculty of Health Sciences, Copenhagen, Denmark; the [2]Department of Endocrinology, Rigshospitalet, Faculty of Health Sciences, Copenhagen, Denmark; and the [3]Department of Obstetrics, Rigshospitalet, Faculty of Health Sciences, Copenhagen, Denmark.
Corresponding author: Lene Ringholm Nielsen, enel@dadlnet.dk.
Received 19 August 2008 and accepted 10 October 2008.
Published ahead of print at http://care.diabetesjournals.org on 22 October 2008. DOI: 10.2337/dc08-1526.

RESEARCH DESIGN AND METHODS

— During the study period 1 September 2004 to 31 August 2006, we conducted a prospective study consecutively including all pregnancies in Danish-speaking Caucasian women with pregestational type 1 diabetes ($n = 121$) referred before 14 completed gestational weeks to the Center for Pregnant Women with Diabetes, Rigshospitalet, which offers a joint service involving only a few experienced obstetricians and endocrinologists. All women were referred from a well-defined geographical area covering 2 million inhabitants in eastern Denmark. Women with a single fetus living beyond 22 completed weeks were included in the present analysis.

Two women with Addison's disease and inflammatory bowel disease, respectively, were excluded to avoid the potential bias of competing disease. If a woman had more than one pregnancy in the study period ($n = 2$), only the first pregnancy was included. A total of 117 women were included in the study and followed until delivery.

Based on the mean of two measurements of 24-h urinary albumin excretions (UAEs) at inclusion, the women were classified as having normoalbuminuria (UAE <30 mg/24 h), microalbuminuria (30–299 mg/24 h), or diabetic nephropathy (UAE ≥300 mg/24 h) accordingly (3). In women with diabetic nephropathy, UAE was also recorded at 14, 21, 27, and 33 weeks. In the remaining women, further analysis of UAE was performed if proteinuria (≥1+) was present in the absence of nitrites and leukocytes on a urinary dipstick (Uristix, Bayer Diagnostics, Bridgend, U.K.), which was checked routinely at each clinical visit. UAE was analyzed by an enzyme-linked immunosorbent assay (14). In a few cases, when 24-h urine samples were not available, albumin-to-creatinine ratio in a random urine sample was performed. We previously reported high concordance between UAE and albumin-to-creatinine ratio with a sensitivity of 94% and specificity of 100% between the two methods (15).

Blood pressure was measured with a digital blood pressure monitor (A&D Instruments, Abingdon, Oxon, U.K.) in a sitting position after 5–10 min of rest. Preeclampsia in women with normoalbuminuria or microalbuminuria was defined as blood pressure >140/90 mmHg accompanied by proteinuria (≥1+) on a sterile urinary dipstick or ≥300 mg/24 h (proteinuria of 300 mg/24 h approximates UAE of 190 mg/24 h) later than 20 weeks. In women with diabetic nephropathy, the diagnosis was based on the same findings accompanied by a sudden increase of ≥15% in systolic or diastolic blood pressure (3).

Antihypertensive therapy was initiated during pregnancy if blood pressure was ≥135/85 mmHg and/or UAE was ≥300 mg/24 h. When ACE inhibitors were withdrawn during prepregnancy planning or in the first weeks of pregnancy, antihypertensive therapy was initiated unless UAE was normal or very low in the microalbuminuric range, in which case the women were observed without antihypertensive therapy (5). Treatment goals were blood pressure <135/85 mmHg and UAE <300 mg/24 h.

Methyldopa (5,11–13) was first-choice therapy in most cases and, when indicated, labetalol and/or nifedipine (5) were added. If given before pregnancy, furosemide was continued during pregnancy to reduce the risk of rebound fluid retention with increased blood pressure and UAE when discontinuing the drug (16).

The majority of women were treated with a basal-bolus insulin regimen. All women registered their self-monitored plasma glucose (SMPG) readings in diabetes diaries, which were evaluated at each clinical visit. Routine SMPG was recommended at least seven times daily to obtain preprandial SMPG of 4.0–6.0 mmol/l, 90-min postprandial SMPG of 4.0–8.0 mmol/l, and prebedtime SMPG of 6.0–8.0 mmol/l (17).

All women visited our and/or their local diabetes center at 1- or 2-week intervals for diabetes control and blood pressure monitoring. Folic acid supplementation during the first 12 weeks of pregnancy was recommended. Structured preconceptional care was not offered systematically.

At median 8 (range 5–13), 14 (12–16), 21 (20–23), 27 (25–29), and 33 (31–35) weeks, weight, A1C, serum creatinine, insulin dose, and blood pressure were recorded, as was the last recorded value of A1C and blood pressure at ~36 weeks. Median SMPG was calculated as previously described (17). A1C was assayed at our center by a latex immunoagglutination inhibition method on the same analyzer (DCA 2000, Bayer, England). Normal A1C range outside pregnancy was 4.7–6.3%, in early pregnancy 4.5–5.7%, and in late pregnancy 4.4–5.6% (18). Serum creatinine was assayed on a routine basis.

Diabetic retinopathy was diagnosed with retinal photos at inclusion and at 28 weeks. Obstetrical ultrasound scanning was performed on a routine basis at inclusion; at 14, 21, 27, and 33 weeks; and when indicated.

Gestational age was estimated based on early ultrasound scanning. Labor was routinely induced after 37–40 completed weeks based on an individual evaluation including duration of diabetes, presence of diabetic complications, previous obstetric history, and fetal size aiming at getting as close as possible to full term. Preterm delivery comprised delivery before 37 completed weeks and included spontaneous delivery and delivery based on medical indications, mainly preeclampsia, fetal distress, and large-for-gestational-age infants. Small-for-gestational-age was defined as <10th centile and large-for-gestational-age was defined as >90th centile for gestational age and sex for a Danish standard population (19). Perinatal mortality was defined as fetal death after 22 weeks or neonatal death the first week after delivery.

Selective serotonin reuptake inhibitors were given in four women. Thyroid dysfunction was treated with levothyroxine in 16 and with thiamazole in 2, resulting in normal thyroid function in all 18 women during pregnancy.

From the midwifery consultation at Rigshospitalet, 25 healthy pregnant women matched for parity and age and with uncomplicated pregnancies were recruited in the first part of pregnancy. Blood pressure was recorded at median 14 (range 10–19), 28 (20–29), and 34 (32–38) weeks, and pregnancy outcome was collected from patients' records.

Mean systolic and diastolic blood pressures were calculated for values at 8, 14, 21, 27, and 33 weeks for diabetic women and for values at 14, 28, and 34 weeks in healthy pregnant women. The research protocol was approved by the regional committees for ethics and science and by the Danish Data Protection Agency.

Statistical analysis

Data are given as median (range) or *n* (%). Categorical variables were compared by χ^2 or Fisher's exact test, as appropriate. Continuous variables were analyzed by one-way ANOVA after logarithmic transformation or by nonparametric tests when appropriate.

Table 1—*Clinical data in 117 women with type 1 diabetes according to urinary albumin excretion at inclusion in early pregnancy and in 25 healthy pregnant women*

	Normoalbuminuria	Microalbuminuria	Diabetic nephropathy	Healthy pregnant women
n	100	10	7	25
Age (years)	30.5 (21–42)	31 (21–34)	30 (23–39)	31 (26–43)
Duration of diabetes (years)	16 (1–36)	14 (1–31)	20 (5–32)	—
UAE rate at inclusion (mg/24 h)	7 (3–29)	91 (30–198)	690 (450–3,290)	—
Serum creatinine at inclusion (μmol/l)	51 (33–75)	51 (41–69)	57 (42–95)	—
A1C at inclusion (%)	6.7 (4.9–10.8)	6.9 (5.8–10.5)	6.5 (5.7–7.8)	—
BMI before pregnancy (kg/m^2)	24.2 (17.3–43.8)	25.6 (21.0–34.4)	25.0 (20.4–32.4)	—
Weight gain during pregnancy (kg)	15.2 (5.6–34.4)	14.5 (9.3–26.4)	14.6 (9.3–22.8)	—
ACE inhibitor therapy before pregnancy	12 (12)	4 (40)	5 (71)*	—
Number of women on antihypertensive therapy at some point in pregnancy	14 (14)	5 (50)	7 (100)	—
Number of antihypertensive agents used during pregnancy in women treated with these drugs	1.5 (1–3)	1 (1–2)	2 (1–4)	—
Diabetic retinopathy	63 (63)	5 (50)	7 (100)†	—
Preeclampsia	7 (7)	0	3 (43)‡	0
Gestational age (days)	265 (155–276)	264 (252–272)	258 (220–260)	282 (264–296)
Preterm delivery <34 gestational weeks	1 (1)	0	1 (14)	0
Preterm delivery <37 gestational weeks	20 (20)	2 (20)	5 (71)*	0
Birth weight (g)	3,540 (445–5,620)	3,430 (2,510–4,484)	2,765 (2,040–3,730)‡	3,510 (2,840–4,970)
Small-for-gestational-age infants (<10th centile)	1 (1)	0	2 (29)*	2 (8)
Large-for-gestational-age infants (>90th centile)	50 (50)	5 (50)	1 (14)	2 (8)
Perinatal mortality (*n*)	2 (2)	0	0	0

Data are *n* (%) or medians (range). *$P < 0.01$, †$P = 0.0503$, ‡$P < 0.02$ between women with diabetic nephropathy and the remaining diabetic women.

After logarithmic transformation, repeated measurements of continuous data were analyzed by a variance component model with the continuous variable as the dependent variable, "week" and "group" (normoalbuminuria, microalbuminuria, or diabetic nephropathy) as discrete covariates, and random woman effect as a measure of each woman's level during pregnancy.

Differences were considered to be statistically significant with a two-sided *P* value <0.05. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS — At inclusion in early pregnancy, 100 (85%) diabetic women had normoalbuminuria, 10 (9%) microalbuminuria, and 7 (6%) diabetic nephropathy. Median gestational age at the first visit was 61 days (range 37–94) with no difference between the groups ($P = 0.30$).

During pregnancy, mean systolic blood pressure was 120 mmHg (101–147), 122 mmHg (116–135), and 135 mmHg (111–145) in women with normoalbuminuria, microalbuminuria, and diabetic nephropathy, respectively ($P = 0.0095$). Corresponding mean diastolic blood pressure was 72 mmHg (62–86), 75 mmHg (65–87), and 74 mmHg (71–86) ($P = 0.26$). In women with normoalbuminuria and microalbuminuria, no differences in mean systolic blood pressure ($P = 0.42$) or mean diastolic blood pressure ($P = 0.61$) were detected. Mean systolic blood pressure was higher in women with diabetic nephropathy compared with the remaining women ($P = 0.016$). At inclusion, no differences in systolic ($P = 0.09$) or diastolic ($P = 0.20$) blood pressure were detected between women with diabetic nephropathy and the remaining women (Figures A1a and A1b are available in an online appendix at http://dx.doi.org/10.2337/dc08-1526).

During pregnancy, mean systolic blood pressure and mean diastolic blood pressure were higher in 86 normoalbuminuric women not receiving antihypertensive therapy during pregnancy compared with healthy pregnant women (120 mmHg [101–138] vs. 117 mmHg [102–128], $P = 0.038$; and 72 mmHg [62–82] vs. 70 mmHg [56–78], $P = 0.023$).

The median UAE among women with diabetic nephropathy was maintained well below 2,000 mg/24 h throughout pregnancy (online appendix Figure A1c). However, in late pregnancy, UAE exceeded 2,000 mg/24 h in three women with diabetic nephropathy who delivered preterm, mainly due to preeclampsia ($n = 2$).

In women with normoalbuminuria, six (6%) were treated with antihypertensive therapy before and during the entire pregnancy, whereas eight (8%) initiated antihypertensive therapy at median 30 weeks (range 14–36). Four (40%) women with microalbuminuria were on antihypertensive drugs before pregnancy, whereas one microalbuminuric woman initiated treatment at 19 weeks. All women with diabetic nephropathy received antihypertensive therapy during pregnancy, of which four (57%) were on treatment before pregnancy, whereas treatment was initiated at the first or second visit in the remaining three women (Table 1).

Table 2—*Comparison of pregnancy outcomes in studies of pregnant type 1 diabetic women with microalbuminuria covering the same geographical area in Eastern Denmark*

	Ekbom et al., 2001 (3)	Nielsen et al., 2006 (5)	Current study
Antihypertensive therapy strategy	Preeclampsia Diastolic BP >95 mmHg	BP >140/90 mmHg UAE >2 g/24 h ACE inhibitor before pregnancy	BP >135/85 mmHg UAE ≥300 mg/24 h ACE inhibitor before pregnancy
n	26	20	10
Duration of diabetes (years)	19 ± 5	18 ± 8	15 ± 10
A1C at inclusion (%)	8.1 ± 0.9	6.8 ± 0.5	7.3 ± 1.5
Antihypertensive therapy (week of onset)	29 (20–34)	13 (before to 34)	Before (before to 14)
Patients on antihypertensive therapy during pregnancy (*n*)	9 (35)	10 (50)	5 (50)
ACE inhibitor before pregnancy (*n*)	5 (19)	9 (45)	4 (40)
Systolic BP at inclusion (mmHg)	121 ± 13	121 ± 14	117 ± 14
Diastolic BP at inclusion (mmHg)	71 ± 8	73 ± 8	74 ± 8
UAE (mg/24 h)	69 (16–278)	74 (30–287)	91 (30–198)
Preeclampsia (*n*)	11 (42)	4 (20)	0
Gestational age at delivery (days)	250 (182–270)	259 (244–271)	264 (252–272)
Preterm delivery before 34 weeks (*n*)	6 (23)	0	0
Preterm delivery before 37 weeks (*n*)	16 (62)	8 (40)	2 (20)
Birth weight (g)	3,124 ± 767	3,279 ± 663	3,471 ± 670
Perinatal mortality (*n*)	1 (4)	0	0
Major congenital malformations (*n*)	1 (4)	0	0

Data are means ± SD, medians (range), or *n* (%). BP, blood pressure. Duration of diabetes, A1C, BP, and birth weight in the current study are given as means ± SD to compare results with previous studies from our center (3,5).

Two women with diabetic nephropathy had increased serum creatinine (89 and 95 μmol/l at inclusion, increasing to 101 and 125 μmol/l at 33 weeks, normal nonpregnant range 50–88 μmol/l). Glomerular filtration rate measured before pregnancy was 48 and 56 ml/min, respectively. Two years and one pregnancy later, glomerular filtration rate was 45 and 51 ml/min, respectively. Serum creatinine was within the normal range at inclusion in all other women (Table 1) and remained stable throughout pregnancy in the remaining women with diabetic nephropathy (62 μmol/l [44–74] at 33 weeks, $n = 4$) and in all women with microalbuminuria (52 μmol/l [39–85] at 33 weeks).

Throughout pregnancy, A1C decreased (online appendix Figure A1d), median SMPG levels remained stable (online appendix Figure A1e), and insulin dose increased (data not shown) with no differences between the three groups.

Early preterm delivery before 34 completed weeks occurred in one woman with diabetic nephropathy due to fetal distress and in one woman with normoalbuminuria who experienced rupture of the membranes at 22 completed weeks and delivered an infant that died within 5 min. An unexplained death occurred a few hours after delivery in a term-born infant of a woman with normoalbuminuria. No major congenital malformations or stillbirths were recorded.

None of the women with microalbuminuria developed preeclampsia, and the frequency of preterm delivery among women with microalbuminuria was equal to that in women with normoalbuminuria (Table 1). In women with diabetic nephropathy, three developed preeclampsia resulting in preterm delivery at 35–36 weeks. Median gestational age was 258 days in offspring of women with diabetic nephropathy. A higher frequency of preeclampsia ($P = 0.013$) and preterm delivery ($P = 0.007$) was thus seen in women with diabetic nephropathy compared with the remaining women. Spontaneous preterm labor occurred in three normoalbuminuric women, i.e., in 11% of all preterm deliveries, whereas the remaining preterm deliveries were based on obstetric indications. Birth weight did not differ between infants of women with normoalbuminuria and microalbuminuria but was lower in women with diabetic nephropathy ($P = 0.017$). Furthermore infants of women with diabetic nephropathy more often were small-for-gestational-age ($P < 0.01$).

A comparison of blood pressure control and pregnancy outcome with recent studies (published within 10 years) in women with microalbuminuria or diabetic nephropathy is shown in Table 2 and Table 3.

CONCLUSIONS — In this prospective study of 117 pregnant women with type 1 diabetes, we showed that after early intervention with antihypertensive therapy comparable pregnancy outcome was seen in type 1 diabetic women with microalbuminuria and normoalbuminuria, respectively. Although less severe than in previous studies, diabetic nephropathy was associated with more adverse pregnancy outcomes.

The importance of antihypertensive and renoprotective therapy in nonpregnant type 1 diabetic patients is well established (7,8). However, only a few recent studies have focused on the effect of antihypertensive therapy in pregnant type 1 diabetic women with microalbuminuria (3,5) or diabetic nephropathy (1–3), with each study having limitations due to small numbers of patients (3,5), retrospective design (1,2), or missing information about the antihypertensive therapy strategy (2). Until larger randomized prospective trials might become available, there is

Table 3—*Comparison of pregnancy outcomes in studies of type 1 diabetic women with diabetic nephropathy receiving antihypertensive therapy during pregnancy*

	Dunne et al., 1999 (2)	Ekbom et al., 2001 (3)	Carr et al., 2006 (1)§	Current study
Antihypertensive therapy strategy	Not specified	Preeclampsia diastolic BP >95 mmHg	Mean arterial BP ≥100 mmHg	BP >135/85 mmHg UAE ≥300 mg/24 h ACE inhibitor prepregnancy
n	21	11	43	7
Duration of diabetes (years)	19.5 (12–30)	16 (5)	16.9	20 (5–32)
A1C at inclusion (%)	9.7 (6.7–16.7)‡	8.8 (1.3)	8.1	6.6 (0.6)
Antihypertensive therapy before pregnancy (*n*)	—	6 (55%)	18 (42%)*	5 (71%)
Patients on antihypertensive therapy during pregnancy (*n*)	—	—	39 (90.7%)	7 (100%)
Systolic BP at inclusion (mmHg)	—	129 (11)	138	131 (19)
Diastolic BP at inclusion (mmHg)	—	77 (8)	82	76 (9)
UAE at inclusion (mg/24 h)	—	1,120 (466–5,528)	3,170	690 (450–3,290)
Preeclampsia (*n*)	—	7 (64%)	15 (35%)	3 (43%)
Duration of pregnancy (days)	243 (203–266)	—	238	258 (220–260)
Preterm delivery before 37 weeks (*n*)	12 (57.2%)	10 (91%)	16 (38.1%)†	5 (71%)
Birth weight (g)	2,429 (985–4,140)	2,235 (1,038)	2,200	2,730 (601)
Small-for-gestational-age infants (<10th centile)	—	5 (45%)	—	2 (29%)
Perinatal mortality (*n*)	2 (10%)	0	4 (9%)	0
Major congenital malformations (*n*)	1 (5%)	1 (9%)	—	0

Data are means (SD), median (range), or *n* (%). A1C and birth weight in the current study are given as means (SD) to compare with previous results from our center (3). BP, blood pressure. *Patients using antihypertensive therapy at first visit. †Preterm delivery before 32 weeks. §Modified from Carr et al. (1) to constitute one group. ‡HbA_1 or A1C (2).

a need for clinical studies describing the experience regarding indications for and timing of antihypertensive therapy in pregnant women with type 1 diabetes.

This study supports previous findings that intensified antihypertensive therapy may reduce adverse pregnancy outcomes in women with microalbuminuria (5) or diabetic nephropathy (1,2). In the majority of women with microalbuminuria or diabetic nephropathy receiving antihypertensive therapy during pregnancy, this therapy was indeed initiated before pregnancy. However, three women with diabetic nephropathy did not receive antihypertensive therapy before pregnancy, mainly because of poor compliance. Blood pressure levels within target range (<135/85 mmHg) were obtained in the vast majority of women in all three categories of UAE. The antihypertensive therapy was well tolerated, and side effects were not noted. Compliance was not measured but was estimated to be good.

At our center, we have previously evaluated the effect of antihypertensive therapy in pregnant diabetic women with microalbuminuria (3,5) and gradually over the years intensified our antihypertensive therapy strategy accordingly. The present article describes pregnancy outcomes of three cohorts of unselected type 1 diabetic women with microalbuminuria from the same geographical area treated by the same doctors (P.D., E.R.M.) according to three different antihypertensive therapy strategies. Microalbuminuria was previously associated with a high prevalence of preeclampsia and preterm delivery (3,5). With gradually intensified antihypertensive strategies, a decrease in rates of preeclampsia and preterm delivery was seen (Table 2), resulting in pregnancy outcome comparable with that of women with normoalbuminuria.

With the current antihypertensive strategy, infants of women with diabetic nephropathy were delivered at a notably later gestational age compared with previous studies from our (3) and other (1,2,4,6) centers, which used less intensive antihypertensive strategies. In the current study, birth weight of infants born to women with diabetic nephropathy was substantially higher than in previous studies (1–3) and only two infants were small-for-gestational-age. Nonetheless, the majority of infants of women with diabetic nephropathy were born preterm and were smaller compared with the remaining infants of diabetic mothers. No neonatal deaths were recorded in women with diabetic nephropathy, but because of the low number of women studied, no firm conclusion regarding infrequent pregnancy outcomes can be drawn.

Women with diabetic nephropathy were more prone to develop preeclampsia in agreement with previous studies (1–4,6,20). Hod et al. (21) reported that in eight highly selected type 1 diabetic women with diabetic nephropathy, ACE inhibition before pregnancy offered a prolonged protective renal effect throughout pregnancy with favorable pregnancy outcome. In the current study, however, two of three women with diabetic nephropathy developing superimposed preeclampsia received ACE inhibition before pregnancy.

Serum creatinine was used as an index of renal function as in the study of Dunne et al. (2), who found increasing serum creatinine during pregnancy in women with diabetic nephropathy. In contrast, we found stable serum creatinine in the women with microalbuminuria or diabetic nephropathy if serum creatinine was within normal range in early pregnancy in accordance with

Rossing et al. (22), although the numbers were too small for solid conclusions. Women with diabetic nephropathy were followed with frequent determinations of UAE, whereas in women with normoalbuminuria or microalbuminuria, further analysis of UAE was only performed systematically when dipstick analysis was ≥1+ during pregnancy. Even in the two women with elevated serum creatinine during pregnancy, the annual change in glomerular filtration rate of 1.5–3 ml/min was not different from what could be expected in the most optimally treated women with diabetic nephropathy (22).

Antihypertensive therapy with up to four drugs was indicated in the women with diabetic nephropathy. Nonetheless, their systolic blood pressure was slightly higher compared with the remaining pregnant diabetic women. This may reflect long-term hemodynamic alterations and necessitate an even more intensive antihypertensive therapy strategy before and during pregnancy (1). Blood pressure levels were within target range in the vast majority of women with microalbuminuria. Furthermore, in all women with microalbuminuria and in the majority of women with diabetic nephropathy, median UAE was maintained below 2,000 mg/24 h, the limit for nephrotic proteinuria.

Even in normoalbuminuric diabetic women not receiving antihypertensive therapy during pregnancy, blood pressure was higher compared with the healthy pregnant women as previously described (23). This may be associated with increased activity of the renin-angiotensin system in type 1 diabetes, which has previously been demonstrated in pregnant (L.R.N., U. Pedersen-Bjergaard, B. Thorsteinsson, F. Boomsma, P.D., E.R.M., unpublished data) and nonpregnant (24) patients with type 1 diabetes.

When compared with previous studies at our center (3,5), improved glycemic control was obtained in early pregnancy, which may in part explain the lack of congenital malformations. Notably, no differences in A1C were detected between women with normoalbuminuria, microalbuminuria, or diabetic nephropathy during pregnancy. A combined effect of improved glycemic control and early intensive antihypertensive intervention may explain the improved pregnancy outcome obtained in the majority of women with microalbuminuria and diabetic nephropathy in the current study.

To summarize, early antihypertensive therapy and strict metabolic control in pregnant women with type 1 diabetes and microalbuminuria or diabetic nephropathy was associated with improved pregnancy outcome compared with recent reports from our (3,5) and other (1,2) centers.

Acknowledgments— The study was supported by unrestricted grants from The Danish Diabetes Association and Novo Nordisk A/S, Bagsværd, Denmark. L.R.N. was supported by a fellowship from the Faculty of Health Sciences, Rigshospitalet, Copenhagen, Denmark. No other potential conflicts of interest relevant to this article were reported.

We are indebted to nurses E. Stage and C. Barfred and laboratory technicians K.M. Larsen and M. Wahl for careful handling of the patients and the data.

References

1. Carr DB, Koontz GL, Gardella C, Holing EV, Brateng DA, Brown ZA, Easterling TR: Diabetic nephropathy in pregnancy: suboptimal hypertensive control associated with preterm delivery. *Am J Hypertens* 19: 513–519, 2006
2. Dunne FP, Chowdhury TA, Hartland A, Smith T, Brydon PA, McConkey C, Nicholson HO: Pregnancy outcome in women with insulin-dependent diabetes mellitus complicated by nephropathy. *QJM* 92:451–454, 1999
3. Ekbom P, Damm P, Feldt-Rasmussen B, Feldt-Rasmussen U, Molvig J, Mathiesen ER: Pregnancy outcome in type 1 diabetic women with microalbuminuria. *Diabetes Care* 24:1739–1744, 2001
4. Kimmerle R, Zass RP, Cupisti S, Somville T, Bender R, Pawlowski B, Berger M: Pregnancies in women with diabetic nephropathy: long-term outcome for mother and child. *Diabetologia* 38:227–235, 1995
5. Nielsen LR, Muller 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* 23:426–431, 2006
6. Reece EA, Coustan DR, Hayslett JP, Holford T, Coulehan J, O'Connor TZ, Hobbins JC: Diabetic nephropathy: pregnancy performance and fetomaternal outcome. *Am J Obstet Gynecol* 159: 56–66, 1988
7. 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* 319:24–25, 1999
8. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy: the Collaborative Study Group. *N Engl J Med* 329:1456–1462, 1993
9. 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* 354:2443–2451, 2006
10. Shotan A, Widerhorn J, Hurst A, Elkayam U: Risks of angiotensin-converting enzyme inhibition during pregnancy: experimental and clinical evidence, potential mechanisms, and recommendations for use. *Am J Med* 96:451–456, 1994
11. Montan S, Anandakumar C, Arulkumaran S, Ingemarsson I, Ratnam SS: Effects of methyldopa on uteroplacental and fetal hemodynamics in pregnancy-induced hypertension. *Am J Obstet Gynecol* 168:152–156, 1993
12. Montan S, Anandakumar C, Arulkumaran S, Ingemarsson I, Ratnam S: Randomised controlled trial of methyldopa and isradipine in preeclampsia: effects on uteroplacental and fetal hemodynamics. *J Perinat Med* 24:177–184, 1996
13. Cockburn J, Moar VA, Ounsted M, Redman CW: Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children. *Lancet* 1:647–649, 1982
14. Feldt-Rasmussen B, Dinesen B, Deckert M: Enzyme immunoassay: an improved determination of urinary albumin in diabetics with incipient nephropathy. *Scand J Clin Lab Invest* 45:539–544, 1985
15. Justesen TI, Petersen JL, Ekbom P, Damm P, Mathiesen ER: Albumin-to-creatinine ratio in random urine samples might replace 24-h urine collections in screening for micro- and macroalbuminuria in pregnant woman with type 1 diabetes. *Diabetes Care* 29:924–925, 2006
16. National Institute of Health Publication no. 00-3029. National High Blood Pressure Education Program. Available at: http://www.nhlbi.nih-gov/health/prof/heart/hbp/hbp-preg.htm. 2000
17. Nielsen LR, Pedersen-Bjergaard U, Thorsteinsson B, Johansen M, Damm P, Mathiesen ER: Hypoglycemia in pregnant women with type 1 diabetes: predictors and role of metabolic control. *Diabetes Care* 31:9–14, 2008
18. Nielsen LR, Ekbom P, Damm P, Glumer C, Frandsen MM, Jensen DM, Mathiesen ER: HbA1c levels are significantly lower in early and late pregnancy. *Diabetes Care* 27:1200–1201, 2004
19. Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B: Intrauterine growth curves based on ultrasonically estimated

foetal weights. *Acta Paediatr* 85:843–848, 1996
20. Lauszus 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* 80: 1096–1103, 2001
21. Hod M, van Dijk DJ, Karp M, Weintraub N, Rabinerson D, Bar J, Peled Y, Erman A, Boner G, Ovadia J: Diabetic nephropathy and pregnancy: the effect of ACE inhibitors prior to pregnancy on feto-maternal outcome. *Nephrol Dial Transplant* 10:2328–2333, 1995
22. Rossing K, Jacobsen P, Hommel E, Mathiesen E, Svenningsen A, Rossing P, Parving HH: Pregnancy and progression of diabetic nephropathy. *Diabetologia* 45: 36–41, 2002
23. Napoli A, Sabbatini A, Di BN, Marceca M, Colatrella A, Fallucca F: Twenty-four-hour blood pressure monitoring in normoalbuminuric normotensive type 1 diabetic women during pregnancy. *J Diabetes Complications* 17:292–296, 2003
24. Toop MJ, Dallinger KJ, Jennings PE, Barnett AH: Angiotensin-converting enzyme (ACE): relationship to insulin-dependent diabetes and microangiopathy. *Diabet Med* 3:455–457, 1986