

Diabetic Nephropathy and Microalbuminuria in Pregnant Women With Type 1 and Type 2 Diabetes

Prevalence, antihypertensive strategy, and pregnancy outcome

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OBJECTIVE—To evaluate the prevalence of diabetic nephropathy and microalbuminuria in pregnant women with type 2 diabetes in comparison with type 1 diabetes and to describe pregnancy outcomes in these women following the same antihypertensive protocol.

RESEARCH DESIGN AND METHODS—Among 220 women with type 2 diabetes and 445 women with type 1 diabetes giving birth from 2007–2012, 41 women had diabetic nephropathy (albumin-creatinine ratio ≥ 300 mg/g) or microalbuminuria (albumin-creatinine ratio 30–299 mg/g) in early pregnancy. Antihypertensive therapy was initiated if blood pressure $\geq 135/85$ mmHg or albumin-creatinine ratio ≥ 300 mg/g.

RESULTS—The prevalence of diabetic nephropathy was 2.3% (5 of 220) in women with type 2 diabetes and 2.5% (11 of 445) in women with type 1 diabetes ($P = 1.00$). The figures for microalbuminuria were 4.5 (10 of 220) vs. 3.4% (15 of 445) ($P = 0.39$). Baseline glycemic control was comparable between women with type 2 diabetes ($n = 15$) and type 1 diabetes ($n = 26$). Blood pressure at baseline was median 128 (range 100–164)/81 (68–91) vs. 132 (100–176)/80 (63–100) mmHg (not significant) and antihypertensive therapy in type 2 versus type 1 diabetes was used in 0 and 62%, respectively, at baseline, increasing to 33 and 96%, respectively, in late pregnancy. Pregnancy outcome was comparable regardless type of diabetes; gestational age at delivery: 259 days (221–276) vs. 257 (184–271) ($P = 0.19$); birth weight 3,304 g (1,278–3,914) vs. 2,850 (370–4,180) ($P = 0.67$).

CONCLUSIONS—The prevalence of diabetic nephropathy and microalbuminuria in early pregnancy was similar in type 2 and type 1 diabetes. Antihypertensive therapy was used more frequently in type 1 diabetes. Pregnancy outcome was comparable regardless type of diabetes.

Diabetes Care 36:3489–3494, 2013

Youth onset of type 2 diabetes continues to increase worldwide (1), and pregnancy in women with type 2 diabetes is a substantial clinical problem (2). Cross-sectional studies show a higher prevalence of albuminuria in young adults with type 2 diabetes compared with type 1 diabetes (3–5). Subjects with youth-onset type 2 diabetes have a fourfold increased risk of end-stage kidney disease compared with youth with

type 1 diabetes (6). Literature focusing on kidney involvement in pregnant women with diabetes is scarce (7–11). To our knowledge, no studies using strict diagnostic criteria have described the prevalence of diabetic nephropathy and microalbuminuria in early pregnancy in women with type 2 diabetes. Likewise, recommendations for an antihypertensive strategy during these pregnancies is missing.

In pregnant women with type 1 diabetes, nephropathy is associated with poor pregnancy outcome in terms of increased rates of preeclampsia and preterm delivery (11–13). In these women, intrauterine growth restriction (11) occurs almost twice as often as in the general population (13), and in the late 1990s, preterm delivery before 34 weeks occurred in ~30% (13). In women with type 1 diabetes and microalbuminuria, preterm delivery and preeclampsia are also frequent and serious complications (11,13,14).

In nonpregnant subjects with diabetes, inhibition of the renin-angiotensin system is a cornerstone in the treatment of microalbuminuria and diabetic nephropathy (15–19). However, during pregnancy, antihypertensive therapy is often not indicated until sustained blood pressure elevations >150 mmHg systolic or 100 mmHg diastolic are documented (20), owing to concerns for reduced placental circulation, which may cause fetal hypoxia and intrauterine growth restriction (21).

In Copenhagen, we recommend blood pressure levels $<135/85$ mmHg and urinary albumin-creatinine ratio <300 mg/g during pregnancy in women with diabetes and diabetic nephropathy or microalbuminuria (14,22), regardless of the type of diabetes. Using this strategy, observational studies have shown that early initiation of intensive antihypertensive therapy during pregnancy leads to a reduced prevalence of preterm delivery in women with type 1 diabetes and diabetic nephropathy or microalbuminuria (14,22). Brown and Garovic (23) also recommend a lower threshold for antihypertensive treatment in pregnant women with diabetes and kidney involvement compared with nondiabetic pregnant women.

However, it has not been evaluated whether women with type 2 diabetes benefit from intensive antihypertensive therapy to the same degree as women with type 1 diabetes during pregnancy.

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Received 1 May 2013 and accepted 16 June 2013.

DOI: 10.2337/dc13-1031

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In this study, we evaluated the prevalence of diabetic nephropathy and microalbuminuria as well as pregnancy outcome in a recent cohort of pregnant women with type 2 or type 1 diabetes treated according to the same protocol for intensive antihypertensive treatment during pregnancy.

RESEARCH DESIGN AND METHODS

A retrospective cohort study among 665 singleton pregnancies in women with type 2 or type 1 diabetes with a living fetus at 22 weeks delivering at our center from January 2007 until October 2012 was conducted. The center is a referral center for all pregnant women with type 2 or type 1 diabetes from a geographically well-defined area of 2.5 million inhabitants. All women were asked to bring two urine samples for analysis of urinary albumin excretion at the first pregnancy visit. Urinary albumin-creatinine ratio was used in the majority of cases to evaluate kidney involvement since we previously reported a high concordance between albumin excretion in 24-h urine collection and urinary albumin-creatinine ratio (24). At least two values within the range of microalbuminuria or diabetic nephropathy were required to classify the patients. Forty-one women were identified with kidney involvement defined as presence of diabetic nephropathy (urinary albumin-creatinine ratio ≥ 300 mg/g) or microalbuminuria (urinary albumin-creatinine ratio 30–299 mg/g). At the first pregnancy visit, three women had nephrotic proteinuria (urinary albumin-creatinine ratio $>2,000$ mg/g).

One woman with type 1 diabetes and diabetic nephropathy had two pregnancies in the inclusion period; both pregnancies were included to ensure all available cases in the study period.

Women were recommended to perform self-monitored plasma glucose (SMPG) values seven times daily, before and 90 min after each main meal and before bedtime, and they were instructed to change insulin dose based on the SMPG values of the previous 3 days. Treatment targets were: 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 (25). $HbA_{1c} \leq 5.6\%$ in the second part of pregnancy was recommended (25).

The women visited our and/or their local diabetes clinic mainly at 2-week intervals during pregnancy. At each visit, weight, HbA_{1c} , insulin dose, and blood pressure were recorded, and the urine was screened

for proteinuria with a dipstick test (Urinstix; Bayer Diagnostics, Bridgend, U.K.) on sterile urine. Further analysis of urinary albumin-creatinine ratio was performed if proteinuria ($>1+$ on the dipstick) was present. The urinary albumin excretion was analyzed using an ELISA (26), and the blood creatinine concentration was measured by standard laboratory methods.

Blood pressure was measured with a digital blood pressure monitor (A&D Instruments, Abingdon, U.K.) in a sitting position after 5–10 min of rest.

If urinary albumin-creatinine ratio was ≥ 300 mg/g or blood pressure $\geq 135/85$ mmHg, antihypertensive therapy was initiated or intensified. If ACE inhibitors were withdrawn during pregnancy planning, another antihypertensive therapy was initiated unless the urinary albumin-creatinine ratio was close to normal (22).

Methyldopa (14,27) was the first-choice therapy in most cases, and, when indicated, labetalol and/or nifedipine (14) were added. If given before pregnancy, furosemide or thiazide was continued during pregnancy to reduce the risk of rebound fluid retention with increased blood pressure and urinary albumin excretion when discontinuing the drug (14,22).

Nonstress testing with cardiotocography was used routinely at least once weekly from 32–34 gestational weeks in addition to daily kick-counting. Fetal growth was evaluated routinely by obstetrical ultrasound at 28, 33, and 37 weeks of gestation. On clinical indications as judged by the obstetrician, flow measurements of the umbilical, cerebral, and uterine arteries were performed.

Preeclampsia was defined as two recordings of either systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg and urinary albumin excretion >190 mg/24 h or proteinuria $\geq 1+$ on a dipstick of sterile urine after 20 weeks of gestation. In women with diabetic nephropathy, the diagnosis was additionally based on a sudden increase of $\geq 15\%$ in systolic or diastolic blood pressure (12).

Neonatal outcomes included early preterm delivery before 34 weeks, preterm delivery before 37 weeks, major congenital malformations (responsible for death, causing a significant future handicap, or requiring surgery), perinatal death (death occurring between 22 completed weeks and 1 completed week after delivery), low 5-min Apgar score (<7), transient

tachypnea of the newborn (the need of continuous positive airway pressure for >1 h), neonatal hypoglycemia (plasma glucose <2.5 mmol/L) on the first plasma glucose value measured 2 h after delivery, or neonatal jaundice (need of photo therapy). Birth weight was evaluated by calculating SD z score to adjust for gestational age and sex and small and large for gestational age (weight for gestational age <10 th percentile and >90 th percentile, respectively) (28).

The study was approved by the Danish Data Protection Agency. According to Danish law, the regional committees for ethics and science did not have to be contacted.

Statistics

Data are given as median (range) or n (%). Differences between groups were analyzed using Fisher exact test and χ^2 test, as appropriate, for categorical variables and Mann-Whitney test for continuous variables as data were nonnormally distributed.

The associations were considered to be statistical significant at a two-sided P value <0.05 . All statistical analyses were performed using SPSS statistics 20.0 (SPSS, Chicago, IL).

RESULTS—The prevalence of diabetic nephropathy at baseline was 2.3% (5 of 220) in women with type 2 diabetes and 2.5% (11 of 445) in women with type 1 diabetes ($P = 1.0$). The prevalence of microalbuminuria was 4.5 (10 of 220) vs. 3.4% (15 of 445), respectively ($P = 0.39$), giving a total prevalence of kidney involvement in early pregnancy of 6.8% for type 2 diabetes vs. 5.8% for type 1 diabetes ($P = 0.62$).

Baseline characteristics (Table 1) were comparable between women with kidney involvement with either type 2 diabetes ($n = 15$) or type 1 diabetes ($n = 26$), except for shorter duration of diabetes in women with type 2 diabetes. Elevated urinary albumin excretion rate was documented with two urine samples before 20 weeks in the majority of cases and with one urine sample in the remaining.

Glycemic control was similar in women with type 2 and type 1 diabetes (Table 1). At first pregnancy visit, antihypertensive therapy was not used in any of the women with type 2 diabetes and in 16 (62%) women with type 1 diabetes ($P < 0.001$).

In women with type 2 diabetes, antihypertensive therapy was initiated during

Table 1—Maternal characteristics among 41 women with type 2 diabetes or type 1 diabetes and kidney affection during pregnancy

	Diabetic nephropathy		Microalbuminuria	
	Type 2 diabetes	Type 1 diabetes	Type 2 diabetes	Type 1 diabetes
<i>n</i>	5	11	10	15
Maternal age (years)	31 (21–39)	32 (28–40)	31 (23–37)	31 (22–37)
Diabetes duration (years)	2 (0.5–13)	19 (10–34)**	2 (0.5–8)	22 (10–31)**
Nullipara	2 (50)	5 (45)	3 (30)	10 (67)
Maternal smoking	0	3 (27)	3 (30)	4 (27)
Folic acid at first visit	2 (50)	10 (91)	6 (60)	12 (92)
Gestational age at first visit (days)	66 (44–69)	68 (49–95)	84 (47–122)	55 (42–147)*
BMI before pregnancy (kg/m ²)	28.2 (24.7–39.3)	23.7 (18.9–34.7)	31.4 (22.5–43.3)	25.8 (21.2–37.5)
HbA _{1c} at first visit (%)	6.8 (5.5–13.2)	7.0 (6.0–9.4)	6.8 (5.8–8.8)	7.1 (6.0–8.3)
HbA _{1c} at first visit (mmol/mol)	51 (37–121)	53 (42–79)	51 (40–73)	54 (42–67)
HbA _{1c} at last visit (%)	5.5 (5.2–5.9)	6.1 (5.5–6.7)	6.2 (5.6–8.2)	6.3 (5.3–6.6)
HbA _{1c} at last visit (mmol/mol)	37 (33–41)	43 (37–50)	44 (38–66)	45 (34–49)
Diabetic retinopathy at first visit	3 (75)	5 (56)	2 (20)	11 (85)**
Serum creatinine at first visit (μmol/L)	52 (40–73)	61 (34–168)	40 (31–63) ^a	51 (35–87)*
Albumin-creatinine ratio at first visit (mg/g)	474 (350–2,950)	712 (350–3,000)	110.5 (51–206)	84.5 (33–222)
Two urine samples collected before 20 weeks	5 (100)	11 (100)	7 (70)	12 (80)
Antihypertensive therapy at first visit	0	7 (64)	0	9 (60)**
Systolic blood pressure at first visit (mmHg)	132 (100–164)	140 (97–176)	128 (108–149)	132 (107–155)
Diastolic blood pressure at first visit (mmHg)	88 (73–91)	80 (63–100)	78 (68–88)	80 (68–87)
Weight gain during pregnancy (kg)	16.7 (2.5–28)	9.25 (1.3–16.2)	8.25 (–2.2 to 15.1)	11.7 (–1.5 to 24.9)
Insulin dose at first visit (IU/kg)	0.40 (0–0.62)	0.68 (0.37–1.17)	0.35 (0–1.23)	0.72 (0.46–1.51)

Data are median (range) or *n* (%). ^aOnly few data available (3 of 10). **P* < 0.05, ***P* < 0.001.

pregnancy in four (80%) women with diabetic nephropathy and in two (20%) women with microalbuminuria. Antihypertensive therapy was mainly initiated in early pregnancy. In two (40%) women with diabetic nephropathy, at least three classes of antihypertensive drugs were indicated.

Among women with type 1 diabetes, nine were treated with ACE inhibitors before pregnancy, and eight continued this treatment during the organogenesis. Antihypertensive therapy was initiated or continued during pregnancy in 25 of 26 women, and 14 (54%) women received at least two classes of drugs. In women with diabetic nephropathy, six (55%) received at least three classes of drugs. The maximum number of antihypertensive drugs given was four.

Blood pressure was stable during pregnancy in all groups without statistically significant differences (Fig. 1).

In early pregnancy, serum creatinine was within normal range in all women, except three (Table 1), and remained stable during pregnancy. No women developed end-stage kidney disease. Development of nephrotic proteinuria during pregnancy occurred in one (2.4%) woman with type 1 diabetes and diabetic nephropathy.

Among all 41 women, 11 (27%) received low-dose aspirin during pregnancy evenly distributed among the four groups. Five (20%) women with type 1 diabetes were treated with thyroid hormone replacement for hypothyroidism during pregnancy. None received antidepressant therapy.

Abnormal flow was measured by ultrasound in four women with type 1 diabetes (three with nephropathy and one with microalbuminuria) and was a contributing factor to induced preterm delivery based on obstetrical judgment. Three of these four women received antihypertensive treatment.

None of the routine nonstress tests alone led to induction of labor or cesarean section before planned.

Pregnancy outcome was comparable in women with type 2 and type 1 diabetes (Table 2). The main causes for preterm delivery were preeclampsia, macrosomia, or suspected placental insufficiency. In women with type 2 and type 1 diabetes, birth weight was 3,304 g (1,278–3,914) and 2,850 (370–4,180), respectively (*P* = 0.67). Birth weight was <2,000 g in four (10%) infants of women with kidney involvement.

Major congenital malformations were recorded in two infants (5%); one live-born

with hypospadias (the mother received ACE inhibitor during the organogenesis), and one stillborn with multiple kidney and heart malformations (no inhibition of

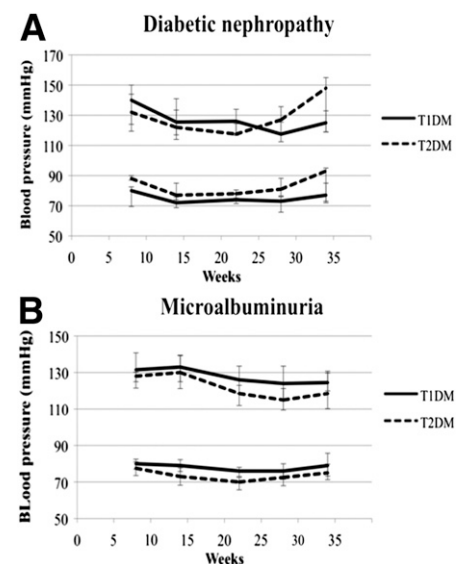


Figure 1—Blood pressure during pregnancy among 41 women with type 2 (T2DM) or type 1 diabetes (T1DM). A: Women with nephropathy. B: Women with microalbuminuria. Data are expressed as median and interquartile range.

Table 2—Pregnancy outcome among 41 pregnancies in women with type 2 or type 1 diabetes and kidney affection during pregnancy

	Diabetic nephropathy		Microalbuminuria	
	Type 2 diabetes	Type 1 diabetes	Type 2 diabetes	Type 1 diabetes
<i>n</i>	5	11	10	15
Preeclampsia	2 (40)	4 (36)	1 (10)	3 (20)
Cesarean section	3 (60)	10 (91)	8 (80)	12 (80)
Gestational age at delivery (days)	250 (233–276)	249 (184–259)	260 (221–275)	259 (224–271)
Delivery before 37 weeks	3 (60)	9 (82)	3 (30)	7 (47)
Delivery before 34 weeks	2 (40)	3 (27)	1 (10)	1 (7)
Birth weight (g)	2,460 (1,835–3,314)	2,506 (370–3,740)	3,355 (1,278–3,914)	3,229 (2,138–4,180)
Admission to neonatal special care unit	3 (60)	7 (64)*	4 (44)	5 (33)
Neonatal hypoglycemia (<2.5 mmol/L)	1 (25)	8 (89)	3 (33)	5 (36)
Weight <i>z</i> score (SD units)	−0.51 (−1.6 to 0.9)	−0.84 (−5.3 to 3.0)	1.21 (−2.8 to 2.4)	1.40 (−1.3 to 3.8)
Large-for-gestational-age infants	0	2 (18)	3 (30)	8 (53)
Small-for-gestational-age infants	2 (40)	4 (36)	2 (20)	1 (7)

Data are median (range) or *n* (%). **P* < 0.05.

the renin angiotensin system during organogenesis). One infant with severe intrauterine growth restriction (*z* score −5.25) and abnormal umbilical flow was delivered at 30 weeks and died 3 days postpartum. The mother had type 1 diabetes and diabetic nephropathy and was treated with three antihypertensive agents during pregnancy. One year later, this woman completed an uneventful pregnancy while receiving four types of antihypertensive agents.

CONCLUSIONS—This study demonstrates that the prevalence of diabetic nephropathy and microalbuminuria in pregnant women with type 2 diabetes was comparable to the prevalence in pregnant women with type 1 diabetes. Using the same antihypertensive strategy, pregnancy outcome was comparable regardless type of diabetes in women with kidney involvement. Antihypertensive therapy was used more frequently in women with type 1 diabetes and did not seem to affect pregnancy outcome negatively.

The women with type 2 diabetes and kidney involvement had a relatively shorter diabetes duration compared with the women with type 1 diabetes. This is in accordance with the findings in the nonpregnant population of children and young adults with type 2 diabetes in whom microalbuminuria and diabetic nephropathy are also present in subjects with a relatively shorter duration of diabetes (3–5).

In Danish pregnant women with type 1 diabetes, the prevalence of diabetic nephropathy has declined from 5% in

the late 1990s (12) to 2.5% in the current study, in which the same diagnostic criteria was used. The prevalence of diabetic nephropathy in type 1 diabetes in the current study is in accordance with a prevalence of 0.5–5.0% in other recent studies using slightly different diagnostic criteria for diabetic nephropathy (7–9,29). The figures for type 2 diabetes were 0.8 and 2.6% (8,9).

The prevalence of microalbuminuria in Danish pregnant women with type 1 diabetes has declined from 11% in the 1990s (12) to 4.5% in the current study, using the same diagnostic criteria. This is in accordance with international findings reporting prevalence of microalbuminuria in pregnant women with type 1 diabetes between 10 and 30% in the late 1990s (11,30) and recent findings of 4.5% (29).

For pregnant women with type 2 diabetes, the prevalence of microalbuminuria in the late 1990s was 13 (2) and 33% (31).

The decline in prevalence of diabetic nephropathy and microalbuminuria in women with type 1 diabetes is in line with a general trend toward lower prevalence of diabetic nephropathy in the Danish diabetic population (32). This may be explained by improved glycemic control (33,34) and more frequent use of inhibitors of the renin angiotensin system (16,17,35).

Preconceptionally, women with type 2 diabetes are mainly followed at the general practitioner and were rarely followed at a specialized diabetes center. This may explain the lack of antihypertensive treatment in women with type 2

diabetes and diabetic nephropathy or microalbuminuria at the first pregnancy visit.

The strength of this study is that the data are unselected from one large center covering the entire eastern part of Denmark. The same intensive antihypertensive strategy was used during the whole period, and the same few doctors treated all patients. Blood pressure was almost stable during pregnancy in all groups without statistically significant differences, but numbers were too small for firm conclusions. Glycemic control was generally good, contributing to affect pregnancy outcome positively (36).

The low number of cases, despite the long inclusion period, and the retrospective design of the study are weaknesses. We asked all women for two urine samples at the first pregnancy visit. The majority of women were compliant to this request; in women with diabetic nephropathy, it was 100%, but among women with microalbuminuria, two samples were obtained in 70–80% of the cases. Some of these women might have had normal urinary albumin excretion in the next sample, which could lead to a slightly lower prevalence of microalbuminuria. For clinicians caring for these high-risk pregnancies, it is clinically relevant to describe the prevalence and pregnancy outcome in pregnant women with type 2 diabetes and diabetic nephropathy or microalbuminuria, as this group of patients is expected to increase in the near future. Pregnancy outcome, especially preterm delivery and preeclampsia, were in accordance to our previous results (22) using the same antihypertensive protocol in pregnant

women with type 1 diabetes and diabetic nephropathy or microalbuminuria. Thus, this study supports that intensified antihypertensive treatment reduces adverse pregnancy outcome as previously described in women with type 1 diabetes and nephropathy (11,37) or microalbuminuria (14).

Serum creatinine was used as an index of renal function. We found stable serum creatinine levels during pregnancy for both women with diabetic nephropathy and microalbuminuria, regardless of type of diabetes in accordance with earlier findings (22,38).

The use of intensive antihypertensive therapy during pregnancy may raise concern about fetal intrauterine growth restriction by lowering the placental blood flow. In women with microalbuminuria, median birth weight z score was positive in both groups, indicating sufficient fetal growth despite antihypertensive therapy given in 68% of these women.

The prevalence of small-for-gestational age infants in women with diabetic nephropathy was 40 and 36% for type 2 and type 1 diabetes, respectively, which is in accordance with our earlier findings (12). The high rate of small-for-gestational-age infants is most likely explained by the diabetic microangiopathy per se (39).

To evaluate properly whether initiation of antihypertensive therapy affects uteroplacental and fetal hemodynamics in diabetic pregnancy, a prospective study with nonstress tests and careful ultrasound examinations before and after initiation of antihypertensive therapy is needed.

In women with increased risk of preeclampsia, including pregestational diabetes mellitus complicated with diabetic nephropathy or microalbuminuria, treatment with low-dose aspirin initiated before 12 weeks of gestation may slightly reduce this risk (20,40). In this study, only one-fourth (11 of 41) of patients received aspirin during pregnancy, a factor that should be improved in the future with the purpose to reduce the rate of preeclampsia.

In conclusion, the prevalence of diabetic nephropathy and microalbuminuria in early pregnancy among women with type 2 diabetes is comparable to that in pregnant women with type 1 diabetes. Pregnancy outcome was comparable in women with kidney involvement regardless of type of diabetes. It seems reasonable to assume that pregnant women with diabetic nephropathy or microalbuminuria could

be treated and controlled in a similar way regardless of type of diabetes.

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

J.A.D. researched data, wrote the manuscript, and contributed to discussions. B.Á. and N.F.C. researched data, contributed to discussions, and reviewed and edited the manuscript. J.M.M., L.R., and B.W.P. contributed to discussions and reviewed and edited the manuscript. E.R.M. contributed to the idea, researched data, contributed to discussions, and reviewed and edited the manuscript. E.R.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

This study was presented as a poster at Diabetes, Hypertension, Metabolic Syndrome and Pregnancy, Florence, Italy, 14–16 March 2013; and in abstract form at the North Europe Young Diabetologists meeting, Korsør, Denmark, 28–30 August 2013.

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