Poor Pregnancy Outcome in Women With Type 2 Diabetes

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OBJECTIVE — To evaluate the perinatal outcome and the frequency of maternal complications in pregnancies of women with type 2 diabetes during 1996–2001.

RESEARCH DESIGN AND METHODS — Medical records of 61 consecutive singleton pregnancies in women with type 2 diabetes from 1996 to 2001 were studied. Pregnancy outcome was compared with that of pregnant women with type 1 diabetes during 1996–2000, the background population, and pregnant women with type 2 diabetes during 1980–1992 from the same department.

RESULTS — The perinatal mortality in pregnancies complicated by type 2 diabetes (4/61, 6.6%) was increased four- and ninefold, respectively, and the rate of major congenital malformations (4/60, 6.7%) was more than doubled, although not statistically significant, compared with type 1 diabetic pregnancies and the background population. The glycemic control was similar or better in women with type 2 diabetes compared with women with type 1 diabetes. Multivariate logistic regression analysis in the pooled group of pregnancies with pregestational diabetes from 1996 to 2001 showed that high HbA_{1c} at admission and type 2 diabetes were independently associated with a serious adverse fetal outcome (perinatal mortality and/or major congenital malformations). The perinatal mortality and the rate of major congenital malformations in type 2 diabetic pregnancies have increased during the last decade.

CONCLUSIONS — The perinatal outcome of pregnancies in women with type 2 diabetes during 1996–2001 is poor. It is worse than the outcome of pregnancies in women with type 1 diabetes and the background population in the same period, as well as in women with type 2 diabetes studied during 1982–1990.

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T he prevalence of type 2 diabetes is increasing rapidly in all age-groups. In line with this, it is a general clinical observation that the number of pregnant women with pregestational type 2 diabetes has become more frequent in the recent years; however, little knowledge exists concerning the prevalence and outcome of these pregnancies (1,2).

A study from Birmingham, U.K., showed a similar perinatal mortality but a higher frequency of congenital malformations, preterm delivery, large-for-gestational-age infants, and fetal loss before 24 weeks' gestation in 57 pregnancies in women with type 2 diabetes compared with pregnancies in women with type 1 diabetes (3,4). In 182 pregnancies in women with type 2 diabetes compared with the general population, there was a 2.5-fold greater risk of perinatal mortality and an 11-fold greater risk of a congenital malformation (5). A study from New Zealand reported a threefold increased perinatal mortality rate in pregnancies related to type 2 diabetes compared with pregnancies related to type 1 diabetes. In addition, the study indicated that the outcome was poorer if type 2 diabetes was diagnosed during pregnancy compared with before pregnancy (6). The prevalence of type 2 diabetes in pregnancy was the highest in non-Caucasian women, who had a nonsignificantly higher HbA_{1c} during pregnancy (3,4,6).

The aims of the present study were to evaluate the frequency of maternal complications and serious adverse fetal outcome in a group of women with type 2 diabetes who gave birth between 1996 and 2001 and to compare the outcome in this group to the outcome in three other groups, namely a group of women with type 1 diabetes who gave birth at our clinic in the same period, the background population in the same period, and a group of women with type 2 diabetes who gave birth at our clinic during 1982–1990 (7). To our knowledge, this is the first report that compares outcome in pregnancies in a recent group of women with type 2 diabetes to a former group of women with type 2 diabetes.

RESEARCH DESIGN AND METHODS — We retrospectively studied all women with pregestational type 2 diabetes referred to the Department of Obstetrics, Copenhagen University Hospital, Rigshospitalet, Denmark, from January 1996 to December 2001 for antenatal care and delivery. A total of 80 singleton pregnancies in women with pregestational type 2 diabetes referred from either general practitioners (44%) or a hospital unit (56%) were registered. To exclude possible type 1 diabetes, type 2 diabetes was defined as diabetes in pa-

tients who were able to manage on diet alone or on oral hypoglycemic agents before (possible) commencement of insulin treatment. Secondary causes of diabetes were excluded (e.g., chronic pancreatitis). Ten of the pregnancies were excluded: 9 spontaneous abortions <12 weeks' gestation and 1 because the medical record was lost. If a woman had more than one pregnancy in the study period (*n* = 9), only the first pregnancy was included, leaving 61 pregnancies for calculations. Of these 61 pregnancies, 60 were deliveries ≥22 weeks' gestation and one was a pregnancy terminated in 14 weeks' gestation due to major congenital malformations identified by ultrasonography.

The type 2 diabetic pregnancies were managed according to our routine procedures for type 1 diabetic pregnancies (8). Current treatment with oral hypoglycemic agents was stopped at admission, and the women were treated with diet alone or diet and insulin. Women treated with diet alone performed home blood glucose measurements before and 1.5 h after breakfast and lunch, respectively, 2–3 days per week. Goals were preprandial capillary blood glucose levels <6 mmol/l, postprandial levels <8 mmol/l, and a mean <7 mmol/l. If these goals were not obtained, insulin treatment with insulin twice (Mixtard; Novo Nordisk, Princeton, NJ) or four times (Actrapid and Insulatard; Novo Nordisk) daily was instituted. Women on insulin treatment were asked to perform home blood glucose measurements before each principal meal and before bedtime during pregnancy and to adjust insulin doses accordingly; the goal was preprandial blood glucose levels of 3–6 mmol/l. HbA_{1c}, analyzed by antibody immunoassay (reference interval in nonpregnant individuals: 4.1–6.4%), was measured at the first visit to the clinic and several times during pregnancy (9). Three values of HbA_{1c} were chosen to represent the metabolic control during pregnancy: at admission and around 21 and 32 weeks' gestation.

Microalbuminuria was defined as urinary albumin excretion of 30–300 mg/24 h, and diabetic nephropathy was defined as >300 mg/24 h, based on two consecutive measurements. Hypertension was defined as pregestational treatment for hypertension or blood pressure >140/90 mmHg, based on three consecutive measurements early in pregnancy. An ophthalmologist evaluated presence or

absence of retinopathy at first visit and around 28 weeks' gestation.

Complications during pregnancy were defined as follows. Pregnancy-induced hypertension was defined as blood pressure >140/90 mmHg, based on three consecutive measurements in pregnancy, and a normal pregestational blood pressure. Preeclampsia was defined as development of hypertension and proteinuria >0.3g/24 h after 20 weeks' gestation. Severe maternal hypoglycemia was defined as hypoglycemia that required help from another person. Preterm delivery was defined as delivery <37 weeks' gestation. Large for gestational age was defined as birth weight >90th percentile, and small for gestational age was defined as <10th percentile for gestational age and sex according to Danish standard population (10).

Neonatal morbidity was defined as follows. Neonatal jaundice was defined as hyperbilirubinemia requiring phototherapy. Respiratory difficulties in the newborn represented the need for continuous positive airway pressure for more than 60 min. Perinatal mortality was defined as fetal death later than 22 weeks' gestation or death within 1 week after delivery.

Major congenital malformations were those responsible for death, those causing a significant future disability, or those requiring major surgery for correction (11). Serious adverse fetal outcome represented was major congenital malformations or perinatal death.

Ethnic origin was defined as Nordic-Caucasian if the woman originated from Denmark, Sweden, or Norway.

For comparison, a group of 240 pregnant women with type 1 diabetes from the same time period and department was used. This population has been described in detail previously (12–14). Likewise, a study of 72 pregnancies in women with type 2 diabetes during 1980–1992 from the same department was used for comparison (7).

Statistical analyses

For categorical variables, comparisons were performed by either Fisher's exact test or χ^2 test or by presenting the relative risk (RR) or odds ratio (OR) and 95% CIs. Continuous variables are given as median and interquartile range. Differences between medians were analyzed with the Mann-Whitney *U* test. The Bonferroni correction was used to allow for multiple

comparisons when more than two groups were compared.

Multivariate logistic regression analysis was performed, including the dependent variable serious adverse fetal outcome. First, analysis was performed in the group of women with type 2 diabetes, including the following variables in the full model: HbA_{1c} at admission, parity, duration of diabetes, maternal age, pregestational BMI, and ethnical background. Second, an analysis was performed in the pooled group of women with type 2 and type 1 diabetes from 1996–2001, including the following variables in the full model: HbA_{1c} at admission, maternal age, type of diabetes, and BMI. The variables were entered in the models as follows: HbA_{1c} and maternal age as binary variables over and under the median, parity as either nulliparous or multiparous, duration of diabetes categorized in quartiles, BMI (0–24.9, 25–29.9, ≥30 kg/m²), ethnic background as either Nordic-Caucasian or non–Nordic-Caucasian and type of diabetes as either type 2 or type 1 diabetes. We used manual backwards elimination (likelihood ratio test). The significance level used was *P* < 0.05 (two tailed). Data were processed using the following software programs: Access2000, Excel 2000 (Microsoft, Redmond, WA), SPSS (version 11.0; SPSS, Chicago, IL), and Prism (version 3.0; Prism Software, Irvine, CA).

RESULTS

Outcome of pregnancies in women with type 2 diabetes during 1996–2001

Baseline data for the women are shown in Table 1. The first visit of the type 2 diabetic women to the obstetric clinic was at 13.1 weeks' (10–16) gestation and only three (5%) pregnancies were planned. Two women had pregestational hypertension. Treatment at admission was diet alone in 29 (48%), oral hypoglycemic agents in 22 (36%), and insulin in 10 (16%) women. During pregnancy, 52 (85%) needed insulin, which was initiated at 13.0 weeks' (8–20) gestation. The maximum daily requirement of insulin was 54 IU (36–95); 54% of the women had insulin twice daily while 46% had insulin four times daily.

Two women experienced ketoacidosis with bicarbonate <17 mmol/l. Both were in poor metabolic control with

Table 1—*Baseline data for pregnant women with diabetes (1996–2001)*

	Type 2 diabetes	Type 1 diabetes	P
n	61	240	
Maternal data at admission			
Age (years)	33.4 (31–38)	30.0 (27–33)	<0.0001
Nordic-Caucasian	36 (59)	240 (100)	<0.0001
Pregestational BMI (kg/m^2)	29.4 (27–35)	23.0 (21–26)	<0.0001
Multiparous	42 (69)	111 (46)	0.002
Smoking	16 (26)	69 (29)	0.52
Systolic blood pressure (mmHg)	115 (108–126)	118 (110–123)	0.96
Diastolic blood pressure (mmHg)	70 (61–80)	70 (60–75)	0.21
Duration of diabetes (years)	2.0 (1–5)	14.0 (6–19)	<0.0001
Microalbuminuria/macroalbuminuria	8 (13)/0 (0)	26 (11)/11 (5)	0.52/0.13
Simplex/proliferative retinopathy	3 (5)/0 (0)	75 (31)/25 (10)	<0.0001/0.01
Glycemic control during pregnancy			
HbA$_{1c}$ at admission (%)	6.8 (6.1–7.7)	7.0 (6.5–7.8)	0.41*
HbA$_{1c}$ second trimester (%)	5.7 (5.2–6.2)	6.3 (5.8–6.8)	0.002*
HbA$_{1c}$ third trimester (%)	5.9 (5.5–6.2)	6.3 (5.9–6.7)	0.005*

Data are medians (interquartile range) or *n* (%). *Bonferroni correction was used to allow for multiple comparisons.

HbA$_{1c}$ of 8.4 and 11.7%, respectively, at the first admission in pregnancy. Type 1 diabetes was excluded in both women based on C-peptide measurements before pregnancy, and both were treated with oral hypoglycemic agents before and after pregnancy. The first woman had been shifted to insulin therapy four times daily from 6 weeks' gestation and developed ketoacidosis in relation to an acute gastroenteritis in the third trimester. Findings were drowsiness, ketonuria >15 mmol/l, pH 7.31, bicarbonate 15.0 mmol/l, base deficit −12 mmol/l, and blood glucose 10.1 mmol/l. The patient needed 13 l of fluid for rehydration. After acute intervention, which continued for 48 h, pregnancy continued uneventfully. The other woman had skipped treatment around conception and did not attend any antenatal medical or obstetrical care before she was admitted at ~26 weeks' gestation, presenting in advanced labor with pregnancy-induced hypertension as well as clinical ketoacidosis. The fetus was in a breech position; therefore, an emergency caesarean section was performed. Findings were pronounced labor pain and anxiety, ketonuria >15 mmol/l, pH 7.42 (PCO$_2$ 3.6 kPa; normal range 4.3 kPa-5.7 kPa), bicarbonate 16.8 mmol/l, base deficit −7 mmol/l, and blood glucose 23.7 mmol/l. The situation was interpreted as a case of respiratory-compensated ketoacidosis, and acute intervention continued for 36 h. Both children did well in the neonatal period.

No cases of severe maternal hypoglycemia were seen.

Maternal pregnancy complications and perinatal outcome are shown in Table 2. A total of 18 of 59 live born infants (31%) were born preterm due to either spontaneous onset of labor (7%) or termination of pregnancy due to obstetrical

reasons (24%). Four pregnancies (6.6%), including one induced abortion at 14 weeks' gestation, were complicated by major congenital malformations (two cardiac malformations, one with multiple additional malformations; one gastroschisis; and one anencephaly). HbA$_{1c}$ at admission was 7.3% (range 5.7–8.5%) in these women. Two of the four women who gave birth to children with malformations were treated with oral hypoglycemic agents. The first woman had HbA$_{1c}$ of 7.3% at admission and was on metformin, 1 g twice a day until 15 weeks' gestation. She had a child with multiple malformations, including cardiac malformations, who died at 6 months of age. The other woman, who had HbA$_{1c}$ of 8.5% at admission, had taken metformin, 1 g three times daily until 10 weeks' gestation. The pregnancy was terminated after 14 weeks' gestation due to fetal anencephaly. The perinatal mortality was 6.7% (4/60) and, in one case, was related to major congenital malformations. Overall, 7 of the 61 pregnancies (11%) were complicated by serious adverse fetal outcome. In these pregnancies, median HbA$_{1c}$ at admission was 7.4 (range 5.7–10.3%) compared with 6.6% (4.9–11.7%) in the remaining pregnancies (*P* = 0.14). In the multivariate regression analyses among the type 2 diabetic pregnancies, no independent variable associated with serious adverse fetal outcome was found.

Table 2—*Complications in pregnancy and perinatal outcome*

	Type 2 diabetes	Type 1 diabetes	P
n	61	240	
Complications in pregnancy			
Pregnancy-induced hypertension	6 (10)	12 (5)	0.22
Preeclampsia	4 (7)	30 (13)	0.26
Caesarean delivery	22 (36)	123 (51)	0.04
Perinatal outcome			
Congenital malformations	4 (6.6)	7 (2.9)	0.24
Perinatal mortality	4 (6.7)	4 (1.7)	0.05
Gestational age (weeks)*	38.0 (37–39)	37.3 (36–38)	0.03
Birth <34 weeks' gestation*	8 (14)	17 (7)	0.19
Birth <37 weeks' gestation*	18 (31)	87 (38)	0.29
Birth weight (g)*	3,600 (3,095–3,990)	3,595 (3,064–3,925)	0.79
Large for gestational age*	33 (56)	117 (51)	0.54
Small for gestational age*	1 (2)	9 (4)	0.35
Birth weight >4,500 g*	5 (8)	11 (5)	0.27
Neonatal jaundice*	13 (22)	40 (18)	0.35
Respiratory difficulties*	12 (20)	52 (23)	0.79

Data are medians (interquartile range) or *n* (%). *The total of live-born singleton infants was 59 for type 2 diabetes and 228 for type 1 diabetes.

Outcome of pregnancies in women with type 2 diabetes compared with type 1 diabetes during 1996–2001

Women with type 2 diabetes were significantly older, were more obese, were more often of non–Nordic-Caucasian background, were more parous, and had fewer caesarean deliveries. Median duration of diabetes was significantly lower, and metabolic control, as judged by HbA_{1c}, was better during pregnancy in women with type 2 diabetes than women with type 1 diabetes (Table 1). Gestational age at birth was significantly higher in pregnancies of women with type 2 diabetes compared with women with type 1 diabetes ($P = 0.03$), and the perinatal mortality was increased compared with both women with type 1 diabetes (RR 4.0, 95% CI 1.0–15.5) and the background population (8.9, 3.4–23.0). Likewise, there was a tendency toward a higher malformation rate compared with women with type 1 diabetes (2.3, 0.7–7.4) and the background population (2.3, 0.9–6.0). Maternal complications in pregnancy as well as neonatal outcomes other than those mentioned above were comparable in the two groups (Table 2).

In multivariate logistic regression analysis in the pooled group of women with either type 2 or type 1 diabetes during 1996–2001, high HbA_{1c} at admission and type 2 diabetes were found to be independently associated with serious adverse fetal outcome (OR 5.3, 95% CI 1.5–19.0 and 3.4, 1.2–9.6, respectively).

Comparison of pregnancy outcome for women with type 2 diabetes during 1996–2001 and women with type 2 diabetes during 1980–1992

In the new group, we found higher rates of perinatal mortality (6.7 vs. 0%, $P = 0.04$), major congenital malformations (6.6 vs. 0%, $P = 0.04$), and preterm delivery (31 vs. 15%, $P = 0.04$). Women in the new group were more overweight (29.4 vs. 27.6 kg/m², $P = 0.005$), and diabetes seemed to be more complicated, as indicated by an increasing number of women needing medical treatment before pregnancy (52 vs. 24%, $P < 0.0001$) and medical treatment during pregnancy (85 vs. 67%, $P = 0.01$). Furthermore, the women tended to be older (33 vs. 32 years, $P = 0.12$) and more often of non–Nordic-Caucasian origin (41 vs. 33%, $P = 0.37$).

Ethnic differences in pregnancies in women with type 2 diabetes during 1996–2001

A total of 25 women (41%) were of non–Nordic-Caucasian background: 13 from Mediterranean countries, 7 from Pakistan, 4 from Somalia, and 1 from Bangladesh. There were no data on whether the women were born in Denmark, but according to their need for linguistic interpretation, it was our impression that most of them were first-generation immigrants. The non–Nordic-Caucasian women were older (35.7 vs. 32.2 years, $P < 0.05$), more parous (96 vs. 51%, $P = 0.0002$), smoked less (4 vs. 42%, $P = 0.002$), and had a lower systolic blood pressure (110 vs. 120 mmHg, $P = 0.007$) and diastolic blood pressure (65 vs. 70 mmHg, $P < 0.05$) at admission. There was a statistically nonsignificant trend toward higher median HbA_{1c} in the non–Nordic-Caucasian women compared with Nordic-Caucasian women both at admission (7.2 vs. 6.5%, $P = 0.23$) and during pregnancy (data not shown), as well as a poorer outcome in the non–Nordic-Caucasian pregnancies regarding perinatal mortality (12.9 vs. 2.6%, $P = 0.17$) and major congenital malformations (9.4 vs. 5.2%, $P = 0.65$), but numbers were small. No differences concerning BMI, gestational age at admission or at birth, birth weight, maternal complications in pregnancy, or rates of caesarean delivery were identified.

CONCLUSIONS — The present study of women with type 2 diabetes during 1996–2001 emphasizes that type 2 diabetes in pregnancy comprises a serious problem. A very high perinatal mortality rate was found: four and nine times increased, respectively, compared with women with type 1 diabetes and the background population, and the rate of major congenital malformations was more than doubled compared with these two groups.

Therefore, our data are in line with recent papers from very different parts of the world, indicating that maternal and perinatal morbidity as well as the perinatal mortality are higher in pregnancies complicated by type 2 diabetes compared with type 1 diabetes (2). In addition, we found that the perinatal mortality and the rate of major congenital malformations related to type 2 diabetes in pregnancy have become more frequent than in our previous study covering the years 1980–1992.

HbA_{1c} and home blood glucose monitoring have been used more frequently in the 1996–2001 group; however, over the years 1980–2001, there were no major changes in either management or referral pattern of pregnant women with type 2 diabetes that could explain this rise in serious adverse fetal outcome.

It is not unexpected that the complication rate in pregnancies in women with type 2 diabetes is increased compared with the background population, but it is not obvious why the outcome is so markedly poorer than in pregnancies complicated by type 1 diabetes. In women with type 1 diabetes who do not have diabetic nephropathy, it is well documented that the best predictor of poor pregnancy outcome is high HbA_{1c} early in pregnancy as well as an inappropriate reduction in HbA_{1c} during pregnancy (15–18). In concordance with this, the HbA_{1c} levels were significantly elevated in pregnancies in women with type 2 diabetes during the entire pregnancy compared with the normal range. However, compared with our well-characterized population of pregnant women with type 1 diabetes, women with type 2 diabetes had comparable or better glycemic metabolic control but nevertheless a poorer pregnancy outcome. A few other studies find tendencies toward higher HbA_{1c} and fructosamine, among women with type 1 diabetes compared with women with type 2 diabetes, but only in the first part of pregnancy (4,6,19). This indicates that factors in addition to glycemic control are related to the poor outcome of pregnancies complicated by type 2 diabetes.

Today ketoacidosis is very infrequent in pregnant women with type 1 diabetes due to the intense attention on these women. In contrast, we observed two cases of ketoacidosis in 61 pregnant women with type 2 diabetes. These two women had known type 2 diabetes for 11 years and 2 years, respectively. Neither of them had been treated with insulin before pregnancy, and both were in poor metabolic control at admission and needed insulin treatment during pregnancy. Therefore, our findings indicate that the pregnancy-induced insulin resistance can cause severe metabolic derangement in noncompliant pregnant women with type 2 diabetes.

Planning of pregnancy and early ad-

mittance for antenatal care are associated with a reduction in complications (15,20–23). Figures for planned pregnancies and the exact gestational age at admission among our women with type 1 diabetes have not been systematically recorded for this study, but it is estimated to be ~70% and 10 weeks' gestation. In contrast, only three (5%) of the pregnancies in women with type 2 diabetes were planned, and more than half of the women attended the obstetrical department for the first time after the first trimester. Furthermore, women with type 2 diabetes were older, multiparous, and especially more obese than women with type 1 diabetes. Increasing age has been described as a risk factor for pregnancy complications, and several studies during the recent years have documented that maternal overweight and obesity in normoglycemic women are associated with an increased rate of complications such as stillbirth, operative delivery, hypertensive complications, and maybe even major congenital malformations (24,25). Obese women and women with type 2 diabetes, in particular, are characterized by insulin resistance, which is further aggravated during pregnancy, and insulin resistance has been associated to pregnancy complications (26). Therefore, it is likely that presence of the metabolic syndrome per se, characterized by insulin resistance, overweight, hyperlipidemia, and microalbuminuria, among the women with type 2 diabetes might to some extent explain the very high perinatal morbidity in these pregnancies. When comparing the new group with the old group of women with type 2 diabetes, our data indicate that the incidence of the metabolic syndrome has increased, showing a higher BMI and more women needing medical treatment before and during pregnancy. The multivariate logistic regression analyses showed no statistically significant association between serious adverse fetal outcome and maternal BMI, maternal age, or parity (data not given). However, the relatively small number of women with type 2 diabetes in this study implies a risk of type 2 errors.

In accordance with previous studies, we found a very high proportion (41%) of non–Nordic-Caucasians among pregnant women with type 2 diabetes. For comparison, the non–Nordic-Caucasian women comprise 7% of the women in the Danish background population (4,6,27). The present study implies that increased morbidity might be related to pregnancies in non–Nordic-Caucasian women with type 2 diabetes compared with Nordic-Caucasian women, but differences were not statistically significant.

What can be done to improve the outcome of these pregnancies? It seems obvious to apply some of the experience gained from pregnancies in women with type 1 diabetes. Important elements are planning of pregnancy, good metabolic control, interdisciplinary teamwork, and centralization of the care.

Women with type 2 diabetes and their health care professionals should be aware of the importance of optimizing metabolic control and treating diabetic complications before safe contraception is stopped. We found a very low risk of severe hypoglycemia in pregnant women with type 2 diabetes, most likely due to their considerable insulin resistance. The risk of hypoglycemia is therefore not expected to give the same limitations for strict metabolic control as in type 1 diabetes. Although the number of pregnant women with type 2 diabetes is increasing, the absolute number is still relatively small, and it seems appropriate to centralize the treatment of these women. This would enable gathering of experience and a more standardized management, which may improve the outcome.

In conclusion, the present study demonstrated a four- and ninefold higher rate of perinatal mortality in women with type 2 diabetes compared with women with type 1 diabetes or the background population during 1996–2001, and the rate of major congenital malformations were more than doubled compared with these two groups. In multivariate logistic regression analysis, HbA_{1c} at admission and having type 2 diabetes were found to be independently associated with serious adverse fetal outcome in pregnancies with pregestational diabetes. The perinatal mortality and the rate of major congenital malformations in pregnancies with type 2 diabetes have increased from 1980–1992 to 1996–2001.

Further prospective studies are needed to elucidate whether the high prevalence of serious adverse fetal outcome of pregnancies in women with pregestational diabetes is related to the rising prevalence of the metabolic syndrome, a high proportion of women of non–Nordic-Caucasian background, or other unknown factors associated with type 2 diabetes.

References

1. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, Marks JS: Diabetes trends in the U.S.: 1990–1998. *Diabetes Care* 23:1278–1283, 2000
2. Feig DS, Palda VA: Type 2 diabetes in pregnancy: a growing concern. *Lancet* 359:1690–1692, 2002
3. Brydon P, Smith T, Proffitt M, Gee H, Holder R, Dunne F: Pregnancy outcome in women with type 2 diabetes mellitus needs to be addressed. *Int J Clin Pract* 54:418–419, 2000
4. Dunne FP, Brydon PA, Proffitt M, Smith T, Gee H, Holder RL: Fetal and maternal outcomes in Indo-Asian compared to caucasian women with diabetes in pregnancy. *Q J Med* 93:813–818, 2000
5. Dunne F, Brydon P, Smith K, Gee H: Pregnancy in women with type 2 diabetes: 12 years outcome data 1990–2002. *Diabet Med* 20:734–738, 2003
6. Cundy T, Gamble G, Townend K, Henley PG, Macpherson P, Roberts AB: Perinatal mortality in type 2 diabetes mellitus. *Diabet Med* 17:33–39, 2000
7. Hellmuth E, Damm P, Molsted-Pedersen L: Maternal and fetal complications in pregnancies of women with pregestational NIDDM. *Int J Diabetes* 5:79–84, 1997
8. Molsted-Pedersen L, Damm P: How to organize care for pregnant diabetic patients. In *Concepts for the Ideal Diabetes Clinic* Mogensen CE, Standl E, Eds. New York, Walter de Gruyter, 1993, p. 199–214
9. Rumley AG, Kilpatrick ES, Dominiczak MH, Small M: Evaluation of glycaemic control limits using the Ames DCA 2000 HbA_{1c} analyser. *Diabet Med* 10:976–979, 1993
10. Larsen T, Petersen S, Greisen G, Larsen JF: Normal fetal growth evaluated by longitudinal ultrasound examinations. *Early Hum Dev* 24:37–45, 1990
11. Miller E, Hare JW, Cloherty JP, Dunn PJ, Gleason RE, Soeldner JS, Kitzmiller JL: Elevated maternal hemoglobin A1c in early pregnancy and major congenital anomalies in infants of diabetic mothers. *N Engl J Med* 304:1331–1334, 1981
12. 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
13. Ekbom P: Pre-pregnancy microalbuminuria predicts pre-eclampsia in insulin-dependent diabetes mellitus: Copenhagen Pre-eclampsia in Diabetic Pregnancy Study Group. *Lancet* 353:377, 1999

14. Ekbom P, Damm P, Nogaard K, Clausen P, Feldt-Rasmussen U, Feldt-Rasmussen B, Nielsen LH, Molsted-Pedersen L, Mathiesen ER: Urinary albumin excretion and 24-hour blood pressure as predictors of pre-eclampsia in type 1 diabetes. *Diabetologia* 43:927–931, 2000

15. Damm P, Molsted-Pedersen L: Significant decrease in congenital malformations in newborn infants of an unselected population of diabetic women. *Am J Obstet Gynecol* 161:1163–1167, 1989

16. Lauenborg J, Mathiesen E, Ovesen P, Westergaard JG, Ekbom P, Molsted-Pedersen L, Damm P: Audit on stillbirths in women with pregestational type 1 diabetes. *Diabetes Care* 26:1385–1389, 2003

17. Kovilam O, Khoury J, Miodovnik M, Chames M, Spinnoto J, Sibai B: Spontaneous preterm delivery in the type 1 diabetic pregnancy: the role of glycemic control. *J Maternal Fetal Neonatal Med* 11:245–248, 2002

18. 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* 43:1534–1539, 2000

19. Sacks DA, Chen W, Greenspoon JS, Wolde-Tsadik G: Should the same glucose values be targeted for type 1 as for type 2 diabetics in pregnancy? *Am J Obstet Gynecol* 177:1113–1119, 1997

20. Suhonen L, Hiilesmaa V, Teramo K: Glycaemic control during early pregnancy and fetal malformations in women with type 1 diabetes mellitus. *Diabetologia* 43:79–82, 2000

21. Dunne FP, Brydon P, Smith T, Essex M, Nicholson H, Dunn J: Pre-conception diabetes care in insulin-dependent diabetes mellitus. *Q J Med* 92:175–176, 1999

22. Kitzmiller JL, Gavin LA, Gin GD, Jovanovic-Peterson L, Main EK, Zigrang WD: Preconception care of diabetes: glycemic control prevents congenital anomalies. *JAMA* 265:731–736, 1991

23. Boulot P, Chabbert-Buffet N, d'Ercole C, Floriot M, Fontaine P, Fournier A, Gillet JY, Gin H, Grandperret-Vauthier S, Geudj AM, Guionnet B, Hauguel-de-Mouzon S, Hieronimus S, Hoffet M, Jullien D, Lamotte MF, Lejeune V, Lepercq J, Lorenzi F, Mares P, Miton A, Penfornis A, Pfister B, Renard E, Rodier M, Roth P, Sery GA, Timsit J, Valat AS, Vambergue A, Verier-Mine O: French multicentric survey of outcome of pregnancy in women with pregestational diabetes. *Diabetes Care* 26:2990–2993, 2003

24. Jensen DM, Damm P, Sorensen B, Molsted-Pedersen L, Westergaard JG, Ovesen P, Beck-Nielsen H: Pregnancy outcome and prepregnancy body mass index in 2459 glucose-tolerant Danish women. *Am J Obstet Gynecol* 189:239–244, 2003

25. Cnattingius S, Bergstrom R, Lipworth L, Kramer MS: Prepregnancy weight and the risk of adverse pregnancy outcomes. *N Engl J Med* 338:147–152, 1998

26. Innes KE, Wimsatt JH: Pregnancy-induced hypertension and insulin resistance: evidence for a connection. *Acta Obstet Gynecol Scand* 78:263–284, 1999

27. *Statistical Yearbook 2001.* Copenhagen, Statistics Denmark, 2001