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ORIGINAL ARTICLE

Glycemic control and pregnancy outcomes in women with type 2 diabetes from Poland. The impact of pregnancy planning and a comparison with type 1 diabetes subjects

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Abstract The number of pregnancies complicated by type 2 diabetes mellitus (T2DM) is growing; however, their clinical characteristics remain incomplete. We aimed to assess clinical characteristics, glycemic control, and selected pregnancy outcomes in pregestational T2DM from Poland and to compare them with those of T1DM. We analyzed 415 consecutive singleton pregnancies; among them, there were 70 women with T2DM and 345 with T1DM. As compared to T1DM patients, women with T2DM were older (mean age 33.1 years vs. 27.8, respectively), heavier before pregnancy (mean BMI 30.8 kg/m^2 vs. 23.9), and had a shorter duration of diabetes (mean 3.3 years vs. 11.4); ($P < 0.0001$ for all comparisons). The gestational age at the first visit was higher in T2DM (mean 11.4 weeks vs. 8.6; $P = 0.0004$). Nevertheless, they had better glycemic control in the first trimester (mean HbA1c 6.2% vs. 7.0; $P = 0.003$); in subsequent months, the differences in HbA1c were no longer significant. T2DM women gained less weight during pregnancy (mean 9.9 kgs vs. 14.1; $P < 0.0001$). The proportion of miscarriages (10.0 vs. 7.3%; $P = 0.32$), preterm deliveries (12.7 vs. 17.8%; $P = 0.32$), combined infant deaths, and congenital malformations were similar in both groups (9.5 vs. 8.8%; $P = 0.4$) as was the frequency of caesarean sections (58.7 vs. 64.1%; $P = 0.30$). Macrosomic babies were more than twice less frequent in T2DM and the difference reached borderline significance (7.9 vs. 17.5%, $P = 0.07$). Pregnancy planning in T2DM had a significant impact on HbA1c in the first trimester (5.7 vs. 6.4% in the planning vs. the not planning group, $P = 0.02$); the difference was not significant in the second and third trimester. T2DM women had better glycemic control in the first trimester than T1DM subjects and gained less weight during pregnancy. This could have been the reason for the slightly lower number of macrosomic babies but did not affect other outcomes. In T2DM, pregnancy planning had a beneficial glycemic effect in the first trimester.

Keywords Pregnancy · Type 2 diabetes · Type 1 diabetes · Outcomes

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Introduction

The prevalence of type 2 diabetes mellitus (T2DM) increases worldwide [1]. This disease affects younger and younger individuals of both genders [2], including women of childbearing age [2, 3]. This rise is attributable to the epidemic of obesity afflicting all generations. The main causes of this phenomenon are unhealthy diet and sedentary lifestyle. In addition, in many countries, women postpone pregnancy, for example, to develop a professional career. As a result, pregnant women are more likely than previously to be older, overweight, or obese and consequently diagnosed with

T2DM [2–4]. A pregnancy complicated by one of the major types of pregestational diabetes, type 1 (T1DM) or type 2 (T2DM), has an increased risk of unfavorable outcomes for the mother and infant, such as spontaneous miscarriages, preeclampsia, premature delivery, perinatal mortality, congenital malformations, and macrosomia [5–13]. This risk is strictly related to the level of glycemic control during pregnancy [14–16]. There is a clear evidence that optimized metabolic control, from preconception to the delivery, can reduce the danger of maternal and fetal complications in women diagnosed with pregestational diabetes [5, 9, 10, 13, 17, 18]. Thus, maintaining glucose levels as close as possible to those seen in healthy women is highly recommended [19].

There have been some number of articles comparing pregnancy outcomes in both major forms of pregestational diabetes and a recent meta-analysis of clinical studies has suggested that despite a milder glycemic disturbance, women with T2DM did not have better outcomes than those with T1DM [20]. Nevertheless, pregnancy complicated by T2DM is less characterized than that complicated by T1DM or gestational diabetes and data from some populations are not available. Moreover, as diabetes care before and during pregnancy has improved over recent years, new data are needed.

We have recently reported observational clinical data of pregnant T1DM women from Poland that were treated with different therapeutic approaches [21]. Our research has stressed the significance of pregnancy planning. In this article, we show clinical characteristics, glycemic control, and selected pregnancy outcomes of T2DM women and compare them with those of T1DM subjects. We also investigate the impact of pregnancy planning in T2DM.

Materials and methods

Patients

This study was performed at the Department of Metabolic Diseases, Krakow, Poland that is an academic reference center for diabetes care in South-Eastern Poland. All the pregnant women with pre-existing diabetes were registered between the years 1999 and 2009 and their data were collected at that time. Overall, we included 415 consecutive singleton pregnancies complicated by pregestational diabetes. All the subjects were Caucasian residents in South-Eastern Poland. Women with diabetes who were pregnant or planning pregnancy received intensive diabetes management, which involved education, frequent outpatient visits, and hospitalization if necessary. The use of the term "pregnancy planning" in this article refers to entering the program before conception. There were 22 (31.4%) planned pregnancies in women with T2DM and 144 (41.1%) in the T1DM group. The following glycemic therapeutic targets were defined: (a) HbA1c $< 6.1\%$, (b) fasting self-monitored blood glucose within 60–90 mg/dl, and (c) subsequent pre- and 1-h postprandial glucose self-measurements within 60–120 mg/dl. The inclusion criteria of T1DM patients had been recently reported by us [21]. We considered T2DM women if a diagnosis of this disease was established according to the current WHO criteria and no insulin therapy had been used for at least 1 year after the diagnosis. For a patient to be included in the study, a complete follow-up, from booking until the end of pregnancy, was required. In the T2DM group, there were 70 pregnancies in 63 women; 6 women had two or more consecutive pregnancies. Oral glucose-lowering drugs had been used before pregnancy in 36 (51.4%) cases and in the rest of them diabetes was controlled with diet only. During pregnancy, most of the women with T2DM ($n = 66$, 94.3%) were transferred to a MDI insulin regimen, while four of them continued on diet only. Most of them used human prandial insulin ($n = 61$, 93.9%). Insulin therapy was started on average at 13.8 ± 7.3 weeks of pregnancy. There were 345 pregnancies in the 275 women with T1DM; 61 women had two or more subsequent pregnancies. In more than half of the T1DM cases, a multiple daily injections (MDIs) regimen was used ($n = 187$, 54.2%) throughout the whole period of gestation. The rest were treated with continuous subcutaneous insulin infusion (CSII) via an insulin pump ($n = 158$, 45.8%). Most of T1DM subjects used human prandial insulin ($n = 209$, 59.7%).

The pregnant women had a check-up with a diabetologist and an obstetrician at least for every 4 weeks. All women received a thorough education covering self-monitoring of blood glucose, glycemic targets, diet, and self-adjustment of insulin doses. They were also advised by a dietician. The recommended standard calorie intake was 35 kcal/kg of body weight, of which 40–50% was to be covered by carbohydrates, 20–30% by fats, and 30% by proteins. Excessive weight gain was addressed by reducing daily food intake accompanied by a regular daily self-assessment of urine ketones [22]. A glucometer for self-control was provided to all women together with education from a diabetes specialist nurse. The patients were asked to measure fasting glycaemia and 1-h postprandial plasma glucose daily. The subjects treated with CSII received additional instructions regarding pump use. All patients received additional individual education if necessary.

Baseline characteristics

The baseline characteristics were assessed during the initial visit and included the patients' age, duration of diabetes, weight and BMI before conception, and presence of

diabetic complications. Retinopathy was diagnosed by ophthalmoscopy, while the diagnosis of nephropathy was based on the albumin excretion rate (with values between 30 and 300 mg/24 h classified as albuminuria).

Outcomes

We analyzed the following study outcomes: (a) HbA1c throughout the first, second, and third trimester of pregnancy, (b) mothers' weight gain during gestation (based on weight before pregnancy and the last weight measurement within a week before delivery), (c) frequency of acute diabetes complications (severe hypoglycemic episodes and diabetic ketoacidosis), (d) frequency of caesarian deliveries, (e) frequency of pre-term births (<37th week) and early pre-term deliveries (<34th week), (f) children's birth weight (term deliveries), (g) frequency of macrosomia (>4000 g), (h) frequency of low birth weight (<2500 g), (i) frequency of spontaneous miscarriages, and (j) infant deaths and congenital malformations analyzed separately and combined. Only singleton pregnancies were examined.

Statistical analysis

The comparisons between both continuous and categorical variables were carried out in the framework of generalized estimating equations to accommodate for women who had more than one pregnancy during the course of the study. Logarithmic transformations were carried out to obtain a more symmetric distribution (for pregestational body weight, BMI, gestational age at first visit, weight gain, and birth weight). Comparisons of outcomes between T2DM and T1DM were adjusted for the frequency of pregnancy planning, and women on CSII were excluded as sensitivity analysis. To compare changes in HbA1c over time, we used a repeated measures model, comparing corresponding HbA1c levels at the first, second, and third trimester. All computations were performed with SAS 9.2 software. *P*-values <0.05 were considered significant.

Results

The baseline clinical characteristics of both study groups are presented in Table 1. We found significant differences in subjects' age, as women with T2DM were on average 5.3 years older than those with T1DM, the duration of their diabetes was shorter by 8.1 years, and they were heavier before pregnancy by 16.3 kg (or 6.9 BMI units). In T2DM women, the mean gestational age at the first outpatient visit was older by 2.8 weeks, even among women planning their pregnancies (by 1.9 weeks). There were 22 (31.4%) subjects in the T2DM group who started intensive diabetes management before conception ("pregnancy planning") as compared to 144 women (41.1%) in the T1DM group. The rest of both study groups entered the intensive diabetes management program in the first trimester.

Women with T2DM had significantly lower HbA1c than T1DM subjects in the first trimester (6.2 vs. 7.0%, $P = 0.003$) (Table 2). Subsequently, HbA1c significantly decreased in both groups between the first and second trimester ($P = 0.007$ in T2DM and $P < 0.0001$ in T1DM), reaching similar levels in both groups (5.6 vs. 5.8%, $P = 0.10$); this was sustained in the third trimester (5.6 vs. 5.7%, $P = 0.27$). Adjusting for different percentages of planned pregnancies in the two groups or excluding CSII-treated women from the analysis did not change the described pattern of HbA1c changes. There were neither severe hypoglycemias nor diabetic ketoacidosis episodes in T2DM group, while their frequencies in T1DM group were 14 and 2, respectively.

Women with T2DM were significantly heavier at the last weight check before labor (by 13.3 kg, $P < 0.0001$), but they gained 4.2 kg less weight than those with T1DM (9.9 vs. 14.1 kg, $P < 0.0001$). There was no difference in duration of pregnancy and mean newborn birth weights (3453 g vs. 3554 g, $P = 0.23$). Adjusting for pregnancy planning or exclusion of CSII-treated T1DM women from the analysis did not have impact on statistical inferences about these outcomes.

Table 1 Baseline clinical characteristics of the study participants with T2DM and T1DM

	T2DM	T1DM	*P*
No. of individuals, *n* (%)	70	345	N.A.
Age (years)	33.1 (31.9, 34.4)	27.8 (27.2, 28.4)	<0.0001
Diabetes duration (years)	3.3 (2.4, 4.3)	11.4 (10.5, 12.3)	<0.0001
Weight before pregnancy (kg/m^2)	80.7 (76.4, 85.2)	64.4 (63.2,65.6)	<0.0001
BMI before pregnancy (kg/m^2)	30.8 (29.2, 32.5)	23.9 (23.5, 24.3)	<0.0001
Retinopathy, *n* (%)	2 (2.9)	89 (25.8)	0.0008
Nephropathy, *n* (%)	0 (0.0)	6 (1.7)	0.39*
Week of gestation at the first visit	11.4 (9.8, 13.2)	8.6 (8.1, 9.1)	<0.0004
Pregnancy planning, n (%)	22 (31.4)	144 (41.1)	0.23

* Fisher exact test

Table 2 Clinical outcomes in T1DM and T2DM group

Outcome	T2DM	T1DM	*P*
Maternal			
HbA1c (%) at admission	6.2 (5.8, 6.7)	7.0 (6.8, 7.2)	0.003
HbA1c (%) second trimester	5.6 (5.4, 5.9)	5.8 (5.7, 5.9)	0.10
HbA1c (%) third trimester	5.6 (5.4, 5.8)	5.7 (5.6, 5.8)	0.27
Weight gain during pregnancy (kg)[a]	9.9 (7.8, 11.9)	14.1 (13.4, 14.9)	<0.0001
Weight at the end of pregnancy (kg)[a]	91.6 (86.5, 96.8)	78.3 (76.9, 79.8)	<0.0001
Perinatal			
Gestational age (weeks)	38.1 (37.2, 39.0)	38.2 (37.9, 38.5)	0.87
Birth weight (g)[a]	3453 (3302, 3603)	3554 (3482, 3626)	0.23
Caesarean delivery, *n* (%)[b]	37 (58.7)	205 (64.1)	0.30
Preterm deliveries, *n* (%)[b]	8 (12.7)	57 (17.8)	0.32
Early preterm deliveries, *n* (%)[b]	3 (4.7)	13 (4.1)	0.6
Miscarriages, *n* (%)	7 (10.0)	25 (7.3)	0.44
Infant death, *n* (%)[b]	1 (1.6)	7 (2.2)	0.99[c]
Malformations, *n* (%)[b]	5 (7.9)	21 (6.6)	0.78[c]
Macrosomia, *n* (%)[b]	5 (7.9)	56 (17.5)	0.07
Low birth weight, *n* (%)[b]	5 (7.9)	24 (7.5)	0.99[c]

Data presented as means (95% confidence interval) or counts (percent)

[a] Term pregnancies

[b] In 320 T1DM and 63 T2DM, miscarriages excluded

[c] Fisher exact test

The rates of cesarian deliveries in T2DM and T1DM (58.7 vs. 64.1%, $P = 0.30$) were similarly high, and so was the proportion of miscarriages (10.0 vs. 7.3%; $P = 0.32$), preterm deliveries (12.7% vs. 17.8%; $P = 0.32$), early preterm deliveries (4.7 vs. 4.1%; $P = 0.6$), and combined number of infant deaths and congenital malformations (9.5 vs. 8.8%; $P = 0.4$), as shown in details in Table 2. The proportion of infants with birth weight >4000 g was over two times less frequent in T2DM than in T1DM (7.9 vs. 17.5%); however, this difference was not significant at this sample size ($P = 0.07$). There was no such difference between the proportions of birth weights <2500 g (7.9 vs. 7.5%, $P = 0.91$). Adjusting for pregnancy planning or CSII treatment did not change inferences about these outcomes.

Pregnancy planning in T2DM had a significant impact on HbA1c recorded in the first trimester. In women who entered the intensive care program before conception, its level was 5.7% (95% CI: 4.5, 6.9) as compared to 6.4% (95% CI: 5.6, 7.3) in women not planning, $P = 0.02$ (Fig. 1). In the second and third trimesters, the HbA1c levels were similar: 5.5% (95% CI: 4.7, 6.4) vs. 5.7% (95% CI: 5.0, 6.3), $P = 0.63$, and 5.6% (95% CI: 4.8, 6.3) vs. 5.6% (95% CI: 5.1, 6.1), $P = 0.78$, respectively (Fig. 1). Except for those in the HbA1c levels in the first trimester, we did not observe any other differences in outcomes between planning and not planning T2DM women. A similar effect of pregnancy planning was observed in T1DM women, where planning women had significantly ($P < 0.0001$) lower HbA1c in the first trimester: 6.3% (95% CI: 6.1, 6.6) than not planning: 7.5% (95% CI: 7.2, 7.7). However, in this group the differences in both second

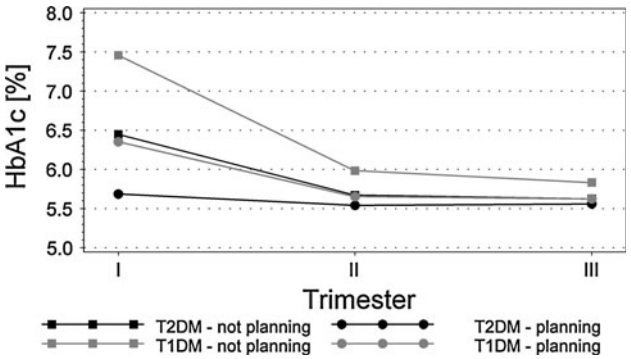

Fig. 1 HbA1c changes during pregnancy in T2DM and T1DM group, with effect of planning. Mean HbA1c level in T2DM (*squares*) and T1DM (*circles*) groups stratified by pregnancy planning (*black lines* connect values in planning strata and *gray lines* connect values in not planning strata) are shown

[5.6 (95% CI: 5.5, 5.8) vs. 6.0 (95% CI: 5.8, 6.1), $P = 0.0003$] and third trimester reached statistical significance: [5.6 (95% CI: 5.4, 5.8) vs. 5.8 (95% CI: 5.7, 6.0), $P = 0.047$] (Fig. 1).

Discussion

This is the first article from the Polish population on pregnancy complicated by T2DM and its comparison with T1DM. We showed that in general the maternal and fetal pregnancy outcomes were similar in T2DM and T1DM women. However, some interesting differences have also been observed. T2DM women had better glycemic control

than T1DM subjects at the beginning of pregnancy and gained less weight. Moreover, the number of macrosomic babies was slightly lower than in T1DM. We also observed that in T2DM, pregnancy planning had a beneficial effect on glycemic control in the first trimester. This data should be seen in the context of the reports that have recently been included in the systematic review and meta-analysis comparing maternal and fetal outcomes in women with T2DM and T1DM [20]. In general, most of those studies were smaller than our current report, many of them originally published more than a decade ago, when different standards and treatment methods were used in pregnancy diabetes care. They also did not include any information concerning the importance of pregnancy planning. It should be noticed that we have examined a relatively large number of outcomes; although, some important data were not available in this study. For example, information on the prevalence of hypoglycemia, hyperbilirubinemia, and other important perinatal fetal complications was missing.

In general, in this study, the maternal baseline characteristics were very similar to those presented in Balsells's et al. meta-analysis [20], although, in spite of a similar age at the examination, our patients had slightly shorter mean T2DM duration (3.3 vs. 5.9 years). This could have, probably only partially, contributed to much better initial HbA1c in this study than in the reports coming from other populations (6.2 vs. 7.2%) [20]. Nevertheless, this explanation cannot clarify similar differences between T1DM groups (7.0 vs. 8.06%) [20]. An improvement in diabetes care over the recent years, as well as a relatively high proportion of T1DM women in our cohort planning pregnancy could elucidate this observation. The fact that in our study metabolic control in the first trimester was significantly better in T2DM than in T1DM patients is consistent with many previous reports [23–31]. The improvement in glycemic control in subsequent trimesters is an obvious result of the treatment intensification during the pregnancy [32]. Interestingly, mean HbA1c in T2DM and T1DM subjects in the second and third trimesters was within the goal of glycemic control as set by international and local guidelines [19, 33–36].

An interesting outcome of the current study is the fact that the number of macrosomic babies in the T2DM cohort was two times lower than in the T1DM one (although, this result is not statistically significant at this sample size). This observation differs our study from most of earlier reports; however, a similar observation has recently been reported from the British population [37]. Such a result could have been associated with our recommendation of daily food intake reduction in case of maternal body mass excess. This could have directly and indirectly, through the improvement of HbA1c level, influenced the birth weight of newborns. Another factor that should be taken into account is a larger pre-pregnancy BMI in T2DM. Noticeably, like in many previous reports, there was no difference in respect to other maternal and fetal outcomes between T2DM and T1DM [20, 23–31]. There are two factors that may help interpret this observation. First, most of the pregnancy period, excluding the first trimester, there was no significant difference in glycemic controls between the analyzed cohorts. Second, as postulated earlier, other factors that are typical for T2DM, such as obesity, might have influenced the pregnancy outcomes [38–43].

Our data clearly demonstrated that pregnancy planning allowed to enter gestation with substantially better HbA1c in the first trimester in both types of diabetes. This effect was sustained in the second and third trimester in T1DM [21]; however, in the T2DM group, unlike in T1DM cohort, the difference in HbA1c between the planning and not planning cohort became statistically non significant. There were less T2DM women than T1DM subjects that started intensive diabetes management before conception, although this difference was not significant at this sample size. However, as the number the pregnancy planning women with T2DM in our study was low, these results should be interpreted with caution. In the France [24] and in the UK [39], the percentage of planned pregnancies in T2DM women had been reported slightly lower (24%) than in our study. Not planning women had a poorer attendance for effective preconception care, later booking for antenatal care, and poorer glycemic control during pregnancy which could have contributed to the high rate of congenital malformations and perinatal mortality [24, 25]. In the meta-analysis published more than a decade ago [44] confirmed by the recent British multicenter report [45], preconception care and planning pregnancy were associated with a lower number of major and minor congenital abnormalities among the offspring of women with pregestational diabetes.

As mentioned above, one of the shortcomings of the current report is the lack of data on some important, mainly fetal, outcomes. In addition, this report is a typical observational study, and as such it is prone to many biases. In the statistical analysis, we tried to address some possible sources of such confounding biases, such as the unequal proportion of planned pregnancies. Nevertheless, it cannot be entirely excluded that our results were influenced by factors that we were unable to access. For example, T1DM and particularly T2DM women who experienced early miscarriage might not be ascertained for this study, taking into account the relatively late average week of gestation at the first visit. One of the limitations of this report is the fact that we were not able to use current percentile charts for the Polish population to evaluate the number of large for gestational age (LGA) newborns. However, a threshold of 4 kg has sometimes been used in recent publications [46].

It was also shown that in women with diabetes a threshold of 4000 g was associated with some clinical outcomes, such as fetal death [47]. It should be emphasized that this study was not based on a formal registry. The relative proportion of women with pre-gestational T1DM and T2DM in this cohort does not necessarily reflect their actual ratio in the Polish population. The current article was based on data collected during routine clinical practice of the Department of Metabolic Diseases in Krakow over the last 10 years. Our criteria for T2DM ascertainment included 1 year without insulin therapy. The justification was based on the finding that a positive GADab test result (indicating T1DM) was strongly associated with the start of insulin treatment within 1 or 2 years from diabetes diagnosis, more so than characteristics such as level of obesity and age at diagnosis [48]. We cannot entirely exclude that this criterion could have, at least to some degree, influenced the study outcomes.

In summary, in spite of a better glycemic control in the first trimester, T2DM women had most of pregnancy outcomes similar to T1DM subjects. Noticeably, they gained less weight during the pregnancy and had lower number of macrosomic babies, what could be a result of caloric restrictions recommended to overweight or obese women. Pregnancy planning had a beneficial effect on the HbA1c level in T2DM women in the first months of pregnancies.

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