ORIGINAL ARTICLE

Changes in preconception treatment and glycemic control in women with type 1 diabetes mellitus: a 15-year single-center follow-up

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KEY WORDS

metabolic control, pregnancy, type 1 diabetes

ABSTRACT

INTRODUCTION Pregnancy in women with type 1 diabetes mellitus (T1DM) is associated with higher risk of complications. Strict glycemic control before conception reduces the risk of unfavorable outcomes.

OBJECTIVES The aim of the study was to assess changes in clinical characteristics, preconception treatment, and glycemic control of women with T1DM at the first antinatal visit.

PATIENTS AND METHODS We analyzed the records from the first antenatal visit of 524 women with T1DM in the years 1998–2012. The follow-up period was divided into 3 5-year periods.

RESULTS Differences in the age of patients between the 3 follow-up periods were observed (28.2 ±5.7 years for 1998–2002; 27.3 ±4.5 years for 2003–2007; and 29.4 ±4.8 years for 2008–2012; P <0.0001). The number of women planning pregnancy did not change and reached 32.1% in the first, 44.4% in the second, and 40.4% in the third period (P = 0.2). The use of rapid-acting insulin analogues increased from 2.6% to 46.5% and then to 95.6% (P <0.001). The rate of therapy with personal insulin pumps before pregnancy increased from 4.6% in the first, through 23.5% in the second, to 33.3% in the third period (P <0.001). Over the subsequent periods, we observed a decrease in hemoglobin A_{1c} (HbA_{1c}) levels at the first antenatal visit (from 7.4% ±1.6%, through 6.9% ±1.4%, to 7.0% ±1.4%; P = 0.06), as well as a decrease in HbA_{1c} levels between the subgroups of women planning pregnancy (6.8% ±1.4%, 6.6% ±1.2%, and 6.1% ±0.8%, P = 0.015).

CONCLUSIONS In the years 1998–2012, an increase in the use of insulin analogues and personal insulin pumps by women with T1DM before conception was observed, and these changes were accompanied by a slight improvement in glycemic control, particularly among women planning pregnancy. The percentage of women planning pregnancy did not change during the follow-up.

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INTRODUCTION Diabetes is the most common metabolic disease complicating pregnancy, and the number of women in childbearing age facing this problem is rising worldwide.[1] One of the reasons is an increase in the incidence of type 1 diabetes mellitus (T1DM); in particular, the countries of Central and Eastern Europe, including Poland, have experienced a substantial growth since 1989.[2,3] Pregnancy complicated by T1DM is a serious medical and social challenge, as it is associated with a large risk of obstetric and neonatal complications. The list of the most common complications in the newborn includes congenital malformations, large- and small-for-gestational age deliveries, neonatal hypoglycemia, and respiratory distress syndrome.[4-6]

Despite improvements in medical care, including new tools for diabetes treatment and monitoring, the risk of poor pregnancy outcomes in women with T1DM is still substantially larger than that reported for the general population.[7-9] A meta-analysis of 12 population-based studies

showed that the probability of these events was 2 to 5 times higher in patients with T1DM as compared with nondiabetic women.[9] One of the reasons may be the limited participation of these women in preconception care and counseling. Periconception glycemia is a critical modifiable risk factor for limiting adverse obstetric outcomes, but more than a half of all pregnancies are unplanned, which contributes to suboptimal glycemic control at the beginning of pregnancy in the majority of women with T1DM.[10-12] Several studies have shown that preconception counseling in women with T1DM was associated with better glycemic control during 3 months before conception and in the first pregnancy trimester, as well as with reduced risk of adverse pregnancy outcome.[13-15] Thus, it is important to monitor shifts occurring in this aspect of diabetes care.

In this large observational study conducted at a single Polish university center, we assessed the changes that occurred over a period of 15 years in the clinical characteristics of women with T1DM during their first pregnancy visit, as well as in their preconception treatment and glycemic control.

PATIENTS AND METHODS This study was performed at the Department of Metabolic Diseases, Kraków, Poland, a tertiary academic referral center for diabetes in South-Eastern Poland. All pregnant women with pre-existing T1DM were registered between the years 1998 and 2012, and their data were collected at the time of the first antenatal visit. All participants were Caucasians and residents of South-Eastern Poland. Data from medical records about the patients' pregestational characteristics, mode of treatment, glycemic control, and presence of microvascular complications as well as other clinical data were collected during the first pregnancy visit, as described earlier.[14,15]

All women with diabetes who entered the pregnancy planning program received intensive diabetes management in the clinic at our department.[14,15] According to the recommendations of the Polish Diabetes Association that were in force when these data were collected,[16] the therapeutic targets for women planning pregnancy were: 1) hemoglobin A_{1c} (HbA_{1c}) <6.1%, 2) fasting self-monitored blood glucose (SMBG) measured using a glucose meter within the range of 60 to 90 mg/dl, and 3) subsequent preprandial and 1-hour postprandial glucose self-measurements within the range of 60 to 120 mg/dl. The monitoring of SMBG was structured. Women who did not plan their pregnancies entered the intensive diabetes care program after conception, at the first antenatal visit clinic visit. Their clinical characteristics reflect the effects of routine diabetes management in nonpregnant patients. Two insulin regimens were used before pregnancy: multiple daily injections or continuous subcutaneous insulin infusion (CSII) with a personal insulin pump.[14]

The HbA_{1c} level was measured during the first pregnancy visit with high-performance liquid chromatography on a Variant apparatus (Bio-Rad, Hercules, California, United States) and was DCCT-adjusted at the central laboratory. The inter- and intra-assay coefficient of variation was less than 2%. Retinopathy was diagnosed by ophthalmoscopy, while the diagnosis of nephropathy was based on the albumin-to-creatinine ratio, with values 30 mg/g or higher classified as albuminuria, and creatinine-derived estimated glomerular filtration rate, with values of less than 60 ml/min/1.73 m^2 defined as abnormal.

Statistical analysis A statistical analysis was performed to determine the difference between 2 groups (*t* test) and several groups (analysis of variance), where applicable. If necessary, nonparametric tests were used as equivalents (Wilcoxon test, Kruskal–Wallis test with post hoc tests). Normality was tested with the Shapiro–Wilk test. For categorical variables, we used the χ^2 test or the Fisher exact test, as appropriate. The analysis was performed with the R statistical software v. 3.2.4 (The R Foundation, Vienna, Austria). *P* values of less than 0.05 were considered significant.

This observational study was concordant with the Helsinki Declaration and was approved by the Jagiellonian University Bioethical Committee.

RESULTS The patients' characteristics for each study period are presented in TABLE 1. We observed differences between the 3 groups in terms of the women's age at the initial pregnancy visit (P <0.0001). In the post hoc analysis, women signing up for the first antenatal appointment in the years 2008–2012 were older than those in the previous 2 time periods (29.4 ±4.8 years vs 28.2 ±5.7 years in 1998–2002 and vs 27.3 ±4.5 years in 2002–2008, P = 0.03 and P <0.0001, respectively). We did not observe differences in T1DM duration (mean, 11.7 ±7.5 years for the entire study period) and prepregnancy body mass index (mean, 23.9 ±4.4 kg/m^2). We also found no differences in the week of pregnancy at the first visit in an outpatient clinic (8.7 ±4.4 weeks of pregnancy). The clinical characteristics of the study subgroups based on the pregnancy planning status are presented in TABLE 2.

Consistently with long T1DM duration, the mean prevalence of retinopathy in the whole group was high: 26.7% (n = 136). The 3 groups differed in terms of the prevalence of retinopathy (P = 0.003). The proportion of this complication changed from 35.8% in the first analyzed period, through 18.2% in the second period, to 27.6% in the third period; the prevalence of this complication was lower in the second period (2003–2007) than in the other periods (P <0.001 and P = 0.03, respectively). The proportion of diabetic nephropathy as defined in this analysis remained low and stable throughout the entire follow-up.

We observed substantial changes in the types of insulin and treatment models used. The use of rapid-acting analogues increased from 2.6% in the first period to 46.5% in the second period,

TABLE 1 Clinical characteristics of study groups

Variable	Follow-up period			*P* value
	1998–2002 n = 109	2003–2007 n = 187	2008–2012 n = 228	
age, y	28.2 ±5.7	27.3 ±4.5	29.4 ±4.8	0.001
duration of diabetes, y	11.8 ±7.2	11.3 ±7.6	12.2 ±7.7	0.4
BMI before pregnancy, kg/m^2	24.3 ±3.3	23.8 ±3.4	24.1 ±4.0	0.3
retinopathy (any form)	39 (35.8)	34 (18.2)	63 (27.6)	0.003
proliferative retinopathy	7 (17.9)	3 (8.8)	11 (11.7)	0.09
nephropathy	3 (2.8)	2 (1.1)	9 (3.9)	0.2
planned pregnancy	35 (32.1)	83 (44.4)	92 (40.4)	0.2
Hbd at 1st pregnancy visit	8.9 ±4.5	8.8 ±4.6	8.5 ±4.3	0.9
HbA_{1c} at 1st pregnancy visit, %	7.4 ±1.6	6.9 ±1.4	7.0 ±1.4	0.06
CSII before pregnancy	5 (4.6)	44 (23.5)	76 (33.3)	0.001
treatment with insulin analogues	3 (2.7)	87 (46.5)	218 (95.6)	0.0001

Data are presented as mean ± SD or as number of cases (percentage).

P values were derived from one-way analysis of variance; otherwise, the Wilcoxon test or the Kruskal–Wallis test was used to detect a significant difference between the study groups. *P* values of less than 0.05 were considered significant.

Abbreviations: BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA_{1c}, hemoglobin A_{1c}; Hbd, week of gestation

reaching 95.6% in the third period ($P < 0.0001$ for all 3 groups and for each pairwise comparison). Long-acting analogues were not used over the entire study period by any patient. Additionally, there was a notable increase in the use of insulin pumps in the analyzed period. In the first period, personal pumps before pregnancy were used to treat only 4.6% of women with T1DM, and this rate increased to 23.5% and 33.3% in the periods 2003–2007 and 2008–2012, respectively ($P < 0.0001$ for a 3-group comparison, $P < 0.0001$ and $P = 0.03$ for period 1 vs 2 and period 2 vs period 3, respectively). Over the years, the number of T1DM women planning their pregnancies did not change ($P = 0.2$). Overall, the proportion of patients entering the intensive diabetes care program (pregnancy planning) during the entire follow-up (1998–2012) reached 39.0% (n = 210).

There was a borderline difference in glycemic control before pregnancy as assessed by the HbA_{1c} level at the first antenatal visit ($P = 0.06$ for 3-group comparison). HbA_{1c} levels tended to be higher in the first period as compared with the two other periods ($P = 0.05$ and $P = 0.07$, respectively).

Two additional analyses were performed based on pregnancy planning status. A lower HbA_{1c} level was found at the first visit in patients who entered the pregnancy planning program (**FIGURE 1**). Specifically, in the first period, the HbA_{1c} level in women who planned pregnancies reached 6.8% ±1.4% and was lower than that in women with unplanned pregnancies (7.7% ±1.6%) ($P = 0.003$). For the second and third periods, the following values were recorded: 6.6% ±1.2% vs 7.2% ±1.4% ($P = 0.009$) and 6.1% ±0.8% vs 7.5% ±1.5% ($P = 0.0000$). For the entire study group, the HbA_{1c} level in women who planned their pregnancies was 6.4% ±1.1% as compared with 7.5% ±1.5% in the "non-planning" patients ($P = 0.0000$). Additionally, we searched for potential changes in HbA_{1c} levels in the subsequent time periods for the planning and nonplanning groups. A decrease in HbA_{1c} levels in the planning groups was observed, as they reached 6.8% ±1.4%, 6.6% ±1.2%, and 6.1% ±0.8% in the subsequent periods ($P = 0.015$). This improvement was not seen in the nonplanning group, in whom the values were as follows: 7.7% ±1.6%, 7.2% ±1.4%, and 7.5% ±1.5% ($P = 0.21$). Additionally, women who planned pregnancy were more often treated with CSII before conception in each analyzed period as compared with women who did not plan their pregnancies. For the years 1998–2002, we recorded 7% (n = 4) of patients on CSII in the planning group as compared with 0.9% (n = 1) in the nonplanning group ($P = 0.006$). For the second and third periods, the values were 16.1% (n = 30) vs 7.5% (n = 12), $P = 0.001$, and 22.5% (n = 50) vs 10.6% (n = 25), $P < 0.001$, respectively.

DISCUSSION In this observational study, we assessed the clinical characteristics, preconception care, and glycemic control in women with T1DM treated at the Department of Metabolic Diseases of the Jagiellonian University Hospital, Kraków, Poland, over the years 1998–2012. We observed some important changes in the analyzed features in this study, which was performed on one of the largest single-center databases of T1DM-complicated pregnancies in Europe.

Almost 30 years after the St Vincent Declaration, the risk of fetal and newborn death as well as other unfavorable outcomes in children and

TABLE 2 Clinical characteristics of study subgroups based on pregnancy planning status

Variable	Follow-up period								
	1998–2002 n = 109			2003–2007 n = 187			2003–2007 n = 187		
	planned n = 35	not planned n = 74	*P* value	planned n = 83	not planned n = 103	*P* value	planned n = 91	not planned n = 136	*P* value
age, y	27.8 ±5.0	28.1 ±6.0	0.7	28.3 ±4.3	26.3 ±4.6	0.001	29.9 ±4.0	28.8 ±5.2	0.2
duration of diabetes, y	12.4 ±7.4	11.3 ±7.2	0.5	13.3 ±7.9	9.5 ±6.9	0.0026	11.9 ±8.2	12.4 ±7.3	0.5
BMI before pregnancy, kg/m^2	23.6 ±2.5	24.7 ±3.4	0.2	23.9 ±3.4	23.7 ±3.6	0.5	23.2 ±3.2	24.6 ±4.4	0.4
retinopathy	11 (31.4)	20 (27.0)	0.8	18 (21.7)	14 (13.6)	0.0003	18 (19.8)	45 (33.8)	0.01
proliferative retinopathy	2 (11.2)	3 (15.0)	0.8	1 (5.6)	2 (14.3)	0.6	4 (22.2)	7 (15.6)	0.5
nephropathy	0 (0)	3 (4.1)	0.5	1 (1.2)	1 (1.0)	1.0	2 (2.2)	7 (5.1)	0.3
Hbd at 1st pregnancy visit,%	8.2 ±3.6	8.8 ±4.8	0.57	7.3 ±4.0	10.1 ±4.9	0.2	6.8 ±2.8	9.2 ±4.8	0.6
HbA_{1c} at 1st pregnancy visit,%	6.8 ±1.4	7.7 ±1.6	0.003	6.6 ±1.2	7.2 ±1.4	0.009	6.1 ±0.8	7.5 ±1.5	<0.0001
CSII at 1st pregnancy visit	4 (3.7)	1 (0.9)	0.06	30 (16.1)	12 (7.4)	0.001	50 (22.5)	25 (10.6)	<0.0001
treatment with insulin analogues	2 (5.7)	1 (1.4)	0.55	42 (50.6)	41 (39.8)	0.6	89 (97.8)	124 (91.2)	1.0

Data are presented as mean ± SD or as number of cases (percentage).

P values derived from the *t* test or the χ^2 test to detect significant differences between the study groups. *P* values of less than 0.05 were considered significant.

Abbreviations: see **TABLE 1**

women in pregnancy complicated by T1DM remains increased as compared to the healthy population.[9] One of the reasons seems to be related to suboptimal glycemic control before conception and in early pregnancy. Several studies described a continuous association between first-trimester HbA_{1c} levels and the risk of fetal complications.[17-20] Moreover, poor glycemic control in early pregnancy usually continues in the subsequent trimesters; therefore, high HbA_{1c} values in early pregnancy are significant predictors of adverse perinatal outcomes.[17-23] Thus, reaching optimal glycemic control in early pregnancy should be one of the major targets in women with T1DM.

The importance of pregnancy planning and periconception care in women with pregestational diabetes was shown in several populations.[24-27] A meta-analysis of 12 studies revealed that women who were under periconception care showed HbA_{1c} levels lower by almost 2% in the first trimester of pregnancy in comparison with those who were not.[13] Another meta-analysis of studies proved that prepregnancy care for women with pregestational T1DM or type 2 diabetes mellitus is effective in reducing maternal HbA_{1c} levels in the first trimester of pregnancy and, even more importantly, in improving the rates of outcomes.[28,29] In this study, a slight increase over the years in the number of women with T1DM who planned their pregnancy did not reach significant value. On average, less than 40% of the women recorded at our center planned their pregnancy. These data may not be representative for the entire country, as the current cohort included mostly women from a large city (Kraków), many of whom were under our care long before pregnancy. Observations made in several other populations revealed a trend of an increasing number of women planning pregnancy and receiving preconception counseling. For example, during the ATLANTIC DIP program, the pregnancy planning rate increased almost twice from 28% to 52%, which resulted in an improvement of outcomes for women with pregestational diabetes.[30] The proportion of planning women reached almost 50% in northern England and was as high as 84% in the Netherlands.[24,26] The lack of a significant rise in pregnancy planning rate shows a necessity for further educational efforts in this and other Polish centers providing diabetes care.

Our data showed a slight improvement of glycemic control in the early pregnancy of our patients with T1DM. Interestingly, a larger and significant decline in HbA_{1c} levels was seen in patients who planned pregnancy, which further underlines the importance of pregnancy planning. This progress was accompanied by an increased use of new technologies and therapeutic tools, such as insulin analogues and personal insulin pumps; although, this clinical study cannot prove a causal relationship. We observed a steady rise in the number of women treated with short-acting insulin analogues; in the last analyzed period, most patients used analogues of human insulin. The same trend has been recently described in other populations. It also concerned personal pumps, which were shown to be effective and safe in achieving normoglycemia in all patients

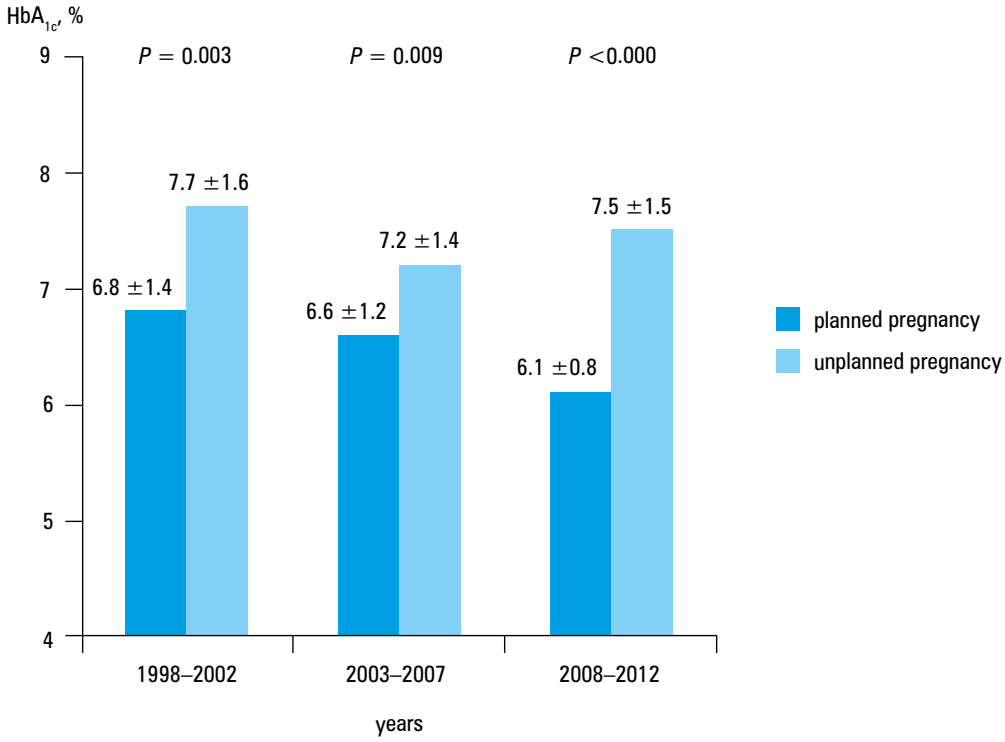

FIGURE 1 Hemoglobin A_{1c} level in the three study periods stratified by the pregnancy planning status

with T1DM,[31] including pregnant women.[31-33] Of note, in our earlier paper we reported that, unlike pregnancy planning, the use of insulin pumps was not associated with lower HbA_{1c} levels as compared with multiple daily injections in T1DM-complicated pregnancy, either in the first trimester or in subsequent months.[12] However, it is important to note that this was an observational study (as is the current one) with the obvious limitations related to this study design and that some recent reports have showed opposite results.[34] Importantly, this clinical practice is linked with a modification of local and international recommendations for diabetes care in pregnancy.[35,36] For example, since 2008, the Polish Diabetes Association has recommended the use of short-acting analogues during pregnancy. Noticeably, none of the studied patients used long-acting insulin analogues, as they were neither recommended nor reimbursed at the time when this study was performed.

One of the strengths of this study is its size and the homogeneity of patients, meaning exclusively Caucasians treated at one center. Another advantage of the report is the long duration of the follow-up carried out continuously in our center. A limitation of this study is related to its observational design, which excludes drawing any conclusions concerning the causality between glycemic control and the use of new technologies. Secondly, we were not able to provide data on folic acid treatment and thyroid status evaluation in the preconception period, as this was not included in standard prepregnancy care in Poland for a considerable part of the follow-up. We also did not have a systematically collected data on maternal hypertension and smoking. Additionally, we did not report later pregnancy data and neonatal outcomes in this paper. However, this lies beyond the scope of the current research as does a search for associations between diabetic complications and clinical and biochemical characteristics. Some of these data were reported earlier.[14,15,37] Additionally, plural comparisons were made in the current report, and it is possible that some of them, particularly those that produced borderline significance, could have produced significant results simply by chance. The lowest prevalence of diabetic retinopathy in the middle time period is probably a random result.

In conclusion, we observed a rise in the use of insulin analogues and personal pumps before conception but not in pregnancy planning in women with T1DM. This was accompanied by a slight improvement in glycemic control.

Contribution statement KC and MTM contributed to study design and protocol development. KC, BK, AHS, IJ, ITM, PW, EK, and JH were responsible for searching medical databases. KC, JS, and BM contributed to data analysis. KC, JS, BK, AHS, IJ, ITM, PW, EK, and MTM contributed to data research and interpretation. KC, JS, and MTM wrote the manuscript. BK, AHS, IJ, ITM, PW, EK, and BM contributed to critical review of the manuscript. MTM coordinated the project and approved the final version of the manuscript. MTM is the guarantor of the data and, as such, has full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis.

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Zmiany w przedkoncepcyjnej terapii i wyrównaniu metabolicznym u pacjentek z cukrzycą typu 1 – 15-letnia jednoośrodkowa obserwacja

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SŁOWA KLUCZOWE

ciąża, cukrzyca typu 1, wyrównanie metaboliczne

STRESZCZENIE

WPROWADZENIE U kobiet z cukrzycą typu 1 (*type 1 diabetes mellitus* – T1DM) ciąża wiąże się ze zwiększonym ryzykiem powikłań. Prawidłowa kontrola glikemii w okresie przedkoncepcyjnym zmniejsza ryzyko wystąpienia zdarzeń niekorzystnych.

CELE Celem badania była ocena zmian w charakterystyce klinicznej, terapii przed ciążą oraz kontroli glikemii u pacjentek z T1DM zgłaszających się na pierwszą wizytę w ciąży.

PACJENCI I METODY Przeanalizowano dane z pierwszej wizyty w trakcie ciąży 524 kobiet z T1DM w latach 1998–2012. Czas obserwacji podzielono na 3 pięcioletnie okresy.

WYNIKI Zaobserwowano różnicę w wieku pacjentek między 3 okresami obserwacji (28,2 ±5,7 roku w latach 1998–2002 *vs* 27,3 ±4,5 roku w latach 2003–2007 *vs* 29,4 ±4,8 roku w latach 2008–2012; p <0,0001). Odsetek kobiet planujących ciążę nie zmienił się i wyniósł 32,1% w pierwszym okresie, 44,4% w drugim oraz 40,4% w trzecim (p = 0,2). Stosowanie szybko działających analogów insuliny wzrosło z 2,6% do 46,5% i ostatecznie do 95,6% (p <0,001). Częstość terapii z wykorzystaniem osobistych pomp insulinowych przed ciążą wzrosła z 4,6% do 23,5%, by w trzecim okresie osiągnąć 33,3% (p <0,001). W kolejnych okresach obserwowano niewielki spadek poziomu hemoglobiny A_{1c} (HbA_{1c}) na pierwszej wizycie ciążowej (odpowiednio z 7,4 ±1,6% do 6,9 ±1,4% i 7,0 ±1,4%; p <0,06) oraz zmniejszenie poziomu HbA_{1c} między podgrupami pacjentek planujących ciążę (6,8 ±1,4%, 6,6 ±1,2% i 6,1 ±0,8%; p = 0,015).

WNIOSKI W latach 1998–2012 zwiększyło się stosowanie szybko działających analogów insuliny oraz osobistych pomp insulinowych przez pacjentki z T1DM w okresie przedkoncepcyjnym, czemu towarzyszyła niewielka poprawa wyrównania metabolicznego, szczególnie w podgrupach planujących ciążę. W analizowanym okresie nie zmienił się odsetek pacjentek z T1DM planujących ciążę.

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