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**Article ID:** doi:10.20452/pamw.3543

**ISSN:** 1897-9483

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**Article type:** Original article

**Received:** May 15, 2016.

**Accepted:** August 29, 2016.

**Published online:** August 29, 2016.

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Changes in preconception treatment and glycemic control in women with type 1 diabetes mellitus – a 15 year long single centre observation

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Short title: Pre-pregnancy glycemic control in T1DM.

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ABSTRACT

Introduction

Pregnancy complicated by type 1 diabetes (T1DM) is associated with a high risk of complications. Strict glycemic control prior to conception limits unfavorable outcomes.

Objectives

We assessed changes occurring in the clinical characteristics of T1DM women, their preconception treatment and glycemic control at the 1st pregnancy visit.

Patients and methods

We analyzed the records of 524 pregnant T1DM women at the first antenatal visit. They received diabetes care at the Department of Metabolic Diseases, Krakow between 1998–2012. This period was analyzed as three 5-year intervals.

Results

Differences in the women's age were identified between the T1DM groups (28.2±5.7 years for 1998–2002 vs. 27.3±4.5 for 2003–2007, and 29.4±4.8 for 2008–2012, P<0.0001). The number of women planning pregnancy did not change and reached 32.1% in the 1st period, 44.4% in the 2nd period and 40.4% in last one (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). Personal pumps before pregnancy were initially used by 4.6% of women, then by 23.5% and finally by 33.3% (P<0.001). HbA1c level at the 1st visit improved slightly from 7.4±1.6% to 6.9±1.4% and 7.0±1.4% (P=0.06), while a decrease in the pregnancy planning subgroups was observed (6.8±1.4%, 6.6±1.2% and 6.1±0.8%, P= 0.015).

Conclusions

We observed a rise in the use of insulin analogues and personal pumps before conception but not in pregnancy planning in T1DM women. These changes were accompanied by a slight improvement in glycemic control, particularly among pregnancy planning patients.
**Key words:** metabolic control, pregnancy, type 1 diabetes
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 the increase of 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 newborn complications includes congenital malformations, large- and small-for-gestational age deliveries, neonatal hypoglycemia and respiratory distress syndrome [4; 5; 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 the one reported from the general population [7; 8; 9]. A meta-analysis of twelve population-based studies showed that the probability of these events was two to five times higher in T1DM patients as compared with non-diabetic women [9]. One of the reasons may be the limited participation of these women in pre-conception 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 T1DM women [10; 11; 12]. Several studies have shown that pre-conception counseling in women with T1DM was associated with better glycemic control during 3 months before conception as well as in the first pregnancy trimester and reduced risk of adverse pregnancy outcome [13; 14; 15]. Thus, it is important to monitor shifts occurring in this aspect of diabetes care.

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

**Patients and Methods**

This study was performed at the Department of Metabolic Diseases, Krakow, Poland, a tertiary academic referral center for diabetes in South-Eastern Poland. All pregnant women with pre-existing T1DM were registered between 1998 and 2012 and their data were collected at the time of clinic attendance. All the subjects were Caucasians resident in South-Eastern Poland. The patients’ medical record information about their pregestational characteristics, mode of treatment, glycemic control and presence of microvascular complications as well as other clinical data were collected during their 1st pregnancy visit, as described earlier [14, 15].

All women with diabetes who entered the pregnancy planning program received intensive diabetes management in the clinic [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: a) A1C <6.1%, b) fasting self-monitored blood glucose measured using a glucose meter within 60–90 mg/dl, and c) subsequent pre- and 1-hour postprandial glucose self-measurements within 60–120 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 clinic visit. The clinical characteristics in these women reflect the effects of routine diabetes management in non-pregnant patients. Two insulin regimens were used before pregnancy: multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) with a personal insulin pump [14].

The HbA1c level was measured during the first pregnancy visit with high performance liquid chromatography (HLPC) on a Variant apparatus (Bio-Rad, Hercules, California, USA) and was DCCT adjusted. 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/creatinine ratio, with values ≥30 mg/g classified as albuminuria and creatinine-derived eGFR, with values <60 ml/min defined as abnormal.

Statistical analysis was performed to determine the difference between two (t-test) and several groups (ANOVA), where applicable. If necessary, non-parametric tests were utilized as equivalents (Wilcoxon test, Kruskal-Wallis with post-hoc tests). Normality was tested with the W Shapiro-Wilk test. For categorical variables we used the chi-squared test or Fisher’s exact test where appropriate. The analysis was performed with R statistical software ver. 3.2.4 (The R Foundation, Vienna, Austria). P-values <0.05 were considered significant.

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

**Results**

The patients’ characteristics for each study period are presented in Table 1. Differences in the women’s age at the initial pregnancy visit were identified between the three groups ($P<0.0001$). In the post-hoc analysis, women booking for the first antenatal appointment in the years 2008–2012 were older than in the two previous time intervals (29.4±4.8 years vs. 28.2±5.7 years in 1998–2002 and vs. 27.3±4.5 years in 2002–2008; $P=0.03$, $P<0.0001$, respectively). We did not observe differences in T1DM duration (the mean for the entire study period 11.7±7.5 years) and pre-pregnancy BMI (mean 23.9±4.4 kg/m$^2$). We also found no differences in the week of pregnancy at 1st visit in out-patient clinic (8.7 ±4.4 weeks of pregnancy). In Table 2, available as an on-line appendix, we present the clinical characteristics of the study subgroups based on the pregnancy planning status of the T1DM patients.
Consistently with long T1DM duration, the mean prevalence of retinopathy in the whole group was high – 26.7% (n=136). The three groups differed in terms of the prevalence of retinopathy ($P=0.003$). The proportion of this complication changed from 35.8% in the 1st analyzed period, through 18.2% in the 2nd period to 27.6% in the last one; the prevalence of this complication was lower in the 2nd study period (2003–2007) than in the two other time intervals ($P<0.001$ and $P=0.03$, respectively). The proportion of diabetic nephropathy as defined in this analysis remained low and stable throughout the entire observation.

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 1st period to 46.5% in the 2nd one, reaching 95.6% in the last time interval ($P<0.0001$ for three groups and for each pairwise comparison). Long-acting analogues were not used over the entire study period by any patient. Additionally, there was a spectacular increase of the use of insulin pumps in the analyzed 15 years. In the 1st observed period, personal pumps before pregnancy were used to treat only 4.6% of T1DM women; which increased to 23.5% and 33.3% in the periods 2003–2007 and 2008–2012, respectively ($P<0.0001$ for a three-group comparison, $P<0.0001$ and $P=0.03$ for period I vs. II and period II vs. period III comparison, correspondingly). 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 observed period (1998–2012) reached 39.0% (n=210).

There was a borderline difference in glycemic control before pregnancy as assessed by HbA1c level at the 1st visit ($P=0.06$ for three group comparison). HbA1c tended to be higher in the first time period as compared to the two subsequent time intervals ($P=0.05$ and $P=0.07$, respectively).

Two additional analyses were performed based on pregnancy planning status. A lower level of HbA1c was found at the 1st visit in T1DM patients who entered the pregnancy
planning program (Figure 1). Specifically, in the 1st time period the HbA1c level in women who planned pregnancies reached 6.8±1.4% and was better than in unplanned pregnancies – 7.7±1.6% \((P=0.003)\). For the 2nd and 3rd period, 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 groups, the HbA1c level in the “planning” T1DM women was 6.4±1.1% as compared to 7.5±1.5% in the “non-planning” T1DM patients \((P=0.0000)\). Additionally, we searched for potential changes in HbA1c levels in subsequent time intervals for the planning and non-planning groups. A decrease in HbA1c 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 three subsequent intervals \((P= 0.015)\). This improvement was not seen in the non-planning T1DM patients, in whom the values were as follows – 7.7±1.6%, 7.2±1.4%, 7.5±1.5% \((P=0.21)\). Additionally, women who planned pregnancy were more often treated with the CSII method before conception in each observed period as compared to the “non-planning” pregnancy groups. For the years 1998–2002 we recorded 7% \((n=4)\) of T1DM patients on CSII in the planning group as compared to 0.9% \((n=1)\) among the non-planning group \((P=0.006)\), for the next year intervals, these numbers were as follows: 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, pre-conception care and glycemic control in T1DM women treated at the Department of Metabolic Diseases of the Jagiellonian University Hospital, Krakow, Poland over the years 1998–2012. We found 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 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 HbA1c and the risk of fetal complications [17, 18; 19; 20]. Moreover, poor glycemic control in early pregnancy usually continues in the next trimesters; therefore, high HbA1c values in early pregnancy are significant predictors of adverse perinatal outcomes [17, 18; 19; 20; 21; 22; 23]. Thus, reaching optimal glycemic control in early pregnancy should be one of the major targets in T1DM females.

The importance of pregnancy planning and peri-conception care in women with pregestational diabetes were shown in several populations [24, 25; 26, 27]. A meta-analysis of 12 studies showed that women who were in peri-conception care showed HbA1c levels lower by almost 2% in the 1st trimester of pregnancy in comparison to those who were not [13]. Another meta-analysis of studies proved that pre-pregnancy care for women with pregestational T1DM or type 2 diabetes mellitus is effective in reducing maternal HbA1C in the 1st trimester of pregnancy and, even more importantly, in improving rates of outcomes [28, 29]. In this study, a slight increase in the number of T1DM women with planned pregnancy over the years 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 entire Poland, as the current cohort included mostly women from a large city (Krakow), of whom many 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 pre-conception counseling. For example, during the ATLANTIC DIP program, the pregnancy planning rate increased almost twice from 28% to 52%, which resulted in
improvement of outcomes for women with pre-gestational diabetes [30]. The proportion of planning women reached almost 50% in the North of 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.

This data showed a slight improvement of glycemic control in the early pregnancy of our T1DM patients. Interestingly, a larger, significant decline in HbA1c level was seen in T1DM patients who planned the conception, which underlines further the importance of pregnancy planning. This progress was accompanied by a rise in the 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 T1DM women 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 with T1DM [31], including pregnant women with T1DM [31; 32; 33]. Of note, in our earlier paper we reported that, unlike pregnancy planning, using insulin pumps was not associated with lower HbA1c level as compared to MDI in T1DM-complicated pregnancy, neither in the 1st trimester, nor in subsequent months [12]. One should, however, remember that this was an observational study (as is the current one) with the obvious problems related to this study design and that some recent reports showed opposite results [34]. It is important to note that 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 recommends 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 in one center. Another advantage of the report is the long duration of the observation carried out continuously in our center. A shortcoming of this paper is related to its observational nature, 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 a part of standard prepregnancy care in Poland for a substantial part of the analyzed period. 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 falls beyond the scope of the current research as does a search for association 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 interval is probably random in nature.

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

**Contribution Statement**

KC, MTM: study design, protocol development; KC, BK, AHS, IJ, ITM, PW, EK, JH: searching medical databases; KC, JS, BM: data analysis; KC, JS, BK, AHS, IJ, ITM, PW, EK,
MTM: research data, data interpretation; KC, JS, MTM: writing the manuscript; BK, AHS, IJ, ITM, PW, EK, BM: critical review of the manuscript; MTM: project coordination, final approval of the manuscript. MTM is the guarantor of the data 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.

**Acknowledgements**

The authors would like to express their gratefulness to the Great Orchestra of Christmas Charity; a non-governmental aid organization in Poland, which provided insulin pumps to most women included into this study.

**List of abbreviations**

- T1DM – type 1 diabetes mellitus
- CSII – continuous subcutaneous insulin infusion
- MDI – multiple daily injections
SMBG – self-monitoring of blood glucose

References:


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</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>20.0 (± 5.7)</td>
<td>20.1 (± 4.7)</td>
<td>20.6 (± 4.7)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Duration of diabetes, years</strong></td>
<td>10.5 (± 7.2)</td>
<td>10.6 (± 7.1)</td>
<td>10.6 (± 7.1)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>BMI before pregnancy, kg/m²</strong></td>
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<tr>
<td></td>
<td>23.5 (± 3.3)</td>
<td>23.6 (± 3.4)</td>
<td>23.7 (± 3.5)</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Retinopathy (any form)</strong></td>
<td>39 (35.8)</td>
<td>34 (33.5)</td>
<td>63 (28.2)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Proliphereative retinopathy</strong></td>
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<tr>
<td></td>
<td>7 (17.9%)</td>
<td>3 (8.0%)</td>
<td>11 (11.7%)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Nephropathy</strong></td>
<td>3 (2.8%)</td>
<td>2 (1.1%)</td>
<td>9 (3.9%)</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Planned pregnancy</strong></td>
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<tr>
<td></td>
<td>35 (32.1%)</td>
<td>83 (44.4%)</td>
<td>92 (40.4%)</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Hbd of 1st pregnancy visit</strong></td>
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<tr>
<td></td>
<td>8.9 (± 4.5)</td>
<td>8.8 (± 4.6)</td>
<td>8.5 (± 4.3)</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>HbA1c at 1st pregnancy visit, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>7.4 (± 1.6)</td>
<td>6.9 (± 1.4)</td>
<td>7.0 (± 1.4)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>CSII before pregnancy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>5 (4.6%)</td>
<td>44 (23.5%)</td>
<td>76 (33.3%)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Treatment with insulin analogues</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>3 (2.7%)</td>
<td>87 (46.5%)</td>
<td>218 (95.6%)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*P-value was derived from one-way analysis of variance (ANOVA), otherwise Wilcoxon test or Kruskal-Wallis test to detect a significant difference in the variable levels among study groups.

Abbreviations: BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA1c, glycated haemoglobin A1c; Hbd, week of gestation; n, number of cases.

A P value of <0.05 is considered statistically significant.

*a Data are presented as mean (± standard deviation). b Data are presented as number of cases (percentage).

Table 2. Clinical characteristics of study subgroups based on pregnancy planning status
<table>
<thead>
<tr>
<th></th>
<th>Planned n=35</th>
<th>Not planned n=74</th>
<th>p</th>
<th>Planned n=83</th>
<th>Not planned n=103</th>
<th>p</th>
<th>Planned n=91</th>
<th>Not planned n=136</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years*</td>
<td>27.8 (±5.0)</td>
<td>28.1 (±6.0)</td>
<td>0.7</td>
<td>28.3 (±4.3)</td>
<td>26.3 (±4.6)</td>
<td>0.001</td>
<td>29.9 (±4.0)</td>
<td>28.8 (±5.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>Duration of diabetes, years*</td>
<td>12.4 (±7.4)</td>
<td>11.3 (±7.2)</td>
<td>0.5</td>
<td>13.3 (±7.9)</td>
<td>9.5 (±6.9)</td>
<td>0.0026</td>
<td>11.9 (±8.2)</td>
<td>12.4 (±7.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>BMI before pregnancy, kg/m²*</td>
<td>23.6 (±2.5)</td>
<td>24.7 (±3.4)</td>
<td>0.2</td>
<td>23.9 (±3.4)</td>
<td>23.7 (±3.6)</td>
<td>0.5</td>
<td>23.2 (±3.2)</td>
<td>24.6 (±4.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Retinopathy*</td>
<td>11 (31.4)</td>
<td>20 (27.0)</td>
<td>0.8</td>
<td>18 (21.7)</td>
<td>14 (13.6)</td>
<td>0.0003</td>
<td>18 (19.8)</td>
<td>45 (33.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Proliferative retinopathy*</td>
<td>2 (11.2)</td>
<td>3 (15.0)</td>
<td>0.8</td>
<td>1 (5.6)</td>
<td>2 (14.3)</td>
<td>0.6</td>
<td>4 (22.2)</td>
<td>7 (15.6)</td>
<td>0.5</td>
</tr>
<tr>
<td>Nephropathy*</td>
<td>0 (0)</td>
<td>3 (4.1)</td>
<td>0.5</td>
<td>1 (1.2)</td>
<td>1 (1.0)</td>
<td>1.0</td>
<td>2 (2.2)</td>
<td>7 (5.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>HbA1c at 1st pregnancy visit, %*</td>
<td>8.2 (±3.6)</td>
<td>8.8 (±4.8)</td>
<td>0.57</td>
<td>7.3 (±4.0)</td>
<td>10.1 (±4.9)</td>
<td>0.2</td>
<td>6.8 (±2.8)</td>
<td>9.2 (±4.8)</td>
<td>0.6</td>
</tr>
<tr>
<td>HbA1c at 1st pregnancy visit, %*</td>
<td>6.8 (±1.4)</td>
<td>7.7 (±1.6)</td>
<td>0.003</td>
<td>6.6 (±1.2)</td>
<td>7.2 (±1.4)</td>
<td>0.009</td>
<td>6.1 (±0.8)</td>
<td>7.5 (±1.5)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>CSII at 1st pregnancy visit*</td>
<td>4 (3.7)</td>
<td>1 (0.9)</td>
<td>0.06</td>
<td>30 (16.1)</td>
<td>12 (7.4)</td>
<td>0.001</td>
<td>50 (22.5)</td>
<td>25 (10.6)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Treatment with insulin analogues*</td>
<td>2 (5.7)</td>
<td>1 (1.4)</td>
<td>0.55</td>
<td>42 (50.6)</td>
<td>41 (39.8)</td>
<td>0.6</td>
<td>89 (97.8)</td>
<td>124 (91.2)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*P-value derived from t-student or chi-square test to detect a significant difference in the variable levels among the study groups.

Abbreviations: BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA1c, glycated haemoglobin A1c; Hbd, week of gestation; n, number of cases.
A *P* value of <0.05 is considered statistically significant.

\(^a\) Data are presented as mean (± standard deviation). \(^b\) Data are presented as number of cases (percentage).

Figure 1.