Diabetes control and pregnancy outcomes in women with type 1 diabetes treated during pregnancy with continuous subcutaneous insulin infusion or multiple daily insulin injections

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Abstract: Objectives. The aim of the study was to compare diabetes control and obstetrical outcomes in pregnant women with type 1 diabetes treated during pregnancy with either continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injections (MDII). **Patients and methods.** It was a descriptive, retrospective, observational study of 116 Caucasian pregnant women with type 1 diabetes mellitus. Thirty women were treated during pregnancy with continuous subcutaneous insulin infusion (CSII group) and 86 with multiple daily insulin injections (MDII group). **Results.** Mean age and body mass index did not differ between groups ($p > 0.05$). Duration of diabetes was longer in CSII than in MDII group, 12.7 ±7.20 vs. 7.71 ±6.13 years, respectively ($p = 0.0005$). There were no differences between the studied groups in glycated hemoglobin (HbA_{1c}) levels in the I, II and III trimesters of pregnancy – in CSII group 7.41 ±1.75, 6.57 ±1.09 and 6.46 ±0.87, respectively, in MDII group – 7.71 ±2.37, 6.65 ±1.18 and 6.75 ±1.21, respectively ($p > 0.05$). There were no severe hypoglycemia and diabetic coma. Mean duration of pregnancy, rate of premature deliveries, newborn birth weight, incidence of SGA and LGA, and the frequency of neonatal hypoglycemia did not differ between groups ($p > 0.05$). The total malformation rate was 5.13%, including 2 terminated pregnancies and the frequency did not differ between groups ($p > 0.05$). The rate of spontaneous abortions was 16.7% in CSII group and 10.3% in MDII ($p > 0.05$). **Conclusions.** No apparent relationships between mode of insulin therapy and pregnancy outcome were found in type 1 diabetes patients.

Key words: continuous subcutaneous insulin infusion, metabolic control, multiple daily insulin injections, pregnancy outcome, type 1 diabetes

INTRODUCTION

In 1989 St.Vincent's Declaration set a series of targets for the improvement in the quality of life of people with diabetes mellitus. One of main assumptions of the Declaration was to secure – within 5-year time frame – that diabetic women would be as likely to become pregnant and give birth to healthy offspring as healthy women are [1]. It has been now 18 years since the Declaration was published and many of its goals are far from being achieved. Results of large population studies conducted in the Netherlands [2] and France [3] show higher perinatal mortality rate and greater incidence of malformed babies in diabetic patients than in the background population.

Preconception planning is a key aspect in achieving better obstetrical results [4,5]. During this period medical care should cover assessment and treatment of vascular complications of diabetes and optimalisation of diabetes treatment in order to achieve best metabolic control possible. All non-pharmacological and pharmacological elements of diabetes treatment should be assessed and corrected if necessary.

Continuous subcutaneous insulin infusion (CSII) with the use of personal portable insulin pump is at the moment the most advanced way of insulin delivery in type 1 diabetes patients. In the recently published randomized clinical trials

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Table 1. Characteristics of the study groups

		CSII n = 30	MDII n = 86	p
Age (years)		27.23 ±4.78	28.08 ±4.50	0.3056
BMI (kg/m²)		23.46 ±2.94	23.72 ±4.64	0.5597
BMI	<25	20 (66.7%)	58 (67.4%)	0.9379
	25–30	9 (30.0%)	17 (19.8%)	0.2472
	>30	1 (3,3%)	11 (12.8%)	0.1819
Duration of diabetes (years)		12.70 ±7.20	7.69 ±6.09	0.0005

BMI – body mass index, CSII – continuous subcutaneous insulin infusion, MDII – multiple daily insulin injections

Table 2. Distribution of patients' categories according to White classification [10]

Class		CSII n = 30	MDII n = 86
A	Diabetes treated with diet or drugs	0	0
B	Age of onset >20 years, and duration <10 years	2 (6.7%)	46 (53.5%)
C	Age of onset 10–19 years, or duration 10–19 years	15 (50%)	36 (41.9%)
D	Age of onset <10 years, and duration >20 years or retinopathy	11 (36.7%)	3 (3.5%)
R	Proliferative retinopathy	0	0
F	Nephropathy	2 (6.7%)	0
RF	Proliferative retinopathy and nephropathy	0	1 (1.2%)

Abbreviations – see Table 1

superiority of CSII over the multiple daily insulin injections (MDII) regimen in controlling diabetes was proven; CSII use resulted the lowering glycated hemoglobin (HbA_{1c}) levels without increasing the number of hypoglycaemia as compared with MDII effects [6-8]. There are, however, several limitations to insulin pump use, including high costs and requirement of appropriately developed patients' ability to operate the device on their own.

The aim of study was the assessment of efficacy and safety of insulin pump treatment in comparison to MDII in pregnant type 1 diabetes patients, with particular reference to obstetrical outcomes.

PATIENTS AND METHODS

A descriptive, retrospective, observational study of 116 Caucasian pregnant women with diabetes mellitus type 1 treated at a university teaching hospital was conducted. All women treated at the Diabetes Care Centre at the Polish Mother's Memorial Hospital – Research Institute, Łódź, Poland, between 2003 and 2006 were included into the study. During this period time 30 pregnant women with type 1 diabetes were treated with CSII and 86 – with MDII.

While pregnant, all patients were under care of the same team, consisting of a diabetologist, obstetrician, diabetes educator and dietician. All patients received dietary counselling and were provided with glucose meters. Episodes of severe hypoglycemia (defined as an episode that required treatment with parenteral glucagon administered either by a family member or emergency medical personnel) were noted. Glycated hemoglobin was measured every trimester, using immunoturbimetric method (Cobas Integra 400 plus analyser, Roche Diagnostics).

Treatment in both groups aimed at near-normoglycemia as recommended by the Polish Diabetes Association: fasting and preprandial plasma glucose 3.3–5.0 mmol/l, and <6.7 mmol/l two hours after meal [9].

For the duration of pregnancy personal insulin pumps (MiniMed 507C, MiniMed 508, Medtronic, USA) were lent to randomly selected patients, based on availability of insulin pump in the clinic at the time of patient's visit. Admittingly, this random selection process was biased by several independent factors including level of patient's education as those who were deemed to be unable to handle pump operation on their own were not offered pump treatment.

Fourteen of 30 patients treated with CSII started the regimen before conception, while 16 women started CSII therapy at 10.0 ±3.6 week of pregnancy. Ninety percent women in CSII group were using lispro insulin. In MDII group 30% of patients used lispro and the 70% human insulin, always in combination with neutral protamine hagedorn (NPH) insulin.

Following data from pregnancy course were analyzed: mother's age, body mass index (BMI), duration of diabetes, category according to White classification [10], HbA_{1c} levels, time and mode of delivery, and labour results (miscarriage, premature labour, perinatal mortality, neonatal weight, Apgar score, neonatal hypoglycaemia, presence of congenital abnormalities).

Data were expressed as a mean value and a standard deviation (mean ±SD).

The statistical analysis was performed with STATISTICA 6.0 PL software package (Tulsa, OK, United States), using non-parametric tests for independent samples (Mann-Whitney's test) and χ^2 or Fischer exact test to assess the differences in distribution (proportions) of qualitative parameters. A value $p < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the study groups are shown in Table 1. Mean age and BMI did not differ significantly between groups, however diabetes duration was longer in CSII group than in MDII ($p = 0.0005$).

Table 3. Comparison of obstetrical outcomes in women with type 1 diabetes treated during pregnancy with continuous subcutaneous insulin infusion (CSII) or with multiple daily insulin injections (MDII)

	CSII, n = 30 (25 deliveries)	MDII, n = 86 (78 deliveries)	p
Duration of pregnancy (weeks)	36.6 ±2.4	36.3 ±3.2	0.5805
Abortion – spontaneous/ therapeutic*	4/1 (16.6%)	8/1 (10.5%)	0.4788
Preterm labour	6 (24.0%)	17 (21.8%)	0.7890
Caesarean section	14 (46.0%)	54 (69.2%)	0.2354
Newborn weight (g)	3191 ±903	3270 ±894	0.7030
SGA	3 (12.0%)	7 (9.1%)	0.7818
LAG	3 (12.0%)	22 (28.6%)	0.1159
Apgar score – 1 min	8.32 ±1.0	8.15 ±1.5	0.5984
Apgar score – 5 min	8.52 ±1.89	8.16 ±2.0	0.4308
Newborn hypoglycemia (<40 mg/dl)	4 (16.0%)	11 (14.1%)	0.8902
Congenital abnormalities**	4	2	0.050

* Therapeutic abortion was indicated in the case of congenital abnormalities in foetus according to ultrasound examination.

** Including terminated pregnancies

Abbreviations: LGA – large for gestational age, SGA – small for gestational age

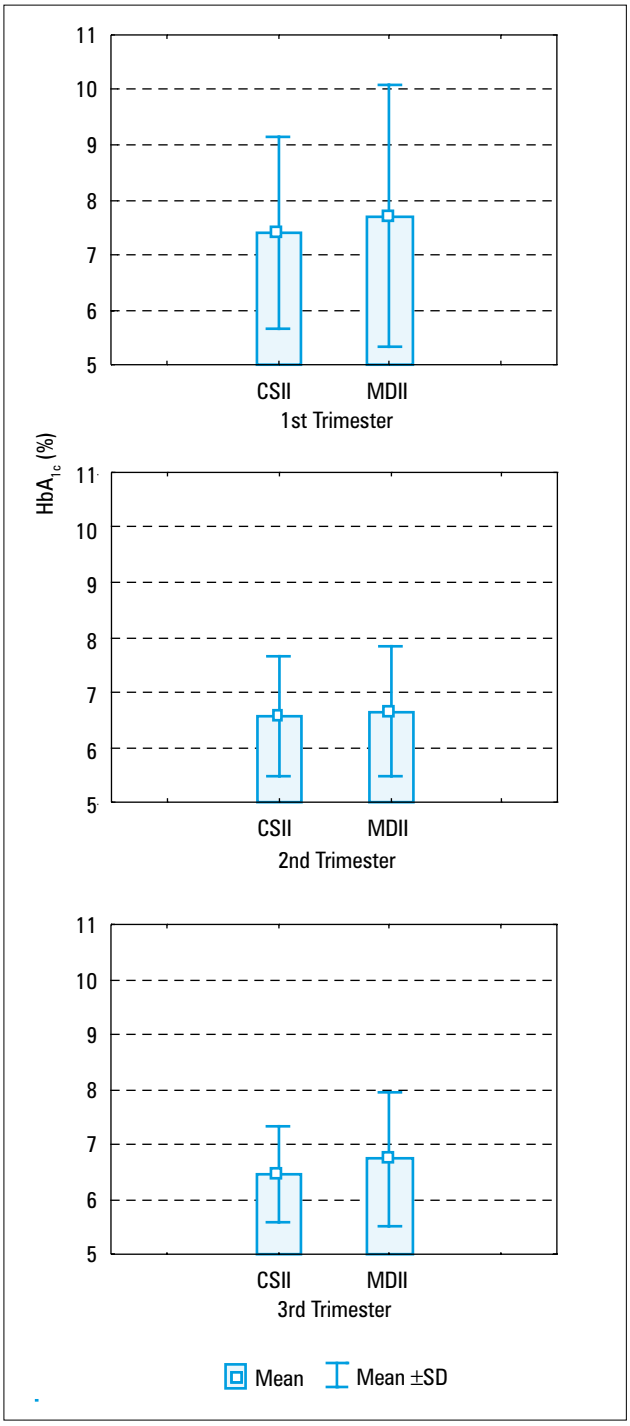

Fig. 1. Mean glycated haemoglobin (HbA_{1c}) levels in women with type 1 diabetes treated during pregnancy with continuous subcutaneous insulin infusion (CSII) or with multiple daily insulin injection (MDII). SD – standard deviation

The number of patients with chronic diabetes complications including retinopathy, nephropathy or both was higher in CSII than in MDII group (43.4% vs. 4,7%, p ≤0.00001). The number of patients with diabetes duration longer than 10 years was 24 in MDII group and 19 in CSII group. Distribution of patients' categories according to White classification is shown in Table 2.

There were no significant difference in HbA_{1c} levels measured in consecutive pregnancy trimesters between studied groups (p >0.05) (Fig. 1). There were also no significant difference in HbA_{1c} levels between CSII and MDII in subgroups with long lasting diabetes (more than 10 years) (Fig. 2). There were no episodes of severe hypoglycemia and diabetic coma during the observation period.

Data concerning obstetrical outcomes are presented in Table 3.

One stillbirth and one newborn death were noted in MDII group and 1 newborn death in CSII group. Mean duration of pregnancy, incidence of premature labour, caesarean section rate and mean newborn birth weight were similar in both groups (p >0.05).

A higher rate of large for gestational age (LGA) (28.6% vs. 12%) was found in MDII group, however the difference failed to reach statistical significance. Apgar score was similarly high in both groups (p >0.05). The total malformation rate was 5.2%.

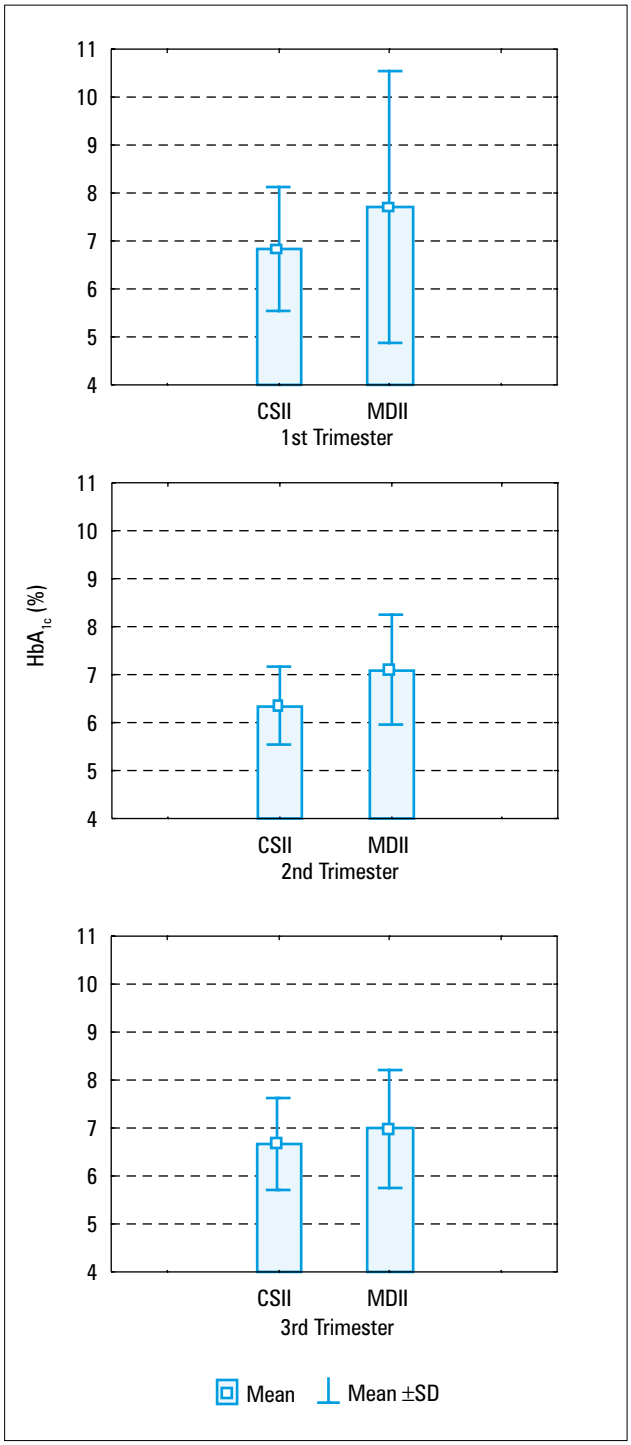

Fig. 2. Mean glycated hemoglobin (HbA_{1c}) levels in women with type 1 diabetes duration more than 10 years treated during pregnancy with continuous subcutaneous insulin infusion (CSII) or with multiple daily insulin injection (MDII). SD – standard deviation

When comparing within CSII group no significant differences in outcomes were observed between patients who started CSII before and during first trimester of pregnancy ($p > 0.05$).

DISCUSSION

Arrival of personal insulin pumps in 1990s offered new option to control blood glucose in type 1 diabetic patients. Pickup et al. in the meta-analysis of 12 randomized clinical studies clearly demonstrated greater efficacy of CSII than MDII, confirmed by modest but significant reduction of HbA_{1c} level without concomitant increase in hypoglycemic events incidence. This beneficial effect of CSII was noted regardless of whether recombinant human insulin or rapid-acting insulin analogs were used [8]. Upon clinical observations it seems that certain groups of patients may experience greater benefits with insulin pump treatment than others [7].

Recently several large prospective studies assessing the risk of complications of pregnancy in patients with diabetes mellitus type 1 have been published, and all of them emphasized the increased risk of perinatal complications, stillbirths, perinatal mortality, congenital defects and macrosomia in type 1 diabetes patients as compared with the general population risk [11-17]. Jensen et al. [18] reported significantly greater relative risk of obstetric failures in women with diabetes – relative risk (RR) 2.3 (8.0% vs. 3.4%), perinatal mortality – RR 4.1 (3.1% vs. 0.75%) and congenital malformation – RR 1.7 (5.0% vs. 2.8%).

Patients with type 1 diabetes who want to become pregnant are of special interest in this regard as achieving the best possible control of diabetes is a prerequisite of giving birth to a healthy child [4]. Until 2003 the efficacy of insulin pump treatment in relation to standard multiple injection regimen has been studied only in very small groups of type 1 diabetic pregnant women, no randomized trial was performed.

In 1986 Carta et al. [19] compared 15 pregnant women with diabetes type 1 treated with CSII or MDII. There were no differences in mean glycemia and HbA_{1c} level between both groups, however in 62.5% of newborn in the CSII group there were perinatal complications – hypoglycemia and hyperbilirubinemia, with no single episode of complications noted in the reference group. Nosari et al. [20] who compared 16 patients treated with the CSII and 16 patients treated with the MDII failed to observe any significant differences in HbA_{1c} values or in obstetric outcomes between the groups. In 2000 Gabbe at al. published the results of the study comparing obstetric results and the effectiveness of treatment in the group of 24 patients who began CSII during pregnancy, 24 women treated with MDII, and 12 subjects who were already using CSII before pregnancy. No significant differences in perinatal outcomes or health care costs were observed among groups [21]. Recently Lapolla et al., Gimenez et al. and Hieronimus et al. [22-24] also did not reveal the superiority of CSII when compare to MDII. Chen R et al. in their paper revealed additionally that CSII may be associated with higher rate of both maternal diabetic ketoacidosis and neonatal hypoglycemic events [25].

The results of our study are in agreement with these findings, indicating that individual or economic rather than clin-

ical aspects of insulin pump treatment should be considered when selecting the best method of treating diabetes in pregnant patients.

It should be noted that our study has certain limitations. It is a retrospective analysis but patients were not (as they actually could not be) subject to proper randomization. Also, CSII group was less numerous than the MDII group, but this disproportion closely reflects everyday clinical practice in many countries, when the minority of pregnant women with type 1 diabetes are offered pump therapy. The results presented by Chen et al. [25] came also from the observational, retrospective study and represented the same, not randomised population.

Interestingly, in our study women treated with CSII had longer duration of diabetes and accordingly presented more often with chronic complications of diabetes. However, this unfavourable difference did not result in worse glucose control or obstetrical outcomes than in the group treated with MDII, in fact efficacy and safety of both treatment regimens was similar. From our own clinical experience we may add that some patients find it easier to achieve improved metabolic control of diabetes with the use of CSII, but determining clear criteria of the selection CSII or MDII is at present not possible. Thus, our study confirms that in type 1 diabetes patients who become pregnant main optimal glycemia control is of paramount importance while method of achieving thereof is of secondary value.

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