ORIGINAL ARTICLE

Association between preconceptional treatment with insulin pumps and improved metabolic status in early pregnancy in women with type 1 diabetes

Paweł Gutaj, Agnieszka Zawiejska, Jacek Brązert, Ewa Wender-Ożegowska

Department of Obstetrics and Women's Diseases, Poznan University of Medical Sciences, Poznań, Poland

KEY WORDS

insulin infusion systems, insulin resistance, lipids, pregnancy, type 1 diabetes

ABSTRACT

INTRODUCTION An adverse intrauterine environment in early pregnancy in women with type 1 diabetes is associated with several perinatal complications including spontaneous abortions, fetal congenital defects, and preeclampsia.

OBJECTIVES We compared metabolic parameters in the first trimester of pregnancy between women with type 1 diabetes treated with continuous subcutaneous insulin infusion (CSII) and those treated with multiple daily injections (MDI).

PATIENTS AND METHODS A total of 168 women in the first trimester of pregnancy (33 using CSII and 135 using MDI) were enrolled in this cross-sectional single-center study. Anthropometric parameters, fasting serum levels of hemoglobin A_{1c} (HbA_{1c}), lipid profile, and estimated glucose disposal rate (eGDR) were determined.

RESULTS Patients did not differ in gestational or maternal age, diabetes duration, and the frequency of planned pregnancies. Women using CSII before pregnancy had lower body mass index and waist-to-hip ratio than those using MDI (22.3 vs 23.3 and 0.77 vs 0.79, respectively, $P = 0.01$). A similar number of women had hypertension; however, the CSII group had lower diastolic blood pressure ($P = 0.02$). Moreover, the CSII group had a significantly lower insulin requirement (0.54 vs 0.63 units/kg; $P = 0.02$), significantly higher eGDR (11.3 vs 10.5 mg/kg/min; $P = 0.0007$), and significantly lower serum triglyceride levels (53.1 vs 61.8 mg/dl; $P = 0.004$). In a multiple regression analysis, CSII therapy was associated with higher eGDR, lower HbA_{1c}, and lower serum triglyceride levels.

CONCLUSIONS The use of CSII before pregnancy in patients with type 1 diabetes is associated with better metabolic profile in the first trimester.

Correspondence to:
Paweł Gutaj, MD, Klinika Położnictwa i Chorób Kobiecych, Uniwersytet Medyczny w Poznaniu, ul. Polna 33, 60-535 Poznań, Poland, phone: +48 61 841 93 34, fax: +48 61 659 96 47, e-mail: pgutaj@o2.pl
Received: February 1, 2015.
Revision accepted: March 23, 2015.
Published online: April 1, 2015.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2015; 125 (5): 329-336
Copyright by Medycyna Praktyczna, Kraków 2015

INTRODUCTION Diabetes mellitus, especially when uncontrolled, has adverse effects on maternal and fetal health. The effects of early exposure to altered diabetic intrauterine environment might be devastating for the developing fetus. Therefore, the prevention of major complications of diabetic pregnancy should start before pregnancy. Several studies have demonstrated that pregnancy planning reduces the risk of congenital malformations and overall perinatal mortality.[1-3] However, only a relatively small number of patients receive preconception care, and we are still far from reaching the goals established at the St Vincent's Declaration in 1989.[4,5] Insulin pumps for treatment of type 1 diabetes were designed to mimic physiological pancreatic insulin secretion. In several studies, continuous subcutaneous insulin infusion (CSII) was found to improve glycemic control compared with multiple daily injections (MDI) in patients with type 1 diabetes.[6-8] However, studies in pregnant women with type 1 diabetes, including 1 meta-analysis and a recent multicenter study, have failed to show any difference in pregnancy outcomes between women using CSII and MDI.[8-12]

Metabolic changes associated with diabetes represent a broad spectrum of abnormalities including hyperglycemia, dyslipidemia, and insulin resistance (IR).[13] The first trimester is considered the most critical period for fetal development, and maternal metabolic status at this time might affect the perinatal outcome. Indeed, studies have correlated the incidence of miscarriage and fetal anomalies with hemoglobin A_{1c} (HbA_{1c}) levels in early pregnancy.[14,15] The HbA_{1c} level in the first trimester is also predictive of late complications such as preeclampsia and preterm delivery.[16] In addition, another study showed that lipid abnormalities in the first half of pregnancy are associated with fetal macrosomia in nondiabetic women, independent of body mass index (BMI) and gestational weight gain.[17]

Data on the role of IR on the course of pregnancy in women with type 1 diabetes are limited.[18,19] However, Wolf et al.[20] found that among nulliparous nondiabetic patients, IR was significantly higher in women destined to develop preeclampsia, suggesting that IR may play an important role for perinatal outcomes.

Our objective was to compare metabolic parameters in the first trimester of pregnancy between women with type 1 diabetes using CSII and those using MDI. We aimed to investigate whether women using CSII before pregnancy achieved better metabolic control in early pregnancy.

PATIENTS AND METHODS This cross-sectional study was performed at the Department of Obstetrics and Women's Diseases, Gynecologic and Obstetrical University Hospital in Poznań, Poland, between June 2012 and June 2014 in a population of pregnant women with type 1 diabetes. Clinical, anthropometric, and laboratory data for the present study were collected during the first perinatal hospitalization (<12 weeks of gestation). The department is the biggest perinatal center for pregnant women with diabetes in Poland, providing care for patients from the Wielkopolska province.

According to the Polish Diabetes Association (in Polish, Polskie Towarzystwo Diabetologiczne, [PTD]), clinical recommendations, and our internal hospital standards, all pregnant women with diabetes from the Wielkopolska province are immediately referred to our center once pregnancy is confirmed. This enabled us to investigate an unselected population of patients in the early stages of pregnancy. Women with concurrent diseases unrelated to diabetes that could affect metabolic control of the disease were excluded.

Among 179 pregnant women with type 1 diabetes admitted to our department during the study period, 168 were eligible for the study. Nine patients were excluded because of the following: newly diagnosed type 1 diabetes in early pregnancy (1 patient), diagnosed polycystic kidney disease with coexisting secondary hypertension (1 patient), and newly diagnosed hypothyroidism (7 patients). Two patients refused to participate in the study.

All study participants were Caucasians. They were all treated with functional intensive therapy before pregnancy; 135 patients received MDI and 33—CSII. All CSII users had been using this method of therapy for at least 6 months. A basal-bolus protocol used in patients on MDI involved 3 injections of short-acting insulin analog before meals and 1 or 2 injections of intermediate-acting insulin at bedtime or at bedtime and in the morning. Women on CSII received short-acting insulin analog (continuous basal rate and 3 premeal boluses).

Of all patients, 61 women using MDI and 20 women using CSII received prepregnancy counseling delivered by a diabetologist or an obstetrician with a special interest in diabetic pregnancy. These data were self-reported by participants. The remaining women received standard care for nonpregnant patients with type 1 diabetes delivered by diabetologists as recommended by the PTD. According to the PTD, blood glucose and HbA_{1c} targets for women planning their pregnancies or already pregnant compared with those nonplanning and nonpregnant were as follows: 3.3–5.0 mmol/l vs 3.9–6.1 mmol/l for fasting glucose levels, <7.5 mmol/l vs <7.8 mmol/l for postprandial glucose levels, and 6.1% (43 mmol/mol) vs (6.5%, 48 mmol/mol) for HbA_{1c} levels.[21]

Blood samples were collected during the first perinatal hospitalization after overnight fasting and immediately transported to the laboratory for analysis. All measurements were performed in the Central Laboratory of Gynecologic Obstetrical University Hospital in Poznań.

The percentage of HbA_{1c} in whole blood was estimated using a turbidimetric inhibition immunoassay (TINIA, Tina-quant® Hemoglobin A_{1c} II test, Roche Diagnostics, Rotkreuz, Switzerland) in a Cobas c311 analyzer. The normal range for this test is between 4.8% and 6.0% (29–42 mmol/mol) for a nonpregnant population.

Total serum cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured with appropriate reagents (cholesterol CHOD-PAP, HDL-C plus, and triglycerides GPO-PAP, respectively, Roche Diagnostics) in a Cobas c501 analyzer. Low-density lipoprotein (LDL) cholesterol levels were calculated using the following formula: LDL cholesterol = total cholesterol – HDL cholesterol – (triglicerydes / 5).

Anthropometric (weight, height, waist circumference, and hip circumference) and blood pressure measurements were performed according to standardized protocols. A detailed medical history, including the course of diabetes, its complications, and comorbidities, was taken from all patients.

All participants were examined by an ophthalmologist in the first trimester of pregnancy.

A 24-hour urine collection test was performed in every patient to assess urinary protein excretion. Diabetic nephropathy was defined as

TABLE 1 Characteristics of patients using continuous subcutaneous insulin infusion and multiple daily injection

Characteristic	MDI n = 135	CSII n = 33	*P* value
gestational age at baseline, wk	8 (7–10)	8 (6–10)	0.3
maternal age at baseline, y	29 (26–32)	29 (24–32)	0.5
primipara	74 (54.8)	21 (63.6)	0.4
prepregnancy counseling	61 (45.2)	20 (60.6)	0.1
age at diagnosis of diabetes, y	17 ±8	15 ±7	0.1
duration of diabetes, y	11.8 ±7.2	12.8 ±6.6	0.5
duration of CSII therapy, mo	–	33 ±32 (6–96)	–
baseline BMI, kg/m^2	23.3 (21.1–26.7)	22.3 (20.5–23.2)	0.01
baseline WHR	0.79 (0.76–0.85)	0.77 (0.73–0.80)	0.01
systolic blood pressure, mmHg	116 ±11	112 ±9	0.06
diastolic blood pressure, mmHg	72 ±8	68 ±6	0.02
patients with chronic hypertension	12 (8.9)	0 (0)	0.13
patients with diabetic nephropathy	6 (4.4)	2 (6.1)	0.7
patients with diabetic retinopathy	28 (20.7)	7 (21.2)	1.0
cigarette smoking	22 (16.3)	5 (15.1)	0.9
family history of type 2 diabetes	59 (43.7)	16 (48.5)	0.7
severe hypoglycemia during the previous 6 months	6 (4.4)	1 (3.03)	1.0
diabetic ketoacidosis during the previous 6 months	1 (0.74)	0 (0)	1.0

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage).

Abbreviations: BMI, body mass index; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injection; WHR, waist-to-hip ratio

the presence of proteinuria exceeding 0.3 g/24 h in the absence of urinary tract infection on admission or as a diagnosis of this disorder documented previously.

A positive family history of type 2 diabetes was defined as the presence of the disease in any of the 3 generations, ie, siblings, parents, and grandparents.

Severe hypoglycemia was defined as any event requiring assistance from another person that occurred during the 6 months before the inclusion to the study.

According to the guidelines, women were tested for thyroid dysfunction (measurement of thyroid-stimulating hormone).[22] Except for the 7 women who were not included into this study because of newly diagnosed hypothyroidism, the remaining women were euthyroid either spontaneously (n = 128) or following levothyroxine treatment (n = 40). There were no patients with hyperthyroidism in the study group.

IR was quantified using the estimated glucose disposal rate (eGDR) (mg/kg/min), calculated using the following equation:

$$eGDR = 24.31 - 12.22 \times (WHR) - 3.29 \times (HTN) - 0.57 \times (HbA_{1c})$$

where WHR is waist-to-hip ratio and HTN is hypertension (0 = no; 1 = yes).

It is worth noting that a decreasing eGDR correlates with increasing IR.[23]

Statistical analysis The statistical analysis was performed using MedCalc for Windows, version 12.1.3.0 (MedCalc Software, Mariakerke, Belgium). The D'Agostino–Pearson test was used to test for normality of data distribution. The *t* test was used to measure the significance of the difference between 2 continuous variables when data fitted normal distribution, with results expressed as mean ± standard deviation. In case of nonnormally distributed data, comparisons were made using the Mann–Whitney test, with results expressed as median and interquartile range. χ^2 and Fisher exact tests were used for the comparison of categorical variables. The Spearman rank correlation coefficient was used to test the relationship between 2 variables when data did not follow normal distribution.

Stepwise multiple regression was used to assess the effect of CSII therapy on maternal HbA_{1c}, eGDR, and lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides). Based on clinical judgment, we included the following confounders into the stepwise models: maternal age (years), diabetes duration (years), nulliparity (yes/no), family history of type 2 diabetes (yes/no), cigarette smoking (yes/no), BMI at baseline (kg/m^2), and prepregnancy counseling (yes/no). The models examining the effect of CSII therapy on lipid fractions additionally included HbA_{1c} and hypertensive status (yes/no) as confounders. According to the stepwise method, variables were entered into the model if their associated *P* values were lower than 0.05 and then sequentially removed if their associated *P* values became greater than 0.2. A *P* value of less than 0.05 was considered statistically significant (2-tailed).

The ethics committee of the Poznan University of Medical Sciences (no. 673/12; June 12, 2012) approved the study protocol, and written informed consent was obtained from every patient before inclusion to the study.

RESULTS The clinical characteristics of the study groups are shown in TABLE 1. The groups did not differ in terms of the gestational age at baseline, maternal age at baseline, nulliparity, rates of patients receiving preconception care, age at diagnosis of diabetes, diabetes duration, smoking status, family history of type 2 diabetes, and number of episodes of severe hypoglycemia/ketoacidosis during the 6 months before pregnancy. A similar number of patients in each group suffered from diabetic vascular complications. Finally, there were no significant differences in the number of patients with chronic hypertension between the groups.

In the CSII group, the mean duration of CSII therapy was 33 months, ranging from 6 to

TABLE 2 Laboratory characteristics of patients using continuous subcutaneous insulin infusion and multiple daily injection

	MDI (n = 135)	CSII (n = 33)	*P* value
HbA_{1c}, %, mmol/mol	6.8 (5.9–8.0), 51 (41–64)	6.1 (5.8–7.1), 43 (40–54)	0.09
total cholesterol, mg/dl	170.6 ±28.3	164.9 ±24.3	0.3
HDL cholesterol, mg/dl	71.6 (61.7–83.4)	73.0 (60.5–84.5)	0.9
LDL cholesterol, mg/dl	81.3 (68.4–94.8)	78.5 (65.2–96.6)	0.6
triglycerides, mg/dl	61.8 (49.2–86.3)	53.1 (42.8–67.3)	0.004
urinary protein excretion/24 h, g	0.13 (0.09–0.20)	0.13 (0.08–0.19)	0.9
creatinine clearance, ml/min	126.7 (100.1–149.1)	127.0 (109.3–145.6)	0.8
total daily insulin requirement, units/kg	0.63 (0.46–0.80)	0.54 (0.44–0.63)	0.02
eGDR, mg/kg/min	10.5 (9.2–11.4)	11.3 (10.7–11.9)	0.0007

Data are presented as mean ± standard deviation or median (interquartile range).

Conversion factors to SI units are as follows: for total cholesterol, 0.0259; HDL, 0.0259; LDL, 0.0259; triglycerides, 0.0113

Abbreviations: eGDR, estimated glucose disposal rate; HbA_{1c}, hemoglobin A_{1c}, HDL, high-density lipoprotein; LDL, low-density lipoprotein, others, see TABLE 1

TABLE 3 Effect of continuous subcutaneous insulin infusion before pregnancy on estimated glucose disposal rate after adjustment for confounders

	Coefficient (standard error)	*P* value
model 1	0.79 (0.29)	0.007
adjusted for maternal age, diabetes duration, nulliparity (yes/no), family history of type 2 diabetes (yes/no), cigarette smoking (yes/no)[a], and BMI at baseline[a]	R^2 adjusted = 0.1387	
model 2	0.66 (0.28)	0.019
adjusted for maternal age, diabetes duration, nulliparity (yes/no), family history of type 2 diabetes (yes/no), cigarette smoking (yes/no), BMI at baseline[a], and prepregnancy counseling (yes/no)[a]	R^2 adjusted = 0.2052	

a variables that were retained in stepwise multiple regression models

Abbreviations: see TABLE 1

96 months. CSII users had lower BMI (P = 0.01), WHR (P = 0.01), and diastolic blood pressure (P = 0.02). There was no significant difference in systolic blood pressure; however, a trend for lower values was noted in the CSII group (P = 0.06).

Laboratory characteristics and IR indexes of the study groups are shown in TABLE 2. HbA_{1c} was lower in the CSII group compared with the MDI group (6.1% vs 6.8%, 43 vs 51 mmol/mol; P = 0.09), but the difference did not reach statistical significance. In a subsequent analysis using multiple regression, CSII was found to be significantly associated with decreased HbA_{1c} levels after adjustment for maternal age, diabetes duration, nulliparity (yes/no), family history of type 2 diabetes (yes/no), cigarette smoking (yes/no), BMI at baseline, and hypertensive status (coefficient = –0.64 [standard error, 0.29]; P = 0.03). However, the association was no longer present after additional adjustment for prepregnancy counseling (yes/no) (data not shown).

The serum levels of total cholesterol, HDL cholesterol, and LDL cholesterol were not different between the CSII and MDI groups; however, serum triglyceride levels were significantly lower in the CSII group (P = 0.004). There was no difference in daily urinary protein excretion and renal clearance between the groups.

CSII users had lower insulin requirements (units/kg) than MDI users (P = 0.02). eGDR was significantly higher (P = 0.0007) in women using CSII, suggesting that they had lower IR. This group also showed a significant negative correlation between eGDR and triglyceride levels (rho = –0.34; P <0.0001).

In the multiple regression analysis, CSII treatment was significantly associated with a higher eGDR when adjusted for maternal age, diabetes duration, nulliparity (yes/no), family history of type 2 diabetes (yes/no), cigarette smoking (yes/no), BMI at baseline (model 1 coefficient = 0.79; P = 0.007). The association became weaker after additional adjustment for prepregnancy counseling (yes/no) (model 2 coefficient = 0.66; P = 0.019). The results are shown in TABLE 3.

The CSII treatment was also associated with the reduction in serum triglyceride levels when adjusted for maternal age, diabetes duration, nulliparity (yes/no), family history of type 2 diabetes (yes/no), cigarette smoking (yes/no), BMI at baseline, hypertensive status (yes/no) (model 1 coefficient = –16.36; P = 0.008). This association became weaker after additional adjustment for HbA_{1c} levels (model 2 coefficient = –15.69; P = 0.01) and prepregnancy counseling (yes/no) (model 3 coefficient = –14.23; P = 0.02). The results are shown in TABLE 4.

The CSII treatment was not associated with changes in the levels of total cholesterol, HDL cholesterol, and LDL cholesterol.

DISCUSSION

As numerous obstetric diseases have their origin in the first trimester, we aimed to investigate whether the mode of insulin therapy before pregnancy is associated with any changes in metabolic status in women with type 1 diabetes during early pregnancy.

We demonstrated that the CSII treatment may have several beneficial effects, not only in terms of HbA_{1c} reduction, but also in a broader metabolic context.

Using the multiple regression analysis, we found that the use of CSII before pregnancy was associated with a decreased HbA_{1c} level. This is an important clinical finding because these women had lower mean glycemia during the critical period for fetal development, namely, embryogenesis. These results are in line with previous

TABLE 4 Effect of continuous subcutaneous insulin infusion before pregnancy on maternal serum triglyceride levels after adjustment for confounders

	Coefficient (standard error)	*P* value
model 1	−16.36 (6.09)	0.008
adjusted for maternal age, diabetes duration, nulliparity (yes/no), family history of type 2 diabetes (yes/no), cigarette smoking (yes/no), BMI at baseline, and hypertensive status (yes/no)	R^2 adjusted = 0.0373	
model 2	−15.69 (6.14)	0.01
adjusted for maternal age, diabetes duration, nulliparity (yes/no), family history of type 2 diabetes (yes/no), cigarette smoking (yes/no), BMI at baseline, hypertensive status (yes = 1/no = 0), and HbA_{1c} at baseline[a]	R^2 adjusted = 0.0666	
model 3	−14.23 (6.20)	0.02
adjusted for maternal age, diabetes duration, nulliparity (yes/no), family history of type 2 diabetes (yes/no), cigarette smoking (yes/no), BMI at baseline[a], hypertensive status (yes/no), and prepregnancy counseling[a] (yes/no)	R^2 adjusted = 0.0547	

a variables that were retained in stepwise multiple regression models

Abbreviations: see **TABLES 1** and **2**

observational studies conducted in both pregnant and nonpregnant patients where pump therapy was associated with the reduction of HbA_{1c} levels.[6-8] Importantly, lower HbA_{1c} in the CSII group was achieved without impacting the rate of severe hypoglycemia during the 6 months before the study. However, it should be emphasized that the association between the CSII treatment and lower HbA_{1c} levels was no longer observed after adjustment for prepregnancy counseling. It further confirms that any therapeutic tool cannot replace preconception care as an integral part of the strategy to achieve optimal metabolic control from the early beginning of pregnancy.

Weight gain is a common metabolic adverse effect of improved glycemic control and is related to hyperinsulinization.[24] In this study, we showed that women treated with CSII had a significantly lower BMI at the beginning of pregnancy. However, the influence of the CSII treatment on gestational weight gain requires further studies as literature yields conflicting results—either no change[8,10,12] or larger weight gain in comparison[9] with the use of MDI. We also measured WHR—a useful clinical parameter of fat distribution—and it was also lower in the CSII group. Since WHR has not been examined in previous prospective and retrospective studies comparing CSII and MDI, this is a completely novel finding. It should be also noted that better metabolic control was achieved with lower doses of insulin (units/kg) in the CSII group. One may suggest that beneficial changes in body fat distribution, together with lower insulin requirements observed in women using CSII, might have been attributed to the more physiological method of insulin delivery.[25] Moreover, increased WHR or abnormal fat distribution in the first trimester has been linked with macrosomia and preeclampsia, irrespective of overall adiposity.[26-28]

IR is a decreased response to normal insulin concentrations and might be observed in both diabetic and nondiabetic individuals. As the gold standard of IR assessment—the clamp technique—cannot be used in pregnancy because of its invasiveness, the eGDR is used as an alternative. It has been found to closely correlate with the clamp technique for measuring IR.[23,29] eGDR has not been used previously in pregnancy. However, as our study group consisted of patients in the early first trimester, when their WHR has not yet been affected by the enlarging uterus (located below the symphysis pubis until the 12th week of gestation), the eGDR seems to be a good indicator of IR.

We found that treatment with an insulin pump before pregnancy was significantly associated with decreased IR, as indicated by increased eGDR. Importantly, this beneficial effect of the CSII treatment was independent of prepregnancy counseling.

There are some data linking increased IR with pregnancy complications. For example, in patients with polycystic ovary syndrome, higher IR altered the implantation rate after in-vitro fertilization.[30] Similarly, Paretti et al.[31] demonstrated that preeclampsia can be predicted by simple insulin sensitivity indexes measured independently in both early and late pregnancy. Hauth et al.[32] confirmed these findings in a large cohort of patients tested between the 22nd and 26th weeks of gestation. Importantly, these studies have been conducted in nondiabetic patients, and there are no similar reports in a population of women with type 1 diabetes. Nevertheless, bearing in mind the higher incidence of early pregnancy loss and preeclampsia in this group, there is a clear need for further studies on the role of IR in pregnancy complicated by type 1 diabetes, in which the mode of insulin therapy would be considered as a confounder.

Type 1 diabetes predisposes patients to dyslipidemia, which further contributes to increased cardiovascular risk.[33] In pregnancy, there is a physiological elevation of maternal lipid levels to meet the energy needs of the growing fetus.[34] In this study, we showed that CSII used before pregnancy was associated with a significant reduction in maternal triglyceride levels in the first trimester. Moreover, we demonstrated that triglyceride levels are negatively correlated with eGDR, supporting a close association between IR and adipose tissue metabolism.[35,36] There is strong evidence from recent meta-analyses that maternal hypertriglyceridemia is associated with and precedes the onset of preeclampsia.[37,38] However, the vast majority of the studies eligible for inclusion to these meta-analyses excluded patients with diabetes as an independent risk group for preeclampsia. Nonetheless, there is an association between diabetes and preeclampsia, as both diseases are associated with oxidative stress and

endothelial dysfunction.[39,40] Thus, hypertriglyceridemia may represent an additional factor that exacerbates these pathological processes and it should be taken into consideration, especially if present in early pregnancy.[41]

During the Banting Lecture in 1980, Norbert Freinkel[42] suggested that nutrients other than glucose could be linked with excessive fetal growth. Since this hypothesis was formed, several studies have shown that high maternal triglyceride levels are associated with fetal macrosomia in nondiabetic women.[17,43] Such associations have also been observed in patients with gestational diabetes.[44,45] However, data on triglyceride levels during pregnancy in women with type 1 diabetes are limited.[13]

There is a paucity of data from human trials exploring the role of CSII on the lipid profile in patients with type 1 diabetes. Available data come from interventional studies carried out on relatively small groups of patients.[46,47] These studies demonstrated beneficial changes in serum lipids, including a reduction in serum triglyceride and LDL cholesterol levels and an increase in HDL cholesterol levels in patients using CSII. These changes can probably be attributed to a significant improvement in glucoregulation after initiation of pump treatment as was suggested by the available studies.[46,47]

In our study, we confirmed that a reduction in serum triglyceride levels in patients treated with CSII was independent of HbA_{1c} and BMI. We believe that this is an important clinical finding because lipid abnormalities observed in early pregnancy tend to be accentuated by advancing gestation.[48] However, further studies are required to confirm whether beneficial changes associated with the use of CSII are sustained throughout pregnancy.

Our study is limited by a relatively small sample size. However, its prospective design and the inclusion of the whole population of pregnant women with type 1 diabetes admitted to our department in the first trimester and within a narrow time frame add to the study's generalizability in this particular population. Nonetheless, this is a "snapshot" study, and further longitudinal studies are needed to explore the mechanisms behind the beneficial effect of the CSII treatment on the metabolic profile in all patients with type 1 diabetes, including pregnant women and children.

In conclusion, we demonstrated that women using CSII before pregnancy achieved better metabolic profile in the first trimester; however, the effect of these beneficial changes on the perinatal outcome requires further research.

Contribution statement PG contributed to study design, data collection, data analysis, data interpretation, and preparation of the manuscript; AZ contributed to data interpretation and reviewed the manuscript; JB reviewed and accepted the final version of the manuscript; EW-O contributed to study design, data analysis, data interpretation, and preparation of the manuscript.

Acknowledgments We are grateful to our patients for their participation in the study.

This study was supported by Poznan University of Medical Sciences (Grant No. 502-14--01110141-99677, granted to PG) and the Polish Diabetes Association (PG is a recipient of the Professor Artur Czyżyk Scientific Grant).

REFERENCES

1 Wender-Ozegowska E, Gutaj P, Szczepanek U, et al. [Influence of pregnancy planning on obstetrical results in women with pregestational diabetes mellitus]. Ginekol Pol. 2010; 81: 762-767. Polish.

2 Wahabi HA, Alzeidan RA, Esmaeil SA. Pre-pregnancy care for women with pre-gestational diabetes mellitus: a systematic review and meta-analysis. BMC Public Health. 2012; 12: 792.

3 Cyganek K, Klupa T, Szopa M, et al. Medical care of pregnant women with type 1 diabetes: current guidelines and clinical practice. Pol Arch Med Wewn. 2013; 123: 59-65.

4 Tripathi A, Rankin J, Aarvold J, et al. Preconception counseling in women with diabetes: a population-based study in the north of England. Diabetes Care. 2010; 33: 586-588.

5 Diabetes care and research in Europe: the Saint Vincent declaration. Diabet Med. 1990; 7: 360.

6 Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med. 2008; 25: 765-774.

7 Mameli C, Scaramuzza AE, Ho J, et al. A 7-year follow-up retrospective, international, multicenter study of insulin pump therapy in children and adolescents with type 1 diabetes. Acta Diabetol. 2014; 51: 205-210.

8 Kallas-Koeman M, Kong J, Klinke J, et al. Insulin pump use in pregnancy is associated with lower HbA1c without increasing the rate of severe hypoglycaemia or diabetic ketoacidosis in women with type 1 diabetes. Diabetologia. 2014; 57: 681-689.

9 Cyganek K, Hebda-Szydlo A, Katra B, et al. Glycemic control and selected pregnancy outcomes in type 1 diabetes women on continuous subcutaneous insulin infusion and multiple daily injections: the significance of pregnancy planning. Diabetes Technol Ther. 2010; 12: 41-47.

10 Wender-Ozegowska E, Zawiejska A, Ozegowska K, et al. Multiple daily injections of insulin versus continuous subcutaneous insulin infusion for pregnant women with type 1 diabetes. Aust N Z J Obstet Gynaecol. 2013; 53: 130-135.

11 Mukhopadhyay A, Farrell T, Fraser RB, Ola B. Continuous subcutaneous insulin infusion vs intensive conventional insulin therapy in pregnant diabetic women: a systematic review and metaanalysis of randomized, controlled trials. Am J Obstet Gynecol. 2007; 197: 447-456.

12 Bruttomesso D, Bonomo M, Costa S, et al. Type 1 diabetes control and pregnancy outcomes in women treated with continuous subcutaneous insulin infusion (CSII) or with insulin glargine and multiple daily injections of rapid-acting insulin analogues (glargine-MDI). Diabetes Metab. 2011; 37: 426-431.

13 Barrett HL, Dekker Nitert M, et al. Normalizing metabolism in diabetic pregnancy: is it time to target lipids? Diabetes Care. 2014; 37: 1484-1493.

14 Gutaj P, Zawiejska A, Wender-Ozegowska E, Brazert J. Maternal factors predictive of first trimester pregnancy loss in women with pregestational diabetes. Pol Arch Med Wewn. 2013; 123: 21-28.

15 Wender-Ozegowska E, Wroblewska K, Zawiejska A, et al. Threshold values of maternal blood glucose in early diabetic pregnancy: prediction of fetal malformations. Acta Obstet Gynecol Scand. 2005; 84: 17-25.

16 Jensen DM, Damm P, Ovesen P, et al. Microalbuminuria, preeclampsia, and preterm delivery in pregnant women with type 1 diabetes results from a nationwide Danish study. Diabetes Care. 2010; 33: 90-94.

17 Clausen T, Burski T, Oyen N, et al. Maternal anthropometric and metabolic factors in the first half of pregnancy and risk of neonatal macrosomia in term pregnancies. A prospective study. Eur J Endocrinol. 2005; 153: 887-894.

18 Wender-Ozegowska E, Zawiejska A, Michalowska-Wender G, et al. Metabolic syndrome in type 1 diabetes mellitus. Does it have any impact on the course of pregnancy? J Physiol Pharmacol. 2011; 62: 567.

19 Gutaj P, Sawicka-Gutaj N, Brazert M, Wender-Ozegowska E. Insulin resistance in pregnancy complicated by type 1 diabetes mellitus. Do we know enough? Ginekol Pol. 2015; 86: 219-223.

20 Wolf M, Sandler L, Munoz K, et al. First trimester insulin resistance and subsequent preeclampsia: a prospective study. J Clin Endocrinol Metab. 2002; 87: 1563-1568.

21 Czech A, Grzeszczak W, Gumprecht J. [Clinical recommendations for the management of diabetes. Consensus of the Polish Diabetes Society]. Diabetol Prakt. 2006; 7 (Suppl A): A1-A44. Polish.

22 Sowinski J, Czupryniak L, Milewicz A, et al. Recommendations of the Polish Society of Endocrinology and Polish Diabetes Association for the management of thyroid dysfunction in type 1 and type 2 diabetes. Endokrynol Pol. 2013; 64: 73-77.

23 Williams KV, Erbey JR, Becker D, et al. Can clinical factors estimate insulin resistance in type 1 diabetes? Diabetes. 2000; 49: 626-632.

24 Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes-causes, effects and coping strategies. Diabetes Obes Metab. 2007; 9: 799-812.

25 Lauritzen T, Pramming S, Deckert T, Binder C. Pharmacokinetics of continuous subcutaneous insulin infusion. Diabetologia. 1983; 24: 326-329.

26 Salem W, Adler AI, Lee C, Smith GC. Maternal waist to hip ratio is a risk factor for macrosomia. BJOG. 2012; 119: 291-297.

27 Li S, Rosenberg L, Palmer JR, et al. Central adiposity and other anthropometric factors in relation to risk of macrosomia in an African American population. Obesity. 2013; 21: 178-184.

28 Taebi M, Sadat Z, Saberi F, Kalahroudi MA. Early pregnancy waist-to-hip ratio and risk of preeclampsia: a prospective cohort study. Hypertens Res. 2015; 38: 80-83.

29 Tam CS, Xie W, Johnson WD, et al. Defining insulin resistance from hyperinsulinemic-euglycemic clamps. Diabetes Care. 2012; 35: 1605-1610.

30 Chang EM, Han JE, Seok HH, et al. Insulin resistance does not affect early embryo development but lowers implantation rate in in vitro maturation-in vitro fertilization-embryo transfer cycle. Clin Endocrinol (Oxf). 2013; 79: 93-99.

31 Parretti E, Lapolla A, Dalfra M, et al. Preeclampsia in lean normotensive normotolerant pregnant women can be predicted by simple insulin sensitivity indexes. Hypertension. 2006; 47: 449-453.

32 Hauth JC, Clifton RG, Roberts JM, et al. Maternal insulin resistance and preeclampsia. Am J Obstet Gynecol. 2011; 204: 327 e321-326.

33 Perez A, Wagner AM, Carreras G, et al. Prevalence and phenotypic distribution of dyslipidemia in type 1 diabetes mellitus: effect of glycemic control. Arch Intern Med. 2000; 160: 2756-2762.

34 Mankuta D, Elami-Suzin M, Elhayani A, Vinker S. Lipid profile in consecutive pregnancies. Lipids Health Dis. 2010; 9: 58.

35 Ginsberg HN, Zhang YL, Hernandez-Ono A. Regulation of plasma triglycerides in insulin resistance and diabetes. Arch Med Res. 2005; 36: 232-240.

36 Kraegen EW, Cooney GJ, Ye J, Thompson AL. Triglycerides, fatty acids and insulin resistance-hyperinsulinemia. Exp Clin Endocrinol Diabetes. 2001; 109: S516-526.

37 Gallos ID, Sivakumar K, Kilby MD, et al. Pre-eclampsia is associated with, and preceded by, hypertriglyceridaemia: a meta-analysis. BJOG. 2013; 120: 1321-1332.

38 Spracklen CN, Smith CJ, Saftlas AF, et al. Maternal hyperlipidemia and the risk of preeclampsia: a meta-analysis. Am J Epidemiol. 2014; 180: 346-358.

39 Avogaro A, Albiero M, Menegazzo L, et al. Endothelial Dysfunction in Diabetes: The role of reparatory mechanisms. Diabetes Care. 2011; 34: S285-S290.

40 Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. Circulation. 2011; 123: 2856-2869.

41 Ceriello A, Taboga C, Tonutti L, et al. Evidence for an independent and cumulative effect of postprandial hypertriglyceridemia and hyperglycemia on endothelial dysfunction and oxidative stress generation: effects of short- and long-term simvastatin treatment. Circulation. 2002; 106: 1211-1218.

42 Freinkel N. Banting Lecture 1980. Of pregnancy and progeny. Diabetes. 1980; 29: 1023-1035.

43 Kulkarni SR, Kumaran K, Rao SR, et al. Maternal lipids are as important as glucose for fetal growth: findings from the Pune Maternal Nutrition Study. Diabetes Care. 2013; 36: 2706-2713.

44 Olmos PR, Rigotti A, Busso D, et al. Maternal hypertriglyceridemia: A link between maternal overweight-obesity and macrosomia in gestational diabetes. Obesity (Silver Spring). 2014; 22: 2156-2163.

45 Schaefer-Graf UM, Graf K, Kulbacka I, et al. Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. Diabetes Care. 2008; 31: 1858-1863.

46 Lawson P, Trayner I, Rosenstock J, Kohner E. The effect of continuous subcutaneous insulin infusion on serum lipids. Diabete Metab. 1984; 10: 239-244.

47 Dunn FL, Pietri A, Raskin P. Plasma lipid and lipoprotein levels with continuous subcutaneous insulin infusion in type I diabetes mellitus. Ann Intern Med. 1981; 95: 426-431.

48 Merzouk H, Madani S, Korso N, et al. Maternal and fetal serum lipid and lipoprotein concentrations and compositions in type 1 diabetic pregnancy: relationship with maternal glycemic control. J Lab Clin Med. 2000; 136: 441-448.

ARTYKUŁ ORYGINALNY

Związek między stosowaniem osobistej pompy insulinowej w okresie prekoncepcyjnym a poprawą parametrów metabolicznych we wczesnej ciąży u pacjentek z cukrzycą typu 1

Paweł Gutaj, Agnieszka Zawiejska, Jacek Brązert, Ewa Wender-Ożegowska

Klinika Położnictwa i Chorób Kobiecych, Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu, Poznań

SŁOWA KLUCZOWE

ciąża, cukrzyca typu 1, lipidy, oporność na insulinę, systemy infuzji insuliny

STRESZCZENIE

WPROWADZENIE Nieprawidłowe środowisko wewnątrzmaciczne we wczesnej ciąży u pacjentek z cukrzycą typu 1 jest związane z występowaniem takich powikłań położniczych, jak samoistne poronienia, wady wrodzone płodu oraz stan przedrzucawkowy.

CELE Celem badania było porównanie parametrów wyrównania metabolicznego w I trymetrze ciąży między pacjentkami z cukrzycą typu 1 stosującymi w okresie przedciążowym osobistą pompę insulinową (*continuous subcutaneous insulin infusion* – CSII) a pacjentkami leczonymi metodą wielokrotnych wstrzyknięć (*multiple daily injections* – MDI).

PACJENTKI I METODY 168 kobiet w I trymestrze ciąży (33 stosujące CSII i 135 stosujących MDI) zostało włączonych do jednoośrodkowego badania przekrojowego. Dokonano pomiarów antropometrycznych, a także oznaczono stężenie hemoglobiny A_{1c} (HbA_{1c}) na czczo, profil lipidowy oraz wskaźnik eGDR (*estimated glucose disposal rate*).

WYNIKI Pacjentki nie różniły się pod względem wieku ciążowego, wieku matki, czasu trwania cukrzycy oraz częstości planowania ciąży. Kobiety stosujące CSII przed ciążą miały niższy wskaźnik masy ciała oraz niższy wskaźnik talia–biodro w porównaniu z kobietami stosującymi MDI (odpowiednio: 22,3 *vs* 23,3; p = 0,01 oraz 0,77 *vs* 0,79; p = 0,01). Porównywalna liczba pacjentek chorowała na nadciśnienie tętnicze, jednakże u pacjentek stosujących CSII zaobserwowano niższe rozkurczowe ciśnienie tętnicze (p = 0,02). Pacjentki stosujące CSII miały także istotnie mniejsze zapotrzebowanie na insulinę (0,54 *vs* 0,63 jednostek/kg; p = 0,02), niższą insulinooporność manifestującą się wyższym wskaźnikiem eGDR (11,3 *vs* 10,5 mg/kg/min; p = 0,0007) oraz niższe stężenie triglicerydów w surowicy (53,1 *vs* 61,8 mg/dl; p = 0,004). W analizie regresji wielorakiej insulinoterapia z użyciem CSII związana była z wyższy wskaźnikiem eGDR, niższym stężeniem HbA_{1c} oraz niższym stężeniem triglicerydów w surowicy.

WNIOSKI Stosowanie CSII w okresie przedciążowym u pacjentek z cukrzycą typu 1 ma związek z lepszą kontrolą metaboliczną w I trymestrze.

Adres do korespondencji:
lek. Paweł Gutaj, Klinika Położnictwa i Chorób Kobiecych, Uniwersytet Medyczny w Poznaniu, ul. Polna 33, 60-535 Poznań, tel.: 61 841 93 34, fax: 61 659 96 47, e-mail: pgutaj@o2.pl

Praca wpłynęła: 01.02.2015.
Przyjęta do druku: 23.03.2015.
Publikacja *online*: 01.04.2015.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2015; 125 (5): 329-336

Copyright by Medycyna Praktyczna, Kraków 2015