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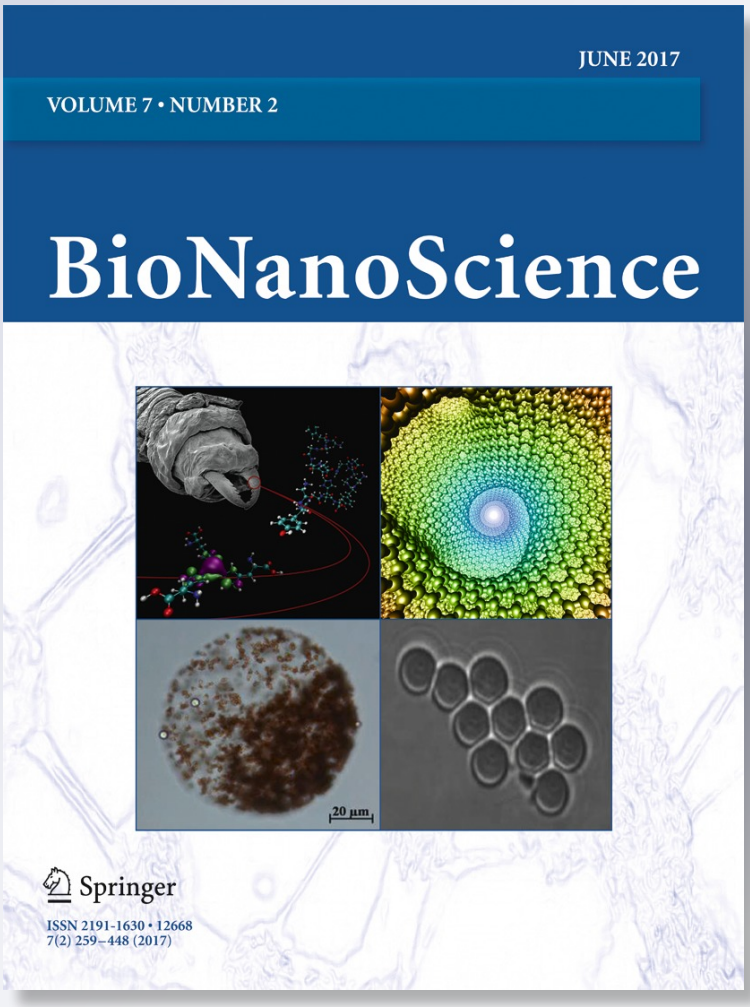

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Pregnancy Outcomes in Women with Type 1 Diabetes Depending on the Different Modes of Insulin Therapy

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Abstract The aim of the study was to evaluate the features of the effect of different modes of insulin therapy on pregnancy outcomes in women with type 1 diabetes mellitus (T1DM) with different levels of albuminuria. The study involved 155 women with T1DM during pregnancy, using various modes of insulin, and 42 infants born to women with T1DM. In order to identify a possible relationship between the level of proinflammatory cytokines and growth factors in pregnant women with T1DM and terms of delivery, we measured the daily urinary excretion of IL-1β, MCP-1, and TGF-β1 in 21 women at different trimesters of pregnancy. The use of continuous subcutaneous insulin infusion (CSII) in pregnant women with T1DM allows to prolong the pregnancy for 2–4 weeks as compared to the timing of delivery of pregnant women with T1DM receiving multiple subcutaneous injections of insulin (MPII). Pregnant women with MPII in 100% cases of the presence of microalbuminuria and proteinuria had premature delivery. Elevated levels of proinflammatory cytokines (IL-1β and MCP-1) and TGF-β1 may possibly serve as a predictor of pre-term delivery in pregnant women with diabetes type 1, starting with the early stages of pregnancy. The use of insulin by CSII in pregnant women with T1DM reduces the percentage of pre-term deliveries, regardless of the stage of diabetic nephropathy. It improves the condition of infants born at term in women with T1DM using a therapy with insulin pumps compared to that with MPII such as less common manifestation of diabetic fetopathy as macrosomia and hypoglycemia at birth, reducing the need for resuscitation in newborns.

Keywords Pregnant women with type 1 diabetes · Outcomes of pregnancy · Insulin pump · IL-1β · MCP-1 · TGF-β1

1 Introduction

Every year, the number of women of reproductive age with type 1 diabetes mellitus (T1DM) increases, thus expanding the range of issues related to the prenatal care. According to the perinatal center of the Republic Clinical Hospital No. 1 (Kazan, Russian Federation) in the period from 1999 to 2015, the number of births to women with type 1 diabetes dramatically increased. For example, in 1999, the number of births to women with type 1 diabetes was 9; in 2008, this figure had increased to 16 patients. In 2014, the number of patients with T1DM who have given birth was 21 women; in the 2015—42 women.

The combination of pregnancy with diabetic complications such as diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, and decompensation of carbohydrate metabolism is the cause of obstetrical pathologies and pathological conditions of the mother and the child such as spontaneous abortions and premature births [1, 2]. The lack of diabetes compensation during pregnancy leads to the hyperinsulinemia, macrosomia, severe hypoxia, and acidosis in the fetus determining the development of central nervous system dysfunction—hypertensive syndrome, psychomotor and intelligence retardation, as well as high perinatal mortality [3]. The outcome of pregnancy depends on the motivation, sufficient knowledge about T1DM, as well as providing timely quality medical care by endocrinologist and obstetrician-gynecologist.

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2 Material and Methods

In this study, we conducted a comprehensive clinical and laboratory examination of 155 pregnant women with T1DM (during different trimesters of pregnancy) at the age of 19 to 36 years and diabetes duration of 1 to 26 years. Clinical and laboratory methods included the following: blood and urine tests, bacterial urine culture, and daily urinary albumin excretion (with quantitative method NycoCard U-Albumin test systems for in vitro diagnostical use of low concentrations of albumin in the urine). Glomerular renal function was assessed by the level of endogenous serum creatinine, which was determined by a color reaction Jaffe, with the calculation of glomerular filtration rate (by Cockcroft-Gault, MDRD). To assess the adequacy of insulin therapy, we assessed the level of glycemia in the capillary blood, glycosylated hemoglobin (HbA1c, %), and daily monitoring of glucose with the CGMS MiniMed Medtronic on different terms of pregnancy: 10–12, 22–24, and 32–34 weeks.

In our study, 62 pregnant women with T1DM used the standard intensified basal-bolus insulin therapy in the mode of multiple subcutaneous insulin injections (MPII) and 93 women used continuous subcutaneous insulin infusion by a portable dispenser (CSII)—insulin pump.

In 21 pregnant women, we studied the excretion of proinflammatory cytokines (IL-1β and MCP-1) and transforming growth factor (TGF-β1) in daily urine by enzyme immunoassay (ELISA) at 10–12, 22–24, and 32–34 weeks of pregnancy using tests of "Bender MedSystems GmbH," Austria.

In 42 children born on term of 38–40 weeks to mothers with T1DM, we estimated the weight, the Apgar score at birth, the need for resuscitation and frequency, and duration of hypoglycemia.

3 Statistical Analyses

Statistical analysis was held using standard STATISTICA package (version 8.0). Statistical significance of differences was assessed by probability of null hypothesis less than 0.05 ($p < 0.05$). Data in the text are presented as M (25.75) (where Me—median, and 25 and 75—interquartile range of the 25th and 75th percentiles). Intra- and intergroup differences were tested by Wilcoxon's signed-ranks and Mann–Whitney *U* tests, respectively.

4 Ethical Considerations

The study protocol was reviewed and approved by the local ethics committee, and written informed consent was obtained from all the patients prior to any medical procedure.

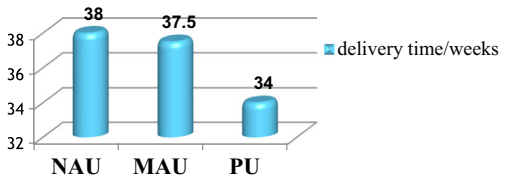

Fig. 1 The terms of delivery in pregnant women with T1DM using insulin therapy in the CSII mode with different levels of albuminuria

5 Results and Discussion

Analysis of pregnancy outcomes in the 155 women with T1DM with different levels of daily albuminuria receiving different types of insulin therapy showed that pregnant women with T1DM using MPII had premature delivery compared with pregnant women using continuous subcutaneous insulin infusion via an insulin dispenser (insulin pumps). All the pregnant women were matched for age and duration of T1DM (p 0.05). Women with normoalbuminuria using CSII had the ability to carry her pregnancy to term of physiological delivery—38 (37; 38.5) weeks of pregnancy; in the presence of microalbuminuria, the average time of delivery was 37.5 (35; 39) weeks of pregnancy. In the presence of proteinuria, the average time of delivery was 34 (32; 35) weeks of pregnancy (Fig. 1). At the same time, pregnant women with normoalbuminuria receiving MPII deliver earlier—at 37 (34; 38) weeks of pregnancy, in the patients with microalbuminuria, childbirth often began at 36 (33; 38) weeks of pregnancy, and if the pregnant woman had diabetic nephropathy with proteinuria, the average term of delivery was 31 (28; 33) weeks of pregnancy (Fig. 2).

Thus, the use of continuous subcutaneous insulin infusion in pregnant women with T1DM allows to prolong the pregnancy for 2–4 weeks as compared to the timing of delivery of pregnant women with T1DM receiving multiple subcutaneous injections of insulin. All the pregnant women using insulin in the MPII mode in the presence of microalbuminuria and proteinuria had premature deliveries (Table 1).

The change of insulin therapy for continuous subcutaneous insulin infusion using an insulin pump allows to achieve and maintain glycemic control throughout pregnancy [4]. The ability to program the dose of basal and bolus insulin depending on the time of day, the diet, physical activity, continually changing hormonal levels in pregnant women, the presence or absence of toxemia and preeclampsia, and intercurrent

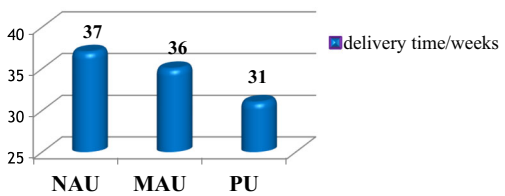

Fig. 2 The terms of delivery in pregnant women with T1DM using insulin therapy in the mode MPII with different levels of albuminuria

Table 1 The time of delivery depending on the mode of insulin administration and albumin excretion

Delivery time/weeks	NAU		MAU		PU	
	Insulin pump	MPII	Insulin pump	MPII	Insulin pump	MPII
Delivery at term 38–40 weeks, %	86.6 ($n = 48$)	71.4 ($n = 25$)	75.0 ($n = 20$)	–	21.5 ($n = 3$)	–
Premature Delivery, %	13.4 ($n = 7$)	28.5 ($n = 10$)	15.0 ($n = 4$)	100 ($n = 14$)	78.5 ($n = 11$)	100 ($n = 13$)

diseases allows patients with diabetes to improve the quality of life, to lead an active lifestyle, and to prevent hypoglycemic and hyperglycemic episodes [2] (Fig. 3).

At the same time, by reducing glycemic variability and increasing the duration of normoglycemia during the day, it is possible to save and prolong pregnancy even with severe diabetic complications such as diabetic nephropathy with proteinuria.

It is well known that the reasons for premature delivery in women with T1DM are often severe preeclampsia, gestational toxicosis, chronic fetoplacental insufficiency, and intrauterine fetal hypoxia [3, 5]. When the duration of diabetes was longer than 10 years, pregnant women more likely to have symptoms of preeclampsia: in 15–37.5% cases, there is a hypertension; in 50% of cases—edema; and in almost 90–100% of cases—proteinuria (Fig. 4). Based on data from this study, we can say that a group of pregnant women with the duration of T1DM more than 10 years and proteinuria had delivered prematurely.

We studied the excretion of proinflammatory cytokines (IL-1β and MCP-1) and transforming growth factor (TGF-β1) with daily urine in 21 pregnant women with T1DM to detect a possible relationship between the urinary level of these markers and the timing of delivery. The pregnant women with T1DM were matched for age, duration of diabetes, and the degree of compensation of carbohydrate metabolism ($p > 0.05$). All the pregnant women with T1DM included in these two groups had no obstetrical pathology. Two pregnant women with T1DM received drug therapy for hypertension with methyldopa. Term of delivery before 38 weeks of pregnancy was seen as early delivery, delivery at term determined as delivery at 38–40 weeks of pregnancy.

Studying the urinary excretion levels of transforming growth factor-β1 in pregnant diabetic women with early delivery, we found that its level in the first trimester of pregnancy (1320.6 (1000.2, 2671.2) pg/ml) is higher than that of pregnant women who gave delivery at term (621 3 (444, 1013.4) pg/ml, $p = 0.07$); in the second trimester, pregnant women who gave birth prematurely also have higher levels of transforming growth factor-β1 (2744.7 (1404, 7557.1) pg/ml) than the pregnant women who delivered at term (1049.6 (487.2, 1497.6) pg/ml, $p = 0.002$); in the third trimester, the level of urinary excretion of TGF-β1 in pregnant women who gave birth prematurely is significantly higher (3900.0 (1386, 4647) pg/ml) compared to the level in the group of pregnant women with delivery at term (1088 (605.4, 1205.7) pg/ml, $p = 0.002$) (Fig. 5).

Urinary excretion of proinflammatory cytokines (IL-1β and MCP-1) in pregnant women with T1DM also significantly increased in the group of the pregnant women with pre-term delivery, compared with the pregnant women who gave birth at 38–40 weeks (Figs. 6 and 7). At the same time, the level of excretion of IL-1β, monocyte chemoattractant protein-1, and transforming growth factor-β1 in healthy pregnant women is comparable with the level of excretion in the women with T1DM who gave birth at term, but significantly lower compared with excretion of these factors in the pregnant women with T1DM who gave birth prematurely.

The analysis of the dynamics of urinary albumin excretion throughout the pregnancy in diabetic women with different terms of delivery showed that out of seven pregnant women who gave birth prematurely (before 38 weeks of pregnancy), two patients had normoalbuminuria throughout the whole pregnancy (Table 2). In two patients, the pregnancies terminated prematurely on the background of diabetic nephropathy deterioration (MAU stage) while initially, the pregnancy started with normal urinary albumin excretion. During pregnancy of one diabetic woman, the diabetic nephropathy progressed from MAU to PU. Two patients were diagnosed with diabetic nephropathy with proteinuria before pregnancy.

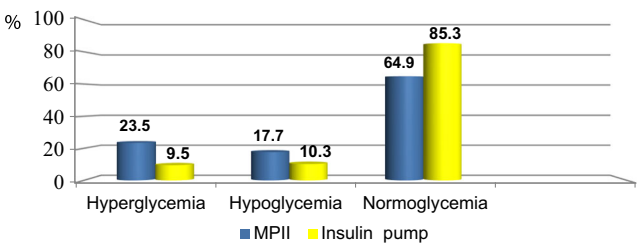

Fig. 3 Hyperglycemia, hypoglycemia, and normoglycemia (%) ratio in pregnant women with T1DM at MPII and after transfer to CSII

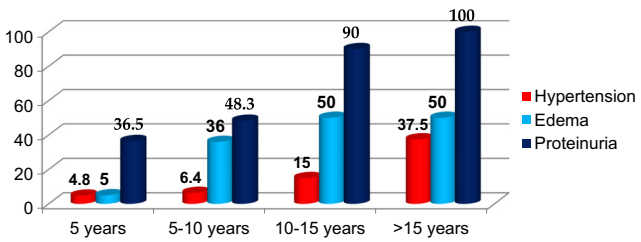

Fig. 4 Frequency of preeclampsia symptoms (hypertension, edema, proteinuria), depending on the duration of T1DM (%)

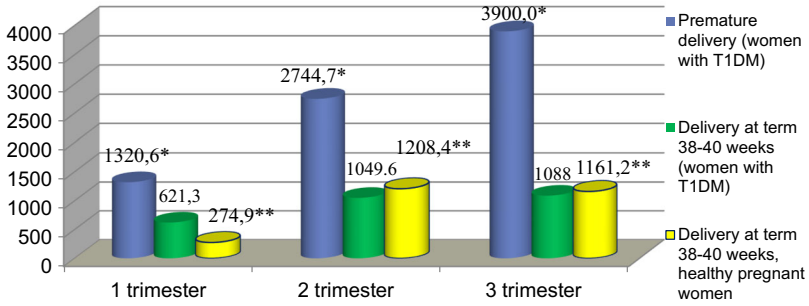

Fig. 5 Urinary excretion of transforming growth factor-β1 in pregnant women with T1DM with different terms of delivery in different trimesters of pregnancy

Note: * - significant difference ($p<0,05$) between groups of pregnant women with T1DM with the premature delivery and pregnant women with delivery at term; ** - significant difference ($p<0,05$) between the group of healthy pregnant women and pregnant women with T1DM who gave birth prematurely.

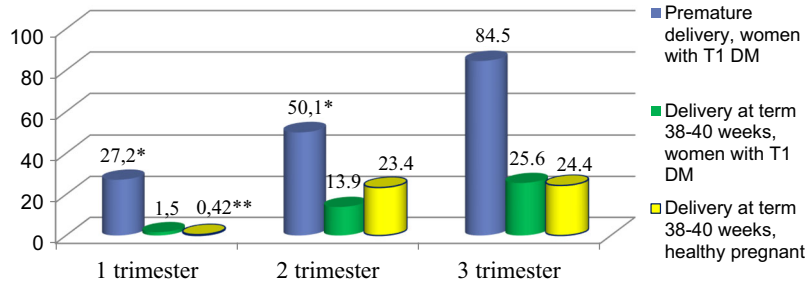

Fig. 6 Urinary excretion of proinflammatory cytokines (IL-1β) in pregnant women with T1DM with different terms of delivery in different trimesters of pregnancy

Note: * - significant difference ($p<0,05$) between groups of pregnant women with T1DM with the premature delivery and pregnant women with delivery at term; ** - significant difference ($p<0,05$) between the group of healthy pregnant women and pregnant women with T1DM who gave birth prematurely.

Four pregnant women received insulin at MPII mode; three—in the mode of CSII. It should be noted that the indication for premature delivery of all the pregnant women with T1DM was the development of preeclampsia.

Thus, all the pregnant women who gave birth at term ($n = 14$) at baseline and throughout the pregnancy had normal urinary albumin excretion. Out of these women, 12 were receiving insulin in CSII mode; two women in MPII mode.

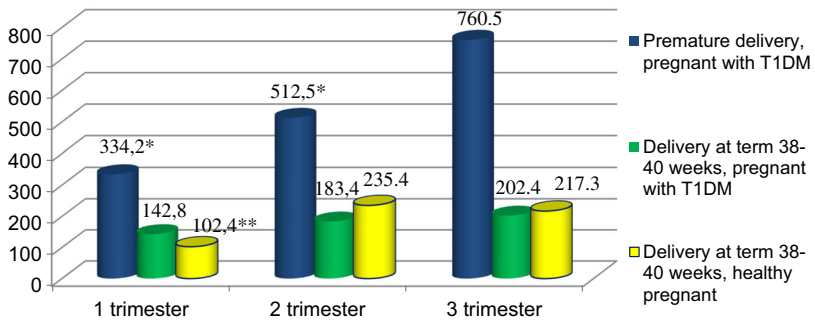

Fig. 7 Urinary excretion of monocyte chemoattractant protein-1 (MCP-1) in pregnant women with T1DM, with different terms of delivery in different trimesters of pregnancy

Note: * - significant difference ($p<0,05$) between groups of pregnant women with T1DM with the premature delivery and pregnant women with delivery at term; ** - significant difference ($p<0,05$) between the group of healthy pregnant women and pregnant women with T1DM who gave birth prematurely.

Table 2 Dynamics of urinary albumin excretion during pregnancy in women with T1DM with different terms of delivery

Premature delivery in women with T1DM ($n = 7$)		Delivery at term (38–40 weeks) in women with T1DM ($n = 14$)	
Excretion of albumin with urine before the pregnancy	Excretion of albumin with urine before delivery	Excretion of albumin with urine before the pregnancy	Excretion of albumin with urine before delivery
NAU ($n = 2$)	NAU	NAU ($n = 14$)	NAU ($n = 14$)
NAU ($n = 2$)	MAU	–	–
MAU ($n = 1$)	PU	–	–
PU ($n = 2$)	PU	–	–

Overall, the study of pregnancy outcomes in women with T1DM revealed that the pregnant women with premature delivery (before 38 weeks of pregnancy) had more than twofold increase in the excretion of IL-1β, monocyte chemoattractant protein-1, and transforming growth factor-β1 compared to the pregnant women who gave birth at term (38–40-week gestation), in all the trimesters of pregnancy. Furthermore, in the group of pregnant diabetic women with premature delivery, we observed the significant increase of these markers along with the progression of diabetic nephropathy. This was also found in women with normoalbuminuria throughout the pregnancy.

Elevated levels of proinflammatory cytokines (IL-1β and MCP-1) and TGF-β1, which are the mediators in the immune cascade of reactions that are running on the background of hyperglycemia and related to metabolic disorders [6], may possibly serve as a predictor of pre-term birth in pregnant women with T1DM, starting with the 1st trimester of pregnancy.

In 42 infants born at term of 38–40 weeks to mothers with T1DM, we estimated the weight and the Apgar score at birth, need for resuscitation, and the incidence of hypoglycemia. We allocated two study groups depending on the method of insulin administration: the first—18 infants born to mothers using MPII and the second—28 newborns of women who used CSII during pregnancy. Both the groups were comparable ($p > 0.05$) by the age of the mother, duration of diabetes, the degree of compensation, and stage of diabetic nephropathy.

In the group of women treated with MPII, the weight of newborns was 3615.0 (3512.5; 4142.5) grams, which was significantly higher than that in the group of newborns of mothers who received CSII—3060.0 (2900.0, 3707.5) grams ($p = 0.01$). Apgar scores between the two groups are statistically different: 7.5 (7.5, 8.0) points in the group of pregnant women in the MPII and 7.8 (7.5, 8.5) points in the CSII group ($p = 0.4$). The need for resuscitation in newborns in the group on MPII appeared in 20% of cases and was associated with asphyxia. In the group on CSII, resuscitation was not used in any child. Hypoglycemia in infants born to mothers who used MPII found in more than half of the children, in contrast to the newborns of mothers who used insulin in the form of CSII (64.3 and 22.2%, respectively) ($p = 0.04$) (Table 3).

The reduction of glycemia variability and achieving its stability during pregnancy by using insulin pump prevents the development of hyperinsulinemia in the fetus and hypoglycemia in newborn, and reduces the risk of macrosomia, severe fetal hypoxia, and acidosis [7].

6 Conclusions

Administration of insulin with a continuous subcutaneous insulin infusion via portable dispenser (CSII) reduces the percentage of pre-term deliveries, regardless the stage of diabetic nephropathy in pregnant women with T1DM. It improves the condition of infants born at term in women with T1DM using insulin pumps compared to that using multiple subcutaneous injections of insulin, which shows as rarer manifestations of diabetic fetopathy as macrosomia and hypoglycemia in newborns, and reduced need for resuscitation in newborns. Elevated levels of urinary excretion of proinflammatory cytokines (IL-1β and MCP-1) and TGF-β1, which are the mediators in the immune cascade of reactions that are running on the background of hyperglycemia and related metabolic disorders, may possibly serve as a predictor of preterm delivery

Table 3 Status of infants born at term in women with T1DM depending on the mode of administration of insulin in the mother

Parameters	Insulin pump	MPII	p
The weight of the newborns at birth, g	3060.0 (2900.0; 3707.5)	3615.0 (3512.5; 4142.5)	0.01
Assessment according to the Apgar score, points	7.8 (7.5; 8.5)	7.5 (7.5; 8.0)	0.4
The need for resuscitation measures, %	–	20	–
Hypoglycemia in newborns, %	22.2	64.3	0.04

in pregnant women with T1DM starting from the early stages of pregnancy.

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Compliance with Ethical Standards

Competing Interests The authors declare that they have no competing interests.

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