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The impact of diabetes mellitus on the course and outcome of pregnancy during a 5-year follow-up

Uticaj dijabetesa melitusa na tok i ishod trudnoće u 5-godišnjem praćenju

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Abstract

Background/Aim. Women with diabetes, especially diabetes type 1, have worse pregnancy outcomes, as well as increased incidence of spontaneous abortions, pre-eclampsia, fetal macrosomia, preterm delivery, congenital anomalies and perinatal mortality. The aim of this study was to analyze the course and outcome of pregnancy in the patients with diabetes in relation to the group of healthy women regarding preterm delivery, perinatal morbidity and mortality. Also, the aim was to compare pregnancy outcomes in the patients with pre-existing diabetes type 1 and the patients with gestational and diabetes type 2. **Methods.** This retrospective study included 156 diabetic women treated at the Clinic of Endocrinology, Diabetes and Metabolic Diseases and Gynecology and Obstetrics Clinic of the Clinical Center of Vojvodina from 2006 to 2010. There were 94 patients with gestational diabetes, 48 with type 1 diabetes, and 14 patients with type 2 diabetes. The control group included 106 healthy women hospitalized at the Gynecology and Obstetrics Clinic. **Results.** The women with type 1 diabetes presented with a statistically significantly higher incidence of cesarean section than those without diabetes, or with type 2 or gestational diabetes ($p < 0.0001$); the women with type 1 diabetes delivered at an earlier week of gestation (WG) in regard to women without diabetes, or with type 2 or gestational diabetes ($p = 0.0017$ and $p = 0.02$, respectively). The incidence of perinatal morbidity: hypoglycemia ($p < 0.001$), pathological jaundice ($p = 0.0021$), and other neonatal pathologies at birth ($p = 0.0031$), was statistically significantly higher and Apgar scores after 1 minute ($p = 0.0142$) and after 5 minutes ($p = 0.0003$) were statistically significantly lower in the patients with diabetes compared to the healthy women. The women with type 2 and gestational diabetes were statistically significantly older than those with type 1 diabetes ($p = 0.001$). A higher incidence of fetal macrosomia in the women with gestational and type 2 diabetes compared to those with type 1 diabetes was at the borderline of statistical significance ($p = 0.07$), whereas the incidence of hypoglycemia of newborn was statistically significantly higher in the patients with type 1 diabetes ($p < 0.0001$). Glycosylated hemoglobin (HbA1c) levels were statistically significantly higher in the diabetic women giving birth during and before the week of gestation 36 ($p = 0.0087$), but there were no differences in HbA1c levels in regard to fetal macrosomia ($p = 0.45$) and congenital abnormalities ($p = 0.32$). **Conclusion.** The results of our study show a higher incidence of perinatal fetal morbidity (hypoglycemia, jaundice, respiratory distress syndrome) in the patients with type 1, type 2 and gestation diabetes than in the healthy controls. Also, we found a higher incidence of cesarean section in the patients with type 1 diabetes than in those with type 2, gestation diabetes and healthy controls. Although delivery in the patients with type 1, type 2 and gestational diabetes was completed approximately one to two weeks earlier compared to the healthy controls there was no statistically significant difference in the incidence of preterm delivery (≤ 36th week of gestation) between the women with diabetes and healthy controls. Preterm delivery associated with poorer glycaemic control reflected through higher values of HbA1c in third trimester. Risks from adverse pregnancy outcomes may be reduced to minimum by adequate preconception counseling of diabetic patients and early diagnosis of diabetes in pregnancy, in order to achieve glycemic control during organogenesis and within pregnancy and through the teamwork of endocrinologists, gynecologists and pediatricians.

Key words:
diabetes mellitus; pregnancy; fetal development; obstetric labor, premature; morbidity.

Apstrakt

Uvod/Cilj. Žene sa dijabetesom, a posebno one sa tipom 1, imaju lošiji ishod trudnoće u odnosu na žene bez dijabetesa, pre svega zbog veće učestalosti spontanih pobačaja, preekalmpsije, makrozomije ploda, prevremenog porođaja, kongenitalnih malformacija i perinatalnog mortaliteta ploda. Cilj ispitivanja bio je analiza toka i ishoda trudnoće kod bolesnica sa dijabetesom u odnosu na kontrolnu grupu zdravih žena, a u odnosu na prevremeni

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porođaj, perinatalni morbiditet i mortalitet, kao i ishod trudnoće kod bolesnica sa preegzistentnim dijabetesom tipa 1 u odnosu na bolesnice sa gestacijskim i dijabetesom tipa 2. **Metode.** Retrospektivno istraživanje sprovedeno je na 156 žena sa dijabetesom lečenih na Klinici za endokrinologiju, dijabetes i bolesti metabolizma i Klinici za ginekologiju i akušerstvo Kliničkog centra Vojvodine tokom perioda 2006–2010. godine. Gestacijski dijabetes imalo je 94 ispitanice, dijabetes tip 1 48, a dijabetes tip 2 14 ispitanica. Kontrolnu grupu činilo je 106 zdravih žena hospitalizovanih u Klinici za ginekologiju i akušerstvo tokom 2011. i 2012. godine. **Rezultati.** Kod trudnica sa dijabetesom tipa 1 porođaj se statistički značajno češće završavao carskim rezom u odnosu na trudnice bez dijabetesa i trudnice sa dijabetesom tipa 2 i gestacijskim dijabetesom ($p < 0,0001$), kao i ranijoj nedelji gestacije u odnosu na trudnice bez dijabetesa i trudnice sa tipom 2 i gestacijskim dijabetesom ($p < 0,0017$, $p = 0,02$). Kod trudnica sa dijabetesom statistički značajno veća bila je učestalost hipoglikemije ($p < 0,0001$), patološkog ikterusa ($p = 0,0021$) i druge patologije ploda na rođenju ($p = 0,0031$) u odnosu na kontrolnu grupu zdravih trudnica uz lošije vrednosti Apgar scora u 1. minuti kod novorođenčadi ($p = 0,0142$) i 5. minutu ($p = 0,0003$). Trudnice sa dijabetesom tipa 2 i gestacijskim dijabetesom bile su statistički značajno starije nego trudnice sa dijabetesom tipa 1 ($p = 0,001$). Veća učestalost makrozomije ploda kod trudnica sa gestacijskim i dijabetesom tipa 2 u odnosu na tip 1 bila je na granici statističke značajanosti ($p = 0,07$), dok su hipoglikemije bile statistički značajno češće u grupi trudnica sa dijabetesom tipa 1 ($p < 0,0001$). Vrednosti glikozilovanog hemoglobina (HbA1c) bile su statistički značajno više kod trudnica sa dijabetesom porođenih tokom i pre 36. gestacijske nedelje ($p = 0,0087$), bez razlike u vrednostima HbA1c u odnosu na makrozomiju ploda ($p = 0,45$) i kongenitalne malformacije ($p = 0,32$). **Zaključak.** Rezultati našeg ispitivanja pokazuju višu učestalost perinatalnog fetalnog morbiditeta (hipoglikemije, ikterusa, respiratornog distres sindroma) kod bolesnica sa tipom 1, tipom 2 i gestacijskim dijabetesom u odnosu na kontrolnu grupu zdravih trudnica. Takođe, kod trudnica sa dijabetesom tipa 1 porođaj se češće završavao carskim rezom nego kod trudnica sa dijabetesom tipa 2 i gestacijskim dijabetesom i zdravih trudnica. Iako se trudnoća kod trudnica sa dijabetesom tipa 1, tipa 2 i gestacijskim dijabetesom završavala jednu do dve nedelje ranije nego kod zdravih trudnica, nije bilo statistički značajne razlike u učestalosti prevremenog porođaja (≤ 36. nedelje gestacije) između žena sa dijabetesom i zdravih trudnica. Prevremeni porođaj bio je povezan sa lošijom glikemijskom kontrolom iskazanom kroz više vrednosti glikoziliranog hemoglobina u trećem trimestru. Rizik od neželjenih ishoda trudnoće može se redukovati adekvatnim prekoncepcijskim savetovanjem bolesnica sa dijabetesom i pravovremenom dijagnozom dijabetesa u trudnoći, uz imperativ postizanja gotovo normoglikemijskog stanja kako u periodu organogeneze, tako i tokom cele trudnoće uz timski rad endokrinologa, ginekologa i pedijatra.

Ključne reči:
diabetes melitus; trudnoća; trudnoća, razvoj fetusa; porođaj, prevremeni; morbiditet.

Introduction

Impaired glucose metabolism is among the most common pregnancy-associated metabolic disorders occurring in 3–10% of all pregnancies. Gestational diabetes accounts for 88% of cases of diabetes in pregnancy, pre-existing diabetes type 2 accounts for 8%, and pre-existing type 1 for 4% [1, 2]. Epidemiological studies show that the prevalence of diabetes among reproductive-age women is increasing, probably due to insufficient physical activity, inadequate diet, and a great number of obese children and adolescents. That is why today more attention is paid to the problem of pre-existing diabetes type 2 in pregnancy and increasing incidence of gestational diabetes [3–5]. Up to the discovery and use of insulin, only a small number of pregnancies in diabetic women have been reported. In the 80's of the last century, risks of diabetes-related complications during pregnancy were 50% higher than in healthy pregnant women [2]. Although current insulin therapy has improved the quality of glycemic control, women with diabetes, especially those with type 1 diabetes compared with women without diabetes, have worse pregnancy outcomes, as well as increased incidence of spontaneous abortions, pre-eclampsia, fetal macrosomia, preterm delivery, congenital anomalies and perinatal mortality [5–8]. Numerous studies have shown that the incidence of adverse pregnancy outcomes in women with type 2 diabetes is the same as in women with type 1 diabetes, and worse than in the population of healthy women [3, 6, 7]. Gestational diabetes is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [1, 2]. The most important risk factors for gestational diabetes include sedentary lifestyle, unbalanced diet, poor physical activity, obesity, family history of diabetes, and previous history of macrosomia. That is why oral glucose tolerance test (OGTT) is recommended to all pregnant women at risk for gestational diabetes. Women are recommended to take a 2-hour OGTT with 75 grams of glucose between their 24th and 28th week of pregnancy, and those at high risk of establishing pregnancy as well [1, 4, 5]. For diagnosis of gestational diabetes it is sufficient to detect only one pathological value during 2 hour OGTT: blood glucose ≥ 5.1 mmol/L at the start, ≥ 10.0 mmol/L after first hour and ≥ 8.5 mmol/L after second hour of the test. In diagnosis of pre-existing diabetes mellitus (type 1 and type 2) a few criteria are in the use: fasting blood glucose ≥ 7.0 mmol/L, postprandial blood glucose ≥ 11.1 mmol/L and/or glycosylated hemoglobin (HbA1c) ≥ 6.5% [1].

Many studies showed that adverse pregnancy outcomes (congenital anomalies, spontaneous abortions and perinatal mortality) were associated with poor glycemic control in the early pregnancy [6–8]. The critical period is before 7 weeks of gestation, that is during organogenesis. Preconception counseling is of utmost importance aiming at good glycemic control during preconception and in the early weeks of gestation (WG). According to the recommendations of the American

Diabetes Association, target glycemic control parameters are clearly defined: fasting blood glucose < 5.3 mmol/L; 1 h postprandial blood glucose < 7.8 mmol/L; 2h postprandial blood glucose < 6.7 mmol/L; HbA1c between 6.0% and 6.5% [1].

There are clearly defined protocols and recommendations for monitoring diabetic pregnant women, depending on the gestational age of pregnancy [2, 5, 9]. In the first trimester it is recommended to attend control of an endocrinologist and gynecologist once a month, to control HbA1c value every 4–6 weeks, regular day-night blood glucose profile control (glycemia daily inspection before each meal and at bedtime, and also 2–3 times weekly 1–2 hours after each meal and during the night), control of TSH, free T4 (before conception and in the first trimester), control of urea, creatinine, 24 hour proteinuria, complete blood count, urine, arterial tension and cardiovascular status, monitoring body weight, and ophthamological examination.

In the second, and especially in the third trimester controls become more frequent. Monitoring of glycemic profile becomes daily and control of glycosuria, acetonuria and HbA1c, as well as control of endocrinologist is recommended firstly every four weeks and later every two weeks. Control of urea, creatinine, 24 hour proteinuria, hepatogram (in suspected preeclampsia), urine, arterial tension, cardiovascular status and weight control is recommended at each visit to the doctor. Ophthalmological examination is obliged in the week of gestation 28, and in the presence of retinopathy in the period between the week of gestation 16 and 20.

Pregnant women with diabetes should be offered ultrasound monitoring of fetal growth and amniotic fluid volume every 4 weeks from 28 to 36 weeks. Women with diabetes and macrovascular disease and/or nephropathy will require an individualised approach to monitoring fetal growth and wellbeing [2, 5].

Diabetes mellitus is not an indication for cesarean section unless there are some other obstetric indications (fetal macrosomia, feto-pelvic disproportion, etc.) or maternal complications (advanced chronic complications of diabetes, eclampsia). But, evidence shows that women with diabetes are more likely to undergo induction of labour and/or caesarean section at 38–39 week of gestation than women without diabetes to prevent stillbirth and shoulder dystocia, which are associated with fetal macrosomia [5].

Elective birth should be offered after completed the week of gestation 38 in the cases of a good metabolic control of diabetes, absence of abnormalities of the fetus, respiratory distress syndrome and other obstetric and maternal complications. Preterm delivery is indicated in cases of poor metabolic control of diabetes, fetal growth acceleration or intrauterine fetal growth retardation, fetal respiratory distress syndrome, polyhydramnios or other obstetric and/or maternal complications [3, 5].

The aim of this study was to analyze the components of maternal and perinatal morbidity in pregnant women with diabetes in relation to the group of healthy pregnant women and separately among the groups with pre-existing type 1 diabetes and gestational and type 2 diabetes, as well as to assess a correlation of components of metarnal and perinatal outcomes in regard to glycemic control, duration of diabetes and chronic complications.

Methods

This retrospective study included 156 diabetic women in the week of gestation 28–32 treated at the Clinic of Endocrinology, Diabetes and Metabolic Diseases and Gynecology and Obstetrics Clinic of the Clinical Center of Vojvodina, Novi Sad, from 2006 to 2010. There were 94 patients with gestational diabetes, 48 with type 1 diabetes, and 14 with type 2 diabetes. Considering a small number of women with type 2 diabetes diagnosed with diabetes mellitus before pregnancy and treated only with diet and/or metformin therapy, bearing in mind similar etiopathogenetic mechanism as gestational diabetes, we included them in the same group for statistical analysis. The control group included 106 healthy women also in the week of gestation 28–32 giving birth at the Gynecology and Obstetrics Clinic of the Clinical Center of Vojvodina during 2011 and 2012. The control group was randomly selected among healthy pregnant women hospitalized in 2011 and 2012 considering the fact that socioeconomic living conditions, health care system and management of pregnancy were not changed in relation to the period 2006–2010. The following parameters were studied: maternal age, arterial hypertension (blood pressure over 140/90 mmHg or use of antihypertensive therapy), and pre-eclampsia during pregnancy (the diagnosis of pre-eclampsia was made after the week 20 of gestation in cases with a arterial hypertensia and proteinuria > 300 mg/24 h), type of delivery (vaginal or cesarean), gestational age at delivery, and the number of spontaneous abortions in previous pregnancies. Neonatal characteristics included Apgar scores, birth weight, birth length, hypoglycemia, jaundice or any other perinatal morbidity and perinatal mortality. These groups were also examined for differences in HbA1c levels, whereas in patients with diabetes type 1 types of insulin therapy and incidence of microvascular complications of diabetes were investigated as well. Statistical data processing was carried out by *t*-test and test of proportion.

Results

Table 1 shows perinatal and maternal outcomes among the pregnant women with type 1 diabetes and the healthy control. The incidence of delivery by cesarean section was statistically significantly higher compared to the non-diabetic women ($p < 0.0001$), and the women with type 1 diabetes were more likely to deliver earlier than women without diabetes (37.9 weeks of gestation *vs* 39.09 weeks of gestation, respectively, $p < 0.0017$). In addition, perinatal morbidity was statistically significantly higher in the diabetic women compared to the healthy controls: hypoglycemia ($p < 0.001$), pathological jaundice ($p = 0.0021$), and other causes of neonatal morbidity ($p = 0.0031$). Accordingly, Apgar scores after 1 minute ($p = 0.0142$) and after 5 minutes ($p = 0.0003$)

Table 1

Perinatal and maternal outcomes observed among the pregnant women with type 1 diabetes and the healthy controls

Parameters	Patients with type 1 diabetes	Healthy controls	*p*
Age (years), $\bar{x} \pm SD$	28.83 ± 5.13	30.57 ± 5.15	0.0537
Arterial hypertension (%)	8.51	10.38	0.9450
Pre-eclampsia (%)	2.13	6.60	0.4443
Spontaneous abortions in previous pregnancies (%)	25.40	14.15	0.1422
Gestational age at delivery (weeks), $\bar{x} \pm SD$	37.90 ± 1.55	39.09 ± 2.36	0.0017
Delivery ≤ 36 WG (%)	14.58	9.43	0.5047
Cesarean section (%)	78.26	35.85	< 0.0001
Apgar score I, $\bar{x} \pm SD$	7.91 ± 1.33	8.57 ± 1.61	0.0142
Apgar score II, $\bar{x} \pm SD$	8.78 ± 0.97	9.39 ± 0.93	0.0003
Birth weight (g), $\bar{x} \pm SD$	3463.62 ± 576.57	3396.60 ± 697.28	0.5617
Birth length (cm), $\bar{x} \pm SD$	50.32 ± 2.41	49.70 ± 3.24	0.2380
Fetal hypoglycemia (%)	52.17	1.88	< 0.0001
Fetal jaundice (%)	50.00	23.58	0.0021
Other fetal morbidity at birth (%)	68.75	41.51	0.0031
Congenital malformations (%)	6.83	13.21	0.3755
Fetal macrosomia (%)	10.42	16.98	0.4157
Stillbirth (%)	4.20	0.00	0.1743

were statistically significantly lower in the diabetic than in non-diabetic women. There were no differences in birth weight and birth length of newborns between the two examined groups. However, in regard to birth weight, one must bear in mind that pregnancies in the women with diabetes completed on the average 1–2 weeks earlier than in the women without diabetes, so it may be assumed that the newborns of the women with diabetes would have had a statistically significantly higher birth weight if they had been born in the same week of gestation as the newborns of the healthy controls. There were no statistically significant differences between these two groups of women in relation to the incidence of congenital abnormalities, spontaneous abortions in previous pregnancies and stillbirths.

complications, lower glucose control, but these differences were not statistically significant. In addition, there were no statistically significant differences regarding the incidence of cesarean section and lower gestational age at birth, birth weight and birth length. A statistically significant difference was only found in Apgar score value in the 1 minute (p = 0,036).

Table 3 shows perinatal and maternal outcomes observed among the pregnant women with type 1 diabetes compared with women with type 2 diabetes and gestational diabetes.

The patients with type 2 diabetes and gestational diabetes were statistically significantly older than the patients with type 1 diabetes (p = 0.001). The glycemic control was better in the

Table 2

Characteristics of the patients with type 1 diabetes related to perinatal fetal morbidity

Parameters	Without fetal morbidity	With fetal morbidity	*p*
Age (years), $\bar{x} \pm SD$	29.93 ± 4.73	28.36 ± 5.29	0.3426
Duration of diabetes (years), $\bar{x} \pm SD$	8.00 ± 5.71	11.91 ± 6.86	0.0608
Insulin analogue therapy (%)	33.33	45.45	0.9470
Microvascular diabetic complications (%)	13.33	25.81	0.5614
HbA_1c (%), $\bar{x} \pm SD$	6.48 ± 0.90	7.10 ± 1.14	0.1139
Arterial hypertension (%)	6.67	9.37	0.8014
Pre-eclampsia (%)	6.67	0.00	0.6945
Spontaneous abortions in previous pregnancies (%)	26.67	24.24	0.8577
Gestational age at birth (weeks), $\bar{x} \pm SD$	38.09 ± 0.81	37.81 ± 1.81	0.5712
Cesarean section (%)	85.71	75.00	0.6731
Apgar score I, $\bar{x} \pm SD$	8.47 ± 0.99	7.61 ± 1.38	0.0367
Apgar score II, $\bar{x} \pm SD$	9.00 ± 0.53	8.68 ± 1.11	0.2970
Birth weight (g), $\bar{x} \pm SD$	3362.67 ± 386.97	3510.94 ± 646.85	0.4172
Birth length (cm), $\bar{x} \pm SD$	50.07 ± 1.83	50.44 ± 2.66	0.6292

Table 2 shows characteristics of the patients with type 1 diabetes related to perinatal fetal morbidity. The women whose infants exhibited perinatal morbidity (hypoglycemia, jaundice, diabetic fetopathy, respiratory distress syndrome) had longer duration of diabetes, higher incidence of chronic

patients with type 2 diabetes and gestational diabetes than in the patients with type 1 diabetes (p < 0.0001). The incidence of hypertension and pre-eclampsia was higher in the patients with type 2 diabetes and gestational diabetes, but the difference was not statistically significant. The incidence of cesar-

Table 3

Perinatal and maternal outcomes observed among the pregnant women with type 1 diabetes compared with the women with type 2 and gestational diabetes

Parameters	Patients with type 1 diabetes	Patients with type 2 diabetes and gestational diabetes	*p*
Age (years), $\bar{x} \pm SD$	28.83 ± 5.13	31.89 ± 5.32	0.0010
HbA_1c (%), $\bar{x} \pm SD$	6.85 ± 1.14	5.85 ± 0.79	< 0.0001
Arterial hypertension (%)	8.51	15.32	0.3701
Pre-eclampsia (%)	2.13	4.54	0.7895
Spontaneous abortions in previous pregnancies (%)	25.40	17.86	0.3816
Gestational age at delivery (weeks), $\bar{x} \pm SD$	37.90 ± 1.55	38.50 ± 1.19	0.0093
Delivery ≤ 36 WG (%)	14.58	5.35	0.1004
Cesarean section (%)	78.26	41.28	0.0001
Apgar score I, $\bar{x} \pm SD$	7.91 ± 1.33	8.10 ± 1.16	0.3760
Apgar score II, $\bar{x} \pm SD$	8.78 ± 0.97	8.93 ± 0.91	0.3616
Birth weight (g), $\bar{x} \pm SD$	3463.62 ± 576.57	3570.72 ± 579.48	0.2892
Birth length (cm), $\bar{x} \pm SD$	50.32 ± 2.41	50.58 ± 2.18	0.5077
Fetal hypoglycemia (%)	52.17	16.51	< 0.0001
Fetal jaundice (%)	50.00	49.54	0.9017
Other fetal morbidity at birth (%)	68.75	45.54	0.0117
Congenital malformations (%)	6.83	7.14	0.7896
Fetal macrosomia (%)	10.42	24.11	0.0770
Stillbirth (%)	4.20	0.00	0.1721

ean section ($p = 0.0001$) and completion of pregnancy 1–2 weeks before full-term ($p = 0.0093$) were statistically significantly higher in the patients with type 1 diabetes than in those with type 2 and gestational diabetes. Perinatal morbidity was statistically significantly higher in the patients with type 1 diabetes, especially hypoglycemia ($p < 0.0001$). There were no statistically significant differences in relation to birth weight, birth length, and Apgar scores of newborns between the patients with type 1 diabetes and those with type 2 diabetes and gestational diabetes. The incidence of fetal macrosomia was higher in the patients with gestational and type 2 diabetes (24.11%) than in those with type 1 diabetes (10.4%), that is considered as borderline statistical significance. The incidence of preterm delivery was higher in the patients with type 1 diabetes (14.58%) in relation to the patients with gestational and type 2 diabetes (5.35%), but the difference was not statistically significant. In addition, there was no statistically significant difference in the incidence of congenital abnormalities and spontaneous abortions in previous pregnancies between the patients with diabetes type 1 and those with diabetes type 2 and gestational diabetes.

Table 4 shows perinatal and maternal outcomes observed among the pregnant women with type 2 diabetes and gestational diabetes in relation to the healthy controls.

There were no statistically significant age related differences between the patients with diabetes and healthy controls. There were also no statistically significant differences in the incidence of hypertension, pre-eclampsia and cesarean

Table 4

Perinatal and maternal outcomes observed among the pregnant women with type 2 diabetes and gestational diabetes in relation to the healthy controls

Parameters	Patients with type 2 and gestational diabetes	Healthy controls	*p*
Age (years), $\bar{x} \pm SD$	31.89 ± 5.32	30.57 ± 5.15	0.0643
Arterial hypertension (%)	15.32	10.38	0.3762
Pre-eclampsia (%)	4.54	6.60	0.7126
Cesarean section (%)	41.28	35.85	0.4941
Spontaneous abortions in previous pregnancies (%)	17.86	14.15	0.5747
Delivery ≤ 36 WG (%)	5.35	9.43	0.3708
Gestational age at delivery (weeks), $\bar{x} \pm SD$	38.50 ± 1.19	39.09 ± 2.36	0.0197
Apgar score I, $\bar{x} \pm SD$	8.10 ± 1.16	8.57 ± 1.61	0.0138
Apgar score II, $\bar{x} \pm SD$	8.93 ± 0.91	9.39 ± 0.93	0.0003
Birth weight (g), $\bar{x} \pm SD$	3570.72 ± 579.48	3396.60 ± 697.28	0.0457
Birth length (cm), $\bar{x} \pm SD$	50.58 ± 2.18	49.70 ± 3.24	0.0190
Fetal hypoglycemia (%)	16.51	1.88	0.0005
Fetal jaundice (%)	49.54	23.58	0.0001
Other fetal morbidity at birth (%)	45.54	41.51	0.6433
Congenital malformations (%)	7.14	13.21	0.2069
Fetal macrosomia (%)	24.11	16.98	0.2574
Stillbirth (%)	0.00	0.00	–

section between these two groups. In the patients with type 2 diabetes and gestational diabetes, pregnancies ended at the week of geastation 38.5, that was statistically significantly earlier compared to the control group – the week of gestation 39.09 (p = 0.02). However, Table 4 also shows that the patients with diabetes exhibited a statistically significantly higher incidence of hypoglycemia (p = 0.0005), pathological jaundice (p = 0.0001), birth weight (p = 0.0457), and birth length (p = 0.019), first minute Apgar score (p = 0.0138), and 5 minute Apgar score (p = 0.0003), compared to healthy controls. Nevertheless, we should keep in mind that pregnant women with diabetes completed their pregnancies on the average one week earlier than the healthy controls, which probably affected lower incidence of fetal macrosomia.

Table 5 shows HbA1c values in relation to birth weight, week of gestation at delivery and congenital anomalies among the pregnent women with diabetes.

Table 5

HbA_1c as a parameter of glycemic control, among the pregnant women with diabetes (type 1, type 2 and gestational) in relation to birth weight, week of gestation (WG) at delivery and congenital anomalies

Parameters	HbA_1c (%), $\bar{x} \pm SD$	p
Birth weight > 4000 g	6.04 ± 0.88	0.4515
Birth weight < 4000 g	6.26 ± 1.07	
Delivery ≤ 36 WG	6.78 ± 1.31	0.0087
Delivery > 36 WG	6.18 ± 1.00	
With congenital anomalies	6.55 ± 1.47	0.3255
Without congenital anomalies	6.19 ± 1.01	

HbA_1c (%) – glycosylated hemoglobin

The women giving birth before the week of gestation 36 presented with a statistically significantly higher levels of HbA1c in relation to those completing their pregnancies after the week of gestation 36 (p = 0.0087), but there were no statistically significant differences in the levels of HbA1c in relation to macrosomia and congenital anomalies.

Discussion

In recent decades, due to current insulin therapy, monitoring of pregnant women with diabetes, counseling, preconception care and strict glucose control, the incidence of perinatal mortality and congenital abnormalities showed a significant reduction in diabetic patients [9–12]. However, despite improvements in glycemic control, the incidence of fetal macrosomia is still 20–40%. Fetal macrosomia is usually defined as birth weight over 95% [13, 14]. Macrosomia is recognized as a cause of fetal morbidity and mortality and despite relatively good glycemic control, its incidence is statistically higher in mothers with diabetes in relation to non-diabetic mothers. Macrosomia also increases maternal morbidity, frequently requiring instrumental delivery or cesarean section. It seems that accelerated fetal growth is determined by HbA1c levels in the first half of pregnancy and it continues despite improved glycemic control in the second half of pregnancy.

Maternal hyperglycemia leads to fetal hyperglycemia and consequently to fetal pancreatic beta-cell hyperplasia. Poon et al. [15] investigated 33,602 women and found that infant birth weight was associated not only with pre-existing and/or gestational diabetes, but also correlated with maternal weight and height, and that it was higher in multipara in regard to nulipara. In our study, there were no statistically significant differences in infant birth weights of mothers with type 1 diabetes and those of healthy controls. This is partly a consequence of the fact that pregnancies in women with type 1 diabetes are completed on the average one or two weeks earlier compared to healthy controls. Our results show that the incidence of neonatal macrosomia was highest in patients with type 2 diabetes and gestational diabetes (24.11%) compared to patients with type 1 diabetes (10.5%) and healthy controls (16.98%), but these differences were not statistically significant. These results can be explained by the fact that on the average glycemic control in our diabetic patients (HbA1c of 6.5%) was satisfactory, and it is well-known that fetal macrosomia is mostly associated with high HbA1c levels in the second and third trimesters of pregnancy. This is certainly contributed by the fact that delivery in patients with diabetes type 1 is usually planned between the week of gestation 36 and 38 and particularly in those with obstetrically verified accelerated fetal growth. A higher incidence of fetal macrosomia in patients with type 2 diabetes and gestational diabetes than in patients with type 1 diabetes may be because fetal macrosomia is affected not only by diabetes, but also by maternal obesity, which is more often associated with type 2 diabetes and gestational diabetes.

During labor and birth process, infants of mothers with diabetes are at increased risk for neonatal hypoglycemia, due to interrupted glucose supply and hyperinsulinism [2, 16]. Perinatal stress is also associated with neonatal hypoglycemia, in part because of catecholamine and glycocorticoid-stimulated mobilization and depletion of glycogen stores. Reactive hypoglycemia occurs within 2 hours after childbirth and persists up to 72 hours, but may last up to one week. Up to 50% of infants of mothers with type 1 diabetes experience hypoglycemia after birth. The results of our study are in accordance with these results showing that the incidence of neonatal hypoglycemia was 52% in mothers with type 1 diabetes, and 16.5% in mothers with type 2 diabetes or gestational diabetes. Both groups of diabetic mothers presented with a statistically significantly higher incidence of neonatal hypoglycemia compared to healthy controls without recorded hypoglycemia. Hrabovski et al. [16] also established a higher incidence of hypoglycemia, hypocalcemia and hypomagnesemia in infants of diabetic mothers compared to healthy controls.

The incidence of hypoglycemia is higher in macrosomic infants, but also in infants with low birth weight in relation to infants with normal birth weight. Neonatal hypoglycemia in infants small-for-date is the consequence of intrauterine growth retardation, often found in mothers with long-term diabetes and chronic vascular complications [2, 17, 18]. Newborn infants of diabetic mothers are also at increased risk of hyperbilirubinemia, which is explained by increase in the red blood cell count and mass, ineffective erythropoiesis and relative immaturity of hepatic conjugation and bilirubin excretion [2, 17, 18]. Both groups of diabetic women (type 1 and type 2 or gestational diabetes) presented with 50% of pathological neonatal jaundice, which is statistically significant in regard to healthy controls. These results are in agreement with the results of numerous previous studies, which confirmed the occurrence of pathological jaundice in neonates of diabetic women [17, 18].

The perinatal mortality is about five times higher in women with diabetes than in those without diabetes. Apart from carbohydrate metabolism disorders, diabetes is also associated with metabolic disorders involving fats, proteins, and amino acids, all of which inevitably affects fetal gene expression and increases teratogenicity. Risks of fetal death are certainly associated with maternal obesity, hypertension, advanced age and long-term diabetic complications [19, 20]. In our study, stillbirths were recorded only in patients with type 1 diabetes (4.2%), whereas the percentage of stillbirths in previous pregnancies was 1.7%, that was not statistically significant in relation to healthy controls and patients with type 2 diabetes and gestational diabetes, where the percentage of stillbirths in previous pregnancies was 0.9% and there were no recorded stillbirths in actual pregnancies. Spontaneous abortion is the best indicator of glycemic control in the preconception period and the early weeks of pregnancy. Investigations have documented that HbA1c levels above 11% increase risks of early spontaneous abortions by over 40% [21, 22] Although the incidence of spontaneous abortions was higher in patients with type 1 diabetes compared to patients with gestational, and type 2 diabetes, and healthy controls, the difference was not statistically significant. The incidence of congenital malformations is 3–5 times higher in women with pre-existing diabetes than in healthy controls, and there is no difference between patients with type 1 and type 2 diabetes. Congenital anomalies often cause stillbirth, especially cardiovascular anomalies and neural tube defects. However, according to the same data, maternal diabetes alone is not a predictive factor of specific anomalies [2, 21]. Although literature data mostly suggest that the incidence of congenital anomalies is higher in women with diabetes, our study showed no statistically significant differences in relation to the healthy controls [21, 22]. HbA1c levels were higher in women with fetal congenital abnormalities in regard to those without them, but the difference was not statistically significant. Major congenital malformations are most commonly associated with hypeglycemia in the preconception period and during organogenesis, but some authors reported about certain nervous system malformations associated with hypoglycemia in the first trimester. Preterm births are closely associated with perinatal mortality and morbidity. One third of preterm births are among mothers with pregestational diabetes. It is believed that the percentage of preterm deliveries (spontaneous and induced) in women with diabetes type 1 is about 45%. The most important predictive factors for preterm delivery include poor glycemic control and vascular complications (pre-eclampsia and nephropathy) [23]. In our study, there was statistically significantly poorer glycemic control in the women which gave birth before the week of gestation 36, and that matches with literature data [23]. Type 1 diabetic patients had more frequent preterm delivery and the most of the cases occurred between the week of gestation 34–36, in regard to patients with type 2 and gestational diabetes and healthy subjects, but without a statistically significant difference. The Confidential Enquiry into Maternal and Child Health (CEMACH) has also reported that the preterm delivery rate is 5 times higher in patients with type 1 and type 2 diabetes compared to general population [5]. About 2/3 of preterm deliveries are medically induced, most often due to fetal complications. The occurrence of hypertension in patients with diabetes type 1 is commonly the consequence of the onset and/or progression of diabetic nephropathy, whereas patients with diabetes type 2 mostly present with essential hypertension, as part of the cardiometabolic syndrome. Both groups of patients are at higher risk for developing pre-eclampsia, especially patients with pre-existing diabetic nephropathy [23, 24]. The above-mentioned maternal vascular complications have been consistently associated with pre-term delivery, perinatal fetal morbidity and mortality [25]. In patients with type 1, type 2 and gestational diabetes, the incidence of hypertension and pre-eclampsia was not statistically significantly different compared to healthy controls. The incidence of hypertension and pre-eclampsia was slightly higher in patients with gestational and type 2 diabetes in relation to patients with diabetes type 1, but the difference was not statistically significant. These results can be explained by the fact that the majority of patients with type 1 diabetes, compared to those with type 2 diabetes or gestational diabetes, get pregnant at a younger age, with a shorter duration of diabetes, without diabetic nephropathy or in its incipient phase. Patients with type 1 diabetes and perinatal morbidity presented with longer duration of diabetes, higher incidence of microvascular complications (macrovascular complications were not diagnosed), hypertension and higher HbA1c levels. The above-mentioned differences were not statistically significant, maybe due to a small number of patients with type 1 diabetes included in the study.

Conclusion

The results of our study show a higher incidence of perinatal fetal morbidity (hypoglycemia, jaundice, respiratory distress syndrome) in the patients with type 1, type 2 and gestation diabetes than in the healthy control. Also, we found a higher incidence of cesarean section in the patients with type 1 diabetes than in those with type 2 diabetes, gestation diabetes and healthy control. Although delivery in the pa-

tients with type 1, type 2 and gestational diabetes was completed approximately one to two weeks earlier compared to the healthy control group there was no statistically significant difference in the incidence of preterm delivery (before the week of gestation 36) between the women with diabetes and the healthy control group. Preterm delivery associated with poorer glycaemic control reflected through higher values HbA1c in third trimester. Bearing in mind that the mentioned complications are usually associated with hyperglycemia, it is necessary to provide adequate preconception counseling of diabetic patients, timely diagnosis of diabetes, and good glycemic control both during organogenesis and throughout pregnancy, in order to reduce adverse pregnancy outcomes to minimum.

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