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Revisiting type II diabetes mellitus in pregnancy and pregnancy outcomes such as in thyroidology: do you mind?

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SUMMARY

OBJECTIVE: There is an increase in the prevalence of pre-gestational diabetes in the past decades, mainly due to the increase in the prevalence of obesity in the general population and consequently type 2 diabetes among women of reproductive age.

METHODS: This study purposed to describe the delivery characteristics, pregnancy complications, and outcomes among women in Serbia with the pre-gestational type 2 diabetes in the past decade, as well as their pregnancy complications, deliveries, and neonatal outcomes. The study included data from all the pregnant women with pre-gestational type 2 diabetes in Belgrade, Serbia during the period between 2010 and 2020. The final sample consisted of 138 patients.

RESULTS: More than half, i.e., 70 (50.7%) had a vaginal delivery, while 48 (34.8%) had elective and 20 (14.5%) had emergency caesarean sections. Throughout the period, there was 1 patient with preeclampsia (0.7%), 5 with pregnancy-induced hypertension (3.6%), 7 had newborns with small for gestational age (5.1%), 28 with macrosomia (20.3%), 12 (8.7%) had preterm births, and one-fifth, i.e., 28 (20.3%) of the newborns had Apgar score under 8.

CONCLUSION: The present study revealed that women with type 2 diabetes in pregnancy have a significant burden of pregnancy complications, related to pregnancy, delivery, and newborns.

KEYWORDS: Diabetes mellitus. Diabetes mellitus, type 2. Pregnancy. Thyroid gland. Pregnancy outcome.

INTRODUCTION

Diabetes, *per se*, is the most common chronic illness affecting pregnant women. Approximately 85% of diabetic cases in pregnancy are gestational diabetes mellitus (GDM)[1]. There has been an increase in the prevalence of pre-gestational diabetes (pre-GDM) in the past decades, mainly due to the increase in the prevalence of obesity in the general population and consequently type 2 diabetes (T2DM) among women of reproductive age[2,3]. A study from the United Kingdom (UK) showed that the prevalence of T2DM in pregnancy increased by 354% in the period between 1995 and 2012, from 0.2% in 1995 to 1.06% in 2012[3]. According to the national UK data, T2DM in 2016 represented half of all cases of pre-GDM[4]. Of note, pregnancies with pre-GDM have a higher frequency of pregnancy complications compared to pregnancies with GDM. Another dimension important for the increase in the prevalence of pre-GDM is that if the diabetes is diagnosed in the first trimester or early in the second trimester, it is considered pre-GDM[5]. This increase also has a societal influence, as diabetes is associated with a decrease in quality of life[6].

Prevalence of pre-gestational diabetes (pre-GDM) is associated with a decrease in fertility[1], but there are more data on the type 1 diabetes mellitus (T1DM), though the same is presumed with T2DM due to the higher prevalence of obesity and polycystic ovarian syndrome among women with T2DM compared to the general population[1,6-9]. Pre-GDM is associated with maternal and neonatal morbidity and mortality[2]: higher likelihood of spontaneous abortions, caesarean deliveries, operative vaginal deliveries, lacerations, perinatal asphyxia, different congenital anomalies, and higher perinatal mortality or venous

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thromboembolism[3,5,10]. As such, the adverse pregnancy outcomes among women with pre-GDM are more frequent than among women with GDM[11,12]. Women with T2DM are at higher risk for adverse pregnancy outcomes compared to women with T1DM, with four times higher perinatal mortality[13] and generally poorer pregnancy outcomes[14]. Pregnancies with pre-gestational T2DM are commonly complicated by chronic hypertension, the main risk factor for preeclampsia that is reported in almost one in five pregnancies with pre-gestational T2DM[11]. Additionally, chronic hypertension is also a risk factor for uteroplacental insufficiency and stillbirth. There is also a higher rate of preterm births, small for gestational age (SGA) infants, large for gestational age (LGA) infants, hypoglycemia and cardiac anomalies in infants[2,11,15], respiratory distress syndrome, polycythemia, organomegaly, electrolyte disturbances, and hyperbilirubinemia[2].

The important issues for the obstetricians in charge of patients with T2DM during pregnancy are the timing and type of delivery. The factors influencing this decision include, but are not limited to, fetal size, the presence of medical comorbidities, and placental insufficiency[16]. T2DM in pregnancy, *per se*, is associated with uteroplacental malperfusion, which can be presented as placental infarction, vasculopathy in deciduas, and earlier maturation of villi[17]. The adequate timing and mode of delivery aim to reduce the rates of intrauterine death, which are higher among women with T2DM compared to women with other types of diabetes in pregnancy and healthy populations. Consequently, the most common timing for delivery of infants of mothers with T2DM is between 37+0 and 38+6 weeks, compared to the usually targeted timing of 40 weeks among women with GDM[16].

At present, there is growing evidence that many consider T2DM a benign condition, and it seems that there is a general lack of concern among patients[17]. The present study aimed to describe the delivery characteristics, pregnancy complications, and outcomes, including thyroidology, among women in Serbia with pre-gestational T2DM over the past decade, as well as their pregnancy complications, deliveries, and neonatal outcomes.

METHODS

Study design

The study included data from all the pregnant women with pre-gestational T2DM in Belgrade, Serbia, during the period between 2010 and 2020. The final sample consisted of 138 patients, and the study was approved by the Ethical Committee of the Faculty of Medicine, University of Belgrade, Serbia (No. 1322/IX-80). The data for this study were routinely gathered for all the pregnant patients in the health care system in Belgrade. The data from the Birth database for Belgrade, City Institute of Public Health were the age, type of delivery, the presence of chronic hypertension, preeclampsia, pregnancy-induced hypertension (PIH), newborns' birth weight, newborns' birth length in centimeters, gestational age at delivery, and Apgar score.

To this end, the type of delivery was classified as vaginal (including spontaneous vaginal, forceps, and vacuum-assisted vaginal delivery), elective caesarean section, and emergency caesarean section. Based on the newborn's birth weight, newborns were classified as small for gestational age (SGA), adequate for gestational age (AGA), and large for gestational age (LGA). The pre-term birth was defined as birth before 37 weeks of gestation[18]. The ponderal index was calculated using the following formula:

[PI=birth weight×100/(birth height in centimeters)^3][19].

Statistical analyses

Statistical analyses were done using the methods of descriptive and analytical statistics. The numerical data were presented as means± standard deviations, and the categorical data were presented as relative numbers (percentages). The differences between the groups on numerical variables were examined using the Student's t-test and univariate variance analysis (ANOVA). The statistical analyses were done using Statistical Software for Social Sciences (SPSS) 22.0.

RESULTS

There were a total of 138 pregnant women with T2DM treated in any health care facility in Belgrade, Serbia, during the 11 years. The average age of the patients was 31.88±5.38 years. More than half, i.e., 70 (50.7%) had a vaginal delivery, 48 (34.8%) had elective caesarean sections, and 20 (14.5%) had emergency caesarean sections. There was 1 patient with preeclampsia (0.7%), 5 with pregnancy-induced hypertension (3.6%), 7 had newborns with SGA (5.1%), 28 with macrosomia (20.3%), 12 (8.7%) had preterm births, and one-fifth, i.e., 28 (20.3%) newborns had Apgar score under 8. The characteristics of the women included in the study are presented in Table 1.

There were significant differences in the average Apgar scores between the newborns of women with different types of delivery, women with and without preeclampsia, and women with a gestational age of under and over 37 weeks at delivery. There were significant differences between the women with preeclampsia and the women without preeclampsia in the average newborns' birth weight. The newborns' birth weight differed significantly between the women with gestational age at delivery of <37 weeks and >37 weeks. The differences in Apgar scores and newborns' birth weights between the patients with different medical and obstetric complications are presented in Table 2.

DISCUSSION

A posteriori, reproductive functions are affected by some conditions, such as T2DM, L-thyroxine (3,5,3′,5′-tetraiodothyronine, T4), and L-triiodothyronine (3,5,3′-triiodothyronine, T3), which are crucial for the normal reproductive function of human and animals *via* the ovarian, uterine, and placental tissues through specific nuclear receptors, modulating their development and metabolism in thyroidology[20-22].

The present study incorporated a total of 138 women with T2DM during the study period, comprising 2% of the total population of women with diabetes in pregnancy in Belgrade, Serbia. The average age of pregnant women with T2DM in Belgrade in our study was 31.9 years, similar to the age reported in the studies in the UK[3] and Denmark[13]. In addition, the prevalence of elective cesarean sections has increased in recent decades[23]. The data from 15 years in Scotland showed the prevalence of elective caesarean sections at 30.5%, which is similar to our results of 34.8%, but the prevalence of emergency caesarean sections in the present study was two times lower compared to the Scottish data, 14.5 vs. 29%, respectively[24]. The treatment and control of diabetes in pregnancy have been improved since the beginning of the data gathering in Scotland, and the differences in the prevalence of emergency caesarean sections can be explained by these improvements, as the start of our data collection was delayed for more than a decade[2,17,18].

Table 1. The characteristics of women in the study design.

Characteristics	n (%)
Age in years (X±SD)	31.88±5.38
Type of delivery	
Vaginal delivery	70 (50.7)
Elective caesarean section	48 (34.8)
Emergency caesarean section	20 (14.5)
Chronic hypertension	
Yes	14 (10.1)
No	124 (89.9)
Preeclampsia	
Yes	1 (0.7)
No	137 (99.3)
Pregnancy-induced hypertension	
Yes	5 (3.6)
No	133 (96.4)
Newborns' birth weight in grams (X±SD)	3423.01±596.27
Newborns' birth weight	
SGA	7 (5.1)
Normal weight	103 (74.6)
Macrosomia	28 (20.3)
Newborns' birth lenght in cms (X±SD)	51.11±2.95
Gestational age at delivery in weeks (X±SD)	38.53±1.78
Gestational age at delivery	
<37 weeks	12 (8.7)
≥37 weeks	126 (91.3)
Apgar score (X±SD)	8.71±0.88
Apgar score	
<8	28 (20.3)
≥8	110 (79.7)
Ponderal index (X±SD)	2.55±0.27

More than 1 in 10 pregnant women in our study reported pre-gestational chronic hypertension, and an additional 3.6% were diagnosed with PIH, which is more than three times lower prevalence of hypertension compared to the TODAY study[11] and similar to the prevalence of hypertension in the cohort of women in California[14]. The risk factors for preeclampsia among pregnant women with T2DM are less examined than the risk factors for preeclampsia among pregnant women with T1DM[16], as the risk for preeclampsia is higher among women with T1DM[19]. Preeclampsia is considered a significant complication associated with both maternal and fetal adverse pregnancy outcomes[16] and the frequency of preeclampsia among women with T2DM is just below 10%[19]. Only one case in the present study had preeclampsia, comprising less than 1% of the sample, but the differences between the studies can be explained by the sample size in our study, which may be insufficient in order of describing the actual prevalence of preeclampsia in this population. The low prevalence of preeclampsia in our study may also indicate improvements in glycemic and cardiovascular control among women with T2DM achieved in recent years[2].

One in five newborns in our study were LGA, similar to the study from California[14], and the prevalence was almost two times lower than that in the Scottish study, although the mean birth weight was almost identical in both studies[24].

The mean gestational age at delivery was above 38 weeks in the present study, which is in the range of the advised time for adequate delivery for women with T2DM for minimization of the risks for stillbirth, and the prevalence of preterm birth in our cohort was below 10%, significantly lower than previously reported for women with T2DM in pregnancy. This prevalence was significantly higher compared to the prevalence of preterm birth among all livebirths in neighboring Bosnia and Herzegovina. One-fifth of the newborns in our study had an Apgar score of less than 8, and the average score of 8.7 is likely previously reported. Finally, newborns of women with emergency caesarean sections had significantly lower Apgar scores compared to the newborns

Table 2. The differences in the Apgar scores and newborns' birth weight.

Characteristics	Apgar score (X±SD)	p	Newborns' birth weight (X±SD)	p
Type of delivery				
Vaginal delivery	8.81±0.80	**0.001**	3397.57±475.90	0.876
Elective caesarean section	8.85±0.46		3454.06±562.45	
Emergency caesarean section	8.00±1.45		3437.50±976.50	
Chronic hypertension				
No	8.69±0.92	0.330	3423.63±560.97	0.971
Yes	8.93±0.27		3417.50±877.14	
PIH				
No	8.71±0.89	0.777	3407.63±590.53	0.119
Yes	8.60±0.55		3832.00±672.40	
Preeclampsia				
No	8.74±0.79	**<0.001**	3437.77±572.57	**<0.001**
Yes	4.00		1400.00	
Gestational age at delivery				
<37 weeks	8.08±1.50	**0.009**	2769.17±858.21	**<0.001**
≥37 weeks	8.77±0.78		3485.28±529.06	

Bold indicates statistically significant p-values.

of women with vaginal and elective caesarean deliveries, as did preterm newborns compared to term newborns. One newborn born to a mother who developed preeclampsia had a significantly lower birth weight compared to the other newborns and a lower Apgar score, but this was the newborn born at 30 weeks of gestation, compared to the average of 38+3 weeks[14,16,24,25].

Limitations

This study has a few possible limitations. First of all, it possesses a descriptive study design. The differences between the examined groups are cross-sectional, and we could not establish a causal relationship. The number of women included in the study is low, which limits the possibility of the statistics. The aforementioned study encompasses the largest study on pregnancies with T2DM in the Serbian population, and the longitudinal design allowed us to describe the large cohort covering the entire decade. Unlike the majority of studies examining the characteristics of pregnant women with pre-GDM that obtain data from clinical settings, the data included in this study are obtained from a population-based registry and reflect the general population of pregnant women with T2DM.

CONCLUSION

This study revealed that women with T2DM in pregnancy have a significant burden of pregnancy complications related to pregnancy, delivery, and newborns. Herewith, we might recommend adequate follow-up and strict glycemic control, which must be enforced among these patients in order to minimize the risks for both mothers and their newborns. This issue merits further investigation.

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AUTHORS' CONTRIBUTIONS

JT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, and Writing—original draft. **SD:** Data curation, Investigation, Methodology, Project administration, Resources, Software, Validation, and Visualization. **DS:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, and Writing—review & editing. **DSt:** Investigation, Methodology, Project administration, Validation, and Visualization. **DAD:** Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, and Writing—review & editing. **IS:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization,

Writing—original draft, and Writing—review & editing. **ECAV:** Investigation, Methodology, Project administration, Validation, Visualization, and Writing—review & editing. **ZTS:** Project administration, Resources, Validation, and Visualization. **BD**: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, and Visualization. **MG**: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, and Visualization.

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