PERINATAL OUTCOMES OF PREGNANT WOMEN WITH TYPE 1 DIABETES MELLITUS: COMPARISON OF MULTIDOSE INJECTION AND CONTINUOUS SUBCUTANEOUS INSULIN INFUSION

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Abstract

Objective. To evaluate obstetric and neonatal outcomes of patients with type 1 diabetes mellitus (T1DM) and compare multidose injection (MDI) and continuous subcutaneous insulin infusion (CSII).

Study Design. Retrospective study of 53 pregnant patients with T1DM reaching at least 24th gestational week.

Results. Fourteen patients (26.4%) hospitalized for insulin dose regulation. Ten patients had hypertensive diseases. Perinatal mortality occurred in 2 neonates owing to cardiac malformations. Neonatal hypoglycemia, small for gestational age, large for gestational age, and neonatal jaundice were demonstrated in 8, 4, 12 and 19 newborns, respectively. Sixteen newborns were admitted to the NICU for various reasons. Congenital malformations were detected in 7 newborns (6 cardiovascular and 1 central nervous system anomaly). Despite lack of statistical significance, total daily insulin doses were higher in the MDI group than in the CSII group with doses of 62 IU (18–166) and 51 IU (20–114), respectively ($p=0.119$). Gestational and perinatal outcomes also showed no statistical significance. However, all congenital abnormalities and perinatal deaths occurred in the MDI group.

Conclusion. T1DM in pregnancy is a challenging problem in terms of having better obstetric and perinatal results. CSII may be used safely instead of MDI in appropriate patients.

Key words: diabetes mellitus, pregnancy.

INTRODUCTION

The management of type 1 diabetes mellitus (T1DM) in pregnancy is challenging because of the increased risk of fetal and maternal complications. The ultimate aim of treatments is to reduce maternal and fetal complications by achieving better glucose levels (1).

The management of T1DM in pregnancy

is more challenging than that of other types of carbohydrate metabolism disorders because it is not only an autoimmune disorder but also requires intense management (2). Prenatal counseling and “special antenatal care program” are required and necessary for better obstetric and perinatal outcomes. Appropriate preconception counseling, including that on glucose level control and folic acid supplementation, is also shown to lead to a decrease in congenital malformations (3).

Perinatal outcomes of these patients are one of the main concerns of the neonatologists. Decreasing these complications with appropriate management of blood glucose is the key. Stillbirth, perinatal mortality, and congenital abnormalities seem to be the most critical outcomes of these pregnancies. Stillbirths are significantly increased in patients with T1DM according to the literature, and there is a 2- to 10-times increase in congenital abnormalities (4, 5). Macrosomia is another complication of T1DM in pregnancy and it has a great impact on obstetric complications such as shoulder dystocia, brachial plexus injury, and increased cesarean section rates. Appropriate management of blood glucose is necessary for overcoming that complication (6).

Maternal complications are also challenging in pregnancies in women with T1DM. Progression of diabetic complications like retinopathy, nephropathy, and keto-acidotic or hypoglycemic episodes may be critical in terms of maternal and fetal complications (7, 8). Regulation of blood glucose becomes also more complicated with the altered metabolic status and changing body mass index during the pregnancy.

T1DM is an insulin-dependent disease and may be managed by multiple daily injections (MDI) of insulin as the regular therapy. Insulin doses are mostly revised all along the pregnancy to achieve ideal glucose levels.

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Most regimens include long-acting baseline insulin injections at night hours with or without additional dose of long-acting insulin at morning hours and short-acting bolus injections during meals (9). With advancing technologies, continuous subcutaneous insulin infusion (CSII) is also becoming more common and thought to be providing a more physiologic insulin therapy. Patients on CSII therapy are also shown to require lower doses of insulin and have better glycemic control according to recent studies (10, 11). There are many studies comparing MDI and CSII in the non-pregnant population and evaluating the effectiveness of both modalities, but there are a limited number of studies evaluating and comparing these modalities in pregnant patients (12). Recent few studies are carried out to compare patients with CSII and MDI in terms of fetal and maternal complications (10).

In this study, we aimed to demonstrate the characteristics of pregnant patients with T1DM and compare patients on CSII and MDI treatments in terms of maternal and fetal complications.

MATERIAL AND METHODS

This retrospective study included 53 pregnant patients with T1DM who underwent regular follow-up in the antenatal period and delivered at Hacettepe University between 2010 and 2017. The required data were obtained from Hacettepe University delivery room registry records and electronic database of our institution. Singleton pregnancies reaching 24 weeks were included in the study. Patients with multiple pregnancies, without regular follow-up, or pre-gestational co-existing diseases (chronic hypertension, renal disease, systemic autoimmune disease, etc.) and those with pregnancies not reaching 24 weeks were excluded from the study. Newly diagnosed patients or those with CSII applications during the pregnancy were also excluded. Patients with at least 3 months of CSII application were included in this study. According to these inclusion criteria, 11 patients with CSII and 42 patients with MDI are included for further evaluation.

Patient follow-ups were performed by the perinatology and endocrinology divisions of our institution. Patients were hospitalized in case of glucose level dysregulations (including hypoglycemic attacks or ketoacidosis) or any obstetric complication. Insulin dose regulations were performed by the Endocrinology Department. Total insulin dose was recorded according to the third trimester regimens of the patients. Majority of the patients had bolus doses

of insulin during meals and long-acting insulin doses at 10 p.m. Patients requiring additional dose also had long-acting insulin injections at morning hours. CSII-using patients had changes in basal insulin infusion doses according to daytimes and bolus insulin infusions during meals.

Worsening of blood sugar regulation was defined as increasing HbA1c or proteinuria levels (microalbuminuria level at 24-h urine analysis or albumin/creatinine ratio at spot urine analysis) (13). Hypertensive disorders are defined as repeated blood pressure measurements of over 140/90 mmHg with/without proteinuria according to recent literature (14). Cesarean section and preterm birth ratios are presented as gestational outcomes. Perinatal mortality is also defined as neonatal deaths before the 28th postpartum day.

Neonatal hypoglycemia is defined as blood glucose levels below 40 mg/dL (15). Small for gestational age (SGA) and large for gestational age (LGA) were also defined by the percentiles of birthweights for gestational age as lower than 10 percentile and greater than 90 percentile, respectively (16). Neonatal jaundice is also defined as the need for phototherapy with increased total bilirubin levels adjusted by gestational week (over 95 percentile) (17). Respiratory problems are defined as any problem necessitating invasive respiratory support at any duration. Admissions to the neonatal intensive care unit (NICU) right after the delivery and major congenital anomalies are also recorded.

The obtained data was used for descriptive analysis of the whole cohort. Further analyses were performed to compare patients having CSII and MDI at all terms.

We have analysed the normality of distribution by visual and quantitative analysis and determined a lack of normal distribution. The results were presented as median and minimum-maximum values according to the data structure. Further analyses between CSII and MDI groups were performed by Mann-Whitney U test or chi-square test according to the data structure. A P-value less than 0.05 was evaluated as statistically significant.

Descriptive statistics and comparative analysis were performed by using IBM SPSS Statistics for Windows version 23.0 (IBM Corp.).

This retrospective study was approved by Hacettepe University Ethics Committee (GO 17-426). Written consent was obtained from all patients who participated in the study.

RESULTS

Table 1 demonstrates the data of all patients with T1DM. The median dose of total insulin at the third trimester was 59 IU. Fourteen out of 53 patients (26.4%) necessitated hospitalization for insulin dose regulation during the pregnancy. Clinical worsening as defined in the Materials and Methods section was demonstrated in 7 patients. Ten patients had developed hypertensive disorders of pregnancy (both hypertension disease and preeclampsia). The median gestational age was 37 weeks with median birth weight of 3150 g. Cesarean section and primary cesarean section rates were 86.8% and 82.5%, respectively. Out of 53 patients, 24 had preterm birth, while 7 had early preterm deliveries. Perinatal mortality occurred in 2 neonates due to severe cardiac malformations. Median APGAR scores were 9 and 10 at 1 and 5 min, respectively.

Neonatal hypoglycemia, SGA, LGA, and neonatal jaundice were demonstrated in 8 (15.1%), 4 (7.5%), 12 (22.6%), and 19 (35.8%) newborns,

respectively. Out of 53 fetuses, 11 (20.7%) had respiratory problems requiring ventilatory support. Sixteen newborns (30.1%) were admitted at the NICU due to various reasons. Congenital malformations were detected in 7 newborns (13.2%), in which 6 had cardiovascular anomalies and 1 had central nervous system anomaly.

Further analyses were carried out to compare the CSII and MDI groups (Table 2). None of the variables showed a statistically significant difference between the groups. Although they did not reach statistical significance, total insulin doses were shown to be different between the MDI and CSII groups, at 62 IU (18–166) and 51 IU (20–114), respectively ($p=0.119$). Gestational and perinatal outcomes also showed no statistical significance. Despite absence of statistical significance, all congenital abnormalities and perinatal deaths occurred in the MDI group.

DISCUSSION

Pregnancy among women with T1DM is associated with an increased risk of congenital malformations and obstetric complications, together with increased neonatal mortality and morbidity (4). Preconception counselling is the key to achieving better pregnancy outcomes. Potential adverse effects of the disease on pregnancy outcomes, medication-related risks, impact of pregnancy on glycemic control, and presence of diabetes-related complications should be discussed with the patients. However, many pregnancies are unplanned, and many women do not receive appropriate counselling before conceiving (18). Thus, the management of T1DM during pregnancy is challenging for the physicians because it is not only a metabolic disorder but also an autoimmune disorder (2). The main goals of physicians in the management of pregnancies complicated by T1DM should be achieving optimal glycemic control and preventing maternal medical complications (retinopathy, nephropathy, hypertension, ketoacidosis, etc.) and overwhelming fetal and obstetrical complications (congenital anomalies, preeclampsia, macrosomia, etc.) (1, 4, 19). A multidisciplinary team that consists of a perinatologist, endocrinologist, endocrinology nurse, and nutritionist should be established to provide optimal patient care. In this study, we have shown that 13.2% of the patients demonstrated clinical worsening during gestation. Glucose level abnormalities required hospitalization in 26.4% of all patients, but none of them demonstrated keto acidotic events. This may be

Table 1. Demographic and obstetric characteristics of the patients with Type 1 Diabetes Mellitus

Demographic Information	
Age [‡]	27 (19 – 38)
Gravida [‡]	2 (1–5)
Parity [‡]	0 (0 – 3)
Living Child [‡]	0 (0 – 3)
Maternal Information	
Insulin Type	
CSII	11 / 53 (20.7 %)
MDI	42 / 53 (79.3 %)
Total Insulin Dose (IU) [‡]	59 (18 – 166)
Hospitalization for Regulation	14 / 53 (26.4 %)
Clinical Worsening	7 / 53 (13.2 %)
Hypertensive Disorder	10 / 53 (18.1 %)
Gestational Outcome	
Birthweight (g) [‡]	3150 (1200 – 4320)
Birth Week [‡]	37 (30 – 39)
Cesarean Section Rate	46 / 53 (86.8 %)
Preterm Birth	24 / 53 (45.2 %)
Perinatal Mortality	2 / 53 (3.7 %)
Perinatal Outcome	
APGAR score at 1 st minute [‡]	9 (0 – 10)
APGAR score at 5 th minute [‡]	10 (0 – 10)
5th minute APGAR < 7	7 / 53 (13.2 %)
Neonatal Hypoglycemia	8 / 53 (15.1 %)
SGA	4 / 53 (7.5 %)
LGA	12 / 53 (22.6 %)
Neonatal Jaundice	19 / 53 (35.8 %)
Respiratory Problems	11 / 53 (20.7 %)
Admission to NICU	16 / 53 (30.1 %)
Major Congenital Anomalies	7 / 53 (13.2 %)

[‡]: Median (Minimum – Maximum).

Table 2. Comparison of patients treated with MDI or CSII

Demographic Information			
	MDI (n = 42)	CSII (n =11)	p
Age [‡]	28 (19 – 38)	25 (19 -34)	0.156
Gravida [‡]	2 (1- 5)	2 (1 - 2)	0.119
Parity [‡]	0 (0 – 3)	0 (0 - 1)	0.374
Living Child [‡]	0 (0 – 3)	0 (0 -1)	0.399
Maternal Information			
Total Insulin Dose (IU) [‡]	62 (18 – 166)	51 (20 – 114)	0.119
Hospitalization for Regulation ^a	11 (26.2 %)	3 (27.3 %)	0.608
Clinical Worsening ^a	5 (11.9 %)	2 (18.2%)	0.626
Hypertensive Disorder ^a	9 (21.9 %)	1 (9.1 %)	0.667
Gestational Outcome			
Birthweight (g) [‡]	3095 (1200 – 4320)	3540 (2490 – 4110)	0.167
Birth Week [‡]	37 (30 – 39)	36 (32 – 38)	0.692
Cesarean Section Rate ^a	37 (88.1 %)	9 (81.8 %)	0.626
Preterm Birth ^a	18 / 42 (42.9 %)	6 / 11(54.5 %)	0.518
Perinatal Mortality ^a	2 (4.8 %)	0 (0 %)	0.442
Perinatal Outcome			
APGAR score at 1 st minute [‡]	9 (0 – 10)	9 (6 – 9)	0.596
APGAR score at 5 th minute [‡]	10 (0 – 10)	10 (8 – 10)	0.749
5 th minute APGAR < 7 ^a	6 (14.2 %)	1 (9.1 %)	0.314
Neonatal Hypoglycemia ^a	6 (14.2 %)	2 (18.2 %)	0.490
SGA ^a	4 (9.5 %)	0 (0 %)	0.382
LGA ^a	8 (19 %)	4 (36.4 %)	0.244
Neonatal Jaundice ^a	14 (33.3 %)	5 (45.5 %)	0.342
Respiratory Problems ^a	9 (21.4 %)	2 (18.2 %)	0.590
Admission to NICU ^a	13 (31 %)	3 (27 %)	0.564
Major Congenital Anomalies ^a	7 (16.7 %)	0 (0 %)	0.322

‡: Median values (Minimum – Maximum), Mann-Whitney U test, a; Frequency, chi-square test.

explained by close multidisciplinary antenatal follow-up and exclusion of pregnancies not reaching 24 weeks, which may have a worse prognosis.

Bartsch *et al.* reported an increased risk of preeclampsia in their systematic review and meta-analysis including 92 cohort studies (pooled preeclampsia rate 11%, 95% CI 8.4–13.8%; pooled relative risk 3.7, 95% CI 3.1–4.3) (20). In our study, 18.1% of the patients had hypertensive disorders during the pregnancy, which is comparable to previous studies (21).

A higher risk of major congenital malformations and miscarriage for pregnancies with T1DM were reported in various studies (22, 23). Especially, increased first trimester glycated hemoglobin values were found to be associated with these obstetric complications (22, 23). Neural tube and cardiac defects were the most common congenital abnormalities reported in pregnancies with T1DM (5). Macintosh *et al.* reported a 4.2-fold increased risk for neural tube defects and a 3.4-fold increased risk for congenital heart diseases in their national population-based pregnancy cohort (5). Our cohort also consisted of 7 of 53 pregnancies with major congenital anomalies

(13.2%). A slightly increased rate may be explained by the specifications of our hospital (tertiary referral center) and the relatively small number of total cases.

Risk of macrosomia and having a LGA neonate was found to be increased in pregnancies with diabetes, especially in women with excess gestational weight gain (24). Heavier birthweights increased obstetric complications such as labour trauma, uterine atony, and brachial plexus injury as well as neonatal complications like hypoglycemia, jaundice, hypocalcemia, and polycythemia (25, 26). We have demonstrated that 22.6% of all pregnancies ended up with a LGA neonates, and none of the deliveries were complicated with shoulder dystocia or brachial plexus injury. Low rates of such complications may be explained by the slightly higher cesarean section rates in patients with T1DM, as in our cohort (27). The relatively higher cesarean section rates are also a result of the recent increase in the medicolegal concerns.

Growth restriction, polyhydramnios, preterm labor, and stillbirth are other obstetric complications associated with diabetes in pregnancy (4, 8, 19). Preterm delivery rate in our cohort was demonstrated as 45.2% including induced and spontaneous preterm

births. Out of 24 preterm deliveries, 16 deliveries were late preterm deliveries.

Infants of patients with diabetes are also at risk in terms of respiratory distress, jaundice, and hypoglycemia (28-30). In our cohort, rates of respiratory distress and jaundice are found to be similar to those in the previous literature, despite the much lower rates of hypoglycemia in our cohort (4). Our neonatal results are also compatible with those of more recent studies (31). NICU admission rates are also similar to those in previous cohorts, and the main indications are specific problems related to infants of mothers with diabetes (31). Five-minute APGAR scores below 7 are also used for evaluating neonatal outcomes and found to be complicating the 13.2% of all pregnancies.

T1DM is an autoimmune-mediated metabolic disease which causes systemic vascular injury together with placental inflammation. We believe that metabolic disorders and immune-mediated diseases like T1DM may cause placental inflammation which goes together with injury to the syncytiotrophoblasts, endovascular trophoblasts covering the tip of the spiral arteries, endothelial cells of the spiral veins, and superficial/glandular epithelial cells of the decidua (intervillous space of the placenta) and the entrance of cell degradants of these tissues into the maternal circulation. These biological events result in placental inflammation and disturbed fetal perfusion. These mechanisms might be the reason for fetal hypoxia-related complications in patients with T1DM (32). These alterations were also previously reported in the placentas of the mothers with T1DM and pathologic findings were correlated with impaired functioning according to a previously published study (33). These alterations also documented in the amniotic fluid by the existence of increased levels of erythropoietin which also supports the close association between diabetes and fetal hypoxia (34).

Optimal glycemic control is mandatory in order to prevent maternal and fetal complications in pregnancies with diabetes (1, 9, 19). Glycemic control can be achieved by either MDI or CSII, depending on the patient characteristics and experience of the physicians (35-37). However, meta-analyses have not demonstrated a significant improvement in maternal or neonatal outcomes (35-37). Mukhopadhyay *et al.* reported that pregnancy outcomes and glycemic control were not significantly different among treatment groups in their meta-analysis including six randomized clinical trials (36). Furthermore, Ranasinghe *et al.*

reported no difference in maternal and fetal outcomes for CSII *versus* MDI (35). Additionally, Farrar *et al.* concluded that there was no evidence to support the use of one particular form of insulin administration over another for pregnant women with diabetes (37). Our cohort had similar results in means of comparison in both treatment modalities. We have not shown any statistically significant difference between the groups. Despite the lack of any statistical significance, lower rates of congenital anomalies and perinatal mortalities in the CSII group are remarkable. The lack of statistical significance may be associated with a relatively lower number of cases in both arms of the study.

CSII is becoming more popular in recent years, and further multicenter randomized controlled studies are required for a more definitive comparison of perinatal and maternal outcomes of these patients with the MDI group.

The strengths of this study are the involvement of the CSII group, long-term and single-center follow-up of the patients, and a relatively high number of parameters compared. The limitations of the study are the relatively small number of cases and retrospective design.

In conclusion, T1DM in pregnancy is a challenging problem in terms of having better obstetric and perinatal results. Preconception counseling and strict follow-up of the patients by the endocrinology and perinatology divisions are necessary for better pregnancy outcomes. Increased risk of hypertensive states of pregnancy, congenital abnormalities, and poor neonatal outcome must be kept in mind. In this series, we could not demonstrate a significant difference between CSII and MDI modalities in terms of maternal and fetal outcomes, thus we may conclude that CSII may be used safely instead of MDI in appropriate patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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