Perinatal outcome in pregnancies complicated with gestational diabetes mellitus and very preterm birth: case–control study

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Abstract
Preterm birth is defined as all births before 37 completed weeks of gestation. Preterm birth can be further sub-divided based on gestational age: extremely preterm (<28 weeks), very preterm (28 to <32 weeks) and moderate preterm (32 to <37 weeks). Retrospective observational case–control study review (1 year i.e., 2015) is to assess pregnancy outcome among women with gestational diabetes mellitus (GDM) delivering very preterm (28 +0/7 to 31 +6/7 weeks of gestation). The study group included all women diagnosed with GDM and were compared to a control group of women delivering at the same gestational age period but without GDM. In all, 30 women were included in the study, of whom 15 were diagnosed with GDM and 15 were not. All women had a cesarean delivery. Neonates of mothers with GDM had higher ponderal index. Birth weight had the positive associations with blood glucose of newborn (r = 0.37, p = 0.047) and term of births (r = 0.52, p = 0.003). Birth weight had the negative associations with maternal systolic pressure (r = −0.7, p < 0.05), pre-eclampsia (r = −0.6, p < 0.05) and maternal pre-pregnancy body mass index (r = −0.5, p < 0.05). There were no differences in mortality or other parameters for neonatal morbidity, including bronchopulmonary dysplasia, prematurity retinopathy, neonatal anemia. According to our data, very preterm delivery occurring in women with GDM does not confer an increased risk for neonatal complications.

Keywords
Fetal macrosomia, gestational diabetes mellitus, pregnancy outcome, premature birth

Introduction
Preterm birth, defined as childbirth occurring at less than 37 completed weeks or 259 days of gestation, is a major determinant of neonatal mortality and morbidity and has long-term adverse consequences for health [1–4]. Preterm birth can be further sub-divided based on gestational age: extremely preterm (<28 weeks), very preterm (28 to <32 weeks) and moderate preterm (32 to <37 completed weeks of gestation) [2]. Of all early neonatal deaths that are not related to congenital malformations, 28% are due to preterm birth [1]. Children who are born prematurely have higher rates of cerebral palsy, sensory deficits, learning disabilities and respiratory illnesses compared with children born at term [1,2]. The morbidity associated with preterm birth often extends to later life, resulting in enormous physical, psychological and economic costs [1,2]. The severity of complications associated with prematurity is proportional to the gestational age. Preterm birth rates have been reported to range from 5% to 11.6% of live births [1,5,6].

Events leading to preterm birth are still not completely understood although epidemiology is thought to be multifactorial. It is, however, unclear whether preterm birth results from the interaction of several pathways or the independent effect of each pathway. Causal factors linked to preterm birth include medical conditions of the mother or fetus, genetic influences, environmental exposure, infertility treatments, behavioral and socio-economic factors, and iatrogenic prematurity [1]. Approximately, 45–50% of preterm births are idiopathic, 30% are related to preterm rupture of membranes and another 15–20% are attributed to medically indicated or elective preterm deliveries [1,7,8]. Factors possibly contributing to but not completely explaining this upward trend include increasing rates of multiple births, greater use of assisted reproduction techniques, increases in the proportion of births among women over 34 years of age and changes in clinical practices, such as greater use of elective cesarean section. For example, the increasing use of ultrasonography rather than the date of the last menstrual period to estimate gestational age may have resulted in larger numbers of births being classified as preterm [1]. Changes in the definitions of fetal loss, stillbirth and early neonatal death may also have contributed to the substantial increases in preterm birth rates recorded in developed countries in the past 25 years [1,6,9].

High levels of blood glucose, or hyperglycemia, is one of the most common health problems of pregnancy today. The International Diabetes Federation estimates that 20.9 million or 16.2% of live births to women in 2015 had some form of

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hyperglycemia in pregnancy [10]. The majority (85.9%) is due to gestational diabetes mellitus (GDM) [10]. The occurrence of GDM is increasing in the context of the pandemic in obesity and type 2 diabetes in the modern world [10]. Changes in diagnosis and classification of hyperglycemia in pregnancy have contributed to the substantial increases incidence of GDM [11–16].

GDM is a serious medical and social problem as largely increases the frequency of adverse perinatal outcomes, chronic placental insufficiency, pre-eclampsia, premature birth, chronic hypoxia and fetal macrosomia [8,17–21]. GDM is associated with perinatal complications, which are more common among premature babies, such as respiratory distress syndrome, hypocalcemia, hypoglycemia [8,17–21].

The relationship between maternal hyperglycemia during pregnancy and premature babies is controversial. Some investigators did not report an increased risk for preterm birth among women with GDM [22], others demonstrated that GDM by itself is a risk factor for prematurity [8]. Therefore, we aimed to assess pregnancy outcome among women with GDM delivering at the very preterm period, and to investigate whether they have a synergistic additive effect on obstetrical and neonatal outcomes.

Methods

We conducted a retrospective observational cohort study of all women with GDM who delivered at “Ural Scientific Research Institute of Maternity and Child” in 2015 at the very preterm birth period (28 + 0/7 to 31 + 6/7 weeks of gestation). The study was approved by the local institutional review board. Eligibility was limited to pregnant women with GDM, delivering at the very preterm period between 28 + 0/7 and 31 + 6/7 weeks of gestation. Women with a fetus or a newborn having confirmed chromosomal and/or structural congenital anomalies were excluded, as well as pregnancy with pre-gestational diabetes. Data were retrieved from the databases of the delivery ward and the child clinic. Collected data included demographical data as well as obstetrical data, sonographic biometric measurements, labor and delivery outcome and neonatal data. In all, 3648 women delivered in our institution during the study period. We excluded women with pre-gestational diabetes (n = 118) and those who delivered prior to 28 completed weeks of gestation or beyond 32 completed weeks of gestation. The study group included all women diagnosed with GDM and were compared to a control group of women delivering at the same gestational age period but without known GDM. Of the eligible women, 15 were diagnosed with GDM and 15 were not diagnosed with GDM. There were three multiple pregnancy in each group. In the compared groups, there were no significant differences in maternal age, pre-gestational body mass index, parity, severity of extra genital pathology (Table 1). Gestational age was determined based on maternal reported last menstrual period and was affirmed by the crown-ramp length measured at a first trimester ultrasound [3]. Hypertension present at or prior to 20 weeks of gestation that did not progress to pre-eclampsia was classified as chronic hypertension. After 20 weeks of gestation, hypertensive disorders in pregnancy were categorized according to the international society for the study of hypertension in pregnancy guidelines [3].

Diagnosis of GDM was based on the consensus of Russian Association of Endocrinologists and Russian Society of Obstetrician-Gynecologists [14] accepted in 2012. This consensus [14] is based on the recommendations of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [12] and included a two-phase strategy for the detection and diagnosis of hyperglycemic disorders in pregnancy. The first is detection of women with overt diabetes not previously diagnosed or treated outside of pregnancy. If fasting plasma glucose value in early pregnancy ≥5.1 mmol/L but <7.0 mmol/L that diagnose as GDM. The second phase is a 75-g oral glucose tolerance test at 24–28 gestational weeks in all women not previously found to have overt diabetes or GDM. One or more of the three values from a 75-g oral glucose tolerance test (fasting ≥5.1 mmol/L; 1-h plasma glucose ≥10.0 mmol/L; 2-h plasma glucose ≥5.5 mmol/L) must be equaled or exceeded for the diagnosis of GDM. Women diagnosed with GDM were treated with appropriate diet and lifestyle modification without Insulin.

Birth weight percentile was calculated using gender-specific local population-based birth weight curves [3,23]. Large-for-gestational age babies were defined as newborns with birth weight above the 90th percentile for gestational age. All newborns were evaluated ponderal index [24]. All neonatal outcomes were determined by the attending pediatrician according to international and national definitions [3].

Statistical analysis was performed using the Statistics software (version 10). Comparison between continuous variables was performed with Student’s t-test, Mann–Whitney U test, and categorical data were compared using χ² test. Correlation was assessed using Pearson’s (r) and Spearman’s (rₛ) coefficients. Data are presented as mean ± SD or median (25th; 75th percentiles). A p value < 0.05 was considered significant.

Results

Characteristics for women with or without GDM at very preterm birth are presented in Table 1. GDM was diagnosed at 17.3 ± 8.3 gestational weeks. All women with GDM were managed by dietary regulation and had a good glycemic control. All women had a cesarean delivery. Pre-eclampsia was the most common cause of premature delivery among 60.0% (9/15) and 66.7% (10/15) of the women with GDM and control groups, respectively (p > 0.05). The second most common cause was a combination of preterm premature rupture of membranes in multiple pregnancies and fetal malpresentation (20% (3/15) in both groups). The third reason was the newborn hemolytic disease (6.7% (1/15) in both groups). Placental abruption as the cause of an emergency very premature delivery was observed only if GDM in 6.7% (1/15).

Apgar score at the first and fifth minute did not have significant differences depending on the presence or absence of GDM (Table 2). We have not identified large-for-gestational age newborns in both groups. But newborns from women with GDM had a lower rate of intrauterine growth restriction (14.6% (6/41) versus 31.7% (13/40), p = 0.02). Infants from mothers with GDM had a slightly lower blood glucose level (2.40 [2.2; 3.2] mmol/L versus 2.45 [1.6; 2.7] mmol/L, p > 0.05). But cases of neonatal hypoglycemia had occur in both groups (p > 0.05). There were no differences in mortality and any of the parameters for neonatal
morbidity. Although the identified trends, we have not identified significant differences in the anthropometric parameters and the level of glucose in the newborn (Table 2).

A positive association was found between the level of neonatal blood glucose and birth weight \( r = 0.37, p = 0.047 \). Birth weight had a positive correlation with gestational age at delivery \( r = 0.52, p = 0.003 \) and a negative correlation with the maternal level of systolic blood pressure \( r_s = -0.7, p < 0.05 \), preeclampsia \( r_s = -0.6, p < 0.05 \) and pre-pregnancy body mass index \( r = -0.5, p < 0.05 \). We found no significant association between birth weight and maternal weight gain \( r = 0.2, p > 0.05 \). We found no significant differences between the study groups in the incidence of bronchopulmonary dysplasia (GDM 9.5% (2/21) versus 15.0% (3/20), \( p < 0.05 \)), retinopathy (GDM 66.7% (14/21) versus 70.0% (14/20), \( p < 0.05 \)) and anemia (GDM 38.1% (8/21) versus 60% (12/20), \( p < 0.05 \)). The severity and duration of respiratory disorders and brain hypoxia-ischemias depend on the gestational age and did not depend on the presence or absence of maternal GDM. Thus, according to our limited data, very preterm birth occurring in women with GDM does not confer an increased risk for neonatal complications.

### Discussion

The incidence of complications in infants from mothers with GDM according to different sources ranging from 12 to 28% [8,11,16–21]. As we know, the main problems in newborns from mothers with GDM in early neonatal period are macrosomia, neonatal hypoglycemia, polycythemia, prolonged hyperbilirubinemia, hypocalcemia, respiratory distress syndrome, newborn transient tachypnea, diabetic cardiomyopathy, damage to the central nervous system [17–19]. Early diagnosis and treatment of GDM can play a significant role in the preservation of the health of mother and child. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, an international multicenter study of a cohort of 25 505 pregnant women tested with a 2-h 75 g OGTT and followed through pregnancy, generated an expectation of universal convergence for the adoption of a 75-g OGTT for the diagnosis of gestational diabetes, as well as for the formulation of diagnostic criteria for GDM [11]. In 2010, International Association of Diabetes in Pregnancy Study Groups (IADPSG) proposed consensus derived cutoff values for fasting, 1-h and 2-h 75-g OGTT threshold values, defining GDM based on odds ratio thresholds of 1.75 in comparison with the mean, for markers of diabetic fetopathy in the multinational observational HAPO study [12]. These criteria have been widely accepted and recently adopted by the World Health Organization [15].

We know that macrosomia is the most significant effect of maternal of hyperglycemia on the fetus [18,21]. The Pedersen’s hypothesis, formulated more than 50 years ago, suggested that fetal overgrowth was related to increased placental transfer of maternal glucose, stimulating the release of insulin by the fetal pancreatic beta cells. Because insulin is a major fetal growth factor, subsequent macrosomia occurs [19]. We did not reveal cases of macrosomia in our study. Infants from mothers with GDM at very preterm birth had a lower rate of intrauterine growth restriction. We used ponderal index to assess fetal growth especially for the evaluation of asymmetric intrauterine growth restriction. The ponderal index is a method of measuring human leanness. The ponderal index is calculated as weight divided by height raised to the third power [24]. This index in children from mothers with GDM was slightly higher than children of mothers without GDM. These differences were not significant \( p > 0.05 \). This can be explained by a small number of groups and short duration prenatal exposure of maternal hyperglycemia in the case of early preterm birth. Children from mothers with pre-pregnancy diabetes have a risk throughout the pregnancy, but the children from mothers with GDM have especially risk only at the end of pregnancy, when the regulation of maternal metabolism could exceed its ability to synthesis of insulin [16].

Hypoglycemia is a common symptom of newborns from mothers with GDM. Newborns from mothers with GDM had slightly lower blood glucose levels than infants from the group without GDM \( p > 0.05 \). But incidents of neonatal hypoglycemia had occurred in both groups. Because of prematurity, intrauterine growth restriction, small-for-gestational age, inadequate glycogen stores in the liver and muscles, insufficient amount of adipose tissue are the causes of transient neonatal hypoglycemia.

Newborns to diabetic mothers are at increased risk of neonatal respiratory distress syndrome, a major cause of admission in neonatal intensive care units. The principal mechanism of this complication relies in altered lung surfactant synthesis, due to fetal hyperinsulinism. Insulin has been shown to alter prenatal surfactant synthesis also after 34 weeks [17]. We have not revealed more severe respiratory disorders in infants from mothers with GDM. It is possible that the active synthesis of surfactant occurs after the 34 weeks of intrauterine development, but the effect of maternal hyperglycemia was not prolonged and not had time to render

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**Table 2. Neonatal outcome for women with or without GDM at very preterm birth.**

| Parameter                        | GDM (n = 21) | Non-GDM (n = 20) | \( p \) |
|---------------------------------|------------|----------------|--------|
| Male neonate                    | 11 (52.4)  | 15 (72.0)      | >0.05  |
| Birth weight (g)                | 1460 [1210; 1800] | 1355 [1200; 1595] | >0.05  |
| Birth weight < 1500 g           | 10 (47.6)  | 12 (60.0)      | >0.05  |
| Birth weight < 1000 g           | 1 (4.8)    | 2 (10.0)       | >0.05  |
| Birth weight percentile <10th   | 4 (19.0)   | 6 (30.0)       | >0.05  |
| Birth weight percentile >90th   | 0 (0)      | 0 (0)          | NA     |
| Birth length (sm)               | 38.0 [37.0; 42.0] | 38.5 [36.8; 39.0] | >0.05  |
| Ponderal index, kg/m\(^3\)     | 25.0 [22.2; 26.8] | 24.8 [22.6; 26.6] | >0.05  |
| 1-min Apgar < 7                 | 21 (100.0) | 20 (100.0)     | >0.05  |
| 5-min Apgar < 7                 | 3 (14.3)   | 8 (40.0)       | >0.05  |
| Blood glucose (mmol/L)          | 2.40 [2.2; 3.2] | 2.45 [1.6; 2.7] | >0.05  |
| Blood glucose < 2.6 mmol/L      | 12 (57.1)  | 12 (60.0)      | >0.05  |
| Blood glucose < 2.2 mmol/L      | 5 (23.8)   | 8 (40.3)       | >0.05  |
| Blood glucose < 1.7 mmol/L      | 3 (14.3)   | 7 (35.0)       | >0.05  |
| NICU admission                  | 21 (100.0) | 20 (100.0)     | >0.05  |
| Perinatal death                 | 0 (0)      | 0 (0)          | NA     |

Data are presented as \( n \) (%) or median (25th; 75th percentiles).

NA: not available; GDM: gestational diabetes mellitus; NICU: neonatal intensive care unit.
considerable influence on infants from mothers with GDM at very preterm birth. A recent study assessed pregnancy outcome among women with GDM delivering at the late preterm period [22]. The results of this study showed that the women with GDM had a higher rate of cesarean delivery and neonates of mothers with GDM had significant higher mean birth weight and birth weight percentile, including higher rate of large-for-gestational age newborns [22]. There were no differences in mortality or other parameters for neonatal morbidity. Authors concluded that late preterm occurring in women with GDM does not confer an increased risk for neonatal complications [22].

The rate of pre-pregnancy body mass index >24.9 kg/m² was 46.7% (14/30) among women with very preterm delivery and was not related to GDM. It is known that maternal overweight and obesity during pregnancy were associated with increased risks of preterm delivery, especially extremely preterm delivery [25]. We confirmed the presence of a negative relationship between maternal pre-pregnancy body mass index and birth weight in our study. Awareness has increased in recent years that maternal diet may influence the outcome of pregnancy as well as the long-term health of the child. Several studies indicate associations between maternal diet and preterm delivery [26].

**Conclusion**

According to our data, very preterm occurring in women with GDM does not confer an increased risk for neonatal complications. The health of children born in the period of early preterm birth depended more on the term of births and the degree of their morphological and functional immaturity than on maternal GDM. However, the problem, of course, requires further study.

**Declaration of interest**

The authors report no conflict of interest.

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