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**ORIGINAL ARTICLE**

**Comparison of neonatal prognosis in gestational diabetic and healthy mothers**

**Running Title: Neonatal prognosis in diabetic and healthy mothers**

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## ABSTRACT

**Objective.** Gestational diabetes mellitus (GDM) is the most common medical disorder complicating pregnancy, which can have serious consequences for mothers and infants. This study was performed with the aim to compare the neonatal and maternal outcomes of two groups of pregnancies: complicated and uncomplicated by diabetes facing a preterm birth.

**Materials and Methods.** This case-control study was undertaken on 196 healthy mothers with preterm birth and 99 premature infants of diabetic mothers referred to Ghaem Hospital in the 2019-21 period. Maternal characteristics including age, rate of pregnancy, type of delivery, delivery complication, and prolonged rupture of the membrane (PROM), along with neonatal characteristics including gestational age, Apgar score, weight, the need for mechanical ventilation, ophthalmic examinations, and laboratory results of neonates including nucleated red blood cell (NRBC), white blood cell (WBC), and venous blood gas were recorded in the checklist.

**Results.** In this study, the mean gestational age of neonates in the groups of healthy and diabetic mothers were  $35.03 \pm 2.46$  and  $33.88 \pm 2.73$  weeks, respectively. Maternal age, type of delivery, prolonged rupture of the membrane, need for cardiopulmonary resuscitation (CPR) and need for ventilation, first minute Apgar score, and retinopathy of prematurity (ROP) exhibited significant differences between the two groups ( $P$ -value  $< 0.05$ ).

**Conclusions.** According to the results of our study, diabetic mothers had pregnancy at an older age, had a longer prolonged rupture of the membrane, and were more likely to have a cesarean-section. Moreover, the preterm infants of diabetic mothers had lower Apgar scores and a greater need for resuscitation at birth. They also run a higher risk of retinopathy of prematurity.

### Key words

Gestational Diabetes; Neonatal Screening; Delivery; Newborn; Apgar Score.

## Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during gestation. It is the most common medical disorder diagnosed during pregnancy. GDM usually disappears after delivery although mothers remain at high risk for type 2 diabetes mellitus during life [1].

The prevalence of GDM varies in different societies, and its global average is estimated at 13.5%[7]. During pregnancy, insulin resistance in women is amplified because the placenta secretes the insulin-antagonistic hormone. GDM usually affects women who are genetically predisposed to type-2 diabetes or whose lifestyle, including obesity and low activity, makes them vulnerable to GDM[8-11]. During pregnancy, although the pancreas produces increased volume of insulin, functional reserves are not sufficient to overcome insulin resistance. After delivery, with placental abruption, insulin production and pancreatic function return to the pre-pregnancy levels [12]. The risk of gestational diabetes increases with maternal age, subsequent pregnancies, increased body mass index (BMI), a history of gestational diabetes, and a family history of diabetes, also demonstrated that higher maternal age, obesity before pregnancy, type of delivery C-section, and body weight to gestational age LGA were significantly associated with increased risk of GDM [6, 7].

Diabetes is also a risk factor for preeclampsia, C-section, preterm delivery, type two DM, cancer risk, and nephropathy in these mothers [1, 8, 9]. Neonatal morbidity in diabetic mothers is about 5% -10% [10]. Outcomes of gestational diabetes for infants may include macrosomia, postpartum trauma, shoulder dystocia, preeclampsia, hypoxia, hypoglycemia, hyperbilirubinemia, and ultimately increased prenatal mortality [11].

So far, many studies have evaluated the outcomes of gestational diabetes in mothers and infants, but few studies have addressed the risk of retinopathy of prematurity (ROP), prolonged rupture of membrane (PROM), and neonatal need for cardiopulmonary resuscitation (CPR) and ventilation. Due to changes in people's lifestyles and the growing rate of obesity in communities, the prevalence of GDM has soared by 30% in the last two decades [16]. It is known as an epidemic and the most common complication during pregnancy. A proper assessment of the consequences and complications of gestational diabetes in mothers and their infants can provide a suitable approach to managing procedures related to the follow-up, monitoring, and prevention of these complications in the healthcare system. Finally, we compared the outcomes of preterm infants and mothers in the two groups of mothers with gestational diabetes and healthy mothers.

## Methods and Materials:

Study design, setting, and population with selection criteria:

This case-control study was conducted on 295 premature infants admitted to the neonatal intensive care unit (NICU) at Ghaem Hospital, Mashhad, during the 2019 - 22 period. The premature neonates whose mothers had a history of diabetes in late stages of pregnancy were assigned to the case group and premature infants whose mothers had no problems during pregnancy were assigned to the control group.

Data collection and Statistical analysis:

Demographic characteristics of mothers including maternal age, gravidity, gestational problems, type of delivery, complications during delivery, and PROM as well as characteristics of newborns including gestational age, birth weight, 1-minute Apgar score, 5-minute Apgar score, need for mechanical ventilation, follow-up neonatal retinal examination along with neonatal laboratory results including the mean count of nucleated red blood cell (NRBC), white blood cell (WBC), and venous blood gas were examined in both groups and recorded in a checklist.

Gestational diabetes is defined as the fasting glucose level of a pregnant woman  $\geq 92$  mg/dl (5.1 mmol / l) once or more,  $\geq 180$  mg/dl (10.0 mmol / l) after 1 hour, and  $\geq 153$  mg/dl (8.5 mmol / l) after 2 h, it is positive if one of the values is equal or more than cut offs [13].

A CBC sample and peripheral blood smear were taken from all hospitalized infants and then a complete blood cell count was performed in the laboratory using a Cismax automatic counter. In the next step, to control the results, a peripheral blood smear device was prepared and the cells were examined morphologically before being separated. The number of NRBC was reported per 100 WBC (NRBC/100).

The retinologist examined the neonate at 32 weeks of pregnancy or 4 weeks after birth and a follow-up was conducted to assess of ROP. The stages and severity of ROP were determined based on the international classification.

After entering data in SPSS 21, we used tables, graphs, and statistical indicators to describe the results. After normality control, the Pearson correlation coefficient test and the independent t-test were used for parametric variables, and Spearman and Mann-Whitney correlation coefficients were used for nonparametric variables. The chi-square test was utilizing to analyze the relationships of variables with a nominal scale. A significant level of less than 0.05 was considered.

Ethical approval:

This study was approved by the Organizational Ethics Committee of Mashhad University of Medical Sciences, (research code: 990515 - and code of ethics: IR.MUMS.MEDICAL.REC.1399.258).

## Results:

In this study, 196 infants (66.4%) were born to mothers without a history of gestational diabetes, and 99 were born to diabetic mothers. Table 1 compares the characteristics of mothers and infants in the two groups. There was a significant difference between the two groups of neonates in terms of independent t-test, maternal age, and 1-minute Apgar score ( $P$ -value < 0.05)(Table1).

The Apgar score of the first minute in babies born to mothers without diabetes was  $1.65 \pm 7.08$  and in the diabetic group it was  $6.39 \pm 2.30$ . The average number of mothers in the group without diabetes was  $27.72 \pm 6.42$  and in the diabetes group was  $32.26 \pm 5.93$ .

Table 2 compares the outcomes of gestational diabetes in mothers and infants during childbirth, including the type of delivery, ROP, PROM, and finally the consequences for the infant in the delivery room in the two groups of neonates born to healthy and diabetic mothers. According to Chi-square test and Fisher's exact test, all five variables were significantly different ( $P$ -value

<0.05). Also, according to the independent t-test, the results of neonatal blood test and peripheral blood smear did not show a significant difference in the mean serum levels of NRBC/100\*, WBC, and mean blood pH in the two groups (P-value>0.05) (Table 2).

Of course, the average white NRBC/100\*, WBC were higher in the group of infants born to diabetic mothers, and the blood pH level of the umbilical cord was lower in the group of babies born to diabetic mothers.

## Discussion

In this study, there was a significant difference between the two groups of neonates in terms of independent t-test, maternal age, and 1-minute Apgar score. Compares the outcomes of gestational diabetes in mothers and infants during childbirth, including the type of delivery, ROP, PROM and finally the consequences for the infant in the delivery room in the two groups of neonates born to healthy and diabetic mothers. Results of neonatal blood test and peripheral blood smear did not show a significant difference in the mean serum levels of NRBC/100\*, WBC, and mean blood pH in the two groups.

According to the results of our study, diabetic mothers were older than healthy mothers. (P-value <0.001) In several studies, diabetic mothers have been reported to be significantly older than mothers without gestational diabetes [14, 16]. However, some studies have not reported a difference in maternal age between groups [8, 17]. In fact, research shows that maternal age is an independent factor that increases the risk of gestational diabetes. However, there is no consensus about the age at which this risk increases. Age over 25 years is significantly associated with increased risk of gestational diabetes in mothers [18].

In this study, the long-term rupture of the membrane in diabetic mothers was three times greater than in healthy mothers (P-value = 0.014). According to Mamta et al., PROM is reported as the most common complication in diabetic mothers [17]. Wahi et al. and Kalra et al. introduced PROM as one of the most common complications [19, 20]. In a systematic review, the most important risk factors of PROM were diabetes and maternal hypertension, which were associated with neonatal and maternal complications, especially infection [21]. Although prematurity is the most common complication associated with PROM, other complications such as sepsis, asphyxia, and respiratory distress syndrome may also occur. Timely detection of maternal risk factors and their proper management, especially diabetes, can reduce the incidence and severity of PROM complications (p <0.001) [21, 22].

In our study, diabetic mothers were 1.5 times more likely to have C- section compared to healthy mothers (P-value < 0.001). Many studies show that C-section is more common in diabetic mothers [15, 23, 24], though some other studies have not reported any significant relationship. Pregnancy complications such as preeclampsia in diabetic mothers may force medical staff to opt for C-section delivery [28]. The higher prevalence of premature amniotic membrane rupture and abnormal monitoring during labor and the greater need for resuscitation in the neonates born to diabetic mothers may explain the higher rate of C-sections in these mothers.

According to this study, acidosis was more severe in the infants of diabetic mothers than in the control group. Various studies have reported a lower pH in the blood of diabetic neonates [29,

30]. According to our findings, high NRBC, and low blood pH in infants born to diabetic mothers may explain acute and chronic uterine acidosis in this group.

In this study, the mean NRBC/100 in the neonates of diabetic mothers was three times higher than in healthy mothers. Other studies have also reported that NRBC is higher in infants born to diabetic mothers compared to the infants of healthy mothers [29, 34]. Infants of diabetic mothers are exposed to intrauterine hypoxia, which increases erythropoietin production, resulting in elevated NRBC levels [36]. Many studies have shown that chronic and acute hypoxia and asphyxia increase NRBC/100 WBC in the fetus and newborns [32, 33]. High NRBC and low blood pH in infants born to diabetic mothers may indicate chronic intrauterine acidosis in this group [29].

In this study, the 1-minute Apgar score of diabetic mothers was low (P-value=0.013). In the study of Levy et al., the 1-minute Apgar score was lower, but the 5-minute Apgar score was not significantly different [14]. In the study of Wahabi et al., the 5-min Apgar score was no different. In the study of Keshavarz et al., no significant difference was reported between the two groups in terms of the 1-minute Apgar score [23]. Low Apgar score of neonates in the case group reflects fetal complications during childbirth, which can be linked to diabetes in the mother and fetus. The survival of these infants in extrauterine life is another problem, which is not unexpected considering high NRBC in the blood of infants and acidosis.

In this study, a threefold increase was observed in the need for resuscitation and ventilation in the delivery room for infants of diabetic mothers (P-value <0.001). In the study of Foeller et al., NICU hospitalization and the need for ventilation in infants born to diabetic mothers were higher than in the control group [34]. Gestational diabetes increases the risk of resuscitation in these infants by raising the risk of prematurity. According to the findings of these studies, there is a significant need for ventilation in these infants, which calls for close monitoring.

In this study, ROP in infants born to diabetic mothers was about 1.5 times higher than in the control group (P-value = 0.042). In the study of Tunay et al., the incidence of ROP in infants of diabetic mothers was 20 percent higher in infants born to healthy mothers [35]. Mohamed et al. found a significant relationship between ROP and hyperglycemia [36]. In the study of Kavurt et al. on neonates with ROP and healthy ones, maternal gestational diabetes was not reported as a risk factor for neonatal retinopathy [37]. ROP takes place in two phases of pathological changes. The first phase begins with the hampered growth of retinal artery after the birth of premature infant. When the preterm infant is exposed to high concentrations of oxygen, it provokes a relative hyperoxic condition, which leads to the vascular endothelial growth factor (VEGF) and subsequent regression of the retinal arteries. In the second phase of ROP, a relative hypoxic state emerges after the oxygen is cut off and the oxygen pressure is normalized. Also, the metabolic needs of the vascular retina increase as the newborn grows. Therefore, increased oxygen demand inflicts ischemic damage to the retina. This relative hypoxia in the retina leads to abnormal vascular proliferation and neovascularization. The neonatal hypoxia of diabetic mothers can exacerbate this condition. On the other hand, severe asphyxia in these infants and a greater need for resuscitation and oxygen prescribed during resuscitation can lead to an intensification of retinal vascularization and ROP due to the production of free radicals [38]. One of the limitations of this study was that we neither evaluated maternal diabetes status during pregnancy nor performed screening to control and treat GDM.

## **Conclusion**

The results of this study suggested that diabetic mothers tend to be older and more vulnerable to PROM, the risk of preterm delivery, and C-section. Also, the infants of these mothers need more resuscitation and are at higher risk of ROP. Therefore, monitoring mothers for prevention and early diagnosis of diabetes and its treatment may mitigate the complications facing these mothers and their fetus. Moreover, the presence of a stand-by resuscitation team at the bedside of a diabetic mother may help resolve newborn complications.

## **COMPLIANCE WITH ETHICAL STANDARDS**

### **Author contribution:**

Dr. Boskabadi and Dr. fatemeh bagheri Conceived and designed the analysis; Contributed data or analysis tools; Performed the analysis and Wrote the paper.

Nazgol Behgam and Dr. fatemeh bagheri Collected the data.

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### **Study registration:**

This study doesn't need registration

### **Disclosure statements:**

The authors declared no potential or actual interests relevant to the research, authorship, and publication of this study.

### **Ethical Approvals:**

This study approved by the Organizational Ethics Committee of Mashhad University of Medical Sciences, (research code: 990515 - and code of ethics: IR.MUMS.MEDICAL.REC.1399.258 -).

### **Informed consent:**

This study doesn't need patient informed consent.

### **Data sharing:**

The datasets generated and/or analyzed during this study included in the results.

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Table 1. Comparison of maternal and neonatal characteristics of the two groups.

<b>Variables</b>	<b>Group</b>	<b>Mean <math>\pm</math> SD</b>	<b>P-value</b>
<b>Maternal age (year)</b>	Normal	27.72 $\pm$ 6.42	< 0.001
	Diabetic	32.26 $\pm$ 5.93	
<b>Parity</b>	Normal	2.10 $\pm$ 1.37	0.538
	Diabetic	2.22 $\pm$ 1.23	
<b>Gestational age (week)</b>	Normal	35.03 $\pm$ 2.46	0.108
	Diabetic	33.88 $\pm$ 2.73	
<b>1-min Apgar</b>	Normal	7.08 $\pm$ 1.65	0.013
	Diabetic	6.39 $\pm$ 2.30	
<b>5-min Apgar</b>	Normal	8.18 $\pm$ 1.58	0.871
	Diabetic	8.15 $\pm$ 1.50	
<b>Weight (gr)</b>	Normal	1869.76 $\pm$ 810.52	0.123
	Diabetic	1716.47 $\pm$ 742.95	

Table 2. Comparison of maternal and neonatal outcomes in the two groups.

Parameters	GDM group (N =99 )	Control group (N = 196)	P-value
PROM* (%)	11.1	3	<b>0.014</b>
C-section (%)	78.8	52.6	<b>0.001</b>
ROP* (%)	74.5	55.1	<b>0.042</b>
CPR in the delivery room* (%)	29.2	9.4	<b>0.001</b>
Ventilation in the delivery room (%)	9	3.6	<b>0.031</b>
Cord PH	7.25 ± 0.11	7.28 ± 0.11	<b>0.124</b>
WBC*	14350 ± 1279	13720 ± 820	<b>0.771</b>
NRBC/100*	121.70 ± 31.89	45.54 ± 34.77	<b>0.156</b>

(Fisher's exact test was used to analyze variables such as type of delivery and ROP and Chi-square test was utilized to examine variables of PROM, CPR, and ventilation in both groups. Independent t-test was used to compare WBC, NRBC, and PH factors in the two groups. \*PROM: Prolong Premature Rupture of membrane, \* ROP: Retinopathy of Prematurity, \* CPR: Cardiopulmonary Resuscitation, \*WBC: White blood cell, \*Nucleated red blood cell)