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Diabetes Consequences on Preterm Premature Rupture of Membrane Complications

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ABSTRACT

Background and Objective: Diabetes mellitus and gestational diabetes are complications that may be associated with preterm premature rupture of the membrane (i.e. PPROM) during pregnancy. We have investigate the impact of gestational and overt diabetes on PPROM through a statistical campaign.

Methods: This study was conducted in two parts: In the first part, the PPROM patients (211 cases) were classified into three groups, without diabetes (W/ODM=126 cases), gestational diabetes (GDM=69 cases consist of 44 cases under insulin therapy and 25 cases of diet controlled), and diabetes mellitus (ODM=16 cases). PPROM complications were studied and compared between these three groups. In the second part, GDM patients under insulin therapy or diet control were compared to W/ODM patients in terms of PPROM complications.

Results: There were no significant statistical differences between the groups regarding pregnancy outcomes, except, for mean gestational age at rupture of membrane and delivery. For maternal outcomes, there were significant changes between groups in terms of labor duration, hospital stay after childbirth, and severe preeclampsia. Fetus and neonatal outcomes suggested that the newborn weight, neonatal hyperglycemia, Apgar score, revive need, infant death, and umbilical cord blood gas test results (except BE) were significantly different between the three groups. Results of the second part of the study, in terms of statistically significant differences between insulin therapy, diet control, and W/ODM are consistent with the first part, for all discussed factors.

Conclusion: Results revealed that PPROM protocol management on PPROM cases who have gestational or overt diabetes is applicable and does not have any further risk.

Keywords Diabetes, Premature rupture of the membrane (PPROM), Insulin therapy, Gestational diabetes

Introduction

Preterm premature rupture of membrane takes place in up to three percent of pregnancies, which is accounts for 35 percent of all preterm births **(1)**. The pathogens and leading causes of PPROM (i.e. spontaneous rupture of membrane before 37 weeks of pregnancy and before labor) are not completely understood. PPROM likely has various causes, but intrauterine infection is believed by many to be a major predisposing event **(1,2)**. Intrauterine infection activates the matrix metalloproteases by creating an inflammatory environment that disrupts membrane strength and leads to membrane rupture **(3)**. In addition to prematurity which is one of the most important causes of infant mortality, PPROM increases the risk of maternal complications such as chorioamnionitis, placental abruption, high rate of csarean section (C/S), increasing hospital stay, postpartum Hemorrhage, etc. As a result, pregnancies complicated by PPROM are associated with significant neonatal and maternal mortality and morbidity, with high immediate and long-term costs.

Diabetes is the most common medical complication of pregnancy. Of all pregnancies, 9 to 10 percent are involved with diabetes **(4)**. Approximately 1-2 percent of women had overt

diabetes before their pregnancy and 3-21 percent of pregnant women were diagnosed with gestational diabetes (GDM) during their pregnancy **(5)**. Diabetes prevalence in Iran is approximately 6% of pregnancies **(6–8)**. Complicated pregnancy with diabetes either overt diabetes (ODM) or gestational diabetes (GDM) seriously endangers the embryo, fetus, and mother's health **(9,10)**. Some fetal and neonatal complications are as follows: increasing chance of preterm birth (either preterm labor and PPROM or indicated preterm birth) **(11)**, macrosomia **(12–14)**, hypoglycaemia. **(15)**, cardiomyopathy **(16)**, etc. Diabetes also is problematic for mothers such that maternal welfare can be seriously jeopardized by increasing infection risk **(17)**, csarean rate **(18–20)**, and pregnancy-induced hypertension (HTN) **(18,21)**. In addition, a significant increase in type 2 diabetes is expected in women with GDM. It is estimated that half of these women will develop diabetes over the next 20 years **(22,23)**.

In conclusion, diabetes probably increases the risk of PPROM prevalence and maternal/neonatal complications during pregnancy **(24)**. Despite the importance and vitality of diabetes and PPROM in pregnant women, there have been few studies that specifically investigated PPROM complications among different kinds of diabetic (GDM or ODM) gravidas. This could be due to the complexity and number of different factors involved in this issue.

Kari *et al.*, **(25)** studied PPROM cases between three groups of pregnant women who were with diabetes (ODM or GDM) and without diabetes (W/ODM) between 2014 and, 2015 (for 15 months). They showed that the three groups were similar for the remaining endpoints, except for length of maternal hospital stay, duration of vaginal delivery, and significantly lower incidence of neonatal hypoglycemia in normoglycemic mothers **(25)**.

In the first part of this study, following Kari *et al.*, **(25)**, we decided to investigate maternal and neonatal complications of a wider range of PPROM and diabetic cases during the following years from April 2016 to September 2020 who attended the same medical center. In the second part of the study, in order to assess the severity of diabetes on PPROM complications, we comparted the maternal and neonatal outcomes between the two subgroups of GDM patients which were insulin and diet-controlled PPROM patients

This paper aims to investigate the impact of being diabetic and the variation of diabetes control approaches in PPROM cases through an extensive statistical campaign. We proposed to revisit many criteria related to both PPROM and diabetic pregnant women and to study the risk factors and outcomes.

Materials and Methods

This retrospective cross-sectional study included target population pregnant women who were hospitalized between 24 and 34 weeks of pregnancy in Al-Zahra Medical-Educational Center of Tabriz from April 2016 to September 2020 (about 53 months). During these 53 months, all diabetic (ODM or GDM) pregnant women who have been admitted with PPROM diagnosis and without exclusion criteria were selected for the study. Due to the diabetes prevalence in Iran, screening gestational diabetes is performed by OGTT 75 gr GLC test for all pregnant women at gestation age between 24 and 28 weeks. According to the Diabetes and Pregnancy Research Association consensus panel **(26)**, by using a one-step approach gestational diabetes is diagnosed in case of the following conditions **(27)**:

$$\begin{cases} \text{FBS} \geq 92\,\text{mg/dl} \\ 1-\text{hr OGTT} \geq 180\,\text{mg/dl} \\ 2-\text{hr OGTT} \geq 153\,\text{mg/dl} \end{cases} \quad (1)$$

For the control group, an estimated sample size of 126 PPROM cases who were without diabetes were selected and compared in terms of maternal and neonatal consequences. Exclusion criteria from the study were multiple pregnancies, congenital anomalies, placental complications, fetal growth restriction, and polyhydramnios. All collected patients received local standard PPROM management protocol. According to the PPROM protocol of Al-Zahra Medical-Educational Center, patients were managed expectantly until the end of 34 weeks of pregnancy, and if the labor has not been started, the pregnancies were terminated.

The patients were classified into three groups, without diabetes (W/ODM): 126 cases, gestational diabetes (GDM): 69 cases which consist of 44 cases with insulin therapy and 25 cases with diet control, and overt diabetes (ODM): 16 cases all with insulin therapy. The patients' information was kept confidential.

In this study, the investigated baseline maternal characteristics are the patient's age, BMI, gravid, and history of premature delivery. The analyzed maternal factors in the study are: mean gestational age at rupture of membrane, latency hours between PPROM and labor onset, and mean gestational age at delivery, labor duration, hospital stay after childbirth, blood transfusion, severe preeclampsia, and chorioamnionitis. Fetal and neonatal analyzed factors are newborn's weight, Apgar score, umbilical cord blood gas (ABG) test results, reviving newborns, infant death, respiratory distress, hypoglycemia, jaundice, and neonatal infection. Also, the possibility of emergency

csarean section (C/S) and other kinds of delivery (e.g. natural vaginal delivery and surgical delivery) were studied. For a more detailed study of diabetes severity and the effect of insulin and diet control on PPROM gravidas, we investigated the maternal and neonatal complications in two subgroups of GDM (consist of diet and insulin controlled).

Data were analyzed using SPSS version 16. The normality of continuous variables was tested using the One-Sample Kolmogorov–Smirnov Test. One-way analysis of variance (ANOVA) with Tukey's test was used for normal distributions to compare the quantitative variables. Meanwhile, for abnormal distributions, the Kruskal-Wallis test was used. Categorical variables were compared by chi-square test or Fisher's exact test where appropriate. The significant level was $P < 0.05$.

Results

Characteristics of Patients

Baseline characteristics of study subjects are shown in Table 1. It could be observed that for both GDM and ODM groups, the mean age and body mass index (BMI) of mothers were significantly higher than the W/ODM group (P = 0.003 and 0.004 respectively). As shown, no statistical differences were observed regarding gravid and history of preterm delivery between the three groups (P > 0.05). However, the prevalence history of preterm delivery for both GDM and ODM is about (0.2/0.08=2.5) 2.5 times higher than W/ODM women.

Table 1. Baseline maternal characteristic in three study groups

	Age	BMI (kg/m^2)	Gravid	History of preterm delivery
W/ODM	29.5 ± 7.5	28.2 ± 4.2	2.2 ± 1.5	0.08 ± 0.5
GDM	33.0 ± 5.4	30.1 ± 3.2	2.4 ± 1.2	0.2 ± 0.4
ODM	30.6 ± 5.3	31.2 ± 6.4	2.7 ± 7.5	0.2 ± 0.3
Total	30.7 ± 6.9	28.9 ± 4.2	2.3 ± 1.4	0.1 ± 0.4
P-value	0.003	0.004	0.23	0.22

Pregnancy Outcomes

As shown in Table 2, both mean gestational age at PPROM onset and delivery in W/ODM were less than two other diabetic groups (P = 0.04). However, no significant statistical difference was found between the three groups in terms of latency period between PPROM and labor onset &/or delivery (P = 0.12).

Table 2. Primarily pregnancy outcomes between W/ODM, GDM, and ODM

	W/ODM	GDM	ODM	P-value
Mean gestational age at PPROM onset	30.8 ± 3.3	32.1 ± 2.3	31.4 ± 3.9	0.047
Mean gestational age at delivery	31.3 ± 3.3	32.4 ± 2.0	31.6 ± 3.9	0.04
Latency hours*	91.6	56.9	18.6	0.12

* Between PPROM and labor onset or C/S delivery

The same results were obtained between GDM with diet control and insulin therapy Table 3. For latency hours, no considerable difference has been shown between the three groups and the average gestational age at PPROM and delivery was significantly higher in W/ODM (P =0.04).

Table 3. pregnancy outcomes between W/ODM, diet control, and insulin therapy

	W/ODM	Diet control	Insulin therapy	P-value
Mean gestational age at PPROM onset	30.8 ± 3.3	32.1 ± 2.5	32.1 ± 2.3	0.01
Mean gestational age at delivery	31.31 ± 3.3	32.46±2.2	32.43±1.9	0.04
Latency hours*	91.6	51	60.2	0.4

* between PPROM and labor onset or C/S delivery

The reasons for pregnancy termination are shown in Table 4. According to this table, the most common reasons for pregnancy termination are preterm labor (PTL) and the end of 34 weeks, which were not significantly different among the three groups (P = 0.9 and P = 0.3, respectively). However, the W/ODM group had significantly higher indicated termination cases than ODM and GDM patients (P = 0.03). For the indicated termination, fetal distress is the most common reason among others.

Table 4. Pregnancy termination reasons between ODM, GDM, and W/ODM groups

Cause	W/ODM No (%)	GDM No (%)	ODM No (%)	p-value
End of 34 week	46 (37)	32 (46)	8 (50)	0.3
PTL	59 (47)	34 (49)	7 (44)	0.91
Indicated termination	21 (17)	3 (4)	1 (6)	0.03
total number	126	69	16	-

In this study, in terms of delivery methods, Table 4 showed that the prevalence of csarean section (C/S) and vaginal delivery (NVD) cases were not significantly different between all groups (P > 0.05). Also, no considerable difference was observed for the emergency C/S among the three groups (P = 0.17). Moreover, Table 5 demonstrated that the total C/S and NVD cases are 117 (55%) and 94 (45%), respectively. Thus, the average csarean section cases were about 1.2 times higher than vaginal delivery cases. Csarean section surgery reasons are presented in Table 6 between ODM, GDM, and W/ODM groups. The childbirth methods for GDM subgroups of diet control and insulin therapy, Table 7 are the same as Table 5. Thus, there are no significant changes for childbirth methods between the subgroups and the control group.

Table 5. Delivery method of ODM, GDM and W/ODM groups

	W/ODM (%)	GDM (%)	ODM (%)	P-value
Emergency C/S	40 (62)	14 (33)	6 (60)	0.17
Total C/S section	65 (52)	42 (61)	10 (62.5)	0.39
Total NVD	61 (48)	27 (39)	6 (37.5)	0.39
Total cases	126	69	16	

Table 6. Summary of the reasons for having csarean section surgery between ODM, GDM, and W/ODM groups

Cause	W/ODM No (%)	GDM No (%)	ODM No (%)
The history of C/S section	25 (38.5)	28 (66.7)	4 (40)
Meconium	3 (4.6)	4 (9.5)	0 (0)
Cardiotocographic abnormalities	20 (30.8)	4 (9.5)	2 (20)
Placental abruption	2 (3.1)	1 (2.4)	0 (0)
Malpresentation	11 (16.9)	4 (9.5)	3 (30)
Failure of induction	3 (4.6)	1 (2.4)	0 (0)
Severe preeclampsia	1 (1)	1 (2.4)	3 (30)
Umbilical cord prolapse	1 (1.5)	0 (0)	0 (0)
Total C/S section	65	42	10

Table 7. Delivery method of diet control, insulin therapy and W/ODM groups

	W/ODM (%)	Diet control (%)	Insulin therapy (%)	P-value
Emergency C/S	40 (32)	4 (16)	10 (23)	0.19
Total C/S section	65 (52)	14 (56)	28 (64)	0.39
Total NVD	61 (48)	11 (44)	16 (36)	0.39
Total cases	126	25	44	

Maternal Outcomes

Table 8 shows maternal outcomes among PPROM patients. Based on the results of the statistical tests, there were no significant differences between the three groups in terms of blood transfusion (P = 0.96) and chorioamnionitis in labor cases (P = 0.77). However, the W/ODM and GDM group had a significantly lower rate of severe preeclampsia than ODM patients (P = 0.002). There was a considerable statistical difference between the groups in terms of NVD labor duration (P = 0.004). This difference was significant between the W/ODM and both diabetic groups. While the hospital stay after childbirth is significantly higher in diabetic groups compared to the W/ODM group (P < 0.001).

Table 8. Maternal outcomes

	W/ODM No (%)	GDM No (%)	ODM No (%)	P-value
Blood transfusion	6 (4.8)	8 (11.6)	2 (12.5)	0.96
NVD labor duration	4.7	3.2	1.5	0.004
Severe preeclampsia	1 (1)	1 (3)	3 (19)	0.00
Chorioamnionitis	3 (2.4)	1 (1.4)	0 (0)	0.77
Hospital stay period after childbirth	1.1 ± 0.4	1.4 ± 0.8	1.7 ± 0.6	0.00

Fetus and Neonatal Outcomes

The primarily neonatal outcomes are summarized in Table 9. Neonates from the GDM and ODM groups had a significantly higher birth weight (P < 0.001) than the control group. The average fifth Apgar was significantly higher (about 20%) in GDM than in the two other groups (P < 0.001). Need to revive newborns cases were significantly lower in GDM, as well as the ODM than W/ODM cases (P < 0.001). The umbilical cord blood gas pH was significantly lower in the ODM group than the other groups, while for BE, the ODM had the largest average amount.

Table 9. Primarily fetus and neonatal outcomes

	W/ODM	GDM	ODM	P-value
Newborn weight (gr)	1870.8	2417.4	2157.5	0.00
The mean Apgar score of the fifth minute	8.1 ± 2.8	9.5 ± 0.9	8.1 ± 2.9	0.00
Need to revive newborns	80 (63.5%)	11 (15.9%)	2 (12.5%)	0.00
BE *	no data	6.3 ± 2.8	10 ± 0.0	0.22
PH *	7.3 ± 0.1	7.3 ± 0.1	7.2 ± 0.1	0.02
HCO^3 (mE/L)*	19.8 ± 4.1	21.2 ± 3.9	21.8 ± 4.5	0.07
PCO^2 (mmHg)*	39.4 ± 10.1	44.1 ±13.2	58.0 ± 18.6	0.00

* Umbilical cord gas test results

Table 9 showed secondary fetus and neonatal outcomes. hypoglycemia and infant death are both statistically different between the three groups. The ODM group had significantly higher hypoglycemia cases (P < 0.001) compared to W/ODM and GDM. There was a statistically considerable difference in terms of infant death cases between GDM and two other groups, with P = 0.008. For all cases, the most common cause of infant death was preterm birth. According to Table 10, the three groups were not statistically different in terms of respiratory distress (P = 0.59) and infection (P = 0.65) as well as neonatal jaundice (P = 0.8).

Table 10. Secondary fetus and neonatal outcomes

	W/ODM	GDM	ODM	P-value
Respiratory distress	85 (67.5%)	48 (69.6%)	10 (62.5%)	0.59
Hypoglycemia	0 (0%)	3 (4.3%)	3 (18.8%)	0.00
Infant death	16 (12.7%)	0 (0%)	2 (12.5%)	0.008
Neonatal jaundice	72 (57.2%)	36 (52.2%)	9 (56.3%)	0.801
Infection	53 (42.1%)	33 (47.8%)	6 (37.5%)	0.653

The maternal and neonatal outcomes for the GDM subgroups (i.e. diet and insulin therapy) and control group are summarized in Table 11. From this table, it could be concluded that the results between the two subgroups of insulin therapy and diet control are the same as the three general groups (ODM, GDM, and W/ODM). Therefore, as also shown in Table 11 the maternal and neonatal outcomes with statistically significant differences are: mean gestational age at delivery (P = 0.04), newborn weight (P = 0.00), need to revive newborns (P = 0.00), and infant death (P = 0.01). The mean gestational age at delivery in the W/ODM group is significantly lower than diet and insulin groups. Neonates from the insulin therapy group had a significantly higher newborn weight compared to other groups. The average birth weight in the insulin group is about 530 gr and 110 gr higher than W/ODM and diet group respectively. The W/ODM group has significantly the highest need to revive and infant death cases.

Table 11. Maternal and neonatal outcomes of diet control, insulin therapy, and W/ODM groups

Outcomes	W/ODM	Diet control	Insulin therapy	P-value
Mean gestational age at delivery	31.31 ± 3.3	32.46±2.2	32.43±1.9	0.04
PTL	59 (47)	14 (56%)	20 (45.5%)	0.67
Chorioamnionitis	3 (2.4)	0 (0%)	1 (2.3%)	0.74
Severe preeclampsia	1 (0.8%)	0 (0%)	1 (2.3%)	0.61
Newborn weight (gr)	1870.8±662.4	2291.2±638	2489.1±727.1	0.00
Need to revive newborns	80 (63.5%)	5 (20%)	8 (18.2%)	0.00
Infant death	16 (12.7%)	0 (0%)	2 (4.5%)	0.01
PH	7.32 ± 0.10	7.31 ± 0.09	7.28 ± 0.11	0.14
Neonatal jaundice	72 (57.1%)	14 (56%)	22 (50%)	0.72
Infection	53 (42.1%)	11 (44%)	22 (50%)	0.66
Respiratory distress	85 (67.5%)	18 (72%)	30 (68.2%)	0.91

Discussion

Diabetes, either gestational or pre-gestational, is a serious medical problem that causes common maternal and neonatal mortality and morbidity. Moreover, its complications will continue after pregnancy ends for both mothers and newborns **(28,29)**. Therefore, the study of diabetes (GDM or ODM) and its controlling approaches (i.e. insulin or diet control) is important in finding appropriate therapies which could decrease the adverse pregnancy outcomes. On the other hand, some previous studies have indicated that mothers with diabetes had higher risk of PPROM compared to women without diabetes (W/ODM) **(30)**. Bouvier *et al.*, **(31)** performed a prospective study of risk factors and outcomes of PPROM, based on a large, unselected cohort. Their study confirmed the biggest risk factors of PPROM are gestational ODM (GDM), low BMI, history of PPROM, and low education level. Also, Bhat *et al.*, **(24)** compared pregnant women with GDM and W/ODM in terms of PPROM occurrence. Their results showed that the probability of developing PPROM in the first group was much greater than that in the second group. Similarly, Köck *et al.*, **(30)**, Al Riyami *et al.*, **(32)**, and Muche *et al.*, **(33)** noted that the risk of PPROM was significantly higher in the diabetic group than in the normal group. As seen in previous studies, the maternal and neonatal consequences of simultaneous PPROM and diabetes and most importantly the effects of diabetes therapy approaches were not studied completely. Therefore, a better understanding of the relationships between these conditions can lead to a more effective strategy implementation to decrease maternal and neonatal morbidities of PPROM among diabetic gravidas.

In the first part of this study, increased BMI and maternal age were significant in diabetic groups. For both GDM and ODM groups, the BMI was more than 30 which is considered obesity. Bouvier *et al.*, **(31)** suggested that factors such as maternal age and increased BMIs, might interact with other factors (e.g. hard-working) and increase PPROM risk factors and prematurity. Nohr *et al.*, **(34)** Showed that the risk of PPROM and of induced preterm birth were higher in obese females (BMI ≥ 30), about twice, than in normal-weight females, especially by the end of 34th week of gestation. In this study, as well as previous studies, the history of preterm labor (PTL) is higher (but not significant) in the GDM group (see 0) than in the control group, while at the same time, the mean gestational age at delivery for W/ODM is lower than diabetic groups.

In our study, the most common reasons for pregnancy termination in every group were preterm labor and reaching the end of 34 weeks of pregnancy. The latency period and the incidence of chorioamnionitis were not varied between ODM, GDM, and W/ODM groups. The only considerable difference in terms of pregnancy termination was the indicated termination in which fetal distress was the most common reason. The significant difference in indicated termination between groups may be due to the greater number of control group cases. The same results were observed for the GDM subgroups (i.e. insulin and diet control). These results demonstrate that the expectant management of PPROM until the end of 34 weeks in both diabetic groups has not increased the maternal infection and the risk of preterm labor, compared to non-diabetic gravidas. Yogev **(35)** showed that the rate of spontaneous preterm birth in GDM does not increase compared to patients without GDM, but achieving established glycemic control levels may reduce the rate of spontaneous preterm birth in GDM. As shown in 0 their results are consistent with our results, as the emergency C/S is lower for GDM compared to the control group. Sheiner *et al.*, **(36)**, Torres **(37)**, and Kessous *et al.*, **(38)** demonstrated that the ODM in PPROM cases has an increased risk of chorioamnionitis in parallel with the increased risk of other infections; whereas Kari *et al.*, **(25)** observed no significant relationship between maternal chorioamnionitis and PPROM occurrence in the diabetic patients rather the women in the nondiabetic group. The results from our study are consistent with those

obtained by Kari *et al.*, **(25)** in terms of the relationship between PPROM and diabetes and the occurrence of maternal infection.

As shown, for all groups, the rate of C/S was more than NVD, but there was no considerable difference between the three groups regarding overall C/S and emergency C/S prevalence. We found that the csarean delivery for PPROM cases is 50% more common in pregnant women with GDM or ODM than nondiabetic women. Previous studies have also shown that the risk of csarean section is higher (about 30% to 35%) among diabetics than W/ODM patients **(13,14,39)**. Diabetes alone is not an indication for C/S before 38 weeks of gestation, it becomes evident that C/S may be the preferred choice for many obstetricians due to the various maternal and fetal complications associated with diabetes **(40)**.

The interesting point about our study is the long labor duration (active phase of labor) in W/ODM groups. The newborn weight and gestational age were both higher in GDM and ODM groups, but the labor duration was higher in the W/ODM group. Although it's impossible to get an accurate conclusion because of the small number of NVD cases, we could approximately explain this result as follows: 1) the smaller size of neonates of W/ODM may cause lower head compression pressure on the cervix which can make the active phase of labor longer, 2) another possible reason is that because of the lower gestational age of the control group; the existing number of oxytocin receptors are less than both diabetic groups.

The results suggested, for maternal outcomes, one of the significant differences among the groups was the shorter stay duration of W/ODM mothers after delivery, which was consistent with the Kari *et al.*, **(25)**. ODM group has the highest hospital stay of all other groups. Also, serve preeclampsia was found significantly higher in ODM groups compared to others. Wen *et al.*, **(41)** demonstrated that preeclampsia is associated with a longer postoperative length of stay during delivery hospitalizations. Thus, in our study, the mean longer hospital stay for ODM might due to the higher preeclampsia cases in this group. Another reason that could explain the longer hospital stay for ODM is the longer time needed to control the serum blood glucose after delivery and change the insulin to the oral anti-glycemic agent.

As is shown in the result part, the considerable differences in neonatal outcomes were lower birth weight, lower fifth Apgar score, higher rate of reviving neonates, and more infantile death in the W/ODM group which all could be explained by the less gestational age at delivery of this group. The rate of neonatal respiratory distress was not significantly different between the three groups. However, Kari *et al.*, **(25)** reported that the gestational age at delivery, Apgar score, need to revive newborn, fetal distress, and NICU admission were not significantly different between the three groups. When we compared the mentioned neonatal outcomes between subgroups of the GDM and the W/ODM group, we reached the same results. Therefore, it seems that the only leading cause of significant differences in neonatal outcomes is the less gestational age at delivery of the W/ODM group.

Regarding neonatal infections in PPROM cases, unlike Hollingsworth *et al.*, **(42)**, our results indicated that there is no significant relationship between neonatal infection and PPROM occurrence in diabetic women rather the women in the control group.

In our study, the rate of neonatal hypoglycemia was considerably higher in the groups with GDM and ODM compared to the diabetes-free group. Consistent with our study, Magee *et al.*, **(43)**, Boriboonhirunsarn *et al.*, **(20)**, and Bhat *et al.*, **(24)** implied that hypoglycemia is the most prevalent neonatal complication related to maternal diabetes. However, Kari *et al.*, **(25)** reported in their study that the relationship between diabetes and hypoglycemia was only found in ODM rather than GDM.

The umbilical cord blood gas test results showed significantly lower pH levels with high base excess and PCO2 for neonates of the ODM group. This mixed metabolic mild acidosis could be due to chromic stress in the uterine environment of the fetal life of these cases. This chronic stress as Aalipour *et al.*, **(44)** showed in their study could be due to pre-existing hyperinsulinemia and hypoglycaemia in the uterine environment because of pregestational maternal diabetes.

In the second part of this study, the influences of diet and insulin therapy on neonatal and maternal consequences of PPROM cases were studied. Previous studies highlighted the fact that insulin therapy, effective treatment regimens consisting of dietary and exercise are beneficial approaches for the wellbeing of mothers, the growing fetus, and the new-born health **(29,45)**. However, little is known about the effects of diabetes therapy approaches on PPROM cases. It is interesting to note that our results in the second part of the study confirm the first part.

Conclusion

The strengths of our study are the big size of PPROM patients conducted for the first time, and about 20 different maternal and neonatal study factors. The effects of gestational/mellitus diabetes and PPROM on the occurrence of maternal/neonatal sequelae were separately compared in this study. More importantly, the

effect of the different types of GDM management (i.e. insulin and diet-controlled) on PPROM maternal and neonatal consequences were studied.

Our study demonstrates that conducting PPROM protocol management on PPROM cases who have gestational or overt diabetes do nothave any further risk on maternal and neonatal consequences. Due to the retrospective nature of this study, unfortunately, the past ODM patients' records were incomplete, and also the diabetes severity based on HbA1C and FBS average was not available, accordingly the comparison of PPROM complications was not possible. Therefore, in further prospective studies, it is necessary to compare the complications of PPROM in ODM patients with diabetes type I and type II. Also, studies with larger sample sizes especially with more overt diabetic patients which could be matched in terms of baseline characteristics and the gestational age of PPROM onset must be designed to assess maternal and neonatal complications and to evaluate long-term follow-up of mothers and children. However, it seems that until then, there is no need to change the PPROM management protocol for diabetic gravidas.

Compliance with Ethical Standards

Ethical Issues

This study was approved by the ethical committee of Tabriz University of Medical Sciences (approval number: IR.TBZMED.REC.1400.136/ date: 2021/05/03).

Informed consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

Acknowledgment

None.

Conflict of interest

Authors declared that they have no conflict of interest.

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