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Neonatal Outcomes in Gestational Diabetes Mellitus

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Abstract

Background Gestational diabetes mellitus (GDM) is a common and serious maternal complication, in which hyperglycemia develops at any time during pregnancy due to progressive insulin resistance. It affects about 14% of pregnancies worldwide. There are many adverse effects of GDM that compromise the fetus and neonate.

Objective To compare neonatal outcomes according to type of treatment for GDM.

Methods A prospective study conducted at the Department of Pediatrics, (Neonatal Intensive Care Unit; NICU) and Obstetric in Al-Imamein Al-Kadhimein Medical City in Baghdad during a period from 1st of march 2019 to 1st of January 2020. The study included 100 neonates delivered by mothers with GDM, divided in to four groups according to their mothers' therapy; (diet group: 18 neonates, metformin group: 36, insulin group: 26, mixed group: 20).

Results Neonates in metformin group had a higher chance of having normal birth weight comparing with others, but neonates in insulin group have higher percent of prematurity, macrosomia, large for gestational age or small for gestational age, hypoglycemia and jaundice among others. No significant statistical difference between metformin and insulin, in mode of delivery, Apgar score, respiratory distress syndrome, hypocalcaemia, anomalies, and NICU admission but can occur more in insulin group.

Conclusion Metformin was able to reduce the risk of neonatal complications, therefore, it can be a good alternative for insulin in the treatment of GDM.

Keywords Gestational diabetes mellitus, macrosomia, metformin, insulin

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List of abbreviations: ANC = Antenatal care, CHD = Congenital heart disease, GDM = Gestational diabetes mellitus, HR = Heart rate, IDF = International diabetes federation, LGA = Large for gestational age, NICU = Neonatal intensive care unit, OFC = Occipital frontal circumference, PCV = Packed cell volume, RR = Respiratory rate, RDS = Respiratory distress syndrome, SGA = Small for gestational age

Introduction

Gestational diabetes mellitus (GDM) is one of the most common and serious conception complications, in which spontaneous hyperglycemia develops at any time during pregnancy [(1)]. According to the most recent (2017) International Diabetes Federation (IDF) estimates, GDM affects approximately 14% of pregnancies worldwide, representing approximately 18 million births annually [(2)]. Risk factors include overweight/obesity, westernized diet and micronutrient deficiencies, advanced maternal age, a family history of insulin resistance and/or diabetes, and ethnicity among women [(3)]. Pregnancy itself is characterized by insulin resistance [(4)]; placental production of diabetogenic hormones such as human placental lactogen in late pregnancy, leading to

progressive insulin resistance; when adaptation of β-cell hyper functionality during pregnancy fails to compensate maternal insulin resistance, GDM develops [5,6]. In utero, exposure to maternal hyperglycemia increases the incidence of perinatal complications. There are many adverse effects of GDM that compromise the fetus including, fetal anomalies or intrauterine death, macrosomia, birth injuries and asphyxia, respiratory distress syndrome, metabolic disorders, growth imbalance, hypoglycemia, hyperbilirubinemia, polycythemia, hypocalcaemia, and some long-term complications. More significantly, GDM places the offspring at risk of insulin resistance and type 2 diabetes mellitus, obesity and cardiovascular disease in adulthood [7-9]. Considering adverse effects mentioned, GDM treatment seems to have great importance and benefits [10]. Medical treatment is initiated if glucose control levels are not achieved by lifestyle modifications such as exercise and dietary changes [11]. Traditionally, insulin has been the golden key for treatment in GDM patients. No placental passage and fine glucose level control, are established benefits of insulin administration in pregnancy [12]. On the other hand, insulin usage has some disadvantages and doubts remain about insulin consumption inconveniences in pregnancy. These include the need for multiple injections, maternal hypoglycemic risk, higher maternal weight gain during pregnancy (possibly due to increased appetite), and increased treatment cost [13]. Various studies have shown that an oral anti glycemic drug may not only have better maternal and fetal consequences but also could bring patients' acceptance [14]. Metformin has been introduced as an alternative drug for insulin in GDM treatment theoretically [15]. This agent induces less gluconeogenesis and higher peripheral glucose uptake. Reducing insulin resistance is of great concern as well many studies approved that metformin did not induce maternal hypoglycemia, excessive maternal weight gain during pregnancy, and major fetal anomalies [16]. In some other studies, it has been shown that metformin administration in GDM has not been accompanying neonatal disorders [4,17].

This study aimed to compare neonatal outcomes according to type of treatment for GDM.

Methods

A cross-sectional study conducted at Department of Pediatric and Obstetric in Al- Al-Imamein Al-Kadhimein Medical City in Baghdad during a period from 1st of March 2019 to 1st of January 2020. The study included 100 neonates delivered by mothers with GDM, the mother's age between 18-45 years old, who had been already diagnosed by obstetrician and gynecologist and on treatment with exclusion of mothers with type 1 and type 2 diabetes mellitus, other chronic diseases and with still birth. All mothers were selected from post-delivery ward in the hospital. Mother data was collected from the mothers themselves by direct questionnaire included the following: Mother age, last menstrual period (LMP), expected date of delivery (EDD), gravity, mode of delivery, type of therapy, antenatal care (ANC), their compliance with therapy, HbA1c was recorded in some of mothers. The evaluated neonatal outcomes data were collected by the neonatal intensive care unit (NICU) doctors or patients case sheets, soon post-delivery or during first week of life if admitted to NICU and included the following: Neonatal age, sex, birth weight, length, occipital frontal circumference (OFC), heart rate (HR), respiratory rate (RR), gestational age, weight in relation to gestational age, Apgar score at 1 and 5 minutes and any obvious congenital anomalies. After neonatal resuscitation, the blood glucose level of them checked during the first 2 hour after birth to detect hypoglycemia, specific investigations should be done according to the cause, such as packed cell volume (PCV) and total serum bilirubin in plethoric or jaundiced neonate, serum calcium if there is suspicion of hypocalcaemia, chest x-ray and echo study in respiratory distress syndrome (RDS) or

congenital heart disease (CHD). Finally, the neonates were divided in to four groups according to types of their mothers' therapy: diet group 18 neonates, metformin group 36, insulin group 26, and mixed group 20, and we evaluate their characteristic, complications and compare them among groups, according to their mother's treatment. All mothers were verbally informed about the study and they were asked permission to make their neonates being part of the study.

Statistical analysis

This is a cross-sectional study; data were presented as frequency and percentage. Comparison of variables between types of therapy of gestational diabetes using Fisher exact test, chi square and Yates chi square test were used. P value < 0.05 considered as level of significance. Statistical package for social sciences (SPSS) version 23 were used.

Results

The study sample consisted of 100 neonates of mothers diagnosed as gestational diabetes mellitus, and on treatment. After data collection they were grouped according to maternal therapy into four groups: 1. dietary therapy, 2. metformin, 3. insulin, 4. metformin and insulin. From a hundred mothers, eighteen mothers were treated with diet, thirty sex with metformin, twenty-six with insulin, and twenty with mixed (insulin and metformin). The neonatal outcomes were analyzed depend on the mother therapy used. The mean age of neonates was 2.01 days (SD±1.62).

Regarding sex of newborns, 53 (53%) of them were females, 47 (47%) were males, and 70 (70%) of them were delivered by cesarean section, 39 (39%) were preterm, 35 (35%) were macrocosmic babies, and 44 (44%) were of normal birth weight, and according to weight for gestational age chart, 45 (45%) of neonates were adequate for gestational age, 37 (37%) large for gestational age, and 18 (18%) small for gestational age.

Apgar score at five minutes was low in 54 (54%) of newborns and 78% of neonates need admission to NICU due to single or multiple complications and the remainder 22% were normal.

Diet and metformin treatment groups show higher rate of term delivery (72.2%) for both comparing to higher rate of prematurity in insulin treatment group (65.4%), also, there was significant difference in gestational age according to type of mother therapy (p value = 0.014) (Table 1).

Table 1. Comparison of gestational age according to maternal therapy

Parameter		Maternal therapy				P value*
		Insulin N=26	Mixed N=20	Diet N=18	Metformin N=36	
Gestational age	Preterm	17 (65.4%)	7 (35.0%)	5 (27.8%)	10 (27.8%)	0.014
	Term	9 (34.6%)	13 (65.0%)	13 (72.2%)	26 (72.2%)	
P value**	Insulin vs other groups		0.073	0.031	0.005	
	Mixed vs other groups			0.734	0.762	
	Diet vs metformin				1.000	

* Chi square test, ** Fisher exact test

Mothers who were treated with metformin had a higher chance of having babies with normal birth weight (55.6%) comparing with those treated with other therapies, but neonates in insulin group have higher percent of low birth weight (26.9%) and macrosomia (50%) among others (p value=0.038), which mean that there is a relation between neonatal birth weight and mothers' therapy (Table 2).

Table 2. Comparison of birth weight according to maternal therapy

Parameter		Maternal therapy				P value*
		Insulin N=26	Mixed N=20	Diet N=18	Metformin N=36	
Birth weight	Low	7 (26.9%)	5 (25.0%)	3 (16.7%)	6 (16.7%)	٠.٢٩٧
	Normal	6 (23.1%)	9 (45.0%)	9 (50.0%)	20 (55.6%)	
	Macrosomia	13 (50.0%)	6 (30.0%)	6 (33.3%)	10 (27.8%)	
P value*	Insulin vs other groups		0.249	0.179	0.038	
	Mixed vs other groups			0.820	0.184	
	Diet vs metformin				0.233	

* Chi square test

Regarding weight for gestational age, neonates who delivered to mothers treated with metformin have a lower chance of having SGA and also had slightly about twice the chance of having a baby AGA, comparing with insulin group which show higher percent of having LGA or SGA babies (p value=0.045) (Table 3**).**

Table 3. Comparison of weight for gestational age according to maternal therapy

Parameter		Maternal therapy				P value*
		Insulin N=26	Mixed N=20	Diet N=18	Metformin N=36	
Gestational age	Preterm	17 (65.4%)	7 (35.0%)	5 (27.8%)	10 (27.8%)	0.014
	Term	9 (34.6%)	13 (65.0%)	13 (72.2%)	26 (72.2%)	
P value**	Insulin vs other groups		0.073	0.031	0.005	
	Mixed vs other groups			0.734	0.762	
	Diet vs metformin				1.000	

* Chi square test, ** Fisher exact test, SGA=small for gestational age, AGA=adequate for gestational age, LGA=large for gestational age

The type of therapy did not significantly affect the mode of delivery in metformin and insulin groups, but in diet and mixed therapy groups there is a significant higher percentage of cesarean section comparing with metformin (P value=0.006) (Table 4).

We found that, there is no significant statistical difference between the four groups in neonatal Apgar score at five minutes (Table 5).

Neonatal complications in general, which also considered as causes for admission to NICU, can be single or multiple in the same admitted neonate, and can developed in all infants of diabetic mother, regardless the type of mother's therapy, in our study, we found that, hypoglycemia can occur in neonates of insulin group with highest percentage than others (76.9%), and in lowest with metformin group (44.4%) (p value=0.035), which is significant. Regarding hyperbilirubinemia, also the neonates in insulin group have the highest percent among the others with significant difference (50.0%), (p value=0.008). At the end, the same results were found regarding respiratory distress syndrome, hypocalcaemia, congenital heart disease, neural tube defect, and NICU admission, which showed that there is no significant statistical difference between

the four groups, but RDS, CHD and NICU admission can occur more in insulin group than others (Table 6).

Table 4. Comparison of mode of delivery according to maternal therapy

Parameter		Maternal therapy				P value*
		Insulin N=26	Mixed N=20	Diet N=18	Metformin N=36	
Mode of delivery	CS	19 (73.1%)	17 (85.0%)	16 (88.9%)	18 (50.0%)	0.006
	NVD	7 (26.9%)	3 (15.0%)	2 (11.1%)	18 (50.0%)	
P value**	Insulin vs other groups		0.476	0.270	0.115	
	Mixed vs other groups			1.000	0.011	
	Diet vs metformin				0.007	

* Chi square test, ** Fisher exact test

Table 5. Comparison of Apgar score according to maternal therapy

Parameter		Maternal therapy				P value*
		Insulin N=26	Mixed N=20	Diet N=18	Metformin N=36	
Apgar score	Low	15 (57.7%)	12 (60.0%)	12 (66.7%)	15 (41.7%)	0.284
	Normal	11 (42.3%)	8 (40.0%)	6 (33.3%)	21 (58.3%)	
P value**	Insulin vs other groups		1.000	0.754	0.303	
	Mixed vs other groups			0.745	0.266	
	Diet vs metformin				0.148	

* Chi square test, ** Fisher exact test

Table 6. Comparison of complication according to maternal therapy

Complications	Maternal therapy				P value*
	Insulin N=26	Mixed N=20	Diet N=18	Metformin N=36	
Hypoglycemia	20 (76.9%)	15 (75.0%)	11 (61.1%)	16 (44.4%)	0.035
Respiratory distress syndrome	15 (57.7%)	7 (35.0%)	5 (27.8%)	12 (33.3%)	0.145
Jaundice	13 (50.0%)	6 (30.0%)	4 (22.2%)	4 (11.1%)	0.008
Hypocalcaemia	8 (30.8%)	8 (40.0%)	2 (11.1%)	7 (19.4%)	0.151
Congenital heart disease	7 (26.9%)	3 (15.0%)	0 (0.0%)	2 (5.6%)	0.090
NTD	1 (3.8%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	0.164
NICU admission	23 (88.5%)	17 (85.0%)	13 (72.2%)	25 (69.4%)	0.473

* Chi square and Yates chi square test

Discussion

The occurrence of GDM is increasing in the context of the pandemic in obesity and type 2 diabetes in the modern world, so early diagnosis and treatment can play a significant role in the preservation of the health of mother and her newborn [4]. In this study we compared the different neonatal outcomes according to

the treatment of choice for gestational diabetes mellitus.

Regarding prematurity, there was a statistical significance of preterm labor between metformin and insulin groups (65.4% in the insulin group versus 27.8% in the metformin group), (P value =0.005), which nearly similar to findings in a study at Kashan University of Medical Sciences, Iran, by Mesdaghinia et al. [18], which found a statistical significance of preterm labor between metformin and insulin groups (8 in the insulin group versus 0 in the metformin group (P = 0.007), and the same results in Balani et al. study [19], but Gui et al. study in 2013 [20] mentioned that preterm labor in metformin group is higher than insulin group and this could be due to phenomenon of chance or an unknown effect of metformin on labor cycle. As we know, neonates who are born prematurely have higher rates of cerebral palsy, sensory deficits, learning disabilities and respiratory illnesses compared with those born at term [21]. Regarding neonatal birth weight, we found in this study that the incidence of macrosomia or low birth weight in the metformin group was significantly less than the group receiving insulin (P=0.035) and this agreed with some studies, such as Behrashi et al. [22], their results showed that the incidence of macrosomia in the metformin group was significantly less than the group receiving insulin (P=0.005). Others like Dhulkotia et al. [23] and Zangeneh et al. [24] showed no significant difference between the groups in the prevalence of macrosomia. But Balsells et al. study in 2015 [25], and Cheng et al. [26], found that metformin was associated with a higher birth weight and macrosomia than insulin, suggested that uncontrolled diabetes can lead to fetal macrosomia.

Regarding weight for gestational age, we found also, the percentage of SGA and LGA newborns was higher in the insulin group, compared to metformin group with a significant statistical difference (P=0.045) and this result is in agreement with Simeonova-Krstevska et al. study in Macedonia [8], Goh et al. [27] and Rai et al. [28]. Surprisingly, although mean glycemic values were higher in the insulin group, the percent of SGA newborns was higher. It can be explained by a high incidence of prematurity in the insulin group, as we know, being SGA is as complicated as being LGA, since both are associated with higher morbidity and mortality in the short- and long-term, among the perinatal complications of an LGA newborn, are noteworthy the increased risk of meconium aspiration, clavicle fracture, perinatal hypoxia, hypoglycemia, hyperbilirubinemia, transient tachypnea, brachial plexus injury, shoulder dystocia, and even neonatal death, therefore, preventing the occurrence of both is important [29]. AGA is the treatment goal, and in our study, metformin was associated with high percent (58.3%) rather than insulin therapy (26.9%), and the difference was significant (P=0.045) and this agreed with Goh et al. [27] and Silva et al. study in Brazil in 2017 [30], and like our study, they also, found that there is no significant statistical difference between metformin and insulin in mode of delivery but higher percent of caesarean delivery associated with insulin group than metformin, probably, due to a higher percent of LGA newborns in insulin group, in addition to these results we also found that there is significant statistical difference between diet, mixed groups and metformin group (P=0.007, 0.011) respectively, in cesarean section delivery, this difference may be due to the dissemination of cesarean practice in our country, unlike others.

Fifth minute Apgar score revealed no difference between the four groups statistically, similar results were reported by Rowan et al. [31], and Ijäs et al. [32].

Regarding hypoglycemia, we found that neonates of mothers treated with insulin therapy have higher percentage among other groups (76.9%) and lower in metformin group (44.4%) and this statistically significant (P=0.035), these results were in agreement with the results of Tertti et al. [33], which showed that, the incidence of neonatal hypoglycemia was significantly higher in the insulin group than in the metformin group (P= 0.03), similar results also found by Hellmuth et al. [34], But Gilson and Murphy study in USA [35] showed that the neonatal hypoglycemia was less in the metformin group than insulin, but there was no statistically significant difference

between the two groups. Other studies reported a higher incidence of neonatal hypoglycemia in the metformin group compared with the insulin group and others, but the difference between the groups was not significant, like the results in study by Conway et al. [36] and Ramos et al. in USA [14], they found that this difference may be related to the level of glycemic control in patients in the various studies.

Regarding hyperbilirubinemia, in our study, we found a significant statistical difference among the groups, higher percent was in insulin therapy (50.0%) and lower percent in metformin (11.1%), which considered a significant difference (P=0.008), similar result found by Mesdaghinia et al. [18] and Hyer et al. [37], but regarding respiratory distress syndrome, hypocalcaemia we found that, there is no significant statistical difference between the four groups but can occur more in insulin and mixed groups, which are nearly similar to the results of other studies like Jacobson et al. [38], Behrashi et al. [22] and Tempe et al. [39], findings of these studies showed that there was no statistically significant difference among groups in the prevalence of hypocalcaemia, respiratory distress syndrome and neonatal jaundice. Others such as Mesdaghinia et al. [18], and Hyer et al. [40], found that respiratory distress syndrome and hypocalcaemia among neonates of the insulin group were significantly more rather than the metformin group, this is believed to be related to higher rates of preterm labor in their studies.

Congenital anomalies such as Congenital heart disease and neural tube defect in our study associated more with insulin and mixed therapy group than others, but it revealed no statistical differences between groups and this results agreed with Tertti et al. [33] and Hawthorne [41], but Ramos et al. [14], and Homko et al. [42] reported greater incidence of congenital anomalies in patients treated with metformin than the insulin group, suggested that risk of major congenital abnormalities may be related to maternal glycemic control before and during pregnancy.

In our study, neonatal admission to neonatal intensive care unit up to 1 week after birth due to single or multiple complications has been recorded in the four groups as a high total percentage 78%, and there is no significant statistical value among groups but Insulin group newborns were admitted in more percent than metformin group, Rowan et al. [51] reported similar results, they assumed that higher rate of NICU admission in the insulin group could be due to higher prevalence of preterm labor.

In general, the findings of this study showed that metformin as a treatment of gestational diabetes mellitus has fewer side effects on fetus and newborns with better short- and long-term outcomes than others. This was corroborated in the study carried out by Elliott et al. [43]; in their study, they observed that very low level of metformin could pass through the placenta, also it had the lowest concentration in infants' umbilical cord blood of diabetic mothers under treatment. The reason behind this observation was the strong tendency of the drug to bind to proteins (it is reported as 99.9%) and a very short half-life of 4-6 h [8], in another study carried out by Kraemer et al. [44] to assess the binding effect of metformin to proteins, they found that by removing albumin, blood levels of metformin in umbilical cord still remained undetectable. They concluded that a specific pump actively pumps it into the maternal blood against the direction of fetal blood concentration. This pump, with the two above mentioned mechanisms, has made metformin a suitable drug for the treatment of gestational diabetes with minimal transmission to the fetus.

In conclusion, the pediatrician in the delivery room should expect different neonatal outcomes according to maternal therapy for GDM and their compliance during pregnancy. So, the results of our study, found that metformin can be a good alternative for insulin and others types of maternal therapy in the treatment of GDM. It is associated with better outcomes and less complications for fetuses and neonates.

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Author contribution

Dr. Rashed and Dr Al-Omrani collected the data, Dr. Mohmmed and Dr. Al-Bahadle wrote the first draft of manuscript, all of them share in statistical analysis and discussion.

Conflict of interest

Authors declare that there is no conflict of interest.

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