Original Article

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To Compare the Outcomes of Neonates Born to Diabetic Mothers who Received Insulin versus Metformin

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Abstract

Background: Metformin is being increasingly recognized as a viable and cost-effective substitute for insulin in the management of gestational diabetes mellitus (GDM) across various nations. Nevertheless, the effects of administering metformin to mothers on the developmental patterns of fetal, infant, and childhood growth remain uncertain. Aim: To compare the outcomes of neonates born to diabetic mothers who received insulin versus metformin. **Materials and Methods:** This study included all neonates who were born alive and whose mothers had pre-existing diabetes mellitus (DM) or gestational diabetes mellitus (GDM) during pregnancy and were registered at the institute during the study period. Mothers were categorized into three distinct groups according to the treatment they received for blood sugar regulation. These groups were as follows: group I, which consisted of mothers who were solely on a meal plan; group II, which included mothers who were prescribed Metformin; and group III, which encompassed mothers who were administered insulin. **Results:** Among the 150 neonates, 85 (56.67%) were males. Term neonates constituted 125 (83.33%) while preterm and post term neonates accounted to 23(15.33%) and 1(1.33%) respectively. The outcomes of neonates born to mothers across different categories of treatment for their blood sugar levels were compared. It was observed that complications like NICU admission, RD, hypoglycemia, hypocalcemia, NNH and congenital anomalies were significantly increased in the category of mothers receiving insulin. **Conclusion:** No significant correlation was found between the treatment regimens administered to mothers (insulin, metformin, or diet) and neonatal outcomes, with the exception of neonatal hyperbilirubinemia.

Keywords: Neonates, Diabetic mothers, Insulin, Metformin.

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Introduction

Diabetes Mellitus (DM) is a prevalent medical complication that can arise during pregnancy. Around 90% of women who experience diabetes mellitus (DM) during pregnancy can be classified as having gestational diabetes mellitus (GDM), while the remaining individuals are categorized as having overt or pre-gestational DM.[1] Neonates born to mothers with diabetes are more susceptible to the occurrence of congenital anomalies, being small for gestational age (SGA), having macrosomia, experiencing metabolic abnormalities such as hypoglycemia, hypocalcemia, and hypomagnesemia, facing hematological complications like neonatal hyperbilirubinemia (NNH), encountering hyper viscosity resulting from polycythemia, and developing respiratory distress (RD) due to the opposing impact of hyperinsulinemia on cortisol-mediated surfactant synthesis. There are several recommendations provided by various governing organizations for the diagnosis of diabetes mellitus (DM) during pregnancy.[2] According to the National guideline for diagnosis and management of Gestational Diabetes in India (2018), the recognized method for screening gestational diabetes is a single step screening using the Diabetes in Pregnancy Study Group of India (DIPSI) criteria. This involves conducting an oral glucose tolerance test (OGTT) with 75 g glucose, regardless of the timing of the last meal. A threshold level of ≥ 140 mg/dL is used to determine the presence of gestational diabetes.[4]

Insulin, as the primary endogenous hormone accountable for regulating glucose homeostasis, has demonstrated efficacy as a therapeutic intervention for gestational diabetes mellitus (GDM). Nevertheless, the effectiveness of insulin is evaluated in light of notable drawbacks. The utilization of insulin has the potential to induce maternal hypoglycemia, enhance the propensity for maternal weight gain, necessitate injection, and present challenges in terms of administration and monitoring.[5] The cost of insulin therapy and the challenges associated with refrigerated storage render it less viable for implementation in low and middle development index settings, which are currently experiencing significant rises in the prevalence of gestational diabetes mellitus.[6] Hence, the investigation into the potential utilization of oral glucose-lowering agents as a therapeutic approach for

gestational diabetes mellitus (GDM) has garnered significant scholarly attention.[7]

Metformin, also known as N,N-dimethylbiguanide, is an oral glucose-lowering drug classified as a biguanide. It has achieved extensive recognition and acceptance within the medical community. Metformin has been granted approval for the treatment of gestational diabetes mellitus (GDM) in numerous countries worldwide. It is included in the 20th edition of the World Health Organization's essential medicines list and has been endorsed by the Society for Maternal-Fetal Medicine (SMFM) as the primary therapeutic option for GDM. Based on the existing body of evidence, it can be inferred that metformin demonstrates efficacy in the maintenance of maternal glycaemic control and potentially serves as a means to restrict gestational weight gain.[10] In contrast to insulin, metformin has the ability to traverse the placental barrier, resulting in its presence at levels of clinical significance in fetal and placental tissues. These concentrations typically range from 50% to 100% of the corresponding maternal concentrations. Hence, it is plausible that the exposure to metformin may have an impact on the developing feto-placental unit through pathways that are not solely related to the regulation of maternal hyperglycemia. Since then, there have been a limited number of studies conducted in India.[10,11] that have examined the comparative efficacy of metformin and insulin in the management of diabetes mellitus during pregnancy. However, the role of metformin was not widely accepted in India until 2014, as the national guidelines at that time only endorsed insulin as the preferred medication for managing diabetes mellitus in the country.[12]

The national guidelines for the diagnosis and management of gestational diabetes mellitus (GDM) in India in 2018 incorporated the use of metformin as a treatment option for GDM cases diagnosed after the 20th week of pregnancy.[4] Following the implementation of revised national guidelines, there is currently a lack of research examining the comparative outcomes of neonates born to mothers who received metformin or insulin treatment for diabetes mellitus during pregnancy in India. This study was designed to assess and compare the outcomes of neonates born to mothers with diabetes who were subjected to different treatment regimens, specifically those involving meal plans only, metformin, and insulin.

Materials and Methods

The present study was conducted in neonates at a tertiary care hospital, employing a prospective observational design. The study was conducted subsequent to obtaining ethical committee clearance from the institute.

Upon obtaining informed written consent from the parents or legal guardians, the neonates were enrolled in the study based on predetermined inclusion and exclusion criteria. This study included all neonates who were born alive and whose mothers had pre-existing diabetes mellitus (DM) or gestational diabetes mellitus (GDM) during pregnancy and were registered at the institute during the study period. The study excluded cases of stillbirth and intrauterine deaths among mothers with diabetes, as well as neonates born outside of the study institute who were subsequently admitted to the neonatal intensive care unit (NICU).

The study institute employed the DIPSI criteria3 to diagnose pregnant mothers, classifying them as either having pre-gestational or overt diabetes mellitus (DM) or gestational diabetes mellitus (GDM). During the time of delivery, data pertaining to mothers who had been diagnosed with overt diabetes mellitus (DM) or gestational diabetes mellitus (GDM) were obtained from the case sheets. The variables considered in this study were age, parity, gestational month at the time of diagnosis of gestational diabetes mellitus (GDM) or overt diabetes mellitus (DM), fasting blood glucose levels at the time of GDM diagnosis or before treatment intervention, 2nd hour oral glucose tolerance test (OGTT) values based on theDIPSI criteria, and glycosylated hemoglobin (HbA1C) levels at GDM diagnosis or before treatment intervention. Mothers were categorized into three distinct groups according to the treatment they received for blood sugar regulation. These groups were as follows: group I, which consisted of mothers who were solely on a meal plan; group II, which included mothers who were prescribed Metformin; and group III, which encompassed mothers who were administered insulin.

The pertinent information of the neonates who were recruited for the study, including their age, sex, gestational age, birth weight, and mode of delivery, was documented in a pre-established case record form. Upon delivery, the medical team recorded the infant's APGAR scores at both the 1-minute and 5-minute marks. If the neonates exhibited APGAR scores below 7 at 5 minutes, their APGAR scores were subsequently assessed every 5 minutes for a duration of up to 20 minutes following birth. The gestational age (GA) of the neonates was assessed using a modified Ballard's score within the first 24 hours after birth. The neonates were then categorized as either preterm (≤36+6 weeks completed GA) or term (≥37 weeks completed GA). The measurement of birth weight was conducted utilizing a digital weighing scale, which possessed a margin of error of ± 10 grams. According to the available literature, neonates were categorized as having low birth weight (LBW) if their weight fell within the range of 1500g to 2499g. Neonates were classified as very low birth weight (VLBW) if their weight ranged from 1000g to 1499g, while neonates with a weight of 999g or less were considered extremely low birth weight (ELBW) neonates. According to the charts developed by Fenton and the World Health Organization's Intergrowth 21 project, neonates were categorized as appropriate for gestational age (AGA) if their weight fell within the 10th-90th percentile range. Neonates were classified as small for gestational age (SGA) if their weight was below the 10th percentile, and as large for gestational age (LGA) if their weight exceeded the 90th percentile, taking into account their gestational age and sex. Once recruited, the neonates were observed for complications like hypoglycemia, hypocalcemia, NNH, birth asphyxia, polycythemia, respiratory distress, birth injuries and were examined for congenital anomalies. Glucose levels were checked at 0,2,6,12, 24,36 & 48 hours by capillary blood

glucose. Hypoglycaemia was defined as blood glucose level of less than 40 mg/dL. If any hypoglycemia was noted with capillary blood glucose, plasma glucose was estimated for confirmation. Neonates with hypoglycemia were managed according to unit protocol. Complete blood picture with haematocrit and serum calcium levels were measured through automated analyser, for all neonates at 24 hours of life and later if needed or symptomatic. Hypocalcemia was defined as total serum calcium <8 mg/dL for term infants or preterm infants weighing >1500 g at birth and total serum calcium <7 mg/dL for very low birth weight infants weighing <1500 g. A neonate was diagnosed to have RD when one or more of the following was present- respiratory rate of more than 60/minute, retractions (subcostal, intercostal, sternal, suprasternal) or noisy respiration in the form of a grunt. The distress may or may not be associated with cyanosis and desaturation on pulse oximetry. NNH was defined as total serum bilirubin >95th percentile on the hour specific Bhutani nomogram. Birth asphyxia was defined according to American College of Obstetricians and Gynecologists (ACOG) guidelines.[13] Polycythaemia was defined in neonates as a venous haematocrit greater than 65% (0.65) or a haemoglobin value greater than 22 g/dL (220 g/L). All the neonates underwent 2D Echocardiography and ultrasonogram of abdomen. The neonates without any complications at birth were monitored regularly in postnatal ward during daily postnatal rounds. Neonates admitted to NICU were managed according to unit protocol. All neonates were monitored up to 7th day of life. Those discharged from hospital earlier than 7 days, were followed at outpatient department on day 3, 5, and 7 of life.

Statistical Analysis

The pertinent data were gathered using a case record form and organized in Microsoft Excel. Subsequently, the analysis was conducted using the computer program SPSS version 25.0, developed by SPSS Inc. in Chicago, IL, USA. Descriptive statistics, such as the mean and standard deviation (SD), were used where appropriate. The ANOVA (Analysis of Variance) test and the post hoc Tukey's HSD (Honestly Significant Difference) test were used to evaluate the disparities among the means of more than two groups. The statistical methods used to assess the significance of categorical variables were Fisher's exact test and the Chi-square test. Binary logistic regression (BLR) was used to account for confounding factors and assess their impact on neonatal outcomes. A significance level of 0.05 was used to determine statistical significance.

Results

Out of the total 1987 neonates born during the designated research period, a subgroup of 155 neonates were delivered by women diagnosed with diabetes mellitus (including both overt diabetes mellitus and gestational diabetes mellitus). The current research found that the incidence of infants born to diabetes mother was 7.80%. Out of the total sample size of 155 newborns, three neonates were unable to be included in the follow-up analysis due to loss of contact, and one pair of twins was omitted from the study. Therefore, a total of 150 newborns were included in the research. Out of the total sample size of 150 neonates, 135 neonates were born to women who were diagnosed with gestational diabetes mellitus (GDM), while the remaining 15 neonates were born to mother who had pregestational diabetes mellitus. A total of 150 women were divided into three groups, with each group consisting of 50 mothers. The first group got a meal plan as their therapy for diabetes mellitus (DM), while the second group received metformin, and the third group received insulin. The demographic features of the mothers in the three therapy groups are outlined in Table 1. There was a statistically significant disparity among the three groups of women in terms of the average number of children born, average duration between diagnosis of diabetes mellitus and pregnancy, average level of glycated hemoglobin (HbA1C), average fasting blood glucose levels, and average oral glucose tolerance test (OGTT) results.

Table 1: Basic profile of mothers of neonates

Parameters	Group I	Group II	Group III	P value
Age	25.87 ± 3.25	26.71 ± 3.11	27.15 ± 2.89	0.15
Parity	1.8 ± 0.88	2.1 ± 0.86	2.6± 0.99	0.07
duration of gestation	8.1 1± 1.25	5.99± 1.15	5.01± 1.06	0.001
FBG (mg/dL)	102.25 ± 3.69	112.15± 6.67	130.33± 11.19	0.001
2nd hr OGTT glucose	152.85 ± 11.58	169.99 ± 13.59	211± 15.59	0.001
HbA1C	5.75 ± 0.77	6.36 ± 0.59	7.77 ± 1.36	0.001
No. of Mothers with PIH n (%)	10 (20)	3 (6)	11(22)	0.23
No. of Mothers with Hypothyroidism n (%)	5 (10)	5 (10)	3 (6)	0.15
No. of Mothers with Anemia n (%)	11 (22)	8(16)	30 (60)	0.22

DM = Diabetes mellitus, FBG = Fasting blood glucose, OGTT = Oral glucose tolerance test, PIH = Pregnancy induced hypertension,

Among the 150 neonates, 85 (56.67%) were males. Term neonates constituted 125 (83.33%) while preterm and post term neonates accounted to 23(15.33%) and 1(1.33%) respectively. The outcomes of neonates born to mothers across different categories of treatment for their blood sugar levels were compared as shown in table 2. It was observed that complications like NICU admission, RD, hypoglycemia, hypocalcemia, NNH and congenital anomalies were significantly increased in the category of mothers receiving insulin.

Table 2: Neonatal outcomes across the three groups of treatment regimens

Parameters	Group I	Group II	Group III	Total (n=150)		P value
Mode of Delivery						0.21
Instrument (Forceps+ Vacuum)	2	5	3	10	6.67	
LSCS	24	25	41	90	60	
Vaginal	24	20	6	50	33.33	
Congenital anomalies	4	10	26	40	26.67	0.001
birth weight (Kg)	2.9 ± 0.7	2.9 ± 0.6	3.0 ± 0.8	-	-	0.25
LBW	9	14	12	35	23.33	0.48
Macrosomia	2	0	2	4	2.67	0.22
SGA	10	14	6	30	20	0.34
LGA	0	3	7	10	6.67	0.002
Preterm	7	6	7	20	13.33	0.356
Number of NICU admissions	25	30	47	102	68	0.004
Duration of NICU stay > 72 hours	6	24	30	60	40	0.0006
Birth Trauma	0	0	2	2	1.33	0.15
Birth Asphyxia	2	3	3	8	5.33	0.29
Respiratory Distress	16	20	34	70	46.67	0.01
Hypoglycemia	2	4	10	16	10.67	0.02
Hypocalcemia	1	3	16	20	13.33	0.001
Hyperbilirubinemia	15	15	45	75	50	0.001
Polycythemia	2	15	20	37	24.67	0.54

LSCS= Lower section ceaserean section, S.D.= Standard deviation, LBW= Low birth weight, SGA= Small for gestational age, LGA= Large for gestational age, NICU= Neonatal Intensive care unit.

Table 3: Binary logistic regression of neonatal outcomes according to different treatment regimens of diabetes mellitus in mothers

Outcome	Therapeutic Modality	Estimate (β)	Standard Error (S.E)	Adjusted Odds Ratio *(e^{β})	P value
NNH	Diet	---			
	Metformin	-2.69	0.16	0.79	0.07
	Insulin	3.69	1.26	10.85	0.04
Hypoglycemia	Diet	---			
	Metformin	0.36	1.39	2.06	0.19
	Insulin	-0.39	1.27	0.63	0.77
Hypocalcemia	Diet	--- 0.52			
	Metformin	1.89	1.37	1.22	0.52
	Insulin		0.27	3.67	0.07
Respiratory Distress	Diet	-			
	Metformin	-0.44	0.44	0.52	0.19
	Insulin	0.49	0.69	2.47	0.27
LGA	Diet	-			
	Metformin	20.36	258.94	3336.25	0.33
	Insulin	0.66	1.22	3.48	0.47
Congenital anomalies	Diet	-			
	Metformin	0.63	0.79	2.18	0.45
	Insulin	0.67	0.63	1.19	0.53
NICU admission	Diet	-			
	Metformin	-0.58	0.41	0.71	0.39
	Insulin	1.26	1.19	4.15	0.41

The adjusted OR was for the following variables: Age of mother, gravidity, mode of delivery, gestational month at diagnosis of DM; maternal fasting blood glucose; maternal oral glucose tolerance test levels; maternal HbA1C levels at diagnosis of DM.

NNH = Neonatal hyperbilirubinemia, LGA = Large for gestational age; NICU = Neonatal intensive care unit.

Following the application of logistic regression analysis, as indicated in Table 3, it was determined that the specific treatment administered to mothers for the purpose of regulating their blood sugar levels did not yield any statistically significant impact on the incidence of hypoglycemia, hypocalcemia, respiratory distress, the need for neonatal intensive care unit (NICU) admission, the presence of congenital anomalies, and large for gestational age (LGA) in neonates, with the exception of neonatal hypoglycemia (NNH). The study findings indicated a significantly higher likelihood of neonatal hyperbilirubinemia admission and treatment in the insulin and Meal plan group, with odds approximately ten times greater than those observed in the other groups.

Discussion

The objective of this research was to assess the newborn outcomes among mothers diagnosed with diabetes mellitus who received various treatment regimens. A significant rise was reported in the rates of neonatal intensive care unit

(NICU) admission, length of NICU stay, presence of congenital malformations, incidence of hypoglycemia, hypocalcemia, neonatal hypoglycemia (NNH), respiratory distress (RD), and large for gestational age (LGA) among neonates delivered to women who were following a meal plan and receiving insulin for diabetes mellitus (DM). However, there is a limited number of Indian research that have conducted comparisons of neonatal outcomes among pregnant individuals with diabetes mellitus (DM) in relation to their treatment. Table 4 presents a comprehensive overview of research conducted both in India and internationally, which have similarities with the current study.

Table 4: Previous studies comparing outcome of neonates

Authors	Year of study	Sample Size	Agents used for DM compared	Neonatal Outcomes
Arshad R et al.[14]	2010	32/39	Metformin/ Insulin	Statistically higher mean birth weight in insulin group
Mesdaghinia E etal.[15]	2013	100/100	Metformin/ Insulin	Significantly more NNH, RD and NICU admissions in insulin group. Lower risk of preterm birth with metformin.
Rai L et al.[16]	2009	30/30	Metformin/ insulin	Mean NICU stay >24 hrs significantly higher in Insulin group. Incidence of NNH higher in Insulin group though not significant.
Thomas N et al.[17]	2008	141/137	Oral hypoglycemics/ Insulin	NNH significantly less with oral hypoglycemic agents.
Munshi S et al.[11]	2014	50/50	Metformin/ insulin	No difference in perinatal complication
Landi SN et al.[18]	2019	3818/ 3450	Metformin/ Insulin	Reduced LGA and neonatal hypoglycemia with metformin. No difference in mean birth weight among the groups.
Ainuddin et al.[19]	2015	43/32/75	Metformin alone/ Metformin plus insulin/ Insulin alone	The utilization of metformin as opposed to insulin has been found to result in a notable decrease in both NICU admissions and cases of neonatal hypoglycemia. There was no statistically significant variation observed among the groups in terms of the preterm birth rate.
Present Study	2023	50/50/50	meal plan/ Metformin / Insulin	The third group exhibited a statistically significant increase in the occurrence of Congenital anomalies, LGA (large for gestational age), RD (respiratory distress), hypoglycemia, hypocalcemia, NNH (neonatal hyperbilirubinemia), NICU (neonatal intensive care unit) admission, and duration of stay in the NICU.

In the current study, a total of 150 neonates were included, of which 102 (68%) were admitted to the Neonatal Intensive Care Unit (NICU). The predominant factors leading to admission to the Neonatal Intensive Care Unit (NICU) were Neonatal Hyperbilirubinemia (NNH) and Respiratory Distress (RD). Consistent with the findings of this study, Ainuddin et al. (19) also reported a statistically significant increase in the rate of admission to the neonatal intensive care unit (NICU) among infants born to mothers who received insulin treatment. Similarly, Rai L et al.[16] observed a prolonged duration of NICU stay exceeding 24 hours in the neonates of mothers who were treated with insulin.

Among the metabolic complications, NNH accounted for the highest proportion at 50%, followed by polycythemia at 24.67%, hypocalcemia at 13.33%, and hypoglycemia at 10.67%. The current investigation exhibited a statistically significant increase in the occurrence of hypoglycemia among newborns whose mothers were administered insulin. Similar findings were also reported by Landi et al. (2018) and Ainuddin et al. (2019) in their studies involving mothers who received insulin treatment. The present study found that the neonates of mothers receiving insulin had a significantly higher number needed to harm (NNH), as noted by Thomas N et al.[17] and Rai L et al.[16] Neonatal hypoglycemia (NNH) was the sole complication found to have a significant association with the treatment regimen administered to mothers, specifically in cases where insulin was received. This association resulted in an increased likelihood of NNH occurrence in neonates born to mothers who received insulin. The current investigation documented a notable increase in rates of RD, which aligns with the findings reported by Mesdaghinia et al.[15] The study findings did not reveal any statistically significant disparity in the average birth weight, which aligns with the observations made by Landi SN et al.[18] and Mesdaghinia E et al.[15] However, Arshad R et al.[14] reported a notably higher average birth weight in the insulin group. In the study conducted by Landi et al. (2018), it was observed that there was a significantly higher incidence of large for gestational age (LGA) infants among mothers who received insulin treatment. The incidence of congenital anomalies was found to be significantly higher in neonates born to mothers in the insulin group, as observed in the current study. In a study conducted by Thomas et al.[17] it was observed that there was a higher occurrence of congenital anomalies in the group receiving insulin. However, it is important to note that this difference did not reach statistical significance.

Conclusion

No significant correlation was found between the treatment regimens administered to mothers (insulin, metformin, or diet) and neonatal outcomes, with the exception of neonatal hyperbilirubinemia.

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