Original Research Article

Comparison of Outcomes Among Neonates Born to Diabetic Mothers Receiving Insulin and Metformin: A Prospective Observational Study

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Abstract

Background: Indian national guidelines (2018) adopted treatment with metformin as first choice of pharmacological agent next to medical nutritional therapy during pregnancy for diabetic mothers after 20 weeks of gestation. **Objectives:** A prospective observational study was planned to compare outcome of neonates of diabetic mothers categorized across different treatment regimens (I: meal plan only, II: meal plan and metformin or III: meal plan and insulin). **Materials and methods:** 100 neonates born to mothers with diabetes mellitus (DM) were included; early neonatal outcomes such as hypoglycemia, hypocalcemia, neonatal hyperbilirubinemia (NNH), birth asphyxia, polycythemia, respiratory distress (RD), birth injuries, congenital anomalies, large for gestational age (LGA) and admission to neonatal intensive care unit (NICU) were compared across the different categories of treatment in mothers. **Results:** Among the 100 included neonates, 37 were born to mothers who received only meal plan; 44 to mothers who received meal plan and metformin; 19 to mothers with meal plan and insulin. There was statistically significant (Fisher's exact test) increase in incidence of congenital anomalies (P value= 0.0000); hypoglycemia (P value= 0.023), hypocalcemia (P value= 0.00004), NNH (P value= 0.0001), RD (P value= 0.013), LGA (P value= 0.0027) and NICU admissions (P value= 0.005) in meal plan and insulin group (Group III). Binary logistic regression analysis revealed that neonates of mothers treated with meal plan and insulin had 11 times increased odds of experiencing NNH. **Conclusion:** There was no difference in outcomes of neonates born to mothers receiving different treatments for DM (meal plan only/ meal plan and metformin/ meal plan and insulin) except NNH.

Keywords: infant of diabetic mother, insulin, meal plan, metformin, neonatal hyperbilirubinemia.

Introduction

Diabetes Mellitus (DM) is a common medical complication during pregnancy. Approximately 90% of women with DM during pregnancy, belong to the category of gestational diabetes mellitus (GDM), while the rest fall into the category of overt or pre-gestational DM.[1] Neonates born to diabetic mothers are at higher risk for developing congenital anomalies, small for gestational age (SGA), macrosomia, metabolic abnormalities like hypoglycaemia, hypocalcaemia, hypomagnesemia, haematological complications like neonatal hyperbilirubinemia (NNH), hyper viscosity secondary to polycythemia, and respiratory distress (RD) due to antagonistic effect of hyperinsulinemia on cortisol mediated surfactant synthesis. [2]

Multiple recommendations from different governing organisations exist for diagnosis of DM during pregnancy. [2] But a single step screening with 75 g glucose – Diabetes in Pregnancy Study Group of India (DIPSI) criteria [3] through oral glucose tolerance test (OGTT) irrespective of the last meal (with a threshold level of ≥ 140 mg/dL) is the recognised tool according to National guideline for diagnosis and management of Gestational Diabetes, 2018 in India.[4]

Regarding the management of DM during pregnancy, the role of metformin gained importance after the publication of the MiG trial in 2008. [5] There have been few studies [6-8] from India since then, comparing the use of metformin and insulin in the management of DM during pregnancy. But there was no widespread acceptance of role of metformin till 2014 in India as the then national guidelines supported only insulin as the drug of choice for management of DM in India. [9]

The guideline recommendations from different organisations like American Diabetes Association (ADA) in 2020 and American Congress of Obstetricians and Gynecologists (ACOG) in 2018 endorse insulin as the first line of management while organisations like International Federation of Gynecology and Obstetrics (FIGO) in 2015 and the National Institutes of Health Care Excellence (NICE) in 2015 have accepted metformin for use in management of DM when control is not achieved by meal plan.[10] In India, the national guidelines for diagnosis and management of GDM in 2018, [4] adopted metformin for management of GDM when diagnosed after 20 weeks of pregnancy.

After the change in national guidelines, there has been no study comparing the outcomes of neonates born to mothers treated with metformin and insulin for DM during pregnancy in India. So, this study was planned to compare the outcome of neonates born to diabetic mothers across different treatment regimens (meal plan only / meal plan and metformin / meal plan and insulin).

Materials and Methods

This prospective observational study was done in neonates at a rural tertiary care teaching hospital in Telangana, India from 1st January 2019 to 31st Dec 2019. The study was conducted after obtaining ethical committee clearance of the institute (Mediciti Ethics Committee: Approval No: EC/17/XI/2K18/18). The procedures

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followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

The prevalence of GDM varies widely in our country and ranges from 4.0% - 9.5%. [11-13]Based on this, the sample size was calculated using the formula: $n=[Z^2\times p\times(1-p)]/d^2$.

Where Z stands for confidence level (1.96 for 95.0% CI); p stands for prevalence and d stands for precision. Based on a prevalence of 9.5% and precision of 6%, the sample size calculated was 91. With an error of 10% the estimated sample size was 100.

After obtaining informed written consent from the parents, the neonates were included in the study according to inclusion and exclusion criteria.

Inclusion criteria:

All live born, neonates of mothers with pre-existing DM or GDM during pregnancy registered at the institute during study period.

Exclusion criteria:

- Still born and intrauterine deaths of diabetic mothers.
- Neonates born outside the study institute and admitted in neonatal intensive care unit (NICU).
- Twins born to mothers with DM.
- All unregistered deliveries with DM at the study institute.

At the study institute, DIPSI criteria[3] were followed to diagnose pregnant mothers were classified to have pre gestational or overt DM and GDM. At the time of delivery, data of the mothers diagnosed with overt DM or GDM were collected from the case sheets. It included age, parity, month of pregnancy when diagnosis of GDM/ overt DM was done, fasting blood glucose at the time of diagnosis of GDM/ before intervening with treatment, 2nd hour OGTT values according to DIPSI criteria, glycosylated hemoglobin (HbA1C) values at diagnosis of GDM or before intervening with treatment. Mothers were classified into 3 categories based on the treatment they received for controlling blood sugar such as category I: on Meal plan only; category II: on Meal plan and T. Metformin (irrespective of dose of metformin) and category III: Meal plan and insulin (irrespective of the dose of insulin).

The recruited neonates' details such as age, sex, gestational age, birth weight, mode of delivery was recorded in a predesigned case record form. At birth, appearance, pulse, grimace, activity, and respiration (APGAR) scores were noted at 1minute and 5 minutes. In case the neonates had low APGAR scores (<7) at 5 min, APGAR was recorded for every 5 minutes, up to an extended period of 20 minutes after birth. Gestational age (GA) of the neonates was determined by modified Ballard's score within 24 hours of life and classified as preterm (≤36+6 weeks completed GA) or term (≥ 37 weeks completed GA). Birth weight was measured using a digital weighing scale with an error of ± 10 grams. Based on BW, neonates were classified as LBW if they weighed ≥1500g and ≤2499g; very low birth neonates if they weighed ≥1000g and ≤1499g and extremely low birth weight neonates if they weighed ≤ 999g. Based on Fenton's and WHO Intergrowth 21 charts for preterm and term neonates respectively, they were classified as appropriate for gestational age (AGA) if their weight was between 10th-90th centile; SGA if their weight was <10th centile and large for gestational age (LGA) if their weight was > 90th centile with respect to their GA 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 [14] by capillary blood glucose (Accu- Check Extra Care Roche Diabetes Care India Pvt. Ltd). Hypoglycaemia was defined as blood glucose level of less than 40 mg/dL. [15] 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. [16] 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. [17] NNH was defined as total serum bilirubin >95th percentile on the hour specific Bhutani nomogram. [18] Birth asphyxia was defined according to American College of Obstetricians and Gynecologists (ACOG) guidelines.[19] 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). [20] 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 relevant data were collected in a case record form and tabulated in Microsoft Excel and analysis was done by using computer software SPSS version 28.0. (SPSS inc., Chicago, IL USA). Descriptive statistics like mean and Standard Deviation (S.D.) were used wherever suitable. ANOVA (Analysis of Variance) test and post Hoc Tukey's HSD (Honestly significant difference) test was used to assess difference between the means of greater than 2 groups. Fisher's exact test and Chi square test were used as tests of significance for categorical variables. Binary logistic regression (BLR) for the neonatal outcomes were done to adjust the effect of confounders. A P value less than 0.05 was taken as significant.

Results

Among 1531 live born neonates during the study period, 104 neonates were born to mothers with DM (overt DM and GDM) The prevalence of infant of diabetic mothers in the present study was 6.79%. Among the 104 neonates, 2 neonates were lost to follow up and one pair of twins were excluded. Hence 100 neonates were included in the study.

Among the 100 neonates, 93 neonates' mothers were diagnosed with GDM, while 7 mothers had pregestational diabetes mellitus. Figure 1 shows the distribution of mothers classified according to the type of DM and the treatment received for the same during pregnancy. 37 mothers had received meal plan only, 44 mothers had received meal plan and metformin while 19 mothers received meal plan and insulin for treatment of their DM.

The baseline characteristics of the mothers across the three categories of treatment regimens is as described in Table 1. There was statistically significant difference among the three categories of mothers with respect to mean parity, mean gestation of diagnosis of DM, mean HbA1C, mean fasting blood glucose and mean OGTT values.

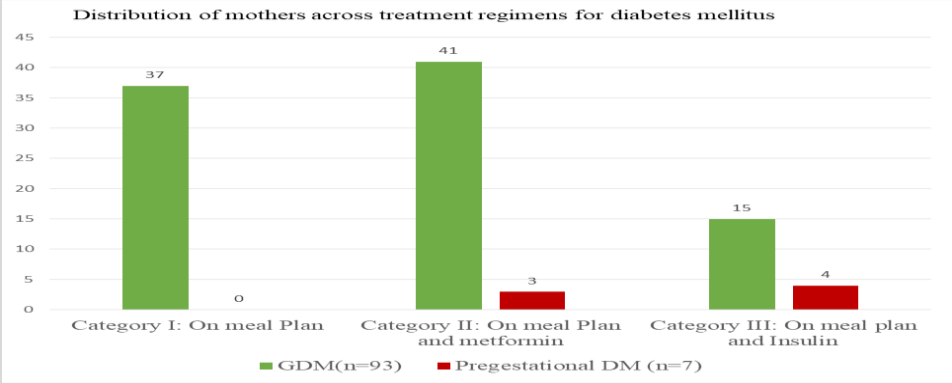

Figure 1: Distribution of mothers across treatment regimens for diabetes mellitus

Table 1: Baseline characteristics of mothers of neonates included in the study

Parameters	Category 1: On meal plan (n=37)	Category 2: meal plan and metformin (n=44)	Category 3: meal plan and insulin (n=19)	P value
Mean Age ± S.D. (years)	26.0 ± 4.7	26.5 ± 4.3	28.0 ± 5.7	0.33 (ANOVA)
Mean Parity ± S.D.	1.9 ± 1.0	2.0 ± 0.9	2.5 ± 1.1	0.069 (ANOVA)
Mean duration of gestation after which diagnosis of DM was made ± S.D. (months)	7.7 ± 0.9	6.3 ± 1.5	4.7 ± 2.7	<0.00001* (ANOVA)
Mean FBG ± S.D. (mg/dL)	101.1 ± 7.56	111.4 ± 11.9	129.1 ± 19.0	<0.00001* (ANOVA)
Mean 2nd hr OGTT glucose ± S.D. (mg/dL)	151.0 ± 15.6	172.5 ± 23.0	212.4 ± 27.5	<0.00001* (ANOVA)
Mean HbA1C± S.D.	5.6 ± 0.6	6.2 ± 0.6	7.6 ± 1.2	<0.00001*(ANOVA)
No. of Mothers with PIH n (%)	7 (18.9)	3 (6.8)	4 (21.1)	0.17 (Fisher's exact)
No. of Mothers with Hypothyroidism n (%)	4 (10.8)	4 (9.1)	1 (5.3)	0.9 (Fisher's exact)
No. of Mothers with Anemia n (%)	8 (21.6)	7 (15.9)	7 (58.3)	0.19 (Fisher's exact)

* Statistically significant

S.D. = Standard deviation, DM = Diabetes mellitus, FBG = Fasting blood glucose, OGTT = Oral glucose tolerance test, PIH = Pregnancy induced hypertension, ANOVA = Analysis of Variance.

Among the 100 neonates, 54.0% (54) were males. Term neonates constituted 84.0% (84) while preterm and post term neonates accounted to 15.0 % (15) and 1.0% (1) 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 and Meal plan.

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

Parameters	Total (n=100)	Category 1: On Meal plan (n=37) n (%)	Category 2: Meal plan and metformin (n=44) n (%)	Category 3: Meal plan and insulin (n=19) n (%)	P value (Fisher's exact test)
Mode of Delivery					
Instrument (Forceps+ Vacuum) LSCS Vaginal	6 55 39	1 (2.7) 18 (48.7) 18 (48.7)	3 (6.8) 23 (52.3) 18 (40.9)	2 (10.5) 14 (73.7) 3 (15.8)	0.337
Congenital anomalies	28	2 (5.4)	12 (27.3)	14 (73.7)	0.0000*
Mean birth weight (Kg) ± S.D.	-----	2.8 ± 0.6	2.8 ± 0.5	2.9 ± 0.7	0.7116**
LBW	26	9 (24.3)	12 (27.3)	5 (26.3)	0.955
Macrosomia	2	1 (2.7)	0	1 (5.3)	0.31
SGA	23	8 (21.6)	12 (27.3)	3 (15.8)	0.64
LGA	7	0	2 (4.5)	5 (26.3)	0.0027*
Preterm	15	5 (13.5)	5 (11.4)	5 (26.3)	0.356
Number of NICU admissions	66	20 (54.1)	28 (63.6)	18 (94.7)	0.005*
Duration of NICU stay > 72 hours	32	5 (13.5)	15 (34.1)	12 (63.2)	0.0007*
Birth Trauma	1	0	0	1 (5.3)	0.19
Birth Asphyxia	5	1 (2.7)	2 (4.5)	2 (10.5)	0.416

Respiratory Distress	45	12 (32.4)	19 (43.2)	14 (73.7)	0.013*
Hypoglycemia	10	1 (2.7)	4 (9.1)	5 (26.3)	0.023*
Hypocalcemia	14	1 (2.7)	4 (9.1)	9 (47.4)	0.00004*
Hyperbilirubinemia	53	16 (43.2)	19 (43.2)	18 (94.7)	0.0001*
Polycythemia	24	1 (2.7)	11 (25)	7 (36.8)	0.229

**By ANOVA test, * statistically significant.
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

S. No	Outcome	Therapeutic Modality	Estimate (β)	Standard Error (S.E)	Adjusted Odds Ratio *(e^{β})	P value
1.	NNH	Diet Meal plan and metformin Meal plan and insulin	--- -1.015 2.421	 0.580 1.131	 0.348 **11.257**	 0.069 **0.032**
2.	Hypoglycemia	Diet Meal plan and metformin Meal plan and insulin	--- 0.420 -0.200	 1.270 1.174	 1.521 0.818	 0.741 0.865
3.	Hypocalcemia	Diet Meal plan and metformin Meal plan and insulin	--- 0.471 1.460	 1.249 0.837	 1.601 4.305	 0.706 0.081
4.	Respiratory Distress	Diet Meal plan and metformin Meal plan and insulin	--- -0.385 0.348	 0.598 0.844	 0.680 1.416	 0.520 0.620
5.	LGA	Diet Meal plan and metformin Meal plan and insulin	--- 19.906 0.771	 3394.3 1.483	 4416 2.161	 0.996 0.603
6.	Congenital anomalies	Diet Meal plan and metformin Meal plan and insulin	--- 0.593 0.577	 0.934 0.919	 1.809 1.780	 0.526 0.530
7.	NICU admission	Diet Meal plan and metformin Meal plan and insulin	--- -0.457 1.100	 0.564 1.168	 0.633 3.004	 0.418 0.346

*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.

After logistic regression analysis, (table 3) it was observed that the type of treatment in mothers for controlling their blood sugar levels did not have any significant effect on occurrence of hypoglycemia, hypocalcemia, RD, requirement for NICU admission, presence of congenital anomalies and LGA in neonates except NNH. It was observed that the odds that a neonate will be admitted and treated for neonatal hyperbilirubinemia was 11 times more in the insulin and Meal plan group compared to other groups.

Discussion

The present study was done to evaluate the neonatal outcomes in mothers with DM receiving different treatment regimens. It was observed that there was a significant increase in rates of NICU admission, duration of NICU stay, presence of congenital anomalies, incidence of hypoglycemia, hypocalcemia, NNH, RD and LGA in the category of neonates born to mothers on Meal plan and insulin for DM. But few Indian studies have compared the neonatal outcome of pregnant DM with respect to their treatment. Table 4 outlines the details of studies from India and abroad that are similar to the present study.

Table 4: Outline of previous studies comparing outcome of neonates of mothers with diabetes mellitus across various treatment regimens

S. No	Authors	Period of Study/Country	Sample Size	Type of Study	Agents used for DM compared	Neonatal Outcomes
1.	Rai L et al. [6]	2009/ Karnataka, India	30/30	Prospective observational	Metformin/ insulin	Mean NICU stay >24 hrs significantly higher in Insulin group. Incidence of NNH higher in Insulin group though not significant.
2.	Thomas N et al. [7]	November 2008 - October 2009/ India	141/137	Prospective observational cohort	Oral hypoglycemics/ Insulin	NNH significantly less with oral hypoglycemic agents.
3.	Munshi S et al. [8]	----/ West Bengal, India	50/50	Prospective comparative	Metformin/ insulin	No difference in perinatal complication
4.	Landi SN et	2019/ New	3818/	Retrospective	Metformin/ Insulin	Reduced LGA and neonatal

	al. [21]	Zealand	3450	cohort population based		hypoglycemia with metformin. No difference in mean birth weight among the groups.
5.	Ainuddin et al. [22]	2015/ Karachi, Pakistan	43/32/75	RCT	Metformin alone/ Metformin plus insulin/ Insulin alone	NICU admissions and neonatal hypoglycemia significantly lower in metformin compared to insulin. No significant difference among groups for preterm birth rate.
6.	Arshad R et al. [23]	2010-2012/ Karachi, Pakistan	32/39	Prospective observational study	Metformin/ Insulin	Statistically higher mean birth weight in insulin group
7.	Mesdaghinia E etal. [24]	----/ Iran	100/100	Prospective RCT	Metformin/ Insulin	Significantly more NNH, RD and NICU admissions in insulin group. Lower risk of preterm birth with metformin.
8.	Present Study	Jan – Dec 2019	37/44/19	Prospective observational study	meal plan/ meal plan and metformin / meal plan and Insulin	Statistically higher incidence of Congenital anomalies, LGA, RD, hypoglycemia, hypocalcemia, NNH, NICU admission and duration of stay in NICU in the third group.

DM = Diabetes Mellitus, NICU = Neonatal intensive care unit, NNH = Neonatal hyperbilirubinemia, LGA = Large for gestational age, RD = Respiratory distress.

Among the100 neonates, 66.0% were admitted to NICU in the present study. The most common reasons for admission to NICU were NNH and RD. Similar to the results seen in this study, Ainuddin et al. [22] also observed a significantly higher rates of admission to NICU in the neonates born to mothers treated with insulin, while Rai L et al. [6] observed an increased duration >24 hours of NICU in the neonates of insulin treated mothers.

Among the metabolic complications, NNH (53.0%), contributed the maximum, followed by polycythemia (24.0%), hypocalcemia (14.0%) and hypoglycemia (10.0%). The present study demonstrated a significantly higher rate of hypoglycemia in neonates born to mothers receiving insulin, and Meal plan. Landi SN et al. [21] and Ainuddin et al. [22] also observed similar results in mothers managed with insulin. As observed by Thomas N et al. [7] and Rai L et al. [6] NNH was significantly higher in the neonates of mothers receiving insulin and Meal plan in the present study. NNH was the only complication that was strongly associated with treatment regimen received by the mother with increased odds of NNH in neonates of mothers receiving insulin. The present study observed significantly higher rates of RD similar to results reported by Mesdaghinia E et al. [24] as shown in table 5. There was no significant difference in mean birth weight in this study which was similar to results observed by Landi SN et al. [21] and Mesdaghinia E et al. [24] But Arshad R et al. [23] reported significantly higher mean birth weight in insulin group.

Landi SN et al. [21] observed a significantly higher incidence of LGA in the mothers treated with insulin as observed in this study. Congenital anomalies were significantly higher in the neonates born to category III (meal plan and insulin) mothers in the present study. Cardiac anomalies were the highest among them (23/28). Atrial septal defect and patent ductus arteriosus were the most common cardiac anomalies observed. Thomas N et al. [7] reported an increased incidence of congenital anomalies in the insulin group, but it was not statistically significant.

Limitation

The data on glycemic control of mothers with DM after initiation of drugs/ Meal plan was not included.

Conclusion

There was no association between the treatment regimens (insulin or metformin or diet) received by mothers and neonatal outcomes except neonatal hyperbilirubinemia.

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