Advances in Bioresearch
Adv. Biores., Vol 13 (1) January 2022: 14-19
©2022 Society of Education, India
Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.13.1.1419

Advances in Bioresearch

ORIGINAL ARTICLE

Neonatal Complications in Metformin Versus InsulinTreated Gestational Diabetic Mothers

Nadipalli Sravani[1], Jagadeeswari S[2]*, M.G. Ravanagoman[3], S. Harivasudevan[4], S.Sundari[5]
Department of Paediatrics, Sree Balaji Medical College & Hospital, Chennai – 600044

ABSTRACT
Gestational Diabetic Mother (GDM) is a frequently observed pregnancy complication characterized by glucose intolerance, and incidence is expected to increase with raise in maternal obesity. This study is done to measure the comparative effectiveness of treating Gestational Diabetic Mothers with metformin versus insulin on immediate complications in new-born and to compare the incidence of adverse neonatal outcomes in pregnancies treated with metformin versus those treated with insulin and estimated the association of treating GDM with metformin versus insulin with adverse child health outcomes. The study had analyzed the relative risk ratio and found that insulin treated group was highly susceptible to get neonatal complications.
Keywords: *Pregnancy, Blood Glucose, Diabetes, Gestational, Obesity, Maternal, Insulin's*

Received 08.06.2021 Revised 16.09.2021 Accepted 11.11.2021

How to cite this article:
N Sravani, Jagadeeswari S, M.G. Ravanagoman, S. Harivasudevan, S.Sundari. Neonatal Complications in Metformin Versus Insulin Treated Gestational Diabetic Mothers. Adv. Biores. Vol 13 [1] January 2022. 14-19

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of dysglycaemia that occurs for the first time or is first detected during pregnancy. It has become a global public health burden [1, 2]. Up to now, there has been no gold standard criterion for the diagnosis. Different countries use different diagnostic criteria in determining its prevalence. InAsia, the prevalence of GDM ranges from 0.7 to 51.0% [3]. Due to the large differences in living conditions, socio-economic levels and eating habits, it is difficult to predict whether the prevalence of GDM in India is unified [4]. American Diabetes Association (ADA), International Diabetes and Pregnancy Research Group (IADPSG) and Diabetes in Pregnancy Study Group of India (DIPSI) recommend that GDM should be screened universally [5]. In India, the prevalence of diabetes is very high, and the chance of detecting previous diabetes through screening is very high. GDM is a frequently observed pregnancy complication characterized by glucose intolerance, and incidence is expected to increase with raise in maternal obesity 6, 7]. Women with elevated blood glucose are at increased risk for delivery of large-for-gestational ageinfants, and there is a strong monotonic association between maternal glucose control and infant birthweight [8, 9]. Up to one-third of women with GDM require pharmacologic treatment to achieve adequate glucose control [10.11]. While glucose control greatly improves pregnancyoutcomes [12-14], the question of whether OHAs are as safe and effective as injectable insulin for the mother and her infant remains unanswered. Injectable insulin has previously been the standard of care for GDM; however, glyburide and metformin (both OHAs) have become increasingly used for this indication.10 Treatment of GDM is always based on diet modifications. If fasting and postprandial glucose target values are not met with diet alone, medication is needed. Historically, insulin has been used most. It is effective and does not affect the fetus.13 However, the subcutaneous administration route, the risk of hypoglycaemia and the tendency to increase appetite and weight gain are disadvantages of insulin. There is growing evidence favouring the use of the oral agents glibenclamide (sulfonylurea) [15] and particularly metformin [12] as an alternative to insulin in GDM patients. Metformin crosses the placenta in late pregnancy according to ex vivo human term placental perfusion studies and in vivo studies where maternal and cord blood metforminconcentrations have been measured and compared. However, the exact mechanism and the degree of placental metformin transfer are unclear [8].

MATERIAL AND METHODS

Study design:

Hospital based prospective study.

Study site:

The study was conducted at Department of Paediatrics, Sree Balaji Medical College and Hospital, Chennai from January 2019 to December 2019.

Source and study population:

Neonates of mothers diagnosed to have gestational diabetes mellitus delivered in Sree Balaji medical college and hospital, Chennai during study period. The Neonates of GDM mothers who fulfilled the inclusion criteria were enrolled in the present study. Minimum sample size needed for adequate statistical power was considered as 150 and eachgroup consists of 75.

Eligibility criteria

Inclusion criteria

- Singleton neonates of diabetic mothers.

Exclusion criteria

Neonates of diabetic mothers with medical complications such asheart disease and renal disease.

- Neonates of diabetic mothers with pregnancy induced hypertensionand eclampsia.
- Twin neonates of diabetic mothers.
- Neonates of GDM mothers treated with medications other thanMetformin and insulin
- Patients were categorised into two groups consecutively based on their treatment modalities. Patients of Group A were treated with Metformin and Group B were treated with Insulin. Compared the neonatal complications of GDM mothers belongs to these two groups.

Data collection

After taking the informed written consent from the parent or guardian, the relevant information from the history, physical examination and investigation findings were recorded in a predesigned proforma. Maternal characteristics recorded include age, parity, BMI gestational age, h/o previous abortions, stillbirths, and mode of delivery. Diabetic status and treatment abstracted from the antenatal records ,all these mothers registered and followed up at SBMCH and were diagnosed as GDM by single step non-fasting 2nd hour OGCT performed around 22-28 weeks and classified as GDM according to DIPSI criteria. These study population underwent glucose challenge test with 75 grams of glucose dissolved in 250-300 ml of water irrespective of last meal and second hour plasma glucose was measured by glucose oxidase-peroxidase method and values ≥140 mg/dl are considered dysglycaemia.

Mothers diagnosed as gestational diabetes were started on either Metformin or insulin according to the mother's convenience and their blood sugar control was monitored using the 6 point profile and who had blood glucose levels in the range of 70 to 110 mg/dL throughout the day are considered to have good glycaemic control and above this are considered to have poor glycaemic control.

After the infant is born, assessment was made based on APGAR scores to determine the need for any resuscitative efforts. The infant was dried and placed under a warmer. Baby was weighed immediately after birth using the Phoenix digital infant weighing scale, noted as birth weight and the gestational age was assessed using new Ballard scoring system and were classified as birth weight appropriate for gestational age or not by plotting on Fenton's foetal-infantgrowth charts.

A screening physical examination for the presence of major congenital anomalies was performed. Blood glucose levels were checked at 1, 2, 3, 6, 12, 24, 36, and 48 hours by glucostix. Cord blood samples are collected, and serum calcium levels were measured by Arsenazo 3 method from cord blood initially and later from venous samples if the baby remains hypo calcaemic or symptomatic. Complete hemogram was done from cord blood samples and haematocrit values were recorded. Hypoglycaemia as blood glucose levels less than 45 mg/dl (IMNCI criteria), hypocalcaemia as serum calcium level less than 7.5 mg/dl. Polycythaemia as haematocrit higher than 65%.

Visual inspection of icterus in the baby was done regularly and bilirubin levels were measured using VOX method after 72 hours of life or earlier if required on venous samples and hyperbilirubinemiaconsidered as TB(total bilirubin) >95th percentile on hour specific Bhutani nomogram and phototherapy was initiated based on hour specificTB modified by any risk factors by AAP(American academy of paediatrics) guidelines for phototherapy.

RESULTS

Totally, 150 GDM Mothers were enrolled and equally categorised in to two groups such as Insulin and Metformin treated groups which had 75 patients each. The baseline maternal characteristics of the two groups were illustrated in table 1:

 © 2022 Society of Education, India

Table-1: Baseline Maternal Characteristics

Maternal Characteristics	Metformin (N=75)	Insulin (N=75)	*P* Value
Maternal Age in years	28.48 ±2.62	28.49 ± 2.41	0.9741
BMI	28.8±2.9	29.64 ±2.83	0.0789
GCT at 2 hours	152.06 ± 13.19	175.73±16.33	<0.0001
Obstetrics score			
G2P1L1	37	35	-
PRIMI	36	35	-
G3P2L2	02	05	-
Mode of Delivery			
EL. LSCS	13	14	-
NVD	44	33	-
EM. LSCS	17	25	
Vacuum Assisted	1	2	-
Outlet Forceps	0	1	-

The oral glucose challenge test was lower in metformin treated group than insulin treated group (*P*<0.0001). The BMI of both the groups were not significantly different (*P*=0.0789).

The maternal age was not significantly different between two groups (p=0.9741). The obstetrics scores were almost similar with two groups. The mode of delivery has shown difference between the two groups (Fig.5). The NVD was higher in the metformin group and LSCS were lower in the same group than insulin group. Assisted delivery was higher in insulin group than metformin group.

NEONATAL CHARACTERISTICS:

Table 2 depicted the baseline characteristics of the neonates who were born to GDM mothers. The birth weight of the neonates was not significantly different between two treatment groups (*P*=0.4120). The appropriate gestational age (AGA) of the neonates were observed higher in metformin group (80 %) than insulin group (76 %). The small for gestational age (SGA) were higher in insulin group (9.33%) than metformin treated GDM mothers (4 %). However, the large for gestational age (LGA) were almost same in both the groups.

The neonatal blood glucose was estimated till 48 hours of life with some intervals. The blood glucose at 1 hour, metformin group showed lower than insulin group which was statistically significant (*P*<0.0001). Similarly, at 24 and 48 hours showed significant difference between the two groups (*P*<0.0001). The other intervals did not differ between the groups. The serum calcium levels were significantly different between the metformin and insulin treated groups. Metformin group showed higher calcium levels than insulin group (*P*=0.0190). The packed cell volume (PCV) had significantly higher in metformin treated group than insulin treated group (*P*=0.0120)

Table 2: Neonatal characteristics

Neonatal characteristics	Metformin (N=75)	Insulin (N=75)	*P* value
Birth Weight	2.92 ±0.55	2.98 ± 0.59	0.4120
Gestational Age Birth Weight			
AGA	60	57	-
SGA	3	7	-
LGA	12	11	-
Blood glucose			
1 hr	61.62 ±10.87	73.34 ±17.54	<0.0001
2 hr	64.76 ±16.36	70.2± 21.74	0.0854
3 hr	71.88 ±17.19	75.06 ±17.22	0.2586
6 hr	88.22 ±20.72	86.77 ±25.12	0.7049
12 hr	81.84 ±12.56	84.08 ±11.58	0.2581
24 hr	98.06 ±23.20	81.81 ±17.36	<0.0001
48 hr	84.85 ±14.18	93.45 ±10.26	<0.0001
Serum Calcium	9.53 ±1.51	8.95 ±1.45	0.0190
PCV	51.49 ±6.14	48.85 ± 6.57	0.0120

 © 2022 Society of Education, India

NEONATAL COMPLICATIONS

The clinical outcome of the GDM mother was observed in both the treatment groups (Table 3). The macrosomia has observed in low number of patients in the metformin group (10.66 %) than in insulin group (14.66%). The RDS occurred in 4% patients and 9.33 % patients in metformin and insulin group respectively. The metformin group had minimal percentage than insulin group. Transient tachypnoea of the new-born (TTN) has observed almost same in both the groups. In the insulin group neonates had higher prevalence of hypoglycaemia (28 %) than occurred in metformin group (25 %). The hyperbilirubinemia has been observed 5% in metformin group and two-fold higher in insulin group (10.66 %). Similarly, hypocalcaemia was twofold higher in insulin group (12.5%) than in the metformin treated group (6.66 %). There was no difference in the occurrence of polycythaemia in both the groups. Both groups had 6.66 % each. The NICU stay was higher in insulin group (32 %) than in the metformin group (26.66 %).

Table 3: NEONATAL COMPLICATIONS

Complications	Metformin N (%)	Insulin N (%)
Macrosomia		
Yes	8 (10.66)	11 (14.66)
No	67 (89.33)	64 (85.33)
Respiratory Distress		
RDS	3 (4)	7 (9.33)
TTN	7 (9.33)	8 (10.66)
No	65 (86.66)	60 (80)
Hypoglycemia		
Yes	19 (25.33)	21 (28)
No	56 (74.66)	54 (72)
Hyperbilirubinemia		
Yes	4 (5.33)	8 (10.66)
No	71(94.66)	67 (89.33)
Hypocalcaemia		
Yes	5 (6.66)	9 (12)
No	70 (93.33)	66 (88)
Polycythaemia		
Yes	5 (6.66)	5 (6.66)
No	70 (93.33)	70 (93.33)
NICU Stay		
Yes	20 (26.66)	24 (32)
No	55 (73.33)	51 (68)

THE RELATIVE RISK ANALYSIS OF NEONATAL COMPLICATIONS

The relative risk analysis showed that metformin treated GDM mother's neonates had least relative risk of the development of the below mentioned neonatal complications**.** However, in insulin treated GDM Mother's neonates had almost one-fold higher chance of the development of these complications. The development of polycythaemia had the equal relative risk and odds ratio in both the groups. The detailed relative risk and odds ratio of the respective neonatal complications were displayed in the table 4.

DISCUSSION

Given the various complications to which the child of a mother with GDM is predisposed, sometimes a more intensive therapy is necessary. Reasons for NICU admission include congenital abnormalities (such as cardiovascular malformations), prematurity, perinatal asphyxia, respiratory distress, and metabolic complications (hypoglycaemia, hypocalcaemia, polycythaemia, and hyperbilirubinemia), among others.135 In the present study, the NICU admission rate was 29.33%. This value corroborates other values found that the need for NICU admission ranged from 15% to 23.5%.16 In the present study, the type of treatment affect the need for NICUadmission, while other authors also found that infants born to women treated with insulin had higher rates of NICU admission when compared with pregnant women who received treatment with metformin.15 these results were coincide with the present study results. The present study had analysed the relative risk ratio and found that insulin treated group was highly

 © 2022 Society of Education, India

susceptible to get neonatal complications. To best of our knowledge, there was no studies available pertaining to relative risk ratioto compare the present study results.

Table 4: Relative risk analysis of neonatal complications

Neonatal Complications		Metformin	Insulin
Macrosomia	Relative risk	0.73	1.38
	Odds ratio	0.69	1.44
RDS	Relative risk	0.43	2.3
	Odds ratio	0.41	2.45
TTN	Relative risk	0.96	1.04
	Odds ratio	0.92	1.09
Hypoglycaemia	Relative risk	0.9	1.11
	Odds ratio	0.87	1.15
Hyperbilirubinemia	Relative risk	0.5	2
	Odds ratio	0.47	2.12
Hypocalcaemia	Relative risk	0.56	1.8
	Odds ratio	0.52	1.91
Polycythaemia	Relative risk	1	1
	Odds ratio	1	1
NICU Stay	Relative risk	0.83	1.2
	Odds ratio	0.77	1.29

CONCLUSION

The conclusion of this study is that compared with insulin, initial metformin is effective and safe for GDM drug treatment. Metformin treatment in GDM patients is not associated with an increased incidence of adverse foetal or neonatal outcomes, indicating thesafety of metformin.

The relative risk ratio of neonatal complications in metformin treated group was lower and higher in insulin treated group.

REFERENCES

1. Wendland, E.M., Torloni, M.R., Falavigna, M., Trujillo, J., Dode, M.A., Campos, M.A., et al. (2012). Gestational diabetes and pregnancy outcomes-a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy study groups (IADPSG) diagnostic criteria. BMC Pregnancy Childbirth. 12(1):23
2. Guariguata, L., Linnenkamp, U., Beagley, J., Whiting, D., Cho, N. (2014) Global estimates of the prevalence of hyperglycaemia in pregnancy. Diabetes Res Clin Pract.103(2):176–85.
3. Nguyen, CL., Pham, N.M., Binns, C.W., Duong, D.V., Lee, A.H. (2018) Prevalence of Gestational Diabetes Mellitus in Eastern and Southeastern Asia: A Systematic Review and Meta-Analysis. JDiabetes Res.;2018:10.
4. Rajput, R., Yadav, Y., Nanda, S., Rajput, M. (2013). Prevalence of gestational diabetes mellitus and associated risk factors at a tertiary care hospital in Haryana. Indian J Med Res ;137:728-33.
5. Mohan, V., Usha, S., Uma, R. (2015). Screening for gestational diabetes in India: Where do we stand? J Postgrad Med ;61:151-4.
6. International Diabetes Federation. (2017). IDF Diabetes Atlas, Eighth Edition. Brussels, Belgium: International Diabetes Federation. .
7. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Gestational Diabetes Bethesda, MD: National Diabetes Information Clearinghouse (NDIC); 2017
8. Kim, S.Y., England, L., Wilson, H.G., Bish, C., Satten, G.A., Dietz, P. (2010). Percentage of gestational diabetes mellitus attributable to overweight and obesity. Am J Public Health. 100(6): 1047- 52.
9. Landon, M.B., Mele, L., Spong, C.Y., Carpenter, M.W., Ramin, S.M.,Casey, B., et al. (2011) The relationship between maternal glycemia and perinatal outcome. Obstet Gynecol. 117(2 Pt 1):218-24.
10. Coustan, D.R. (2007). Pharmacological management of gestational diabetes:an overview. Diabetes Care. ;30 Suppl 2:S206-8.
11. ADA. 13. Management of Diabetes in Pregnancy. Diabetes Care.2017;40(Supplement 1):S114-S9.
12. Crowther, C.A., Hiller, J.E., Moss, J.R., McPhee, A.J., Jeffries, W.S., Robinson, J.S. (2005) Effect of treatment of gestational diabetes mellitus onpregnancy outcomes. The New England journal of medicine. 2005;352(24):2477-86.
13. Landon, M.B., Spong, C.Y., Thom, E., Carpenter, M.W., Ramin, S.M., Casey, B., et al. (2009). A multicenter, randomized trial of treatment for mild gestational diabetes. The New England journal of medicine.

;361(14):1339-48
14. Alwan, N., Tuffnell, D.J., West, J. (2009). Treatments for gestational diabetes. Cochrane Database Syst Rev. (3):CD003395.
15. Goh, J.E., Sadler, L., Rowan, J.(2011). Metformin for gestational diabetes inroutine clinical practice. Diabet Med. ;28:1082-7.
16. Mesdaghinia, E., Samimi, M., Homaei, Z., Saberi, F., Moosavi, S.G.A.,Yaribakht, M. (2013). Comparison of newborn outcomes in women withgestational diabetes mellitus treated with metformin or insulin: arandomised blinded trial. Int J Prev Med. 4:327-33.

Copyright: © 2022 Society of Education. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.