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Original Research Article

Adverse perinatal outcome in diabetic mother treated with oral hypoglycemic agents vs. insulin

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ABSTRACT

Background: Insulin has been the primary mode of therapy in diabetic mother for glycemic control as oral hypoglycemic agents (OHA) were initially thought to have teratogenic effect. Recent data supports the use of certain OHA; this study was designed to compare the perinatal outcomes in infants born to diabetic mother treated with insulin vs. oral hypoglycemic agents and to find out the relation of adverse perinatal events to glycemic control in both groups.

Methods: This prospective observational study was conducted in a tertiary care hospital. 108 neonates born to diabetic mother between October 2014 to September 2016 were taken for study immediately after delivery after excluding the mothers who were treated with lifestyle modification and/or dietary modification alone only. 60 mothers had received insulin and 48 OHA for glycaemic control. Glycemic control was assessed by HbA1C estimation on the day of delivery. The infants were followed up in neonatal care unit for perinatal complications. Main outcome measure(s): birth weight, gestational age, respiratory problems, birth injury, birth asphyxia, congenital anomalies, hypoglycemia, hypocalcaemia, hyperbillirubinemia.

Results: Out of 108 infants, 27 were born to pregestational and 81 to gestational diabetic mothers. 60(55.5%) were treated with insulin and rest with OHA, 53(49.1%) had optimal glycemic control. Both the groups had similar glycemic control in the third trimester. None of the perinatal outcomes showed significant difference between insulin and OHA group except neonatal hyperbillirubinemia. (p=0.013, RR=8 and OR=0.106). Within the optimal glycemic control (HbA1C <8), LGA has significant association with the insulin group than OHA (p=0.012, RR=2.217 and OR=4.2018).

Conclusions: As compared to insulin, oral hypoglycemic agents have similar glycemic control and no adverse perinatal outcomes and can be used in pregnant mothers with diabetes mellitus from poor socioeconomic and educational background for its low cost and better patient compliance. Within the glycemic control, maternal treatment with insulin showed significant difference in LGA compared to OHA which needs further studies for validation.

Keywords: Gestational diabetes, Insulin, Oral hypoglycemic agent, Outcome

INTRODUCTION

Worldwide prevalence of diabetes mellitus is increasing and gestational diabetes mellitus (GDM) constitutes 88% of all cases of diabetes in pregnancy.[1] Incidence of GDM is significantly greater (15%) in women born on the Indian subcontinent.[2] There is high risk of perinatal morbidity and mortality in offspring of GDM. Insulin has been the primary mode of therapy as oral hypoglycemic agents (OHA) were initially thought to have teratogenic effect. Recent data supports the use of certain OHA, however studies on perinatal morbidity comparing mother using insulin and OHA are limited.[3] OHA are cheaper, patient friendly, don't require injection or refrigerator for storage and well suited to the mothers from low socioeconomic and educational background in developing countries. Hence, this study was designed to study the perinatal outcomes in the mother with GDM treated with insulin vs. OHA and to find out the relation of adverse perinatal events to glycemic control in both groups.

METHODS

This was a prospective study done at special neonatal care unit of a tertiary care hospital at Cuttack, India. As the study was an observational study and don't involve any intervention in the study subjects, approval was not obtained from the ethical committee. Informed consent was obtained from the parents before enrolling for the study.

All neonates born to diabetic mother in SCB Medical College Cuttack between October 2014 to September2016 were enrolled for the study. Data regarding diabetic status were obtained from the antenatal records. Babies presenting after 24hrs of delivery and mothers who were being treated with dietary modification and/or lifestyle modification alone were excluded from the study.

Data Collection

After obtaining informed written consent from the parents, patients were selected from delivery room according to inclusion and exclusion criteria. Babies requiring resuscitation at birth were resuscitated according to National resuscitation programme.[4] All babies were shifted to neonatal care unit for monitoring and treatment. Different variables recorded include name, age, parity, residence, gestational age (GA), and other antenatal problems. Type of diabetes pregestational (Type I, Type II), or gestational was assessed, glucose tolerance test performed earlier were noted. HbA1c estimation of maternal venous blood was done to assess the glycemic status of mother during third trimester.[5]

At admission to neonatal care unit, weight was recorded using digital weighing scale, GA assessment done using New Ballard score. Macrosomia was defined as either birth weight >90th centile for GA or >4000gm independent of gestational age.[6,7] Small for GA was defined as birth weight <10th centile for GA.[8] Congenital anomalies were searched clinically. Babies were monitored for hypoglycemia (defined by blood glucose level <40mg/dl regardless of gestational age).[9] Respiratory distress was defined by respiratory rate of ≥60/min and/or sub costal and intercostal retraction.

Blood glucose estimation was done by heel prick using glucose oxidase method at admission, 1hr, 3hr and 5hr. Estimation of hemoglobin, hematocrit, and serum electrolyte were done in clinical laboratory by automated analyser. Polycythemia was diagnosed if the venous hematocrit exceeds 65%; hypocalcaemia was defined as serum calcium <7mg/dl.[9-12] Billirubin level was estimated at the clinical appearance of jaundice or on day4 if not evident clinically and hyperbillirubinemia was diagnosed based on standard guidelines.[13] Chest X ray was done in all infants with respiratory problems and/or heart murmur. ECG and echocardiography was done in all infants by trained cardiologist. Venous blood of all mothers was sent within 24 hr of delivery for HbA1c estimation.

Patient's hospital course was followed up according to neonatal unit protocol.

Outcomes: Perinatal Outcome variable studied were prematurity, Large for gestational age (LGA), small for gestational age (SGA), macrosomia, hypoglycemia, polycythemia, respiratory problems (TTN, HMD, MAS, Pneumonia), birth asphyxia, hypocalcaemia and hyperbillirubinemia.

Statistical analysis

This study involves comparison of proportion with a dichotomous outcome between two samples using the Chi-squared statistic. As this requires a whole lot of knowledge about estimate of population parameters. But no consistent knowledge about 12 adverse outcomes available from the previous studies. Hence a pilot study with available 108 cases, 60 in insulin and 48 in OHA group which were available during the study period was considered to throw light on the subject and form basis for a more valid study in future.

Frequency procedure has been adopted to calculate the baseline attributes of the cases among insulin and OHA. Association of adverse outcomes with agents and glycemic levels has been studied using cross tabulation procedure along with chi-square test and relative risk analysis.

RESULTS

Out of 108 patients studied, 60 (55.5%) were treated with insulin and 40 (44.5%) with OHA. Mothers were primigravida in 39 (36.1%) and from rural area 37

(34.3%). Type of diabetes was pre-gestational in 28 (25.9%) and gestational in 80 (74.1%). History of diabetes was present in 46 (43%) of the families. Third trimester glycaemic control was optimal (HbA1C <8) in 54 (50%) mothers (Table 1).

Table 2 presents the analysis of different adverse perinatal outcomes for studying the association of adverse outcomes with agents – insulin and oral hypoglycemic agents. None of the adverse perinatal outcome showed significant association at 0.05 level of significance except neonatal hyperbillirubinemia. The relative risk (RR) of neonatal hyperbillirubinemia is 8 in the insulin group than OHA group and OR of 0.106 (p=0.013). MSAF showed lesser significant association with agents p=0.055, in insulin group 4 (6.7%) delivered with MSAF while it was 9 (18.8%) in OHA group (p=0.055, RR=0.356, OR=3.231).

Table 1: Characteristics of diabetic mother both insulin and oral hypoglycemic group.

Variable	Overall (n=108)	Insulin (n=60)	OHA (n=48)	P value
Parity				
Primi	39 (36.1)	21 (35)	18 (37.5)	
Grand multi	14 (12.9)	6 (10)	8 (16.7)	
Residence				
urban	71 (65.7)	45 (75)	26 (54.2)	0.023
rural	37 (34.3)	15 (25)	22 (45.8)	
Type of diabetes				
Pregestational	28 (25.9)	15 (25)	13 (27.1)	0.806
gestational	80 (74.1)	45 (75)	35 (72.9)	
HbA1c				
*Mean±SD	7.91±1.21	7.98±1.12	7.82±1.33	0.499
<8	53 (49.1)	28 (46.7)	25 (52.1)	0.699
>8	55 (50.9)	32 (53.3)	23 (47.9)	
Family history of diabetes	46 (43)	19 (32.2)	27 (56.2)	0.012

Data presented as n (%), *Mean ±SD

Table 2: Analysis of adverse perinatal outcomes by agents

Outcomes	Insulin (n=68)	OHA (n=40)	P value	OR(RR)*
SGA	4 (6.7)	1 (2.1)	0.26	3.357 (3.2)
LGA	22 (36.7)	16 (33.3)	0.719	1.158 (1.1)
MSAF	4 (6.7)	9 (18.8)	0.055	3.231 (0.356)
Birth asphyxia	13 (21.7)	9 (18.8)	0.708	0.834 (1.156)
Birth injuries	8 (13.3)	12 (25)	0.121	2.167 (0.533)
Hairy pinna	43 (71.7)	30 (62.5)	0.312	0.659 (1.147)
Respiratory problems	16 (26.7)	13 (27.1)	0.961	1.021 (0.985)
Congenital anomaly	4 (6.7)	2 (4.2)	0.573	1.643 (1.6)
Hypoglycemia	8 (13.3)	3 (6.2)	0.227	0.433 (2.133)
Polycythemia	1 (1.7)	3 (6.2)	0.21	3.933 (0.267)
Hypocalcaemia	2 (3.3)	0 (0)	0.202	
Hyperbilirubinemia	10 (16.7)	1 (2.1)	**0.013**	0.106(8)

Data presented as n (%);*OR: Odds ratio; RR: Relative risk

In order to isolate the confounding effect of glycemic level on agents, study of association of adverse outcomes with agents was attempted within the glycemic level (Table 3). Within the optimal glycemic level, LGA has significant association with the insulin group having 18 (62.1%) manifestation against 7 (28%) in the OHA (p=0.012, RR = 2.217 OR = 4.208).

In the sub-optimal group, LGA has significant association with OHA with 9 (39.1%) against 4 (12.9%) in the insulin group (p=0.026, RR=0.33 and OR=0.23). MSAF is 0.278 (RR) times less likely in the insulin group than OHA within the sub-optimal glycemic level. Hyperbilirubinemia indicated significant association with the insulin than OHA (p=0.043) within the sub-optimal glycemic level.

Table 4 presents adverse perinatal outcomes are separately analyzed in the insulin and OHA. In the insulin group only LGA was found to be significantly different

between the optimal and sub-optimal glycemic control (p=0.000, OR=11.05 and RR=4.81). In the OHA, MSAF was significantly different between the optimal and sub-optimal glycemic control (p=0.006, OR=12.80 and RR=0.12). The remaining adverse outcomes did not exhibit any significant association with hypoglycemic control.

Table 3: Analysis of adverse perinatal outcome for Insulin and oral hypoglycemic agents within the glycemic control.

Outcomes	HbA1c <8 (Optimal)				HbA1c >=8 (Sub-optimal)			
	Insulin (n=28)	OHA (n=25)	P value	OR (RR)*	Insulin (n=32)	OHA (n=23)	P value	OR(RR)*
SGA	1(3.4)	1 (4)	0.915	0.857 (0.862)	3 (9.7)	0 (0)	0.125	
LGA	18 (62.1)	7 (28)	0.012	4.208 (2.217)	4 (12.9)	9 (39.1)	0.026	0.23(0.33)
MSAF	1(3.4)	1 (4)	0.915	1.167 (0.862)	3 (9.7)	8 (34.8)	0.024	4.978 (0.278)
Birth Asphyxia	9(31)	4 (16)	0.198	0.423 (1.94)	4 (12.9)	5 (21.7)	0.389	1.875 (0.594)
Birth Injuries	3 (10.3)	8 (32)	0.050	4.078 (0.323)	5 (16.1)	4 (17.4)	0.902	1.095 (0.927)
Hairy Pinna	20 (69)	17 (68)	0.939	0.956 (1.014)	23 (74.2)	13 (56.5)	0.173	0.452 (1.313)
Respiratory problems	5 (17.2)	8 (32)	0.206	2.259 (0.539)	11 (35.5)	5 (21.7)	0.274	0.505 (1.632)
Congenital Anomaly	2 (6.9)	0 (0)	0.181		2 (6.5)	2 (8.7)	0.756	0.724 (0.742)
Hypoglycemia	5 (17.2)	2(8)	0.313	0.417 (2.155)	3 (9.7)	1 (4.3)	0.46	0.424 (2.226)
Polycythemia	0 (0)	2 (8)	0.121		1 (3.2)	1 (4.3)	0.829	1.364 (0.742)
Hypocalcaemia	1 (3.4)	0 (0)	0.349		1 (3.2)	0 (0)	0.385	
Hyper-bilirubinemia	5 (17.2)	1 (4)	0.123	0.2 (4.31)	5 (16.1)	0 (0)	0.043	

Data presented as n (%);*OR: Odds ratio; RR: Relative risk

Table 4: Analysis of adverse perinatal outcome for optimal and suboptimal glycemic control within the agent.

Outcomes	Insulin				OHA			
	HbA1c <8 (n=28)	HbA1c ≥8 (n=32)	p value	OR(RR)*	HbA1c <8 (n=25)	HbA1c≥8 (n=23)	P value	OR(RR)*
SGA	1 (3.4)	3 (9.7)	0.334	0.33 (0.36)	1 (4)	0 (0.0)	0.332	
LGA	18 (62.1)	4 (12.9)	**0.000**	11.05 (4.81)	7 (28)	9 (39.1)	0.414	0.61 (0.72)
MSAF	1 (3.4)	3 (9.7)	0.334	3.00 (0.36)	1 (4)	8 (34.8)	**0.006**	12.80 (0.12)
Birth Asphyxia	9 (31.0)	4 (12.9)	0.088	0.33 (2.41)	4 (16)	5 (21.7)	0.611	1.46 (0.74)
Birth Injuries	3 (10.3)	5 (16.1)	0.510	1.67 (0.64)	8 (32)	4 (17.4)	0.243	0.45 (1.84)
Hairy Pinna	20 (69.0)	23 (74.2)	0.653	1.29 (0.93)	17 (68)	13 (56.5)	0.412	0.61 (1.20)
Respiratory problems	5 (17.2)	11 (35.5)	0.110	2.64 (0.49)	8 (32)	5 (21.7)	0.424	0.59 (1.47)
Congenital Anomaly	2 (6.9)	2 (6.5)	0.945	1.07 (1.07)	0 (0)	2 (8.7)	0.132	
Hypoglycemia	5 (17.2)	3 (9.7)	0.389	0.51 (1.78)	2 (8)	1 (4.3)	0.602	0.52 (1.84)
Polycythemia	0 (0.0)	1 (3.2)	0.329		2 (8)	1 (4.3)	0.602	0.52 (1.84)
Hypocalcemia	1 (3.4)	1 (3.2)	0.962	0.93 (1.07)	0 (0)	0 (0.0)		
Hyperbilirubinemia	5 (17.2)	5 (16.1)	0.908	0.92 (1.07)	1 (4)	0 (0.0)	0.332	

Data presented as n (%);*OR: Odds ratio; RR: Relative risk

DISCUSSION

Adverse perinatal outcomes have been studied in the present study. Family history of diabetes was seen in 40.1% in the present study which is higher compared 20% reported by Ranade et al, which may be due to increasing incidence of diabetes in our country.[14] Incidence of prematurity was 15.7% in the present study which varies in different studies with as low as 11% by Gabbe SG et al to 46% by Watson et al.[15,16]

Incidence of perinatal complications reported by different researchers varies in different studies, macrosomia (16% to 41.5%), birth asphyxia (9.1% to 20.4%), congenital anomalies (3.8% to 7.9%) birth injuries (2%), respiratory distress (5.7% to 28.6%), hypoglycemia (8.5% to 50%),

hypocalcaemia (2% to 14%), hyperbillirubinemia (8% to 42.9%) and polycythemia (1.5% to 20%). Our reports are comparable to the above findings.[14,16-20]

The meta-analysis by Dhulkotia JS et al demonstrates no difference in outcomes when OHAs were compared with insulin.[21] Present study also revealed similar results excepting hyerbillirubinemia which is more in the insulin group. Thomas N et al also reported more hyperbillirubinemia in the insulin group.[22] Third trimester HbA1C is the strongest predictor of LGA infants in the study by Herranz L et al. We found significantly more no of babies with LGA in the optimal glycemic control group irrespective of agents and also that in those treated with insulin only which is contrary to the above studies. Further study with large no of subjects may be done to validate the findings.[23]

Limitations

The limitation of present study is that it is an observational study, randomization was not done. The decision to put the baby in two groups was decided by the gynaecologist as per their experience and considering the socioeconomic and educational background of the mothers. As the study sample size is small, outcome with use of different OHA is not compared. Initial hyperglycemia at the start of therapy was not studied, which might alter the interpretation of the results. Further randomized control studies with more no of patients and comparing different OHA and at different initial levels of hyperglycemia are needed to validate these findings.

CONCLUSION

Perinatal outcome and glycemic control in mother treated on oral hypoglycemic agents are not different than that treated with insulin. Oral hypoglycemic agents due to better patient compliance and being cheaper can be used in developing countries with low socioeconomic and educational background mother without any significant adverse effect on perinatal morbidity.

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