RESEARCH PAPER

Perinatal Outcome of Infants Born to Diabetic Mothers in a Developing Country- Comparison of Insulin and Oral Hypoglycemic Agents

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Objective: To study the perinatal outcomes of infants born to mothers with gestational diabetes treated with insulin or oral hypoglycemic agents in a developing country.

Design: Prospective observational cohort study.

Setting: Tertiary-care perinatal center in southern India.

Participants: Babies born to mothers with gestational diabetes.

Methods: Maternal details were obtained and physical examination was performed on the neonates. Babies were given hourly feeds soon after birth and blood glucoses checked at 1, 3, 5, 9 and 12 hours of life; hematocrit and calcium levels were also measured. Perinatal outcomes were compared between mothers who required insulin or an oral hypoglycemic agent for treatment of diabetes.

Results: Of the 10,394 mothers who delivered during the study period, 574 (5.5%) were diagnosed to have gestational diabetes. 137 were treated with insulin and 141 with oral hypoglycemic agents. 44 (15.8%) babies were born preterm, 97 (35%) were large for gestational age, 13 (4.7%) were small for gestational age and 9 (3.2%) were macrosomic. Hypoglycemia was seen in 26 (9.3%) babies, congenital anomalies in 15 (5.4%) and birth injuries in 7 (2.5%). There was no difference between the two groups in any of the outcomes except for hyperbilirubinemia, which was more in the insulin group (13.7% *vs* 6.5%, *P*=0.04).

Conclusions: There was no difference in the perinatal outcome whether the mother received insulin or an oral hypoglycemic agent for treatment of gestational diabetes other than the increased incidence of hyperbilirubinemia in the insulin group

Key words: Gestational diabetes, India, Insulin, Management, Oral hypoglycemic agents, Outcome.

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The World Health Organization (WHO) has predicted that between 1995 and 2025, there will be a 35% increase in the worldwide prevalence of diabetes [1]. Moreover, women born in Asian countries display the highest prevalence of Gestational Diabetes Mellitus (GDM), with up to 17% of women likely to develop GDM, in comparison to 4% of European and white American women [2,3]. The prevalence of gestational diabetes in southern India was recently found to be 17.8% in urban women, 13.8% in semi urban and 9.9% in rural women, a steep rise from the prevalence of 1% reported from a similar population in 1998 [3,4]. In addition to the high perinatal mortality and morbidity associated with diabetes complicating pregnancy, there is an increased risk of birth defects and stillbirths. Infants of diabetic mothers (IDM) have a higher incidence of neonatal complications than those born to non-diabetic women[6].

Insulin has been the primary mode of therapy for diabetes complicating pregnancy for many decades, as oral hypoglycemic agents (OHA) were thought to have a teratogenic effect on the fetus. However, recent data support the use of OHAs, and both insulin and OHAs are now being used in the control of diabetes in pregnant women [7].OHAs are patient-friendly, convenient and cheap compared to insulin. In India, there are 26 million births annually. If 10-12% of pregnancies are affected by GDM and 40% of these pregnant mothers require insulin, OHAs would be a cheap and convenient alternative for more than 1.2 million women every year in India.

There is paucity of data available on outcome of IDMs, especially from developing countries like India and the literature available is primarily from an era when OHAs were not used [8-12].Information from India on the use of OHAs in pregnancy is limited to case-series [13,14].A recent retrospective study suggests that the perinatal morbidity is higher in mothers who received glyburide for the treatment of gestational diabetes as compared to insulin [15]. Hence, there is a need to look at the neonatal outcomes of mothers receiving OHAs.

The aim of the study was to determine the perinatal outcome of IDMs comparing those mothers treated with insulin or OHAs.

METHODS

This prospective observational cohort study was conducted in the neonatology department of Christian Medical College, Vellore, a tertiary-care perinatal center in southern India. All babies born to mothers diagnosed to have GDM from November 2008 to October 2009, and requiring treatment with OHAs or insulin were included. Babies born to mothers with impaired glucose tolerance test (GTT) or gestational diabetes requiring only diet control were excluded. The criteria for diagnosis of gestational diabetes was as laid out by the National Diabetes Data Group (NDDG) [16]. Once GDM was diagnosed, blood glucoses were repeated 3-7 days after diet modification.If the fasting value was >5 mmol/L (90 mg/dL) or 1hour postprandial value >6.6 mmol/L (120 mg/dL) treatment was started with OHA and if the respective values were >7.2 mmol/L (130 mg/dL) or >13.9 mmol/L (250 mg/dL), they were treated with insulin. The blood glucose was regularly monitored and dose of drugs adjusted as required. If blood glucoses were not controlled on OHA, the patients were switched to insulin.

As per the unit protocol, all babies born to diabetic mothers on insulin/OHA were admitted into the special care nursery and hourly feeds started. The first feed was usually given within 30 minutes of birth and babies fed hourly for the first 6 hours and then two-hourly if blood glucose values were normal. Once normoglycemia was established on two-hourly feeds, babies were transferred back to the mother and started on breast feeds.Blood glucose levels of these infants were checked using a glucometer (Accucheck sensor, Roche, Germany) at 1, 3, 5, 9 and 12 hours after birth, and subsequently in babies who were hypoglycemic. If the glucometer value was ≤2.6 mmol/L (47 mg/dL), plasma glucose estimation was performed for confirmation. Babies with hypoglycemia despite adequate feeds were treated with intravenous (IV) dextrose infusion. Bolus IV dextrose was given only if the baby was symptomatic or the blood glucose level was less than 1.4 mmol/L (25 mg/dL). Blood samples for measuring PCV/hemoglobin and serum calcium levels were also sent. All babies had a detailed physical examination within 24 hours of life. The birth weight of the babies was plotted against gestational age and babies were classified as large, small or appropriate for gestational age [17].

Hypoglycemia was defined as a blood glucose level of ≤2.6 mmol/L (47 mg/dL) in any infant regardless of gestational age and whether or not symptoms were present. Polycythaemia was defined as the presence of a venous hematocrit more than 65% or a venous hemoglobin concentration in excess of 22.0 g/dL. Hypocalcemia was defined as total serum calcium level less than 7 mg/dL. Hyperbilirubinemia was defined as a serum bilirubin level of >15 mg/dL. Large for gestational age (LGA) was defined as birth weight greater than 90th percentile for gestational age, small for gestational age (SGA) as birth weight less than the 10th percentile for gestational age and macrosomia as birth weight more than 4000 g. Babies born before 37 completed weeks of gestation were classified as preterm.

Relevant demographic, maternal and neonatal details were filled into a standard proforma and entered into Microsoft excel.Statistical analysis was done using the SPSS software version 16.Differences between the two groups were tested with the chi-square test, Fischerexact test for categorical variables and t-test and Mann-Whitney U test for continuous variables. *P* value of <0.05 was considered as significant.

RESULTS

During the one-year study period, there were 10,394 mothers who delivered in our hospital, of whom 574 (5.5%) were diagnosed to have GDM. Of these, 281 mothers required treatment with either insulin or OHAs while the rest were managed with diet control. Among the 281 babies born to diabetic mothers, there were 278 live births, 3 still births and no neonatal deaths. The perinatal mortality among the IDMs was thus 10.8 per 1000 births.

141 (50.7%) mothers received OHAs for control of blood glucose and 137 (49.3%) received insulin. Four (2.9%) mothers who were initially started on OHAs had to be switched over to insulin to control blood glucose levels. The OHAs used were glyburide (mean daily dose 4.58±2.08 mg/day) and metformin (mean daily dose 895.2±248.1 mg/day) in 110 and 31 mothers, respectively.

***Table* I** shows the maternal characteristics in the two groups.The mean age and parity of the mothers was similar as was the incidence of PIH and anemia. However, there were more hypothyroid mothers in the insulin group (7% *vs* 1.4%, *P*=0.003). Also, there was a significant difference in the GTT values with the insulin group having higher mean blood glucose levels at start of therapy. HbA1c levels were available for 82 mothers, 34 in the OHA group and 48 in the insulin group. The mean HbA1c after treatment was significantly higher in the insulin group.

***Table* II** shows the maternal and neonatal outcomes of the insulin and OHA groups.The babies in both the groups had a similar mean gestational age and birth weight; there was no significant difference in the proportion of LGA, SGA, preterm and macrosomic babies in the two groups.

TABLE I CHARACTERISTICS OF DIABETIC MOTHERS TREATED WITH INSULIN OR ORAL HYPOGLYCEMIC AGENTS

Parameters		*Overall (n=278)*	*Insulin (n=137)*	*OHA (n=141)*	*P value*
Age	Mean ± SD	29.38 ± 4.1	29.2 ± 4.1	29.5±4.1	0.57
	>35 years	23	11 (7.9%)	13 (9.3%)	0.67
Parity	Mean ± SD	1.58 ± 0.66	1.59 ± 0.67	1.56±0.65	0.69
	Primi	141 (50.7%)	69 (50.4%)	72 (51.1%)	
	≥3	20 (7.2%)	8 (5.7%)	12 (8.7%)	
Antenatal Risk Factors	PIH	36	18 (12%)	18 (12%)	1
	Anemia Hb <6gm%	1	0	1 (0.7%)	1
	Hypothyroidism	12	10 (7%)	2 (1.4%)	0.003
	None	199	95 (68%)	104 (74%)	0.28
GTT	AC	108.68 ± 30.9	112.62 ± 37.12	104.3 ± 21.69	0.04
	½ hour	108.8 ± 28.9	123.22 ± 36.49	99.97 ± 16.99	<0.001
	1 hour	220.16 ± 55.18	247.41 ± 67.36	203.27 ± 37.5	<0.001
	2 hour	198.66 ± 63.18	232.78 ± 80	177.49 ± 37.09	<0.001
	3 hour	161.1 ± 60.89	194.29 ± 75.6	140.5 ± 37.4	<0.001
HbA1c*	Mean ±SD	6.8 ±1.5	7.38 ± 1.6	5.97 ± 0.9	<0.001

**HbA1c after instituting treatment was available for only 82 mothers, 34 on OHA and 48 on Insulin; Data given as mean±SD and n(%).*

The overall rate of neonatal complications was low. Hypoglycemia occurred in 26 (9.3%), congenital anomalies in 15 (5.4%), birth injuries in 7 (2.5%), polycythemia in 6 (2.3%), hypocalcemia in 1 (0.5%) and probable sepsis in 7 (2.5%) babies.There was no difference between the insulin and OHA groups in these complications or in the duration of hospital stay (***Table* II**). There were more babies who developed hyperbilirubinemia (13.7% *vs* 6.5%, *P*=0.04) and required phototherapy (25.1% *vs* 13.6%, *P*=0.02) in the insulin group.The congenital anomalies seen were ano-rectal malformations [7], sacral agenesis [2], cardiac anomalies [2] and pre-auricular sinus [4].Of the seven babies with birth injury, four had brachial plexus injury and three had clavicular fractures.

DISCUSSION

In our cohort of IDMs who required treatment with either insulin or OHA, there were very few babies who developed complications with an overall good outcome. Importantly, there was no difference in the perinatal outcomes between the two groups except for the increase in hyperbilirubenemia in the insulin group.

The incidence of gestational diabetes in our study was much lower than that reported by Seshiah, *et al*. [3], from the same region. However, our study was not a community-based study and is not truly reflective of the general population. Other hospital-based studies from India have reported a similar incidence to ours [18]. The perinatal mortality in this cohort was also much lower than what has been reported previously from India and other developing countries [8,12].This probably reflects better perinatal care as our hospital is a tertiary-care centre, where more than 80% of the mothers are booked for antenatal care.

The OHA used were glyburide and metformin. Glycemic control achieved was not an objective of this study but the fact that only 2.9% from the OHA group were switched to insulin suggests that OHAs can be successfully used in the treatment of GDM.Langer et al reported a 4% failure rate of glyburide while other studies have reported failure between 16 to 46.3% [19,22].

There were more mothers with hypothyroidism in the insulin group. However, they formed a very small proportion (7%) of the group and were unlikely to have influenced the outcome. The mothers in the insulin group had higher mean blood glucoses and HbA1c levels. It is the policy of our obstetricians to start insulin rather than OHA as the primary mode of treatment if the GTT was very abnormal (AC> 130 mg%, 1hr PC > 250 mg%).This explains the higher pre-treatment blood glucoses and post treatment HbA1c levels in the insulin group, implying that those treated with OHA in our cohort had a milder degree of hyperglycemia and also accounts for the low failure rate of OHA. It is to be noted that Ramos, *et al*. [20] found that glyburide was not as effective in a subgroup of gestational diabetics with markedly elevated GTT and fasting hyperglycemia.

TABLE II MATERNAL AND NEONATAL OUTCOMES OF DIABETIC MOTHERS TREATED WITH INSULIN AND ORAL HYPOGLYCEMIC AGENTS

Parameters	*Overall (n=278)*	*Insulin (n=137)*	*OHA (n=141)*	*P value*
GA (mean ±SD)	37.49 ± 1.47	37.22 ± 1.59	37.76 ± 1.29	0.63
Preterm Delivery	44 (15.8%)	26 (18.7%)	18 (12.9%)	0.24
Birth Weight (mean ± SD)	2962.9 ± 505.9	2928.7 ± 418	2998.1 ± 492.5	0.25
LGA	97 (35.0%)	51 (36.7%)	46 (33%)	0.61
SGA	13 (4.7%)	9 (6.5%)	4 (2.9%)	0.25
Macrosomia	9 (3.2%)	4 (2.8%)	5 (3.6%)	0.5
Mode of Delivery				
Instrumental	52 (18.7%)	23 (16.5%)	29 (20.8%)	0.44
LSCS	119 (42.8%)	52 (38.8%)	67 (46.7%)	0.22
Birth Injuries	7 (2.5%)	5 (3.6%)	2 (1.4%)	0.25
Congenital anomalies	15 (5.4%)	10 (7.2%)	5 (3.6%)	0.52
Neonatal hypoglycemia				
1 hour	23 (8.2%)	15 (10.7%)	8 (5.7%)	0.13
3 hour	4 (1.4%)	2 (1.4%)	2 (1.4%)	1
5 hour	2 (0.7%)	2 (1.4%)	0	0.15
Polycythemia	6 (2.3%)	3 (2%)	3 (2%)	0.93
Hypocalcemia	1 (0.5%)	1 (0.9%)	0	0.33
Hyperbilirubinemia	28 (10.1%)	19 (13.7%)	9 (6.5%)	0.04
Probable Sepsis	7 (2.5%)	4 (2.9%)	3 (2.1%)	0.27
Phototherapy	54 (19.2%)	35 (25.1%)	19 (13.6%)	0.02
Duration of hospital stay	2.25 ± 0.8	2.26 ± 0.94	2.24 ± 0.82	0.86

Data given as mean±SD and n (%).

We found no significant increase in any of the neonatal complications among those who received OHA as compared to those treated with insulin, other than an increased incidence of jaundice and the need for phototherapy in the insulin group. Two studies have noted increased neonatal jaundice in babies whose mothers received glyburide for gestational diabetes [23,24], but this has not been described in other studies [19-22].

The overall incidence of neonatal hypoglycemia in our study was lower than most studies, probablyreflecting good glycemic control and the effectiveness of the unit policy of early, frequent feeding to prevent hypoglycemia. There was no difference in the incidence of hypoglycemia between the two groups in our study.Similar findings were noted by two previous RCTs comparing insulin and OHA therapy in GDM [19,22]. However, two smaller studies noted a higher incidence of hypoglycemia in the glyburide group [20,21].

The incidence of LGA was high, while that of macrosomia was low in our cohort compared to data from other countries [15,19,20]. This may be because we used the local intrauterine growth chart as a standard to classify the birthweight centiles. The meta-analyses of OHA *vs* insulin for gestational diabetes did not show any difference in the incidence of LGA in the two groups (OR 1.01; 95%CI, 0.61-1.68) [7]. A recent retrospective observational study however, showed an increase in the number of macrosomic babies and neonatal intensive care admission in babies born to mothers treated with glyburide for gestational diabetes [15].

The limitations of our study are that it is an observational study which is prone to several potential biases.In addition, the group that received OHA had a milder degree of hyperglycemia and less hypothyroid mothers compared to the group treated with insulin making the two groups non homogenous. The lack of maternal data like HOMA-IR, maternal lipid profile and complete data on HbA1C is also a lacuna in this study. Despite these limitations, the fact that more than 50% of this cohort of GDMs could be treated safely with OHA is an important observation.

In conclusion, the use of OHA's in mothers with mild

WHAT IS ALREADY KNOWN?

- Oral hypoglycemic agents are increasingly being used for the treatment of gestational diabetes, especially in developing countries.

WHAT THIS STUDY ADDS?

- The perinatal complications are not increased in offspring of mothers with gestational diabetes treated with oral hypoglycemic agents.

to moderate gestational diabetes does not increase perinatal complications. There is a need for more information, especially in the group with marked hyperglycemia at onset and further RCTs may be needed to address this issue.

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