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RESEARCH ARTICLE

SIGNIFICANCE OF THIRD TRIMESTER HbA1c AS A PREDICTOR OF ADVERSE OBSTETRIC OUTCOME IN DIABETIC MOTHERS- A PROSPECTIVE OBSERVATIONAL STUDY

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ABBREVIATIONS
ADA- American Diabetes Association
CGM – Continuous Glucose Monitoring
GDM- Gestational Diabetes Mellitus
HbA1c- Glycosylated Hemoglobin
IADPSG- International Association of Diabetes in Pregnancy Study Group
IGT – Impaired Glucose Tolerance
LGA – Large for Gestation Age
OR – Odds Ratio
OGTT- Oral Glucose Tolerance Test
SMBG – Self Monitoring of Blood Glucose.

ABSTRACT

Background: Diabetes is emerging as a new epidemic in today's era with the increase in obesity and sedentary lifestyles, affecting a large proportion of the female population extending to reproductive age group. It is well known to have short and long term consequences for the fetus and mother. Thus, proper control of diabetes in pregnancy is essential to ensure better obstetric outcomes. O**bjective:** The present study was undertaken to determine the significance of HbA1c levels in third trimester in predicting adverse maternal and fetal outcomes. **Methods:** It was a Prospective observational study of 100 pregnant women with diabetes who attended the antenatal clinic and delivered at St. Isabel's hospital, Chennai from May 2017 to Oct. 2017. Pre-gestational diabetes was diagnosed according to ADA criteria and testing for GDM was done with 75g Oral Glucose Tolerance Test (OGTT) according to IADPSG criteria at the first visit and at 24 -28 weeks. Patients with diabetes were managed according to hyperglycemia control. Hba1c value in late third trimester or at time of delivery was noted and a value of < 6% was considered normal. Obstetrical and perinatal outcomes were noted and the data was compared using Chi-square test. Odds ratio and 95% confidence interval were used to compare association of HbA1c with various maternal and neonatal complications. Regression analysis was used to estimate the relationship among various categorical variables. **Results:** Fetomaternal outcomes were compared among patients with HBA1c ≥6% and <6%. Adverse maternal outcomes when HbA1c was ≥6% included hypertension (42% vs. 6%, p<0.001, OR=11.7) and preterm labour (35% vs. 14%, p=0.01, OR=3.24). Spontaneous onset of labour (19% vs. 42%) when HbA1c was ≥6% with greater percentage of vaginal deliveries when HbA1c <6% (80% vs 20%). Neonatal outcome analysis revealed higher birth weight (51% vs. 39%, p=0.013) and greater incidence of LGA (45% vs. 3%, p<0.001, OR=27.5) with HbA1c ≥6%. Adverse neonatal metabolic complications included hypoglycemia (39% vs. 7%, p=0.001, OR=8.08), hyperbilirubinemia (58% vs. 29%, p=0.006, OR=3.39) and hypocalcemia (16% vs. 3%, p=0.016, OR=6.44). Regression analysis of various maternal and neonatal complications showed highest relation of third trimester HbA1c with maternal hypertension (p=0.002) followed by LGA (p=0.01). **Conclusion:** HbA1c is a sensitive tool for prediction of foetomaternal complication in patients with diabetes and should be advised to ensure optimum outcomes when self monitoring of blood glucose is not feasible.

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INTRODUCTION

Diabetes is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion or insulin action or both. Gestational Diabetes Mellitus (GDM) is defined as carbohydrate intolerance, mostly due to insulin resistance, of variable severity with an onset or first recognition during pregnancy and regardless of whether insulin or only diet modification is used for treatment or if it persists after pregnancy (Matouleibi Chanu et al., 2015). Up to 7% of all pregnancies are complicated by GDM (American College of Obstetrics and Gynaecology, 2013). Optimum monitoring of glycemic control improves fetal and maternal outcomes as both, over correction as well as under correction of blood glucose levels can be detrimental to the fetus. Hence, the need for appropriate screening, diagnosis and timely interventions, along with proper monitoring of glycemic levels to reduce maternal morbidity (pre-eclampsia, polyhydramnios, perineal tears etc.) and neonatal morbidity and mortality.

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In addition to glycosylated hemoglobin (HbA1c) levels, various methods to assess gylcemic control such as self-monitoring of capillary blood glucose (SMBG), continuous glucose monitoring (CGM), periodic fasting and post-prandial blood glucose levels are available. However, these methods are expensive and cumbersome leading to non-compliance and need motivation. Moreover, they do not reflect long term glycemic control. Hence, HbA1c has been a reliable marker for assessment of glycemic control (Rodrigues et al., 2013), as it does not depend on fasting status and gives an average over the last 4-6weeks. According to American Diabetes Association (ADA), the upper limit of normal HbA1c in third trimester should be kept as 5.6% instead of 6.3% (Nielsen et al., 2004). HbA1c levels should be within 1% above the upper limit of the normal range, in order to have a rate of complications no greater than those in pregnancies not complicated by diabetes (American Diabetes Association, 2002). HbA1c is more strongly correlated to the daily mean glucose concentration than to fasting plasma glucose (Mosca et al., 2006). Mothers with GDM have higher HbA1c values as compared to non-diabetic mothers, due to increased proportion of plasma glucose undergoing non-oxidative glycolysis. Hence the need for lower cut-off values which should be trimester specific.

HbA1c represents an integrated measure of glycemic control as it is directly proportional to blood glucose concentration (American Diabetes Association, 2017). As strict control of maternal hyperglycemia before conception is advisable to improve pregnancy outcome, optimum glycemic control throughout pregnancy is required in patients with impaired glucose tolerance (IGT), GDM and pre-gestational diabetes to minimize the adverse outcomes.

MATERIALS AND METHODS

Pregnant women with diabetes who attended the antenatal clinic and admitted for delivery at St. Isabel's hospital, Chennai from May 2017 to Oct. 2017 were enrolled in the study. Informed written consent was obtained prior to enrolment in the study.

Inclusion criteria

- HbA1c level done in 3rd trimester in diabetic mothers
- Singleton pregnancy
- Booked patient

Exclusion criteria

- Medical conditions affecting HbA1c like: Chronic kidney disease, known hemoglobinopathies
- Splenectomy

Pregnant patients who were diagnosed to have diabetes preconceptionally or in the first trimester were labelled as Pre-gestational diabetes.As a protocol, universal screening of all nondiabetic pregnancies was performed at 24- 28 weeks of gestation by 75gm GTT according to the International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria. All diagnosed cases were managed by a multidisciplinary team involving an obstetrician, diabetologist, dietician and a paediatrician. HbA1c level done in 3rd trimester was recorded. If it was not available, HbA1c was done at admission for delivery. Optimum control was taken as <6% according to the ADA recommendation. HbA1c level if done in 1st or 2nd trimester was also noted. Other antenatal details like type of diabetes, gestational age at time of diagnosis, test for diagnosis, treatment modality in different trimesters was recorded. Associated conditions like hypertension, thyroid disorder was noted. Thorough clinical examination was done and any evidence of macrosomia, polyhydramnios or cephalo pelvic disproportion was noted. Intrapartum events like onset of labour, mode of delivery, complications of labour, if any were noted. Routine antenatal and intrapartum care was provided as per protocols. Following delivery, weight of baby, prematurity, large for gestational age (LGA), neonatal hypoglycaemia, hyperbilirubinemia and hypocalcemia was screened for and treated according to hospital protocol and was noted. Neonates were followed up till 7th postnatal day to observe for any complications. Data was analysed using Microsoft Excel and SPSS 20 version. Descriptive statistics was analysed using measures of central tendency and standard deviation. Various categorical variables in relation to HbA1c were analysed using Chi-square test. Comparison of means was done by independent t-test to check for significant difference. Odds ratio and 95% confidence interval were used to compare association of HbA1c with the various maternal and neonatal complications. Regression analysis was done to estimate the relationship among various categorical variables.

RESULTS

The 100 parturient enrolled in our study were further divided into 2 groups based on their third trimester HbA1c levels being less than 6% (<6%) and more than or equal to 6%(≥ 6%). Cut-off was taken as ≥ 6% in accordance with 2017 American Diabetes Association (ADA) recommendations on management of diabetes in pregnancy (American Diabetes Association, 2017). Control group had 69 parturients with HbA1c <6% (well controlled diabetics) and 31 with HbA1c ≥6% (not well controlled). Table 1 shows most of the patients were in the age group of 25 – 35 years and comprised of 54 primigravida and 46 multigravida. 10 parturients had pre-gestational diabetes while 90 had GDM. 72% of GDM were able to achieve optimum HbA1c of <6% as compared to the 40% with pre-gestational diabetes. We found treatment initiated in first or second trimester, it did not significantly reflect on HbA1c levels done in third trimester. When treatment was taken in third trimester, better control of hyperglycemia was achieved irrespective of treatment modality (p=0.003). Table 2 shows maternal hypertension (42% vs 6%, p<0.001) and preterm labour (35% vs 14%, p=0.01) were significantly higher when third trimester HbA1c was ≥6%. However, polyhydramnios (44% vs 56%, p=0.287) was higher when HbA1c was <6% but was not statistically significant. Table 3 shows 42% vs 19% went into spontaneous labour, while 28% vs 55% had an elective LSCS when HbA1c was <6%, which was statistically significant (p=0.012).Incidence of induced labour was comparable in both groups (30% vs 26%). Table 4 shows vaginal deliveries was significantly higher when the HbA1c was <6%, 80% vs 20%, 22 (79%) had spontaneous labour and 15 (83%) were induced as compared to 6 (21%) and 3 (17%) respectively, when HbA1c was ≥6% (p<0.001). Among patients who delivered by LSCS, 59% had HbA1c <6% while 41% had HbA1c ≥6%. However, among the patients with HbA1c <6%, 46% delivered by LSCS as compared to the 71% when HbA1c was ≥6% (p=0.05). intrapartum complications were comparable in the two groups and was not found to be significant (p=0.106).

Table 1. Demographic data

Demographic parameters	Third Trimester HbA1c		Total
	<6% (n=69)	≥ 6% (n=31)	
1.Age (years)			
<25	9(90%)	1(10%)	10
25- 35	53(65%)	28(35%)	81
>35	7(78%)	2(22%)	9
2.Parity			
Primi	41(76%)	13(24%)	54
Multi	28(61%)	18(39%)	46
3.Type of diabetes			
Pre-gestational	4(40%)	6(60%)	10
Gestational	65(72%)	25(28%)	90

Table 2. Maternal complications

Complication	HbA1c <6% (n=69)	HbA1c ≥6% (n=31)	P value	OR
Hypertension	4 (6%)	13 (42%)	<0.001	11.7
Preterm labour	10 (14%)	11 (35%)	0.01	3.24
Polyhydramnios	5 (56%)	4 (44%)	0.287	

Table 3. Onset of Labour

	THIRD TRIMESTER HbA1c			
Onset of labour	<6% (n=69)	≥ 6% (n=31)	TOTAL	P-VALUE
Spontaneous	29 (42%)	6 (19%)	35	0.012
Induced	21 (30%)	8 (26%)	29	
Elective lscs	19(28%)	17(55%)	36	
Total	69	31	100	

Table 4. Mode of Delivery

Mode of delivery	ONSET OF LABOUR	THIRD TRIMESTER HbA1c		TOTAL	P-VALUE
		<6% (n=69)	≥ 6% (n=31)		
1.Vaginal delivery		37 (80%)	9 (20%)	46	<0.001
	SPON-TANEOUS	22 (79%)	6 (21%)	28	
	INDUCED	15 (83%)	3 (17%)	18	
2.lscs		32 (59%)	22 (41%)	54	
Total		69	31	100	

Table 5. Intrapartum complications

Complication	THIRD TRIMESTER HbA1c		TOTAL	P-VALUE
	<6% (n=69)	≥ 6% (n=31)		
Dysfunctional labour	10	5	15	0.106
Perineal tear	-	4	4	
Uncontrolled sugar	-	1	1	
Atonic pph	1	1	2	
High bp	-	1	1	
Total	11	12	23	

Table 6. Neonatal birth weight

Birth Weight (KGS)	Third Trimester HbA1C		TOTAL	P-VALUE
	<6% (n=69)	≥ 6% (n=31)		
< 2.5	7(10%)	3(10%)	10	0.013
2.5 – 3.5	53(77%)	16(51%)	69	
>3.5	9(13%)	12(39%)	21	
TOTAL	69	31	100	

Table 7. Neonatal Complications

Neonatal complications	HbA1c		p VALUE	ODDS RATIO
	<6% (n=69)	≥6% (n=31)		
Lga	2 (3%)	14 (45%)	<0.001	27.5
Hypoglycemia	5 (7%)	12 (39%)	0.001	8.08
Hyperbilirubinemia	20 (29%)	18 (58%)	0.006	3.39
Hypocalcemia	2 (3%)	5 (16%)	0.016	6.44

Table 8. Regression Analysis

				95% Confidence Interval	
Parameter	Standard Error	Wald	Significance	Upper Bound	Lower Bound
Hypertension	0.741	9.909	0.002	0.880	3.785
Poly-hydramnios	1.349	0.33	0.85	-2.890	2.398
Preterm labour	0.696	2.97	0.08	-2.563	0.165
Lga	1.073	6.531	0.01	0.639	4.844
Hypoglycemia	0.891	2.419	0.12	-0.225	2.328
Hyperbilirubinemia	0.729	0.08	0.778	-1.634	1.223
Hypocalcemia	1.070	1.579	0.209	-0.753	3.442

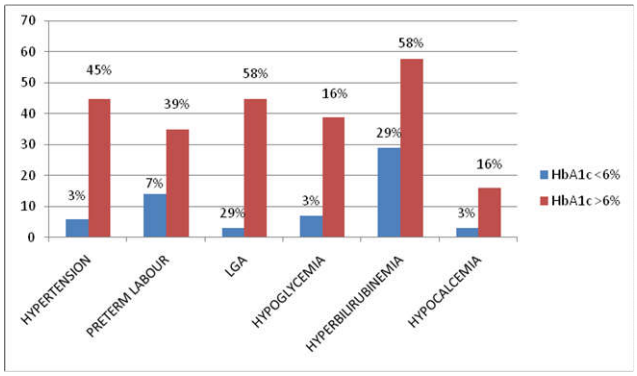

Figure 1. Distribution of Maternal and Neonatal Complications

Table 5 shows intrapartum complications were comparable in the two groups and was not found to be significant (p=0.106). However, perineal tears were more when HbA1c was ≥6%. The higher percentage of birth weight greater than 3.5 Kg, 39%as seen in Table 6 when HbA1c was ≥6% was found to be significant (p=0.013). The average birth weights were 2.95Kg and 3.22Kg when HbA1c was <6% and ≥6% respectively. The difference in the mean birth weight by independent t-test was significant (p=0.004). Table 7 shows LGA (45% vs 3%, p<0.001), neonatal hypoglycemia (39% vs 7%, p=0.001), neonatal hyperbilirubinemia (58% vs 29%, p=0.006) and neonatal hypocalcemia (16% vs 3%, p=0.016) were significantly higher when third trimester HbA1c was ≥6%. Regression Analysis of the various maternal and neonatal complications showed the highest relation of third trimester HbA1c with maternal hypertension (p=0.002) followed by LGA (p=0.01).

DISCUSSION

The effects of hyperglycemia prior to and throughout pregnancy, on the pregnancy outcomes are well known. Serial monitoring of glycaemic levels throughout pregnancy plays a vital role to optimize glycemic control and prevent the adverse outcomes associated with hyperglycemia.Various methods to monitor glycemic control during pregnancy such as SMBG, CGM and HbA1c are available. Strict patient compliance, cost and technical difficulties restrict the use of SMBG and CGM, more so in low income strata of society. In such cases, HbA1c can be used as a reliable alternative to assess glycemic control since it can be assessed irrespective of fasting status of the patient and the sample is relatively stable following collection until it is processed. Majority of the patients in the study population were less than 35 years of age indicating that irrespective of age, all women are at risk of developing diabetes during pregnancy and hence, should be screened for hyperglycemia. 90% patients had GDM while 10% had pre-gestational DM. 59% of patients with GDM were primigravida while 41% were multigravida, indicating that primigravidae as well as multigravida are equally susceptible to hyperglycemia, which reflects the problem of insulin resistance and ethnic preponderance, an epidemiological problem in Indian population necessitating monitoring of hyperglycemia. Among women with GDM, 72% vs 28% were able to achieve optimum third trimester HbA1c level of <6%, as compared to the 40% vs 60% among women with pre-gestation DM. This could be due to some women being unaware of their diabetic state prior to conception and diagnosed only during pregnancy. These women therefore might have higher peri-conceptional HbA1c and trying to maintain glycemic control in the near normal range without producing hypoglycemia might be difficult. Findings were similar to that of Pandey U et al where, 84.6% vs 15.3% of women with GDM and 19.2% vs 80.7% with pre-gestational diabetes were able to achieve HbA1c <6% (p=0.000) (Pandey et al., 2016). Hyperglycemia in pregnancy is associated with increase in maternal complications like asymptomatic bacteriuria, urinary tract infections, increased incidence of pre-eclampsia, preterm birth and LGA and its associated maternal morbidity (Matouleibi Chanu et al., 2015). Hypertension that is induced or exacerbated by pregnancy increases with duration of diabetes and may be related to oxidative stress, which plays a key role in the pathogenesis of diabetic complications and preeclampsia (Cunningham et al., 2014). However, long standing inadequately controlled pre-gestational diabetes can be associated with vasculopathy resulting in fetal growth restriction rather than LGA. Hartling et al found moderate evidence linking treatment of GDM to decrease in Preeclampsia (Hartling et al., 2013). We found the incidence of hypertension to be significantly high, 42% vs 6% when HbA1c was ≥ 6% (p<0.001) with odds ratio of 11.7. Maresh et al found women having Type 1 DM with higher values of HbA1c at 34 weeks gestation had higher incidence of preeclampsia. When HbA1c level was <6%, incidence was 8% which almost doubled to 14% when HbA1c 6.0-6.4% and 28% when HbA1c was ≥ 7.5%. These results were very highly significant (p<0.001) (Maresh et al., 2015) Sarbhai V et al found a higher incidence of pre-eclampsia when HbA1c was ≥ 6% as compared to <6% (44% vs 38%). However, the results were not statistically significant (p>0.05) (Sarbhai, 2016).

Delivery prior to 37 weeks of gestation attributed to maternal hyperglycemia can be primarily due to the polyhydramnios resulting in preterm birth or recurrent infections like vulvovaginitis, UTI or iatrogenic wherein early delivery is planned either due to poor glycemic control (fluctuating sugar levels) or to prevent macrosomia. We found 35% vs 14% delivered preterm when HbA1c ≥ 6% (p=0.01) with an odds ratio of 3.24 (95% CI- 1.19-8.77, p=0.02), equivalent to findings by Maresh MJ et al, where the incidence of preterm birth was 23% when HbA1c at 34 weeks was ≥ 6% (OR-1.4, 95%CI- 0.7–2.9, p<0.001)(11) and Damm P et al, where a 1%-point increase in third trimester HbA1c almost doubled the odds of preterm delivery (OR 1.75, CI-1.08-2.82, p= 0.023).(13)Sengupta R et al found preterm delivery occurred in 24.10% vs 17.64% when third trimester HbA1c was ≥ 6% (p=0.04).(14) However, Sarbhai V et al did not find significant difference in preterm delivery when HbA1c was ≥ 6% (36% vs 32.3%) (Sarbhai, 2016). Maternal hyperglycemia after 20 weeks gestation results in fetal hyperglycemia and causes polyuria leading to increased amniotic fluid volume (Polyhydramnios), fetal urine being the major contributor to amniotic fluid. We found the incidence of polyhydramnios was not markedly different when HbA1c <6% i.e. 56% vs 44% with higher value (p=0.28) which can be attributed to the fact that, most of the patients with HbA1c ≥ 6% had values <7% with only 1 patient having HbA1c value of 8.1%. Sarbhai V et al found incidence of polyhydramnios was 44% when HbA1c was >6% but was also not statistically significant when compared to women with lower HbA1c values (p>0.05) (Sarbhai et al., 2016). However, Capula et al (OR 4.48, 95% CI-1.20–16.73, p = 0.025)(15) and Sengupta R et al (p=0.03)(14) found higher HbA1c levels prior to delivery was significantly associated with polyhydramnios. The present

study showed that 42% vs 19% of women with HbA1c <6% had spontaneous onset of labour.

Similarly, significant difference was found among those who had an elective LSCS, 28% vs 55%with HbA1c <6%. The increased rate of LSCS with higher HbA1c could probably be accounted to a large proportion of women having suboptimal glycemic control requiring high doses of insulin and other obstetric indications like repeat elective LSCS, floating head etc. These differences were found to be significant (p= 0.012). The number of women who were induced was comparable in both the groups, as it is hospital protocol to induce women with GDM having good glycemic control at 40 weeks. No studies were found on the association of third trimester HbA1c and onset of labour. 46 patients had a vaginal delivery and 54 delivered by LSCS. There were higher percentage of successful vaginal deliveries when the HbA1c was <6%, including spontaneous 79% vs 21% or induced labour 83% vs 17% (p<0.001), similar to findings of Sengupta R et al, where 70.6% vs 10.1% of women with HbA1c <6% had a vaginal delivery (p=0.01).(14) Among the patients who underwent LSCS, we found 59% patients had an elective LSCS when HbA1c was <6% as compared to the 77% when HbA1c was ≥ 6%. However, this was not found to be significant (p=0.05). Maresh et al. (2015) and Sengupta et al. (2012), did not find significant association between increasing third trimester HbA1c and rate of caesarean section (p=0.26 and p=0.23 respectively).

However, Malinowska PA et al found spontaneous vaginal deliveries in women with GDM 72.5% and rate of LSCS was 23.2%(p<0.05) (Malinowska-Polubiec et al., 2003). Intrapartum complications are higher in pregnancies complicated by diabetes, but was not found to be significant (p=0.106). The risk of dysfunctional labour is higher with induction of labour and LGA fetuses. LGA neonates predispose the mother to perineal tears and postpartum hemorrhage. In the current study, there was no shoulder dystocia. Sengupta et al. (Sengupta et al., 2012) found a significant association of HbA1c ≥ 6% and shoulder dystocia (p=0.01) while no significant association was found between the other intrapartum complications. Maternal hyperglycemia leading to fetal hyperglycemia and fetal hyperinsulinemia (insulin being a major anabolic hormone) leads to an increase in fetal growth and deposition of subcutaneous fat in the fetus, resulting in an increased fetal birth weight, LGA and macrosomia (Pedersen's hypothesis) (Hod, 2017). LGA can be detected by ultrasound biometry and confirmed following delivery when the birth weight is greater than 90th percentile for the gestational age. We found higher percentage of average weight neonates, 77% vs 23% when HbA1c was <6%. Higher percentage of LGA neonates were born when maternal HbA1c was ≥ 6% (57% vs 43%, p=0.013) with only 1 neonate born at 4kg. Taylor et al. (2002) did not find any association between mean HbA1c and birth weight (p>0.1). The incidence of LGA was 45% vs 3% when HbA1c ≥ 6% (p<0.001), equivalent to study done by Sarbhai et al (52% vs 29.4%, p<0.05) (Sarbhai et al., 2016) and Sengupta et al (18%, p=0.01) (Sengupta et al., 2012) Whereas, Mikkelsen et al found women with GDM and HbA1c >5.6% before delivery had a higher prevalence of LGA infants 39.2% (OR-3.1, 95% confidence interval= 1.3-7.6, p=0.013) (Mikkelsen, 2011) while Subash S et al found incidence of 25% when HbA1c was >5.7% (p<0.05) (Subash, 2016). Barquiel B et al found third trimester HbA1c ≥ 5% in women with GDM an independent predictor of LGA birth weight (Barquiel et al., 2016). In women with Type 1 DM, Damm P et al found LGA/macrosomia increased with increasing third-trimester HbA1c (p=<0.001),(13) and Maresh MJ et al found incidence of 47% with HbA1c ≥ 6% and rising to 68% with HbA1c ≥ 7% (p<0.001) (Maresh et al., 2015). Morrens A et al also identified late pregnancy HbA1c as an independent predictor for LGA (p=0.026, OR 1.70, CI 1.07–2.71) (Morrens et al., 2016). However, Balaji et al. (Balaji, 2007) found a significant number of GDM mothers delivering LGA babies despite good glycemic control in third trimester which was attributed to the influence of maternal hyperglycemia on fetal growth in the early weeks of gestation. Also, Taylor et al did not find a significant association between HbA1c and macrosomia in women with Type 1 DM (p>0.1), which was attributed to episodic spikesof hyperglycemia which do not get reflected in HbA1c values (Taylor, 2002).

Neonatal hypoglycemia occurs due to poor glycemic control in the diabetic mother which causes fetal hyperglycaemia, hyperplasia of the islets of Langerhans, increased peripheral insulin receptors, a decreased glucagon response to hypoglycaemia and a delayed evocation of hepatic gluconeogenic pathway. At delivery, the transplacental supply of glucose is stopped and hypoglycaemia occurs in the neonate. We found a higher incidence of neonatal hypoglycaemia (39% vs 7%, p=0.001, OR= 8.08) when maternal HbA1c was ≥ 6%. Similarly, Sengupta et al. (2012), Maresh et al. (2015) and Sarbhai et al. (2016) found incidence of 38.55% (p=0.02), 25% (p<0.001, OR 1.4, 95% CI 0.8–2.7) and 36.8% (p<0.05) respectively, when HbA1c was ≥ 6%. Subash S et al found incidence of 22.9% when HbA1c was >5.7% (p=0.01) (Subash, 2016) Taylor R et al found that neonatal hypoglycemia correlates with maternal hyperglycemia in labour and not with HbA1c during pregnancy (Taylor, 2002). Hyperglycemia-mediates increase in maternal affinity for oxygen and fetal oxygen consumption, causing a relative hypoxia. This hypoxia leads to increased fetal erythropoietin levels and red cell production. This in addition to the relative immaturity of the hepatic bilirubin conjugation and excretion causes hyperbilirubinemia. We found higher incidence of neonatal hyperbilirubinemia (58% vs 29%, p=0.006, OR-3.39) when HbA1c was ≥ 6%. Maresh MJ et al found incidence of 15% (AOR 1.7, 95%CI-0.9–3.5, p<0.001) which increased to 39% when HbA1c was >7% (AOR 4.1, 95% CI-1.8–9.8, p<0.001) (Maresh et al., 2015) Sengupta et al. (2012) found incidence of 33.73% when HbA1c ≥ 6%(p=0.03). However, Sarbhai V et al did not find any significant association (Sarbhai, 2016). Hypocalcemia in neonates born to diabetic mothers has been attributed to calcium-magnesium imbalance, asphyxia and preterm birth. We found incidence of neonatal hypocalcemia was significantly higher when HbA1c was ≥ 6%, 16% vs 3% (p=0.016, OR= 6.44). Demarini et al found lower infant serum calcium concentration correlated significantly with elevated maternal HbA1c concentration at delivery (p=0.03) (1994). Regression analysis of the present study showed the highest risk of adverse outcome was for maternal hypertension followed by LGA when maternal HbA1c was ≥ 6% in the third trimester. Although the other maternal and neonatal complications were not found to be significant in the regression analysis, the individual analysis of each adverse complication i.e. hypertension and preterm labour in the mother as well as neonatal complications including LGA, hypoglycaemia, hyperbilirubinemia and hypocalcemia was found to be significant. Thus indicating that maternal HbA1c

levels done in third trimester prior to delivery, can serve as a predictor of various adverse obstetric outcomes. Our study has limitations as the sample size was small and the study period short.

Also, serial monitoring of HbA1c in each trimester was not done. Comparison of HbA1c values with healthy non-diabetic patients, in order to determine normal reference range in specific trimester of pregnancy was not done and the contribution of anemia and iron supplementation on HbA1c was not evaluated. All the patients were on prophylactic iron supplementation.

Conclusion

In the present era where diabetes especially GDM is emerging as an epidemic affecting women of child-bearing age, the focus has shifted from diagnostic and management criteria to monitoring euglycemic levels throughout pregnancy. Strict monitoring techniques during pregnancy to maintain euglycemic levels, prevents and decrease the adverse maternal and fetal outcomes well known in pregnancy complicated by diabetes. In the present study, HbA1c levels done in the third trimester at the time of delivery was to determine the glycemic control during pregnancy and its predictive effect on the obstetric outcomes and not for guiding the management. Patients with HbA1c ≥6% are at increased risk of pregnancy and neonatal complications. HbA1c is an effective and sensitive predictor of adverse obstetric outcomes in women with diabetes and hence, should be routinely recommended to ensure better vigilance. Various studies have suggested different cut-off values of HbA1c for pregnant women in each trimester. As yet, the optimum range of HbA1c in healthy pregnant women is uncertain especially in Indian population and larger studies are needed for the same.

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