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MATERNAL-FETAL MEDICINE

Reference range for glycated haemoglobin in full term non diabetic pregnant women: a multicentric cross sectional study

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Abstract

Background There are no large studies to define the normal value of glycated haemoglobin (HbA1c) measured in full term pregnant women measured at the time of delivery.

Research design and methods The study was conducted at three government hospitals in South India. Clinical data, maternal blood sample and foetal cord blood sample were collected from women admitted for safe confinement. Mean (± SD) of HbA1c in participants with no known diabetes (gestational or pregestational) or any complications (maternal or fetal) is described, 2.5th–97.5th centile reference range was derived.

Results From 3 centres, 2004 women participated in the study. Data from 1039 participants who had no history of diabetes or any maternal or fetal complication were used to determine the reference range for HbA1c at term pregnancy. The mean HbA1c in subjects devoid of diabetes and its known complications was 5.0 (±0.39) %. The reference range for normal HbA1c at term in these women was found to be 4.3–5.9%. Maternal HbA1c at term pregnancy in non-diabetic pregnant women is associated with pre-pregnancy BMI, maternal age and 2-h plasma glucose level of 2nd trimester oral glucose tolerance test (OGTT).

Conclusions The mean HbA1c at term pregnancy in non-diabetic women admitted for safe confinement is 5.00 (±0.39) %. An HbA1c of 5.9% or more at term should be considered abnormal and women with such a value may be kept at a close surveillance for development of diabetes.

Keywords Gestational diabetes · Glycated haemoglobin · Delivery · Birth weight · Term pregnancy

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What does this study add to the clinical work

The normative values of HbA1c in full term antenatal women is defined by this study. This will be useful in assessing the composite glycaemic environment faced by the mother and foetus in the final trimester of pregnancy and possibly to predict the risk of future diabetes in parous women.

Introduction

Gestational diabetes mellitus (GDM) is hyperglycemia first detected during pregnancy. It is the most common medical condition which complicates pregnancy [1]. GDM not only increases the risk of complications in pregnancy for both the mother and the fetus, but also increases the risk of future metabolic syndrome and its complications for both mother and the child [2]. The incidence of GDM has increased manifold owing to the raging pandemics of obesity and type 2 diabetes [3, 4]. GDM prevalence ranged between 9 and 26% in the hyperglycemia and adverse pregnancy outcome (HAPO) study [5]. A community-based study conducted in South India reported a prevalence of 17.5% among urban women, 13.8% in semi urban, 9.9% in rural areas based on single two-hour 75-g post glucose values [6].

The fetal effects of GDM are mediated by transplacental passage of glucose and the consequent increased levels of fetal insulin. This results in fetal macrosomia, the chances of which are proportional to the duration and severity of maternal hyperglycaemia to which the foetus is exposed [7, 8]. Glycated Haemoglobin (HbA1c) is a composite marker of glycaemic levels of last 90–120 days in the non-pregnant state. In the pregnant state HbA1c levels fall due to a higher erythrocyte turnover, dilutional effect and lower blood glucose levels. HbA1c levels measured at the time of delivery represent the glycemia experienced by the mother and the foetus in the last trimester of pregnancy and may be useful in identifying women and babies who have been exposed to higher levels of blood glucose in the last trimester with or without the diagnosis of diabetes mellitus earlier. Screening programs for GDM involve evaluation of glycemia at 24–28 weeks' gestation but gestational diabetes can develop even after this time [9]. The normal values of HbA1c in the term pregnant women are not known. The current study was done to find the normative values of HbA1c at term pregnancy in women with no GDM or any of its known complications in the current pregnancy. Secondary objectives of the study were to find the determinants of HbA1c if any, in such women.

Materials and methods

After obtaining the approval of the Human Ethics Committee, (HEC. GMCT/No. 01/44/2018 dated 09/01/2018), the study was done over a period of 30 months starting in February 2018. The study was conducted at 3 tertiary care hospitals in two different districts of Kerala. Using the standard deviation of HbA1c of 0.4% from previous studies and a desired confidence interval of 0.05% the required sample size was calculated as 983 patients, assuming 80% power and alpha error fixed at 5%.

Pregnant women admitted for safe confinement to these hospitals during the study period and willing to give consent were consecutively included in the study. Patients on any type of steroid medication (systemic, topical or inhaled steroids etc.), any other diseases complicating pregnancy were excluded from the study. For calculating the normative value of HbA1c the following exclusion criteria were employed. Previous obstetric complications like gestational diabetes, overt diabetes mellitus, macrosomia, recurrent abortion, previous intrauterine death, still birth were excluded. Women with anemia (haemoglobin < 10 g/dl) gestational diabetes, overt diabetes mellitus, pre-eclampsia, preterm delivery, premature rupture of membranes, antepartum haemorrhage, intrauterine demise of fetus, macrosomia, still birth in the current pregnancy were also excluded. Additionally, women with a pre-pregnancy BMI > 30 kg/m^2 were also excluded from final analysis.

After an informed written consent, demographic details of the mother, family history of diabetes, her previous obstetric history, mode of delivery, details of the newborn, complication in the new-born if any and comorbidities detected during current gestation (including diabetes and hypertension) were collected and entered in a predesigned proforma by trained nurses who were employed for the study. Hospital records were available to the research staff who collected the data. Maternal blood sample was collected for estimation of HbA1c, and random plasma glucose. Cord blood was also collected for estimation of foetal plasma glucose and insulin levels. All biochemical investigations were done using the same analysers for all subjects under a National Accreditation Board for Laboratories (NABL) certified quality control program. Plasma glucose estimation was done with the glucose oxidase-peroxidase method (GOD-POD). HbA1c was estimated using a National Glucose Standardization Program (NGSP) certified high performance liquid chromatography (HPLC) system (BIORAD-D10, USA). For collecting cord blood sample, immediately after the cord was sectioned blood was collected in 2 bottles (one fluoride bottle for glucose estimation and another plain bottle for Fetal insulin

estimation). It was collected from the placental side of the sectioned cord. The samples were stored at 4–8 °C till they were transported to the laboratory. In the laboratory the fluoride sample was centrifuged and glucose estimation was done using Glucose oxidase method. All 3 hospitals involved in the study had policy of universal screening for gestational diabetes mellitus using a 75 g oral glucose tolerance test at 24–28 weeks of gestation.

The demographic, anthropometric, clinical and biochemical data was tabulated in MS Excel 2017. Quantitative variables were summarized as mean ± SD. To find the normative value of HbA1c women with overt diabetes, GDM or any known complication in the current pregnancy were excluded from the analysis. Statistical analysis was done using SPSS version 28. Data from all eligible women was tabulated in MS Excel 2017. Test for skewness of distribution was done in SPSS and found to be normally distributed. Mean and SD was calculated. The upper and lower cut off of 97.5th centile and 2.5th centile was derived using SPSS version 28. Quartiles of HbA1c were also also described. Categorical variables are expressed as number and percentages and compared using chi-square test. To compare two independent groups of continuous variables, one way ANOVA was used. Post-hoc Bonferroni correction was employed to assess the differences within subgroups.

Results

Baseline parameters

A total of 2004 subjects were enrolled in the study from the 3 different participating hospitals. Of these 1196 patients were from Thiruvananthapuram and the rest 808 women from Kottayam district. Mean age of included women was 25.15 ± 4.12 years (Tables 1, 2).

Out of these participants, GDM was diagnosed in 552 and overt diabetes mellitus in 9 women. Patients with recurrent abortions (more than 2 abortions in past), past neonatal deaths, intra-uterine demise of fetus (IUD) preterm delivery (Gestational age < 37 weeks), premature rupture of membranes, antepartum haemorrhage, fever during pregnancy and macrosomia comprised 273 participants. All participants had been classified as those with GDM and those without, based on an OGTT at 24–28 weeks' gestation and actual OGTT values of 1598 of 2004 participants was available for analysis. For finding the normative values of HbA1c at the time of delivery, women with anaemia (Hb < 10 g %), pregestational BMI > 30 kg/m^2, GDM, overt diabetes mellitus, history of recurrent abortions or neonatal deaths or intrauterine deaths, current preterm delivery i.e. Gestational age < 37 weeks, Premature rupture of membranes, Antepartum haemorrhage, fever, Macrosomia, were excluded.

After excluding the above, data from 1039 subjects were available for assessing the normal values for HbA1c in pregnant women at term gestation. Among these non-diabetic, healthy, maternal and fetal complication free mothers, the mean HbA1c at term gestation was found to be 5.00 ± 0.39%. The reference 95 centiles (2.5th centile to 97.5th centile) for the HbA1c values in these complication free, non-diabetic, non-obese mothers was found to be 4.3–5.9% (Table 3).

Among these non-diabetic, healthy, maternal and fetal complication free mothers, the HbA1c level at time of confinement was found to have a statistically significant correlation with 2 h plasma glucose value of 2nd trimester (GTT), First trimester Post prandial plasma glucose (PPPG), Pre-pregnancy BMI, Systolic BP, Diastolic BP and Maternal age (Table 4). On binary logistic regression done by dichotomising HbA1c at the median, only maternal pre-pregnancy BMI (Pearson $r = 0.22$) and 2 h OGTT plasma glucose value of 2nd trimester (Pearson $r = 0.26$) were found to have an independent association. Birth weight and fetal insulin level were not found to have a significant correlation with the HbA1c levels among the apparently normal women.

Further the study participants were divided into 4 quartiles according to the HbA1c levels and the participants in the highest quartile (HbA1c > 5.2%) were compared to those in the lowest quartiles (HbA1c < 4.8%) with regard to relevant demographic, anthropometric obstetric and biochemical parameters (Table 5). Pre-pregnancy BMI, maternal weight at term, Systolic blood pressure, second trimester 2-h post glucose load plasma glucose values and maternal random plasma glucose at delivery were found to be significantly higher in the uppermost quartile when compared to the lowermost quartile. Women in the uppermost quartile of HbA1c were also at risk of an earlier termination of pregnancy compared to those with lesser HbA1c levels. Statistically significant difference was not found in the groups with regard to birth weight of the baby or placental weight.

Discussion

In non-pregnant state, HbA1c is a measure of average glucose values in past 3–4 months. In pregnant women, the utility of HbA1c was earlier challenged due to the relatively faster erythrocyte turnover and hemodilution. Later as normative values for HbA1c for different trimesters became available, the guidelines have suggested trimester specific targets for pregnant women [9]. Although HbA1c level may not be reflective of the glycemic levels of last 3–4 months in pregnant women, it is certainly useful to assess the glycemic status of the last 1–2 months [10]. This physiological change may be useful for clinical follow up in pregnancy because clinic visits in pregnancy especially in those with

Table 1 Clinical characteristics of participants without diagnosed GDM or maternal or fetal complications ($n=1039$) and comparison with women with GDM ($n=552$)

	Women without GDM mean (SD) ($n=1039$)	Women with GDM mean (SD) ($n=552$)	p value
Age (years)	25.15 (4.12)	26.7 (4.89)	< 0.01
Height (cm)	155.22 (6.04)	155.95 (7.08)	0.047
Maternal weight at term (kg)	62.39 (8.61)	64.49	< 0.001
BMI at term (kg/m^2)	25.9 (3.5)	26.6 (4.77)	0.002
Pre-pregnancy BMI (kg/m^2)	21.20 (3.38)	22.3 (4.6)	0.002
HbA1c at term (%)	5.0 (0.39)	5.5 (0.42)	< 0.001
Haemoglobin level (g/dl)	11.68 (1.01)	11.7 (0.62)	0.06
Baby birth weight (kg)	2.96 (0.21)	2.81 (0.48)	< 0.001
Ist trimester fasting PG ($n=547$)	76.50 (9.59)	83.4 (14.1)	< 0.001
Ist trimester post prandial PG ($n=547$)	90.35 (15.64)	112.6 (26.1)	< 0.001
2nd trimester Fasting PG (mg/dl) ($n=890$)	80.77 (10.55)	87.4 (15.13)	< 0.001
2nd trimester OGTT 1 h (mg/dl) ($n=890$)	102.92 (19.64)	138.0 (33.9)	< 0.001
2nd trimester OGTT 2 h (mg/dl) ($n=890$)	98.42 (19.63)	120.7 (29)	< 0.001

PG, plasma glucose; BMI, body mass index; OGTT, oral glucose tolerance test (75 g)

Table 2 Frequency of categorical variables of study participants without GDM ($n=1039$)

Parameter	Frequency (%)
Primiparous	670 (64.5%)
Vaginal delivery	754 (72.5%)
Caesarean	285 (27.4%)
History of abortion	73 (8.7%)
Cephalic presentation	776 (74.7%)
Breech presentation	260 (25.0%)
Transverse lie	3 (0.3%)

Table 3 Percentile of HbA1c at term in full-term term healthy women ($n=1039$)

HbA1c percentile	HbA1c value at delivery (%)
2.5th	4.3
25th	4.8
50th (median)	5.0
75th	5.2
97.5th	5.9

Table 4 Correlation between HbA1c and various other parameters at the time of delivery

Clinical parameter	Correlation with HbA1c (Pearson R)
Age	0.07*
Gestational age	−0.18**
Pre-pregnancy weight	0.13**
Pre-pregnancy BMI	0.22**
Haemoglobin	−0.04
Birth weight	0.06
Maternal plasma glucose at delivery	0.12**
Fetal insulin	0.08
Fetal plasma glucose	0.08*
Maternal fasting PG	0.19**
Maternal post prandial PG	0.18**
Serum thyrotropin	0.00
Ist trimester fasting PG	0.10*
Ist trimester post prandial PG	−0.01
2nd trimester fasting PG	0.07
2nd trimester OGTT (1 h)	0.07
2nd trimester OGTT (2 h)	0.26**
Systolic blood pressure	0.11**
Diastolic blood Pressure	0.08**

PG, plasma glucose; BMI, body mass index; OGTT, oral glucose tolerance test (75 g)

*$P<0.05$, **$P<0.01$

diabetes are more frequent than a non-pregnant patient and it becomes a more accurate indicator of glycemia in the near past without the confounding effect of remote hyperglycemia of 3–4 months back making it more relevant in the context of pregnancy where there can be relatively faster changes in the level of glycemia.

HbA1c measured at term pregnancy reflects the average blood glucose values experienced by the mother and fetus after the 28–32 weeks of gestation. The importance of such a measurement in a patient not diagnosed to have diabetes till third trimester is to assess the glycemic exposure of the mother and the fetus in the last trimester. It may also help in determining the risk of future diabetes in the mother. In pregnant patients diagnosed to have diabetes, the HbA1c

level can help in assessment of adequacy of glycemic control and of risk of maternal and fetal complications.

Maternal hyperglycemia can occur any time during a pregnancy, the risk being higher in the later trimesters. It has been shown that peripheral insulin sensitivity (defined as the ability of insulin to increase glucose uptake in skeletal muscle and adipose tissue) decreases by approximately 50% by late gestation and in women with normal glucose tolerance, there is a 2–3-fold increase in insulin secretion in response to the decreased insulin sensitivity that maintains euglycemia [11, 12]. Despite this higher risk the screening programs do not assess for hyperglycemia after the 28th week of gestation [13].

The current multicentric study was done to find the normative value of HbA1c at term pregnancy in healthy pregnant women admitted for safe confinement. The study determined the mean HbA1c value at delivery in previously normal women, admitted for safe confinement without any maternal or fetal complications to be 5.0 (±0.38) %. As HbA1c levels decrease during pregnancy, in order to ensure optimal glycaemic control in pregnant woman with diabetes, it is necessary to use HbA1c reference values specific for each trimester [14]. With the current study normal value of HbA1c at the end of third trimester at full term has been defined. Previously reference ranges have been studied for the 3rd trimester of pregnancy but the HbA1c estimation was done for different patients at different times during the third trimester ranging from 28 to 36th week of gestation [15, 16].

Some investigation has previously been done on HbA1c at the time of delivery with pregnancy outcomes especially

Table 5 Clinical parameters of participants in different HbA1c Quartiles

	Quartile 1 Mean (SD)	Quartile 2 Mean (SD)	Quartile 3 Mean (SD)	Quartile 4 Mean (SD)	Overall *P* value	Q1 versus Q4 *P* value
Age (years)	25.04 (3.86)	24.69 (3.97)	24.99 (4.22)	25.79 (4.30)	0.02	0.24
Gestational age (weeks)	38.86 (1.91)	38.88 (2.01)	38.71 (1.60)	37.8 (1.95)	< 0.001	< 0.001
Haemoglobin (g/dl)	11.67 (1.02)	11.77 (1.05)	11.67 (1.01)	11.61 (0.95)	0.38	1
1 min APGAR score	8.88 (0.56)	8.9 (0.53)	8.94 (0.40)	8.94 (0.33)	0.37	0.91
HbA1c (%)	4.49 (0.17)	4.85 (0.04)	5.06 (0.04)	5.45 (0.28)	< 0.001	< 0.001
Fetal plasma glucose at delivery (mg/dl)	63.10 (19.32)	61.83 (17.12)	64.52 (25.82)	67.45 (24.88)	0.04	0.20
Maternal Plasma glucose at term (mg/dl)	89.07 (22.19)	90.80 (20.64)	92.54 (23.11)	96.34 (30.13)	0.01	0.01
Diastolic BP (mm of Hg)	73.06 (8.21)	74.81 (7.73)	75.09 (8.38)	74.81 (6.69)	0.01	0.01
Systolic BP (mm of Hg)	113.74 (10.64)	114.85 (11.73)	115.72 (12.27)	117.16 (9.51)	0.005	< 0.01
Pre-pregnancy BMI (kg/m^2)	21.10 (3.36)	21.10 (3.18)	21.45 (3.58)	23.19 (3.28)	< 0.001	< 0.001
Weight at term (kg)	60.65 (8.23)	60.89 (7.90)	61.81 (8.64)	65.72 (8.56)	< 0.001	< 0.001
2nd trimester OGTT (2 h) (mg/dl)	92.04 (17.04)	95.42 (17.83)	97.39 (17.33)	108.17 (22.15)	< 0.001	< 0.001
2nd trimester OGTT (1 h) (mg/dl)	102.51 (16.53)	100.39 (20.43)	103.77 (17.21)	107.44 (28.49)	0.12	0.64
2nd trimester FPG (mg/dl)	79.17 (10.42)	82.22 (10.94)	80.72 10.68)	81.3 (9.52)	0.06	0.67
1st trimester FPG (mg/dl)	75.62 (10.09)	76.99 (9.79)	76.54 (8.97)	77.54 (9.44)	0.50	1
1st trimester 2 h Post prandial PG (mg/dl)	91.6 (14.56)	89.34 (16.55)	88.19 (14.33)	94.20 (17.93)	0.03	1
S. TSH (mIU/ml)	1.45 (1.23)	1.38 (0.98)	1.37 (0.90)	1.45 (1.15)	0.77	1
Baby birth weight (kg)	2.77 (0.50)	2.79 (0.49)	2.77 (0.46)	2.83 (0.44)	0.46	1

SD, standard deviation; HbA1c, glycated haemoglobin; BP, blood pressure; BMI, body mass index; OGTT, oral glucose tolerance test; FPG, fasting plasma glucose; PG, plasma glucose

caesarean delivery, but again normal values in non-diabetic pregnant women has not been defined [17]. In a study by Enzenauer et al. the primary objective was to compare the HbA1c level among obese non diabetic pregnant women and non-obese diabetic pregnant women at the time of delivery. But in this study also the reference range (2.5th–97.5th centile) or the upper cutoff (97.5th centile) has not been calculated and presented [18]. Punoose et al. have also evaluated trimester specific levels of HbA1c. Again a specific point of delivery was not chosen as the time for HbA1c estimation [19]. He et al. the consequences of a late pregnancy hyperglycaemia as evidenced by an HbA1C > 5.7% at delivery was studied for difference in fetal outcomes [20]. The study again doesn't mention a reference range. Worth et al. have done HbA1c at the time of delivery but the study had only 17 and 19 participants with HbA1c measured using 2 methods (colorimetric and column) [21]. Consequently the variability was also higher (standard deviation 0.7%. The mean was also higher probably due to the assay with a lack of international standardisation at the time of the study (year 1985).

The current study finds that the upper limit of reference interval for HbA1c at full term pregnancy is 5.9%. It is in consistence with the American Diabetes association target for HbA1c which recommend a level of < 6% to be optimal during pregnancy if it can be achieved without hypoglycemic episodes [22]. In the 2nd and 3rd trimesters, HbA1c < 6% has been proposed to have lowest risk of large for gestational age infants, preterm delivery, and preeclampsia [23]. It is also recommended that HbA1c should be monitored more frequently i.e., monthly, during pregnancy [23].

Regarding the determinants of HbA1c at full term gestation, the current study found that 2nd trimester GTT, 2 h glucose value, FPG and Post prandial PG of first trimester, Pre-pregnancy BMI, Systolic BP, Diastolic BP, and Maternal age have significant correlation with HbA1c levels at term. As only women with normal BMI, without GDM or overt diabetes and those without any fetal and maternal complications were included in the analysis the relation between HbA1c and the birthweight and fetal insulin levels may have been masked as those with high BMI, diagnosed GDM or overt diabetes. Pre-pregnancy BMI exerts its influence on HbA1c even in the third trimester of pregnancy highlighting the importance of adiposity in the pathogenesis of GDM. This association has been consistently observed in many previous studies on HbA1c in all trimesters of pregnancy. This highlights the importance of normalizing BMI, prior to conception for possible prevention of GDM. 2nd trimester OGTT 2 Hour glucose value association with HbA1c is important as it may be evaluated as a sensitive predictor of hyperglycemia in the third trimester of pregnancy.

Intrauterine hyperglycaemia through its effects on fetal β-cells and adipose tissue can lead to late development of metabolic complications in the offspring. In a follow-up study [24] from Denmark, offspring's (18–27 years of age) of women with GDM, 21% of the offspring had pre-diabetes or diabetes accounting for an eight-fold increased risk compared with the background population. Furthermore, the risk of overweight and the metabolic syndrome was higher (twofold and fourfold, respectively) and insulin sensitivity and secretion were reduced. The 'HAPO-Follow up study' confirmed these findings but suggests that although maternal adiposity is a strong risk factor for offspring obesity, GDM remains a significant risk factor, even after adjustment for maternal BMI [25]. Further studies correlating the effects of sustained third trimester hyperglycaemia (as reflected by HbA1c at term) in offspring are needed.

Anemia and iron deficiency can lead to slight elevation of HbA1c levels in non-pregnant state with more prominent increase in the pregnant state where glycated albumin may be a better choice [26]. In spite of the above, mild anemia and iron deficiency may not affect the HbA1c levels by a large margin [27].

The current study had a strength of multicentric data collection and a large sample size. The study had the novelty of defining HbA1c levels at term in normal pregnant women for the first time. The limitations of the study included lack of fetal C peptide level estimation which would have been a better marker for fetal endogenous insulin secretion.

Conclusions

The mean HbA1c at term pregnancy in normal women, without any maternal or fetal complications admitted for safe confinement is 5.00 (±0.38)%. The 95% reference range for HbA1c at term is 4.3–5.9%. Pre-pregnancy BMI and 2nd trimester OGTT 2-h glucose value, are independently associated with the HbA1c levels at term in non-diabetic women.

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Author contributions Author RVJ conceived the project and reviewed the manuscript. AN, CJ and PKJ conducted the study. And JC analyzed the data. AG reviewed the literature and prepared the manuscript. CN, CPV, AB contributed to data acquisition, discussion and reviewed the manuscript.

Data availability The data that support the findings of this study are available on requestfrom the corresponding author.

Declarations

Conflict of interest The authors have nothing to disclose and there are no conflict of interest.

Guarantor statement Dr. Abilash Nair and Dr. Jayakumari C are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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