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ORAL GLUCOSE TOLERANCE TEST OR MEASUREMENT OF HBA1C OR BOTH FOR SCREENING AND DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS: A HOSPITAL-BASED STUDY FOR PREVALENCE ASSESSMENT

Biochemistry

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ABSTRACT

Introduction: Gestational diabetes mellitus (GDM) is described as any degree of glucose intolerance first recognized during pregnancy. Women with GDM and their offspring have a risk to develop Type 2 diabetes mellitus in later life. For diagnosis of GDM, criteria such as ADA, WHO, DIPSI etc., are followed. In 2013 WHO reformed its criteria for GDM, followed by development of IADPSG criteria. In this study an attempt was made to compare these criteria with an emphasis to study the role of HbA1C in the diagnosis of GDM and overt diabetes during pregnancy.

Methods: 289 pregnant women were screened for GDM by 75 g OGTT in fasting, and HbA1C during first ANC visit and at 24 to 28th week of gestation. Women with thyroid and other disorders were excluded. Relevant clinical information was collected. Plasma glucose was analyzed by autoanalyzer and HbA1C by NGSP certified method. SPSS 24 was used for statistical analysis

Results: 13.6, 18.3, 32.9, and 31.2 percent prevalence of GDM respectively was observed according to DIPSI, WHO 1999, IADPSG and WHO 2013 criteria. Applying HbA1C cutoff values (%) of > 6.5, and 6.0 - 6.49, there were 6 (2.0%) with diabetes and 11 (3.8%) subjects with impaired glucose tolerance respectively. Approximately 4% women were found to be suffering from overt diabetes based on both HbA1C and FPG values as recommended by IADPSG.

Conclusion: Screening with HbA1C along with OGTT for the diagnosis of GDM would be a significant marker to rule out pre-existing or overt diabetes in pregnant population and calculation of reliable existing prevalence rate of GDM in pregnant population.

KEYWORDS

gestational diabetes mellitus, glycated hemoglobin, prevalence, OGTT, HbA1C

Introduction:

Gestational diabetes mellitus (GDM) is described as any degree of glucose intolerance first observed during pregnancy. This definition applies irrespective of insulin or only dietary modification is used for treatment and whether or not the condition persists after pregnancy. It does not exclude the possibility that undiagnosed glucose intolerance may have antedated or begun concomitantly with the pregnancy [1]. Thus, this definition includes a subgroup of women with more severe hyperglycemia, similar to overt diabetes.

According to American Diabetic Association (ADA), approximately 7% of all pregnancies are complicated by GDM resulting in more than two lakh cases annually, whereas its total incidence is estimated up to 17.8% [1]. One of the most important aspects of GDM is its increasing prevalence in several race/ethnicity groups. There have been a trend of increasing prevalence of GDM over the decades and also varied prevalence throughout the world. Definition of GDM, which reflects in the diagnostic criteria for GDM has changed periodically due to technical advances in the methodologies of estimations [2]. Looking into the definition of GDM, it is difficult to distinguish between preexisting but undiagnosed diabetes before pregnancy and hyperglycemia that is induced during pregnancy. Various diagnostic criteria exist for the diagnosis of gestational diabetes which includes WHO criteria [3], ADA criteria [1] and the most recent IADPSG criteria [4], and DIPSI criteria [5] in India. The designated plasma glucose cutoff values according to these criteria has been stated in Table1. Obviously, varied prevalence rates are expected due to different diagnostic criteria.

Recently IADPSG consensus panel in their position statement had recommended the criteria for the diagnosis of overt diabetes in pregnancy in addition to criteria for GDM. They further strategized that pregnant women during their first antenatal visit should be screened for overt diabetes by the measurement of HbA1C, fasting plasma glucose, and random plasma glucose. If random plasma glucose exceeds 200mg/dl, overt diabetes needs to be confirmed using the data obtained by FPG or HbA1C [4].

On the other hand, use of HbA1C during pregnancy for screening and diagnosis of GDM has not yet been established. Historically studies have been conducted but no definitive conclusions were arrived at for use of HbA1C for the screening of GDM [6]. During pregnancy longitudinal changes in HbA1C levels have been reported. The pattern of changes may be the elevation in early pregnancy and a dip in the third trimester [7,8]

Table No 1: Diagnostic criteria for gestational diabetes mellitus

Time of glucose measurement	WHO 1999	IADPSG	WHO 2013	DIPSI India
	Glucose thresholds mg/dl (mmol/L)			
Fasting	126.0 (7.0)	92.0 (5.1)	92.0 - 125.0 (5.1 – 6.9)	--
1 hour	--	180.0 (10.0)	180.0 (10.0)	--
2 hour	140.0 (7.77)	153.0 (8.5)	153.0 – 199.0 (8.5 - 11.0)	140.0 (7.77)

Note: *Any one value exceeding the thresholds to be considered as diagnosis of GDM.*

In the present study an attempt has been made to categorize separately GDM cases from that of overt diabetes using the data collected and applying laid down criteria of segregation. In addition to above, the present study has also explored the utility and contribution of glycated haemoglobin i.e HbA1C in identifying subjects with pre-existing diabetes or pregnancy induced diabetes i.e GDM.

Material and Methods:

Present study was carried out in a tertiary care 750 bedded teaching hospital after obtaining ethical clearance from the institutional ethical committee. Pregnant women at their first antenatal clinic visit for routine pregnancy checkup were selected and enrolled for the study after informed and written consent. Pregnant women were asked to report in fasting condition for the OGTT test, prior to which they underwent clinical assessment by Obstetrician and Gynecologist. Details of demographic information, present, and past clinical history were recorded, and blood samples were collected. Blood samples were

immediately sent for laboratory analysis.

Plasma glucose was estimated by ERBA XL 640 autoanalyzer by TransAsia Biomedical Pvt. Ltd. Mumbai, India. Glycated hemoglobin (HbA1C) was estimated by NGSP accredited method on D-10 hemoglobin testing system by Bio-Rad Ltd. USA.

All the data was collected and compiled in Excel software by Microsoft Mac version 2011. Data was analyzed using SPSS version 24 using appropriate tools.

Results:

A total of 289 pregnant women after informed and written consent were enrolled for study. On the first visit, women were screened for anthropometric observations, clinical examination and risk factors for GDM. On another day women were called in fasting condition and 75 g OGTT was carried out for two hours and samples were collected and analyzed for plasma glucose, and HbA1C, and other required investigations as part of antenatal care.

According to DIPSI, WHO 1999, IADPSG and WHO 2013 criteria, prevalence of 13.6% (40), 18.3% (54), 32.9% (97), and 31.2% (92) of GDM respectively was observed. When diagnostic criteria for overt diabetes during pregnancy [4] was applied to the collected data, 4% (12) women were found with overt diabetes mellitus among total pregnant women screened. Whereas among women with GDM and NGT by DIPSI, WHO-1999, IADPSG, and WHO-2013 criteria, respectively 20% (08), 18% (10), 10% (10), and 5% (5) women in GDM, and about 1 to 4% women in NGT group were observed with overt diabetes.

Based on HbA1C values alone, 6 (2.0%) women with diabetes with above cut off values of 6.5% and 11 (3.8%) women with impaired glucose tolerance with cut off values between 6.0 to 6.49% were observed out of total pregnant women screened. Among women with GDM by these four criteria, about 3 to 10% and among women with NGT about 1% women were found to have overt diabetes as per HbA1C cutoff value of 6.5% for overt diabetes in pregnancy. And about 2.5% women in GDM, and 1% women in NGT by four criteria were found to be with impaired glucose tolerance based on HbA1C values of 6.0 to 6.49% (Table 3, Chart1).

On the basis of the concentration of only fasting plasma glucose, we have found approximately 3.1% (9), and 4.1% (12) women with fasting hyperglycemia (FPG 126.0 mg/dl), and fasting impaired glucose (FPG 110.0 to 126.0 mg/dl) respectively in the total screened pregnant women. Percentage of women with fasting hyperglycemia, and impaired fasting glucose among women with GDM and NGT by these four criteria are presented in Table 3 and Chart 1.

After exclusion of 12 women with overt diabetes, a group of 277 pregnant women was placed as a separate group, in which the prevalence of GDM was 12.4% (31), 17.1% (43), 32.7% (82) by DIPSI, WHO-1999 and by both IADPSG and WHO-2013 criteria respectively. A clear-cut difference of 2% was observed in the prevalence of GDM before and after exclusion of women with overt diabetes by DIPSI and WHO-1999 criteria but not by WHO-2013 and IADPSG criteria in which no such difference was observed.

Mean age, BMI, glucose values in fasting and OGTT, and HbA1C values in women with GDM and NGT by four criteria before and after exclusion of women with overt diabetes are shown in Table 4 and 5.

Table No 2: Prevalence of GDM in different groups (before and after exclusion) as per the different criteria

Criteria/ Groups	Groups	DIPSI (n) %	WHO 1999 (n) %	IADPSG (n) %	WHO 2013 (n) %
Total Cohort before exclusion for diabetes (289)	GDM (n) %	(40) 13.6%	(54) 18.3%	(97) 32.9%	(92) 31.2%
	NGT n	249	235	192	197
Cohort after Exclusion for overt diabetes (277)	GDM (n) %	(31) 12.4%	(43) 17.1%	(82) 32.7%	(82) 32.7%
	NGT n	236	224	185	185

Table 3: Incidence of hyperglycemia of variable degree based on HbA1C and/ or OGTT, and fasting plasma glucose among women with GDM and NGT by various criteria

Criteria	DIPSI				WHO-1999				IADPSG				WHO-2013			
Category	GDM		NGT		GDM		NGT		GDM		NGT		GDM		NGT	
n	40		249		54		235		97		192		92		197	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
DM	8	20	4	2	10	18	2	1	10	10	2	1	5	5	7	4
IGT	1	2.5	15	6	13	24	3	1	14	14	2	1.1	14	15	2	1
IFG	0	0	12	5	12	22	0	0	12	12	0	0	12	13	0	0
HbA1C 6.5%	4	10	2	0.8	4	7	2	0.9	4	4	2	1.1	3	3	3	1.5
HbA1C 6.0 to 6.49%	1	2.5	3	1.2	1	2	3	1	2	2	2	1.1	2	2	2	1

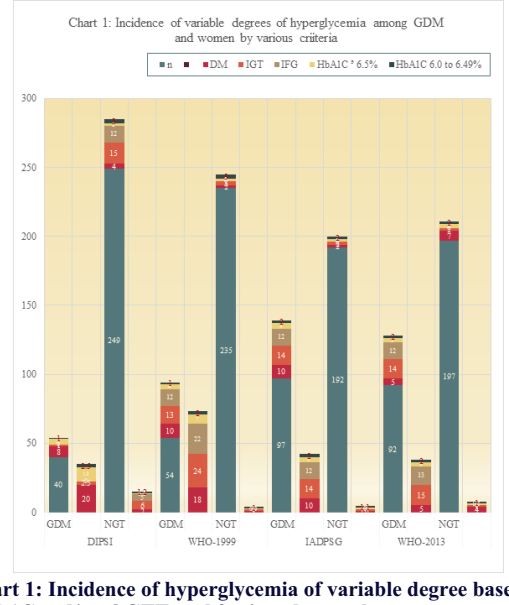

Chart 1: Incidence of hyperglycemia of variable degree based on HbA1C and/ or OGTT, and fasting plasma glucose among women with GDM and NGT by various criteria

Table 4: Age, BMI, OGTT and HbA1C in women with GDM and NGT before exclusion of cases with overt diabetes based on HbA1C and OGTT values

Criteria	Parameter	Age (Years)	BMI (kg/m^2)	OGTT		HbA1C (%)
				FPG (mg/dl)	Pp2 (mg/dl)	
DIPSI	**NGT (248)**	24.50 ± 3.96	22.82 ± 4.52	86.28 ± 11.61	104.70 ± 17.97	5.05 ± 0.48
	GDM (40)	26.28 ± 4.13	25.63 ± 4.45	96.76 ± 31.07	173.17 ± 45.46	5.50 ± 0.90
p value		0.008	0.001	0.263	0.000	0.001
WHO-1999	**NGT (230)**	24.35 ± 3.83	22.66 ± 4.47	84.39 ± 8.82	104.38 ± 18.00	5.04 ± 0.47
	GDM (54)	26.44 ± 4.34	25.67 ± 4.45	102.12 ± 28.37	157.18 ± 48.38	5.40 ± 0.84
p value		0.001	0.000	0.000	0.000	0.002
IADPSG	**NGT (185)**	24.34 ± 3.88	22.21 ± 4.17	80.97 ± 6.31	105.86 ± 19.74	5.40 ± 0.48
	GDM (97)	25.55 ± 4.19	25.19 ± 4.81	100.88 ± 20.78	131.21 ± 46.18	5.25 ± 0.71
p value		0.019	0.000	0.000	0.000	0.017
WHO-2013	**NGT (195)**	24.39 ± 3.90	22.34 ± 4.31	82.02 ± 10.43	104.38 ± 18.00	5.04 ± 0.47
	GDM (92)	25.47 ± 4.23	25.01 ± 4.72	102.12 ± 28.37	157.18 ± 48.38	5.40 ± 0.84
p value		0.44	0.000	0.000	0.000	0.097

Table 5: Age, BMI, OGTT and HbA1C in women with GDM and NGT after exclusion of cases with overt diabetes based on HbA1C and OGTT values

Criteria	Parameter	Age (Years)	BMI (kg/m^2)	OGTT		HbA1C
				FPG (mg/dl)	Pp2(mg/dl)	
DIPSI	NGT (219)	24.58 ± 3.98	22.93 ± 4.53	86.33 ± 11.03	104.42 ± 18.21	5.03 ± 0.46
	GDM (31)	25.90 ± 3.88	24.72 ± 3.67	85.17 ± 11.70	159.45 ± 19.46	5.24 ± 0.48
p value		0.053	0.027	0.767	0.000	0.018
WHO-1999	NGT (207)	24.43 ± 3.87	22.73 ± 4.47	84.65 ± 8.76	103.99 ± 18.12	5.03 ± 0.45
	GDM (41)	26.23 ± 4.25	25.14 ± 3.87	93.55 ± 16.91	146.16 ± 28.81	5.17 ± 0.52
p value		0.010	0.002	0.002	0.000	0.049
IADPSG	NGT (167)	24.36 ± 3.91	22.27 ± 4.11	81.15 ± 6.12	105.75 ± 20.18	5.02 ± 0.46
	GDM (80)	25.54 ± 4.06	24.89 ± 4.62	96.58 ± 11.76	123.03 ± 31.31	5.12 ± 0.48
p value		0.025	0.000	0.000	0.000	0.100
WHO-2013	NGT (167)	24.33 ± 3.91	22.39 ± 4.11	81.09 ± 6.17	105.75 ± 20.18	5.02 ± 0.46
	GDM (80)	25.54 ± 4.06	24.89 ± 4.62	96.58 ± 11.76	123.03 ± 31.31	5.12 ± 0.48
p value		0.021	0.000	0.000	0.000	0.105

Discussion:

GDM affects both mother and fetus in various ways, results in adverse pregnancy outcome as well as the long-term effect of development of Type 2 diabetes in later life. As per the available literature, it is clearly known that existence of GDM will lead to a number of adverse outcomes such as preeclampsia and caesarian section, macrosomia, neonatal hypoglycemia [9, 10], shoulder dystocia, hypoglycemia and hyperbilirubinemia [11,12], and history of adverse outcomes of GDM also come along with the history of GDM. In 1960s, O'Sullivan first established the criteria for interpretation of OGTT during pregnancy and found that the degree of glucose intolerance during pregnancy was related to the risk of developing diabetes after pregnancy based on statistical calculations [13]. Over the period of several decades, modifications were made in these criteria as there have been developments in technology in the diagnostic methods. Various regional criteria also exist for diagnosis of GDM, like DIPSI (India), ADPIS (Australia), and JSOG (Japan) etc., Recently HAPO study was carried out in a large multiethnic, multicentric worldwide way, and they inferred new cut off values for glucose in 75 g OGTT at 24 to 28 weeks of gestation, but were unable to define and recommend these for the diagnosis of GDM. Hence, IADPSG, an umbrella organization, studied extensively the data of HAPO group, by considering adverse pregnancy outcomes such as neonatal anthropometric parameters at a predefined odds ratio of 1.75 [4] and then defined the diagnostic criteria for GDM, now known as IADPSG criteria. Table No 1 shows various diagnostic criteria for GDM.

In the present study, we have applied four diagnostic criteria for GDM as DIPSI, WHO-1999, IADPSG, and WHO-2013 on cohort before and after excluding women with overt diabetes cases, based on HbA1C and FPG values for diagnosis of overt diabetes in pregnant population. About 2% of cases were identified as overt diabetes alone by HbA1C (cut off of 6.5%), and 4% by HbA1C and FPG values (Table 3, Chart 1). After exclusion of cases of overt diabetes, an average of two percent lower prevalence rate of GDM was observed in remaining pregnant women across these four diagnostic criteria (Table 2). Thus, this 2% of cases detected as GDM by these four criteria actually might be of Type 2 diabetes from the preceding period of pregnancy, and presently categorized as overt diabetes being detected during pregnancy. This group of women is at higher risk for adverse outcomes of pregnancy and requires immediate preventive and interventional steps than women with GDM. At the same time, about 1% of women were observed by each cut off of HbA1C 6.5% and 6.0 to 6.49% i.e. with diabetes and impaired glucose tolerance among women defined as NGT by these four criteria, based on OGTT values only (Table 3, Chart1). Looking into these observations it is evident that about 1% of screened pregnant population based on OGTT plasma glucose values may be categorized as normal though they can be diagnosed as overt diabetes if HbA1C test is applied.

The definition of GDM itself [1] shall be a cornerstone for using the observations for interpretation. The subgroup of women with more severe hyperglycemia that is similar to Type 2 diabetes, might have had existing diabetes prior to antenatal period and in the scenario of non-detection prior to pregnancy and there is a high possibility that this fraction is most likely counted as pregnant women with GDM leading to false projection of prevalence rates. Contemplating all these aspects, only glucose values in the 75 g OGTT were considered for the diagnosis of GDM as per existing guidelines. But after introduction of HbA1C estimation for the diagnosis of diabetes mellitus outside pregnancy i.e. in general population, it is possible to detect the hidden cases of pre-existing diabetes being surfaced as overt diabetes during pregnancy by screening with this parameter. This type of selective screening was not possible before the introduction of HbA1C.

This issue of women with likely pre-existing diabetes first noted during pregnancy has been extensively discussed during IADPSG consensus panel meeting in 2008 [4]. It has been recommended to consider that during pregnancy, HbA1C value of 6.5% (by DCCT/UKPDS standardized methods) [14], and FPG values of 126.0 mg/dl as diagnostic criteria for overt diabetes in pregnancy. In the present study, we estimated HbA1C by NGSP method, values of which have been linked to DCCT/UKPDS and IFCC values by master equation [15]. Thus, NGSP values obtained in the present study are equally correct to diagnose diabetes as compared to clinically meaningful DCCT/UKPDS values.

According to hypothesis of HAPO study, not only plasma glucose levels but also the levels of HbA1C would act as a guide regarding likely occurrence of adverse pregnancy outcomes and tried to use HbA1C as an alternative to OGTT measurement but did not find HbA1C as a suitable marker to replace OGTT. However, an association was observed between HbA1C and primary and secondary outcomes such as neonatal anthropometric measurements in the subjects which were part of HAPO study, when not adjusted for glucose. Whereas, on adjustment for glucose values in OGTT in case of pre-term delivery, an association of HbA1C was found to be varied. A strong association was observed if fasting plasma glucose was considered but not so if postprandial glucose concentration was considered. However, HbA1C was very well correlated with all the glucose values in the study [16]. In the present study also, a similar pattern of correlation between glucose values and HbA1C was observed.

In another study [8] of healthy pregnant women, mean HbA1C was observed to be 5.0% in first trimester and 5.9% in third trimester of pregnancy against upper limit of 6.3%. In addition to the above findings, this study also concluded that for prevention of congenital malformations and macrosomia in diabetic pregnancies, HbA1C levels should be below 5.0% & 6.0% in first and third trimester respectively. Others have reported that in women with HbA1C between 5.9 to 6.4% had high rate of GDM (75%) by IADPSG criteria in third trimester and worse outcomes of pregnancy as compared to women with HbA1C 5.8% [17]. In another study by these workers, it was reported that addition of HbA1C test for screening in the first antenatal visit should be beneficial to identify hidden cases of diabetes and prediabetes in early pregnancy [18]. The present study supports the contention by these workers regarding the benefit to use HbA1C for screening of GDM and overt diabetes in pregnant women. The results of our study correlate with the results reported by Hughes et. al. 2014 [18].

In the present study, we have also observed the marginal but statistically significant difference in HbA1C levels between women with and without GDM (Table 4), which again cannot be underestimated or neglected and be judiciously treated in view of incidence of GDM in pregnant women. Also, a statistical difference in HbA1C levels between NGT and GDM women by DIPSI and WHO-1999 criteria was observed in a group of women after excluding women with overt diabetes, but not so when IADPSG and WHO 2013 criteria were applied.

The present study and the number of other studies clearly give an indication of beneficial role of HbA1C as an adjunctive diagnostic

parameter in addition to OGTT in the pregnant women with GDM to assess possible adverse outcomes, but none of the studies including our study did prove the utility of HbA1C singularly for this purpose [19, 20]. The moot point is that will OGTT or HbA1C individually suffice for diagnosis or both shall be applied. Can these parameters be used singularly for definitive diagnosis of GDM and correct prediction of outcomes or is there any justification to apply OGTT for diagnosis though many times it fails to indicate possible outcomes or HbA1C utility as less proven diagnostic marker but more useful for indication of possible outcomes? when we have to do OGTT for diagnosis, is it justifiable to make the subject to incur additional cost for the analysis of HbA1C? Keeping in mind regarding the health of pregnant women and healthy child without any adverse outcomes, in the direction of prevention of such eventuality, clinicians have to apply discretion whether to go for OGTT only or for both, but the advice for the analysis of HbA1C cannot be applied universally by imposing additional unnecessary financial burden on subjects with pregnancy, though HbA1C offers an advantage of the subjects not necessarily being on fasting, ensuring compliance. We cannot overlook the fact that so far, no such definitive data is available regarding HbA1C as a diagnostic marker without depending upon OGTT. It is appropriate to comment that whenever a clinician suspects a possibility of adverse outcomes, it is advisable to go for both OGTT and HbA1C to protect both mother and fetus for any impending harm. While interpreting, taking the basis of the concentration of HbA1C in the pregnant subjects, a caution has to be exercised as the levels of HbA1C are suggested to be not reliable in the presence of hemoglobinopathies or the conditions of varied turnover rate of RBCs such as hemolytic anemia, iron deficiency anemia and blood transfusions [21]. HbA1C levels are reported to be elevated in the presence of iron deficiency anemia, which is more frequent in women [22] especially among the middle and lower middle-class population of India. Another aspect we have to take into consideration is that the condition of haemodilution in pregnant population which might affect all biochemical parameters.

Based on only glucose levels in fasting and in OGTT, about 1% of women among NGT by WHO-1999, IADPSG, and WHO-2013 criteria and 6% by DIPSI criteria were with impaired glucose tolerance. Whereas 5% women among NGT by DIPSI criteria were with impaired fasting glucose were observed but not by other three criteria (Table 3). These observations clearly indicate that DIPSI criteria, in which only one glucose value of OGTT without taking into the consideration of fasting concentrations are considered, providing no opportunity of possibility of detecting fasting hyperglycemia or impaired fasting glucose for systematic diagnosis of GDM. Hence, it can be stated that it is an inefficient criterion to diagnose GDM in a true spirit of the definition of GDM. A study by Mohan et. al. [23] similarly concluded that DIPSI criteria was not suitable for the diagnosis of GDM and suggested to perform fasting OGTT for the diagnosis. Higher incidence of GDM based on fasting glucose value in IADPSG criteria has also been reported in a cohort of HAPO study [24], which cannot be completely neglected in view of GDM cases.

Conclusions:

- So far, we have not found any suitable parameter apart from the OGTT, which can be singularly used in the diagnosis of GDM, of course, many workers have used fasting blood sugar for this purpose.
- The analysis of glycated haemoglobin would offer additional an advantage in the diagnosis of GDM and possible outcomes but as of now it cannot replace OGTT
- For better diagnosis of possible outcomes in the pregnant women with GDM, along with OGTT, it is advisable to analyze HbA1C but caution and necessary discretion has to be applied while advising for the analysis of HbA1C as it incurs high cost to the subjects and strain on resources in Indian conditions.
- More data is required using a large population of pregnant women to correlate HbA1C, haemoglobin status and iron status with GDM cases. The data shall come from both hospital and population-based studies

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