ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 02 | February - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CORRELATION BETWEEN HAEMOGLOBIN LEVELS DURING FIRST TRIMESTER OF PREGNANCY & RISK OF GESTATIONAL DIABETES MELLITUS & PRE-ECLAMPSIA-LONGITUDINAL STUDY

Obstetrics & Gynaecology

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ABSTRACT

Background: Pre-eclampsia(PE) and Gestational diabetes mellitus (GDM) are two of the most medical complication during pregnancy and contribute significantly to maternal, fetal & neonatal morbidity and mortality.
Objective: This study is a longitudinal study to evaluate associations between hemoglobin levels in the first trimester and the risk of GDM and preeclampsia.
Methods: A longitudinal study was conducted on 324 pregnant women at tertiary care hospital between December2018 –October2020. The demographic data and medical information of each participant were collected individually through questionnaires. The Hematological investigation was performed on a fully automated Beckman coulter hematology analyzer in Department of Pathology at our tertiary care hospital . Association among the study groups was assessed with the help of the Fisher test, student't' test, and Chi-Square test. 'P' value of less than 0.05 was taken as the significant and relative risk was generated.
Results: 1) The relative risk of developing pre eclampsia and GDM in pregnant women with high first trimester hemoglobin level (>13g/dl) is 1.41 times and 1.71 times respectively more than pregnant women who had normal or low first trimester hemoglobin level.(95% CL p=< 0.0203 and p = <0.0012 respectively). 2) Incidence of pre eclampsia and GDM was 14.44% and 9.7% respectively. 3) Women with high pre pregnancy BMI (overweight and obese) are at increased risk of developing GDM further in pregnancy.(p=<0.0001HS).
Conclusion: These findings suggest that Hemoglobin levels during early pregnancy play a role in predicting the risk of GDM and pre eclampsia

KEYWORDS

Hemoglobin, Gestational diabetes mellitus, Pre-eclampsia, Body mass index

INTRODUCTION

Pre-eclampsia(PE) and Gestational diabetes mellitus (GDM) are two of the most medical complication during pregnancy, affecting 0.2–9.2% and 9.3%–25.5% of pregnancies, respectively, in different global populations. [1-2]. In India, the overall incidence of PIH is 5-15% [3] and GDM is 4.6 to 14% [4]. Preeclampsia is a disorder of pregnancy, associated with new-onset hypertension which occurs most often after 20 weeks gestation & frequently near term[5]. It is the leading cause of maternal mortality worldwide [3]. The basic underlying pathology in pre-eclampsia is vascular endothelial injury by free radicals and oxidative stress due to exaggerated maternal inflammatory response which presents as atherosis, microvascular coagulation & increased permeability [5]. Preeclampsia patients are confronted with the risk of developing fetal growth restriction, premature termination of pregnancy, placental abruption, & caesarean delivery.

GDM is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy.GDM patients have an increased risk of malformation, polyhydramnios, preterm birth, preeclampsia, macrosomia, caesarean delivery, neonatal hypoglycemia, hyperbilirubinemia [6]. Both GDM and preeclampsia contribute significantly to maternal, fetal & neonatal morbidity and mortality. Thus, predicting GDM, PE, is essential and imperative for improving the health quality of populations. Recent studies have suggested an increased risk of preeclampsia and GDM in pregnant women with high hemoglobin levels at their 1st-trimester antenatal visit. Hemoglobin measurement among pregnant women during the first trimester visit is considered standard practice according to the World Health Organization (WHO) to evaluate physical status & anemia [7].

High hemoglobin concentration could be a marker of inadequate plasma volume expansion which is associated with the development of preeclampsia later in pregnancy. Many studies have shown that Haemoglobin in circulation after oxidation could be the cause of methemoglobin-derived heme deposition on vessels[10]. Also, heme as a catalyst acts to oxidize LDL (low-density lipoprotein) and induce toxicity on the vascular walls[11]. Wang et al hypothesized that high Hemoglobin levels may reflect iron overload because iron supplementation in high doses has been confirmed to have a role in the occurrence of GDM [12]. Accumulating evidence has demonstrated that iron is a strong pro-oxidant, and iron overload can increase β-cell oxidative stress, thus causing insulin resistance and impaired glucose metabolism [13].Further research is needed to better understand this relationship. This study is a longitudinal study to evaluate the association between hemoglobin levels in the first trimester and the risk of GDM and preeclampsia.

MATERIAL AND METHODS

This was a hospital-based longitudinal study, a total of 449 pregnant women were enrolled, and who registered in the first trimester at our tertiary care hospital. Among them, 22 were ineligible due to multifetal pregnancy, Sickle cell disease, known case diabetes or hypertension & who refused o give consent for the study. The remaining 427 eligible pregnant women entered into the study after obtaining their informed consent. Then, their demographic characteristics and gestational age, Body mass index were recorded in the first trimester. The hematological investigation was performed on a fully automated Beckman coulter hematology analyzer in the Department of Pathology at our tertiary care hospital.

Pregnant women were grouped into 3 cohorts i.e. low hemoglobin (<11 gm/dl), normal hemoglobin (11-12.9 gm/dl), and high hemoglobin (>13 gm/dl). 17, 11, and 6 pregnant women were excluded from low hemoglobin, normal hemoglobin, and high hemoglobin cohort respectively due to abortion, fetal anomalies, did not perform OGTT or loss o follow up. 127 pregnant women were randomly selected from each cohort and underwent blood pressure recording in each trimester and OGTT was performed between 24-32 weeks of gestation and were followed up until delivery.

The number of pregnant women with gestational diabetes and preeclampsia was documented in each group. The women were considered preeclampsia according to ACOG guidelines. Diagnosis of gestational diabetes was based either on two- step ACOG. Oral glucose tolerance test (OGTT) was perform initially regardless of the interval between the test and last meal, 50 g of glucose given to the patient and blood glucose levels was measured one hour later. If the obtained value was equal to or greater than 140 milligrams per deciliter, then the three-step test was perform.

Comparison among the study groups was done with the help of the student 't' test, and Chi-Square test. 'P' value of less than 0.05 is taken as significant. All pregnant women were followed till delivery and the mode of delivery, baby birth weight was recorded. Very low birth weight was defined as < 1.5 kg and low birth weight were defined as < 2.5 kg. Macrosomia was defined as birth weight >3.5 kg(>90th percentile in India) [14].

Approach	Criteria	Fasting mg/dl	One-hour mg/dl	Two-Hour mg/dl	Three-hour mg/dl
Two-step (100-gram load)	**ACOG**	95	180	155	140

RESULTS:

381 eligible pregnant women were finally included in the study and were grouped as low hemoglobin (11g/dl), normal hemoglobin (11-13g/dl), and high hemoglobin (>13g/dl). 127 pregnant women (33.33%) were enrolled in each group. Mean hemoglobin was 11.09 ± 1.79 (6.3–13.4). Baseline characteristics of total pregnant women stratified by hemoglobin are given in table 1. The mean age of the study population was 25.46 ± 4.24 (17-38) years. Among the study group, 234 (61.42%) were primigravida and 147 (38.58%) were multigravida. 173 (45.41%) had normal BMI followed by 107 (28.08%) were underweight, 69 (18.11%) were overweight & 32 (8.4 %) were obese.

ACOG Diagnostic criteria for Pregnancy- Associated Hypertension	
Preeclampsia- Hypertension and any one of following	BP >140/90 mmhg after 20 weeks in previously normotensive women
Proteinuria	>300 mg/24h, or Protein: creatinine ratio ≥0.3 or Dipstick 1+ persistent
Thrombocytopenia	Platelets < 100,000/ µL
Renal Insufficiency	Creatinine > 1.1 mg/dl or doubling from baseline
Liver involvement	Serum transaminase levels twice normal
Cerebral symptoms	Headache, visual disturbances, convulsion
Pulmonary edema	

Table1

	Hemoglobin<11g/dl	Hemoglobin (11-13g/dl)	Hemoglobin>13g/dl	P value
Age in years				
≤20	52%(25)	20.83%(10)	27.08%(13)	P=0.305,NS
< 35	30%(3)	30%(3)	40%(4)	
Parity				
Primigravida	33%(78)	35.04%(82)	31.62%(74)	P=0.588 NS
Multigravida	33%(49)	30.61%(45)	36.05%(53)	
Pre-pregnancy BMI				
Underweight (BMI< 18.5)	59.81%(64)	21.50%(23)	18.69%(20)	P<0.0001,HS
Normal BMI(18.5-22.9)	20.81%(36)	37.57%(65)	41.62%(72)	
Overweight (BMI23-24.9)	23.19%(16)	39.13%(27)	37.68%(26)	
Obese (BMI>25)	34.38%(11)	37.50%(12)	28.13%(9)	

In our study, the incidence of preeclampsia and GDM was 14.44% (55) and 9.7%(37) respectively. Out of 55 women with preeclampsia 29(15.95%) were from high haemoglobin(>13g/dl) group, 15(8.25%) from normal haemoglobin group (11-13g/dl), and 11 (6.05%) from low haemoglobin(<11g/dl) group. Among 37 GDM patients 18(48.64%), 13(35.13 %), and 16 (43.24 %) were from high, normal, and low hemoglobin cohort respectively. As shown in table 2, there is a significant association between the incidence of pre-eclampsia and GDM with high hemoglobin with p=< 0.0203 and p = <0.0012 respectively.

The relative risk of developing preeclampsia and GDM in pregnant women with high first-trimester hemoglobin level is 1.41 times and 1.71 times respectively more than pregnant women who had normal or low first trimester hemoglobin levels. Among 37 GDM patients, 1(2.7%), 4(10.82%), 18(48.64%) and 14(37.83%) were underweight (BMI <18.5), normal weight (BMI 18.5-22.9), overweight (23-24.9) and obese (>25) according to pre- pregnancy BMI. Women with high pre-pregnancy BMI (overweight and obese) are at increased risk of developing GDM further in pregnancy. And this association was found statically significant (p=<0.0001HS). Out of 55 patients with preeclampsia 14 (25.45%), 22(40%), 12 (21.81 %), and 7(12.72 %)were underweight, normal, overweight, and obese respectively according to pre pregnancy BMI. But the association of low BMI (underweight) and high BMI (overweight, obese) were not found to be statically significant (p=0.476) due to the small sample size.

Table No.2 Association Of Haemoglobin Level With Risk Of Pre-eclampsia

Haemoglobin level	Pre-eclampsia		RR	95% Confidence Interval	p-value
	Yes	No			
>11 Low	11	116	0.83	0.52-1.32	0.4077,NS
(11 – 13) Normal	15	112	1.00	-	-
>13 High	29	98	1.41	1.09-1.82	**0.0203, Significant**

Table No.3 Association Of Haemoglobin Level With Risk Of Gestational Diabetes Mellitus.

Haemoglobin level	Gestational diabetes mellitus		RR	95% Confidence Interval	p-value
	Yes	No			
>11 Low	6	121	0.61	0.31-1.20	0.095,NS
(11 – 13) Normal	13	114	1.00	---	---
>13 High	18	109	1.75	1.40-2.18	0.0012,HS

Table No.4 Association Of Maternal BMI with GDM, Pre-eclampsia And Pre Term Birth.

BMI	No. of Cases	GDM		Pre-eclampsia	
		Yes	No	Yes	No
<18.5 Underweight	107	1(0.9)	106(99.1)	14(13.1)	93
18.5 – 22.9 Normal	173	4(2.3)	169(97.7)	22(12.7)	151
23 – 24.9 Overweight	69	18(26.1)	51(73.9)	12(17.4)	57
≥25 Obese	32	14(43.8)	18(76.2)	7(21.9)	25
p-value		<0.0001, HS		0.476,NS	

A higher caesarean and preterm delivery rate were found in our study among patients with GDM and preeclampsia. Among 37 GDM patients, 8(21.4%) delivered vaginally and 29(78%) delivered by caesarean section. (p=<0.0001HS). 11(29.73%) of GDM patients underwent preterm delivery (29.73% vs. 15.12% p=<0.023S). Among 55 women with preeclampsia 9(16.36%) and 46(83.6%) delivered by vaginal and caesarean delivery respectively (p=<0.0001HS) and the incidence of preterm delivery in women with preeclampsia was 29.09% (16) (p=<0.007). In our study, we also found an increased incidence of very low birth weight (VLBW) and low birth weight (LBW) among babies born to mother with preeclampsia and it was found statistically significant (p=<0.0001) Among babies born to mother with preeclampsia, 2 (3.63%), 21(38.18%) and 33(57.89%) were very low birth weight, normal and low birth weight respectively. One of the adverse neonatal outcomes, macrosomia was also found higher among babies born to mothers with GDM compared to non-GDM patients. (27.30 % vs. 1.74%, p<0.001)

This study showed that pregnant women with high hemoglobin levels (>13g/dl) have 1.71 times more chance of developing GDM than pregnant women with low and normal hemoglobin levels. Also, the risk of preeclampsia in pregnant women with high hemoglobin level is 1.41 times higher than women with normal or low hemoglobin levels. Furthermore, it was also found that women with high pre pregnancy BMI (overweight and obese) were associated with a higher risk of GDM. But the association of low BMI (underweight) and high BMI (overweight, obese) was not found with preeclampsia due to the small sample size.

Similar to our results, a retrospective cohort study on 21,577 pregnant women was conducted by Wang et al in 2013-2015 and revealed that high maternal hemoglobin level in the first trimester (>13g/dl) was associated with a higher incidence of GDM and preeclampsia with odds ratio 1.27 and 1.30 respectively for hemoglobin > 13 g/dl. Their study also found an association between high pre-pregnancy BMI (>24 kg/m2) with GDM [15].

Similarly, in the report by Mehrabian and Hosseini [16] on 973 pregnancies during 2011–2012, significantly higher incidences of GDM and PE were found among women who had early pregnancy hemoglobin values ≥12.5 g/dl than those with hemoglobin values < 12.5 g/dl. The OR values were 3.7 (95% CI; 2.2 to 6.4) and 5.4 (95% CI; 2.8 to 10.5), respectively [16].

Also, a longitudinal study was conducted on the 400 pregnant women

by Manjunatha S et al. in 2015 and found a significant association between high hemoglobin level (13 g/dl) and risk of pre-eclampsia ($p < 0.0001$).

CONCLUSION

Our study shows high hemoglobin levels during the first trimester of pregnancy play a role in predicting the risk of GDM and PE. It will help the clinicians to be aware of complications of GDM & Preeclampsia early in pregnancy before the development of overt signs and symptoms later in pregnancy.

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