A CLINICAL STUDY ON THE RELATIONSHIP BETWEEN MATERNAL HEMOGLOBIN AND GESTATIONAL DIABETES MELLITUS IN HYDERABAD POPULATION

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ABSTRACT :
Type 1 Diabetes Mellitus is a metabolic disease where the insulin producing β-cells in the pancreatic islets of Langerhans are progressively destroyed. When the insulin production is no longer sufficient to keep the appropriate blood glucose concentration, hyper glycaemia with subsequent glycosuria occurs. The objective of this study was to determine the relationship between the hemoglobin levels during the first trimester of pregnancy with gestational diabetes incidence in pregnant women. This is an analytical, prospective, cohort study conducted with convenience sampling from December 2017 to March 2018. Sample size was determined as follows: 50 people with a confidence interval of 95%, relative accuracy of 25% and a probability of exclusion of 10%. The Ethics Committee approved for our study. Analysis of the different groups (in terms of hemoglobin levels) did not indicate any significant differences among them regarding the above variables, as well as the type and duration of complement intake in pregnancy (p>0.05). As Table II depicts, 5 (8.2%) of all cases developed gestational diabetes, among which 50 (83.67% of those afflicted) were in the High group (hemoglobin levels of 1.25 and higher). All cases were followed up to the delivery due to developing gestational diabetes and the supplements, duration of intake and their types were recorded on each visit. It appears that hemoglobin level during the first trimester of pregnancy may be considered as a selective screening factor for gestational diabetes.
Keywords: gestational diabetes, confidence interval, probability

I.INTRODUCTION

Diabetes mellitus [1, 2]

Type 1 Diabetes Mellitus is a metabolic disease where the insulin producing β-cells in the pancreatic islets of Langerhans are progressively destroyed. When the insulin production is no longer sufficient to keep the appropriate blood glucose concentration, hyper glycaemia with subsequent glucosuria occurs. Type 1 diabetic patients require exogenous insulin administration in order to restore a normal metabolic state.

Gestational diabetes

Gestational diabetes (or gestational diabetes mellitus, GDM) is a condition in which women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy (especially during their third trimester). GDM usually becomes apparent during the 24th to 28th weeks of pregnancy. It is associated with both impaired insulin secretion and the blocking effects of other hormones on the insulin that is produced, a condition referred to as insulin resistance. Diabetic symptoms usually disappear following delivery.

EPIDEMIOLOGY [2,3,4]

The prevalence of GDM in India varied from 3.8 to 21% in different parts of the country, depending on the geographical locations and diagnostic methods used. GDM has been found to be more prevalent in urban areas than in rural areas. For a given population and ethnicity, the prevalence of GDM corresponds to the prevalence of impaired glucose tolerance (IGT) (in nonpregnant adult) within that given population.

CLASSIFICATION [2, 3]

Diabetes mellitus can occur during pregnancy in 2 forms: pregestational and gestational diabetes. World

Health Organization (WHO) have classified diabetic pregnancies according to etiology

Classification of diabetes in pregnancy

Pregestational diabetes

Type 1 diabetes

Type 2 diabetes

Secondary diabetes

Gestational diabetes

Impaired glucose tolerance of pregnancy

Undiagnosed pre-existing diabetes

Undiagnosed pre-existing impaired glucose tolerance

HISTORY AND PATHOPHYSIOLOGY [3, 4, 5, 6]

Pregnancy is a diabetogenic state. The exact cause of gestational diabetes is not known, but there are some theories as to why the condition occurs. The endocrine regulation of carbohydrate metabolism changes during pregnancy. Levels of insulin antagonists and steroid hormones increase along with the level of some enzymes with insulinase activity like oxytocinase, histaminase, and alkaline phosphatase. Up to the 37th to 38th gestational weeks, insulin demand may intensify 3- to 4-fold compared with that prior to pregnancy. The elevated insulin need is compensated by the hypertrophy and hyperplasia of the β-cell mass. The changes in maternal metabolism during normal pregnancy include

- decreased fasting plasma glucose level
- increased postprandial plasma glucose level
- increased preprandial and postprandial insulin levels
- β-cell hypertrophy and hyperplasia
- decreased insulin sensitivity
- improved lipolysis

Glycemic control in normal pregnancy is characterized by 'accelerated starvation'. Accelerated starvation leads to lower fasting glucose levels. The normal decrease in maternal insulin sensitivity during pregnancy is beneficial for the growth of the fetus, since post-prandial hyperglycemia enhances glucose transer to the fetus. Enhanced glucose transfer to the fetus is referred to as 'facilitated anabolism' and is a result of enhanced maternal lipolysis, which occurs because of the inability of insulin to suppress lipolysis in adipose tissue. However, these alterations in the metabolism of carbohydrates and lipids may lead to hyperglycemia and ketosis. However, patients with insulin-dependent diabetes mellitus (IDDM, type 1) are more prone to develope diabetic ketoacidosis during pregnancy than are patients with noninsulin-dependant diabetes mellitus (NIDDM, type 2) or gestational diabetes.

Some hormones produced by the placenta (estrogen, cortisol, and human placental lactogen) can have a blocking effect on insulin, which usually begins about 20 to 24 weeks into the pregnancy. As the placenta grows, more of these hormones are produced, and insulin resistance becomes greater. Normally, the pancreas is able to make additional insulin to overcome insulin resistance, but when the production of insulin is not enough to overcome the effect of the placental hormones, GDM results. The hormones that lead to fetal growth and development do so by mobilizing the mother's nutritional resources, primarily glucose, making them available to the fetus. The plasma levels of the critical anabolic hormones (human chorionic gonadotropin, human placental lactogen, progesterone, estrogen) present during pregnancy increase in the last 20 weeks of gestation. Human placental lactogen plays a vital role in triggering the changes that lead to glucose intolerance. It has strong anti-insulin and lipolytic effects. Peripheral insulin sensitivity during the third trimester decreases to 50% and basal hepatic glucose output is 30% higher than that seen in the first trimester, despite higher insulin levels. This combination of increased mobilization of glucose and decreased sensitivity to insulin places women at risk of developing diabetes during pregnancy. There is evidence that women who develop GDM secrete less insulin in response to a glucose load

than women who do not acquire the disease.

The aim of the study is to evaluation the Relation between Hemoglobin Concentration in patient with GDM. The objective of this study was to determine the relationship between the hemoglobin levels during the first trimester of pregnancy with gestational diabetes incidence in pregnant women

II. EXPERIMENTAL WORK

Study Condition: Gestational diabetes in Pregnancy

Study Period: Planned enrolment during 2 months

Planned study duration: 3 months

Study type: Observational study

Inclusion:

Criteria of being included in the study:

Conception with a living fetus amounts of FBS and HB in the first 14 weeks of conception and GCT in weeks 24-28 of conception.

All women gave their written informed consent. Data were collected using a questionnaire containing personal data and obstetric history. The validity and reliability of the questionnaire were assessed using content validity and test re-test, respectively. Researchers completed the questionnaires through interviews with the cases. Complete blood counts (CBC) were obtained from all cases to measure the hemoglobin level of the first trimester. In addition, glucose challenge test (GCT) with 50 g of glucose was performed as the national routine test for pregnant women in 24- 28 weeks of gestational age.

Exclusion:

Criteria for being excluded from the study were:

Development of known fetal anomalies, abortion, stillbirth, consumption of alcohol, cigarettes or non-routine drugs during the present pregnancy or receiving pregnancy care or tests in other center

Statistical analysis:

All the data was entered in SPSS version 22 software and analyzed for statistically significant outcomes. Chi-square tests and percentiles were used for gathering the findings of the results.

This is an analytical, prospective, cohort study conducted with convenience sampling from December 2017 to March 2018. Sample size was determined as follows: 50 people with a confidence interval of 95%, relative accuracy of 25% and a probability of exclusion of 10%. The Ethics Committee approved for our study (license number 116/995). Once all the necessary authorizations were acquired, the researchers referred to the Om Sai Hospital, Hyderabad, in order to explain the nature and objectives of the study and to recruit 50 pregnant women who were referred to the pregnancy care clinics and fulfilled the inclusion criteria. All women gave their written informed consent. Data were collected using a questionnaire containing personal data and obstetric history. The validity and reliability of the questionnaire were assessed using content validity and test re-test, respectively. Researchers completed the questionnaires through interviews with the cases. Complete blood counts(CBC) were obtained from all cases to measure the hemoglobin level of the first trimester. In addition, glucose challenge test (GCT) with 50 g of glucose was performed as the national routine test for pregnant women in 24- 28 weeks of gestational age. For those women who had blood sugar levels higher than 140 mg/dL on the GCT, oral glucose tolerance test (OGTT) was performed at the laboratory of the Om Sai Hospital in order to establish a diagnosis of gestational diabetes, and the results were extracted by the researchers and recorded on data sheets. Based on hemoglobin level, the samples were categorized in three groups of Low (<1.1 g/l), Normal 1.1-1.24g/l) and high(≥ 1.25g/L)

All cases were followed up to the delivery due to developing gestational diabetes and the supplements, duration of intake and their types were recorded on each visit. The inclusion criteria were: a pregnant woman with a single fetus, aged 18-35 years with a gestational age of 1-13 weeks (calculated using the first day of the last regular menstruation or a sonography report during the first trimester), a parity of 3 or less, lack of known systemic diseases, and lack of gestational diabetes during previous pregnancies. The Carpenter and Coustan criteria were used for diagnosing diabetes – fasting blood sugar of 95 mg/dL, 1-hour, 2-hour, and 3-hour blood sugar levels of 180, 155, and 130 mg/dL, respectively, following oral consumption of 100 g of glucose). The researcher and 3 trained colleagues determined the type of delivery, gestational age and neonatal weight in the labor room and recorded the information on data sheets. The reliability of data measurement and recordings was assessed by 4 midwives using the inter rater consistency. The exclusion criteria were: development of known fetal anomalies, abortion, stillbirth, consumption of alcohol, cigarettes or non-routine drugs during the present pregnancy or receiving pregnancy care or tests in other centers. Hemoglobin levels were measured by a laboratory expert at the laboratory of the Om Sai Hospital by flow cytometry on a Sysmex XT 1800i cell counter (Adons Electronics, Japan). Blood sugar was measured using the GOD/PAP method and kits prepared by ParsAzmoon (licensed by Germany) on Hitachi 902 instruments manufactured in Japan. All the instruments were calibrated every morning by a laboratory expert and their accuracy and reliability were ascertained. Data analysis was performed using the SPSS software version 18 with statistical tests of Kruskal-Wallis, chi-square, one-way ANOVA, relative risk and logistic regressionmodel.The confidence interval and level of significance were 95% and 0.05 respectively.

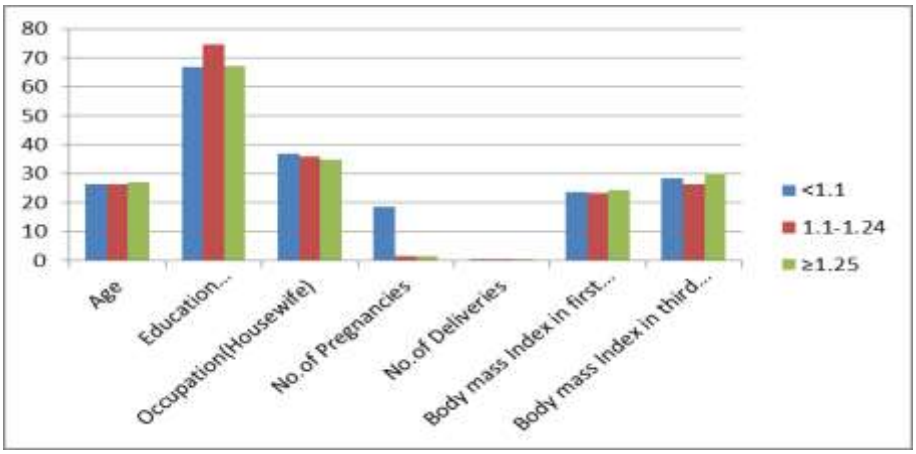
III.RESULTS AND DISCUSSION

Results From the 70 women who entered our study, a total of 10 were excluded due to lack of compliance (2 cases), abortion (2 cases), intrauterine fetal demise (1 cases), oligohydramnios

Table I. Demographic and obstetric characteristics of study case

Group	<1.1(20)	1.1-1.24(18)	≥1.25(22)	P value
Age	26.35±2.1	26.34±3.65	26.98±3.64	-
Education (Intermediate/High School)	13	13	15	-
Occupation(Housewife)	7	6	8	-
No.of Pregnancies	18.63±0.59	1.54±0.54	1.35±2.3	0.03
No.of Deliveries	0.6±0.46	0.45±0.54	0.34±0.32	0.01
Body mass Index in first trimester	23.45±3.24	23.14±4.3	24.36±3.64	-
Body mass Index in third trimester	28.36±3.54	26.35±3.47	30.21±3.94	-

Group I. Demographic and obstetric characteristics of study case



(1 cases), polyhydramnios (1 cases), placenta previa (2 cases), placental abruption (1 cases), and thus leaving 60 women for investigation. The demographic and obstetric characteristics of our cases are summarized in Table I 34 (57.2%) of the patients fell in the age range of 25-30 years. Their mean age was 27-28 years, with a standard deviation of 3.64. 41 (69.8%) of the study participants had intermediate/high school education and 50 (83.7%) were housewives. 30 (48.2%) were primigravidas. BMI during the first trimester was within the normal range (19.8-26 kg/m2) for 32 (54.3%) of the women. 51(86%) did not have a history of abortion and 33 (55.3%) did not

have a history of delivery.

Table II. Distribution of hemoglobin groups and occurrence of gestational diabetes.

Group	**<1.1(12)**	**1.1-1.24(16)**	**≥1.25(32)**	**Total**
Gestational Diabetes	Number (%)	Number (%)	Number (%)	Number (%)
Yes	11(96.7)	15(96.8)	28(88.4)	54(90%)
No	1(3.3)	1(3.2)	4(11.6)	6(10%)
Total	13(100%)	16(100%)	32(100%)	60(100%)

Groupt II. Distribution of hemoglobin groups and occurrence of gestational diabetes.

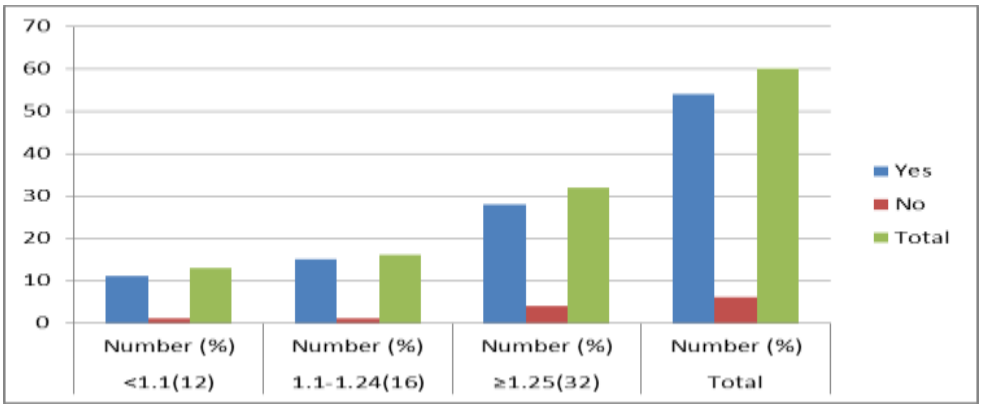
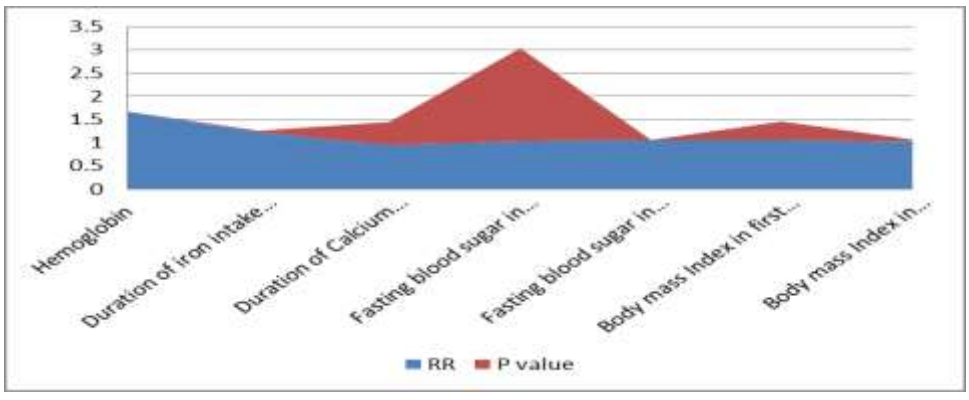


Table III. Risk factors for gestational diabetes using logistic regression model

Incidence related factors	RR	P value	Confidence interval
Hemoglobin	1.67	0.001	1.26-2.46
Duration of iron intake during pregnancy	1.23	0.03	1.02-1.84
Duration of Calcium intake during pregnancy	0.95	0.5	0.83-1.1
Fasting blood sugar in first Trimester	1.04	2	1.01-1.05
Fasting blood sugar in Second Trimester	1.06	0.001	1.03-1.08
Body mass Index in first trimester	1.06	0.4	0.92-1.2
Body mass Index in Third trimester	1.03	0.04	1-1.14

Table III. Risk factors for gestational diabetes using logistic regression model



Analysis of the different groups (in terms of hemoglobin levels) did not indicate any significant differences among them regarding the above variables, as well as the type and duration of complement intake in pregnancy (p>0.05). As Table II depicts, 5 (8.2%) of all cases developed gestational diabetes, among which 50 (83.67% of those afflicted) were in the High group (hemoglobin levels of 1.25 and higher). Using the chi-square test, a statistically significant relationship was discovered between high hemoglobin levels during the first trimester of pregnancy and developing gestational diabetes (p=0.001). The relative risk of developing gestational diabetes was 3.94 times higher for the High group compared to the Normal group (CI=1.74-8.95), while it was 1.03 times higher for the Low group compared to the Normal group (CI=0.12-8.17). Having performed the Bonferroni correction, the chi-square test indicated a significant difference between the High and Normal hemoglobin groups; i.e. gestational diabetes occurred more frequently in the High hemoglobin group (p<0.001)

Comparison of Low and Normal hemoglobin groups with chi-square test failed to indicate any significant difference in terms of the occurrence of gestational diabetes (p=0.3). Moreover, comparing the High and Low hemoglobin groups with chi-square test indicated a significant difference between the two groups in terms of the development of gestational diabetes (p=0.008). The incidence of gestational diabetes was 8.2% in our study, with confidence interval of 5-10%.

DISCUSSION:

The present study indicated that high levels of hemoglobin in the first trimester of pregnancy and progression of pregnancy are significantly related. Phaloprakarn et al., (2008) reported similar results (CI=2.0-7.1, RR=3.8) [7], as well as Lao et al., (2002) whose results were similar to those of our study (CI=1.08-2.78, RR=1.73) [8]. The findings of a study by Vasegh et al[9]., indicated that high hemoglobin levels before 14 weeks of gestational age may be considered to be a risk factor for developing gestational diabetes, what may be accounted for by increased amounts of iron stored in these women.

On the other hand, Gungor et al., (2007) [10] did not observe a significant relationship between high hemoglobin levels of the first trimester and gestational diabetes. However, many confounding variables were not controlled in the Gungor study and hemoglobin levels were assessed in 28-30 weeks of gestations, when the iron supplements received during the second half of pregnancy had probably obscured the true difference of hemoglobin level among the groups.

Our study controlled the confounding variables appropriately and assessed hemoglobin levels during the first trimester. The probable mechanism accounting for the relationship between excessive hemoglobin and development of gestational diabetes is that the increased iron may affect insulin synthesis and secretion, as well as promote lipid oxidation, leading to a decreased glucose uptake and consumption in muscles and increased glucose synthesis in the liver. This condition creates a state of insulin resistance and makes the pregnant woman more prone to gestational diabetes. Furthermore, increased iron stores influence the oxidative stress and may result in lipid peroxidation and tissue injury through creation of highly toxic free radicals such as superoxide and hydroxide anions.

Oxidative stress increases ferritin so that the higher levels of ferritin may neutralize free iron and reduce the oxidative injury. It appears that tissue deposition of iron promotes insulin resistance, increasing ferritin and establishing a vicious cycle of iron overload which renders the patient prone to glucose tolerance disorder. Iron deposition may simultaneously lead to subclinical hemochromatosis, thus compromising pancreas [11,12]. It seems that high levels of hemoglobin during the first trimester may be a warning sign for development of gestational diabetes over the next weeks of pregnancy. Occurrence of certain medical conditions, such as abortion before 20 weeks of gestation and the consequent exclusion of the person were among the limitations of the present study.

The main advantage of the present study is its prospective methodology, with elimination of known risk factors and control of confounding variables for the development of gestational diabetes. In order to enhance the reliability and validity of test results, all tests were performed at the laboratory of the Om Sai Hospital by one person and with one instrument. As was mentioned in the method section, reliability and validity were assessed. Discovering a new risk factor for early diagnosis of gestational diabetes may contribute to early detection of pregnant women at risk. Moreover, timely treatment or referral of patients afflicted may reduce maternal, fetal and neonatal complications.

CONCLUSION

It appears that hemoglobin level during the first trimester of pregnancy may be considered as a selective screening factor for gestational diabetes.

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