

Prediction of Gestational Diabetes Mellitus and Hypertensive Disorders in Pregnancy Using Insulin Resistance at 11-14 Weeks Period of Gestation

Indraneel Jadhav^{*}, Shashikala Bhat² and Maheshwari Indraneel Jadhav³

Abstract

Background: Hypertensive disorders of pregnancy and gestational diabetes (GDM) are all associated with increased risks of poor maternal and perinatal outcomes. It has been hypothesized that the association could be due to at least in part, to insulin resistance. Although insulin resistance is a physiologic phenomenon in normal pregnancy, in predisposed individuals it could lead to hyperinsulinemia with development of GDM, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia and eclampsia) or both. In the present study the role of insulin resistance in early prediction of gestational diabetes mellitus and hypertensive disorders in pregnancy. Researchers attempted to study the correlation of insulin resistance at 11 to 14 weeks period of gestation and outcome in terms of GDM and hypertensive disorders in pregnancy and explore the possible use of insulin resistance in their early prediction.

Objectives: Prediction of gestational diabetes mellitus and hypertensive disorders in pregnancy using insulin resistance at 11-14 weeks of gestation.

To evaluate if combined maternal markers (insulin resistance, mean arterial pressure and uterine artery Doppler pulsatility index) in first trimester of pregnancy (11-14 weeks) is more effective in predicting the same.

Methodology: The study is a prospective observational study carried out from December 2015 to November 2016, in the Department of Obstetrics and Gynaecology at Dr. T.M.A. Pai Hospital, Udupi. The study population consists of pregnant women booked between 11-14 weeks of gestation with viable pregnancy, who are willing for blood investigation to determine insulin resistance and also those women who gave consent to do uterine artery Doppler. Total 165 patients are included in the study. Out of them 118 patients gave consent to do uterine artery Doppler during NT scan. All patients are followed up for presence of development

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of gestational diabetes mellitus and hypertensive disorders of pregnancy with mode of delivery, intrapartum and postpartum complications.

Results: Likelihood ratio by taking HOMA-IR cut off as 1.87 at 11-14 weeks of gestation was 2.5 stating that with HOMA-IR value as 1.87, pregnant women were 2.5 times more likely to develop gestational diabetes mellitus or hypertensive disorders of pregnancy with advancing gestation. It was observed that HOMA-IR values increased with increase in BMI in present study with p value-0.013, thus was found statistically significant. Out of 72 patients having HOMA-IR ≥ 1.87 , 32 patients developed either GDM/HTN which accounted for 45% of women who developed gestational diabetes mellitus or hypertensive disorders in pregnancy. There was an increasing trend in HOMA-IR at 11-14 weeks period of gestation in women who later developed gestational diabetes mellitus or hypertensive disorders in pregnancy. Out of 9 patients having gestational hypertension, 7 patients were having HOMA-IR ≥ 1.87 , which accounted for 78% of patients developing gestational hypertension (HTN) in pregnancy. HOMA-IR was a useful marker in predictive gestational hypertension (p value <0.01). Out of 32 patients having gestational diabetes mellitus, 26 patients were having HOMA-IR ≥ 1.87 , which accounted for 81% of patients developing gestational diabetes mellitus (GDM) in pregnancy. HOMA-IR was a useful marker in predicting gestational diabetes mellitus (P value <0.01). The combined parameters of study showed 100% sensitivity and 100% negative predictive value for predictability of GDM/HTN in pregnancy.

Conclusion: HOMA-IR can be used to predict GDM/Hypertensive disorders of pregnancy at 11-14 weeks gestation with reasonable accuracy. Combined screening algorithm with HOMA-IR, MAP and uterine artery Doppler has limited role and may help only in select high risk population. The prospect of screen positive women being given low dose aspirin (75mg) and advice regarding appropriate dietary management to help prevent the development of hypertensive disorders/GDM in later gestation needs to be explored by larger trials.

Keywords: Insulin resistance; Gestational diabetes mellitus; Hypertensive disorders of pregnancy; Uterine artery doppler.

Introduction

Thousand years of evolution has provided mammals, including humans, with a carefully orchestrated set of metabolic changes during pregnancy that serve to enhance maternal metabolic efficiency and delivery of nutrients to the fetus during feeding, while at the same time accentuating mother's ability to use her own stored fat as an energy source during fasting. Although pregnancy is a carbohydrate intolerant state, only a small proportion of pregnant women (3-5%), develop GDM. Insulin resistance (or inverse of insulin sensitivity) is characterized by diminished

glucose response to the metabolic actions of insulin. As pregnancy advances, the increasing tissue resistance to insulin creates a demand of more insulin. In most women insulin resistance requirements are readily met, so the balance between insulin supply and resistance to the effects of insulin is maintained. However, if resistance becomes dominant due to impaired insulin secretion, hyperglycemia develops.

Gestational diabetes mellitus is defined as glucose intolerance with onset or first recognition during pregnancy [1,2]. The definition applies whether insulin or diet

modification is used for treatment and whether or not the condition persists after pregnancy. It does not exclude possibility that unrecognized glucose intolerance may have preceded or begun concomitantly with pregnancy [3].

In women with limited β cell secretory capacity (e.g. women with diabetes mellitus) maternal metabolic responses to pregnancy are abnormal in ways that can be detrimental to mother and developing infant. Although other metabolic and physiological parameters like lipid metabolism, vascular endothelial function and gene expression are partially regulated by insulin action, these parameters are not considered when assessing insulin sensitivity.

The concept of insulin resistance is relatively easy to understand but determining precisely who has insulin resistance is more complicated. Normal insulin resistance varies widely and is influenced by age, ethnicity and obesity. Over the past decades there has been growing interest in role of insulin resistance related to complications in pregnancy.

Hypertensive disorders of pregnancy are responsible for significant (2-25%) proportion of maternal and perinatal morbidity. It one of the leading causes of maternal deaths in developing countries. Increased insulin resistance leads to poor placental development, with maternal and placental processes contributing in a vicious cycle of inflammation and endothelial dysfunction giving rise to pre-eclampsia. Hence, insulin resistance should be the focus for clinical and research strategies for prevention of pre-

eclampsia and related pregnancy complications and their cardiovascular sequelae [4].

Hypertensive disorders of pregnancy and gestational diabetes (GDM) are all associated with increased risks of poor maternal and perinatal outcomes. Pregnant women with gestational diabetes have been shown in population studies to have increased risk of pre-eclampsia compared with non-diabetic women and vice-versa. It has been hypothesized that the association could be due to at least in part, to insulin resistance. Although insulin resistance is a physiologic phenomenon in normal pregnancy, in predisposed individuals this could lead to hyper-insulinemia with development of GDM, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia and eclampsia) or both.

Increasing amount of data suggests that greater than normal increase in insulin resistance can be a common pathway in development of hypertensive disorders of pregnancy and gestational diabetes (GDM) along with long term risk of cardiovascular disease and diabetes. Lighter needs to be shed on the effect of possible interventions to curb it. Correlation does not necessarily imply causation, but the development of possible preventive strategies and therapeutic interventions. More specifically lifestyle modification such as carefully selected diet, encouraging physical activity, pharmacologic therapy with aspirin, after finding group of individuals with greater genetic predisposition would help to decrease the effects of insulin resistance. In the present

study, the role of insulin resistance in early prediction of gestational diabetes mellitus and hypertensive disorders in pregnancy. Researchers attempted to study the correlation of insulin resistance at 11 to 14 weeks period of gestation and outcome in terms of GDM and hypertensive disorders in pregnancy and explore the possible use of insulin resistance in their early prediction [5].

Aims and objectives

Aim

To find out if insulin resistance can be an effective screening tool to predict gestational diabetes mellitus and hypertensive disorders in pregnancy (gestational hypertension, pre-eclampsia and eclampsia).

Objectives

- **Primary objective**
Prediction of gestational diabetes mellitus and hypertensive disorders in pregnancy using insulin resistance at 11-14 weeks of gestation.
- **Secondary objective**
To evaluate if combined maternal markers (insulin resistance, mean arterial pressure and uterine artery Doppler pulsatility index) in first trimester of pregnancy (11-14 weeks) is more effective in predicting the same.

Materials and methodology

This study was a prospective observational study done from December 2015 to November 2016 in the Department of Obstetrics and Gynecology, Dr. TMA Pai Hospital, Udupi.

The study population consisted of singleton pregnant women booked between 11-14 weeks of gestation with viable pregnancy and excellent dating. It was a Hospital based prospective observational study conducted during 1 Year (01/12/2015-30/11/2016). The inclusion criteria were Low risk antenatal women with singleton pregnancies booked from 1st trimester, willing to deliver in the hospital and also willing to participate in the study.

And exclusions were Women reluctant to participate, Women with multiple pregnancies, Women with pre-gestational diabetes, Women with chronic hypertension, Women with renal disease, Smokers or those with history of illicit drug use.

Prior to enrollment, ethical committee clearance was obtained from Manipal university Institutional ethical committee (MUEC- ECR/191/Inst/KL/2013).

Sample size

- Anticipating a sensitivity (p) of 80%, with precision (d) of 10% and prevalence of 10% of Gestational Diabetes Mellitus/Hypertensive disorders of pregnancy, with ratio of 1:3 for the positives to negatives-

$$n = \frac{\frac{4p(1-p)}{d^2}}{(1 - prevalence)}$$

- a minimum of 40 positives (n) to 120 negatives (3n) was needed.
- Hence sample size required for current study=160.

Data analysis and statistical methods

- Data was entered in Microsoft excel data sheet and analyzed using Scientific Package for Social Sciences (SPSS) 20 software.
- Analysis of demographic data and baseline characteristics was done using percentages for categorical data and mean and standard deviation for continuous data.
- Analysis of categorical variable was done by chi-square test and continuous variables were compared using independent sample T test or The Mann-Whitney U Test and repeated measure ANOVA test.
- Receiver operating character (ROC) curve was used for optimal cut-off points for the maternal and foetal outcomes.
- Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, Likelihood Ratios and area under curve (AUC) were reported.
- P value <0.05 was considered to be statistically significant.

Methodology

All pregnant women meeting inclusion criteria at 11-14 weeks' gestation and were willing to participate were recruited in the study. A written informed consent about patient's participation and consent for prospective data collection of the pregnancy outcomes were taken from the patient. Dating of the pregnancy was checked and patients with excellent dating were included. Dating was considered excellent when patient

had regular cycles with known LMP and first scan was corresponding to period of gestation according to LMP. Detailed maternal history and clinical examination was done. Maternal data collected included age, parity, weight, height, BMI and obstetric history.

Maternal weight was recorded using digital scale; height was measured using a stadiometer at 11-14 weeks period of gestation. Body mass index (BMI) was calculated from these values by using following formula:

$$BMI = \frac{\text{Weight in Kilograms}}{(\text{Height in meters})^2}$$

Blood pressure was measured in semi-recumbent position with arm roughly at the level of heart with mercury sphygmomanometer during 11-14 weeks' period of gestation. First Korotkoff sound was taken as systolic pressure and fifth Korotkoff sound was taken as diastolic pressure.

$$\text{Mean Arterial Pressure} = \frac{2 \times \text{Diastolic pressure} + \text{Systolic P}}{3}$$

After taking consent from pregnant women at 11-14 weeks, during routine first trimester ultrasound to measure nuchal translucency (NT), uterine artery Doppler using ultrasound machine Philips Clearview series 350 was done. Following initial assessment of fetal biometry and NT, utero-placental circulation was assessed.

Uterine artery Doppler measurement was done using color Doppler to visualize the uterine artery ascending at the level of the internal cervical os. Once a consistent uterine artery waveform was recorded, right and left

uterine artery pulsatility indices were measured (over three cycles). At the same time, blood samples were collected for fasting blood sugar and fasting insulin levels. Insulin resistance was calculated by HOMA formula. 4ml of overnight fasting venous sample was taken for fasting blood sugar and estimated using glucose oxidase and peroxidase method by fully automated analyzer Hitachi 902. Fasting insulin was measured by specific chemi-luminescence test [6].

Insulin resistance was calculated by Homeostasis Model assessment (HOMA) formula [7].

HOMA formula

$$HOMA-IR = \frac{\text{Fasting insulin} \left(\frac{mIU}{L} \right) \times \text{Fasting glucose} \left(\frac{mg}{dl} \right)}{405}$$

HOMA-IR at cutoff of ≤ 2 had a sensitivity of 94.5% and NPV of 95.1%. The meaningful part of the acronym is the IR “Insulin Resistance” part. This calculation marks for both the presence and extent of any insulin resistance that you might currently express. It is a terrific way to reveal the dynamic between your baseline (fasting) blood sugar and the responsive hormone insulin. High HOMA-IR relates to your level of insulin resistance. The higher the number, the more resistant you are to the message of insulin.

Patients were followed at each visit with regular blood pressure measurement. If patient was detected to have gestational hypertension, pre-eclampsia/eclampsia, patient was followed up with necessary

investigations (like urine protein, liver function test, renal function test, coagulation profile and growth scan) as per the standard of care for hypertensive disorders of pregnancy.

During antenatal visit at 24-28 weeks' gestation, one step GTT (DIPSI) was done by giving 75g oral glucose load, without regard to the time of the last meal. A venous blood sample was collected at 2 hours for estimating plasma glucose by the glucose oxidase-peroxidase method. GDM was diagnosed if 2hr plasma glucose was ≥ 140 mg/dl. In our hospital, 75g glucose has been customized and made available for patients.

Patients were managed with diabetic diet with or without insulin depending on the blood sugar values.

Feto-maternal outcomes of pregnancy were noted. Birth weights of babies of women who delivered at hospital were noted.

Result

A total of 209 cases booked at 11-14 weeks who had done HOMA-IR were included in study.

- 2 were excluded from the study in view of abortion.
- 9 women were lost to follow up.

Remaining 198 had been monitored with GCT and regular BP monitoring.

165 delivered in the study period and 118 underwent uterine artery Doppler evaluation too.

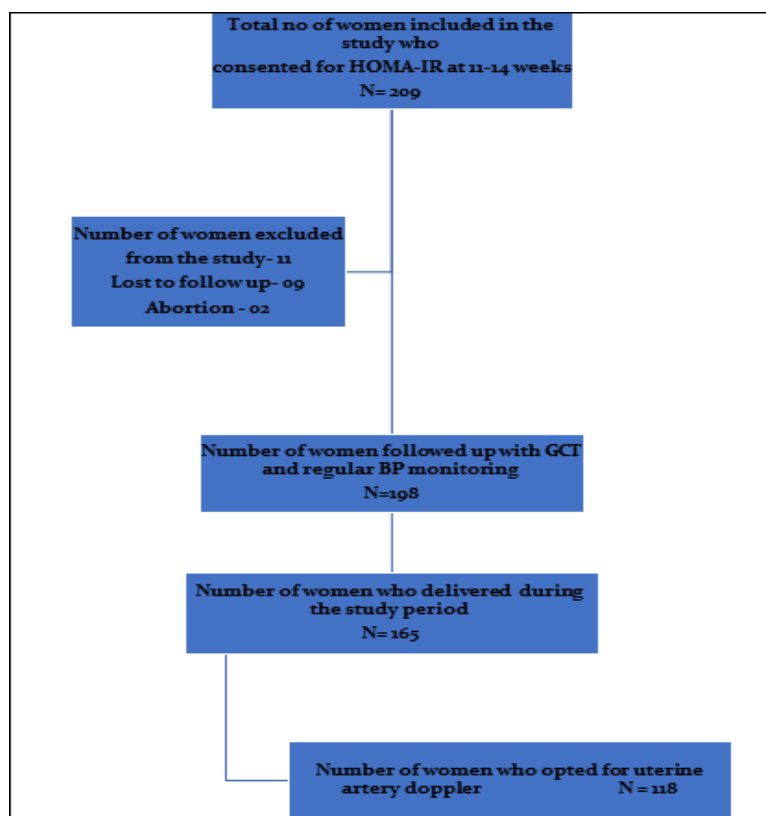


Figure 1: Flowchart of cases recruited.

Baseline characteristics of the study population obtained at the time of their study recruitment

The mean maternal age was 28 ± 4 years with maximum cases (48.5%) distributed between 25-29 years.

Age

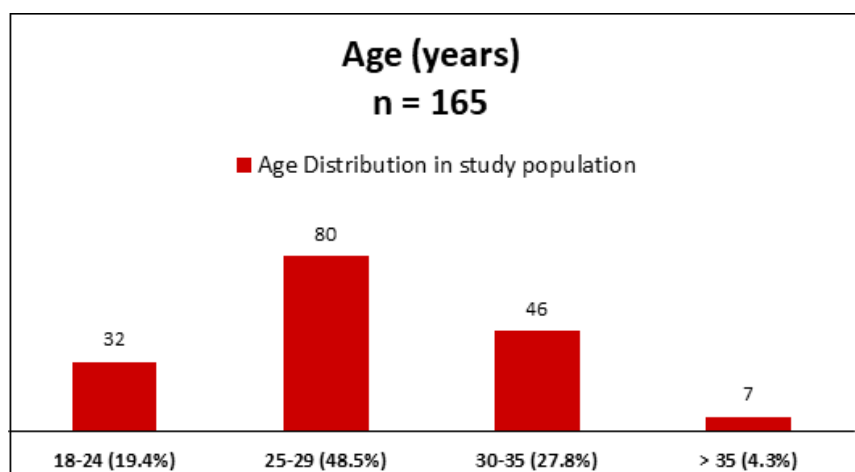


Figure 2: Age distribution in study population.

Parity

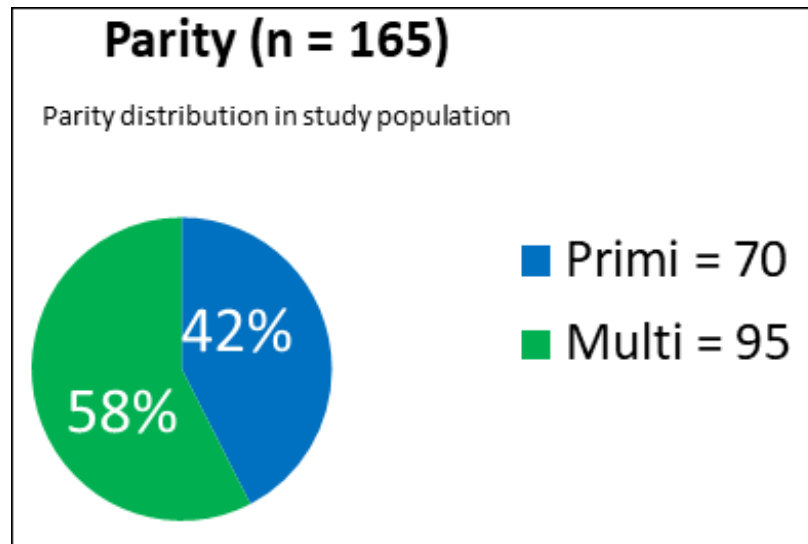


Figure 3: Parity distribution in study population.

Among 165 women finally included in the study, 70 were primi gravidae and 95 were multi gravidae.

Anthropometric characteristics

In the study population,

- Mean BMI was 21.8 ± 4.1 kg/m²
- Mean height was $1.57 (\pm) 0.46$ m
- Mean weight was $53.8 (\pm) 9.8$ kg
- Majority of women (44.8%) had BMI in the range 20-24.9.

	BMI (kg/m ²)	Sample Size (n=165)	Percentage %
Underweight	<18.50	55	33.3
Normal weight	18.50-24.99	74	44.8
Overweight	25.0-29.9	33	20
Obese	>30	3	1.9

Table 1: BMI in study population.

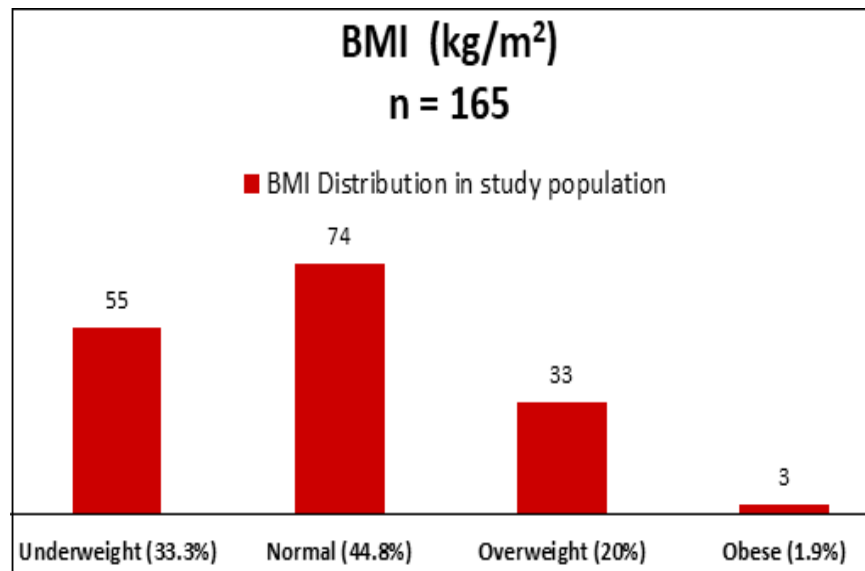


Figure 4: BMI distribution in study population.

Mean arterial pressure (MAP)

BP measurements were taken at 11-14 weeks period of gestation

- The mean Systolic pressure (SBP) mean was 115.9 ± 7.5 mmHg
- The mean Diastolic pressure (DBP) mean was 71.5 ± 3.7 mmHg
- The mean of mean arterial pressure (MAP) was 85.8 ± 3.6 mmHg

Screening parameters of the study participants

HOMA-IR parameters

The mean fasting glucose for entire population was 84.8 ± 7.4 (mg/dL). As mean values for fasting insulin and insulin resistance exceeded the standard deviation, the median and inter-quartile ranges were considered.

Characteristic	Median	Inter-quartile range
Fasting Insulin (mIU/l)	8.4	5.7, 11.7
HOMA-IR	1.7	1.2, 2.4

Table 2: The median and inter-quartile range of fasting insulin and HOMA-IR.

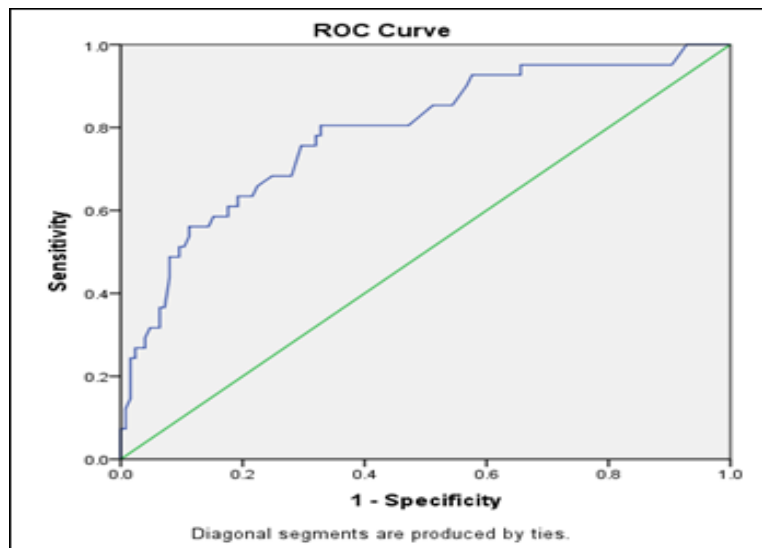


Figure 5: ROC curve for HOMA-IR.

Diagnostic accuracy of HOMA-IR

1.87 as cut-off for HOMA-IR showed sensitivity of 80.5%, specificity of 67.2%, and positive predictive value of 44.6% and negative predictive value of 91.3%. Hence,

HOMA-IR value 1.87 was taken as standard to divide the study population into 2 groups and analyze

- HOMA-IR <1.87
- HOMA-IR $\geq$ 1.87

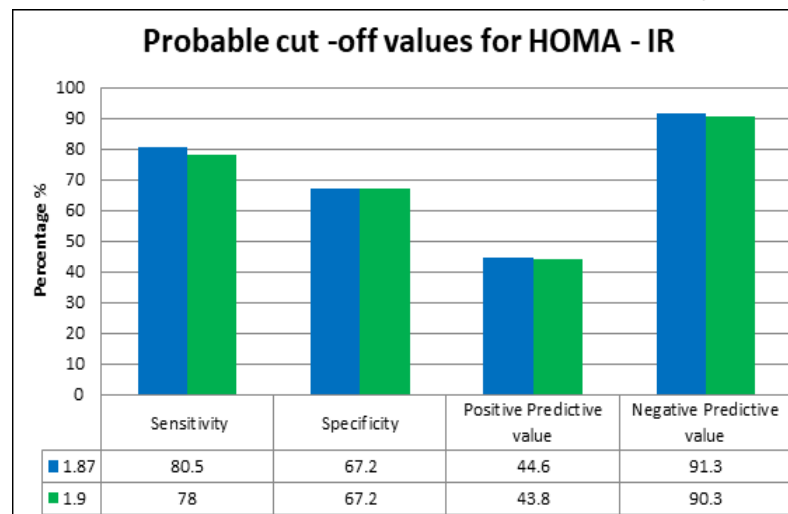


Figure 6: Comparative cut-off for HOMA-IR in study population.

Likelihood ratio by taking HOMA-IR cut off as 1.87 at 11-14 weeks of gestation was 2.5 stating that with HOMA-IR value as 1.87, pregnant women were 2.5 times more likely

to develop gestational diabetes mellitus or hypertensive disorders of pregnancy with advancing gestation.

HOMA-IR in relation to general parameters of study population

It was observed that HOMA-IR values increased with increase in BMI in present study with p value-0.013, thus was found statistically significant.

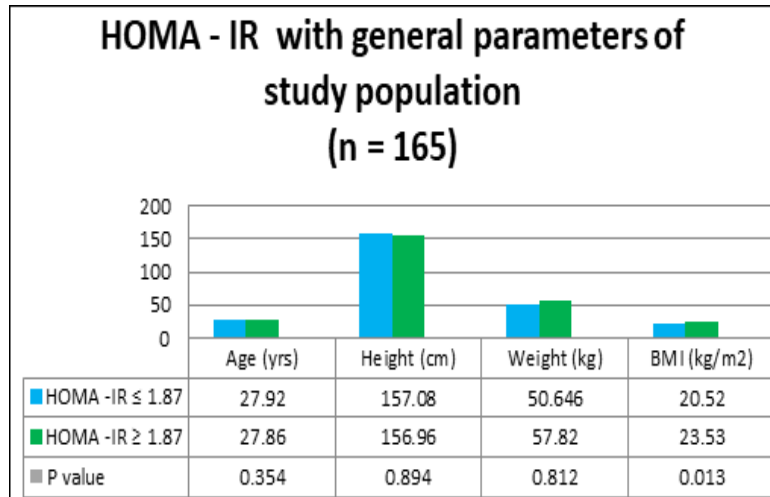


Figure 7: HOMA-IR in relation to general parameters of study population.

HOMA-IR in relation to follow up parameters of study

One step GTT (DIPSI)

The mean blood glucose following one step GTT (DIPSI) at 24 weeks period of gestation was 110.4 ± 26.4 mg/dL. One step GTT (DIPSI) was higher with higher insulin resistance values, but was not statistically significant (p value=0.139).

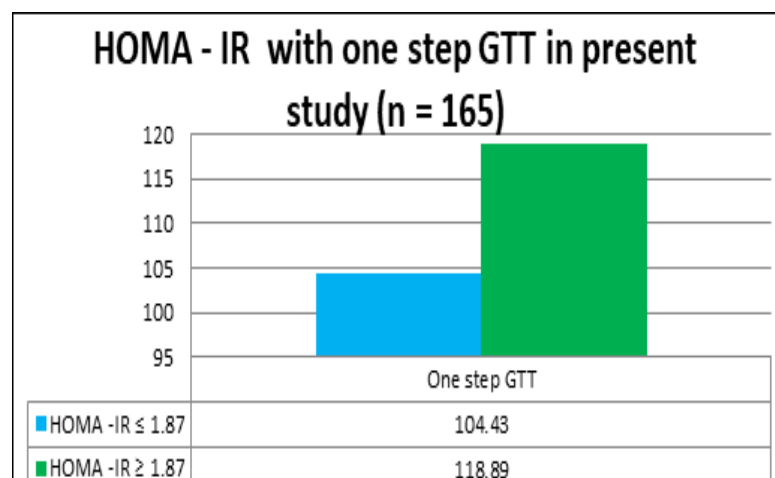


Figure 8: HOMA-IR with one step GTT in study population.

Analysis in relation to obstetrical outcome

Positives were those women who developed either GDM/HTN during their pregnancy period.

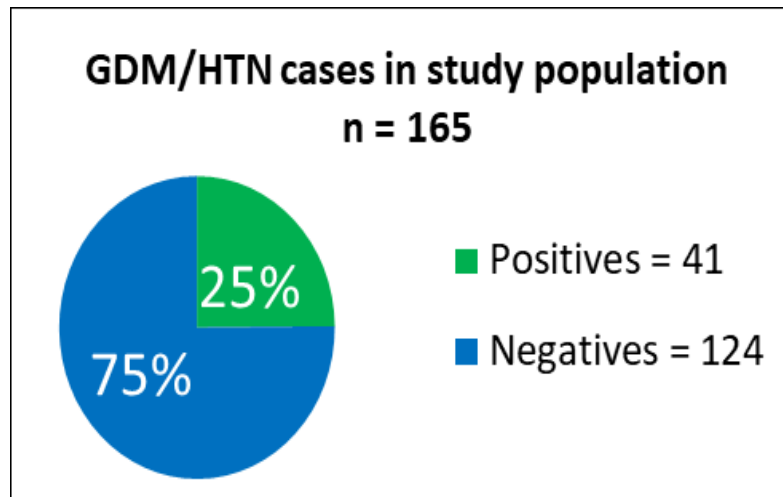


Figure 9: Distribution of cases in study population.

GDM/HTN cases in women with HOMA-IR <1.8

Out of 93 patients having HOMA-IR <1.87 at 11-14 weeks of gestation, 9 patients developed either GDM/HTN in late pregnancy period.

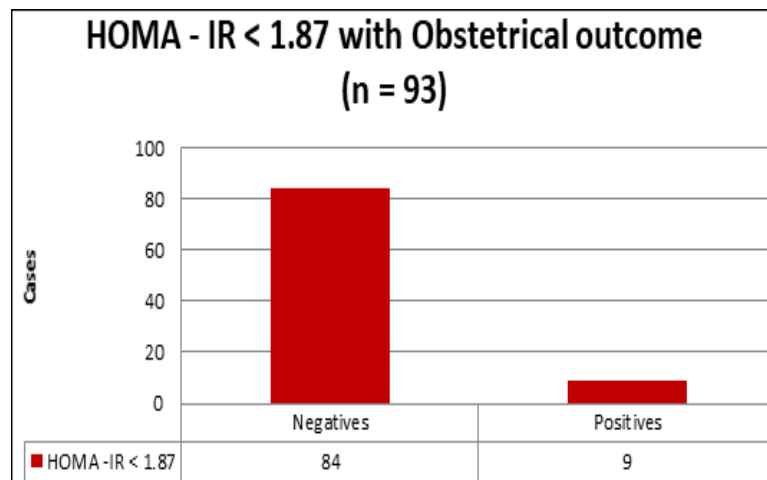


Figure 10: HOMA-IR <1.87 in relation to obstetrical outcome.

GDM/HTN cases in women with HOMA-IR ≥ 1.87

Out of 72 patients having HOMA-IR ≥ 1.87, 32 patients developed either GDM/HTN which accounted for 45% of women who developed gestational diabetes mellitus or hypertensive disorders in pregnancy.

There was an increasing trend in HOMA-IR at 11-14 weeks period of gestation in women who later developed gestational diabetes mellitus or hypertensive disorders in pregnancy.

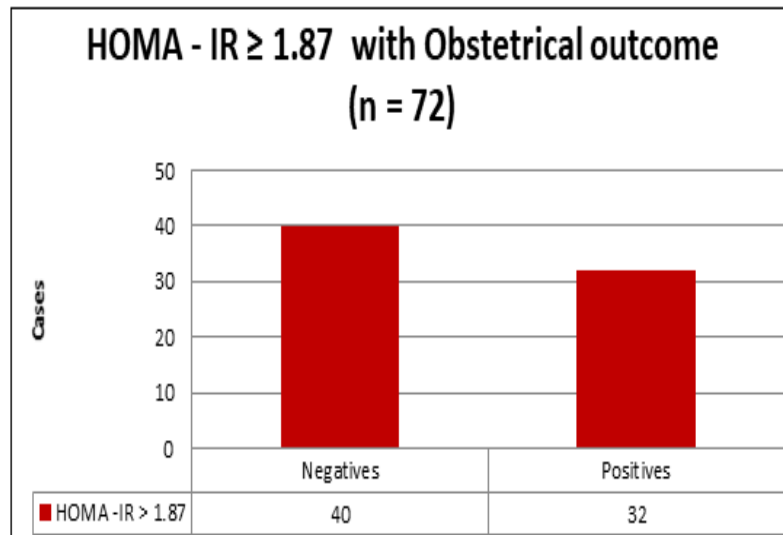


Figure 11: HOMA-IR ≥ 1.87 in relation to obstetrical outcome.

Analysis in relation to specific obstetrical outcome

Gestational hypertension

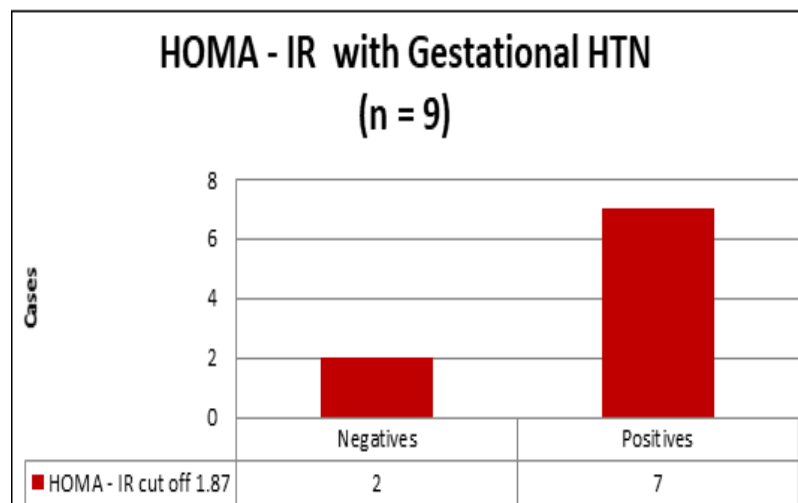


Figure 12: HOMA-IR cut off 1.87 in relation to gestational hypertension.

Out of 9 patients having gestational hypertension, 7 patients were having HOMA-IR ≥ 1.87 , which accounted for 78% of patients developing gestational hypertension (HTN) in pregnancy.

HOMA-IR was a useful marker in predictive gestational hypertension (p value <0.01)

Gestational Diabetes Mellitus (GDM)

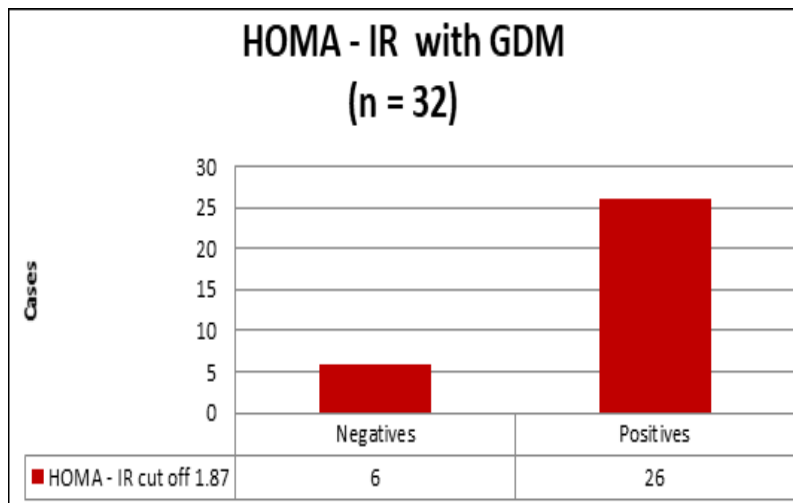


Figure 13: HOMA-IR cut off 1.87 in relation to gestational diabetes mellitus (GDM).

Out of 32 patients having gestational diabetes mellitus, 26 patients were having HOMA-IR ≥ 1.87 , which accounted for 81% of patients developing gestational diabetes mellitus (GDM) in pregnancy.

HOMA-IR was a useful marker in predicting gestational diabetes mellitus (P value <0.01)

IUGR

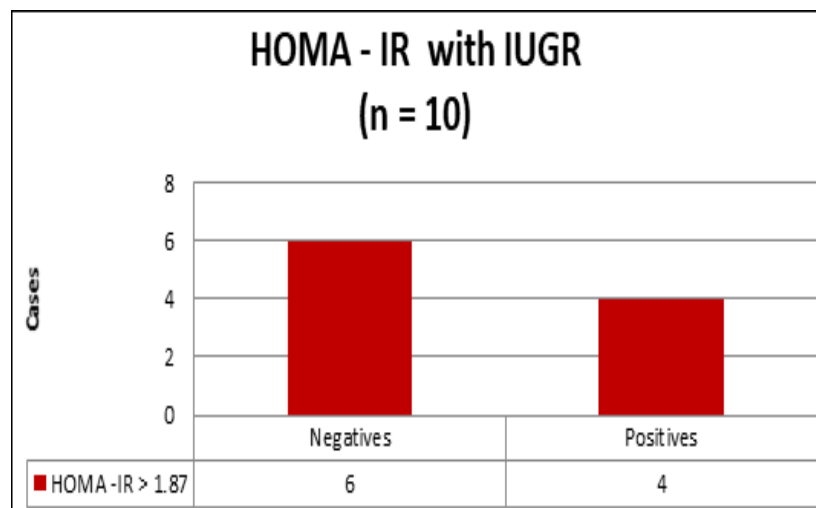


Figure 14: HOMA-IR cut off 1.87 in relation to Intra uterine growth restriction (IUGR).

Out of 10 pregnant women who had IUGR foetuses, 4 were having HOMA-IR ≥ 1.87 which accounted for 40% of antenatal women having IUGR in pregnancy. This was not statistically significant and was not useful for prediction of IUGR.

Oligohydramnios

Oligoamnios was seen in 2 women with HOMA-IR ≥ 1.87 which accounted for 50% of women with oligoamnios in pregnancy. HOMA-IR was not a good predictor of oligoamnios too.

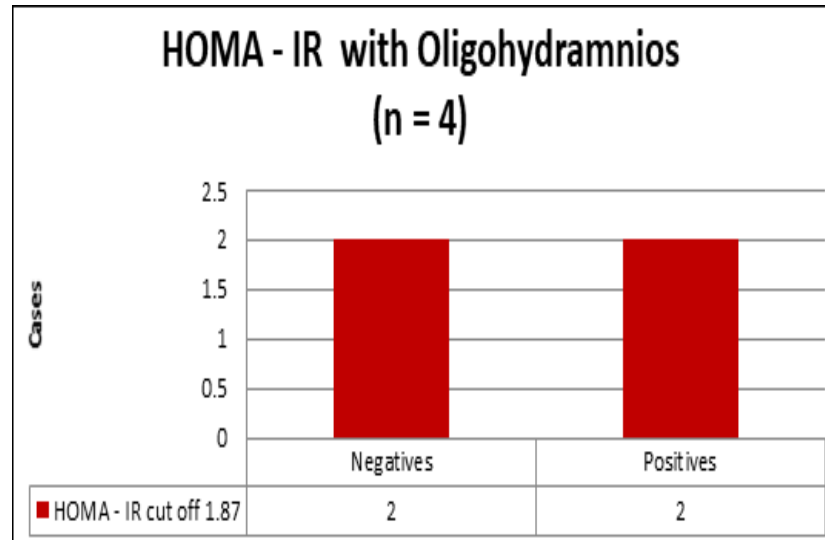


Figure 15: HOMA-IR cut off 1.87 in relation to oligohydramnios.

Analysis in relation to general obstetrical outcome

Mode of delivery

It was observed that HOMA-IR had no correlation with mode of delivery.

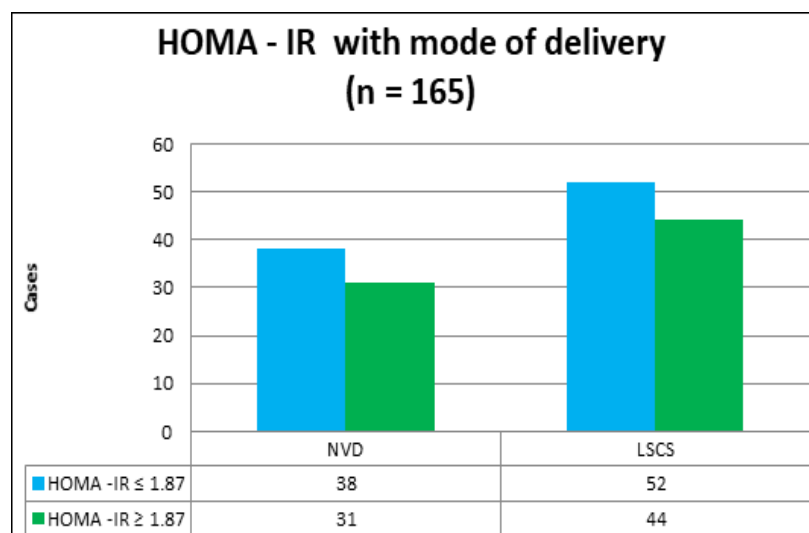


Figure 16: HOMA-IR cut off 1.87 in relation to mode of delivery in study population.

Birth weight

It was observed that HOMA-IR had no correlation to birth weight at delivery too.

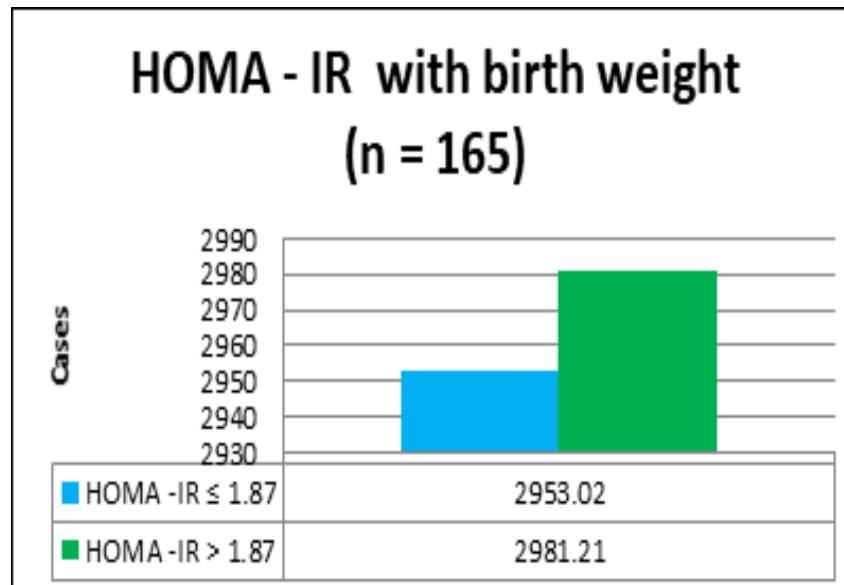


Figure 17: HOMA-IR cut off 1.87 in relation to birth weight in study population.

Uterine artery doppler parameters

As mean values for Right and left uterine artery Doppler pulsatility index (PI) was exceeding standard deviation, the median and inter-quartile were considered.

Parameter	Median	Inter-quartile range
Right uterine artery Doppler	1.3	0.9,1.6
Left uterine artery Doppler	1.3	1.0,1.8

Table 3: Mean values for right and left uterine artery doppler pulsatility index.

ROC curve for uterine artery doppler

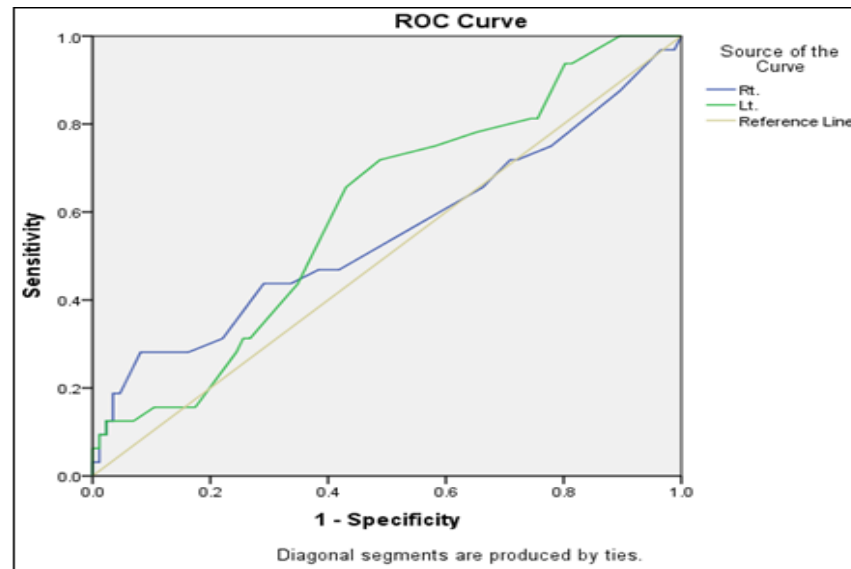


Figure 18: ROC curve for uterine artery doppler.

Diagnostic accuracy of uterine artery doppler

In a study done titled “Uterine artery Doppler at 11-14 weeks of gestation and its prediction of pre-eclampsia and IUGR” on 220 patients at Dr. TMA Pai Hospital, Udupi, the optimal cut-off for uterine artery Doppler PI was found to be 1.3. Likelihood ratio using either right or left uterine artery Doppler PI cut off as 1.3 was 1.14 with diagnostic accuracy of only 55%.

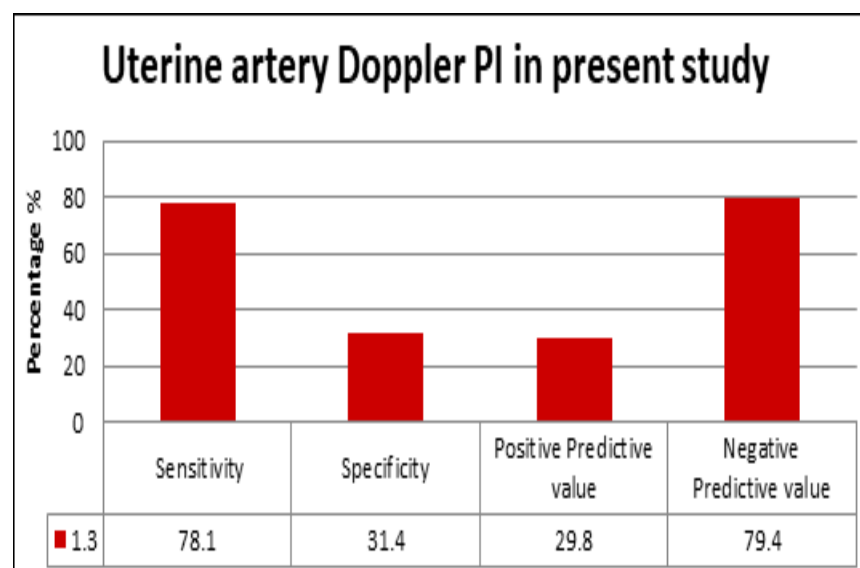


Figure 19: Uterine artery doppler PI in present study.

Analysis in relation to obstetrical outcome

There was no statistically significant correlation of uterine artery Doppler (PI) with positive cases. Hence, it was disregarded as a diagnostic parameter alone.

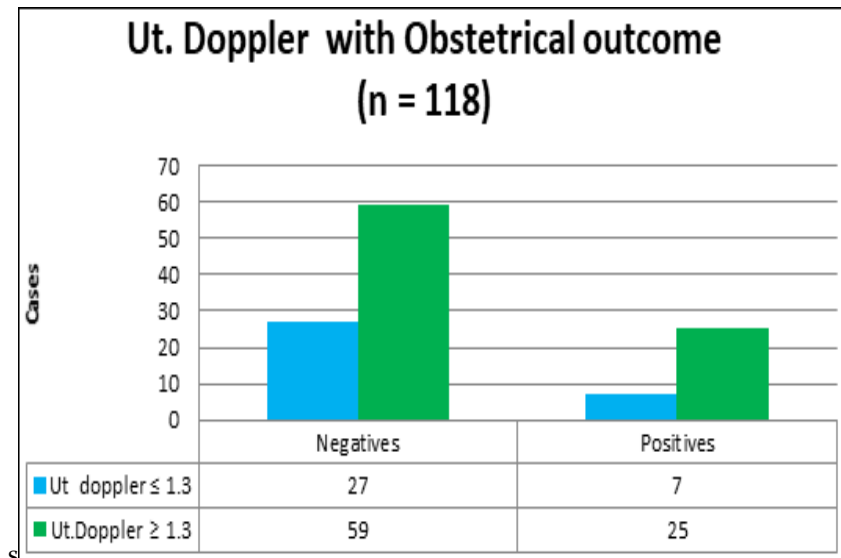


Figure 20: Uterine artery doppler PI in relation to cases in present study.

Efficacy of Mean arterial Pressure (MAP)

With mean arterial pressure alone diagnostic accuracy was only 59%.

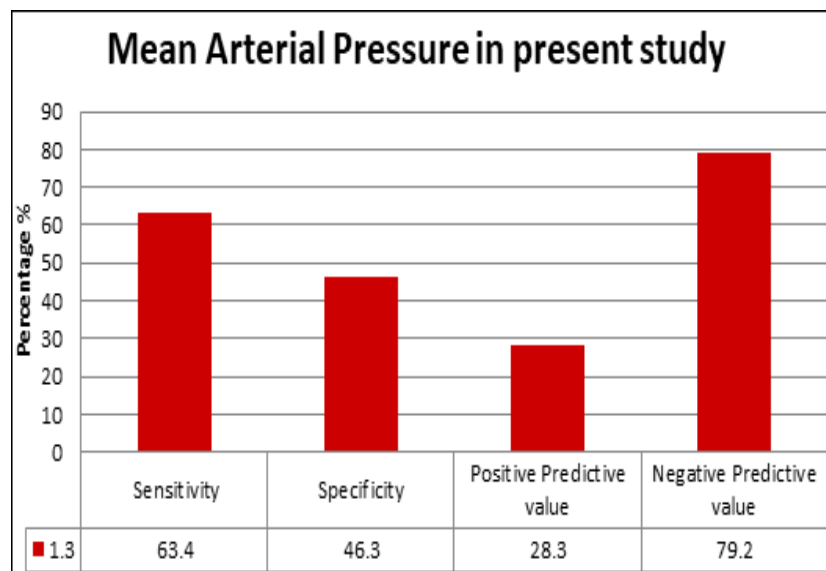


Figure 21: Mean arterial pressure (MAP) in present study.

Diagnostic accuracy combined efficacy of Mean Arterial Pressure (MAP) and HOMA-IR: diagnostic accuracy

The diagnostic accuracy was only 48.2% hence combined disregarded as a prognostic indicator.

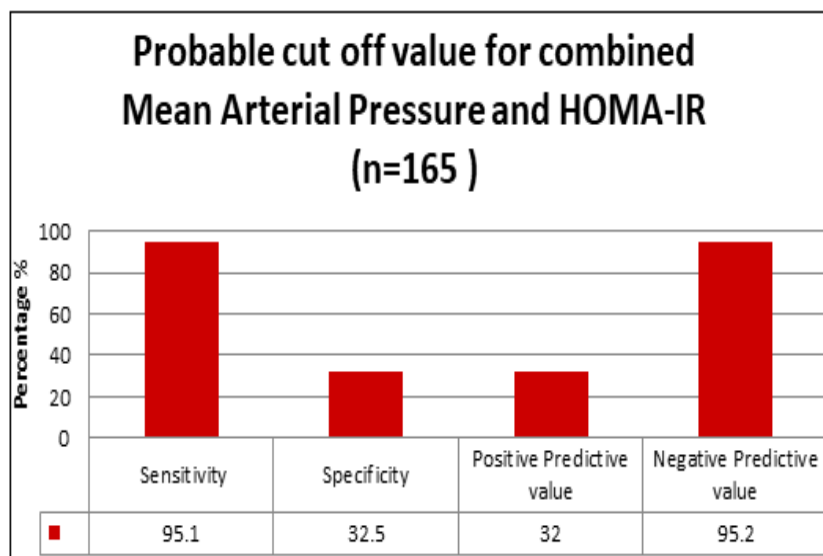


Figure 22: Diagnostic accuracy combined efficacy of Mean Arterial Pressure (MAP) and HOMA-IR.

Combined efficacy of uterine artery doppler and HOMA-IR: diagnostic accuracy

Likelihood ratio with taking combined either right or left uterine artery Doppler PI cut off as 1.3 and HOMA-IR cut-off as 1.87 was 1.4, hence not useful for prediction of GDM/HTN.

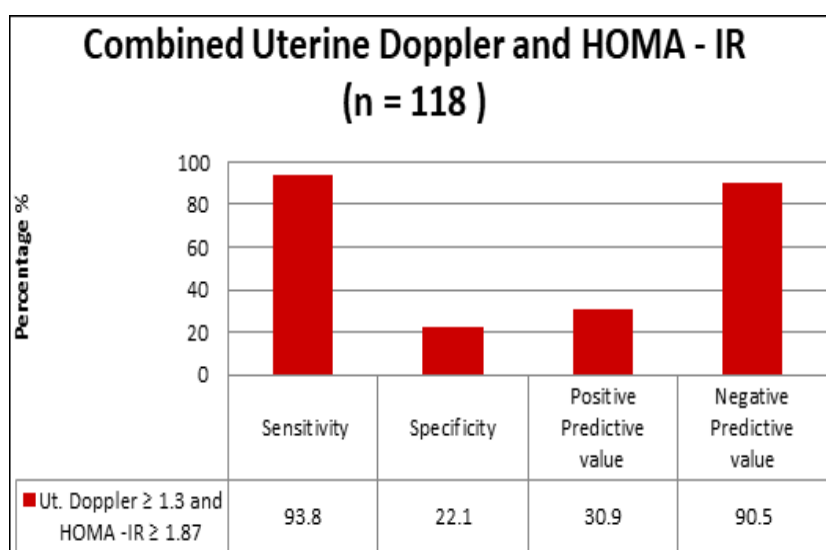


Figure 23: Combined efficacy of uterine artery doppler and HOMA-IR.

Combined efficacy of uterine artery doppler, Mean arterial Pressure (MAP) and HOMA-IR

In the present study

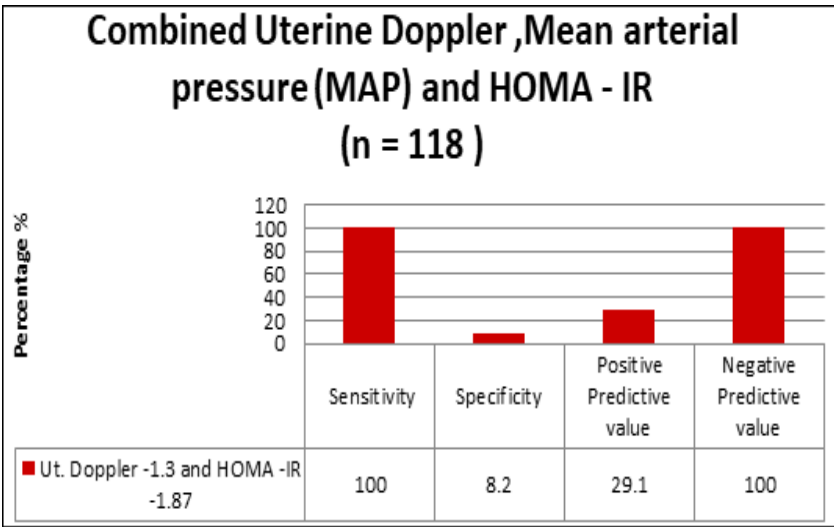


Figure 24: Combined efficacy of uterine artery doppler, Mean Arterial Pressure (MAP) and HOMA-IR.

The combined parameters of study showed 100% sensitivity and 100% negative predictive value for predictability of GDM/HTN in pregnancy. It is not useful for prediction of GDM/HTN in pregnancy in general low risk population. Nevertheless, combined parameters may be used as multivariate screening algorithm in select population at high risk of hypertensive disorders of pregnancy and gestational diabetes mellitus.

Discussion

In the present study, reseachers tried to find the correlation of insulin resistance in pregnancy at end of first trimester with adverse pregnancy outcomes specifically gestational diabetes mellitus and hypertensive disorders of pregnancy. Detection of insulin resistance is difficult clinically and so surrogate markers have been developed. These include fasting glucose to

insulin ratio (G/I) ratio, HOMA and QUICKI. HOMA is an index of insulin resistance while G/I ratio and QUICKI are indices of insulin sensitivity. Hence as the insulin resistance of an individual increases, there is an increase in the HOMA level and decrease in the G/I and QUICKI values. Although each of the above have been advocated in recent studies, HOMA values are most reliable as it has correlated most closely with clamp techniques.

Researchers conducted similar study, in determining the differences in insulin sensitivity in pregnancy [8]. Researchers observed that:

- HOMA-IR values in overweight women with normal glucose tolerance (NGT) and in women with GDM were significantly (p <0.01) higher than

those in normal-weight women with normal glucose tolerance (NGT).

- HOMA-IR in women with GDM increased significantly ($p < 0.05$) during pregnancy, but HOMA-IR values in normal-weight and overweight women with NGT did not change significantly with advancing gestation.

In present study

- In the study also out of 32 patients having GDM 26 patients were having HOMA-IR > 1.87 which accounted for 81% of patients developing GDM in pregnancy.

HOMA-IR was a useful marker in detecting GDM (p value < 0.01)

- It was observed that HOMA IR values positively correlated with BMI in present study with p value -0.013 . This could be due to increased insulin resistance in women who were obese.

Above table clearly shows a difference between Indians and Japanese. For a similar glucose control, the insulin levels required in Indians was much higher to maintain glucose homeostasis. Hence South East Asians have higher threshold for these indices in comparison with other Asians and are more insulin resistant.

Evaluation of glucose in Cowett's study was by prime constant infusion technique to measure the glucose turnover while Butte evaluated glucose levels in fasting state. The study was not comparable to these studies as

these values were recorded in third trimester of pregnancy.

The study by Cowett, et al. depicts that insulin resistance rises as patient advances to the last trimester. On the contrary in the study by Buette, et al. there was less insulin resistance with low HOMA values. This can be explained by the fact that there remains a difference considering the ethnicity of the population included in both groups. The study by Buette had a mixture of whites, Africans, Americans, Hispanics and Asians while the study included only Indians. Also, the sample size considered in the studies was too low to come to a conclusion. A study by Eyal Sivan, et al. had sought to determine the effect of insulin on fat metabolism during and after normal pregnancy by conducting euglycaemic-hyperinsulinemic clamp in combination with infusion of stable isotope and estimating indirect calorimetry and the glycerol turnover. The increased insulin levels of the 3rd trimester in comparison with the 1st and 2nd trimesters may reflect in part the relative insensitivity for insulin peripherally or the presence of human chorionic somatomammotrophin (hCS).

Hence, as the caloric expenditure increases during late pregnancy, it follows that any reduction in maternal carbohydrate utilization resulting from insulin resistance must be accompanied by an increase in utilization of another fuel, presumably fat. This is explainable by the fact that in late gestation, rising concentrations of human chorionic somatomammotrophin, prolactin, cortisol and glucagon exert anti insulinogenic and lipolytic effect that promote greater use

of alternative fuels, especially fatty acids by the peripheral tissues.

In present study

The mechanism may partly explain higher values of one step GTT with higher HOMA-IR values but was not statistically significant (P value=0.139).

Correlation with BMI

In the study, insulin resistance index was higher in obese pregnant women. Hence, obesity was an independent risk factor for insulin resistance.

Studies by Ravi Retnakaran, et al. [9] have shown that ethnicity modifies the effect of obesity on insulin resistance in pregnancy. Three populations of Asians, South Asians and Caucasians (Asian are more predisposed than South Asians) were compared. Asian women compared to Caucasians are independently associated with increased insulin resistance in late pregnancy. Pre-pregnancy BMI has a much greater effect on insulin resistance in pregnancy in Asian women compared to Caucasians. Probably this difference of observation could be due to longitudinal assessment involved in Satoko and study while Ravi, et al. study was a cross sectional assessment.

Researchers found lean GDM characterised by increased insulin resistance and inadequate insulin secretion which persisted even after delivery. But the lean GDM women of study were compared to only normal and IGT (impaired glucose tolerance) women, so the difference obesity made in an already

insulin resistant population like GDM could not be assessed. A similar comparative group are women with PCOS, wherein even the lean population exhibit insulin resistance and obesity is not an additive factor for an individual being insulin resistant.

Correlation with gestational diabetes mellitus (GDM)

GDM typically develops in the second half of pregnancy in parallel with the development of insulin resistance. All pregnant women become relatively insulin resistant in the third trimester but less than 10% develop GDM.

The GDM women of study showed higher fasting blood glucose, insulin levels and HOMA levels. Out of 32 patients having GDM 26 patients were having HOMA-IR >1.87 which accounted for 81% of patients developing GDM in pregnancy. HOMA-IR was a useful marker in predicting GDM (p value <0.01).

In another study by Martinez et al. who sought to evaluate early pregnancy insulin resistance and subsequent gestational diabetes mellitus, it was observed that women with gestational diabetes diagnosed at 24-28 weeks of gestation demonstrated higher levels of fasting glucose, fasting insulin and HOMA at 17 weeks of pregnancy. In the study doctors tried to evaluate even earlier at 11-14 weeks period of gestation. Buchanan, et al. [10] showed that mean fasting glucose and insulin levels were higher for GDM patients, hence insulin resistance was higher in comparison to controls.

In the GDM women, there is relative decrease in first phase insulin response which is the first manifestation of β cell dysfunction. There is also impaired suppression of hepatic glucose production. Both these effects become evident only after progressive decrease in insulin sensitivity which is seen in late gestation, resulting in hyperglycaemia. Early risk stratification of GDM in pregnant women with obesity and targeted intervention using lifestyle advice with or without metformin could improve glucose tolerance compared to standard antenatal care. Probiotics are a relatively new intervention, which are assessed by mothers' metabolism, and can reduce blood sugar levels, prevent gestational diabetes and reduce the maternal and fetal complications resulting from it. Dietary advice interventions for pregnant women may be able to prevent GDM.

Correlation with hypertensive disorders of pregnancy

There is growing evidence that hypertension in pregnancy is related to insulin resistance and carbohydrate intolerance [11,12]. Both proteinuric and non proteinuric hypertension of pregnancy predicts future essential hypertension and diabetes, disorders strongly related to glucose intolerance and insulin resistance. In addition, there is proven elevated incidence of hypertension among women with gestational diabetes mellitus [10,13].

In the study, out of 9 patients having gestational hypertension 7 patients were having HOMA-IR ≥ 1.87 which accounted for

78% of patients developing hypertension in pregnancy. HOMA-IR was a useful marker in detecting gestational HTN (p value <0.01). There were two studies in accordance with pre-eclampsia and insulin resistance by: Ralph N Roberts, et al. and Bjorg Lorentzen, et al. [11]. It can be observed, that the mean fasting glucose and insulin levels in the study by Robert, et al. is much lower than the study values. Doctors concluded that pre-eclampsia is not associated with increase in insulin resistance, while reverse was true in study. Bjorg Lorentzen, et al. investigated the glucose tolerance and insulin resistance in pre-eclampsia compared to normal pregnancies in response to the 75-gram oral GTT. This was comparable to obtained study with regard to increase in HOMA-IR values.

Uterine artery doppler correlation

Establishment of utero-placental circulation in 2nd trimester is not a random phenomenon, but rather a consequence of events in the 1st first trimester. This is supported by the findings of a Doppler study by Kaminopetros P, et al. in 55 pregnancies, which reported a significant decrease in measurement of the uterine artery PI done at 11-14 weeks to those at 19-22 weeks [14].

In the study by Martin, et al. 63 of 3195 pregnancies developed pre-eclampsia, 290 cases had IUGR [15] O Gomez et al. studied 999 pregnancies of which 22 developed pre-eclampsia and 37 pregnancies developed IUGR [16].

In the study, screen positives included cases having gestational diabetes mellitus and

hypertensive disorders of pregnancy but the above-mentioned studies screened only for pre-eclampsia. There were no prospective studies done using mean arterial pressure (MAP) at 11-14 weeks gestation and adverse pregnancy outcomes.

Limitations

Larger sample size would have given more definitive results where the doctors obtained clinically significant observations that were not proven statistically. No trimester specific standard values were available for insulin resistance in pregnancy according to trimesters which were included as novel markers to predict gestational diabetes mellitus and hypertensive disorders of pregnancy in this study. There was no adequate data available for these maternal serum markers.

Uterine artery doppler pulsatility index (PI) had poor patient acceptance. Also, bowel shadowing, thick abdominal wall, obese patients etc. were other hindrances

contributing to the smaller sample size with uterine artery Doppler measurements.

Conclusion

- HOMA-IR can be used to predict GDM/Hypertensive disorders of pregnancy at 11-14 weeks gestation with reasonable accuracy.
- Mean arterial pressure (MAP) and uterine artery Doppler PI when used alone, were not useful markers for prediction of GDM/hypertensive disorder of pregnancy.
- Combined screening algorithm with HOMA-IR, MAP and uterine artery Doppler has limited role and may help only in select high risk population.
- The prospect of screen positive women being given low dose aspirin (75mg) and advice regarding appropriate dietary management to help prevent the development of hypertensive disorders/GDM in later gestation needs to be explored by larger trials.

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