



CORRELATION OF FASTING INSULIN AND HOMA-IR IN EARLY PREGNANCY WITH THE DEVELOPMENT OF GESTATIONAL HYPERTENSION AND GDM

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ABSTRACT

Background: Gestational Diabetes Mellitus (GDM) and Gestational Hypertension (GH) are common pregnancy complications. They are associated with underlying maternal metabolic derangement and increased insulin resistance. The objective of this study was to evaluate the predictive value of early first trimester fasting insulin and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) for the subsequent development of GDM and GH in a Central Indian population.

Methods: The prospective observational cohort study included 60 pregnant women who presented between 10 and 14 weeks gestation at a tertiary care center. Women with pre-existing metabolic or hypertensive disorders were not included. At the first visit, demographic data, Fasting Plasma Glucose and Fasting Serum Insulin were recorded and HOMA-IR was calculated. Participants were followed-up during their pregnancy to diagnose onset of GDM (using a 75g, 2-hour OGTT at 24-28 weeks) and Gestational Hypertension.

Results: Among the 60 participants, 41 had a normal pregnancy, 11 developed GDM and 8 developed GH. Fasting insulin and HOMA-IR were significantly higher in women who subsequently developed GDM (HOMA-IR : 3.34 ± 0.88) and GH (HOMA-IR : 2.84 ± 0.72) compared to women with a normal pregnancy (HOMA-IR : 1.53 ± 0.45) in the first trimester ($p < 0.001$). Also, first-trimester HOMA-IR was strongly positively associated with 2-h OGTT glucose levels ($r = 0.62$, $p < 0.001$) and third-trimester peak systolic blood pressure ($r = 0.54$, $p < 0.001$).

Conclusion: Fasting insulin and HOMA-IR levels in the first trimester are with high sensitivity and specificity early biochemical predictors of development of Gestational Diabetes Mellitus and Gestational Hypertension. Routine early screening with HOMA-IR can help identify patients at high risk to implement preventive interventions in a timely manner and improve maternal and perinatal outcomes.

Key words: HOMA-IR, Gestational Diabetes Mellitus, Gestational Hypertension, Insulin Resistance

INTRODUCTION

Pregnancy introduces a profound set of maternal metabolic adaptations to meet the nutrient needs of the developing fetus. These adaptations comprise a gradual physiologic decline in insulin sensitivity, particularly during the 2nd and 3rd trimesters [1]. In uncomplicated pregnancies, insulin secretion by maternal pancreatic β -cells is enhanced to maintain euglycaemia. In cases where the compensatory hyperinsulinemia does not counteract the pregnancy-induced insulin resistance, pathological metabolic states occur, principally the Gestational Diabetes Mellitus (GDM) and the pregnancy hypertensive disorders, namely the Gestational Hypertension (GH) [1,2]. Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The overall increase in risk of obstetric and perinatal morbidity associated with GDM includes both macrosomia and operative delivery as well as future maternal type 2 diabetes. Gestational Hypertension refers to the condition where a woman experiences high blood pressure during pregnancy. Preterm birth and maternal target-organ damage are caused largely by hypertension [2]. Gestational diabetes mellitus (GDM) and gestational hypertension (GH) are increasingly believed to be not separate diseases but related manifestations of a severe endothelial dysfunction and an exaggerated insulin resistance maternal metabolic syndrome [3]. It is a significant priority in obstetric care nowadays to identify early women facing risk for these complications. The HOMA-IR is a validated mathematical model that uses fasting glucose and fasting insulin to provide a strong, non invasive surrogate for hepatic and peripheral insulin resistance. According to a recent view, while insulin resistance actually peaks late in the second trimester [5], the presence of underlying pre-gravid (pre-conception) or early pregnancy insulin resistance, may be the main (patho)physiological driver for subsequent vascular and glycaemic complications, occurring later on in pregnancy [6, 7]. Though evidence points towards early hyperinsulinemia and high HOMA-IR influencing vascular and metabolic dysfunction, they are not very predictive. Since pathogenesis and aetiology are unique in groups with different dietary and genetic exposures, it was thought of studying them in this population. The current study was designed to determine the association of fasting insulin and HOMA-IR in the first trimester of gestation with the subsequent development of GDM and GH in a tertiary care institute in central India.

MATERIALS AND METHODS

Study Design and Setting

This prospective, observational cohort study was conducted over a 12-month period (January 2014 to December 2014) at Tertiary care center in Central India, Indore. The study protocol was reviewed and approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrollment.

Study Population

The study enrolled 60 pregnant women presenting to the antenatal outpatient department during their first trimester (between 10 and 14 weeks of gestation).

Inclusion Criteria:

Primigravida or multigravida women aged 18–35 years, carrying a singleton pregnancy, and presenting before 14 weeks of gestation.

Exclusion Criteria:

Patients with pre-existing type 1 or type 2 diabetes mellitus, chronic hypertension, essential hypertension, polycystic ovarian syndrome (PCOS), overt thyroid dysfunction, chronic kidney or liver disease, and those on medications known to alter glucose metabolism (e.g., systemic corticosteroids) were strictly excluded from the study.

Data and Sample Collection

At the first antenatal visit (10–14 weeks), detailed demographic, obstetric, and familial histories were recorded. Maternal body mass index (BMI) was calculated. Blood pressure was measured using a standard mercury sphygmomanometer in a seated position.

Following an overnight fast of at least 8 to 10 hours, 5 mL of venous blood was collected.

- **Fasting Plasma Glucose (FPG):** Analyzed using the glucose oxidase-peroxidase (GOD-POD) method.
- **Fasting Serum Insulin (FSI):** Analyzed via a chemiluminescence immunoassay (CLIA) in the central biochemistry laboratory.

HOMA-IR Calculation

Insulin resistance was quantified using the HOMA-IR formula developed by Matthews et al. [4]:

$$\text{HOMA-IR} = [\text{Fasting Insulin } (\mu\text{U/mL}) \times \text{Fasting Plasma Glucose (mmol/L)}] / 22.5$$

(Note: Glucose values in mg/dL were converted to mmol/L by dividing by 18).

Follow-Up and Diagnostic Criteria

Participants were prospectively followed during routine antenatal visits until delivery.

1.Diagnosis of GDM: All participants underwent a 75g, 2-hour Oral Glucose Tolerance Test (OGTT) between 24 and 28 weeks of gestation. Diagnosis was established based on standard criteria (Fasting ≥ 92 mg/dL, 1-hour ≥ 180 mg/dL, or 2-hour ≥ 153 mg/dL) [10].

2.Diagnosis of GH: Monitored throughout pregnancy. Gestational hypertension was diagnosed if the systolic blood pressure reached ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on two occasions at least 4 hours apart after 20 weeks of gestation, without significant proteinuria [20].

Statistical Analysis

Data were compiled using Microsoft Excel and analyzed using appropriate statistical software. Continuous variables were expressed as Mean $\pm$ Standard Deviation (SD). Categorical variables were presented as frequencies and percentages. Group comparisons were performed using the one-way Analysis of Variance (ANOVA) for continuous variables. Pearson's correlation coefficient (r) was used to determine the association between HOMA-IR, fasting insulin, and clinical outcomes. A p-value < 0.05 was considered statistically significant.

Results

Out of the 60 pregnant women enrolled in the first trimester, all completed the follow-up to delivery. Based on clinical outcomes, the cohort was divided into three groups:

- **Normal Pregnancy (n = 41):** Remained normotensive and normoglycemic.
- **Developed GDM (n = 11):** Diagnosed with GDM between 24 and 28 weeks.
- **Developed GH (n = 8):** Developed new-onset hypertension without proteinuria after 20 weeks.

Table 1: Baseline Demographic and Clinical Characteristics (n = 60)

Parameter	Normal Pregnancy (n = 41)	Developed GDM (n = 11)	Developed GH (n = 8)	p-value
Maternal Age (years)	24.3 $\pm$ 3.1	25.8 $\pm$ 3.4	24.9 $\pm$ 3.2	0.315
Nulliparity (n, %)	24 (58.5%)	6 (54.5%)	5 (62.5%)	0.890
Gestational Age at Sampling (weeks)	12.1 $\pm$ 1.2	11.9 $\pm$ 1.1	12.3 $\pm$ 1.0	0.582

Baseline BMI (kg/m ²)	22.8 ± 2.2	26.4 ± 2.9	25.7 ± 2.5	< 0.01*
Systolic BP (mmHg)	112 ± 8	116 ± 6	120 ± 8	0.062
Diastolic BP (mmHg)	72 ± 6	74 ± 5	78 ± 6	0.071

Maternal baseline characteristics at the first sampling (10-14 weeks) are shown in Table 1. Baseline BMI was higher in the group of women who subsequently developed GDM and GH, compared to the group of women with normal pregnancy. There was no statistical difference in maternal age and parity.

Table 2: Comparison of Early Pregnancy Fasting Insulin and HOMA-IR

Biochemical Marker (10-14 wks)	Normal Pregnancy (n = 41)	Developed GDM (n = 11)	Developed GH (n = 8)	p-value
Fasting Plasma Glucose (mg/dL)	84.2 ± 6.4	91.5 ± 7.2	87.1 ± 5.8	0.014*
Fasting Insulin (μU/mL)	7.4 ± 2.1	14.8 ± 3.5	13.2 ± 3.1	< 0.001*
HOMA-IR	1.53 ± 0.45	3.34 ± 0.88	2.84 ± 0.72	< 0.001*

*Statistically significant (p < 0.05).

Table 2 Biochemical parameters in early pregnancy. Mean Fasting Plasma Glucose was marginally higher in the GDM group but was in the normal early pregnancy clinical reference ranges for all groups. Fasting Insulin and calculated HOMA-IR were significantly higher in those developing GDM and Gestational Hypertension in the first trimester as compared to those with a normal pregnancy trajectory.

Table 3: Correlation of First Trimester HOMA-IR with Late Pregnancy Outcomes

Clinical Parameter	Pearson Correlation (r) with HOMA-IR	p-value
2-hour OGTT Glucose (mg/dL)	0.62	< 0.001*
Peak Systolic BP (mmHg)	0.54	< 0.001*
Peak Diastolic BP (mmHg)	0.49	0.001*
Neonatal Birth Weight (grams)	0.41	0.005*

Table 3. Pearson's correlation coefficients for the association between first trimester HOMA-IR and mid to late pregnancy clinical parameters. HOMA-IR was positively correlated with 2h post-load glucose level (determined by OGTT at 24-28 weeks) and peak systolic blood pressure in the third trimester.

DISCUSSION

The rising prevalence of metabolic and hypertensive disorders of pregnancy necessitates a movement toward predictive and preventative obstetric care. The present prospective 12 months study was conducted to evaluate fasting insulin and HOMA-IR profile in early first trimester in 60 women at Tertiary care center in Central India, Indore. The results are unequivocal in demonstrating

an exaggerated state of insulin resistance weeks prior to the clinical presentation of Gestational Diabetes Mellitus (GDM) or Gestational Hypertension (GH). In normal physiology, early pregnancy is usually associated with a slight increase in insulin sensitivity or no change in baseline insulin resistance, with maternal fat deposition being the priority [6]. Significant systemic insulin resistance is induced by placental hormones (e.g., human placental lactogen, cortisol and prolactin) only later in the second and third trimesters, to ensure adequate glucose supply to the growing fetus [5]. Our data suggest that women who eventually had an uncomplicated pregnancy had a mean HOMA-IR of 1.53 in the first trimester. However, the early HOMA-IR values were significantly higher in the progression GDM and GH groups (3.34 and 2.84; $p < 0.001$, respectively). The marked increase in first-trimester HOMA-IR and fasting insulin in the GDM cohort is very consistent with the underlying hypothesis that GDM represents a disease of pre-existing, subclinical metabolic derangement that is unmasked by the physiologic stress of pregnancy [9]. If basal insulin resistance is already impaired in early pregnancy, the subsequent physiological elevation in anti-insulin placental hormones exhausts the pancreatic β -cell reserves prematurely [7, 11]. The HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) study has shown a continuous relationship between maternal hyperglycemia and adverse outcomes [5] but our study highlights the fact that hyperinsulinemia precedes hyperglycemia. This was confirmed by Di Cianni et al. who reported that defects of insulin resistance are present early in gestation in women who will develop GDM [7]. Another interesting finding is the significant increase in HOMA-IR (2.84) and fasting insulin in subjects who developed Gestational Hypertension. Traditionally, hypertension in pregnancy has been viewed as an isolated placental and angiogenic disorder, but recent paradigms firmly place it on the spectrum of metabolic syndrome [12]. Insulin resistance has direct effects on the vasculature, including reduced endothelial vasodilator nitric oxide production, increased sympathetic nervous system activity, and renal sodium retention [13, 14]. Our results agree with those of Bartha et al. who demonstrated that insulin resistance is associated with inflammatory markers and vascular resistance [13]. The strong positive association between first trimester HOMA-IR and peak systolic blood pressure in our cohort ($r = 0.54$, $p < 0.001$) supports the idea that early metabolic derangement initiates the hypertensive cascade long before the classical mid-pregnancy ischemic placental triggers dominates the clinical picture. We also noted a significant difference in baseline BMI between the normal cohort and those with complications (22.8 vs 26.4 and 25.7 kg/m²). This supports the role of adipose tissue in the development of early pregnancy insulin resistance [17]. Adipose tissue is a highly active endocrine organ releasing pro-inflammatory cytokines (TNF- α and IL-6) further interfering with insulin receptor signaling [12]. The biochemical markers of HOMA-IR and fasting insulin were much more directly and biologically linked to the ultimate disease states, even after adjustment for BMI clinically. The incorporation of HOMA-IR into the routine first-trimester screening, particularly in a resource-limited but high-risk population like Central India, provides a strategic advantage. This changes the clinical window from reactive management at 24–28 weeks to proactive intervention at 10–14 weeks. Early detection of HOMA-IR > 2.5 in pregnancy might be a trigger to implement lifestyle changes, early dietary recommendations or more intensive blood pressure surveillance in high risk women and thereby decrease the severity of GDM and GH [15, 16]. The main strength of this study was the prospective study design and a strict exclusion of pre-existing metabolic and hypertensive diseases, so that the increased HOMA-IR values observed were intrinsic to the pregnancy per se. The study is localized to Central India providing much needed regional data where unique dietary patterns (high carbohydrate, low protein) heavily influence metabolic profiles [19]. Limitations The sample size was relatively small ($n = 60$) which limited our ability to perform multivariable logistic regression to establish HOMA-IR independent cut off values adjusting for variables such as parity and accurate gestational weight gain. Moreover, we did not measure specific adipocytokines mediating the association between fat mass and insulin sensitivity. Large, multi-center studies are needed to validate specific HOMA-IR cut-offs for early screening across populations.

CONCLUSION

High fasting insulin and HOMA-IR levels in the first trimester are strong biochemical predictors in early prediction of Gestational Diabetes Mellitus and Gestational Hypertension. The strong association between early insulin resistance and mid- and late-pregnancy glycemic and vascular dysfunction suggests a common metabolic pathophysiology underlying these conditions. Screening for HOMA-IR at early antenatal visits may offer a critical window of opportunity for early preventative interventions, hence improving maternal and perinatal outcomes in high risk populations.

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