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ORIGINAL ARTICLE

Correlation of Insulin Resistance in Pregnancy with Obstetric Outcome

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Abstract

Introduction Pregnancy is characterized by a series of metabolic changes that promote insulin resistance. This could be due to increase in the plasma levels of one or more pregnancy-related hormones such as oestrogen, progesterone, prolactin, cortisol, and human placental lactogen (HPL). The increased insulin resistance in pregnancy is associated with development of diabetes which has implications for the future gestations also.

Aims and Objectives To determine status of insulin resistance in pregnant women and correlate the presence of insulin resistance with obstetric outcome.

Material and Method A prospective cohort study was conducted in the Department of Obstetrics and Gynaecology, KGMU, Lucknow, over a period of one year. Total 150 pregnant women were enrolled from OPD, out of which 136 women were followed up till delivery. Insulin resistance was calculated by HOMA IR index, twice in whole antenatal period (first in early pregnancy and second in late pregnancy). All women were also tested for GDM by DIPSI test (plasma glucose value after 2 h of 75 gm glucose load irrespective of last meal) as per protocol.

Results In our study, we found 71 women out of 136 (52.2%) were GDM. Total 30 women out of 136 (22.05%) were GGI (Gestational Glucose Intolerance), and total 38 out of 136 (27.9%) women were found to have insulin resistance using HOMA IR ≥ 2 as cut off. Significant correlation was found in between BMI and insulin resistance ($p = 0.001$) and between GDM and insulin resistance ($p = 0.001$). Relative risk of development of complications like Preeclampsia, neonatal hypoglycemia, and respiratory distress syndrome was higher in women having insulin resistance and GDM.

Conclusion Obstetric complications like preeclampsia, neonatal hypoglycemia, and respiratory distress syndrome are more likely to occur in women with insulin resistance, but larger studies are required to delineate whether insulin resistance alone without development of GDM will have the same implication

Introduction

Pregnancy is characterized by a series of metabolic changes that promote insulin resistance in pregnancy. With advancing gestation there is around 50–60% decrease in insulin sensitivity [1]. Maternal insulin sensitivity decreases with advancing gestation in order to provide glucose and possibly other nutrients for feto-placental growth and energy needs. During normal pregnancy, there is progressive increase in maternal insulin secretory response to glucose and various other stimuli [1]. In early pregnancy, insulin secretion increases, while insulin sensitivity is unchanged, decreased, or even may increase [2]. However, in late gestation, insulin-mediated glucose disposal decreases [2], ability of insulin to suppress whole-body lipolysis is reduced [3], hepatic glucose production increases, and insulin resistance occurs [4, 5].

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The decreased insulin sensitivity is best characterized by a post-receptor defect resulting in the decreased ability of insulin to bring about GLUT4 mobilization from the interior of the cell to the cell surface [6, 7]. This could be due to increase in the plasma levels of one or more pregnancy-related hormones [8]. Insulin resistance or the decrease in insulin sensitivity during pregnancy is mainly attributed to the increase in the levels of pregnancy-associated hormones like oestrogen, progesterone, prolactin, cortisol, and human placental lactogen (HPL) in the maternal circulation [4]. Normally insulin resistance of the whole body is increased to about three times that seen in the non-pregnant state.

Insulin resistance in the pregnancy may cause several pathogenic effects like gestational diabetes mellitus (GDM), pregnancy-induced hypertension, impaired utero-placental circulation, and foetal growth restriction. GDM is defined as various degrees of glucose intolerance diagnosed or detected for the first time in pregnancy. It is one of the most common complications in pregnancy. Hyperglycemia in pregnancy is associated with increased maternal and foetal morbidity and mortality.

Though there is ample literature on hyperglycemia in pregnancy, there is paucity of studies on insulin resistance in pregnancy. The present study is planned to study outcome of pregnancy complicated by insulin resistance, and to decipher if the insulin resistance itself affects pregnancy outcome even when it does not result in hyperglycemia.

Aims and Objectives

To determine status of insulin resistance in pregnant women and to determine correlation of insulin resistance and obstetric outcome.

Material and Methods

A prospective cohort study was conducted on pregnant women attending the antenatal clinic of the Department of Obstetrics & Gynaecology and in collaboration with Department of Pathology, King George Medical University, Lucknow, over a period of 1 year (from September 2018 to August 2019).Total 150 women fulfilling the inclusion and exclusion criteria were enrolled in this study. Out of these 136 women could be followed up till delivery. GDM testing was done by using DIPSI (Diabetes in Pregnancy Study Group of India) criteria, i.e. by checking plasma glucose level after 2 h of 75 gm glucose load irrespective of last meal at first antenatal visit. Plasma glucose was measured by using a plasma calibrated glucometer. All women were called on next day with overnight fasting. On next day, blood sample for fasting plasma glucose and fasting serum. insulin was taken. Fasting serum insulin was measured by Chemiluminescent Microparticle Immunoassay, and fasting plasma glucose was measured by Glucose Calorimetric Assay Kit (GOD-POD Glucose Oxidase—Peroxidase Method). All enrolled women were followed, and those women who were found to have DIPSI (plasma glucose level after 2 h of 75 gm glucose load) level 140 mg% or more were labelled as GDM in first visit and were managed as per departmental protocol. All recruited women were followed up and repeat DIPSI (plasma glucose level after 2 h of 75 gm glucose load) was done at 24 to 28 week of gestational age and atleast 4 weeks after first visit in those women who were not GDM at first visit. Repeat fasting s. insulin and fasting s. glucose were done in all GDM and non GDM women at 24 to 28 week of gestational age and atleast 4 weeks after first visit.

Homeostasis model assessment—insulin resistance index (HOMA IR) was calculated in first visit and second visit by this formula.

HOMA IR = Fasting S. Glucose (mg/dl) X Fasting insulin (μIU/L)/405 [8].

HOMA IR value ≥ 2 denoted insulin resistance in present study.

Sample size was calculated using following formula.

n = Z 2 X P X(1-P)/d 2.

where

n = required sample size;

Z = statistical value corresponding to confidence level;

P = prevalence from previous study;

d = precision;

It came out to be 153.

One hundred and fifty women recruited, 14 women lost to follow up.

All enrolled women were followed up till delivery and their maternal and foetal outcomes were noted (Fig. 1).

- Maternal outcomes noted were development of Preeclampsia and eclampsia, GDM, recurrent infection, polyhydroamnios, postpartum haemorrhage (PPH), and puerperal sepsis.
- Mode of delivery and period of gestation at which delivery occurred were noted.
- Foetal outcomes noted were birth weight, occurrence of hypoglycemia and respiratory distress syndrome, hypocalcemia, hyperbilirubinemia, polycythemia, congenital malformations, and NICU admissions.

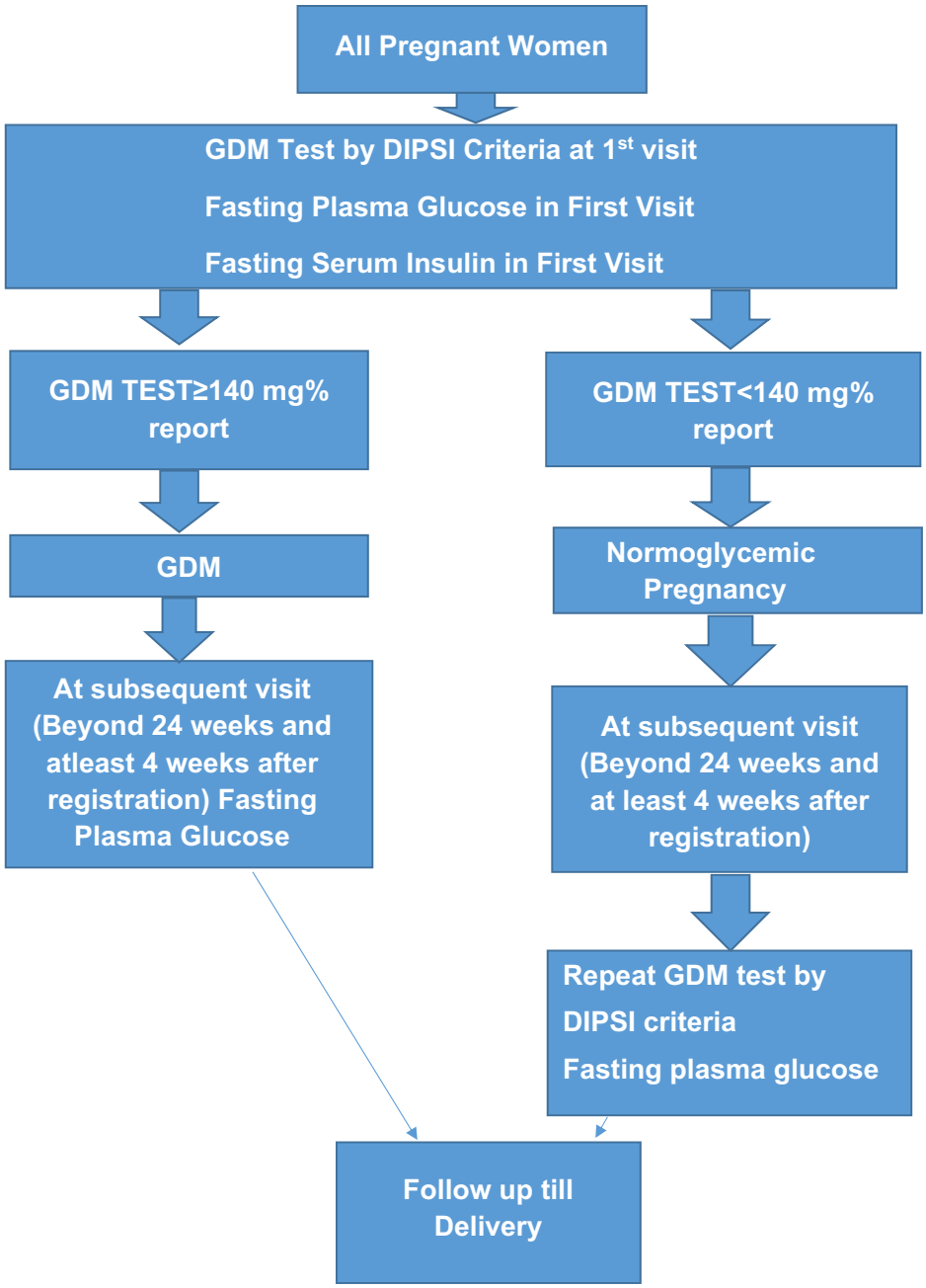

Fig. 1 Methodology and flow of events of the study

Observations and results

In present study, we found total 71 women out of 136, i.e. 52.2% were GDM. Out of 71 women, 46 women were diagnosed as GDM in early gestation, and 25 more were diagnosed as GDM in subsequent visit. In our study, we found 28 women were diagnosed to have GGI at first visit, and 14 were diagnosed to have GGI in second visit. Out of these 14 women, 12 women had GGI in first visit, and two women had normal fasting plasma glucose in first visit. So total 30 out of 136 i.e. 22.05% were found to have GGI. (Table 1).

Table 2 shows that total 38 out of 136 (27.9%) women were found to have insulin resistance using HOMA IR ≥ 2 as cut off. Out of these 22 women were diagnosed in early pregnancy and 16 more were diagnosed in late pregnancy.

Table 3 shows that out of 30 obese women (BMI > = 25 kg/m2) 15 women had insulin resistance, i.e. 50%.So 15 out of 38 (39.47%) of insulin resistant women were obese, 13 out 38(34.21%) were overweight and 10 out of 38(26.31%) had normal BMI. There was significant correlation of BMI with insulin resistance, *P* value was 0.001.

As shown in Table 4 there was a significant correlation of GDM with insulin resistance (*p* value was < 0.001).

Twenty-eight women out of 71, i.e. (39.43%) had insulin resistance.

Table 5 shows that maximum women 20 (14.70%) out of 136 developed preeclampsia, out of which 14 women were GDM and 13 had insulin resistance.

The women who had insulin resistance had a relative risk of developing preeclampsia of 6.76 (95% confidence interval 2.43 to18.74) as compared with women who had no insulin resistance.

The women who were GDM had a relative risk of developing preeclampsia of 2.41 (95% confidence interval 0.87 to 6.7) as compared with women who were non GDM.

Three women developed polyhydroamnios, out of which two were GDM and all three had insulin resistance.

The women who were GDM had relative risk of developing polyhydroamnios of 1.83 (95% confidence interval 0.17 to 19.72) as compared with women who were non GDM.

Six women had PPH after delivery, out of them four were GDM, and two had insulin resistance. None woman developed puerperal sepsis.

Seventy-six (55.88%) women out of 136 women had no complication in present pregnancy, out of which 41 women were GDM, and 13 had insulin resistance.

Two neonates out of 136 had birthweight of ≥ 4 kg. Both mothers were GDM, and both were insulin resistant. However, out of 134 women (mothers of neonates < 4 kg birth weight) 69 women were GDM, and 36 were insulin resistant.

Eighteen(13.27%) neonates out of 136 developed neonatal hypoglycemia, out of which 14 women were GDM, and nine women had insulin resistance. Relative risk for developing neonatal hypoglycemia was significantly higher in those women who had insulin resistance and also in those women who were GDM compared to those women who were non GDM and had no insulin resistance.

Table 6 shows that out of 71 GDM women 28 women also had insulin resistance. Out of these 28 women nine women, i.e. (32.1%) developed preeclampsia and 18 women, i.e. (64.2%) had neonatal morbidity.

43 out of 71 GDM women did not have insulin resistance. Out of these 43 women five women, i.e. (11.6%) developed preeclampsia and 14 women, i.e. (32.5%) had neonatal morbidity. The difference in terms of neonatal morbidity was statistically significant.

So we can say that prevalence of preeclampsia and neonatal morbidity were higher in those women who had GDM with insulin resistance.

Table 1 Distribution of cases according to GDM and GGI diagnosed in 1 visit and 2 visit

S. no	Visit	GDM	%	GGI	%
1	1 Visit	46/136	33.82	28/136	20.58
2	2 Visit	25/90	27.77	14/90	15.55
3	Total	71/136	52.2%	30/136	22.05

Table 2 Distribution of cases according to insulin resistance in 1 visit and 2 visit

Visit	Insulin resistance	No	%
1 Visit	Absent	114	83.84
	Present	22	16.17
2 Visit	Absent	98	72.05
	Present	38	27.9

Discussion

In the present study, incidence of GDM was found to be very high. This may be due to our centre being a tertiary care centre with majority of cases being referred due to complications from other centres in the city and large areas of north India.

In the present study, 38 women out of 136 (27.9%) were found to have insulin resistance in present study, out of which 22 women (16.17%) were diagnosed in early pregnancy at first visit and also had insulin resistance at second visit beyond 24 weeks of gestational age. Sixteen women out of 38 were found normal in early pregnancy, but they were diagnosed as insulin resistant in late pregnancy, i.e. insulin resistance was higher in later gestation. Sonagra et al. 2014 [4] found in their study that mean fasting serum insulin value and HOMA IR were significantly higher in second and third trimester of pregnancy.

Present study found a significant correlation between-BMI (body mass index) and insulin resistance (p value was 0.001). Insulin resistance was found in 50% obese women(BMI > = 25 kg/m2), 34.21% of overweight women (BMI 23 to 24.9 kg/m2), and only 14.70% women with normal BMI.

Ormazabal et al. [9] also found that central obesity is linked to insulin resistance. However, the molecular mechanism by which fat causes insulin resistance is unclear; inflammation due to lipid accumulation, the inhibitory effect of fatty acid oxidation on glucose oxidation, and the secretion of adipocytokines has all been linked to the development of local and systemic insulin resistance [9].

In our study, there were total 38 women with insulin resistance out of which 28 women, i.e. (73.6%) had GDM.

Table 3 Correlation of insulin resistance with BMI

S. no	BMI (kg/m2)	No of cases	Cases with insulin resistance	%
1	< 18.5	0	0	0
2	18.5–22.9	68	10	14.70
3	23.0–24.9	38	13	34.21
4	> = 25	30	15	50.00

Table 4 Correlation of insulin resistance with GDM and GGI

	Visit 1			Visit 2		
	No (136)	Insulin resistance	%	No (90)	Insulin resistance	%
GGI	28	1	3.57%	14	3	21.4
GDM	46	16	34.78	25	12	48
NON GDM	62	5	8.06	51	4	7.8

Table 5 Distribution of cases according to obstetric outcomes

S. no		Obstetric Outcomes	No ($n=136$)	GDM ($n=71$)	IR ($n=38$)	RR d/t GDM	RR d/t IR
1		Preeclampsia	20(14.7%)	14	13	2.41 (0.87–6.7)	6.76(2.43–18.74)
2		Polyhydroamnios	3(2.20%)	2	3	1.83 (0.17–19.72)	NA
3		PPH	6(4.41%)	4	2	1.83 (0.35–9.67)	1.24 (0.24–6.52)
4		Puerperal sepsis	0	0	0		
5		Hypoglycemia	18(13.27%)	14	9	3.20 (1.11–9.24)	2.57 (1.10–6.0)
6		Hyperbilirubinemia	23(16.9%)	12	5	1.00 (0.47–2.11)	0.67 (0.48–55.2)
7	Birth weight (KG)	<4 kg	134	69	36	4.58(.22–93.73)	12.69(.62–258.45)
		≥4 kg	2(1.47%)	2	2		
8		RDS	10(7.35%)	7	7	2.14 (0.58–7.92)	6.01 (1.6–22.07)

Table 6 Comparison of preeclampsia and neonatal morbidity in women of GDM with and without Insulin Resistance

	GDM with IR ($n=28$)		GDM without IR ($n=43$)		Chi-square	p value
	n	%	n	%		
Preclampsia	9	32.14	5	11.63	3.31	0.069
Neonatal morbidity	18	64.29	14	32.56	5.67	0.017

Out of remaining 10 women who had insulin resistance only seven had normal plasma glucose, i.e. (< 120), and three had GGI (plasma glucose 120–139 mg%). So insulin resistance was significantly correlated with GDM. (P value was < 0.001). Ismail et al. [10] found that women who were GDM had higher HOMA IR score and higher fasting serum insulin level. P value in their study was 0.001. Area under ROC curve for HOMA IR score was 0.79 with (95% confidence interval, 0.74–0.84) with optimum cut-off value of 2.92 (sensitivity = 63.5%; specificity = 89.8%).

Not all the patients of GDM had insulin resistance. Hypothesis might be that here we derived IR by the value of fasting blood sugar and fasting insulin. During physiological changes during pregnancy fasting sugar reduces but postprandial blood sugar rises, that's why there is disparity in incidence of GDM and insulin resistance.

In the present study we found most common maternal complication associated with insulin resistance was GDM followed by preeclampsia. Total 20 women out of 136, i.e. (14.70%) women developed preeclampsia, out of which 13 women had insulin resistance and 14 women were GDM. Relative risk for developing preeclampsia in those women who had insulin resistance was found to be 6.76 (95% confidence interval 2.43 to 18.7) as compared with women who had no insulin resistance. Farideh Rezaei Abhari et al. [11] also found a significant association of insulin resistance and preeclampsia, and they found higher HOMA IR in preeclampsia group compared to normal group. It was thus concluded that insulin resistance could be an important risk factor for predicting preeclampsia.

In our study we found that 18 (13.27%) neonates out of 136 developed neonatal hypoglycemia out of which 14 women were GDM and nine women had insulin resistance. Relative risk for developing neonatal hypoglycemia was significantly higher in those women who had insulin resistance and also in those women who were GDM compared with those women who were non GDM and who had no insulin resistance. Relative risk of hypoglycemia due to insulin resistance was found 2.57 (95% confidence interval 1.10 to 6.0), and relative risk of hypoglycemia due to GDM was found 3.20(95% confidence interval 1.11 to 924). This finding of our study was similar to finding of Ismail et al. [10] who found that neonatal

hypoglycemia was a significant complication in GDM women who had insulin resistance. Significant association of neonatal hypoglycemia with GDM was found(P value was 0.02).

In our study, we found that out of 136 women, neonates of two women had birth weight ≥ 4 kg. Relative risk for developing macrosomia was 4.58 (95% CI 0.22–93.73) in GDM women and 12.69 (95% CI 0.62–258.45) in insulin resistant women. Yamashita et al. [12] found in their study that HOMA IR was positively associated with birth weight. Higher HOMA IR value was significantly associated with an increased incidence of large for gestational age infants independent of maternal obesity and glucose levels *P* value was 0.05.

Conclusion

Insulin resistance was found in 38 out of 136 pregnant women, i.e. (27.9%), and GDM was found in 71 out of 136 pregnant women, i.e. (52.2%). Insulin resistance was found to be significantly correlated with development of complications like GDM, Preeclampsia, neonatal hypoglycemia, and respiratory distress syndrome, however, findings of present study need to be validated in a larger study.

As obesity is significantly correlated with insulin resistance, message to general public should be, to optimize BMI before planning pregnancy to reduce adverse outcomes. An awareness should be created regarding lifestyle, diet, exercise, and weight control.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval Ethical approval from institutional ethical committeeKGMU, Lucknow, was taken.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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