Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com/journal/sjams/home

OPEN ACCESS

Obstetrics & Gynecology

Study of Maternal Insulin Resistance in Antenatal Period and its Obstetric Outcome

Dr. Rameshwari Beck[1], Dr. Shashi Dinkar Minj[2*], Dr. Sarita Tirkey[3], Dr. Ajit Kumar[4]

[1]Assistant Professor, Department of Obstetrics and Gynecology, ICARE Institute of Medical Sciences and Research, Haldia, West Bengal, India
[2]Associate Professor, Department of Anaesthesiology, ICARE Institute of Medical Sciences and Research, Haldia, West Bengal, India
[3]Associate Professor, 4Associate Professor, Department of Obstetrics and Gynecology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India

***Corresponding author:** Dr. Shashi Dinkar Minj
| **Received:** 26.12.2018 | **Accepted:** 07.01.2019 | **Published:** 30.01.2019
DOI: 10.36347/sjams.2019.v07i01.009

Abstract | **Original Research Article**

Introduction: Gestational diabetes mellitus (GDM) is a metabolic disorder defined as glucose intolerance with the onset or first recognition during pregnancy. Women with GDM are at increased risk for adverse obstetric and perinatal outcome. This study was done to determine the frequency of insulin resistance in GDM/IGT pregnant women during antenatal population. ***Materials & Methods:*** Patients meeting the inclusion criteria underwent fasting serum insulin and fasting plasma glucose measurements. HOMA calculator (software based) was used to calculate the HOMA-2IR value, which was taken as a measure of insulin resistance. Based on the inclusion criteria, 60 patients were followed up though their antenatal and period, and obstetric outcome measures were documented. Prevalence of insulin resistance was calculated using HOMA-2IR value of more than 1.9 as cut off. Total patients screened and delivered at a tertiary care teaching hospital, Haldia, West Bengal during the period of study were taken as the denominator. ***Results:*** Majority of pregnant women belongs to 18-30 yrs age group (56.12%), followed by 32.09% and 11.80% in 31-40 and above 40 yrs age group. Present study revealed the prevalence of impaired glucose tolerance and GDM in patients delivering at our hospital over a period of 6 months (Jan-June 2016) was 9.31% and 3.11% respectively. The total number of patients with HOMA-2IR>1.9 was found to be 8 (8 out of 100.) The prevalence of insulin resistance is 8% amongst the antenatal patients in the study. Prevalence of Cesarean delivery and assisted vaginal delivery was higher in in study group 13.33% and 31.7% respectively. The percent prevalence of shoulder dystocia (5%) and postpartum hemorrhage (PPH) (25%) were also higher in GDM/IGT patients. ***Conclusion:*** Screening and diagnosis of GDM and treating it effectively not only prevent adverse maternal and perinatal outcome but also future diabetes in both mother and child. Screening for IR can be advised to all pregnant women. Insulin sensitivity can be improved in these women by modifying diet, lifestyle, amount and type of physical activity.

Keywords: Pregnancy, diabetes, gestational diabetes mellitus, impaired glucose tolerance, insulin resistance, Homeostasis Assessment Model (HOMA), outcome.

INTRODUCTION

The prevalence of diabetes in pregnancy has been increasing in worldwide which is having increasing trends in India. The majority is gestational diabetes mellitus (GDM) with the remainder primarily preexisting type 1 diabetes and type 2 diabetes. The rise in GDM and type 2 diabetes in parallel with obesity and may have a connection with maternal insulin resistance. Both type 1 diabetes and type 2 diabetes confer significantly greater maternal and fetal risk than GDM. Specific risks of uncontrolled diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia, and neonatal hyperbilirubinemia, among others. Diabetes in pregnancy may increase the risk of obesity and type 2 diabetes in offspring later in life [1-3].

IFG is defined as FPG levels between 100 and 125 mg/dL (between 5.6 and 6.9 mmol/L) and IGT as 2-h PG during 75-g OGTT levels between 140 and 199 mg/dL (between 7.8 and 11.0 mmol/L). It should be noted that the World Health Organization (WHO) and numerous other diabetes organizations define the IFG cutoff at 110 mg/dL (6.1 mmol/L) [4]. GDM is diabetes that is first diagnosed in the second or third trimester of pregnancy that is not clearly either preexisting type 1 or type 2 diabetes. The International Association of the

Diabetes and Pregnancy Study Groups (IADPSG) GDM diagnostic criteria for the 75-g OGTT as well as the GDM screening and diagnostic criteria used in the twostep approach were not derived from data in the first half of pregnancy, so the diagnosis of GDM in early pregnancy by either FPG or OGTT values is not evidence based [5]. GDM carries risks for the mother and neonate. GDM diagnosis can be accomplished with either of two strategies: 1. "One-step" 75-g OGTT or 2. "Two-step" approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen positive.

Insulin resistance is defined where a normal or elevated insulin level produces an attenuated biological response; classically this refers to impaired sensitivity to insulin mediated glucose disposal [6, 7]. The incidence of gestational diabetes mellitus (GDM) has doubled over the last 6–8 years and is paralleling the obesity epidemic. GDM carries long-term implications for the subsequent development of type 2 diabetes in the mother and increased risk for obesity and glucose intolerance in the offspring. Insulin resistance exists before pregnancy in women with a history of GDM but worsens during gestation. Insulin secretion is inadequate to compensate for the insulin resistance, leading to hyperglycemia that is detected by routine glucose screening in pregnancy. Thus, chronic insulin resistance is a central component of the pathophysiology of GDM [8].

There are a variety of approaches to the laboratory assessment of insulin resistance. Less direct methods include assessments of insulin resistance based on mathematical modelling include the Homeostasis Assessment Model (HOMA) [9] and the Quantitative Insulin Sensitivity Check Index (QUICKI), Continuous Infusion of Glucose with Model Assessment (CIGMA), Frequently Sampled Intravenous Glucose Tolerance Test and minimal modelling[10, 11].

Normal pregnancy is characterised by insulin resistance which is greatest in the third trimester. This appears to be an adaptive response, diverting glucose and lipids to the developing foetus [12] and thought due to the combined effects of human placental lactogen, progesterone, oestradiol and cortisol, which act as counter-regulatory hormones to insulin. Exaggeration of the insulin resistance normally seen in pregnancy is associated with gestational diabetes mellitus and gestational hypertension [13].

The homeostatic model assessment (HOMA) is a validated method to measure insulin resistance from fasting glucose and insulin. The original model HOMA1-IR, first published by Mattews and cols. in 1985 [14], has been widely used, especially in epidemiological and clinical studies. Recently, the model was updated with some physiological adjustments to a computer version (HOMA2-IR) providing a more accurate index [15].

The normal HOMA-IR value of healthy human ranges from 0.5-1.4, in which less than 1.0 means you are insulin-sensitive which is optimal. A value above 1.9 indicates early insulin resistance and above 2.9 indicates significant insulin resistance.

MATERIALS & METHODS

This prospective observational study was conducted at tertiary care teaching hospital in the department of Obstetrics and Gynaecology. Pregnant women attending antenatal clinic in the hospital, were screened for clinical markers for insulin resistance, between Jan 2016 till June 2016 for the study. Patients meeting the inclusion criteria underwent fasting serum insulin and fasting plasma glucose measurements. HOMA calculator (software based) was used to calculate the HOMA-2IR value, which was taken as a measure of insulin resistance. Based on the inclusion criteria, 60 patients were followed up though their antenatal and period, and obstetric outcome measures were documented.

Diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or A1C criteria. Generally, FPG, 2-h PG during 75-g OGTT, and A1C are equally appropriate for diagnostic testing. Weight and height were measured with the subjects wearing light clothing and without shoes on. The waist circumference was assessed at the mid-point between the lowest rib and the iliac crest at the end of a normal expiration [16]. The BMI was calculated and classified according the World Health Organization (WHO) recommendation [17].

Blood samples were obtained after a 12-hour overnight fast and stored in a freezer at -30ºC. Plasma insulin was determined using an ELISA kit (Erba). Glucose was determined by the oxidase method. Total cholesterol, HDL cholesterol and tryglicerides were measured using the colorimetric enzymatic method. LDL cholesterol fraction was calculated by the Friedwald's formula [18]. The HOMA1-IR index was calculated by the formula: HOMA1-IR = fasting plasma insulin (µU/ml) x fasting plasma glucose (mmol/ L)/22.5[19]. The HOMA2-IR index was obtained by the program HOMA Calculator v2.2.2 [20].

Table-1: Diagnostic Criteria for GDM with their respective glucose values[21]

Guidelines	Fasting PG Mg/dl (mmol/l)	Glucose Challenge	1-hour PG Mg/dl (mmol/l)	2-hour PG Mg/dl (mmol/l)	3-hour PG Mg/dl (mmol/l)
WHO 1999	≥ 126 (7.0)	75 g OGTT	Not required	≥ 140 (7.8)	Not required
ACOG	≥95(5.3)	100gOGTT	≥180(10.0)	≥155 (8.6)	≥ 140(7.8)
Canadian Diabetes Association	≥95 (5.3)	75 g OGTT	≥191(10.6)	≥ 160(8.9)	Not required
IADPSG	≥ 92 (5.1)	75g OGTT	≥180(10.0)	≥ 153 (8.5)	Not required
DIPSI	Not required	75g OGTT	Not required	≥140 (7.8)	Not required

Prevalence of insulin resistance was calculated using HOMA-2IR value of more than 1.9 as cut off. Total patients screened and delivered at a tertiary care teaching hospital, Haldia, West Bengal during the period of study were taken as the denominator.

RESULTS

Majority of pregnant women belongs to 18-30 yrs age group (56.12%), followed by 32.09% and 11.80% in 31-40 and above 40 yrs age group [Table 2].

Table-2: Age wise frequency distribution of study subjects [n=483]

Age group	No. of pregnant women	Percentage
18-30	271	56.12%
31-40	155	32.09%
Above 40	57	11.80%

Table-3: Month wise distribution of patients delivered between Jan 2016 and Jun 2016 with impaired glucose tolerance and GDM

Month	Total deliveries	Pts with IGT	Pts with GDM
Jan 2016	78	9 (11.54%)	3 (3.84%)
Feb	83	7 (8.4%)	2 (2.41%)
March	67	5 (7.5%)	3 (4.5%)
April	96	11 (11.46%)	4 (4.2%)
May	84	6 (7.14%)	1 (1.2%)
June 2016	75	7 (9.33%)	2 (2.67%)
Total	483	45 (9.31%)	15 (3.11%)

The above table 3 shows the prevalence of impaired glucose tolerance and GDM in patients delivering at our hospital over a period of 6 months (Jan-June 2016) was 9.31% and 3.11% respectively. In a total of 100 pregnant women HOMA-2 IR test were done and that inclusive all subjects who had diagnosed a case IGT or GDM.

The total number of patients with HOMA-2IR>1.9 was found to be 8 (8 out of 100.) The prevalence of insulin resistance is 8% amongst the antenatal patients in the study [Table 4].

Table-4: Level of HOMA-2 IR in selected subjects in antenatal period

No. of the patients	Number with (HOMA-2 IR 0.5-1.4)	Number with (HOMA-2 IR 1.4-1.9)	Number with (HOMA-2 IR 1.9-2.9)	Number with (HOMA-2 IR >2.9)
100	78 (78%)	14 (14%)	7 (7%)	1 (1%)

Table-5: Clinical and metabolic characteristics of the total studied population

Characteristic	Median (interquartile range) (n = 483)
Age, years	27
BMI, kg/m²	23.5 (19.8 to 33)
Systolic blood pressure, mmHg	122 (106 to 134)
Diastolic blood pressure, mmHg	84 (70 to 96)
Total cholesterol, mg/dL	178 (145 to 224)
Fasting plasma glucose, mg/dL	88 (78 to 120)
Fasting plasma insulin, mU/L	10.1 (6.1 to 18.0)
HOMA2- IR	1.5 (0.9 to 2.9)

The values for waist circumference, BMI, total cholesterol increased in the upper quartiles for HOMA-2 IR indexes [Table 5].

H/o: History of

Risk factors were observed in insulin resistance subjects with pregnancy like family H/O of diabetes, past H/o of GDM, h/o of perinatal losses and h/o of big baby 35%, 21.7%, 16.7% and 11.7% [Table 6].

Table-6: Prevalence of risk factors in GDM and IGT population (N=60)

Risk factors	No. of patients	Percentage
Family H/O of diabetes	21	35%
H/o of perinatal losses	10	16.7
H/o of big baby	7	11.7%
Past H/o of GDM	13	21.7%

Table-7: Delivery outcomes in GDM and IGT population (N=60)

Outcome	No. of patients	Percentage
Caesarean delivery	8	13.33%
Instrumental vaginal delivery	19	31.7%
Spontaneous vaginal delivery	33	55%
Shoulder dystocia	3	5%
Postpartum haemorrhage	15	25%

Prevalence of Cesarean delivery and assisted vaginal delivery was higher in in study group 13.33% and 31.7% respectively. The percent prevalence of shoulder dystocia (5%) and postpartum hemorrhage (PPH) (25%) were also higher in GDM/IGT patients [Table 7].

Table-8: Fetal outcomes in GDM and IGT population (N=60)

Outcome	No. of patients	Percentage
Still Birth	4	6.67%
Hyperbilirubinemia	11	18.33%
RDS	3	5%
Macrosomia	6	10%
Hypoglycemia	5	8.33%
Sepsis	4	6.67%

The prevalence of hyperbilirubinemia, stillbirths, macrosomia, and hypoglycemia was 18.33%, 6.67%, 10% and 8.33% respectively [Table 8].

DISCUSSION

Diabetes can be classified into the following general categories [4]:

- Type 1 diabetes (due to autoimmune b-cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (due to a progressive loss of b-cell insulin secretion frequently on the background of insulin resistance)
- Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
- Specific types of diabetes due to other causes

Any degree of glucose intolerance with the onset or first recognition during pregnancy is defined as Gestational Diabetes Mellitus (GDM)[22]. Women with history of GDM are at an increased risk of adverse maternal and perinatal outcome and also at increased risk of future diabetes predominantly Type II including their children and therefore there are two generations at risk [23].

Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for the treatment for many women. Medications should be added if needed to achieve glycemic targets. Insulin is the preferred medication for treating hyperglycemia in gestational diabetes mellitus, as it does not cross the placenta to a measurable extent. Metformin and glyburide may be used, but both cross the placenta to the fetus, with metformin likely crossing to a greater extent than glyburide. All oral agents lack long-term safety data. Metformin, when used to treat polycystic ovary syndrome and induce ovulation, need not be continued once pregnancy has been confirmed [1]. Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with the onset or first recognition during pregnancy with or without remission after the end of pregnancy [24]. GDM is important in that it poses a risk to the pregnant woman and her baby. GDM is associated with higher incidence of maternal mellitus later in life [25].

Study by Priyanka Kalra *et al*. [26] revealed that the most common complications seen in GDM mothers were gestational hypertension (36.4%) followed by vaginal candidiasis (24.2%), premature rupture of membranes (PROM; 18.1%), and abruptio placentae (12.12%). Study by Gajjar found that most common maternal complication seen in GDM mothers was gestational hypertension (36.4%) followed by abruptio placentae (20%)[27].

In the study done by Buchanan T *et al*. researchers found that there is gradual decline in insulin sensitivity as the pregnancy advances. So the amount of insulin produced in response to glucose concentration also gradually increases [28]. In the total population, HOMA-IR showed a significant positive correlation with placental and birth weights. In contrast, HOMA-IR was negatively correlated with the ratios of fetal to placental weight. Therefore, as maternal insulin resistance increases, the placenta enlarges, but placental efficiency decreases [29].

It is well documented that macrosomia is associated with pregnancies complicated by GDM. This was also the finding by Imoh LC *et al*. [30] where GDM was independently associated with macrosomia. The maternal hyperglycemia in women with GDM increases the gradient of glucose flux into fetus leading to fetal hyperglycemia. This, with the accompanying hyperinsulinemia, results in fetal overgrowth. This explains the increased glucose levels found in women with macrosomic babies compared to those with normal babies. Macrosomia has adverse implications for obstetric practice because it predisposes to labor complications that may result in maternal and fetal adverse outcomes. The degree of increase of the physiologic IR in pregnancy may be related to maternal glucose levels [31]. Indeed, IR in pregnancy usually becomes severe in the context of GDM [31, 32].

CONCLUSION

Gestational Diabetes Mellitus (GDM) is defined as any glucose intolerance with the onset or first recognition during pregnancy. This definition helps for diagnosis of unrecognized pre-existing Diabetes also. Hyperglycemia in pregnancy is associated with adverse maternal and prenatal outcome. Fasting and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and preexisting diabetes in pregnancy to achieve glycemic control. As pregnancy advances, IR increases. Increased IR is associated with poor maternal and fetal outcome. Screening of all pregnancy for IR and early intervention may help to reduce the associated complications.

REFERENCES

1. Management of Diabetes in Pregnancy. American Diabetes Association Diabetes Care 2017 Jan; 40(Supplement 1): S114-S119. Available at http://care.diabetesjournals.org/content/40/Supplement_1/S114.full-text.pdf
2. Holmes VA, Young IS, Patterson CC, Pearson DW, Walker JD, Maresh MJ. Diabetes and Pre-eclampsia Intervention Trial Study Group. Optimal glycemic control, pre-eclampsia, and gestational hypertension in women with type 1 diabetes in the diabetes and pre-eclampsia intervention trial. Diabetes care. 2011;34:1683-8.
3. Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, Roumain J, Bennett PH, Knowler WC. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes. 2000 Dec 1;49(12):2208-11.
4. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes 2018. Diabetes Care 2018; 41(Suppl. 1):S13–S27.
5. McIntyre HD, Sacks DA, Barbour LA, Feig DS, Catalano PM, Damm P, McElduff A. Issues with the diagnosis and classification of hyperglycemia in early pregnancy. Diabetes Care. 2016 Jan 1;39(1):53-4.
6. Cefalu WT. Insulin resistance: cellular and clinical concepts. Exp Biol Med (Maywood). 2001; 226:13–26.
7. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. Endocrinol Metab Clin North Am. 2004; 33:283–303.
8. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular Mechanisms for Insulin Resistance in Normal Pregnancy and Gestational Diabetes. Diabetes Care Jul. 2007; 30 (Supplement 2):S112-S119.
9. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004; 27:1487.
10. Wallace TM, Matthews DR. The assessment of insulin resistance in man. Diabet Med. 2002; 19:527–34.
11. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev. 2005; 26(2):19-39.
12. Butte NF. Carbohydrate and lipid metabolism in pregnancy:normal compared with gestational diabetes mellitus. Am J Clin Nutr. 2000; 71(suppl):1256S–61S.
13. Seely EW, Solomon CG. Insulin resistance and its potential role in pregnancy-induced hypertension. J Clin Endocrinol Metab. 2003; 88:2393–8.
14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28(7):412-9.
15. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation

uses the computer program. Diabetes Care. 1998; 21(12):2191-2.
16. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. Geneva: World Health Organization, 2000.
17. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. Geneva: World Health Organization, 2000.
18. Friedwald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18(6):499-502.
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28(7):412-9.
20. The Oxford Centre for Diabetes. Endocrinology & Metabolism. Diabetes Trial Unit. HOMA Calculator. Available from: http://www. dtu.ox.ac.uk/ Accessed March 2018.
21. Rani PR, Begum J. Screening and Diagnosis of Gestational Diabetes Mellitus, Where Do We Stand. J Clin Diagn Res. 2016;10(4):QE01-4.
22. Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. The Organizing Committee. Diabetes Care. 1998; 21(Suppl 2):B161–67.
23. Danam P. GDM and subsequent development of overt Diabetes mellitus. Dan Med Bull. 1998; 45:495–509.
24. Seshiah V, Das AK, Balaji V, Joshi SR, Parikh MN, Gupta S Diabetes in Pregnancy Study Group. Gestational diabetes mellitus-guidelines. J Assoc Physicians India. 2006; 54:622–8.
25. Davey RX, Hamblin PS. Selective versus universal screening for gestational diabetes mellitus: An evaluation of predictive risk factors. Med J Aust. 2001; 174:118–21.
26. Kalra P, Kachhwaha CP, Singh HV. Prevalence of gestational diabetes mellitus and its outcome in western Rajasthan. Indian J Endocrinol Metab. 2013;17(4):677-80.
27. Gajjar F, Maitra K. Intrapartum and perinatal outcomes in women with gestational diabetes and mild gestational hyperglycemia. J Obstet Gynaecol India. 2005; 55:135–7.
28. Buchanan T, Metzger B, Freinkel N, Bergman R. Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. Am J Obstet Gynecol. 1990; 162(4):1008–14.
29. Tanaka K, Yamada K, Matsushima M, Izawa T, Furukawa S, Kobayashi Y, Iwashita M. Increased maternal insulin resistance promotes placental growth and decreases placental efficiency in pregnancies with obesity and gestational diabetes mellitus. Journal of Obstetrics and Gynaecology Research. 2018 Jan 1;44(1):74-80.
30. Imoh LC, Ogunkeye OO, Isichei CO, Gadzama AA, John C, Ocheke AN. Severe maternal insulin resistance in pregnancy: An independent predictor of fetal macrosomia. J Med Trop. 2016;18:73-8.
31. Catalano PM, Kirwan JP, Haugel-de Mouzon S, King J. Gestational diabetes and insulin resistance: Role in short- and long-term implications for mother and fetus. J Nutr. 2003;133 5 Suppl 2:1674S-83S.
32. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. Diabetes Care. 2007; 30 Suppl 2:S112-9.