

## Gestational diabetes mellitus: A risk factor for hypertension in pregnancy

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### Abstract

**Introduction:** It has been reported that worldwide, one in 10 pregnancies is associated with diabetes, 90% of which are GDM. In India rates of GDM are estimated to be 10-15% with it expected to increase to 20%. There is a significant positive association between maternal hyperglycemia and adverse maternal outcome with the strongest association been found for hypertension in pregnancy. The present study is an effort to bring out the association between GDM and hypertension in pregnancy.

**Method:** A prospective observational study was carried out on 1059 pregnant women. Amongst them, 129 who met the revised IADPSG criteria were diagnosed with GDM and rest included in normoglycemic group. Women with preeclampsia and gestational hypertension were included in the pregnancy associated hypertension (PAH) group. The risk of PAH in women with normoglycemia and GDM was calculated and maternal demographic factors associated with it identified.

**Result:** There were 60 (3.8%) women with PAH. Normoglycemic women had lower rate of PAH, as compared to women with GDM (5.4% vs 7.8%,  $p>0.05$ ). The risk of GDM patients developing pre-eclampsia was significantly more than normoglycemic women developing it ( $p<0.05$ ). Also, women with GDM and PAH had the highest rates of pregnancy after 35years, obesity, primiparity, and cesarean sections.

**Conclusion:** This study demonstrates that GDM is associated with a higher incidence of PAH. There is a pre-pregnancy predisposition to dysfunction of beta cells which may be unmasked by the progressive insulin resistance of pregnancy and this is the common pathophysiology postulated with both GDM and hypertension in pregnancy. There is a necessity for early diagnosis and intensive monitoring of women with GDM for the development of PAH.

**Keywords:** Pregnancy, GDM, Hypertension, Pre-eclampsia, Pregnancy complications

### Introduction

Gestational diabetes mellitus has been defined as “glucose intolerance with onset or first recognition during pregnancy.”<sup>(1)</sup> It is reported that worldwide, one in 10 pregnancies is associated with diabetes and 90% of these have GDM. In India, one of the most populous country globally, incidence of GDM have been estimated to be 10-15% which is higher than the west.<sup>(2,3)</sup> The incidence of GDM is expected to increase to 20% i.e. one in every 5 pregnant women is likely to have GDM.<sup>(2)</sup> In case GDM goes undiagnosed it can lead to significant maternal & fetal complications.<sup>(2)</sup> Of the various adverse maternal outcome reported in pregnant women with hyperglycemia, the strongest association has been found for hypertension in pregnancy.<sup>(4)</sup>

Hypertensive disorder of pregnancy is diagnosed by the level of a blood pressure exceeding 140/90mm Hg with or without proteinuria greater than 0.3g/24 h urine, after 20weeks’ of gestation. A revision in this definition has been made by the Task Force appointed by American College of Obstetricians and Gynecologists in 2013.<sup>(5)</sup> The development of this disorder leads to dysfunction of the endothelial function which is responsible for many abnormalities in the mother<sup>(6)</sup> along with high risk (approximately 12%) of maternal mortality during pregnancy and the puerperium.<sup>(7)</sup>

Insulin resistance is a physiological process in a normal pregnancy and the resulting hyperinsulinemia in predisposed women, can manifest as gestational diabetes mellitus and hypertension in pregnancy.<sup>(8)</sup> Hence, insulin

resistance plays an important role in development of hypertensive disorders of pregnancy, and also in these women having an increased risk of future hypertension and cardiovascular disease.

Gestational diabetes mellitus and hypertension in pregnancy have each been postulated to be an early expression of metabolic syndrome which includes hypertension, diabetes and obesity.<sup>(9)</sup> Also, offsprings of women with GDM are at an increased risk of developing type 2 diabetes mellitus, later in life.<sup>(2)</sup> The present study is an effort to bring out the association between GDM and hypertension in pregnancy, making the common etiologic pathway like insulin resistance and risk factors like age, obesity and parity responsible for the two. However, these common etiologic triggers for appearance of these disorders has not been adequately tested.

### Methodology

This prospective observational study was carried out on all antenatal patients except those who had pre-existing diabetes or overt diabetes, for a period of one year from June 2014 to May 2015 at tertiary care centre in department of obstetrics & gynecology. Diagnosis of gestational diabetes mellitus was made by a single-step approach based on IADPSG recommendations.<sup>(10)</sup> According to that, a standard oral glucose tolerance test (OGTT) was performed between 24 to 28weeks of gestation. In pregnant women with high risk factor for GDM like age >35years, BMI>30kg/m<sup>2</sup>, a family history

of diabetes mellitus (in 1<sup>st</sup> degree relatives), previous H/O intrauterine fetal demise and/or previous H/O macrosomic baby, OGTT was done at 1<sup>st</sup> antenatal visit and then again at 24-28wks if found to be normal.

To determine if gestational diabetes was present in pregnant women, a standard OGTT was done after overnight fasting (8-14 hours) by giving 75 g anhydrous glucose in 250-300 ml water. Plasma glucose was measured fasting, after 1 hour and after 2 hours. All pregnant women who met revised IADPSG criteria for diabetes mellitus were classified as having GDM and others who had normal OGTT as normoglycemics (Table 1). One or more of these values had to be equaled or exceeded for diagnosing GDM. All patients who were diagnosed to have GDM were managed with medical nutritional therapy, oral hypoglycemic or insulin as per their requirement and were followed up as per the standard guidelines of the institution for GDM.

**Table 1: IADPSG Consensus Panel guideline for diagnosing GDM<sup>(10)</sup>**

|         | Plasma Glucose Threshold (mg/dl) |
|---------|----------------------------------|
| Fasting | 92                               |
| 1-hour  | 180                              |
| 2-hours | 153                              |

Gestational hypertension and preeclampsia was diagnosed with information from the usual obstetric examinations, and routine analyses of urine. In women with proteinuria on dipstick test, 24-hour urine was checked for total proteinuria. Gestational hypertension and preeclampsia-eclampsia were defined according to the Report of the National High Blood Pressure Education Program by the Working Group on High Blood Pressure in Pregnancy updated by the Task Force appointed by American College of Obstetricians and Gynecologists definition.<sup>(5)</sup> Diagnosis of gestational hypertension (BP values >140 or >90 mm Hg for systolic or diastolic BP, respectively, after the 20th week of gestation without clinical record of hypertension previous to 20th week of gestation and prior to pregnancy) or pre-eclampsia (gestational hypertension with any one or more of these - proteinuria >300 mg in 24 hours of urine collection/thrombocytopenia with platelets <100,000 per mm<sup>3</sup>/impaired liver functions in form of elevated transaminases twice the normal levels/new development of renal insufficiency in absence of other diseases or pulmonary oedema/new onset of cerebral or visual disturbances, diagnosed after the 20th week of gestation in a previously normotensive women) was done with information from the routine obstetric examinations. Women with preeclampsia and gestational hypertension were included in the pregnancy associated hypertension (PAH) group. Management and follow-up of these women were according to the standard guidelines for the disorder.

The specific objectives of our study were:

1. To document the incidence of GDM and compare the risk of PAH and pre-eclampsia in women with normoglycemia and GDM.
2. To identify maternal demographic factors associated with the incidence of GDM and PAH
3. To examine the difference in maternal and fetal characteristics in the normoglycemia and GDM group with respect to the PAH.

**Statistical Analysis:** Statistical analysis was done by using SPSS version 19 and data statistically analyzed with Chi-square value to find the associations between factors. Also associated p-values were calculated assuming significance at p value <0.05 & Confidence Interval Used (CI) = 95%.

### Results

All the pregnant women tested for GDM between June 2014 to May 2015 were included in the study. The total number of women who were included in the study were 1059, of which 930 had normal OGTT and 129 were diagnosed with GDM. The incidence of GDM was found to be 12.2%. The mean age of women with GDM was 25.61 years (SD-4.038), which was significantly higher in comparison to women with normal oral glucose tolerance in whom it was found to be 24.43 years (SD-3.817). Also there were significantly more number of women with age >35 yrs in GDM group (p<0.05) (Table 2).

In the study population, it was found that there were 60 (3.8%) women with pregnancy associated hypertension (PAH), which included patients with gestational hypertension and pre-eclampsia. In the normoglycemic women, 50 (5.4%) had PAH as compared to 10 (7.8%) women with GDM (Fig. 1). Of the 50 women with PAH in the normoglycemic group, 28 had gestational hypertension and 22 had pre-eclampsia. In the GDM group there were 3 and 7 women with gestational hypertension and pre-eclampsia, respectively. Chronic hypertension was detected in 7 women and they were not included in the comparison of outcome within the two groups. The risk of association of GDM with PAH was higher than normoglycemia with PAH but it was not statistically significant (p=0.27). However, the risk of GDM with pre-eclampsia was found to be significantly more than normoglycemia with pre-eclampsia (p<.05).

On comparison of women with or without hypertension within the GDM and normoglycemics, specifically women with GDM and PAH had the highest rates of pregnancy after 35 years, obesity, and primiparity. This indicates that these risk factors increase the occurrence of PAH in women with GDM. The babies of women with normoglycemia and PAH had the least mean birth weight amongst all the groups. Birth weight of babies of women with GDM and PAH was observed to be normal (Table 3). The study also revealed that if the GDM is well controlled then the adverse effect on the

fetal outcome in the form of abnormal birth weight and intrauterine fetal demise is not observed.

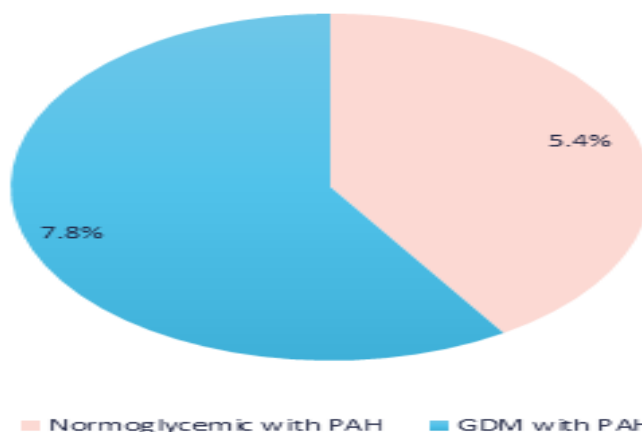


Fig. 1: Distribution as per presence of pregnancy associated hypertension in women with Normoglycemia & GDM

Table 2: Characteristics of women with or without gestational diabetes mellitus

| S No. | Characteristics                  | Normoglycemic (n=930 women) | GDM (n=129 women) | p-value |
|-------|----------------------------------|-----------------------------|-------------------|---------|
| 1.    | Associated PAH, Gest HT & PE (%) | 50(5.4%)                    | 10(7.8%)          | .27     |
| 2.    | Mean Age(yrs)                    | 24.43(SD-3.82)              | 25.61(SD-4.03)    | .001    |
| 3.    | Age>35(%)                        | 14(1.5%)                    | 2(1.5%)           | .02     |
| 4.    | BMI (%)                          | 6(0.6%)                     | 2(1.5%)           | .26     |
| 5.    | Nulliparas(%)                    | 522(56.1%)                  | 66(51.1%)         | .28     |

Table 3: Comparison of characteristics in women with normoglycemia & GDM with respect to presence or absence of PAH

|                           | Normoglycemic | Normoglycemic with PAH | p-value |
|---------------------------|---------------|------------------------|---------|
| Age >35yrs (%)            | 12(1.4%)      | 2(4%)                  | .13     |
| BMI>30(%)                 | 4(0.5%)       | 2(4%)                  | .00     |
| Nulliparas (%)            | 487(55.3%)    | 35(70%)                | .04     |
| Caesarean deliveries (%)  | 201(22.8%)    | 21(42%)                | .001    |
| Mean Birth Weight, kg(SD) | 2.87(0.48)    | 2.56(0.64)             | .000    |
|                           | GDM           | GDM with PAH           | p-value |
| Age >35yrs (%)            | 1(0.8%)       | 1(10%)                 | .02     |
| BMI>30(%)                 | 1(0.8%)       | 1(10%)                 | .02     |
| Nulliparas(%)             | 59(49.6%)     | 7(70%)                 | .21     |
| Caesarean deliveries (%)  | 40(33.6%)     | 6(60%)                 | .17     |
| Mean Birth Weight, kg(SD) | 2.65(0.68)    | 2.91(0.48)             | .14     |

### Discussion and Conclusion

It has been observed that pregnant women diagnosed with GDM have a higher risk of developing hypertension in pregnancy. Bryson et al found a significantly increased risk of gestational hypertension, mild preeclampsia, and severe preeclampsia among women with gestational diabetes. The researcher found that there was 1.5 times more risk of developing these disorders amongst women with gestational diabetes.<sup>(11)</sup>

In the present study this risk was 5.4% in normoglycemic women increasing to 7.8% on association with GDM, although the difference was not significant. This may be due to a smaller sample size of our study. However, the risk of developing pre-eclampsia in women with GDM was found to be significantly increased as compared to the normoglycemics, in the study. This was comparable to the result of the cohort study which reported significantly increased risk of preeclampsia among

mothers with gestational diabetes compared with mothers without gestational diabetes.<sup>(12)</sup> Hossein-Nezhad A et al has also elucidated the correlation between GDM and hypertensive disorders after matching for age, BMI, parity and pregnancy age variable and found the prevalence of hypertension in pregnancy to be significantly higher in GDM patients [OR=3.18, (95% CI: 1.13-8.94), RR=1.03, (95% CI: 1.004-1.06), P=0.03].<sup>(13)</sup>

With various studies suggesting an association between GDM and hypertension in pregnancy, there is a likelihood of common pathology associated with the two disorders. GDM has pre-pregnancy origins in beta cell dysfunction that may be unmasked by the progressive insulin resistance of pregnancy.<sup>(14)</sup> This insulin resistance leading to hyperglycemia may be a cause of endothelial damage and inflammation.<sup>(6)</sup> In fact, it has been postulated that insulin resistance during pregnancy could be the common trigger leading to GDM and/or PAH in predisposed women.<sup>(7)</sup> There are also documented several common maladaptations of pregnancy which may be responsible for association between the two disorders. These include endothelial dysfunction (e.g. lower flow-mediated dilation),<sup>(15)</sup> increased oxidative stress (e.g., low total antioxidant status, high free radicals),<sup>(16)</sup> and dyslipidemia (e.g., increased triglycerides),<sup>(17)</sup> which may all be resulting from inflammation and endothelial damage due to hyperglycemia. However, none of these pathophysiologicals is confirmed.

Another outcome demonstrated in our study is that the risk factors which increase the incidence of GDM like age >35yrs, obesity and nulliparity are observed maximum in women with associated PAH indicating that all these factors are also associated with increased risk of PAH. The results from a relatively large prospective Brazilian study have also suggested that gestational diabetes and hypertension in pregnancy increases with increasing age and adiposity, and decreases with decreasing parity<sup>(18)</sup> illustrating that these risk factors are common to both the disorders supporting the concept that the causes for the development of the two disorders are similar.

Together, gestational diabetes and hypertension in pregnancy, have been postulated to be an expression of future development of metabolic syndrome which includes hypertension, diabetes and obesity.<sup>(19)</sup> This can be due to increased presence of risk factors in pregnancy with GDM and/or PAH, common with risk factors of the metabolic syndrome like advanced age, obesity and excessive weight gain. Hence, the increased risk of hypertension in pregnancy in women with gestational diabetes may indicate an underlying common pathophysiology related to the development of metabolic syndrome in future life. There is also an increased association of pregnancy associated hypertension with increased risk of development of hypertension, ischaemic heart disease, thromboembolic episodes, and

diabetes in later life.<sup>(20)</sup> If an intervention for a good control of GDM during pregnancy is able to reduce the risk of PAH, it can reduce these long term adverse effects seen with these two disorders.

This study concludes that GDM is associated with a higher rate of hypertension in pregnancy. There is a need for early diagnosis and increased monitoring and follow-up of women with GDM for the development of this disorder. Further research on the progressive insulin resistance as the underlying common pathophysiology of these two disorders of pregnancy may help clinicians to improve early detection, prevention and treatments of GDM and hypertension in pregnancy, and their long term adverse effects.

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