

Comparison of incidence of pregnancy induced hypertension in gestational diabetes mellitus and healthy pregnant women

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Abstract

Background: Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance occurring or detected for the first time during pregnancy also hypertension is one of the major complications of pregnancy. Hypertension occurring as a result of pregnancy is called pregnancy-induced hypertension (PIH), which is itself divided into two groups: gestational hypertension and pre-eclampsia. The aim of this study is to compare the incidence of hypertensive disorders in pregnant women with GDM and healthy group.

Methods: In a cohort study, 615 pregnant women including 293 GDM patients as exposed group were recruited. Gestational diabetes mellitus was diagnosed based on Carpenter and Coustan criteria. On the other hand, 322 women with a normal glucose challenge test were chosen as un-exposed.

Results: Mean age, BMI, and parity in GDM and control groups were 27.64 ± 5.80 and 25.71 ± 4.93 years, 26.98 ± 5.38 and 25.63 ± 5.08 kg/m², and 1.34 ± 0.84 [1(3)] and 0.25 ± 0.43 [1(1)] births, respectively. Women with GDM had a significant higher prevalence of PIH than matched controls [OR=3.18, (95% CI: 1.13-8.94), RR=1.03, (95% CI: 1.004-1.06), P=0.03]. The prevalence of pre-eclampsia and essential hypertension was also higher in women with GDM than matched controls but not significant.

Conclusion: Our results show that hypertensive disorders are more common in women with GDM than in normoglycaemic controls of similar age, parity and BMI. It has been hypothesized that this association, at least in part, could be due to insulin resistance, which is a physiologic phenomenon and adaptation in normal pregnancy but that in the predisposed individual with other risk factors could lead to pathologic procedures for instance the development of PIH, GDM, or both. Correlation does not necessarily imply causation, but the development of possible preventive strategies and therapeutic interventions based on this data could be beneficial

Keywords: Pregnancy, GDM, Hypertension

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Introduction

The prevalence of type 2 diabetes is rapidly increasing and recent studies have clearly proved diabetes as an important risk factor of cardiovascular diseases worldwide (1, 2). Hypertension demonstrated to play a similar role in the pathogenesis of the disease. Therefore, hypertension and diabetes, being two major defining criteria for the metabolic syndrome, are inextricably interlinked showing an upward trend in their incidence worldwide (3).

Regardless of the close relationship between hypertension and type 2 diabetes, little information exists on the relationship between pregnancy induced hypertensive disorders and Gestational diabetes mellitus (GDM).

GDM is defined as a glucose intolerance status initiated or diagnosed for the first time during pregnancy (4). GDM was proposed to complicate approximately 4.7 percent of all pregnancies in Iran (5). It is demonstrated that gestational diabetes is associated with a great number of perinatal complications, both maternal and offspring (6); as GDM increases the risk of hypertension and dyslipidaemia, and thereby, increasing the risk for atherosclerosis and coronary heart disease (7).

Hypertension in pregnancy is usually correlated with a constellation of complications classified as hypertensive disorders in pregnancy and they are generally termed as "pregnancy-induced hypertension" (PIH). These disorders include gestational hypertension and pre-eclampsia, and they complicate up to 8% of all pregnancies (8). Besides, they are proved to be leading causes of various maternal and perinatal morbidities (9) including seizures, stroke, hepatic failure, renal failure, intrauterine growth retardation, fetal distress, premature delivery, as well as maternal and offspring mortalities (10).

Although several epidemiological studies have successfully demonstrated a correlation between GDM and hypertension, a causal relationship between them is not well demonstrated hitherto (11). Moreover, there are some controversy surrounding the subject as some studies failed to demonstrate any such

correlation at all (12, 13). Moreover, having not yet been defined universal criteria for diagnosis of PIH; it is difficult to compare results of different studies on the subject.

It has been suggested that this association, at least in part, might be due to insulin resistance, which is a physiologic adaptation mechanism in normal pregnancies. As we know, pregnancy is associated with some degree of physiological resistance to insulin that fades out after delivery (14). However, it could lead to pathologic conditions such as PIH and GDM in individuals with certain risk factors (15, 16).

As we described, different definitions of PIH in different studies, make the task of clarifying the association between gestational diabetes and pregnancy-induced hypertension seem elusive. Moreover, the common etiology of two diseases such as insulin resistance, age, obesity, and high parity makes this association even more complicated. Therefore, in this study, we endeavored to take a stride to clarify any potential relationship between gestational diabetes and different presentations of pregnancy-induced hypertension, by comparing the incidence of hypertensive disorders in patients with GDM and our healthy control group.

Methods

Study design and participants

In a cohort study, pregnant women who referred to five university educational hospital clinics were recruited. In this cohort study, GDM patients as exposed and healthy pregnancies as unexposed groups were followed up until delivery. The study protocol was approved by ethics committee of Endocrinology and Metabolism Research Center (EMRC). All women signed informed consent forms before entering the study. Exclusion criteria were chronic liver disease, diabetes or any other endocrine disease such as hyperthyroidism. Each participant completed a questionnaire, which recorded the results of a general medical examination and any relevant obstetric or endocrine history. Every patient

was followed up until delivery at the clinic whenever possible or otherwise by phone. Demographic, anthropometric and clinical data, e.g. age, pre-pregnancy body weight, weight gain during pregnancy, family history of diabetes and obstetric history were recorded for all participants. Weight and height were measured directly. Gestational age was estimated from the last menstrual period and confirmed or corrected by ultrasonography. BMI calculated for all patients.

Protocol

The pregnant women were studied via universal screening for GDM. Universal screening for GDM was done with a glucose challenge test (GCT) between the 24th and 28th weeks of gestation. Every woman attending the antenatal clinic was screened in this way between the 24th and 28th weeks of her pregnancy. In cases with one or more GDM risk factors (family history of type 2 diabetes, history of GDM and/or impaired glucose tolerance, obesity, glycosuria); screening was done earlier, as soon as it was feasible to do so. If her plasma glucose on screening was equal to or greater than 130 mg/dL, she underwent a 100-g 3-hour oral glucose tolerance test (OGTT) to confirm the diagnosis of GDM, as defined by the criteria proposed by Carpenter and Coustan (16,17). Women with a positive GCT test and two or more abnormal OGTT readings were diagnosed with GDM. Blood sampling took place in the participating clinics by trained personnel under the supervision of a trained midwife. All blood samples were centrifuged no more than 30 minutes, sampled, refrigerated, and then transferred at the end of every day under appropriate storage conditions to Dr Shariati Hospital. Measurement was by the glucose oxidase method, using Hitachi 704 autoanalyzer.

We diagnosed chronic hypertension as a diastolic blood pressure equal to or higher than 90 mmHg, or systolic blood pressure equal to or higher than 140 mmHg, or both, at least twice before 20th gestational weeks. Diagnosis of gestational hypertension and pre-eclampsia

was done with information from the usual obstetric examinations, including monthly ambulatory blood pressure monitoring, and routine analyses of urine, including 24-hour urine collection in women with suspicion of proteinuria from dipsticks. Pregnancy-induced hypertension, pre-eclampsia and 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.

Diagnosis of gestational hypertension (BP values >140 or >90 mm Hg for systolic (SBP) or diastolic (DBP) BP, respectively, after the 20th week of gestation without clinical record of hypertension previous to pregnancy after the 20th week of gestation for further corroboration of hypertension in pregnancy without clinical record of hypertension previous to pregnancy) or pre-eclampsia (gestational hypertension and proteinuria, >300 mg in 24 hours of urine collection, with or without edema, diagnosed after the 20th week of gestation in a previously normotensive women) was done with information from the conventional obstetric examinations and routine analyses of urine (18). Subjects with documented normotensive pregnancies participated in current study as a control group. Control group were matched for age, body mass index, number of pregnancy and the year of delivery by GDM patients.

Statistical analysis

The data gathered were analyzed according to results obtained with Carpenter and Coustan's criteria for diagnosis of GDM. Chi-square test was used to compare the frequency of variables and the restrictive factors between two groups and Fisher's exact test for contingency tables with minimum expected frequencies of less than 5. Odds ratios (ORs) with a 95% confidence interval (CI) were screening approaches calculated. Multivariable logistic regression method was used to investigate the independent effect of GDM on hypertensive disorders in pregnancy. The level of significance was set at a probability of ≤ 0.05 for all tests. All statistical

analyses were performed using SPSS version 16.0 software.

Results

Totally 615 pregnant women participated in current study. From all subjects 293 pregnant women had diagnosed with GDM that classified as exposed group. Also 322 healthy pregnancies participated as an unexposed group in our study.

Our results demonstrated that in the similar assessment time during pregnancy in two groups the mean \pm SD of age, BMI and the number of delivery in GDM patients vs. healthy group were 27.64 \pm 5.8 and 25.71 \pm 4.93 years, 26.98 \pm 5.38 and 25.63 \pm 5.08 kg/m², and 1.34 \pm 0.84 and 0.25 \pm 0.43 births, respectively. As shown in Table 1, we found significant differences in mention characteristics between two groups.

Women with GDM had a significant higher prevalence of PIH than unexposed group [OR=3.18, (95% CI: 1.13-8.94), RR=1.03, (95% CI: 1.004-1.06), P=0.03]. The prevalence of pre-eclampsia and essential hypertension was also higher in exposed than unexposed group but not significant (Table 2).

In the case of the differences between PIH patients and healthy pregnant women, a significant difference was observed regarding BMI and parity. Considering pre-eclampsia, significant difference was seemed in terms of age, parity, FBS and BMI.

In multivariable logistic regression method, GDM predicted PIH independent of age, BMI and parity (P=0.03). Regarding prediction of pre-eclampsia this model demonstrated that the effect of GDM on pre-eclampsia associated with FBS. These results indicated that GDM could not predicted pre-eclampsia independent of fasting blood sugar.

Table 1. The characteristics comparison between two groups.

Characteristic	participants		P-value
	Exposed* (293 subjects) mean \pm SD	Unexposed** (322 subjects) mean \pm SD	
Age (years)	27.64 \pm 5.80	25.71 \pm 4.93	0.01
parity	1.34 \pm 0.84 1(3)	0.25 \pm 0.43 1(1)	0.01
BMI (kg/m2)	26.98 \pm 5.38	25.63 \pm 5.08	0.02
FBS(mg/dl)	96.07 \pm 21.44	78.58 \pm 9.36	0.01

* Gestational diabetes mellitus patients recruited as exposed group.

**Healthy pregnant women recruited as unexposed group.

Table 2. The prevalence of hypertensive disorders in two study groups.

Hypertension disorders		Exposed* (293 subject)	Unexposed** (322 subject)	P	Odds Ratio [CI %95]	Relative Risk
PIH	%	4.8	1.6	0.03	3.18	1.03
	Number of patients	14	5		[1.13 to 8.94]	[1.004 to 1.06]
Pre-eclampsia	%	3.1	0.9	0.07	3.37	1.02
	Number of patients	9	3		[0.9 to 12.56]	[0.99-1.04]
Essential hypertension	%	3.4	1.9	0.3	1.86	1.01
	Number of patients	10	6		[0.66 to 5.18]	[0.99-1.04]

* Gestational diabetes mellitus patients recruited as exposed group.

**Healthy pregnant women recruited as unexposed group.

Discussion

Unfortunately, there is a scarcity of longitudinal research using control groups to demonstrate a potential association between hypertension and GDM from during the whole period of pregnancy. However, the longitudinal study by Ralph et al. measuring blood pressure before, during, and after pregnancy shed some light on the possible relationship between those two pregnancy complicating conditions (19). We believe that such investigations that demonstrate a possible correlation between hypertension and GDM could result in a better understanding of the increased preterm delivery rate as well as of the increased perinatal and maternal morbidity rate (20, 21).

In the present study, the prevalence of essential hypertension in those with GDM was 2.5 times higher compared to that of the control group. This clearly indicates a correlation between previous hypertension and GDM. Previous studies have demonstrated that pregnant patients with hypertension are at an increased risk for developing gestational diabetes mellitus (22, 23).

Various studies have suggested an association between GDM and essential hypertension. For instance, Hedderson and colleagues (23) successfully demonstrated that during early pregnancy, women with mild hypertension had a small increased risk of GDM, and women with pre-existing severe hypertension showed a twofold increased risk of GDM as compared to women with normal BP, after adjusting for age, race/ethnicity, gestational week of BP, BMI, and parity. Similar results were reported by Lao and Ho that are consistent with those of our study (24). Moreover, a study by Negrato et al. (25) showed that pregnant women with hypertension had higher glucose levels on an oral glucose tolerance test.

A different study demonstrated a different finding regarding the relationship between gestational diabetes and blood flow. Brachial artery post-occlusion flow-mediated vasodilatation is demonstrated to be reduced in patients with GDM although this was not the case regarding nitrate-dependent vasodilatation (26).

Apart from the effect of high blood sugar on blood pressure, there are several common pathogeneses leading to hypertension and GDM that may shed some light on the association between the two conditions. One of these potentially important underlying pathologies could be due to insulin resistance. Although insulin resistance is a physiologic condition in a normal pregnancy, in vulnerable individuals this could lead to hyperinsulinemia, and eventually, to gestational hypertension, gestational diabetes mellitus, or both (22).

Markers of inflammation such as C-reactive protein have been demonstrated to be associated with increased BP levels (27). Moreover, high levels of CRP in early pregnancy stages have been shown to be correlated with an increased risk of GDM (28). Our results are generally consistent with those of previous studies of BP and the risk of GDM (24) and explain some possible correlation between two pregnancy complicating conditions.

It is demonstrated that insulin resistance can result in hypertension via different cellular, circulatory, and neurological mechanisms. For instance, Insulin resistance is recognized as a key pathologic mechanism in type 1 diabetes mellitus (29, 30). Moreover, endothelial damage has been demonstrated in women with GDM during pregnancy (31) and its close relationship with hypertension is well documented (32). Similarly, in pregnant women, it is proved that insulin resistance can lead to the development of PIH, GDM, or both especially when other risk factors exist (33). Therefore, it seems that both hypertension and vascular disease could be related to, and possibly originated from GDM.

Furthermore, some studies have provided evidence indicating that pregnancies complicated by GDM are characterized by an increased insulin resistance in comparison with normal pregnancies (34). For instance, one study using similar methods reported that women with GDM showed a significant decrease in sensitivity to insulin (35). Besides, Caruso et al. (36) results showed that women with gestational hypertension had a 40%

reduction in insulin sensitivity index level compared with the control subjects. Suhonen et al. (37) showed that the prevalence of essential hypertension was considerably higher in their case group in comparison with the controls, a finding consistent with our results. Another subgroup of hypertensive disorders in pregnant women is PIH. GDM pregnancy is demonstrated to predispose women to PIH (38). The main hurdle to explain any association between GDM and PIH seems to be due the same risk factors responsible for two complications. Comparing PIH prevalence difference between GDM and healthy pregnant women, Nordlander et al. (39) demonstrated higher PIH prevalence in the GDM group. In the mentioned study, two groups were matched for age and pregnancy age characteristic, but unfortunately, not for weight. Similar findings were reported by Greco et al (40), although they matched merely age and parity in the case and control groups.

High insulin resistance during pregnancy could be a potential culprit for pathogenesis of PIH and GDM. Increasing evidence from different studies have successfully demonstrated an increased insulin resistance in women with PIH compared to healthy pregnant women, and thereby, suggesting a role for insulin resistance in PIH similar to that of the essential hypertension. It is noteworthy that the underlying pathologic mechanism of GDM is believed to be insulin resistance and pregnancy complicated by GDM is characterized by higher longitudinal insulin resistance increase compared to normal pregnancies (41).

It could be suggested that pregnancies complicated by PIH have the same characteristics as those complicated by GDM. Increased insulin resistance could be a common link between PIH and GDM as insulin resistance in a non-pregnant state is supposed to be associated with an elevated blood pressure through a sympathetic response, leading to vascular smooth muscles contracture and effects on the epithelium and on the cellular membrane pump (22).

To evaluate the correlation between GDM and PIH, the differences between pre-eclampsia and PIH in terms of diagnosis criteria should be considered. Pre-eclampsia is defined as a sympathetic over-activity state (42) and some inflammatory conditions (43), both closely related to insulin resistance. Moreover, recently, Sattar et al. (44) have demonstrated that high levels of the pro-inflammatory adhesion molecules and higher HbA1c levels complicated pregnancies with pre-eclampsia but not the control group.

Our results demonstrated that glucose intolerance was more common in patients with pre-eclampsia and those with gestational hypertension. Interestingly, Parretti et al. (45) have even proposed a model suggesting that prediction of pre-eclampsia is possible by measuring fasting insulin and glucose levels.

However, it appears that predisposing mechanisms to pre-eclampsia are different from those of essential hypertension (19, 46), a difference with a direct impact on related studies. Therefore, in current study, we took a further stride to elucidate the correlation between GDM and hypertensive disorders. Besides matching for age, BMI, parity and pregnancy age variable, enabled us to analyze PIH and pre-eclampsia independently between two groups.

The prevalence of pre-eclampsia was significantly higher in GDM patients in the current study, a finding similar to that of Sowers et al. (47). However, results reported by Gobbe et al. (48), were contrary to us, a discrepancy which might be due to the apparently confounded criteria for pre-eclampsia used in their study. The contradicting results of different studies, however, might be a result of their not matching variable between groups and their not defining clear criteria for hypertension and its diagnosis.

In conclusion, the current study demonstrated a clear correlation between hypertensive disorders in pregnancy and GDM, whilst providing a clear definition and setting proper criteria for each subgroup such as pregnancy

hypertension, pre-eclampsia and PIH separately with matched characteristic between groups.

In summary, our results demonstrated that pregnancies complicated with gestational diabetes mellitus are at increased risk of developing various pregnancy related hypertension disorder, and therefore, having in mind potential grave consequences of every

single disorder, it is worthwhile to make the diagnosis as early as possible to intervene.

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