Perveen et al., International Current Pharmaceutical Journal, October 2015, 4(11): 453-456
http://www.icpjonline.com/documents/Vol4Issue11/01.pdf

International Current Pharmaceutical Journal

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

Relationship between gestational diabetes and pregnancy induced hypertension (PIH)

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ABSTRACT
Pregnancy-induced hypertension (PIH) and gestational diabetes mellitus (GDM) both have no adequate classification in addition to nomenclature that creates difficulties for researchers to find link between them. Aim of this work was to review the most recent data available on PIH and GDM and find the association between both conditions during gestation. Epidemeologies and whole studies which have done till now days, could not satisfy that what is association between PIH and GDM. The main issue to solve is how to find the association between GDM and PIH. Very limited data and research studies are available, creating hindrance to find any association. The one way to find the association now, can be that it should be checked the level of hypertension before, during and after gestation. According to the available data and research, it could be deduced that insulin resistance, present in non-insulin dependent diabetes mellitus (NIDDM), may provide association more frequently. However, no direct evidential data is available for this link.

***Key Words*:** Gestational diabetes, hypertension, pregnancy.

INTRODUCTION

Gestational diabetes

Any degree of glucose intolerance that has its onset or is first detected during pregnancy indicates gestational diabetes. It occurs in approximately 2-7% of pregnant women, generally during the second or third trimester. Occurrence of gestational diabetes mellitus (GDM) increases future risk for developing type 2 diabetes mellitus (Bellamy *et al.*, 2009). GDM can be managed by meal planning, physical activity and insulin as well, to decrease the complications in maternal and fetus. Over weighed diabetes in family history, race/ethnicity, 25 years or more age, previous delivered baby with weight 9 pounds or pre-diabetic gestational patients are risk factors and may increase the complications of GDM in any pregnant woman. Tight glycemic control with normal HBA1c levels is very important during pregnancy.

Diagnostic criteria

The most commonly used standard oral glucose tolerance test (OGTT), should be performed after overnight fasting (8-14h) by using 75 g anhydrous glucose in 300 ml water and after 2 h plasma glucose level is measured (Alberti *et al.*, 1998; Metzger *et al.*, 1998). The most commonly used OGTT to diagnose GDM is the 3-hour, 100-g OGTT. According to the recommendations for diagnostic criteria by American Diabetes Association (ADA), GDM is diagnosed if, two or more plasma glucose levels, equal to or greater than the brink (table 1): at fasting 95 mg/dl of glucose concentration, at 1 hr 180 mg/dl of glucose concentration, at 2 hr 155 mg/dl of glucose concentration or at 3 hr 140 mg/dl of glucose concentration (Tracyl. Setji *et al.*, 2005; American *et al.*, 2000; Metzger *et al.*, 1998). Most recently, panel of WHO, characterizes GDM as Impaired Glucose Tolerance (IGT) or Fasting Glucose level ≥ 7.0 mmol/L or 2 hr glucose ≤ 7.8 mmol/L (WHO, 1999). OGTT is more sensitive as compared to fasting plasma glucose (FGP). FGP is more accepted in women due to less time period and easiness of tolerance. Both the ADA and WHO criteria are valid options for the diagnosis of GDM and the prediction of unfavorable pregnancy outcomes. Throughout pregnancy, hyperglycemia may lead to congenital abnormalities in the fetus, so a tight glycemics control should be there in gestational patient.

Complications & risks of gestational diabetes mellitus

Poor glycemic control in early on pregnancy increases the unplanned abortion as well as innate malformations. While, late in pregnancy, poor management of glycaemia may possibly lead towards polyhydranomias, preterm labor, still birth along with fetal macros Omnia with its associated problems. Diabetic retinopathy can first develop for the duration of pregnancy or retinopathy that is already present can be proved as worsen. Diabetic women with microalbumin urea can have worsening albumin urea during pregnancy and are at higher risk for pre-eclampsia. Patients who have pre-existing renal failure are at increased risk of kidney function turn down during pregnancy and this may not reverse after delivery. Diabetic gastroparesis can severely exacerbate nausea and vomiting of pregnancy. Some patients may need nutritional support.

Unless, there are fetal and maternal complications, diabetic women should be capable of carrying the pregnancy up to full term, delivering at 38-41 weeks. Induction of labor before 39 weeks may be cautious if there is concern about increase fetal heaviness.

Major and most common complications are intrauterine growth retardation, fetal depression, abnormal birth weight, premature birth and the very critical is intrauterine death. These complications may be greater hazards in an augmentation of morbidity as well as mortality due to exacerbation in coronary heart diseases (Naveed, 2002). Recently available epidemiological

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evidences shows that intrauterine growth retardation (IUGR), having a greater risk in pre-eclampsia caused by expansion of cardiovascular diseases in the life of adults (Fiona *et al.*, 1996).

Several studies are present which represent that gestational diabetes mellitus GDM is 3-6% risky to develop complications in infants of that mother (Moshehod *et al.*, 1991). During a study, comparison of gestational diabetes mellitus (n = 878) in which 132 mothers with pre-GDM and 380 as control, determined that more incidence of complications, such as: hypocalcaemia, hypoglycemia (neurological damage), macrosomia, birth trauma to mother and neonate (Moshehod *et al.*,1991; Spellacy *et al.*,1985), hyperbilirubinemia, polycythemia (neurological damage and renal vein thrombosis), Thrombocytopenia, and other congenital anomalies (Moshehod *et al.*, 1991).Complications with the rates: preeclampsia or pregnancy induced hypertension (PIH) 24.6%, cesareans 45.2% have been recorded. PIH occurs most frequently with significance of ($p<0.01$) in patients with diabetic micro-angiopathy (Ulfhanson *et al.*, 1993).

Congenital anomalies

Congenital anomalies includes CNS abnormalities (neural tube defects, 4.2 fold greater as compared to other anomalies (atlas *et al.*, 2006; Christofer *et al.*, 2000; Leanny *et al.*, 2007), facial defects 85%, eye anomalies 48%, ear anomalies 95%, gastrourinary anomalies 19%, skeletal anomalies 52%, cardiovascular malformations(CVM) including mitral valve, aortic valve and vascular disruption) (atlas *et al.*, 2006; Christofer *et al.*, 2000), diabetes associated heart malformations, 3.4 fold than other anomalies (Christofer *et al.*, 2000; Leanny *et al.*, 2007); left sided obstructive heart defects (Christofer *et al.*, 2000), gastrointestinal anomalies (pyloric stenosis, small bowel atresia, mekel diverticulum, small colon syndrome),and skin anomalies (Atlas *et al.*, 2006), reno-genital and aneuploidy (Ferral *et al.*, 2002).

Pregnancy induced hypertension (PIH)

A syndrome of hypertension with or without proteinuria and edema during gestation is known as pregnancy induced hypertension (PIH). It usually occurs with some clinical menifestations (Jun Zhang *et al.*, 1997). Hypertension develops after 20 weeks of gestation categorized as PIH. Approximately, all forms of PIH are present combine in 8% of pregnancies by epidemiological point of view (Girouard *et al.*, 2007).

Classification of PIH

Four forms of PIH are present, preeclampsia, eclampsia, chronic hypertension and gestational hypertension. In underdeveloped countries, preeclampsia is a major cause of fetal and maternal morbidity and mortality (Baha *et al.*, 1995; Fiona *et al.*, 1996). In pre-eclampsia, characteristics are high blood pressure in last trimester of gestation (90 mmHg or an increase of 25mmHg with the presence of protein uric level (0.3 g per 24 hr) with instabilities of body systems. It can lead to eclampsia, *i.e.*, grand mal convulsions (Fiona *et al.*, 1996). These all classes of PIH can be defined as in table 2.

Incidence

Multiple pregnancies have more risk of PIH as compared to the single gestational women. The risk in smokers to have PIH has been observed consistently lower than the non-smokers (Jun Zhang *et al.*, 1997).

Table 1: Diagnosis of GDM by OGTT.

	ADA 100-g OGTT	ADA 75-g OGTT	WHO 75-g OGTT
Fasting (mg/dl)	95	95	126
1-hour (mg/dl)	180	180	—
2-hour (mg/dl)	155	155	140
3-hour (mg/dl)	140	—	—

For the ADA criteria, two or more of the values from either the 100- or 75-g OGTT must be met or exceeded to make the diagnosis of GDM. For the WHO criteria, one of the two values from the 75-g OGTT must be met or exceeded to make the diagnosis of GDM.

Source: Tracyl *et al.*, 2005.

Table 2: Widely used definitions of PIH forms.

	American college of Obstetrics and gynaecologist	Oxford
Hypertention	SBP*≥30mmHg or DBP**≥15mmHg or B.P≥140/90mmHg	Initial B.P<90mm Hg giving rise to maximum of ≥90mm Hg
Gestational Hypertension	Hypertension without Proteinuria	Hypertension only
preeclampsia	Hypertension with proteinuria &/or edema	Hypertension with proteinuria
eclampsia	Preeclampsia with seizures	-

SBP*=Systolic blood pressure, DBP**=Diastolic blood pressure

Table 3: characteristic features of insulin resistance syndrome in association with a class of PIH (preeclampsia).

- Hypertension
- Hyperinsulinemia
- Glucose intolerance
- Lipid abnormalities
- Increase leptin
- Increase TNF-α
- Increase PAI-1
- Increase testosterone

Source: Seely *et al.*, 2001.

Epidemeology

Epidemiologies of PIH have a number of factors which are recognized during a number of researches by different researchers at different time and areas of the world. We cannot say that a single or a specific kind of factor will be present in this condition.

Factors for epidemeology

Unlimited and uncountable factors are present to describe the epidemiology of pregnancy induced hypertension. Some of them are genetic factors *e.g.*, family history, immune response, genetic variation, antioxidant enzymes, unprotected sexual intercourse, abortion in past, assisted reproductive technology, anti-phospholipid antibodies, age of maternity, obesity (risky for maternal body mass index) (Jun Zhang *et al.*, 1997), polyhydramnios and hydrops fetalis, multiple pregnancies, race/ethnicity, smoking, low dose aspirin and supplementation, high altitude, stressful environment (Roberts, 2003).

PIH and insulin resistance

A greater degree of insulin resistance is present in PIH, by different mechanisms of insulin such as associated endothelial dysfunction, sodium retention in kidneys, activation of sympathetic nervous system, and increased level of transportation of cations.

GDM provide an increased risk of PIH, due to increase in insulin resistance due to β-cell defects (Thomas *et al.*, 2007) leading to hyperglycemia (non-insulin dependent diabetes mellitus). The results of an approach in China indicated that insulin resistance and hyperinsulinemia are present in severe PIH patients, after an oral glucose load (Gu H *et al.*, 1994; Kim *et al.*, 1999). It is also evident that hyperinsulinemia and insulin resistance play a role in hypertension development (James *et al.*, 2003). Insulin resistance have been associated with some markers in body such as, leptin, adiponeptin, tumor necrotic factor (TNF-α), platelet activating inhibitor (PAI-1), homocysteine (Palomo *et al.*, 2006; Joe *et al.*, 2003), which have been studied during or after pregnancy/in postpartum period (Girourd *et al.*, 2007).

RESEARCH (STUDY DESIGNS) ON PIH

Very limited research and evidential data is available. One of these is given: a retrospective cohort study was conducted by Xu Xiong *et al.*, in 1989-1990 on the basis of births from population based perinatal database in china, which resulted that 0.6 week shorter gestation in state of pre-eclampsia as compared to normotensive women ($p<0.1$). So, it concludes that pre-eclampsia increases the risk of intrauterine growth restriction as well as low birth weight.

Association between gestational diabetes and pregnancy induced hypertension

Some researchers have been trying to find the clear relation between PIH and GDM through their researches, but still the results are unclear due to lack of a number and frequency of studies on these two fetal conditions, in maternal as well as fetuses.

Study designs for relation between PIH and GDM

A study conducted by Chris L. Bryson *et al.*, in 1992-1998 in Washington state to assess the relation between gestational diabetes and pregnancy induced hypertension (n=62,982) by using a birth events records database (BERD). It shows after adjustment for confounders, 1.5 times greater risk for developing serious disorders among gestational diabetics and both ethnicity and prenatal care modify the association between GDM and PIH.

Another study was performed in association between PIH and GDM Mocarski and Savitz DA. in Columbia University, New York (NY), USA on basis of birth certificate data during 2001-2006.To evaluate crude and adjusted OR of GDM, logistic regression was used among all ethnic groups. The adjusted OR ranged from 1.4-2.9 for PIH. Overall, ethnic variations were seen.

In Latin America, a large population based study (n=878,680) was conducted by using a birth event records database (BERD) resulted that association between pre-eclampsia and GDM (relative risk=1.93, 95 percent CI: 1.66, 2.25) with no ethnicity and body mass index accounted in this study (Conde-Agudelo *et al.*, 2000).

Another perspective study of women for calcium supplementation trial to prevent pre-eclampsia showed the degree of abnormal glucose tolerance which was associated with pre-eclampsia. It showed that GDM have an increased risk of preeclampsia (OR=1.67, 95 percent CI: 0.92, 3.05) (Joffe *et al.*, 1998).

Another study have been found in French including 15 maternity units to found an association GDM and almost all forms of PIH (OR=2.86, 95% CI: 1.05, 7.83) (Vambergue *et al.*, 2002). A number of other studies have been examined to understand the association between GDM and PIH.

RESULTS

According to epidemiological tools and the available research data, we have reached to the point that PIH and GDM have no clear association except the way of insulin resistance, present in NIDDM due to β-cells dysfunction. No other evidences are present in available researches studies and clinical data to deduce the association between these two conditions in gestation. But these studies describe that there is some impact of factors; race, ethnicity as well as perinatal care on severity and complications of hypertension state of gestation. In GDM, monitoring of glycaemia as well as blood pressure during before, during and after GDM may provide some data to find the relationship between GDM and PIH.

CONCLUSION

It is concluded that the association between Pregnancy induced hypertension and gestational diabetes mellitus is due to a unifying factor, insulin resistance. Hyperglycemia generates the increase in blood pressure, due to insulin resistance which prolongs the extent of hypertension. That's why GDM may have a role in generating as well as precipitations of the complications of PIH. PIH and GDM have high prevalence, but most of the people do not know about the severity, complications and life threatening results. More researches should be there.

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