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Maternal Lipid Profile Changes in Gestational Diabetes Mellitus

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Abstract

Introduction: *Pregnancy is commonly recognized as a state of physiological and temporary insulin resistance. This condition is driven by high concentrations of steroid hormones such as progesterone, estrogens, prolactin, cortisol and placenta-derived human placental lactogen. All of these are diabetogenic and combined cause for decreased sensitivity of insulin receptors within target tissues. Women with prior GDM are at greater risk for developing hypertension, hyperlipidaemia and electrocardiogram abnormalities.*

Materials and Methods: *seventy five patients with Gestational diabetes mellitus and 75 healthy Normal pregnant women were enrolled for the study after the institutional ethical committee's clearance was obtained. The fasting blood samples of the study subjects were evaluated for the glucose, lipid profile, Glycated Haemoglobin (HbA1c), Malondialdehyde (MDA) and calculated BMI.*

Results: *Lipid peroxidation is enhanced in GDM group as MDA values have elevated significantly ($p < 0.0001$) compared to normal pregnancy. Total cholesterol ($p< 0.001$) and LDL ($p = 0.001$) are found to be significantly higher in GDM, but there are no significant differences in triglycerides and HDL between normal and diabetic pregnant women. Obesity is observed in GDM group as their BMI ($p < 0.001$) is significantly higher than that of the control group.*

Conclusions: *It was found that GDM is associated with hyperlipidaemia as evidenced by the significantly elevated total cholesterol and LDL concentrations. Obesity and lipid peroxidation are significantly high in GDM.*

Keywords: *Gestational diabetes mellitus, HbA1c, lipid profile, lipid peroxidation, BMI.*

Introduction

Gestational diabetes mellitus (GDM) is a risk factor for development of type 2 diabetes mellitus in later life[1]. GDM affects 3 to 5% of pregnancies[2]. It is believed to occur when pancreas fail to produce adequate amounts of insulin in the face of increasing insulin resistance during pregnancy. According to some authors GDM risk factor for metabolic syndrome, may trigger irreversible vascular changes putting patient at risk of cardiovascular diseases[3]. Endothelial dysfunction has been diagnosed in

women with history of GDM[4]. Metabolic syndrome associated with insulin resistance, i.e. dislipemia, is a well-known cardiovascular risk factor.

Pregnancy is a stressful condition in which many physiological and metabolic functions alter to a considerable extent. In recent years, the role of decreasing anti-oxidants and increasing free radicals are gaining importance as these factors lead to maternal and foetal complications. Antioxidants are crucial in pregnancy as they have been shown to have a protective effect against oxidative stress[5]. The exact pro oxidant and antioxidant status in GDM is still unclear. However, lipid peroxidation is suggested to play a role in pathogenesis of GDM[3].

Materials and Methods

This study has been carried out at NRI Medical College and General Hospital, Chinakakani, in the Guntur district. The study was performed after getting approval from the institutional ethics committee. In this study fasting plasma glucose (FPG), postprandial plasma glucose(PPPG), Glucose Challenge Test (GCT), Oral Glucose Tolerance Test (OGTT), Glycated haemoglobin (HbA1c), Lipid profile, Malondialdehyde (MDA) levels in GDM patients attending the Obstetrics and Gynaecology department have been evaluated. Gestational age between 28 and 34 weeks with GDM have been included in this study. The diagnosis of GDM has been established on the basis of clinical profile, biochemical tests like GCT, OGTT and HbA1c. All selected patients belong to the age group of 20 to 30 years. Exclusion criteria is made on the previous clinical history. Patients already having type 1 or type 2 diabetes, before pregnancy are excluded from the study. Those having history of hypertension, renal, liver diseases and other chronic medical diseases are also excluded from the study. Age matched healthy pregnant women with normal plasma glucose concentration and having no past history of diabetes and hypertension are taken as controls.

The total number of 150 subjects are divided into two groups, namely Group-I and Group-II. Group-I includes 75 GDM patients and Group-II consists of 75 Normal glucose tolerance (NGT) pregnant women. GDM is usually detected in the second trimester. Fasting venous blood sample has been used for the estimation of fasting serum glucose, lipid profile and MDA. For the estimation of HbA1c EDTA is used as anticoagulant. Postprandial serum glucose has been estimated 2 hours after breakfast. GCT has been estimated by measuring the serum glucose concentration 1 hour after a 50-g oral glucose load. Diagnostic OGTT has been estimated on that subset of women exceeding the glucose threshold value of 140 mg/dl on the GCT. The diagnosis of GDM is based on an OGTT as per American Diabetic Association (ADA). Diagnostic criteria for the 100-g OGTT are derived from the original work of O'Sullivan and Mahan[6] modified by Carpenter and Coustan[7].

Controls have been excluded from OGTT as it is unethical to conduct OGTT in normal pregnant women. For all the subjects blood pressure also has been recorded. Automated clinical chemistry system of Dade Dimension RxL has been used for estimation of serum glucose and lipid profile by enzymatic methods using Dade (Siemens) kits adapted to Dade autoanalyzer. HbA1c was estimated by BioRad D10 system which was based on the principle of High Performance Liquid Chromatography (HPLC). Lipid peroxides are analysed by quantitative assay of thiobarbituric acid reactive substances, expressed as n-moles MDA/dL[8]. BMI has been calculated by individual's body weight in Kg divided by the square of her height in meters.

Statistical analysis: Values for the variables are expressed as Mean ± Standard Deviation (SD). Comparison of women with GDM against the control group (NGT) has been done using unpaired students t-test, at a level of $p<0.05$ is

considered as statistically significant. SPSS 11.5 (SPSS Inc., United States) has been used for statistical analysis.

Results

The two study groups have similar maternal and gestational age, systolic and diastolic blood pressures. As expected, women with GDM had higher mean fasting ($p<0.001$), 2hr post prandial blood glucose ($p<0.001$) concentrations compared with controls. Mean GCT ($p<0.0001$) and HbA1c ($p<0.0001$) concentrations are also significantly higher in women with GDM (Table-1). Mean values of OGTT are significantly higher in GDM patients when compared with American Diabetic Association (ADA) recommended glucose cut points (Table-2).

Lipid profile in GDM patients exhibited significantly higher total cholesterol ($p<0.001$) and Low Density Lipoprotein (LDL) concentration ($p<0.001$). High Density Lipoprotein (HDL) mean values were slightly lower than controls but the difference was not significant ($p=0.7$). Triglycerides ($p = 0.978$) mean values were elevated in GDM but the difference was not significant (Table-1). MDA concentration ($p<0.0001$) and BMI ($p <0.001$) were significantly higher in GDM patients.

Table 1: Parameters with Mean and SD values of GDM and Controls

Parameters (Units of measurement)	GDM (Mean ± SD)	NGT (Mean ± SD)	p -value
Number of Patients (n)	75	75	
Maternal Age (years)	23.94 ±3.08	23.21 ±2.76	0.193(NS)
Gestational Age (weeks)	30.16±1.608	30.22±1.842	0.855(NS)
Fasting Glucose (mg/dL)	113.62 ± 29.88	85.39 ± 10.28	<0.0001*
Postprandial Glucose (mg/dL)	161.21 ± 45.30	124.83 ± 10.59	<0.001*
GCT (mg/dL)	180.87 ± 64.01	124.35 ± 13.15	<0.0001*
Cholesterol (mg/dL)	204.71 ± 22.54	182.05 ± 28.01	<0.001*
Triglycerides (mg/dL)	166.5 ± 31.7	166.22 ± 51.06	0.978 (NS)
HDL (mg/dL)	46.92 ± 5.13	47.25 ± 6.77	0.7 (NS)
LDL (mg/dL)	123.23 + 18.14	101.32 ± 25	0.001*
VLDL (mg/dL)	33.09 ± 6.32	32.28 ± 10.13	0.92 (NS)
HbA1c %	6.28 ± 0.75	4.974 ± 0.513	<0.0001*
MDA (n moles/dL)	644.93 ± 117.6	381.8 ± 113.2	<0.0001*
Systolic BP (mm Hg)	112.5 ± 8.032	111.13 ± 9.73	0.506 (NS)
Diastolic BP (mm Hg)	76.87 ± 8.2	76.11 ± 10.33	0.724 (NS)
BMI (kg/m^2)	28.51 ± 3.69	24.35 ± 3.63	<0.001*

* - Significant NS - Not Significant

Table 2: OGTT Values of ADA Glucose cut points and Mean and SD of GDM Patients.

OGTT 100g, 3-h (mg/dl)	Fasting	1 st hr	2 nd hr	3rd hr
ADA Glucose cut points	95	180	155	140
GDM (Mean ± S.D)	116.35 ± 27.12	214.46 ± 41.02	184.21 ± 29.72	157.9 ± 30.44

Discussion

GDM is a metabolic disorder affecting carbohydrates, fat, and protein metabolism and characterized by hyperglycaemia resulting from a disorder either in insulin secretion or its action on target tissues or both. Complications such as hypertension, preeclampsia, greater risk of developing diabetes mellitus and need for caesarean at the time of delivery due to big baby may arise. The mother may get DM and obesity in future due to GDM.

The present study evaluated the role of biochemical markers such as fasting plasma glucose, postprandial plasma glucose, GCT, OGTT, HbA1c, total cholesterol, TG, HDL, LDL and VLDL. MDA is estimated as a marker for oxidative stress in gestational diabetes.

Fasting serum glucose and postprandial glucose have been found to increase in GDM patients. Elevated fasting and postprandial glucose levels are associated with insulin resistance, which is common in pregnancy, due to elevation of chorionic gonadotropin and cortisol as well as estrogen and progesterone. Insulin resistance increases in GDM patients more than the normal. Chronic autoimmunity directed at B-cells is one mechanism that may contribute to B-cell failure in GDM, perhaps even in the absence of chronic insulin resistance. However, evidence for such autoimmunity is present in only a small minority of patients. Mechanisms that lead to B-cell failure in the majority of women remain to be identified. The frequent occurrence of chronic insulin resistance in women who have or had GDM suggests that the propensity for B-cells to fail in the presence of insulin resistance may be a common feature of the disease. The same mechanism may be involved in progression from GDM to type 2 DM and in the pathogenesis of type 2 DM in general [9]. Women with GDM demonstrate an increase in insulin resistance beyond that observed in the normal pregnant state. These women have levels of free fatty acids that exceeded than those of pregnant non- diabetic controls. Free fatty acids plays a role in the pathogenesis of insulin resistance and GDM [10]. Tumour necrosis factor (TNF-α) has been recognized as the most prominent factor in insulin resistance in obesity and diabetes [11].

Cholesterol increase in GDM patients is more when compared to normal pregnant women. High maternal cholesterol is associated with increase in LDL cholesterol and Apo-B concentration in maternal blood [12]. The disturbances in glucose metabolism causes lipid profile changes. Cholesterol is used by placenta for steroid synthesis and fatty acid for placental oxidation. Changes in total cholesterol concentration reflect changes in various lipoprotein fractions [13]. Total cholesterol concentration is decreased initially, but increased in 2nd and 3rd trimesters in response to estrogen in normal pregnancy.

The increase of LDL in GDM patients is more when compared with NGT controls (Table-1). Lipolysis is increased as a result of insulin resistance, leading to increased influx of free fatty acids to liver promoting the synthesis of VLDL. VLDL remains in the plasma for a longer period which leads to accumulation of LDL [14,15]. The GDM patients who have the family history of early onset of autosomal dominant type 2 diabetes may be due to defective lipolysis of VLDL. Metabolic studies carried out demonstrated that women with GDM have multiple defects in insulin action together with impaired compensation for insulin resistance. These defects in the regulation of glucose production, glucose clearance and free fatty acid concentrations, along with defects in pancreatic B-cell function, precede the development of type 2 diabetes in women with GDM. Insulin resistance and type 2 diabetes mellitus are associated with a clustering of interrelated plasma lipid and lipoprotein abnormalities, which include decreased HDL cholesterol and a predominance of LDL cholesterol particles [16].

In the present study, the total cholesterol and LDL levels show a significant increase in GDM than normal pregnancies. HDL mean values are lower in GDM than control but not significant. TG mean values are not significantly higher in GDM patients when compared with controls. VLDL mean values are higher in GDM patients but the difference is not significant[15]. This dyslipidaemia profile has also been noted in pregnancies complicated by GDM in various case control studies [17,18,19]. All results from these studies are not in consonant with each other. The discrepancy among these studies may be due to

small sample size, as well as methodological differences [20].

Increased blood glucose levels induce oxidative stress and decrease antioxidant defences apparent in diabetes. Possible source of oxidative stress in diabetes include free radicals generated by auto oxidation of glucose, unsaturated lipids in plasma and membrane proteins. Oxidative stress may be amplified by a continuing cycle of metabolic stress, tissue damage and cell death leading to increased free radical production and compromised free radical scavenger system which further exacerbates the oxidative stress [21].

Abnormality in the regulation of peroxide and transition metal metabolites are postulated to result in establishment of disease as well as its long term complications. In normal pregnancy there is an increase of lipoperoxidation products in serum with advancing gestation which is balanced by an adequate anti oxidative response [22]. But in diabetic pregnancy there is increased oxidative stress leading to increased free radical generation and decreased antioxidant defences. The proposed mechanism for oxygen free radical generation at higher glucose concentration in pregnancy include non–enzymatic protein glycation, which may induce production of oxygen free radicals (23). Free radicals are formed disproportionately in diabetes by glucose auto-oxidation, polyol pathway and non-enzymatic glycation of proteins [14]. In the present study, there is a significant increase in levels of MDA, a marker of lipid peroxidation, in GDM than normal pregnancies.

Women with GDM tend to be obese, so mechanisms promoting obesity and or linking obesity to insulin resistance are likely to play a role. Some studies have revealed increased circulating levels of leptin, the inflammatory markers TNF-α, C-reactive protein and decreased levels of adiponectinin women with GDM. Inherited reduction in the mitochondrial content in skeletal muscle of insulin-resistant pre-diabetic offspring of parents with type 2 diabetes and this reduction may be responsible for decreased oxidative phosphorylation, decreased lipid oxidation and lipid accumulation [24]. These phenomena could lead to a continuing tendency toward both weight gain and excess intra-organ lipid concentrations. Consistent with these findings, the pre-pregnancy body mass index increased progressively from normal glucose tolerance to mild gestational hyperglycemia to GDM [24].

Conclusions

It was found that GDM associated with dyslipidaemia, lipid peroxidation and obesity as evidenced by the significantly elevated total cholesterol, LDL, MDA and BMI. Dyslipidaemia in women with GDM increased their risk of developing preeclampsia is thought to reflect an oxidative stress related mechanism. Diabetes mellitus as complicated by pregnancy may give rise to irreversible vascular changes that put the women at risk of increased cardiovascular morbidity. Hence it is of paramount importance to identify women at risk of GDM and to keep a tight metabolic control in order to avoid immediate and long term consequences for mother and their offspring.

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