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Maternal Serum Biomarkers for the Early Prediction of Gestational Diabetes Mellitus

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Review Article

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Abstract

The prevalence of gestational diabetes mellitus (GDM) is increasing because of the worldwide obesity/diabetes epidemic. The complications of untreated GDM affect both the mother and baby and include complications during pregnancy as well as increased risk of subsequent type-2 Diabetes in mother and offspring. Screening for glucose intolerance during pregnancy provides an opportunity to offer management to those women diagnosed with gestational diabetes mellitus (GDM). Standard tests for hyperglycemia in diabetes, such as fasting glucose and glycosylated hemoglobin (HbA1c) are not currently recommended for GDM screening. Instead, an oral glucose tolerance test (OGTT) is specified, which is invasive, time-consuming, and not easily accessible to many at-risk populations. In this article, we describe a multi-analyte maternal serum profile test that incorporates novel glycoprotein biomarkers include endocrine and metabolic hormones like Myokines & cytokines (Adiponectin, Irisin, HCG, Insulin, Ferritin, PAPP-A, Resistin, CRP, Fibronectin, Leptin and SHBG). Further studies are warranted to determine the Reliability of these markers.

Keywords: Gestational Diabetes Mellitus; Irisin; Fibronectin; Adiponectin; PAPP-A; Leptin

Introduction

Diabetes mellitus is a major global health problem. According to the most recent projections, the worldwide prevalence of diabetes mellitus is expected to reach 300 million in 2025 compared to the current prevalence of around 160 million [1]. About 18% of women may experience gestational diabetes while pregnant but around 7% of those pregnancies will face complications [2,3]. Gestational diabetes mellitus (GDM) or Carbohydrate intolerance, a common medical complication during pregnancy is defined as “any degree of glucose intolorence with onset or first recognition during pregnancy” [4]. GDM is a serious complication of pregnancy that can increase the risks of several maternal-fetal disorders, including macrosomia, shoulder dystocia

or birth injury, premature delivery and preeclampsia [5-8].

In addition to the increased risk of complications associated with gestation and delivery, there are also serious post-natal complications of GDM. About 5-10% of women with GDM are found to have diabetes immediately after pregnancy and women who had GDM have a 10-fold higher chance of developing diabetes within the next 10-20 years [6]. It is now apparent that children of mothers with GDM have an 8-fold higher risk of developing type-2 diabetes mellitus in later life [7]. Thus untreated GDM contributes to the overall diabetic population in both the short and long term. Universal or even widespread GDM screening is hampered by the fact that the standard assessments of diabetes and pre-diabetes, such as fasting insulin/glucose and HbA1c, are not recommended for screening of GDM. Instead, the recommended parameter is an oral glucose tolerance test (OGTT) [8], which is invasive requiring a hospital visit and multiple blood draws. Therefore, improved methods and analytes for GDM screening are needed to increase diagnosis rates and prevent maternal and child risk of future diabetes. Specifically, the development of minimally invasive testing with robust analyte combinations will greatly aid in the identification of GDM [9].

The rates of obesity and diabetes have increased rapidly over the last 20 years in US as well as globally [10]. It is not surprising that the incidence of gestational diabetes mellitus (GDM) is also increasing in parallel to the overall rise in obesity and type-2 diabetes [11]. The adoption of new diagnostic criteria based on the recent HAPO study will increase the prevalence of GDM to approximately 18% of all pregnancies [12]. In light of the fact that 80-90% of women diagnosed with GDM can be managed with lifestyle therapy [13]. However, there is no internationally accepted method of screening for GDM. In UK, it is recommended that an oral glucose tolerance test (OGTT), which is the diagnostic test for GDM, should be offered to women with any one of the following risk factors: body mass index (BMI) >30 kg/m2, previous history of GDM or Macrosomic baby (>4.5 kg), family history of diabetes or Racial origin with a high prevalence of diabetes such as South Asian, African-Caribbean and Middle Eastern (NICE, 2008).[1]The recommendation made by some organization to adopt a 1-step process 2 hrs-75gm OGTT for GDM screening, but currently American congress of obstetricians and gynecologist (ACOG) accepts the 2-step diagnostic process for screening of GDM between 24-28 weeks with a non-fasting 1-hour sample, 50 gram GCT [12,14]. We don't know the causes of gestational diabetes, but we have some clues which cause GDM. The placenta supports the baby as it grows and Placental hormones help the baby to develop. But these hormones also block the action of the mother's insulin. This is what we call insulin resistance. Insulin resistance makes it hard for the mother's body to use insulin and require up to three times higher insulin.

Gestational diabetes develops when your body is not able to produce enough insulin during pregnancy. Insulin is necessary to transport blood glucose into the cells and without enough insulin, high concentration of glucose is accumulated in the blood, leading to a higher-than-normal blood glucose level (hyperglycemia) and perhaps leads to gestational diabetes.

However, untreated or poorly controlled gestational diabetes can hurt the growing foetus. The pancreas works overtime to produce insulin in GDM, but the insulin does not lower your blood glucose levels. Insulin will not cross the placenta, but glucose and other nutrients will cross the placenta, so extra blood glucose will go through the placenta giving high blood glucose levels to the baby. This causes the baby's pancreas to make extra insulin to get rid of increased blood glucose. The extra energy will be stored as fat because the baby is getting more energy than it requires to grow and develop. This will lead to macrosomia, or a "fat" baby. Babies with macrosomia faces health complications, including damage to their shoulders during birth. Because of the extra insulin made by the baby's pancreas, newborns may have very low blood glucose levels at birth and are also at higher risk for breathing problems. The elevated blood glucose level in gestational diabetes is caused by hormones released by the placenta during pregnancy. The placenta produces a hormone called the human placental lactogen (HPL), also known as human chorionic somatotropin (HCS). It's action is similar to growth hormone (so it helps the baby grow), but it actually modifies the mother's metabolism and how she processes carbohydrates and lipids. HPL actually raises maternal blood glucose level and makes a woman's body less sensitive to insulin less able to use it properly. If the body doesn't use insulin as it should, then the blood glucose levels will rise. The HPL hormone increases the blood glucose level so that the baby can get the nutrients it needs from the extra glucose in the blood [15].

At 15 weeks of gestation, another hormone called human placental growth hormone will also increases and

causes maternal blood glucose level to increase. This hormone wills also helps to regulate the mother's blood glucose level to be sure that the baby gets the right amount of needed nutrients. It's normal for women's blood glucose levels to go up a bit during pregnancy because of the extra hormones produced by the placenta. But sometimes, the blood glucose levels goes up and remain high. This leads to gestational diabetes and is associated with an increased risk of type 2 diabetes will be developed in the child [12].

Research Design and Methods

Adiponectin

Adiponectin is an abundant message encoding protein which is specifically expressed in adipose tissues. It is readily detectable in blood and stable upon collection and inversely correlates with multiple metabolic disorders [16]. It sensitizes peripheral tissues to insulin and protects the body against inflammation and apoptosis. The Molecular and Cellular mechanism of Adiponectin is exerted by two adiponectin Receptors 1 & 2 and also by non- signalling binding protein T-cadherin. The Adiponectin receptors acts as Transmembrane signal transducers for Adiponectin ligand [17]. Epidemiological data in some study reveals that Adiponectin may improve Lipoprotein and cholesterol metabolism and protects against coronary lesions [18,19]. It is believed that Adiponectin promotes glucose-stimulated insulin secretion (GSIS), enhances the beta cells under a variety of conditions and prevent apoptosis [20,21].

Adiponectin and SHBG in Early Pregnancy

Adiponectin is an adipocyte-derived polypeptide and Sex Hormone Bing Globulin (SHBG) a liver-derived glycoprotein. In a case-control study conducted between March 2006 to August 2009, they examined 12,283 singleton pregnancies and excluded 819 due to previous pregnancy etc. In the 11,464 included cases 297 cases had developed GDM. They randomly selected 80 cases of GDM and 300 controls. The study involved the measurement of maternal serum concentration of Adiponectin (ELISA) and SHBG (Sex hormone binding globulin) at 11-13 weeks of gestation. SHBG was measured by DELFIA (dissociation-enhanced lanthanide fluorescent immunoassay) [1]. Low levels of Adiponectin have been reported prior to the development of GDM, in overt GDM and in Type II diabetes patients also.

Plasma Insulin and Adiponectin (11week gestation)

A study was conducted at East Melbourne, Australia a total of 250 pregnant women were recruited to the study at their first antenatal visit itself. They are routinely screened for GDM by oral GTT at approximately between 24 to 28 weeks of gestation. Out of 250 participants 14 were diagnosed with GDM, after an overnight fasting followed by a 75g Glucose load test. GDM was diagnosed by a fasting glucose concentration ≥ 6 mmol/L and 2 hour glucose concentration ≥8.0 mmol/L (WHO). For the purpose of the study an equal no of matched (Age, gravidity, parity, ethnicity and BMI matched) and normal pregnant women (non-GDM) were also screened postnatally. Of the 23 biomarkers investigated at 11 weeks Gestation, only Plasma Insulin (ELISA) and Adiponectin were found to be significantly different between those of uncomplicated control women and women destined to develop GDM [22].

Irisin (Improves Glucose Tolerance)

Irisin (also known as FNDC5), is a fat-fighting powerhouse. In the past few years, dysregulation of various adipocytes and hepatocytes derived factors are seen.(Including Adiponectin, Leptin, Adipocyte fatty acid-binding protein and fibroblast growth factor-21) has been reported to mediate insulin resistance and proinflammatory effects in GDM [23,24]. Moreover, Myocytes - secreted proteins, in addition to Adipokines and Hepatokines, renewed interest in the field of metabolic diseases most recently. Bostron introduced the myokine Irisin as an exercise – inducible secreted factor that improves glucose tolerance and increases energy expenditure in mice [25]. So far data about Irisin in humans have been insufficient to evaluate its metabolic effects and association with metabolic disease.

Irisin is an Anti-diabetic hormone that regulates Glucose metabolism and energy consumption via converting White to Brown adipose tissue. Reports on Irisin Regulation in GDM and pregnancy are scant. BMI was determined as weight/ squared ht. Irisin serum concentration were determined by ELISA, according to the manufacturer's instruction at 24-28 gestational weeks. Fasting serum Irisin level was measured 3 days after the oral GTT. Moreover, Glycosylated hemoglobin was also measured [26]. The study was performed at Tertiary care centre Department of O&G between January 2014 – April 2014. A total of 41 pregnant women with GDM and 41

BMI and Age -matched Healthly pregnant women (control group) were included in the study [27].

Serum Ferritin and Maternal Diabetes

A review article published by the Departmentt of Edocrinology , PR China states the following. Ferritin, the major Iron storage protein, plays a key role in Iron metabolism. Serum Ferritin concentration provides an indirect estimation of body iron stores because it is highly correlated with bone marrow iron. Ferritin is also a positive Acute - phase reaction and increases in the various acute and chronic disease condition [28,29]. High levels of Ferritin were a risk for development of GDM in pregnant women. Non Anemic Gravidas from Honk Kong who developed GDM during the course of pregnancy were compared with cases without anemia or diabetes selected at random from the risk population. Studies also showed a significant relation between higher serum Ferritin levels and Insulin resistant syndrome and risk of type II Diabetes [30,31]. Unadjusted concentration of serum Ferritin, Iron and the post natal hemoglobin were significantly higher at 28 – 31 Week gestation in cases with GDM compared with controls [32]. The mechanisms involved in the development of GDM are not completely understood. It is increasingly being recognized that there is a systematic inflammation in GDM, as indicated by higher levels of serum CRP. Inflammation is usually associated with obesity because adiposities from adipose tissue can secrete Proinflammatory cytokines [33].

Pregnancy Associated Plasma Protein-A (11- 14 weeks)

PAPP-A is a Matri metalloproteinase that regulates the extracellular matri remodeling during pregnancy, it is produced by the trophoblast and is detectable in maternal blood from the 28th day of conception in nonpregnant women. PAPP-A is produced by corpus luteum and granulose. A case-control study comparing pregnancies complicated from GDM and selected healthy pregnancies was done at the Department of O&G, University Hospital at Pavia, Itlay in the period of 2007- 2009. During the period of study, out of 3477 patients who received prenatal care, 228 patients were diagnosed with GDM and 228 Euglycemic pregnant women served as control group. Serum free β-HCG and PAPP-A (Pregnancy specific plasma protein-A) were measured by Delfia Xpress Analytical platform. This study is the first investigation suggesting that women who develop GDM had Low First Trimester maternal PAPP-A. In women with GDM both first trimester median and adjusted multiple of median PAPP-A concentrations were lower than in the control group [32]. This hypothesis is supported by Peitero who studied the relationship among PAPP-A, inflammatory cytokines and glucose control in diabetic Non pregnant women [34].

GDM in Twin Pregnancy-A Screening Approach

A study was conducted in 2014 by YOgev.et al for the Screening of GDM in Twin pregnancy. A total of 14,268 pregnant women had participated. Out of that 529 women were Twin pregnancy (by Scan). Glucose challenge test (GCT) was done for 529 twin pregnancies and 14,268 singleton pregnancies between 24-28 weeks of gestation [24]. Patients underwent 1 hour GCT with 50 gm non-fasting oral glucose load test. OGTT was done for the patients who had greater GCT cut-off typically between 130-140 mg/dl [12]. The population was mostly Nonobese. They found that patients with Twin pregnancies had significantly higher GCT ≥ 130 mg/dl and ≥ 140 mg/dl even after the adjustment of fetal sex, maternal age and parity [35,36].

A cohort study was conducted at New York University from 2005 to 2013. Totally 475 patients had twin pregnancies and out of that 31 patients were diagnosed with GDM. They compared 3 different GCT threshold values for the diagnosis of GDM. The GCT values are ≥130 mg/dl, ≥135 mg/dl and ≥140 mg/dl. 1 hour GCT was done for the patients between 24-28 weeks gestation and patients with GCT above 130 underwent a 3 hours OGTT (100 gm glucose). The diagnosis of GDM was conformed if 2 of the 4 values of OGTT were abnormal. Patients with GCT less than 130 mg/dl did not undergo OGTT. They have created ROC cure for all the patients. In this study they found that the GCT cutoff value for twin pregnancies is ≥130 mg/dl and the sensitivity is 100 %. [37,38].

Leptin: Leptin is an adipokine involved in the weight regulation and metabolism. Leptin is produced by the placenta and is increased during pregnancy and maternal hyperliptinemia. Some have reported increased leptin level [39-41]. Decreased leptin level and unchanged serum leptin level in GDM [42]. A case-control study was performed in school of medicine at Iran from July 2007 to October 2008. Blood samples were obtained from 22 normal healthy pregnant women and 26 GDM patients. They have measured the serum leptin concentration and the data's were analyzed by independent sample t-test. There was no significant difference regarding Age, weight, BMI and gestational age at first trimester between the case and control group. No significant weight again is also observed between the two groups. The serum leptin level

in GDM is 9.890 ± 7.764 ng/ml and 13.80 ± 10.32 ng/ml in normal pregnant women. No significant difference was noticed in maternal serum leptin level between the control and case (p=0.14) [43].

Discussion

About 2-5% of all pregnant women develop gestational diabetes mellitus (GDM) during their pregnancies and the prevalence has increased considerably during the last decade. GDM is a heterogeneous disorder that is defined as carbohydrate intolerance with onset or first recognition during pregnancy. It is manifested when pancreatic beta cells are no longer able to compensate for the increased insulin resistance during pregnancy, but the pathogenesis of the disease is still largely unknown. GDM is considered to result from interaction between genetic and environmental risk factors. Old age, obesity and high fat diet represent some important non-genetic factors. Although the true prevalence of GDM is unknown, GDM is estimated to affect 1% to 14% of pregnancies in the United States annually.

The Myokine Irisin is an exercise-inducible secreted factor that improves glucose tolerance and increases energy expenditure. Serum Irisin level might be introduced as marker for GDM, with the decreased levels being indicative of GDM. Lower first trimester PAPP-A in pregnancies destined to develop GDM, suggests that PAPP-A could be a early marker of incipient glucose intolerance. Many Findings shows that in GDM group maternal serum Adiponectin and SHBG levels at 11 to 13 weeks were reduced by about 30% and 20 % respectively. It is believed that Adiponectin promotes glucose-stimulated insulin secretion. Most of the studies says that the risk factors for development of GDM include increased maternal Age and BMI.

Conclusion

The goal of prenatal care is to ensure health of the mother and giving birth to a healthy baby. Pregnancy is the time of more complicated changes, and the common endocrine condition encountered is GDM and thyroid dysfunction. So women with history of GDM should be encouraged to use preventive behavior such as increased physical activity, diet management and maintenance of normal weight. GDM women should be screened for diabetes because they have the risk of getting diabetes in future. We conclude that the first trimester screening for GDM can be done by a combination of maternal characteristics and various novel biomarkers like Adipoonectin, Irisin, HCG, Insulin, Leptin, Ferriti, PAPP-A, Resistin, CRP, Fibronectin and SHBG at 11 -28 weeks. Early diagnosis and early identification of high- risk group can lead to a reduction in the maternal as well as perinatal complications associated with GDM.

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