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Medical Journal of Obstetrics and Gynecology

Research Article

Sex Hormone Binding Globulin in Gestational Diabetes Mellitus

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Abstract

Aims: The aim of this study was to measure and compare maternal plasma SHBG concentrations in normal pregnancy and in GDM patients, and thereafter determine the association between SHBG and GDM.

Materials and Methods: This was a prospective, case-control study with a total of 60 participants in their third trimester of pregnancy. The control group had 28 women versus 32 women in the GDM/case group. Maternal serum SHBG was measured and compared between the two groups.

Results: The mean age in all participants was 28.35±4.38 years. SHBG concentrations were lower in GDM group (n=32, SHBG= 53.64±31.91) compared to the control group (n=28, SHBG= 71.33±30.58) (p <0.05).

Conclusion: SHBG levels were significantly lower in pregnant women with GDM, therefore, SHBG can, in the future, be used as both a diagnostic and monitoring tool in patients with GDM.

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Submitted: 20 March 2015

Accepted: 12 April 2015

Published: 14 April 2015

ISSN: 2333-6439

Keywords

- Gestational diabetes mellitus
- Sex hormone binding globulin
- Diabetes mellitus

ABBREVIATIONS

ADA: American Diabetes Association; BMI: Body Mass Index; CRP: C Reactive Protein; DBP: Diastolic Blood Pressure; DHT: Dihydro Testosterone; DM: Diabetes Mellitus; FPG: Fasting Plasma Glucose; GDM: Gestational Diabetes Mellitus; GH: Growth Hormone; HAPO: Hyperglycemia and Adverse Pregnancy Outcomes; HIV: Human Immunodeficiency Virus; HOMA: Homeostasis Model Assessment; IADPSG: International Association of Diabetes and Pregnancy Study Groups; IGF: Insulin like Growth Factor; mRNA: messenger Ribo Nucleic Acid; OGTT: Oral Glucose Tolerance Test; PCOS: Poly Cystic Ovarian Syndrome; RPG: Random Plasma Glucose; SBP: Systolic Blood Pressure; SHBG: Sex Hormone Binding Globulin; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; WHO: World Health Organization

INTRODUCTION

Sex Hormone

Introduction and structure: A hormone is a chemical structure that is released into the blood stream in small amounts and after delivery, elicits a typical physiologic response in the target cells [1]. Hormones are generally classified into three classes; 1: derivatives of amino acid tyrosine e.g. adrenaline, noradrenaline, thyroxine; 2: steroid hormones e.g. testosterone, estradiol; 3: peptides and proteins e.g. thyrotropin releasing hormone, prolactin releasing hormone [2]. According to Guyton and Hall [2], sex hormones are steroid hormones that are derived from cholesterol and hence their chemical structure is similar to that cholesterol. Sex hormones consist of three cyclohexyl rings and one cyclopentyl ring combined into a single structure and they are lipophilic [2].

Because sex hormones have low water solubility, they are bound to protein carriers in the blood and only the free and unbound fraction is biologically active, that is, is able to enter a cell and activate its receptor [1,3]. The protein carrier for the sex hormone is SHBG and as long as bound to the globulin, sex hormones remain inactive and these serve as a reservoir for future use [3,4]. However, protein binding is a reversible process [1].

Biosynthesis: Production of sex hormones is mainly in three endocrine organs; adrenal cortex, ovary and testis, however, during pregnancy, placenta acts as an additional source of the sex hormones [3].

Regulation: Concentration of the sex hormones fluctuates with a specific periodicity or as a response to either a physiological and/or pathological process [3,5]. Availability also depends on the biosynthesis and catabolism [5].

Sex Hormone Binding Globulin

Structure: SHBG is a plasma glycoprotein that is produced by the hepatocytes and has a high affinity for steroid hormones [6]. The liver is not the only source for SHBG because testes have also been shown to express SHBG mRNA [7]. SHBG exists as a dimer of two essentially identical monomers and the primary structure

of SHBG monomer is a single peptide of 373 amino acids and 3 carbohydrates side chains and this structure binds only one steroid molecule [8].

Functions: SHBG binds sex hormones with high affinity: DHT>testosterone>estrogen [6]. It transports sex steroid hormones within the blood stream to extravascular target tissues [6,8]. It also regulates the bioavailability of sex steroid hormones to target cells [4,6]. Concentration of circulating plasma SHBG also serves as a major determinant of the metabolic clearance of sex hormones [4].

SHBG has been identified as a contributing factor and also implicated in the pathophysiology of T2DM [6-12]. A number of epidemiological studies have also demonstrated an inverse relationship between the lower levels of SHBG with T2DM [9-12]. SHBG concentrations have been consistently found to be lower in GDM patients [13-15]; however, these concentrations are neither related nor reflective of the peripheral insulin insensitivity [15].

Based on some recent molecular epidemiological studies, genetically determined concentrations of SHBG are inversely associated with T2DM and thus supporting evidence of the role of SHBG in the development of T2DM [9,12,16]. The exact mechanism by which SHBG influences the risk of DM is still unclear but according to Nestler and colleagues, SHBG may contribute to the impairment of glucose metabolism through modulation of sex hormones, bioavailability and direct activation of specific receptor for SHBG10. On the other end, Rosner *et al*. [17] found that plasma membranes of different types of cells are capable of binding specifically and with high affinity to SHBG and thus mediating sex hormones.

Regulation: Nestler and fellow authors also found that SHBG influences glucose homeostasis, and factors such as insulin and monosaccharides are implicated as possible regulators of SHBG transcription [10]. There are factors that may increase or decrease the plasma concentration of SHBG. Factors that decrease SHBG levels include, hyperinsulinaemia, high levels of GH, high levels of IGF, PCOS and obesity [6,18-20]. Some of the factors that may increase SHBG concentrations include, liver cirrhosis, hyperthyroidism, anorexia nervosa and high estrogen levels [6,18-21].

Diabetes Mellitus

Definition and classification: Diabetes mellitus is defined as a group of metabolic diseases characterized by hyperglycemia from abnormalities in insulin secretion and/or insulin action [22-25]. DM is divided into two major groups based on the etiopathogenesis [22]; T1DM which is due absolute insulin deficiency and T2DM, due to a combination of insulin resistance and inadequate compensatory insulin secretory responses [22]. Diabetes mellitus can be classified into four clinical cases [26] which are: Type 1: This is secondary to β cell destruction resulting in absolute insulin deficiency.

Type 2: It is due to progressive defects in insulin secretin on the background of insulin resistance.

Type 3: other specific types due to other causes e.g. due to the exocrine pancreas defects such as in cystic fibrosis or chemical induced DM e.g. in treatment of HIV.

Type 4: GDM

Pathophysiology: Insulin is a major hormone that regulates the uptake of glucose from the blood, therefore, deficiency of this hormone or the insensitivity of its receptors plays a central role in all types of DM [27]. The body normally acquires glucose from three main sources; intestinal absorption of food, breakdown of glycogen (glycolysis) and gluconeogenesis [28]. Insulin can either inhibit glycolysis or gluconeogenesis. If insulin is produced in inadequate amounts, or if the cells are resistant to the effects of insulin (that is, insulin insensitivity or insulin resistance), then blood glucose remains high [28,29]. Excess glucose will then be excreted in the urine (glycosuria) [30]. This will in turn result in increased osmotic pressure and subsequent inhibition of reabsorption of water by the kidney, resulting in polyuria and because reabsorption of water by the kidneys is minimal, this will then lead to depleted plasma volume and thus causing dehydration and resultant polydipsia [28].

Diagnosis: According to WHO [31], DM is characterized by recurrent hyperglycemia and is diagnosed by either of the following:

FPG≥7.0mmol/l (≥126mg/dl)

RPG≥11.1mmol/l (200mg/dl)

Gestational Diabetes Mellitus

Definition: Gestational diabetes mellitus is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [22,24]. The American Diabetes Association defines GDM as diabetes that is diagnosed during pregnancy, but that is not overt diabetes [26]. The IADPSG has recently recommended that high risk women found to have diabetes early in pregnancy be classified as 'overt' not as 'gestational' diabetes [25]. Overt diabetes has been described by the IADPSG as pre-pregnancy diabetes that is first noted during pregnancy [25].

Pathophysiology: Insulin resistance has been identified as the hallmark of GDM and therefore, it is etiologically similar to T2DM [32]. According to Bartha Jose and colleagues, because insulinaemia has been shown to be similar between normal and GDM women, they therefore suggested that GDM is characterized by increased peripheral insulin resistance and the development of insulin resistance might be explained by the elevated triglycerides during pregnancy [15]. Based on Alan H. Decheney and colleagues, GDM and T2DM are pathogenetically related and as such, GDM is considered to be T2DM that is unmasked during pregnancy due to the metabolic changes of pregnancy [32]. GDM is secondary to reduced pancreatic β cell function and is therefore characterized by insulin concentrations that are inadequate to meet the insulin demand [23].

Diagnosis: The IADPSG recommends one step approach to diagnose GDM and the diagnosis can be made if there are one or more abnormal values of the 75g OGTT [25].

Below is the table adapted from IADPSG consensus pan [25]

1.At first visit, assign a diagnosis of preexisting diabetes if any of the following is present -FPG ≥6.99mmol/l (≥126mg/dl) -HbA1C ≥48mmol/mol (≥6.5%) -RPG ≥11.1mmol/l (200mg/dl)
2. At first visit, assign a diagnosis of GDM if present: -FPG ≥5.11mmol/l (≥92mg/dl) and <6.99mmol/l (<126mg/dl)
3. At 24-28weeks gestational age, perform 75g OGTT, 2h OGTT and assign a diagnosis of GDM if one or more of the following plasma glucose values is met or exceeded. -FPG ≥5.11mmol/l(≥92mg/dl) and <6.99mmol/l (<126mg/dl) -1h ≥9.99mmol/l (≥180mg/dl) -2h ≥8.49mmol/l (≥153mg/dl)

MATERIALS AND METHODS

This was a prospective, case-control study among pregnant women who were admitted to Fujian Union Hospital in the department of Obstetrics and Gynecology for routine delivery between May 2014 and July 2014. The study population consisted of the patients who eligible for the study during the period. All participants were carrying singleton pregnancies. Patients with known diabetes mellitus and hypertension were excluded from the study and those with multiple pregnancies. Patients with PCOS were also excluded from the study because according to Veltman-Verhulst and colleagues [33], PCOS is associated with lower SHBG levels and these pre-conceptual levels are strongly associated with the development of GDM.

Patients were diagnosed as GDM based on the IADPSG consensus panel. The diagnosis of GDM was made during antenatal visits between 24-28 weeks gestational age. Gestational age was calculated based on the participants` last normal menstrual period and first trimester (described as the first 13 weeks) ultrasound. Maternal weight, height, blood pressure, gestational age and fetal weight were obtained from the patients' medical records. Maternal blood samples were collected into non heparinized tubes as part of the routine work up before admission. Samples were centrifuged by the hospital's laboratory; serum was separated and frozen at -20°C until assayed for SHBG analyses. SHBG was measured by a quantitative sandwich enzyme- linked immunoassay (ELISA) technique. The sensitivity of the SHBG was 1.0nmol/l. The kit for SHBG analysis was supplied by the Shanghai Blue Gene biotech.

Ethical Issues

The research was approved by the Fujian Union Hospital Research Ethics committee. A waiver for informed consent was approved because the participants were not subjected to any study specific investigations beyond the routine clinical care. Participants were identified by their hospital number and names were only used to retrieve the clinical file and the laboratory results.

RESULTS

Data analysis was performed using SPSS for Windows, version 18. Data are shown as mean±SD or median (min-max), where applicable. The mean differences between the study groups were compared by Student's *t*-test. The area under the curve (AUC) and 95% confidence interval (CI) for SHBG was evaluated by receiver-operator curve (ROC) analysis. Odds ratio and 95% CI for each independent variable were also calculated. A *p* value less than 0.05 was considered to be statistically significant.

There were a total of 60 participants and 28 of them were in the control group and the remaining 32 were in the GDM/cases group. The mean age in all participants (n=60) was 28.35±4.38 years. However, the women in the GDM group were found to be older than the control group, 29.63±4.93years in the GDM group versus 26.89±3.14 years in the control group (Table 1). Random plasma glucose levels were found to be statistically higher in the GDM group (5.25± 1.25mmol/l) when compared to the control group (4.71±0.77mmol/l) (Table 1). SHBG concentration in the combined participants was 61.89±32.28nmol/l and in the control group, it was 71.33±30.58nmol/l while in the GDM group it was significantly lowered with a mean of 53.64±31.91nmol/l (p= 0.03). There were no significant differences in the blood pressures between the two study groups. There were no women who were underweight and twenty-two (36.67%) of the participants were in the normal BMI category whilst twenty- seven (45%) were overweight and ten (16.67%) were class 1 obese and 1.67% were class 2 obese (Table 2).The correlation between SHBG levels, RPG, BMI and fetal weight was not statistically significant in both groups (Tables 3 and 4). However, the correlation between these parameters in the GDM group was found to be a slightly positive relationship even though this failed to reach levels of significance (Table 4).The predictive accuracy of SHBG as a marker for GDM was determined by receiver operator curve (ROC) analysis (AUC: 0.677; 95% CI: 0.531-0.803; Figure 1).

DISCUSSION

There are four main findings that can be drawn from our study:

Table 1: Baseline parameters of the control and GDM groups.

Parameters	Combined (n=60)	Control group (n=28)	GDM group (n=32)	*P* values
Age (years)	28.35±4.38	26.89±3.14	29.63±4.93	0.012ŧ
Weight (kg)	68.14±8.51	67.14±7.04	69.02±9.64	NS
Height (cm)	160.32±4.81	160.11±5.53	160.50±4.16	NS
BMI (kg/m2)	26.53±3.26	26.20±2.53	26.82±3.79	NS
SBP (mmHg)	120.48±10.54	120.07±9.85	120.84±11.25	NS
DBP (mmHg)	74.35±8.91	74.11±8.27	74.56±9.565	NS
RPG (mmol/l)	5.00±1.09	4.71±0.77	5.25±1.25	0.05ŧ
SHBG (nmol/l)	61.89±32.28	71.33±30.58	53.64±31.91	0.03ŧ
Gestational Age (weeks)	38.5±1.86	38.96±1.32	38.09±2.18	NS
Gravidity	2 (1-7)	2 (1-3)	1.5 (1-7)	NS
Parity	0 (0-3)	0.5 (0-2)	0 (0-3)	NS

Note: All parameters are mean ± SD except for gravidity and parity which are median (min-max); SD, Standard Deviation; NS, Not Significant; ŧ statistically significant

Table 2: BMI Distribution in the two groups.

BMI Distribution (kg/m2)	Combined (n=60)	Control group (n=28)	GDM group (n=32)
Underweight 16-18.4	0	0	0
Normal 18.5-24.9	22	11	11
Overweight 25-29.9	27	13	14
Obese Class 1 30-34.9	10	4	6
Obese Class 2 35-39.9	1	0	1
Obese Class 3 ≥40	0	0	0

Table 3: Pearson correlation coefficients between SHBG concentration and BMI, RPG and fetal weight in the control group.

Parameters	SHBG Concentration
BMI	0.076 (*P*=0.701)
RPG	0.040 (*P*=0.839)
Fetal Weight	0.045 (*P*=0.820)

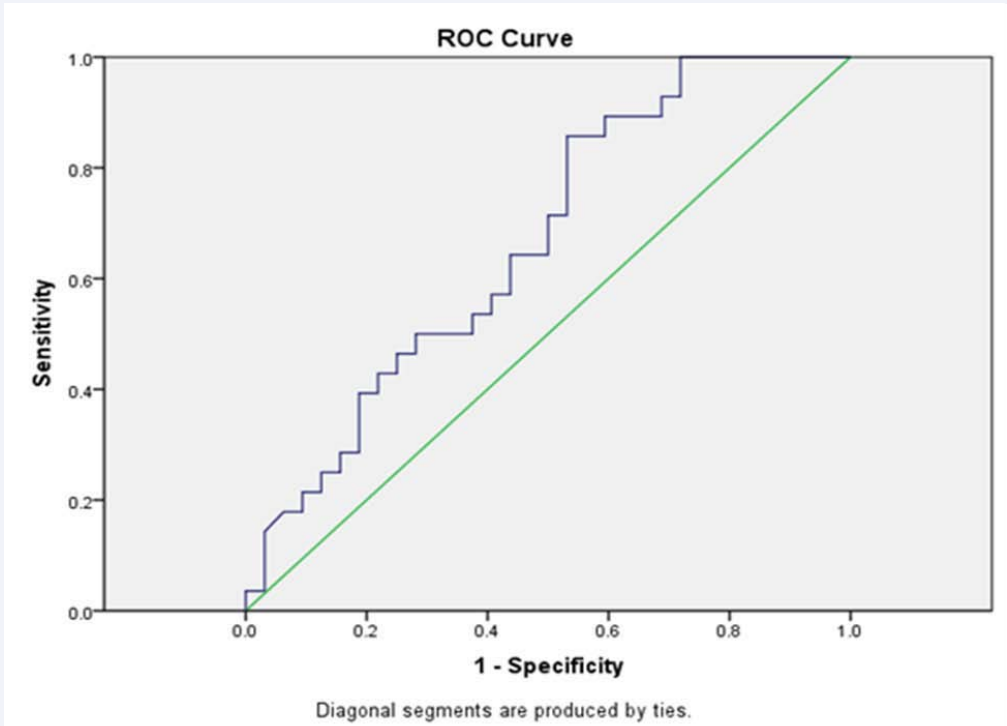
Table 4: Pearson correlation coefficients between SHBG concentration and BMI, RBS, and fetal weight in the GDM group.

Parameters	SHBG Concentration
BMI	0.136 (*P*=0.458)
RPG	0.259 (*P*=0.153)
Fetal Weight	0.282 (*P*=0.118)

1. Women with GDM were significantly older than the women in the control group.
2. Random plasma glucose concentrations were elevated in the GDM group.
3. Sex hormone binding globulin serum concentrations were lower in the GDM group
4. There were no significant differences between the BMI in the two study groups.

In a study by Caglar S and colleagues [34], they found that women in the GDM group were older than those in the control group. And in a different study [14], the authors also found that the females in the GDM group were older. The age differences between the study groups were also observed in this current study. The mean age of the women in the control group was 26.89±3.14 years versus the mean age of 29.63±4.93 (p=0.01). This trend has in fact been shown in various studies done on SHBG and GDM [34-38].

In a study by Nanda S *et al* [35], the authors conducted a study with the objective of developing a model for the prediction of GDM from maternal factors and biochemical markers at 11 to 13 weeks. They found that found that maternal age, BMI, racial origin, history of previous GDM and macrosomic infant were significant independent predictors of the development of GDM. However, they found that in screening for GDM by maternal factors only,



Area Under the Curve			
Test Result Variable(s):SHBG			
		Asymptotic 95% Confidence Interval	
Area	p	Lower Bound	Upper Bound
0.667	0.027	0.531	0.803

Figure 1 ROC showing the predictive probabilities of SHBG for GDM.

the detection rate was ~62% (with a high false positive rate of ~20%). The detection rate increased to ~74% when they added adiponectin and SHBG. Sminakis and colleagues36 compared three biomarkers; CRP, SHBG and measures of fasting glucose and insulin (HOMA) and of the three, SHBG was found to be an optimal marker for prediction of subsequent GDM. In the Saku diabetes study [11], the authors carried out a case-control study of 215 males and 85 females with DM versus 300 matched controls. And they found that after adjustments for age, family history of DM, smoking, physical inactivity, fatty liver index (FLI) and BMI, SHBG concentrations were inversely associated with DM in women but not in men. In contrast, they found that testosterone levels were inversely associated with DM in men but not women. They concluded that low levels of SHBG in females and low levels of testosterone in males are associated with diabetes mellitus.

Various studies have shown that there is a relationship between levels of sex hormones and T2DM. In a systematic review and meta-analysis by Ding EL *et al* [39], they demonstrated a sexually dimorphic relationship between testosterone and risk of development of T2DM, that is, lower testosterone levels in males were associated with diabetes mellitus while increased testosterone concentrations in females correlated with increased risk for diabetes mellitus in females. The authors also observed that females with T2DM had significantly lower SHBG levels compared with the control group [39]. They found that females with serum SHBG greater than 60nmol/l had a ~80% reduction in the risk of developing T2DM in contrast to those with lower levels. Other authors have also demonstrated this relationship [9,12].

SHBG levels have been shown to be consistently lower women with GDM [11,13-15,40]. According to Kim Catherine and co-authors, once diagnosed with GDM, women seemed to progress to T2DM and this progression increased steeply within the first five years after delivery41.In this current study, SHBG levels were found to be significantly lower in the GDM group than in the control group. SHBG concentration in the control group was 71.33±30.58nmol/l while in the GDM group was 53.64±31.91nmol/l. The difference between the two means was found to be statistically significant. The mean in the GDM group was lower than 60nmol/l and as already suggested by Ding *et al* [39], at this concentration, the women are at a higher risk for T2DM. This has also been demonstrated by Morisset AS *et al* [14], the authors observed that SHBG levels were lowered in GDM patients. This trend has been demonstrated by other studies [15,34-38]. In a study which was set to examine cross sectional associations of SHBG with glucose among women with recent GDM, the authors hypothesized that SHBG levels would be associated with both the FPG and 2hours post glucose challenge, however, the results showed that at baseline, lower SHBG levels were associated with higher FPG but no significant association with the 2hours glucose [40]. In our study, there was no measurement of FPG, however, RPG was found to be higher in women with GDM (5.25±1.25 versus 4.71±0.77) and the difference between the two study groups was statistically significant. There were no observed differences in the BMIs between the two study groups in our study, however, according to Morisset AS *et al* [14] they found that BMI was significantly increased in the GDM group. The authors also observed that during GDM screening, BMI was a better predictor for GDM than SHBG level. Sminakis KV *et al* [36] also found BMI to be higher in the GDM groups. But despite this, they concluded that SHBG was a better predictor.

CONCLUSION

In our study, although the sample size was small (n=60) and the serum measurements were done in the third trimester (mean gestational age at the time of screening was 38.50±1.86weeks), SHBG was still observed to be significantly lowered in GDM. SHBG does not exhibit diurnal variations when compared to other biomarkers of insulin resistance [42]. Because of this, SHBG is reliable in non- fasting states. SHBG seems to be a more practical and sensitive tool in clinical situations in which it is not practical to routinely collect fasting blood samples such as during antenatal care. SHBG can thus be implored in both predicting and monitoring GDM. With SHBG, more women with GDM can be identified (if testing is done in early pregnancy) and this can provide an opportunity for interventions that could improve the pregnancy outcome. However, the following recommendations need to be considered:

1. There should be standardization of the laboratory assay for analysis of SHBG and the concentration of the plasma SHBG should be determined for a constant gestational week.
2. If SHBG is to be used as a diagnostic tool and predictor of GDM, screening should be done in early pregnancy, preferably in the first trimester so that there is adequate time for interventions and thus preventing the adverse outcomes of GDM.
3. If SHBG is going to be used as a monitoring tool for GDM, more research is needed to determine SHBG in the puerperium.

ACKNOWLEDGEMENTS

The authors wish to thank the following; Dr Chen Rongrong for her assistance with data collection, Mr Akeem T. Ketlogetswe for data analysis and all the personnel at the Department of Obstetrics and Gynecology in Fujian Union Hospital for their contribution. And all the women who participated in this research study.

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Cite this article

Anderson SS, Zhiqun Z (2015) Sex Hormone Binding Globulin in Gestational Diabetes Mellitus. Med J Obstet Gynecol 3(2): 1057.