ORIGINAL ARTICLE

Serum Sex hormone binding globulin (SHBG) as an accessory diagnostic marker in hypertensive disorders of pregnancy: A cross sectional study in a tertiary care centre.

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Abstract

Background: Hypertensive disorders of pregnancy (HDP), including gestational hypertension and preeclampsia, are major contributors to maternal and fetal morbidity and mortality, particularly in developing countries. Sex Hormone Binding Globulin (SHBG), a glycoprotein involved in the regulation of sex hormones, has been linked to metabolic disturbances and may play a role in placental development.

Objective: To evaluate serum SHBG levels during the third trimester in pregnant women with hypertensive disorders and correlate them with pregnancy outcomes.

Methods: A total of 99 pregnant women were enrolled in this cross-sectional study conducted at a tertiary care center in South India. Participants were grouped into control (n=38), gestational hypertension (GH, n=22), late-onset preeclampsia (LOP, n=21), and early-onset preeclampsia (EOP, n=19). Serum SHBG levels were measured using ELISA. Statistical analysis included ANOVA with Tukey post hoc test and ROC curve analysis.

Results: Serum SHBG levels were significantly reduced in GH, LOP, and EOP groups compared to controls ($p<0.05$). Gestational age at birth was also significantly lower in LOP and EOP groups. ROC analysis identified a SHBG cut-off value of 579.28 mM with 83% sensitivity and 80% specificity (AUC = 0.883; $p<0.001$) for predicting HDP.

Conclusion: Decreased serum SHBG levels are associated with hypertensive disorders of pregnancy. SHBG may serve as a potential early diagnostic biomarker to identify women at risk for preeclampsia and aid in timely interventions to prevent progression to severe forms.

Keywords: Hypertensive disorders of pregnancy, endothelial dysfunction, pregnancy outcome

Running title: Sex hormone binding globulin in hypertensive disorders of pregnancy.

Introduction:

Hypertensive disorders of pregnancy is a pregnancy complications that affect about 10% gestation (1). About 10-15% of maternal deaths are associated with preeclampsia and eclampsia in developing countries such as India (2). Sex Hormone Binding Globulin (SHBG) is a glycoprotein produced primarily in the liver. It plays a crucial role in regulating sex hormone levels by binding to sex hormones, mainly testosterone, dihydrotestosterone (DHT), and estradiol (a form of estrogen)**,** and controlling their bioavailability in the target tissues (3). The SHBG usually tend to decrease in metabolic conditions such as hypothyroidism, obesity, insulin resistance, type 2 diabetes mellitus, Polycystic ovarian syndrome, Gestational diabetes mellitus, steroid use and other hormonal disturbances (4,5). The SHBG levels usually tend to increase during the second trimester helping the hormone regulation and that is essential for placental development and better pregnancy outcomes. An altered SHBG levels may lead to poor oxygen supply and increase the risk of IUGR in newborn (6). In this study, an attempt was to assess the serum Sex hormone binding globulin levels (SHBG) in pregnancy during third trimester and followed till labor to assess the pregnancy outcomes such as gestational age at the time of delivery.

Subjects and methods:

The study subjects were recruited from the Department of Obstetrics and Gynecology in a tertiary centre at South India. The study was approved by the institute human ethics committee and the study subjects were recruited after obtaining informed consent. A total of 99 pregnant women were recruited for this cross sectional study where 38 were control pregnant women who had no history of presence of hypertension anywhere during the pregnancy. Among the study group, Gestational hypertension (GH, n=22), Late onset preeclampsia (LOP, n=21) and Early onset preeclampsia (EOP, n= 19) were also recruited for the study. The preeclampsia group is classified as early onset and late onset based on the ACOG 2016 guidelines. Gestational hypertension refers to the occurrence of hypertension among pregnant women after 20 weeks of gestation. In EOP the pregnant women are diagnosed with onset of hypertension and proteinuria between 20-34 weeks of gestation and in LOP the onset of hypertension were after 34 weeks of gestation. Pregnant women with Gestational diabetes mellitus, chronic hypertension, and preeclampsia superimposed on chronic hypertension were excluded from the study. The study subjects were collected 5 ml of fasting blood and the serum was separated by centrifugation at 3500 rpm for 10 min and stored at -40°C till analysis. Sex hormone binding globulin was analyzed using commercially available ELISA kit (M/s Diagnostic Biochem Canada, Ontario) as per the manufacturer's instructions. The statistical analysis was carried out using ANOVA followed by Post Hoc Analysis of Variance with Tukey method to compare the means across the groups using SPSS v 19.0 software and the P-value < 0.05 was considered statistically significant.

Results:

The study demonstrated no significant change in the mean age across the study groups. There was no significant difference found in the mean age of the study subjects. The gestational age at birth of the baby was found to significantly decreased in LOP and EOP compared to the control and also there is a significant difference between the LOP and EOP itself as shown in table 1. In order to predict the SHBG as a diagnostic marker, an ROC curve was analyzed to assess the diagnostic accuracy of best cut off value of (Figure 2). To assess the diagnostic accuracy of the serum SHBG, an ROC analysis was carried out and the best cut off value was found to be 579.28 mM with 83% sensitivity and 80% specificity with 95% CI; $p<0.001$) with an AUC of 0.883 as shown in figure 3.

Discussion:

Sex hormone binding globulin (SHBG) is expressed in trophoblasic cells of placenta and plays a significant role in placental development and growth of the fetus regulating the secretions of human chorionic gonadotrophin (HCG). It activates cAMP and also activates placental cells for the insulin signaling (7) which regulates the metabolic activity essential for fetal growth (8–10). A lower level of serum SHBG indicates a sign of insulin resistance(7,11). Usually the gestational hypertension is treated

Table 1: The Demographic details of Hypertensive disorders of pregnancy and Control Pregnant Women.

Demographic details and pregnancy outcomes	Control Pregnant women (CPW, n-38)	Hypertensive disorders of pregnancy (HDP, n= 62)		
		Gestational Hypertension (GH, n=22)	Late onset preeclampsia (LOP, n=21)	Early onset preeclampsia (EOP, n=19)
Age (years)	26.61± 2.81	26.77 ± 2.76	27.76 ± 2.87	26.9 ± 26.1
Gestational Age at birth (wks)	38.89 ± 1.09	38.80 ± 0.95	37.70 ±1.31*	35.64 ± 2.78*#
Gestational age at blood sampling (wks)	35.17 ± 0.9	34.33 ± 0.64	35.51 ± 0.56	34.5 ± 2.46

Data are reported as mean ± standard deviation (S.D). Statistically significant differences ($P < 0.05$, one way ANOVA with Tukey *post hoc*) are indicated as follows: * vs Control Pregnant Women (CPW; n=38); # vs Late onset Preeclampsia (LOP; n=21); (Significant differences between other groups are not indicated). EOP: Early Onset Preeclampsia, $P<0.05$ were considered significant.

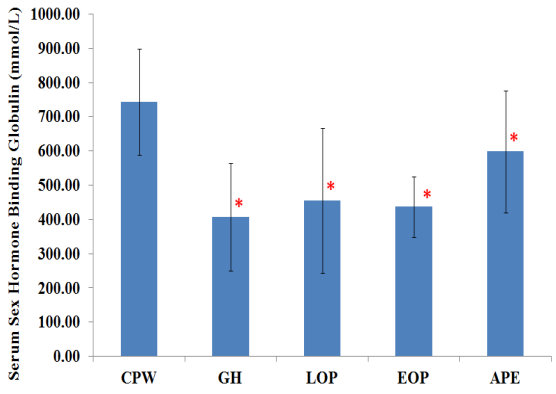

Figure 1: Plasma levels of Sex hormone binding globulin in hypertensive disorders of pregnancy compared to control pregnant women. Data are reported as mean ± S.D. Statistically significant differences ($P < 0.05$, one way ANOVA with Tukey *post hoc*) are indicated as *vs Control Pregnant Women (CPW; n=38); CPW: Control Pregnant Women, GH: Gestational hypertension, LOP: Late Onset Preeclampsia, EOP: Early Onset Preeclampsia, $P<0.05$ were considered significant.

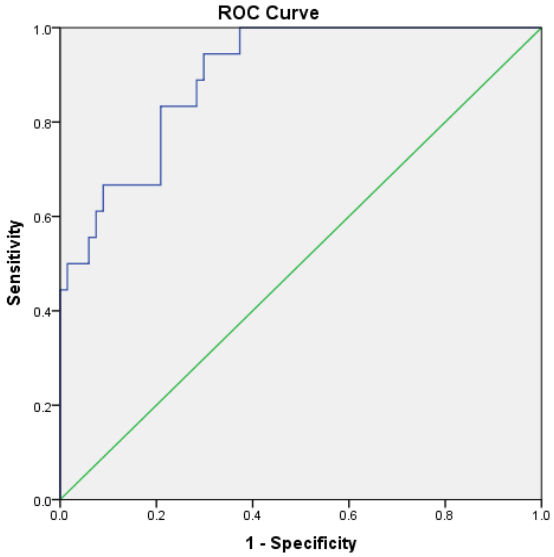

Figure 2: ROC curve analysis of Serum SHBG for predicting cut off value for the diagnosis of hypertensive disorders of pregnancy. The best cut off value was found to be 579.28 mM with 83% sensitivity and 80% specificity with CI, 95%; $p<0.001$) with an Area Under the curve, (AUC: 0.883).

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with conservative management (12) and may tend to be ignored by many pregnant women (13). In our study, it has been found that the serum levels of SHBG were significantly decreased in EOP and LOP compared to control. To our understanding, it is crucial to note that the SHBG values in the serum were significantly decreased in gestational hypertension compared to the control indicating the possibility of insulin resistance and silent metabolic dysfunction that could be leading to sudden onset of severe form of preeclampsia and eclampsia. Moreover, the analysis of serum SHBG is mostly carried out in GDM where the insulin resistance is common, than that of the preeclampsia. Also, studies have found that the low levels of serum SHBG during prepregnancy had high risk of the pregnancy to be gestational diabetes mellitus (14). However, the evidence on the development of preeclampsia is not studied well. This could possibly give a clue that the a central disturbance in the hormone regulation of key players such as SHBG could contribute to the development of PCOS (5), GDM and Preeclampsia during pregnancy(14,15). In our study, although we have a significant decrease in the serum levels of SHBG, the correlation with the pregnancy outcome has not been established well (data not shown) indicating the fact that there could be some intermediate which may play a role in development of preeclampsia. In placental development, the testosterone and estradiol plays an essential role in spiral artery remodeling that is essential for fetal development. SHBG is believed to bind with testosterone and estradiol to regulate their function for the placental development (11). A higher level of testosterone might decrease uterine blood flow, defective spiral artery modeling and poor placentation as evidence from animal experiment on pregnant rats (17). In our study, as we have found a decrease in SHBG levels, this could be a factor that might lead to poor placentation in preeclampsia. These results and evidences, shows that a routine biochemical investigations along with the assessment of Serum SHBG during pregnancy could contribute to early diagnosis and targeted interventions for better management of hypertensive disorders of pregnancy especially at the milder stage itself as seen in Gestational Hypertension. Research that focus on the diagnostic benefits of serum SHBG might contribute to better management of preeclampsia by preventing its progression into severe forms such as eclampsia.

Conclusion:

The present study shows that the serum level of SHBG was significantly decrease in Gestational hypertension, early onset preeclampsia and eclampsia when compared to control. Assessment of serum SHBG might be used as diagnostic marker along with assessment of other risk factors which might be useful for early diagnosis and targeted interventions for the management of sever forms of preeclampsia.

Conflict of interest:

We do not have any conflict of interest

Acknowledgement / Declaration of Interest:

We thank and acknowledge the host institute for funding this project.

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