The difference in serum human chorionic gonadotropin level between preeclamptic pregnant women and normotensive pregnant women

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ABSTRACT

Hypertension remains one of the urgent problems of medicine. Leading to the development of complications, arterial hypertension is accompanied by the development of structural and functional changes in the heart.

The study of insufficient reduction in blood pressure is important. At the same time, at present, using the method of daily monitoring of blood pressure, it has been established that with an insufficient nightly decrease in blood pressure, arterial hypertension is characterized by certain and very significant features of the course, prognosis and pathogenesis. At present, it seems quite reasonable to assume that in patients with uncomplicated hypertension and insufficient nocturnal BP reduction, the use of drugs with sympatholytic activity, that is, beta-blockers, may be especially effective.

Keywords: preeclampsia , serum beta human chorionic gonadotropin ,normotensive pregnant

Introduction

Pre-eclampsia is a pregnancy specific and multi systemic disorder involving the placenta, liver, kidneys, blood and the neurological and cardiovascular system , characterized by newly onset of blood pressure more than 140/90 mmHg ,in at least two consecutive occasion and proteinuria (> 300 mg per 24 hours collection) after 20 weeks gestation of pregnancy in patient who was previously noted to be normotensive (1).patients diagnosed with this condition are at increased risk for maternal and /or fetal mortality or serious morbidity ,It is responsible for 25% of all fetal growth retardation and 15% preterm birth in developed countries (2).Patient present with symptoms of persistent headaches, visual changes, peripheral edema of upper and lower extremities ,and possible right upper quadrant pain. Current criteria for the diagnosis of pre-eclampsia involves sustained high blood pressure associated with thrombocytopenia, altered liver function, the new development of renal insufficiency, pulmonary edema, or new onset cerebral or visual change.(3)

Classification: classification done clinically according to the severity of preeclampsia in to three groups :

Mild pre-eclampsia:
Is defined by the following criteria: systolic BP(140-149) mmHg ,diastolic BP (90-99)mmHg confirmed on two measures at 6 hours interval but not more than 7 days apart and,(Proteinuria ≥ 300 mg) on a 24 hours urine collection or two random urine dipstick results of at least 30mg /dl (1+). Spot urine protein: creatinine ratios are used by some investigators instead of 24 hours urine collection and show excellent predictive value(2,3).

Moderate pre-eclampsia:
Is defined by the following criteria: systolic BP(150-159) mmHg ,diastolic BP (100-109)mmHg , ,(Proteinuria ≥ 300 mg) on a 24 hours urine collection or two random urine dipstick results of at least 30mg /dl (1+). (2,3)

Severe pre-eclampsia:
Severe features of pre-eclampsia includes any of these findings:

- Systolic blood pressure of 160mmHg or higher, or diastolic blood pressure of 110mmHg or higher on two occasions at least four hours apart .
- Progressive renal insufficiency (Serum creatinine concentration>1.1mg dl−1 or a doubling of the serum creatinine concentration in the absence of other renal disease) or ,(Proteinuria ≥ 5 g) on a 24 hours urine collection.
- Thrombocytopenia (platelets <100 000/μl)
- Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnosis, or both
- Pulmonary edema
- New onset cerebral or visual disturbances(2,3)

Etiology
The signs and symptoms of this disorder are well known, but the etiology is still unknown and thus the prevention of the disease is not possible. A number of theories have been put forward where different biochemical markers have been implicated in the causal association of preeclampsia(1). The prevailing theory has been that the subsequent relative placental ischemia causes release of vasoactive factors into the circulation which then give rise to endothelial-mediated end-organ damage and clinical manifestations of the disease. Scientific endeavours to determine these elusive vasoactive factors have largely been responsible for pre-eclampsia(2). Several studies have reported an association between unexplained increases in maternal serum β-HCG levels in the second trimester of pregnancy and subsequent development of preeclampsia.(3)

Risk factors:(1,2,3)
Factors associated with an increased risk of developing pre-eclampsia

- Nulliparity
- Pre-eclampsia in a previous pregnancy
- Age >40 years or <18 years
- Chronic hypertension
- Chronic renal disease
- Antiphospholipid antibody syndrome or inherited thrombophilia
- Vascular or connective tissue disease
- Diabetes mellitus (pre gestational and gestational)
- Multifetal gestation
- High body mass index
- Black race
- Male partner whose mother or previous partner had
- pre-eclampsia
- Hydrops fetalis
- Unexplained fetal growth restriction
- Woman herself was small for gestational age
- Fetal growth restriction, abruptio placentae, or fetal demise in a previous pregnancy
- Prolonged inter pregnancy interval
- Partner related factors (new partner, limited sperm exposure [e.g. previous use of barrier contraception])
- Hydatidiform mole
- Susceptibility genes (1,2,3)

Pathophysiology:

The pathogenesis of pre-eclampsia originates in the placenta. The disease can occur in the absence of fetal tissue (molar pregnancy) and manifestations of the disease will only resolve following delivery of the placenta, The blueprint for establishing pre-eclampsia is determined at outset of pregnancy when placental trophoblast invades the maternal uterine spiral arteries at the time of implantation.(4) .

In pregnancies destined to be complicated by preeclampsia, transformation of the spiral arteries is impaired , with suboptimal remodeling of small-capacitance constricted vessels into dilated large-capacitance conduits.(5) It seems that endothelial cells dysfunction is the main cause of preeclampsia , pregnancy that complicated by preeclampsia typically show 30 to 50 % reduction in utero placental blood flow (6). A typical response to reduced blood flow is an increase in villous capillary number to maximize blood flow which cause accelerated placental maturation(7) . It may also be linked to the trophoblast response to hypoxia with the development of a hyper secretary state compared with normal pregnancies. It is well known that the cytotrophoblast is an undifferentiated stem cell, predominantly found in late trimester of pregnancy(8). The syncitotrophoblast is a differentiated trophoblast found in early gestational period transformed from the cytotrophoblast. In preeclampsia the cytotrophoblast transformed into syncytotrophoblast. Human placenta synthesizes steroid, protein, and glycoprotein hormones throughout gestation (9). Several candidates have been considered in the role of a key circulating vasoactive factor, including interleukins, tumor necrosis factor (TNF)-α and components of the angiotensin pathway. Whilst all these elements are subject to modification in pre-eclamptic pregnancies, it has not been possible to demonstrate that any have an initiating role in the disease process..(10)

Human chorionic gonadotropin hormone:

The human chorionic gonadotropin (HCG) is a glycoprotein composed of two subunits, α and β, and is produced by syncytiotrophoblast cells of the placenta.(11). The free β-subunit can derived from three sources, namely, direct trophoblast cell production, dissociation of HCG into free α- and free β-subunits, and by macrophage or neutrophil enzymes nicking the HCG molecule(12) . Maternal serum HCG peaks at 8 - 10 week of gestation and then declines to reach a plateau at 18 - 20 week of gestation. The free β-HCG circulating in maternal serum corresponds to only about 0.3-4% of the total HCG (13) . High human chorionic gonadotropin combined with low placental growth factor concentrations in the second trimester is associated with strongly increased risk for preterm preeclampsia that HCG is involved in the angiogenic processes that are associated with preeclampsia.(14) Maternal concentrations of HCG are known to change during normal pregnancy, However, it is not known if the changes in HCG throughout pregnancy differ between women who develop preeclampsia and other women, Twin pregnancies and molar pregnancies, produce higher levels of HCG and they are associated with a higher incidence of preeclampsia than uncomplicated singleton pregnancies.(15) . An association has been reported between preeclampsia and elevated third trimester HCG levels. Considerable evidence suggests an association between serum HCG levels and preeclampsia .(16)

The role of serum HCG in pathogenesis of preeclampsia:

The production of HCG by the placenta in early pregnancy is crucial for implantation and maintenance of the blastocyst, Since it is postulated that preeclampsia is a trophoblastic disorder (17), it has become essential to understand this disease, to investigate the pathologic and secretory reaction of the placenta, Physiological concentrations of HCG is significantly increased in vitro capillary formation and migration of endothelial cells in a dose dependent manner and has a novel function in uterine adaptation to early pregnancy (18) . As the possible role HCG in the pathophysiology of preeclampsia is not well-understood and changes in its level can

reflect the placental reaction to preeclampsia (19).

High circulating concentrations of HCG in the second and third trimester of pregnancy have been associated with increased risk of preeclampsia, High levels of soluble fms like tyrosine kinase 1 (sFlt-1) and low levels of placental growth factor (PGF) in the second and third trimester have also been linked to preeclampsia .(20), Both sFlt-1 and PGF are components of the vascular endothelial growth factor (VEGF) system, which is important for placental angiogenesis , and HCG is involved in the regulation of VEGFs Therefore, it seems plausible that HCG is involved in the angiogenic processes that are associated with preeclampsia . (21)

Aim of the study The purpose of the study was to determine the difference in the serum BHCG level between preeclamptic and normotensive pregnant women and it's relation to the severity of preeclampsia.

patients and methods:

Setting &duration:

Study carried out from 1st day of September 2018 to the end day of February 2019 in sulaimani maternity teaching hospital .

Design : case control study .

Patients &methods:

The study included 75 pregnant women with singleton pregnancy between (28-36) weeks gestation who admitted to emergency department of sulaimani maternity teaching hospital and divided in to three groups, 25 normotensive pregnant women who admitted to emergency department because of premature uterine contraction or preterm labour (control group), 25 mild preeclampsia and 25 sever preeclampsia (case group) .

Exclusion criteria:

Cases with diabetes ,chronic hypertension ,twin pregnancy or any other chronic disease were excluded from the study.

Preparation :

After admission to emergency department of maternity teaching hospital taking a verbal consent from each woman full history and examination including obstetrical examination was taken, a questionnaire has been used to record the demographic variable including {Age, Address ,Gravity , Parity, BMI , BP , Proteinuria and Gestational age by weeks}

Blood Pressure measurement : The criteria for sever preeclampsia systolic BP ≥160mmHg and diastolic BP ≥110mmHg. The criteria for mild preeclampsia were BP≥(140-149) mmHg and diastolic BP≥ (90-99)mmHg ,

Measurement of BMI :the measurement of BMI by the balance weight and measure the height by tab measure then divided the weight in Kg by height in squared meter to calculate the BMI .

Blood sampling : after taking the consent from the patient to take a blood sample by researcher or nurse in sitting or lying position . Select a suitable site for venipuncture, about 5 cc blood take by sterile syringe, then send the sample to the laboratory of our hospital to be tested for serum BHCG level. Serum levels of B-HCG were measured by radioimmunoassay and were compared between groups of study.

Test for proteinuria : the patient were asked to collect a MSU by giving the clean (sterile) bottle .(Pass some urine into the toilet. Then, without stopping the flow of urine, catch some urine in a clean (sterile) bottle). The sample was sent to the laboratory of our hospital . Within two hours to investigated for proteinuria by dipstick testing .which reveled 1+ in mild preeclampsia and ≥2+ in sever preeclampsia.

Data entry and analysis :

each questionnaire was given an identity number (ID). Prior to data entry and analysis ,all question of questionnaire were coded . The data was checked and entered into statistical package for social science (SPSS) version 21, the data had collected are presented in simple cell . Frequencies of data are arranged in table. The results were compiled and analyzed to study the level of serum BHCG and comparison between normotensive pregnant women and preeclamptic (mild , sever)pregnant women table was constructed and compared using Chi-square and Fisher exact test with assignment of P- Value of <0.05 as significant level ,then the sensitivity ,specificity , positive predictive value ,and negative predictive value for positive test results and negative test results were calculated .

Ethical consideration :
Approval for doing this study was taken by a written consent from the scientific committee of maternity teaching hospital thankfully .

Results:
The results of the present study revealed that the studied groups (i.e. the group with mild preeclampsia and the one with severe preeclampsia) were significantly different only in terms of their BMI (p=0.01) such that the group with mild preeclampsia had a lower BMI than the group with severe preeclampsia (with 25.4±3.9 and 26.2±3.9, respectively). However, as indicated by the results, there was no significant difference between the two groups regarding their age, Gravity, Parity, Miscarriage, and gestational age (p>0.05) (See Table 1).

Table 1: Comparison of demographic, anthropometric and obstetrical variable between the studied groups

Variable	Normotensive Mean±SD	Mild Preeclampsia Mean±SD	Severe Preeclampsia Mean±SD	P-value
Age(year)	26.4±6.7	29.3±7.2	30.6±7.3	0.09
BMI Kg/m^2	23.1± 3.9	25.4±3.9	26.2±3.9	0.01
Gravity	2.8±1.8	3.0±1.9	2.9±1.8	0.9
Parity	1.7±1.5	1.7±1.6	1.5±1.4	0.8
Miscarriage	1.6±1.3	1.0±1.1	1.4±1.1	0.6
Gestational age by week	32.3±3.2	33.8±2.4	32.3±2.7	0.1

Comparing the level of serum BHCG in the three groups indicated that there was a significant difference between the three groups in terms of their serum BHCG at a p-value of <0.001, such that the group with severed preeclampsia had a higher serum BHCG (80906.80±16826.592) than the group with mild preeclampsia (35569.80±12988.102) and both mild and sever preeclampsia higher than normotensive (24613.8±3515.088). (See Table 2 &3).

Table 2: Comparison of serum BHCG between the studied groups

Variable	Normotensive Mean ± SD	Mild and sever Preeclampsia Mean ± SD	P-value
Serum BHCG IU/mil	24613.8 ± 3515.088	58238.30 ± 27306.591	< 0.001

Table 3 : Comparison of serum BHCG between mild and sever preeclampsia

Variable	Mild Preeclampsia Mean±SD	Severe Preeclampsia Mean±SD	P-value
Serum BHCG IU/ml	35569.80±12988.102	80906.80±16826.592	<0.001

Discussion
In pre-eclampsia the rise of blood pressure is due to vasoconstriction and impaired angiogenesis leading to hypoxia and hyperplasia of trophoblastic cells which causes hyper secretion of placental hormone ultimately leading to high level of circulating β-HCG . Also, there should be an abnormal placental secretary function in patients with severe preeclampsia.(22)

The results of our study revealed that the studied groups (i.e. the group with mild preeclampsia and the one with severe preeclampsia) were significantly different only

in terms of their BMI (p=0.01) such that the group with mild preeclampsia had a lower BMI than the group with severe preeclampsia (with 25.4±3.9 and 26.2±3.9, respectively). However, as indicated by the results, there was no significant difference between the two groups regarding their age, Gravity, Parity, Miscarriage, and gestational age (p>0.05). Comparing the level of serum BHCG in the two groups indicated that there was a significant difference between the two groups in terms of their serum BHCG level at a p-value of (<0.001), such that the group with severed preeclampsia had a higher serum BHCG level (80906.80±16826.592) than the group with mild preeclampsia (35569.80±12988.102).

.Agree with the study done by BEGUM Z1, et al in the Eclampsia ward of Dhaka Medical College Hospital in Bangladesh, (2013)(23).conducted on (75) pregnant women. there was no significant differences between the groups with respect to gestational age, gravida and or history abortion (p= 0.328,p=0.522and p=0.847).in the same study the Association between severity of preeclampsia and serum B-HCG level shows that mean serum BHCG level was the highest in severe preeclampsia and the lowest in the control group, while that in mild preeclampsia lie in between the two (p<0.001) (23).

Our study also agree with study done by Kanika Mandi Choudhurya, et al in (2012)(24) in India. Conducted on the 50 preeclamptic and 50 normotensive women The paired samples of serum samples were estimated for β-HCG level and . The serum level of maternal β-hCG was markedly raised in preeclampsia (18,087.42 ± 2,014.17 mIU/mL) in comparison to controlled (8,391.06 ± 1,909.64 mIU/mL) and parallel with the severity of pre-eclampsia.(24)

Our study agree with another study done by Gubuz A, Karateke A, et al. Value of Serum β-hCG in Pathogenesis of Pre-Eclampsia in (2004)(25) in istanbul , turkey .A study compared B-HCG levels in 80 women suffering from mild preeclampsia, severe preeclampsia and normotensive pregnant women. The B-HCG level reported to be significant higher in mild and sever preeclampsia was significantly more than those in control groups (p<0.001).(25)

Conclusion:

Hypersecretion of human chorionic gonadotropin hormone by placenta reflecting high level of serum circulating beta human chorionic gonadotropin hormone level in preeclampsia disorder and its severity. So in preeclampsia a trophoblastic disease association with the circulating beta human chorionic gonadotropin hormone may have pathogenic role.

Recommendation

- I recommend to measure the BHCG level for pregnant women in the second trimester with one or more risks factors may help in the early diagnosis of the disease.
- we can use serum B-HCG as an indicator of the severity of the preeclampsia.

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