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Original Article

Association of maternal Serum Selenium Binding protein and its effect on fetal outcomes in Pregnancy Induced Hypertensive Disorders: A case-control study.

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Abstract

Background: Pregnancy-induced hypertensive (PIH) disorder represented the primary cause of maternal and fetal morbidity and mortality. The cause of pre-eclampsia is unknown, but ischemic blood supply to the placenta stimulates the inflammatory process which leads to endothelial dysfunction and oxidative stress. Antioxidants like Selenium altered concentration involve in its pathogenesis. This study was proposed to find out the significance of Selenium as a biomarker in the pathophysiology of PIH disorders and its association with fetal outcomes.

Methodology: This case-control study was conducted on 240 pregnant women, 20-40 weeks of gestation, divided into four groups equally. Normotensive control, investigational group 1 PIH, 2 Pre-eclamptic, and 3 Eclamptic. A structured questionnaire was administered and arterial blood pressure was measured and the blood sample was done for serum Selenium assessment through ELISA. A urine sample was collected and the level of proteinuria was assessed. Fetal wellbeing and signs of growth restriction were observed using ultrasound reports.

Results: The mean age of the studied participants was 27.6 ± 5.3 years with the gestational age of 32.11 ± 4.56 weeks. The mean Serum Selenium levels (ng/ml) were significantly lower in investigational groups 67.93 ± 10.54 in PIH, 44.6 ± 13.19 in PE, and 36.38 ± 10.3 in Ec than 78.5 ± 8.2 control ($p<0.05$). The mean systolic, diastolic blood pressure and proteinuria were significantly high in case groups ($p<0.05$). Furthermore, we observed a significant inverse correlation of serum selenium with gestational age, systolic, diastolic blood pressure, proteinuria, fetal weight, and femur length in all four groups, whereas mainly positive significant correlation was elucidated with serum glutathione, PIH ($r= 0.797$, $p<0.001$), PE ($r = 0.617$, $p>0.00$), Ec ($r=0.559$, $p=0.019$) than control ($r = 0.817$, $p<0.001$).

Conclusion: It is concluded that serum selenium level is significantly reduced in Pregnancy-induced hypertensive disorders and it has markedly affected maternal and fetal outcomes.

Keywords

Serum Selenium Binding Protein, Pregnancy-Induced Hypertensive Disorders, Eclampsia, Pre-Eclampsia, Fetal Growth Restriction.

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Introduction

Pregnancy-induced hypertensive disorders are the foremost cause of maternal, fetal, and newborn morbidity and mortality and are 20 times more frequent in developing countries than in developed states[2]. According to the United Nations Population Fund (UNPF), the Maternal mortality ratio (MMR) (186/100,000 live births) is the highest in Pakistan among other countries of South Asia[3], and it is graded as the third-highest country fronting the load of maternal, fetal, and child mortality[1]. It is an illness characterized as a result of the development of arterial hypertension de novo after the 20th week of pregnancy[4]. Pregnancy-induced hypertensive disorders are of three types PIH/Gestational hypertension, Pre-eclampsia, and Eclampsia. PIH/Gestational hypertension is characterized by the onset of new hypertension (140/90 mmHg) without having proteinuria[5]. Whereas characteristics features of Pre-eclampsia are SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, proteinuria ≥ 300 mg/day, non-dependent edema on hands and face, thrombocytopenia, severe epigastric pain, blurred vision, headache, impaired liver, and renal functions, etc[6]. Lastly, Eclampsia involves SBP ≥ 160 mmHg and DBP ≥ 110 mmHg, new-onset tonic-clonic seizures, decreased alertness, and convulsions[7]. Pre-eclampsia is a primary cause of preterm birth because the only known therapy is placental delivery. This leads to increased newborn morbidity and significant increases the healthcare costs[8].

The morbidity and mortality rate of mother and fetus can be decreased and their causes can be prevented through proper understanding, diagnosis, and management of pregnancy-related complications[9]. The disease's etiology is unknown, but researchers have established that early trophoblastic invasion caused hypoxia of the placenta, escalation of oxidative stress which impaired the endothelium's structure and function. Utero-placental insufficiency occurring secondary to impaired remodeling of spiral arteries and serves as a robust stimulus for the production of reactive oxygen species[10]. Normally body cells are acquired to have antioxidant mechanisms. But during oxidative stress syncytiotrophoblast cannot generate antioxidant[11]. Like Selenium which is (nonenzymatic antioxidant) and its altered concentration involves in the pathogenesis of preeclampsia[12].

Selenium is a trace element that exists in two forms inorganic (selenate and selenite) and organic (selenomethionine and selenocysteine) which are nutritionally necessary for humans and have a role in reproduction, DNA synthesis, protection against oxidative harm, infection, apoptosis, and detoxification processes[4]. The presence of such selenoproteins in the uterus as antioxidative agents was observed[13]. Alteration in maternal circulation due to an imbalance between antioxidants and reactive oxygen species leads to interruptions in the normal flow of the growth process of the fetus[14]. Selenium as a fundamental constituent of prenatal care, letting down the complications related to pregnancy[15].

Fetal biometry is very important for fetal growth measurement in obstetrical practice it provides the estimation of gestational age and fetal growth assessment[16]. Around 6-30% of newborn children with restricted change in intrauterine life are observed more in developing countries[17]. This condition is four times more in pre-eclampsia associated with 5% reduced birth weight[18]. 2500 gm birth weight is considered as reduced birth weight at 37 gestational weeks[17,19]. Fetal biometry parameter is usually comprised of biparietal diameter, head circumference, femur length, abdominal circumference, and fetal weights; the biparietal diameter and femur length measurements are broadly used in amalgamation to measure the development of the fetus[20].

Several studies implicated selenium alteration with pre-eclampsia, fetal growth restriction, preterm labor, gestational diabetes, and obstetric cholestasis[21]. In various studies, females with pre-eclampsia have lower levels of Se and lower levels of glutathione peroxidase (GPx), and mitigating selenoprotein SEPP1 in the placenta or serum/plasma, contrasted with those of healthy pregnant women[22,23]. However, some other studies revealed elevated levels of serum selenium during pregnancy[24]. Nevertheless, not all outcomes are unambiguous Selenium levels in women having preeclampsia might be the result

of already-developed disorders[25]. The problem remains uncluttered regarding whether this microelement insufficiency in healthy women (early stage) might be interrelated to the subsequent development of PIH[4]. Whereas, some prospective investigations produced different results because of different procedures[8,21]. Assessment of the Selenium status in the serum is likely to provide the best possibility of recognizing changes. The importance of selenium in preeclampsia and altered fetal development is necessary for developing effective and legal preventative and treatment strategies. The basic purpose of our study was to explore the significance of the serum selenium binding protein in PIH disorders and its association with fetal outcomes.

Methodology

Study Design & Setting

A multicenter, retrospective case-control study (1:1) was conducted on 240 pregnant females aged between 17-38 years from July 2017 to August 2019 through nonprobability sampling. The participants were recruited from six tertiary care hospitals of Karachi including Sindh Government Lyari General Hospital, Civil Hospital, Jinnah Postgraduate Medical Center, Atia General Hospital Malir, Koohi Goath Hospital, and Liaquat National Hospital and medical college.

Study Participants

The pregnant females enrolled in this study were more than twenty-two gestational weeks and singleton pregnancies. The investigational group comprised 180 pregnant females having systolic blood pressure of more than 140 mmHg and diastolic blood pressure of more than 90 mmHg. This gathering was further equally distributed into 3 different groups i.e. Pregnancy-induced hypertensive group that recruits the patients with the beginning of new hypertension Systolic and diastolic blood pressure 140/90 mmHg or more on two occasions at least 4 hours apart after 20 weeks of pregnancy without proteinuria, PE group recruits the patients with SBP of 140 mm Hg or more or DBP of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with an earlier normal blood pressure, 300 mg or more per 24-hour urine collection proteinuria and thrombocytopenia platelet count < 100,000 and Eclamptic group which recruits pre-eclamptic patient with the development of seizures (tonic/colonic convulsions). In contrast, remaining sixty participants were enrolled in the control group which is related to normotensive blood pressure, having no signs of proteinuria, systemic or endocrine and renal disease.

Maternal variables

A self-structured questionnaire was designed to gather the information from participants of each group which was first designed in English and then translated to Urdu. Patient's medical records entailed demographic details, current symptoms, medical history, physical activity level, vital measurements including blood pressure (mmHg) through auscultatory method, pulse rate (beats/min), respiratory rate (breaths/min), blood saturation (%), hematological findings [hemoglobin (gm/dl), platelets count ($x10^9$/L), uric acid (mg/dl) and, creatinine by colorimetry (mg/dl)] and ultrasound findings [gestational age (weeks)]. A urine sample was collected and the level of proteinuria was assessed. 3 ml blood samples were taken from the cubical vein to examine serum selenium binding protein (ng/ml) (human SELENBP1 antibody). The sample were then centrifuged for isolating serum and place in categorized tubes and kept at -20°C. Enzyme-linked immunosorbent assay (ELISA) method was applied via Cat. No E3250Hu test quantifies the serum selenium binding protein. The human SELENBP1 antibody has been pre-coated on the kit plate. A serum sample that contains SELENBP1 is added and binds to pre-coated antibodies on the wells. After that standard biotinylated human SELENBP1 antibody is administered and binds to SELENBP1 in the sample. This Biotinylated SELENBP1 antibody complex binds with Streptavidin-HRP. The washing step removed the unbound Streptavidin-HRP after incubation. The amount of human SELENBP1 is in proportion with the development of color which is observed after the addition of substrate solution. Stop acidic solution is added to terminate the reaction and then absorbs at the wavelength of 450 nm.

Fetal Growth Factors/variables

Fetal prosperity and indications of development limitation were noticed utilizing ultrasound

reports. The parameters utilized from the ultrasound reports were gestational age (weeks) biparietal diameter (cm), femur length (cm), head circumference (cm), abdominal circumference (cm), and weight of fetus (gm).

Statistical Analysis

For data analysis, SPSS version 20.0 was used, the findings were articulated as means and standard deviations considered statistically significant at $p<0.05$. Data were collected at 95% confidence interval, one way ANOVA has been applied for all four-group comparisons, for qualitative parameters assessment. Whereas, Pearson chi-square test was used for quantitate parameters and spearman correlation test was also applied.

Ethical Clearance

The Ethical Review Board of Pakistan medical association permitted the study protocol (Reference no. IJ/357/QWL/23), and the study was planned under the Declaration of Helsinki. Informed consent was obtained from participants before their enrollment.

Results

The mean age of all study participants was 27.6 ± 5.3 years with the gestational age of 32.11 ± 4.56 weeks. The vital measurement and diagnostic characteristics of all groups are presented in table 1, which showed that maternal age was not found statistically significant. SBP was significantly high in all investigational groups (Ec 170.3 ± 17.3 mmHg, PE 155.9± 15.9PIH 137.6 ± 6.7) than control (114.7± 7.05 mmHg) ($p=0.03$) and DBP also followed the same pattern. Furthermore, the mean score of other vitals like pulse rate, breathing rate, and oxygen saturation followed the same trend of having statistically significant different values than the normotensive group ($p<0.05$). The main indicator of investigational group division, level of proteinuria also intensified significantly in a diseased group with ($p<0.05$). A similar trend of having significant differences was observed in hemoglobin level, platelet count, creatinine, and uric acid in all three investigational groups ($p<0.01$).

Table 1: One-way ANOVA comparison in control and investigational groups of clinical characteristics.

Variables	Control	PIH/GH	PE	Eclampsia	p-value
	Mean ±SD				
Maternal Age (years)	28.4±4.63	27.75±5.6	27.48±5.23	27.00±5.08	0.083
Gestational Age (weeks)	33.18±3.7	32.36±2.3.05	33.06±2.7	33.11±2.02	0.03*
SBP (mmHg)	114.75±7.05	137.66±6.75	155.9±15.8	170.3±17.39	0.004*
DBP (mmHg)	78.06±6.84	98.88±8.02	101.4±6.67	104.51±9.58	0.002*
Pulse Rate (beat/min)	85.9±14.7	89.6±13	101.9±6.2	108.7±18.3	0.001*
Respiratory Rate (breath/min)	18.2±2.0	19.11±4.5	19.6±3.5	21.4±5.2	0.003*
Oxygen Saturation (%)	98.01±0.7	96.35±1.16	95.5±0.8	95.21±1.22	0.001*
Proteinuria (mg/day)	168.66±27.07	202.6±23.2	320.6±63.19	423.78±55.6	0.001*
Hemoglobin (g/dl)	10.52±0.91	11.22±0.88	12.37±0.83	12.60±1.19	0.032*
Platelet Count ($x10^9$/L)	293.38±51.1	183.78±43.2	135.5±26.4	113.13±19.5	0.04*
Creatinine (mg/dl)	0.68±0.14	0.89±0.14	0.94±0.14	1.12±0.13	0.021*
Uric Acid (mg/dl)	3.93±0.74	4.01±0.53	4.66±1.16	7.89±0.4	0.001*

Control Normotensive; PIH-pregnancy-induced hypertensive; GH-Gestational Hypertension; PE-preeclampsia; DBP-Diastolic Blood Pressure; SBP-Systolic Blood Pressure

*p≤0.05 is considered significant.

Maternal Serum Selenium and Fetal biometry in control and investigational groups were presented in Table 2, which showed that measurements such as biparietal diameter, femur length, and head circumference showed a significant difference in all three investigational groups. Whereas abdominal circumference and fetal weight measurement were different non-significantly in investigational groups and disease groups.

Moreover, the level of serum selenium binding protein was also found significantly lower in investigational groups as compared to control ($p<0.05$).

Table 2: Maternal serum selenium level and fetal biometry in control and investigational groups.

Parameters	Control	PIH/GH	PE	Eclampsia	p-value
Serum Selenium (ng/ml or µg/l)	78.5±8.2	67.93±10.5	44.6±13.2	36.38±10.3	0.000*
Biparietal Diameter (cm)	7.87±0.41	7.71±0.48	7.14±0.75	7.1±0.64	0.000*
Femur Length (cm)	6.18±0.9	5.97±0.6	5.55±0.5	5.34±0.4	0.000*
Abdominal Circumference (cm)	27.5±3.8	27.4±2.6	26.9±2.4	26.4±2.4	0.122
Head Circumference (cm)	28.4±2.9	29.9±2.4	30.0±2.4	31.5±2.4	0.000*
Fetal Weight (gm)	2005.7±67	1943.9±47.0	1917.4±45	1873.9±26.0	0.513

Control Normotensive; PIH-pregnancy-induced hypertensive; GH -Gestational Hypertension; PE-preeclampsia
*p≤0.05 is considered significant

Table 3 Elucidated the correlation of serum selenium level with maternal variables and fetal biometry. An increase in systolic, diastolic blood pressure, proteinuria and gestational age have been directly associated with the reduced level of serum selenium wherea the positive correlation of platelet count and serum glutathione has been attributed with decreased selenium level. Table 3 also showed a significant correlation of serum selenium reduction with fetal biparietal diameter femur length and fetal weight.

Table 3: Correlation of serum selenium level with maternal and fetal biometry.

Variables	Control		PIH/GH		PE		Eclampsia	
	r	p	r	p	r	p	r	p
SBP (mmHg)	-0.535	0.000*	-0.603	0.000*	-0.926	0.000*	-0.935	0.037*
DBP (mmHg)	-0.348	0.002*	-0.789	0.000*	-0.888	0.002*	-0.941	0.026*
Proteinuria (mg/day)	-0.85	0.001*	-0.878	0.000*	-0.978	0.005*	-0.907	0.037*
Platelet count ($x10^9$/L)	0.632	0.031*	0.869	0.037*	0.949	0.000*	0.836	0.028*
Serum Glutathione (ng/ml)	0.817	0.000*	0.871	0.000*	0.895	0.000*	0.777	0.000*
Gestational Age (weeks)	-0.739	0.000*	-0.833	0.000*	-0.885	0.000*	-0.84	0.037*
Biparietal Diameter (cm)	-0.705	0.002*	-0.869	0.000*	-0.887	0.002*	-0.88	0.000*
Femur Length (cm)	-0.62	0.001*	-0.789	0.000*	-0.856	0.005*	-0.817	0.037*
Head Circumference (cm)	-0.927	0.032*	-0.789	0.003*	-0.829	0.003*	-0.816	0.000*
Fetal Weight (gm)	-0.743	0.06	-0.837	0.000*	-0.897	0.001*	-0.874	0.000*

Control Normotensive; PIH-pregnancy-induced hypertensive; GH -Gestational Hypertension; PE-preeclampsia; DBP-Diastolic Blood Pressure; SBP-Systolic Blood Pressure
*p≤0.05 is considered significant

Discussion

Oxidative stress in pregnancy-induced hypertensive females is described by a significantly reduced level of Serum Selenium binding protein with the severity of the disease, which subsequently produces a hostile impression on maternal health and fetal growth in this current study ($p<0.05$). Several studies have found that an oxidative imbalance causes a significant increase in the production of reactive oxygen species and decline meant in the naturally occurring antioxidants in placental tissues due to impaired remolding of spiral arteries, which are vulnerable to hypoxia and reperfusion injury, causing the production of oxidative substances to greatly increase. This causes apoptosis and misfolding at the placental interface because of low levels of antioxidants which contribute to confinement in the fetal growth in pre-eclamptic females[19]. Cells are acquired to have antioxidant mechanisms to cope with the continued development of free

radicals. As syncytiotrophoblast cannot generate antioxidant in the placenta disrupts redox homeostasis and give rise to oxidative stress[11]. Selenium is a trace element that is nutritionally necessary for humans that take part in reproduction, metabolism of the thyroid hormone, DNA synthesis, as well as in protection against oxidative harm, and detoxification processes[4].

Serum selenium level is significantly decreasing in the pregnancy-induced hypertensive group as compared to the control group in the present study. Similar findings have been observed in multiple studies that supported the association of reduced selenium concentration in the pathogenesis of preeclampsia[8,26]. The severity of the hypertensive disorder is directly related to a lower concentration of selenium[23]. Decreased levels of selenium in early pregnancy could be an indicator of pregnancy complications in later stages and have been related to negative effects on embryo growth[27]. However, some studies showed different perspectives and reported no difference in selenium concentration[25,28], whereas the slightly increased level of selenium in PE pregnant females as compared to normotensive pregnant females was also observed[24].

Selenium levels can be affected by multiple reasons including selenium concentration in drinking water, soil, plant, and animal tissue, and different intakes in different global areas, sample type, and sampling time[26]. As a fundamental constituent of prenatal care, selenium also helps to lessen the risk for maternal and child morbidity and mortality through lowering complications related to pregnancy[15]. A maternal diet which was not containing a sufficient amount of selenium increased the risk of oxidative stress in the placenta which ultimately produces adverse maternal and fetal outcomes with increased chances of offspring chronic illnesses[12].

Fetal biometry is very important for fetal growth measurement in obstetrical practice it provides the estimation of gestational age and fetal growth assessment[16]. 2500 gm birth weight considered as reduced birth weight at 37 gestational weeks or underneath the 10th percentile for the gestational age or more[17,19]. In the present study reduced level of selenium binding protein in pregnancy-induced hypertensive groups showed also decreased fetal weight.

Se levels during pregnancy have been linked to altered fetal growth and increased the risk of delivering a preterm baby by lowering placental antioxidant defensive activity, whereas lower Selenium levels in the third trimester are thought to reflect increased placental stresses, a theory that needs to be confirmed[29]. Furthermore, reduced birth weight has been reported in a pre-eclamptic group of other studies[24,25].

The present work carefully provides fetal biometry evaluation, which shadowed the criteria of this geographical location, particularly for the normotensive group, as well as the substantial variations in fetal biometry parameter measurements in PIH groups[20]. It has been elucidated in our study that statistically significantly reduced femur length and Biparietal diameter in pregnant females of all three hypertensive groups; similar results of a retrospective study speculated that 52.5% of pregnant females were pre-eclamptic and possessed poor BPD growth and its association with an adverse neural developmental outcome in the fetus[30]. However, a reduction in abdominal circumference and fetal weight was also reported in the present study hypertensive group, which highlights the influence of oxidative stress on impaired fetal growth[31]. A similar result of reduced birth weight among preterm Pre-eclamptic, Term Pre-eclamptic than normal pregnant females with increased oxidative stress was also interpreted[32]. While fetal head circumference remained considerably higher in pregnancy-induced hypertension groups, an intriguing tendency of enhanced fetal head development in a pre-eclamptic group at term gestation with lower birth weight was found[33,34]. More exposure of the fetus at term to neurotrophins and BDNF, which are important critical components of brain growth, dictated the uniqueness of our result[35].

Our study results revealed that most of the quantitative parameters in patients were found to be statistically significant like SBP, DBP, uric acid, and proteinuria ($p<0.05$), respectively

similar findings of increased Systolic and diastolic blood pressure uric acid and proteinuria in PE than normally observed in other studies[24, 36]. In contrast to this significant reduction in platelet count level has been notified in a pregnancy-induced hypertensive group ($p<0.05$)[37].

Furthermore, a significant negative relationship between maternal Selenium and systolic and diastolic blood pressure, proteinuria, and gestational age was discovered in this investigation.

The moderate negative relationship with BMI, on the other hand, was confirmed in all three experimental groups, showing that the severity of the issue increases as pregnancy progresses. Along with this significant negative correlation of maternal selenium level with fetal biometry parameters includes head circumference, abdominal circumference, fetal weight, and femur length were described in pregnancy-induced hypertensive groups as compared to normotensive similar findings reported in a recent study with serum glutathione level[34]. It is suggested that the restriction of fetal development in pregnancy-Induced hypertension diseases are due to a reduction in Selenium levels because of ischemic perfusion. Further studies are also required to elucidate the significance of serum selenium in pregnancy-induced hypertensive disorders. This study might be helpful to an enhanced understanding of the causes of pregnancy-induced hypertension.

The large sample size of the investigational group and variety of parameters are the key strengths of this study. It provided a realistic picture of serum selenium levels in Pregnancies complicated by hypertension females and accurately analyzed the connection between Pre-eclampsia and fetal growth. Our study's limitations include its cross-sectional design, the lack of availability of perfectly matched gestational weeks, no follow-up after delivery of participants have taken, and single-site assessment of antioxidants level.

Conclusion

The current research concluded that maternal serum selenium is significantly reduced in hypertensive groups with the severity of disease, resulting in an adverse effect on maternal and fetal health and inversely associated to gestational age, systolic and diastolic blood pressure proteinuria, creatinine level, hemoglobin, fetal head circumference, and fetal weight; additionally, positively serum selenium is associated with platelet count level in complicated pregnancy groups. Serum selenium level assessment's ultimate objective is to anticipate information about a woman and her pregnancy to see how closely serum selenium impacts the fetus's growth.

Conflicts of Interest

The authors have declared that no competing interests exist.

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References

1. Khowaja AR, Qureshi RN, Sheikh S, Zaidi S, Salam R, Sawchuck D, Vidler M, von Dadelszen P, Bhutta Z. Community's perceptions of pre-eclampsia and eclampsia in Sindh Pakistan: a qualitative study. Reprod. Health. 2016;13(1):39-44.
2. Walker JJ. Pre-eclampsia. The Lancet. 2000;356(9237):1260-1265.
3. UNFPA. Maternal mortality decreased to 186 deaths per 100,000 live births: UNFPA Pakistan. [Updated August 21, 2020]. Available at: https://pakistan.unfpa.org/en/news/maternal-mortality-decreased-186-deaths-100000-live-births
4. Rayman MP, Searle E, Kelly L, Johnsen S, Bodman-Smith K, Bath SC, Mao J, Redman CW. Effect of selenium on markers of risk of pre-eclampsia in UK pregnant women: a randomised, controlled pilot trial. BJN. 2014;112(1):99-111.
5. Mammaro A, Carrara S, Cavaliere A, Ermito S, Dinatale A, Pappalardo EM, Militello M, Pedata R. Hypertensive disorders of pregnancy. J. Perinat. Med. 2009;3(1):1-5.

6. Aouache R, Biquard L, Vaiman D, Miralles F. Oxidative stress in preeclampsia and placental diseases. Int. J. Mol. Sci. 2018;19(5):1496.
7. Berzan E, Doyle R, Brown CM. Treatment of preeclampsia: current approach and future perspectives. Curr. Hypertens. Rep. 2014;16(9):473.
8. Ghaemi SZ, Forouhari S, Dabbaghmanesh MH, Sayadi M, Bakhshayeshkaram M, Vaziri F, Tavana Z. A prospective study of selenium concentration and risk of preeclampsia in pregnant Iranian women: a nested case–control study. Biol. Trace Elem. Res. 2013;152(2):174-179.
9. Bernstein PS, Martin Jr JN, Barton JR, Shields LE, Druzin ML, Scavone BM, Frost J, Morton CH, Ruhl C, Slager J, Tsigas EZ. Consensus bundle on severe hypertension during pregnancy and the postpartum period. J. Obstet. Gynecol. Neonatal Nurs. 2017;46(5):776-787.
10. Mert I, Sargın Oruc A, Yuksel S, Cakar ES, Buyukkagnıcı U, Karaer A, Danisman N. Role of oxidative stress in preeclampsia and intrauterine growth restriction. J Obstet Gynaecol Res. 2012;38(4):658-664.
11. Schoots MH, Gordijn SJ, Scherjon SA, van Goor H, Hillebrands JL. Oxidative stress in placental pathology. Placenta. 2018;69:153-161.
12. Habibi N, Grieger JA, Bianco-Miotto T. A Review of the potential interaction of selenium and iodine on placental and child health. Nutrients. 2020;12(9):2678.
13. Qazi IH, Angel C, Yang H, Pan B, Zoidis E, Zeng CJ, Han H, Zhou GB. Selenium, selenoproteins, and female reproduction: a review. Molecules. 2018;23(12):3053.
14. Rashid CS, Bansal A, Simmons RA. Oxidative stress, intrauterine growth restriction, and developmental programming of type 2 diabetes. Physiology. 2018;33(5):348-359.
15. Darnton-Hill I, Mkparu UC. Micronutrients in pregnancy in low-and middle-income countries. Nutrients. 2015;7(3):1744-1768.
16. Shehzad K, Ali M, Zaidi S. Fetal biometry. PJMS. 2006;22(4):503.
17. Shweta DR, Khanna A. The effect of antenatal L-arginine and antioxidant supplementation on oxidative stress marker levels in newborns. JCDR. 2014;8(10):OC10.
18. Ødegård RA, Vatten LJ, Nilsen ST, Salvesen KÅ, Austgulen R. Preeclampsia and fetal growth. Obstetrics & Gynecology. 2000;96(6):950-955.
19. Biri A, Bozkurt N, Turp A, Kavutcu M, Himmetoglu Ö, Durak I. Role of oxidative stress in intrauterine growth restriction. Gynecol. Obstet. Invest. 2007;64(4):187-192.
20. Acharya P, Acharya A. Evaluation of applicability of standard growth curves to Indian women by fetal biometry. JS Asian Fed Obstet Gynecol. 2009;1(3):55-61.
21. Mistry HD, Gill CA, Kurlak LO, Seed PT, Hesketh JE, Méplan C, Schomburg L, Chappell LC, Morgan L, Poston L, SCOPE consortium. Association between maternal micronutrient status, oxidative stress, and common genetic variants in antioxidant enzymes at 15 weeks' gestation in nulliparous women who subsequently develop preeclampsia. Free Radic. Biol. Med. 2015;78:147-155.
22. Mistry HD, Pipkin FB, Redman CW, Poston L. Selenium in reproductive health. AJOG. 2012;206(1):21-30.
23. Haque MM, Moghal MM, Sarwar MS, Anonna SN, Akter M, Karmakar P, Ahmed S, Sattar MA, Islam MS. Low serum selenium concentration is associated with preeclampsia in pregnant women from Bangladesh. J. Trace Elem. Med. Biol. 2016;33:21-25.
24. Cinemre FB, Cinemre H, Erdogan E, Dilaveroglu N, Tuten A, Kaya B, Aydemir B. Association of selenoprotein W1 (rs3786777) polymorphism, maternal plasma selenoprotein W (SelW), and selenium levels in patients with pre-eclampsia. Trace Elem Electrolytes. 2019; 36(2):61-67.
25. Silva AC, Costa SM, Valerio EG, Ramos JG. 73 Comparison of serum selenium levels among hypertensive and normotensive pregnant women from southern brazil: A Case control-study: Risk factors, prediction of preeclampsia. Preg Hypertension: Int J Wom Cardiovas Hea. 2016;6(3):213.
26. Bizerea TO, Dezsi SG, Marginean O, Stroescu R, Rogobete A, Bizerea-Spiridon O, Ilie C. The link between selenium, oxidative stress and pregnancy induced hypertensive disorders. Clin Lab. 2018;64(10):1593-1610.
27. Lewandowska M, Sajdak S, Lubiński J. Serum selenium level in early healthy pregnancy as a risk marker of pregnancy induced hypertension. Nutrients. 2019;11(5):1028.
28. Wilson RL, Bianco-Miotto T, Leemaqz SY, Grzeskowiak LE, Dekker GA, Roberts CT. Early pregnancy maternal trace mineral status and the association with adverse pregnancy outcome in a cohort of Australian women. J. Trace Elem. Med. Biol. 2018;46:103-109.

29. Duntas LH. Selenium and at-risk pregnancy: challenges and controversies. Thyroid Res. 2020;13(1):1-2.
30. Hasegawa Y, Aoki S, Kurasawa K, Takahashi T, Hirahara F. Association of biparietal diameter growth rate with neurodevelopment in infants with fetal growth restriction. Taiwan J Obstet Gynecol. 2015;54(4):371-375.
31. Grantz KL, Kim S, Grobman WA, Newman R, Owen J, Skupski D, Grewal J, Chien EK, Wing DA, Wapner RJ, Ranzini AC. Fetal growth velocity: the NICHD fetal growth studies. AJOG. 2018;219(3):285-e1.
32. Roy S, Dhobale M, Dangat K, Mehendale S, Lalwani S, Joshi S. Differential oxidative stress levels in mothers with preeclampsia delivering male and female babies. The J. Matern.-Fetal Neonatal Med. 2015;28(16):1973-1980.
33. Eviston DP, Minasyan A, Mann KP, Peek MJ, Nanan RK. Altered fetal head growth in preeclampsia: a retrospective cohort proof-of-concept study. Fron pediatrics. 2015;3:83.
34. Arshad S, Ahmed S, Syed S. Assessing the impact of Glutathione on maternal and fetal outcome in pregnancy-induced hypertensive disorders: A case-control study. IJEHSR. 2020;9(1):10-20.
35. Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. Nature Rev Neurosci. 2013;14(1):7-23.
36. Surico D, Bordino V, Cantaluppi V, Mary D, Gentilli S, Oldani A, Farruggio S, Melluzza C, Raina G, Grossini E. Preeclampsia and intrauterine growth restriction: Role of human umbilical cord mesenchymal stem cells-trophoblast cross-talk. Plos one. 2019;14(6):e0218437.
37. Sultana R, Karim SF, Atia F, Ferdousi S, Ahmed S. Platelet count in preeclampsia. J Dhaka Nat Med Col Hospital. 2012;18(2):24-26.