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Evaluation of estriol levels in women with preeclampsia in Nnewi, South-East Nigeria

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Abstract

Preeclampsia is a life-threatening pregnancy-induced disorder characterized by the presence of hypertension and proteinuria occurring after 20 weeks of gestation in a previously normotensive and aproteinuric woman. This study is aimed at investigating the maternal serum levels of estriol in pregnant women with preeclampsia. This is an analytical cross-sectional study including a total of 90 pregnant women aged 18-41years at 26-40 weeks of gestation, according to the last date of menstruation and ultrasonographic measurements. Forty five of these were preeclamptic while the other forty five were apparently healthy individuals. Preeclampsia was determined by proteinuria ≥30mg/dl or ≥1+ using a urine dipstick and sphygmomanometer blood pressure reading of ≥ 140/90 mmHg using ausculatory method. BMI was calculated from weight and height measurements of each participant. Estriol (E3) levels were determined utilizing the double-antibody sandwich enzyme linked immunosorbent assay technique. Hypothesis testing was done using the student's t-test for continuous variables, Chi-square test for categorical variables and Pearson's correlation for the tests of association. Statistical significance was set at $p<0.05$. The mean serum values of E3 were significantly lower in women with preeclampsia (124.18±22.40) compared with the apparently healthy control counterparts (141.41±20.68, $p<0.001$). A moderate negative correlation was observed between maternal serum estriol level and BMI in the preeclamptic group ($r = -0.589$; $p<0.001$). There existed a strong negative correlation between maternal serum estriol level and systolic ($r = -0.738$; $p<0.001$) as well as diastolic ($r = -0.711$; $p<0.001$) blood pressures in women with preeclampsia. Preeclampsia is associated with lower maternal serum levels of estriol which may play a significant role in the pathogenesis of the disorder.

Keywords: BMI; Estriol; ELISA; Preeclampsia; Proteinuria

1. Introduction

Preeclampsia (PE) is one of the major causes of maternal and neonatal morbidity and mortality [1] and complicates 3% to 7% of pregnancies worldwide [2] with higher trends in developing countries (2.8% of live births) compared to developed countries (0.4% of live births) [3]. The incidence of preeclampsia in Nigeria ranges from 2-16% [3] but studies by Onoh *et al.* [4] in Abakaliki indicated an incidence of 3.6% while Ugwu *et al.* [5] reported a prevalence of 3.3% in Enugu.

PE is defined as new onset hypertension (systolic blood pressure ≥140mmHg and a diastolic blood pressure ≥90mmHg after two consecutive measurements 4-6hours apart) that occurs after 20-week gestation with significant proteinuria with or without pathologic edema in a previously normotensive and aproteinuric woman [6, 7]. PE is also characterized by high blood pressure without proteinuria associated with elevated liver enzyme activities, increased blood creatinine, thrombocytopenia, seizures, or intrauterine growth retardation [8, 9]. Two types of PE have been described: early-onset

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PE (type I) and late-onset PE (type II) with occurrence of clinical signs before and after 34 weeks of gestation respectively [10, 11]. The only definitive therapy for either type of PE is delivery of the foetus and placenta [12].

PE is a multi-systemic syndrome, involving genetic and environmental factors in its pathogenesis and pathophysiology [13]. The severity of the pathophysiology associated with PE differs depending on its complications with conditions such as eclampsia, edema, renal failure, liver failure, and HELLP (hemolysis elevated liver enzymes low platelet) syndrome [9]. Risk factors of preeclampsia include obesity, chronic hypertension, maternal age, diabetes mellitus, multiple pregnancies, history of preeclampsia, new paternity, race and in vitro fertilization [7, 14].

Estrogen is a category of sex hormone with various physiological actions responsible for the development and regulation of the female reproductive system and secondary sex characteristics [15]. The three major endogenous estrogens in humans include estrone (E1), estradiol (E2) and estriol (E3) with E2 being the most potent and prevalent estrogen produced by the ovaries in non-pregnant premenopausal women. However, in pregnancy, E3 is produced in notable quantities during which it is the predominant circulating estrogen in terms of serum levels [15]. Levels of E3 increase 1,000-fold during pregnancy whereas levels of E2 and E1 increase 100-fold [16, 17]. E3 is mainly produced by the placenta and accounts for 90% of the total circulating estrogens in pregnant women [17]. Unlike E2, E3 has a much lower affinity for sex hormone-binding globulin (SHBG) hence a greater fraction available for biological activity than the "more potent" hormone [18]. E3 has been proposed to improve pregnancy outcomes and can be measured in maternal blood or urine as a marker of fetoplacental function to predict adverse fetal outcome [19, 20, 21]. Estriol also has anti-inflammatory properties as well as vasculo-protective action [22, 23, 24]. Aberrant production of estriol may play a key role in PE symptoms because it is the predominant estrogen exclusively produced by the placenta in pregnant women [15]; and promotes angiogenesis and vasodilation which contribute in boosting uteroplacental blood flow and placental perfusion during pregnancy [23, 25]. Several studies have associated diminished levels of estriol with preeclamptic pregnancies [23, 26]. However, these findings have not been well characterized in our environment thus limiting the generalizability of the findings to southeastern Nigerian women. Hence, this study was designed to determine maternal serum estriol level in pregnant women with preeclampsia in Nnewi, South-East Nigeria and to compare it with apparently healthy pregnant controls to ascertain whether serum estriol level is associated with preeclampsia in this population.

2. Materials and methods

2.1. Study design and setting

This was an analytical cross-sectional study conducted at the antenatal clinic and labour ward of Nnamdi Azikiwe University Teaching Hospital. The hospital is a federal government of Nigeria teaching hospital located in Nnewi, Southeastern Nigeria. It acts mainly as a referral center for other government-owned and private hospitals in the State and runs four antenatal clinics a week (Tuesday, Wednesday, Thursday and Friday).

2.2. Study population

A total of 90 pregnant women aged between 18–41years at 26-40weeks of gestation were recruited in this study after a written informed consent was sought and obtained upon counselling on the purpose and requirements of the study. The test group comprised 45 pregnant women diagnosed with preeclampsia while the control participants consisted of 45 apparently healthy pregnant women with normal blood pressure who were matched for maternal age and gestational age. Preeclampsia was defined as a blood pressure of ≥140/90 mmHg, measured twice at least 6 hours apart, and proteinuria of ≥30 mg/dl or ≥1+ using a urine dipstick [6]. The test participants were recruited using purposive sampling technique while the apparently healthy pregnant controls were randomly recruited.

2.3. Sample size determination

Sample size was calculated using G*Power software (version 3.0.10). Power analysis for two independent groups was conducted in G*Power to determine a sufficient sample size using an alpha of 0.05, a power of 0.80 and a medium effect size (d=0.50). Based on these assumptions, the calculated total sample size of 90 (45 per group) has 80% power to detect a difference of 0.50 (medium effect size) at significance level of 0.05.

2.4. Inclusion criteria

Preeclamptic and apparently healthy pregnant women aged 18-41 years at 26-40 weeks of gestation attending the antenatal clinics as well as preeclamptic pregnant women admitted into labour ward of Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria.

2.5. Exclusion criteria

Non-pregnant women, pregnant women outside the age range of 18-41 years and gestational age of 26-40 weeks, pregnant women who smoke or drink alcohols, pregnant women who did not give their informed consent, pregnant women with history of diabetes, cardiovascular disease, hepatic disorder, anaemia, cancers, human immunodeficiency virus (HIV) infection and renal dysfunction. The exclusion was done after the filled questionnaire has been reviewed.

2.6. Anthropometric measurements and laboratory analysis

Blood pressure measurement was by ausculatory method as described by Adenekan *et al.* [27]. Using a mercury sphygmomanometer desk type with a long (adult) cuff calibrated in mmHg, the arterial blood pressure in the brachial artery was measured on the left arm in a comfortable sitting position after 10 minutes of rest. A korotkoff sound is used for determination of diastolic blood pressure. All measurements were taken on two occasions at least 4 hours apart and the average of the reading was taken as the final blood pressure to provide a more accurate estimate. Systolic and diastolic blood pressures greater than or equal to 140mmHg and 90mmHg respectively were regarded as high blood pressure [6]. Urinalysis was performed using the Medi-Test Coombi-2 urine strip. The weight and height of each participant were measured in kilograms and metres respectively using a medical grade weighing scale and stadiometer (model Stat Fax 2100, Awareness Technology Inc., Palm City, Fla., USA). The BMI of each woman was then calculated as weight in kilogram divided by height squared in meters [28]. Information on socio-demographic, medical history and lifestyle was obtained using a well-structured questionnaire. Five milliliters of venous blood sample was collected from the cubital vein of each participant in to a plain labelled sample container using standard venepuncture technique and left at room temperature for few minutes to clot. The serum was then obtained by centrifugation for 5 minutes at 4000rpm and stored at -20^{o}c prior to analysis. Double-antibody sandwich enzyme immunoassay technique with ELISA kit (Melsin Medical Company Limited, Jilin Province China) was used for the quantitative determination of serum estriol.

2.7. Statistical analysis

The data were analyzed using statistical package for social sciences (SPSS) version 23.0. The results were expressed as mean plus or minus standard deviation (mean ± SD) in tabular form. Independent student's t-test was used for comparing the differences of continuous variables while Chi-square test was used to compare the differences in proportion of the categorical variables. The tests of association were performed using Pearson's correlation. Statistical significance was set at $p<0.05$.

2.8. Ethical consideration

The ethical approval for this study was obtained from the ethics committee, Nnamdi Azikiwe University Teaching Hospital, Nnewi (Reference number NAUTH/CS/66/VOL. 14/VER.3/289/2021/072). A written informed consent was sought and obtained from the participants after the purpose and requirements of the study have been explained to them.

3. Results

The participants ranged from 18 to 41years with the mean±SD higher in the preeclamptic group (31.76±5.41) compared with the control group (30.84±5.92) and the difference was not statistically significant ($p>0.05$). Majority of the participants were aged 24-29years recording 51.1% in both the test and control group. Gestational age was lower in the preeclamptic group (32.18±3.92) compared with the control counterparts (33.60±3.71) and the difference was not statistically significant ($p>0.05$). The highest number of participants in both groups was at 31-35weeks gestational age accounting for 21(46.7%) in preeclamptic group and 20(44.4%) for apparently healthy controls. There was no statistically significant difference between the test and control participants with regards to parity ($p = 0.181$). With respect to occupation, most of the participants in both test and control group were self-employed, accounting for 44.4% and 40% respectively. The least among them were students, 22.2% and 24.4% of test group and control group respectively. There was no statistically significant difference among the groups ($p = 0.145$). Most of the participants had tertiary education, recording 44.4% and 53.3% of test group and control group respectively. The least number of participants had primary education, accounting for 8.9% in both groups. There was no statistically significant difference among the study groups with respect to education ($p = 0.157$) [Table 1].

As presented in table 2, the mean serum level of E3 was significantly lower in women with preeclampsia (124.18**±**22.40) compared with the apparently healthy control counterparts (141.41**±**20.68, $p<0.001$). The women with preeclampsia had higher mean value of BMI (35.33±6.80) compared with the control group (29.50±5.62) and the difference was found to be statistically significant ($p<0.001$). Also, significantly higher mean values of systolic (160.89±21.41 vs. 108±9.61, $p<0.001$) and diastolic blood pressures (106.53±9.00 vs. 69.84±10.46, $p<0.001$) were observed in the preeclamptic group compared with the control participants.

A moderate negative correlation was observed between maternal serum E3 level and BMI in preeclamptic group (r = -0.589; p<0.001). There existed a strong negative correlation between maternal serum E3 level and systolic blood pressure (r = -0.738; p<0.001). Similarly, a strong negative correlation was observed between maternal serum E3 level and diastolic blood pressure (r = -0.711; p<0.001). There was no correlation between E3 and maternal age (p>0.05). Also, there was no correlation between E3 and gestational age (p>0.05) [Table 3].

Table 1 Demographic data of test participants and controls

Variables	Preeclamptic N (%)	Apparently Healthy N (%)	χ^2	p-value
Age group (years)				
18-23	7(15.6)	7(15.6)		
24-29	23(51.1)	23(51.1)	6.491	0.690
30-35	12(26.7)	8(17.8)		
36-41	3(6.7)	7(15.6)		
Mean±SD	31.76±5.41	30.84±5.92		
Gestational age (weeks)				
26-30	6 (13.3)	12 (26.7)		
31-35	21 (46.7)	20 (44.4)	5.411	0.248
36-40	18 (40.0)	13 (28.9)		
Mean±SD	32.18±3.92	33.60±3.71		
Parity				
Nullliparous	22 (48.9)	23(51.1)		
Parous	23(51.1)	22(48.9)	1.793	0.181
Occupation				
Student	10 (22.2)	11 (24.4)		
Self employed	20 (44.4)	18 (40.0)	6.839	0.145
Civil servant	15 (33.3)	16 (35.6)		
Education				
Primary	4(8.9)	4(8.9)		
Secondary	21(46.7)	17(37.8)	6.629	0.157
Tertiary	20(44.4)	24(53.3)		

Table 2 Comparison of mean values of estriol, BMI, systolic and diastolic blood pressures in preeclamptic and apparently healthy pregnant women

Parameters	Preeclamptic(n=45) Mean±SD	Healthy(n=45) Mean±SD	t-value	p-value
BMI (kg/m^2)	35.33±6.80	29.50±5.62	4.428	<0.001**
SBP (mmHg)	160.89±21.41	108±9.61	15.095	<0.001**
DBP (mmHg)	106.53±9.00	69.84±10.46	17.837	<0.001**
E3 (pg/ml)	124.18±22.40	141.41±20.68	-3.791	<0.001**

**p<0.001 significant Keys: BMI Body mass index SBP Systolic blood pressure DBP Diastolic blood pressure E3 Estriol

Table 3 Correlation of maternal serum E3 in the preeclamptic group with BMI, SBP, DBP, maternal age and gestational age

Parameters	r-value	p-value
BMI ($kg/m^{2)}$	-0.589	<0.001**
SBP (mmHg)	-0.738	<0.001**
DBP (mmHg)	-0.711	<0.001**
Maternal age (years)	-0.116	0.447
gestational age (weeks)	0.685	0.062

**p<0.001 significant p>0.05 not significant Keys: BMI Body mass index SBP Systolic blood pressure DBP Diastolic blood pressure E3 Estriol

4. Discussion

The mean age of 31.76 years recorded in women with preeclampsia recruited in this study is similar to the mean age of 30.91 years reported in preeclamptic women from the same study setting [28] and the mean age of 31.7 years reported by Cantonwine *et al.* [29]. This is also almost the same as the mean ages of 30.19 and 30.0 years reported from similar studies in Owerri and Lagos, Nigeria respectively [27, 30]. Maternal age has been reported as one of the risk factors of preeclampsia [14]. Increased age of women is an important risk factor due to increased villous reaction leading to preeclampsia in a woman greater than 30years [31].

The mean gestational age (GA) of occurrence of preeclampsia in this present study (32.18±3.92) is similar to the mean enrolment GA of 32.5±3.9 weeks recorded by Adekunle *et al.* [27]. The finding of this current study is also not different from the results of similar studies conducted in different clinical settings in Nigeria [30, 32]. This explains why preeclampsia is considered a major cause of perinatal morbidity and mortality mostly because pregnancies complicated with preeclampsia often culminates in preterm delivery of the fetus shortly after the occurrence of the disorder [33].

Majority of women with preeclampsia recruited in this study were self-employed accounting 44.4% of the test participants. The finding of this current study is almost the same as the results of similar study by Emeka-Obi *et al.* [30] who reported that a greater percentage of the test participants were self-employed.

The findings of this study indicated a significantly higher mean value of BMI in the preeclamptic women compared with the apparently healthy individuals. This could be as a result of increased total body water in preeclamptic pregnancies [34]. Decreased nitric oxide (NO) bioavailability associated with endothelial dysfunction results in decreased cardiac output which impairs renal perfusion and function, thereby inducing additional fluid retention [35]. BMI greater than $30kg/m^2$ has been proposed as a risk factor of preeclampsia [14]. Overweight or obesity has been linked with higher prevalence of late-onset preeclampsia [36, 37]. This is possibly, in part, due to the association of preeclampsia with obesity and cardiometabolic dysfunction [38]. Although, weight loss during pregnancy is not recommended, antenatal lifestyle modifications are important to minimize weight gain and reduce the risk of preeclampsia [14]. Our finding is in line with the findings of Shao *et al.* [39] who reported a significantly higher BMI in preeclamptics compared with the normotensive controls in Lanzhou, China. This is also consistent with the findings of [26, 28, 34].

Our study showed a significant increase in the mean systolic and diastolic blood pressures in the preeclamptic group compared with the apparently healthy controls. This could be attributed to placental ischemia resulting from reduced utero-placental perfusion due to abnormal cytotrophoblast invasion of spiral arterioles [13]. Placental ischemia leads to widespread activation/dysfunction of the maternal endothelium that results in enhanced formation of endothelin and thromboxane, imbalance in circulating angiogenic and anti-angiogenic factors, increased vascular sensitivity to angiotensin II, and decreased formation of vasodilators such as nitric oxide and prostacyclin [9]. These endothelial abnormalities induce vasoconstriction and increased vascular stiffness in the systemic and pulmonary circulation, resulting in augmented systolic workload with attendant systemic hypertension [9, 40]**.** This agrees with the findings of Amiri *et al.* [41] and Onuegbu *et al.* [28] who reported significantly higher mean levels of systolic and diastolic blood pressures in preeclamptic individuals compared with the normotensive group**.**

Our study found significantly lower serum levels of estriol in the preeclamptic women compared with their apparently healthy counterparts. The decline in estriol level may be due to decrease in enzyme activities of 3β-hydroxysteroid dehydrogenase type I(3β-HSD1), aromatase and 17β-hydroxysteroid dehydrogenase(17β-HSD) which are essential for

estriol biosynthesis as stated by Strauss and Barbieri [15] and Berkane *et al.* [42]. Ischemic placental circulation and hypoxia due to defective cytotrophoblast uterine vessel invasion may also contribute to the decline in serum level of estriol in preeclampsia [42, 43]. Hypoxia mediates the downregulation of placental aromatase, a key enzyme in estriol synthesis by activating transcription factors that inhibit aromatase expression with aberrant synthesis of estriol contributing to uterine vascular dysfunction in preeclampsia [42, 43, 44]. Low maternal serum estriol level has been associated with adverse pregnancy outcomes [20]. Zhou *et al.* [21] also reported that exposure of pregnant fetal mice to E3 improved adult offspring reproductive and mental health by epigenetically programming the fetus. Estriol has been reported to up-regulate uteroplacental blood flow and placental vascularization which are directly linked to fetal growth and survival [23, 45, 46]. Thus, decreased levels of estriol may contribute in compromising placental perfusion and exacerbating the outcome of the mother and fetus in pregnancies complicated with preeclampsia. This correlates with the findings of Jobe *et al.* [26] who evaluated the patterns of estrogen synthesis, metabolism, and the individual plasma profile of estrogens in preeclampsia and reported that levels of estriol were significantly lower in severe preeclampsia compared with normal pregnancy.

Our findings showed a moderate negative correlation between maternal serum E3 levels and BMI in pregnant women with preeclampsia. These findings suggest that low maternal serum estriol levels may predispose individuals to increased BMI and the link between obesity and preeclampsia appears to be well established [14, 36, 37]. The findings of this current study indicate that just as some of the already established risk factors of preeclampsia, lower serum levels of estriol may be implicated in the occurrence of the disorder [20, 21]. This agrees with the report by Kurylowicz [47] who provided empirical evidence of the link between estrogens and obesity. Our study further observed strong negative correlations between maternal serum E3 concentrations and SDP as well as DBP both of which pose as markers of severity of preeclampsia. These findings suggest the vasculoprotective and anti-hypertensive properties of E3 as reported by Berkane *et al.* [23]. Hence, maternal serum levels of E3 may be related to the severity of preeclampsia as reported by Jobe *et al.* [26]. Estriol has been reported to promote vasodilation and angiogenesis thus promoting uteroplacental blood flow [23]. This is consistent with our findings.

Also, in this current study, there were no significant variations of E3 with maternal age and gestational age in preeclamptic pregnancies. These findings indicate that the maternal serum levels of E3 in preeclampsia may not be directly related to maternal age and gestational age, although serum estrogen levels have been reported to increase with advancing gestational age in normal pregnancy [48].

5. Conclusion

Maternal serum estriol level was significantly lower in women with preeclampsia compared with apparently healthy pregnant women and may play a significant role in the pathogenesis of preeclampsia in southeastern Nigerian women.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declared no conflict of interest

Statement of ethical approval

The ethical approval for this research was obtained from the Ethics Committee of Nnamdi Azikiwe University Teaching Hospital, Nnewi.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, Alkema L. Global causes of maternal death: a WHO systematic analysis. The lancet global health. 2014; 2(6): e323-33.

[2] Savitz DA, Danilack VA, Engel SM, Elston B, Lipkind HS. Descriptive epidemiology of chronic hypertension, gestational hypertension, and preeclampsia in New York State, 1995–2004. Matern child health J. 2014; 18(4): 829-38.

[3] Osungbade K, Ige O. Public health perspectives of preeclampsia in developing countries: Implication for health system strengthening. J Pregnancy. 2011; 2011: 481095.

[4] Onoh R, Mamah J, Umeokonkwo CD, Onwe EO, Ezeonu PO, Okafor L. Severe preeclampsia and eclampsia: A 6-year review at the Federal Teaching Hospital, Abakaliki, Southeast Nigeria. Trop J Obstet Gynaecol. 2019; 36: 418.

[5] Ugwu EO, Dim CC, Okonkwo CD, Nwankwo TO. Maternal and perinatal outcome of severe pre-eclampsia in Enugu, Nigeria after introduction of magnesium sulfate. Niger J Clin Pract. 2011; 14(4): 418-21.

[6] ACOG (2013). Hypertension in pregnancy: report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. Obstet & Gynecol. 122(5): 1122-31.

[7] Al-Jameil N, Aziz KF, Fareed KM, Tobassum H. A brief overview of preeclampsia. J Clin Med Res. 2014; 6(11): 1-7.

[8] ACOG (2020). ACOG practice bulletin, number 222. Gestational hypertention and preeclampsia. Obstet & Gynecol. 135: e237-260

[9] Rana S, Lemoine E, Granger PJ, Karumanchi AS. Preeclampsia: Pathophysiology, Challenges, and Perspectives. Circ Res. 2019; 124(7): 1094-112.

[10] Robillard PY, Dekker G, Scioscia M, Bonsante F, Lacobelli S, Boukerrou M, Hulsey TC. The blurring boundaries between placental and maternal preeclampsia: a critical appraisal of 1800 consecutive preeclamptic cases. J Matern Fetal Neonatal Med. 2020; 35(13): 2450-56.

[11] James MR, Janet WR, Thomas FC, Lana G, Leslie M. Subtypes of preeclampsia: recognition and determining clinical usefulness. J Hypertens. 2021; 77(5): 1430-41.

[12] Romero R, Chaiworapongsa T. Preeclampsia: a link between trophoblast dysregulation and an antiangiogenic state. J Clin Invest. 2013; 123(7): 2775–77.

[13] Cornelius DC. Preeclampsia from inflammation to immunoregulation. Clin Med Insights Blood Disord. 2018; 11: 1-6.

[14] Dimitriadis E, Rolnik Dl, Zhou W, Estrada-Gutierrez G, Koga K, Francisco RPV, Whitehead C, Hyett J, da Silva Costa F, Nicolaides K, Menkhorst E. Preeclampsia. Nat Rev Dis Primers. 2023; 9(1): 8.

[15] Strauss JF, Barbieri RL. Yen and Jaffe's reproductive endocrinology: physiology, pathophysiology and clinical management. 8th edition. St. Louis: Elsevier; 2019.

[16] Lappano R, Rosano C, De Marco P, De Francesco EM, Pezzi V, Maggiolini M. Estriol acts as a GPR30 antagonist in estrogen receptor-negative breast cancer cells. Mol Cell Endocrinol. 2010; 320(1–2): 162–70.

[17] Susan B. Maternal, fetal, & neonatal physiology: a clinical perspective. 5th edition. St. Louis Missouri: Elsevier; 2018.

[18] Jasuja R, Spencer D, Jayaraj A, Peng L, Krishna M, Lawney B, Patel P, Jayaram B, Thayer KM, Beveridge DL, Bhasin S. Estradiol induces allosteric coupling and partitioning of sex-hormone-binding globulin monomers among conformational states. iScience. 2021; 24(6): 102414

[19] Pagana TJ, Pagana KD. Mosby's manual of diagnostic and laboratory tests. St. Louis: Mosby; 2009

[20] Settiyanan T, Wanapirak C, Sirichotiyakul S, Tongprasert F, Srisupundit K, Luewan S, Traisrisilp K, Tongsong T. Association between isolated abnormal levels of maternal serum unconjugated estriol in the second trimester and adverse pregnancy outcomes. J Matern Fetal Neonatal Med. 2016; 29(13): 2093-97.

[21] Zhou Y, Gu B, Brichant G, Singh JP, Yang H, Chang H, Zhao Y, Cheng C, Liu ZW, Alderman III MH, Lu L, Yang X, Gao XB, Taylor HS. The steroid hormone estriol (E3) regulates epigenetic programming of fetal mouse brain and reproductive tract. BMC Biol. 2022; 20(1): 93.

[22] Nadkarni, S., Cooper, D., Brancaleone, V., Bena, S., Perretti, M. Activation of the annexin A1 pathway underlies the protective effects exerted by estrogen in polymorphonuclear leukocytes. ATVB. 2011; 31(11): 2749–59.

[23] Berkane N, Liere P, Oudinet JP, Hertig A, Lefevre G, Pluchino N, Schumacher M, Chabbert-Buffet N. From pregnancy to preeclampsia: a key role for estrogens. Endocr Rev. 2017; 38(2): 123-44.

[24] Vermillion MS, Ursin RL, Attreed SE, Klein SL. Estriol reduces pulmonary immune cell recruitment and inflammation to protect female mice from severe influenza. Endocrinol. 2018; 159(9): 3306-20.

[25] Lan KC, Lai YJ, Cheng HH, Tsai NC, Su YT, Tsai CC, Hsu TY. Levels of sex steroid hormones and their receptors in women with preeclampsia. Repro Biol Endocrinol. 2020; 18(1): 12.

[26] Jobe SO, Tyler CT, Magness RR. Aberrant synthesis, metabolism and plasma accumulation of circulating estrogens and estrogen metabolites in preeclampsia implications for vascular dysfunction. J Hypertens. 2013; 61(2): 480-87.

[27] Adenekan MA, Oluwole AA, Olorunfemi G, Sekunmade AI, Ajepe AA, Okunade KS. Maternal tumour necrosis factor-alpha levels inpreeclamptic pregnancies in Lagos, South-West Nigeria. Pregnancy Hypertens. 2022; 30: 198-203.

[28] Onuegbu AJ, Olisekodiaka JM, Udo JU, Umeononihu O, Amah UK, Okwara JE, Atuegbu C. Evaluation of high-sensitivity C-reactive protein and serum lipid profile in southeastern Nigerian women with preeclampsia. Med Princ Pract. 2015; 24(3): 276-79.

[29] Cantonwine DE, McElrath TF, Trabert B, Xu X, Sampson J, Roberts JM, Hoover RN, Troisi R. Estrogen metabolism pathways in preeclampsia and normal pregnancy. Steroids. 2019; 144: 8-14.

[30] Emeka-Obi OR, Ibeh NC, Obeagu EI, Okorie HM. Evaluation oflevels of some inflammatory cytokines in preeclamptic women in Owerri. J Pharm Res. 2021; 33(42A): 53-65.

[31] Lamminpää R, Vehviläinen-Julkunen K, Gissler M, Heinonen S. Preeclampsia complicated by advanced maternal age: a registry-based study on primiparous women in Finland 1997–2008. BMC Pregnancy Childbirth. 2012; 12(47): 1-5.

[32] Udenze I, Amadi C, Awolola N, Makwe CC. The role of cytokines as inflammatory mediators in preeclampsia. Pan Afri Med J. 2015; 20: 219.

[33] Yang Y, Le Ray I, Zhu J, Zhang J, Hua J, Reilly M. Preeclampsia Prevalence, Risk Factors, and Pregnancy Outcomes in Sweden and China. JAMA. 2021; 4(5): e218401.

[34] Hilesund ER, Seland S, Bere E, Sagedal LR, Torstveit MK, Lohne-Seiler H, Vistad I, Overby NC. Preeclampsia and gestational weight gain in the Norwegian fit for delivery trial. BMC Res Notes. 2018; 11(1): 282.

[35] Puissant C, Abraham P, Durand S, Humeau-Heurtier A, Faure S, Rousseau P, Mahe G. J Mal Vasc. 2014; 39(1): 47-56.

[36] Durst JK, Tuuli MG, Stout MJ, Macones GA, Cahill AG. Degree of obesity at delivery and risk of preeclampsia with severe features. AJOG. 2016; 214: 651.e1-e5.

[37] Wadhani P, Saha PK, Kalra JK, Gainder S, Sundaram V. A study to compare maternal and perinatal outcome in early vs. late onset preeclampsia. Obstet Gynecol Sci. 2020; 63: 270-77

[38] Martinez-Hortelano JA, Cavero-Redondo I, Alvarez-Bueno C, Sanabria-Martinez G, Poyatos-Leon R, Martinez-Vizcaino V. Interpregnancy weight change and hypertension during pregnancy: a systematic review and meta-analysis. Obstet & Gynecol. 2020; 135(1): 68-79.

[39] Shao Y, Qiu J, Huang H, Mao B, Dai W, He X. Pre-pregnancy BMI, gestational weight gain and risk of preeclampsia: a birth cohort study in Lanzhou, China. BMC Pregnancy Childbirth. 2017; 17: 400

[40] Ahmed R, Dunford J, Mehran R, Robson S, Kunadian V. Pre-eclampsia and future cardiovascular risk among women: a review. JACC. 2014; 63(18): 1815-22.

[41] Amiri M, Ramezani TF, Rahmati M, Behboudi-Gandevani S, Azizi F. Changes over-time in blood pressure of women with preeclampsia compared to those with normotensive pregnancies: a 15year population-based cohort study. Pregnancy Hypertens. 2019; 17: 94-99.

[42] Berkane N, Liere P, Lefevre G. Abnormal steroidogenesis and aromatase activity in preeclampsia. Placenta. 2018; 69: 40-49.

[43] Perez-Sepulveda A, Monteiro LJ, Dobierzewska A, Espana-Perrot PP, Venegas-Araneda P, Guzman-Rojas AM, Gonzalez MI, Palominos-Rivera M, Irarrazabel CE, Figueroa-Diesel H, Varas-Godoy M, Illanes SE. Placental aromatase is deficient in placental ischemia and preeclampsia. Plos One. 2015; 10(10): e0139682.

[44] Mandala M. Influence of estrogens on uterine vascular adaptation in normal and preeclamptic pregnancies. Int J Mol Sci. 2020; 21(7): 2592.

[45] Herrera-Garcia G, Contag S. Maternal preeclampsia and risk for cardiovascular disease in offspring. Curr Hypertens Rep. 2014; 16: 475.

[46] Bai J, Qi QR, Li Y, Day R, Makhoul J, Magness RR, Chen DB. Estrogen receptors and estrogen-induced uterine vasodilation in pregnancy. Int J Mol Sci. 2020; 21(12): 4349.

[47] Kurylowicz A. Estrogens in adipose tissue physiology and obesity-related dysfunction. Biomed. 2023; 11(3): 690.

[48] Kim SC, Park MN, Lee YJ, Joo JK, An BS. Interaction of steroid receptor coactivators and estrogen receptors in the human placenta. J Mol Endocrinol. 2016; 56**:** 239-47.