Increased 8-OHdG in umbilical cord blood represents the risk of preeclampsia with Intra-Uterine Growth Restriction (IUGR)

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INTRODUCTION

Preeclampsia is a disease related to pregnancy and involves multiple organs, especially marked by an increase in blood pressure in the second trimester of pregnancy, which can quickly develop into serious complications, including the death of the mother and fetus, both short and long-term. Complications in the mother include cardiometabolic disease (diabetes, ischemic heart disease, metabolic syndrome), cerebrovascular disease, neurological disorders ( eclampsia), and renal impairment. The impact on the fetus can be in the form of IUGR, prematurity, and having a high risk of experiencing hypertension, obesity, metabolic syndrome, dyslipidemia, and cardiovascular disease as an adult. Severe preeclampsia is often associated with adverse pregnancy outcomes, including fetal growth restriction and premature birth, all of which are associated with increased neurodevelopmental delays due to increased oxidative stress in the uterus. Impaired placenta implantation in the uterine wall is understood as a cause of preeclampsia. Impaired uterine spiral artery remodeling by extravillous trophoblasts causes decreased placental perfusion, resulting in intermittent arterial blood flow, causing repeated episodes of ischemia-reperfusion and creating a supportive environment for oxidative stress. Oxidative stress can cause DNA damage with one of the main products, 8-hydroxy-2 deoxyguanosine or 8-OHdG. Previous studies have shown mothers who smoke increase the risk of childhood disorders, including premature delivery, IUGR, low birth weight, cleft lip, congenital heart disease, and attention deficit hyperactivity disorder (ADHD). Furthermore, several studies have reported that the presence of elevated 8-OHdG levels increases the incidence of cancer in children, diabetes mellitus, and coronary heart disease. The current study did not show any association between 8-OHdG levels and various indicators of fetal development outcome. However, additional approaches regarding the characteristics of oxidative stress during the perinatal period are needed to improve fetal and infant health and development.

Oxidative stress plays an important role in cell damage and cell death. When oxidative stress occurs, the number of reactive oxygen species (ROS) will increase and cause mitochondrial dysfunction, disruption of antioxidative defense mechanisms, or a combination of these systems, resulting in damage to DNA, RNA, mitochondria, and other biomolecules, resulting in impaired cellular function or death cell. In preeclampsia, there is an increase in arterial resistance in the uterus, thereby inducing vasoconstriction, and thus

ABSTRACT

Background: Preeclampsia is a pregnancy-related disease involving multi-organs, characterized by increased blood pressure in the second trimester of pregnancy. Preeclampsia can have short-term and long-term consequences for the mother and the fetus, including intra-uterine growth restriction (IUGR). One of the markers of DNA damage due to oxidative stress due to endothelial dysfunction in preeclampsia is the increase in 8-OHdG levels in cord blood. This study aims to see an increase in 8-OHdG levels in preeclampsia.

Methods: This study was a cross-sectional study with a total of 41 patients with preeclampsia and 41 patients with healthy women at Wahidin Sudirohusodo Hospital and its network. Samples were taken using the purposive sampling method according to the inclusion criteria. This 8-OHdG level was examined using the ELISA kit at the HUMRC laboratory of Hasanuddin University Hospital. The data is then processed statistically using SPSS.

Results: This study found 6 patients with PE + IUGR, 31 with PE, and 41 without PE. The examination results of 8-OHdG levels found significant differences between the 3 groups PE + IUGR, PE, and normal pregnancies, which showed a significant relationship between elevated 8-OHdG levels and the incidence of PE accompanied by IUGR (p = 0.006).

Conclusion: Elevated 8-OHdG levels are found in preeclampsia, especially in preeclampsia accompanied by IUGR.

Keywords: IUGR, Preeclampsia, 8-OHdG.


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resulting in chronic placental ischemia and oxidative stress processes. The presence of 8-hydroxy 2-deoxyguanosine (8-OHdG) is a sensitive marker of oxidative damage in cellular DNA. It is thought that maternal stress programs embryonic cell mass, and these cells then migrate and form various organs with abnormal cell metabolism, which will further manifest as clinical disorders in later life. Another study conducted by Fujimaki et al. also showed that 8-OHdG levels were significantly higher in the pre-eclampsia group, pre-eclampsia with IUGR, compared to the normal control group.

Based on the explanation above, the long-term impact caused by preeclampsia is not only on the mother but also on the development of babies born to mothers who suffer from preeclampsia. Factors that can cause this condition are still a question until recently. This is the basis that makes the author conduct this research. This study aims to assess whether there are differences in 8-OHdG levels as a marker for DNA damage in cord blood in mothers who suffer from preeclampsia and mothers who do not have preeclampsia.

METHODS

A study with a cross-sectional study design examined 8-OHdG (ng/mL) levels in a group of pregnant women diagnosed with preeclampsia and healthy pregnant women as control. This research was conducted at Wahidin Sudirohusodo Hospital and Network Hospital of the Department of Obstetrics and Gynecology, Faculty of Medicine, Hasanuddin University from July to November 2022. This study included 6 pregnant women with preeclampsia accompanied by IUGR, 35 without IUGR, and 41 healthy pregnant women. The diagnosis of preeclampsia is based on systolic blood pressure of 140 mmHg and diastolic blood pressure of 90 mmHg with two measurements (after approximately 15 minutes of rest) in pregnancies over 20 weeks accompanied by positive urine protein or other organ dysfunction in pregnant women such as renal insufficiency, liver disorders (increased liver enzymes), neurological disorders (headaches, eclampsia, mental disorders, blindness, stroke due to increased blood pressure), and hematological disorders (thrombocytopenia with platelet levels <150,000/µL, DIC, hemolysis) who previously had normal hypertension. The patient group was divided into 3 groups, i.e., PE + IUGR, PE, and control. The control group comprised healthy pregnant women without increased blood pressure or other systemic diseases.

Demographic data of this study group, such as age, parity, gravidity, and gestational age, were calculated based on the last menstruation. Umbilical cord artery blood samples were collected from research subjects who gave birth at the hospital by double-clamping the umbilical cord and then taking 5 cc of blood and storing it in a tube to be centrifuged to allow separation between serum and blood plasma, which was then analyzed for levels of 8-OHdG. Exclusion criteria were pregnant women diagnosed with other systemic diseases or found to have a history of using alcohol, smoking, or other drugs that are also another important cause of cell oxidative stress, which could be a bias in this research.

Measurement of 8-OHdG levels in blood serum using a specific kit. As a competitive enzyme-linked immunosorbent assay (ELISA) kit, the specific kit used in this study was considered appropriate for measuring oxidative damage in tissues, serum, and plasma. The ELISA test was carried out by the HUMRC laboratory at Hasanuddin University Hospital, Faculty of Medicine, Hasanuddin University.

Statistical method: The Kolmogorov-Smirnov test checks whether the continuous variables are normally distributed. Furthermore, the T-test was used to compare normally distributed variables between two independent groups, while the Mann-Whitney test was used to compare non-normally distributed variables. ANOVA multivariate analysis test was used to compare normally distributed variables between more than two independent groups, and Kruskal Wallis’ T-test was used to compare non-normally distributed variables. Relationships between numerical variables were analyzed using Spearman’s rank correlation coefficient, and a chi-square test was used for non-numeric variables. Statistical analysis was performed using SPSS on Windows 2.0 software, and a p-value < 0.05 was considered statistically significant.

RESULTS

This study was obtained from 94 normal pregnant women diagnosed with preeclampsia. A total of 82 patients divided into 3 groups were analyzed in this study because 12 samples were lysis during the study. Of the 82 samples, 6 samples were included in the group of preeclamptic pregnant women accompanied by IUGR, then 35 samples of pregnant women with preeclampsia, and 41 samples of healthy pregnant women.

The number of nulliparous pregnant women was higher in the preeclampsia group compared to the control group but statistically not significantly different (p = 0.30), a contrast was found in the body mass index (BMI) status of study subjects with excess BMI in the preeclampsia group compared to the control group (p = 0.02) (Table 1).

The pregnancy outcomes in the three groups found that the number of babies with low birth weight was higher in the group of pregnant women with preeclampsia compared to the control group, but the p-value could not be measured (NA = not applicable) because there was a “zero” value in one of the groups. In addition, were 4 babies born at term with low birth weight; these babies were then classified as babies with IUGR.

Statistical analysis was carried out with Kruskal-Wallis, obtaining a statistical value of p<0.05 between 3 groups (p = 0.006), indicating a significant relationship between 8-OHdG levels and preeclampsia. After that, it was followed by a post-hoc analysis with the result that there were significant differences between the PE + IUGR group with preeclampsia and the control group. However, the PE without IUGR and the control groups were not statistically different. This shows that 8-OHdG levels are especially increased in preeclampsia accompanied by IUGR compared to those without IUGR.

DISCUSSION

Preeclampsia is often associated with complications that can have an impact on both the maternal and the fetus.
methods of screening and diagnosing preeclampsia and preventive and curative treatment updates have been found. However, the problem of preeclampsia is still a problem that is often found in pregnancy. Pregnancy is a series of complex events, including decidualization, placentation, and delivery. Chronological changes are very important in normal pregnancy, and any changes may have consequences for the health of the maternal and fetus. Pregnancy is known to increase oxidative stress, an event produced by the normal systemic inflammatory response that produces high levels of circulating reactive oxygen species (ROS). The main source of ROS during pregnancy is the central organ, which is the placenta. In this regard, the increased oxidative stress in pregnancy could lead to tissue damage. However, the increase in oxidative stress is offset by an increase in antioxidant synthesis. When oxidative stress exceeds antioxidant defenses in the placenta, oxidative damage can spread to distal tissues. Until now, the pathogenesis of preeclampsia has been proposed in various theories, such as failure of spiral artery invasion and the theory of inflammation, which is associated with oxidative stress. Oxidative stress has been shown to play an important role in the pathogenesis of preeclampsia, and DNA damage is common.

### Table 1. Demographic and clinical characteristics of research subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preeclampsia (n=35)</th>
<th>PE+IUGR (n=6)</th>
<th>Control (n=41)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>14 (17.07)</td>
<td>3 (3.65)</td>
<td>8 (9.75)</td>
<td>0.28</td>
</tr>
<tr>
<td>Low Risk</td>
<td>21 (25.6)</td>
<td>3 (3.65)</td>
<td>33 (40.24)</td>
<td></td>
</tr>
<tr>
<td>Parity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nullipara</td>
<td>21 (25.6)</td>
<td>4 (4.87)</td>
<td>17 (20.73)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Multipara</td>
<td>14 (17.07)</td>
<td>2 (2.43)</td>
<td>24 (29.26)</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>18 (21.95)</td>
<td>4 (4.87)</td>
<td>12 (14.63)</td>
<td>0.30</td>
</tr>
<tr>
<td>Normal</td>
<td>17 (20.73)</td>
<td>2 (2.43)</td>
<td>29 (35.36)</td>
<td></td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 9 Years</td>
<td>10 (12.19)</td>
<td>2 (2.43)</td>
<td>14 (17.07)</td>
<td>0.13</td>
</tr>
<tr>
<td>&gt; 9 Years</td>
<td>25 (30.48)</td>
<td>4 (4.87)</td>
<td>27 (32.92)</td>
<td></td>
</tr>
<tr>
<td>Employment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>10 (12.19)</td>
<td>1 (1.21)</td>
<td>13 (15.85)</td>
<td>0.09</td>
</tr>
<tr>
<td>Unemployed</td>
<td>25 (30.48)</td>
<td>5 (6.09)</td>
<td>28 (34.14)</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Spacing, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 Years</td>
<td>5 (6.09)</td>
<td>2 (2.43)</td>
<td>1 (1.21)</td>
<td>0.17</td>
</tr>
<tr>
<td>&lt; 10 Years</td>
<td>30 (36.58)</td>
<td>4 (4.87)</td>
<td>40 (48.78)</td>
<td></td>
</tr>
<tr>
<td>PE history, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (2.43)</td>
<td>1 (1.21)</td>
<td>0 (0.00)</td>
<td>NA</td>
</tr>
<tr>
<td>No</td>
<td>33 (40.24)</td>
<td>5 (6.09)</td>
<td>41 (50.00)</td>
<td></td>
</tr>
<tr>
<td>History of PE in mother/sister, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (2.43)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>NA</td>
</tr>
<tr>
<td>No</td>
<td>33 (40.24)</td>
<td>6 (7.31)</td>
<td>41 (50.00)</td>
<td></td>
</tr>
<tr>
<td>History of Chronic Hypertension, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (3.65)</td>
<td>1 (1.21)</td>
<td>0 (0.00)</td>
<td>NA</td>
</tr>
<tr>
<td>No</td>
<td>32 (39.02)</td>
<td>5 (6.09)</td>
<td>41 (50.00)</td>
<td></td>
</tr>
</tbody>
</table>

*Fisher Exact Test: statistically significant if p-value less than 0.05.

### Table 2. Outcomes of pregnancy research subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preeclampsia (n=35)</th>
<th>PE + IUGR (n=6)</th>
<th>Control (n=41)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>8 (9.75)</td>
<td>6 (7.31)</td>
<td>0 (0.00)</td>
<td>NA</td>
</tr>
<tr>
<td>Normal</td>
<td>27 (32.92)</td>
<td>0 (0.00)</td>
<td>41 (50.00)</td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20 (24.39)</td>
<td>4 (4.87)</td>
<td>19 (23.17)</td>
<td>0.65</td>
</tr>
<tr>
<td>Female</td>
<td>15 (18.29)</td>
<td>2 (2.43)</td>
<td>22 (26.82)</td>
<td></td>
</tr>
<tr>
<td>Time of delivery, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term</td>
<td>27 (32.92)</td>
<td>4 (4.87)</td>
<td>41 (50.00)</td>
<td>NA</td>
</tr>
<tr>
<td>Preterm</td>
<td>8 (9.75)</td>
<td>2 (2.43)</td>
<td>0 (0.00)</td>
<td></td>
</tr>
</tbody>
</table>

*Fisher Exact Test: statistically significant if p-value less than 0.05.
Table 3. Levels of 8-OHdG Study Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preeclampsia</th>
<th>PE + IUGR</th>
<th>Control</th>
<th>p</th>
<th>p1</th>
<th>p2</th>
<th>p3</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-OHdG ng/ml (mean ± sd)</td>
<td>3.46±0.76</td>
<td>6.01±2.09</td>
<td>3.49±0.62</td>
<td>0.006c</td>
<td>0.001c</td>
<td>0.67b</td>
<td>&lt;0.0001c</td>
</tr>
</tbody>
</table>

If the *Kruskal Wallis value is positive (p<0.05), then post-hoc analysis can be used. p, between 3 groups; p1, between the PE+IUGR, and Preeclampsia groups; p2, between preeclampsia and control groups (*Mann-Whitney Test); p3, between Preeclampsia + IUGR and control groups (*unpaired T-Test); *statistically significant if p-value less than 0.05.

Figure 1. 8-OHdG Levels between 3 groups.

The oxidative stress that occurs in the circulation of mothers with preeclampsia defines preeclampsia as 2 distinct disease entities: early-onset preeclampsia, which tends to develop before 34 weeks of gestation, and late-onset preeclampsia, which develops at or after 34 weeks. Both early and late-onset preeclampsia are associated with different biochemical markers, genetic and environmental risk factors, prognosis, heritability, and clinical features. Early-onset preeclampsia is considered a fetal disorder that is usually associated with placental dysfunction, reduced placental volume, intrauterine growth restriction, abnormal uterine and umbilical artery Doppler evaluations, low birth weight, multiorgan dysfunction, perinatal death, and adverse maternal and neonatal outcomes. Late-onset preeclampsia is considered a maternal disorder; the result of an underlying maternal constitutional disorder, more often associated with a normal placenta, larger placental volume, normal fetal growth, normal uterine and umbilical artery Doppler evaluation, normal birth weight, and more favorable maternal and neonatal outcomes. However, the relationship between the severity of hypoxic changes and oxidative DNA damage in the placenta of women with early and late-onset preeclampsia and IUGR is unclear. IUGR is defined as the failure of the fetus to reach its full genetic growth potential. In humans, this pathological condition affects about 10% of all pregnancies and can be caused by both genetic and environmental factors. However, in developed countries, placental insufficiency is considered the main cause of IUGR. Placental insufficiency impairs the transfer of substrates to the fetus and causes fetal growth restriction. In turn, substrate transfer and fetal growth changes can result in medical complications, such as perinatal asphyxia, hypothermia, prematurity and death.

A fetus suitable for gestational age is a fetus whose size is within the normal range for its gestational age. These fetuses usually have individual biometric parameters and/or estimated fetal weight between the 10th and 90th percentiles. A fetus with a small gestational age is a fetus whose size is below a predetermined threshold for its gestational age. These fetuses usually have an estimated fetal weight or abdominal circumference (AC) below the 10th percentile. However, the 5th centile, 3rd centile, -2SD and Z-score deviations have also been used as cutoffs in the literature. An IUGR fetus is a fetus that has not yet reached its growth potential. This condition can be associated with poor perinatal outcomes and neurodevelopment. It has been classified into early onset (detected before 32 weeks of gestation) and late-onset (detected after 32 weeks). A fetus with suspected IUGR is not necessarily small for gestational age at delivery and may fail to reach its growth potential. Similarly, not all small gestational fetuses are growth retarded; Most tend to be ‘constitutionally’ small. Traditionally, the symmetry of fetal body proportions has been seen as an indication of the underlying etiology of IUGR.

In the study conducted by Kimura C et al., they examined maternal and umbilical 8-OHdG concentration levels as well as placental localization, which is a marker of oxidative DNA damage and placental hypoxic status, respectively, with histology in early and late-onset preeclamptic women and healthy women with an uncomplicated pregnancy. They found that nearly all preeclamptic women with IUGR had early-onset preeclampsia and that nearly all preeclamptic women without IUGR had late-onset preeclampsia. The condition of prolonged preeclampsia in early-onset disease is impaired uterine arterial flow and reduced placental blood flow. The severity of hypoxic changes and oxidative DNA damage is greater in the placenta, which ultimately leads to IUGR because almost all preeclamptic women with IUGR have preeclampsia of early onset and low-grade preeclampsia. Inadequate trophoblast cell invasion and complete spiral artery remodeling are generally more severe in women with early-onset preeclampsia.

8-OHdG is produced due to the breakdown of DNA by reactive oxygen species, which can be detected in urine, serum, and human and animal tissue samples and is the most sensitive marker of oxidative stress. Furthermore, 8-OHdG levels in tissues reflect oxidative stress in organs. Takagi Y et al. evaluated tissue levels of 8-OHdG, 4-hydroxynonenal, thiorredoxin, and redox factor-1 in healthy pregnant women and pregnant women with PE, IUGR, and PE plus IUGR. Their findings revealed higher scores in patients with PE, IUGR, and PE plus IUGR compared to healthy pregnant women. IUGR has also been analyzed as an association between the occurrence of these events and oxidative...
stress. It has been shown that damage due to ROS activity occurs primarily in membrane lipids, proteins, nuclear DNA and mitochondria. 8-Hydroxy-2′-deoxyguanosine (8-OHdG) is one of the more commonly used oxidation markers for the effects of ROS on tissues. Levels and redox factor-1 (redox regulator, which is responsible for repairing damaged DNA) are much higher in the placenta of patients in pregnancies complicated by IUGR than in uncomplicated pregnancies. In another study, DNA was isolated from placental tissue and 8-OHdG levels were compared between healthy pregnant women and pregnant women with severe PE and IUGR plus severe PE. No differences were identified between healthy pregnant women and women with severe PE; however, 8-OHdG levels are higher in pregnant women with IUGR plus severe PE.

Judging from the onset of preeclampsia, another study showed that the level of 8-OHdG staining in the nuclei of placental trophoblast cells in women with early-onset preeclampsia was greater than in women with late-onset preeclampsia. These results suggest that oxidative DNA damage in placental trophoblast cells of women with early-onset preeclampsia is greater, and these women have an increased incidence of IUGR. Given the prolonged preeclamptic state early in the disease, the condition may impair uterine arterial flow and reduce placental blood flow, and the severity of hypoxic changes and oxidative DNA damage is greater in the placenta and lead to IUGR, thereby increasing oxidative stress in the fetus.

Higher levels of 8-OHdG in cord blood obtained from umbilical cord elements of babies born to PE/eclampsia mothers were also reported compared to healthy pregnant women. The same thing was also stated by Yudianto B et al., that high oxidative stress causes DNA damage as indicated by an increase in 8-hydroxy-2′-deoxyguanosine (8-OHdG), which can cause aging. Higher levels of 8-OHdG in the placenta have previously been associated with other pregnancy complications, that is, preeclampsia, intrauterine growth retardation and fetal death.

In this study, the authors evaluated serum 8-OHdG levels in healthy pregnant women and PE to reveal their association with disease severity. As a potential biomarker in the etiopathogenesis of PE, 8-OHdG levels were measured in cord blood serum using the ELISA method. There were statistically significant differences between the results of 8-OHdG levels in the PE+IUGR, PE and control groups. However, studies show that placental 8-OHdG levels are not significantly associated with oxidative damage in the etiopathogenesis of the disease and the development of IUGR in PE pregnant women. It is also shown in this study that pregnant women with PE have higher BMI than controls but are not statistically significantly different. However, it is known that the pathophysiological mechanisms behind the increase in BMI in PE are not fully understood, although the increased insulin resistance and inflammatory state associated with obesity are possibly an important contributing factor. The contrast is seen in the parity status of the mother, it was found that the number of mothers with nullipara was higher in the preeclampsia group, and there was a significant difference. It is suggested that excess placental secretion of circulating antiangiogenic protein, soluble fms-like tyrosine kinase 1 (sFlt1), may have an important role in the pathogenesis of maternal syndrome in PE. sFlt1 acts by antagonizing vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) signaling in blood vessels. Several human studies have confirmed that changes in circulating angiogenic factors are associated with PE. Our study is limited by the patients selected from various hospitals, resulting in incomplete data regarding laboratory tests such as chemical blood tests. For further studies, gathering research subject data from a single hospital to standardize laboratory results is advisable. Additionally, considering the assessment of placental weight could be beneficial in supporting the diagnosis of IUGR.

In conclusion, measuring 8-OHdG levels in umbilical cord blood for PE seems to be an appropriate method to see the relationship with IUGR and see the relationship between severity of the disease and 8-OHdG levels, in line with previous studies which have shown that 8-OHdG levels in Placenta and umbilical cord blood were high than healthy pregnant women. This substance may play a role in the etiopathogenesis of PE. Further research on a larger number of patients is needed to evaluate the value of 8-OHdG measurement in samples other than serum (i.e., urine) in the early diagnosis of PE. Developing better and more sensitive assays in further research to determine 8-OHdG levels in either blood, urine, or placental pathology may help generate evidence of its role in PE.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ETHICAL CONSIDERATIONS
The Ethics Committee for Health Research, Faculty of Medicine, Hasanuddin University (No: 732/UN4.6.4.5.31/PP36/2022) has examined and approved all research designs.

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AUTHOR CONTRIBUTION
A. Nurul Faizah Tenri Ola conceived and designed the analysis, collected the data, contributed data or analysis tools, and wrote the original paper. Efendi Lukas, Deviana S.Riu, Rina Previana, Isharyah Sunarno, Nasrudin A.M., and Maisuri T.Chalid conceived and designed the analysis, contributed data or analysis tools, and validated the final paper.

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