Placenta Senescence and the Genesis of Preeclampsia: Is There Any Potential Role? – A Review

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Abstract
Introduction: Preeclampsia is a hypertensive disorder of pregnancy and is responsible for around 800 maternal deaths. The etiologies of preeclampsia remain unidentified, although the premature senescence of the placenta is a possible cause. To date, various markers such as oxidative stress and mitochondrial dysfunction have been identified to be related to placental aging.
Method: This study uses a narrative review approach; the search engines used are Scopus, PubMed, and Cochrane. The keyword combinations are placenta senescence AND aging AND preeclampsia, while excluding the results that are correspondence or not written in English.
Results: The senescence of the placenta has a role in the pathophysiology of preeclampsia. The epigenetic alterations marked by the changes in the trophoblast's telomere length as the result of the damage done by ROS to the mitochondria marked by various biomarkers can lead to accelerated cell death.
Conclusion: Preeclampsia is due to premature placental aging and apoptosis, resulting in widespread blood vessel lining dysfunction.

Keywords: Epigenetic Alterations, Oxidative Stress, Placental Senescence, Preeclampsia

Penuaan Plasenta dan Asal Mula Preeklampsia : Adakah Peran Potensial? – Sebuah Tinjauan

Abstrak
Pendahuluan: Preeklampsia adalah gangguan hipertensi pada kehamilan yang menyebabkan sekitar 800 kematian ibu. Penyebab preeklampsia masih belum diketahui, namun penuaan dini plasenta merupakan salah satu penyebabnya. Sampai saat ini, berbagai markah seperti stress oksidatif dan disfungsi mitokondria telah teridentifikasi berhubungan dengan penuaan plasenta.
Metode: Penelitian ini menggunakan pendekatan tinjauan naratif dan mesin pencari yang digunakan adalah Scopus, PubMed, dan Cochrane. Kombinasi kata kunci yang digunakan adalah penuaan plasenta DAN penuaan DAN preeklampsia dan mengecualikan hasil yang bersifat korespondensi atau tidak ditulis dalam bahasa Inggris.
Hasil: Penuaan plasenta memiliki peran dalam patofisiologi preeklampsia. ROS merusak mitokondria dengan mengubah panjang telomer trofoblas. Perubahan tersebut dapat menyebabkan percepatan kematian sel yang bisa ditandai dengan berbagai biomarker
Kesimpulan: Preeklampsia disebabkan oleh penuaan plasenta dini dan apoptosis yang mengakibatkan disfungsi lapisan pembuluh darah yang meluas.

Kata kunci: Perubahan Epigenetik, Stres Oksidatif, Penuaan Plasenta, Preeklampsia

Introduction

Preeclampsia is a hypertensive disorder of pregnancy (HDP) characterized by proteinuria that arises specifically during pregnancy, beginning at the 20th week.[1,2] This condition is significant concern because of its global prevalence, affecting an estimated 8-22% of pregnancies globally, and 800 maternal deaths every day. Furthermore, preeclampsia is responsible for around 800 maternal deaths each day. Furthermore, 99% of all incidents arise from underdeveloped nations, including Indonesia. In Indonesia, preeclampsia is responsible for approximately 30-40% of maternal fatalities. The Case Fatality Rate of Preeclampsia in Hasan Sadikin General Hospital Bandung was 10% in 2022. If prompt interventions are not performed, it is anticipated that the number will persistently rise.[1,2]

The prevailing idea posits that preeclampsia is characterized by two distinct stages, constituting a two-stage illness which underlies the pathophysiology of the condition. The initial phase involves a decrease in placental blood flow, leading to maternal syndrome. The process begins in the first trimester of pregnancy with inadequate invasion of trophoblasts, resulting in diminished placental perfusion. In the second stage, a maternal clinical condition develops, leading to systemic activation of the endothelium system. Components that experience increased activity include cytokines, antiangiogenic factors, excessive syncytiotrophoblast microparticles, and activated blood products within the intervillous cavity. Oxidative stress is another significant factor in the development of preeclampsia.[3-5]

The two-stage disorder theory states that for preeclampsia to occur, it is not necessary to go through stage 1 first. Other factors such as genetics, behavior, and environment play an important role in the pathogenesis of preeclampsia without going through the first stage. Defects in trophoblast invasion of the spiral arteries are related to placental vascular resistance. This resistance will directly lead to ischemia; and if no factors maintain the blood supply, focal necrosis can occur in several areas of the placenta.[4-6] States of resistance, ischemia, and placental necrosis are closely related to stunted fetal growth, abruption, placenta, and even fetal death.[4-6]

To date, developing biomarkers to identify pregnancy complications in maternal body fluids, such as for preeclampsia, has proven to be a significant obstetric challenge. Early biomarkers for pregnancy disorders have been studied, including oxidative stress and various markers of mitochondrial dysfunction related to placental aging. Every tissue inevitably experiences aging as a unidirectional phenomenon. However, the placenta ages prematurely in preeclampsia due to the continuous oxidative stress that accelerates this process.[7] Previous research show a correlation between the process of telomere shortening, cellular senescence, mitochondrial dysfunction, and the occurrence of premature placental aging.[8,9]

Objectives

This study aims to review the role of placental senescence and the genesis of preeclampsia that could become a basis and direction for further preeclampsia clinical studies.

Method

This study uses a narrative review approach. Articles were obtained from international databases, including PubMed, Scopus, and the Cochrane Library, without restricting publications' time. The combination of keywords used is "placenta Senescence" AND "aging" AND "preeclampsia" or their synonyms. The inclusion criteria of our studies include (1) studies investigating

placental senescence and preeclampsia and (2) Experimental or observational studies. However, the studies were excluded if they were found to be correspondence or were not published in English.

Results

It has been a major obstetric problem to find biomarkers in maternal body fluids to diagnose pregnancy issues including IUGR and preeclampsia. According to Table 1, Various oxidative stress and mitochondrial dysfunction markers have been observed as putative early markers for pregnancy problems. Qiu et al. reported the first instance of increased amounts of mtDNA in the blood of pregnant women with preeclampsia in 2012. These results imply increased oxidative stress and impaired mitochondrial function.18 A recent case-control study by Williamson, McCarthy, and Kenny showed that during the first 15-20 weeks of pregnancy, preeclamptic women had greater levels of mitochondrial DNA (mtDNA) in their maternal plasma than those women with uncomplicated pregnancy.19-20

Discussion

Pathogenesis of Preeclampsia: Roles of Placenta

Preeclampsia is defined by extensive impairment of endothelial cells, which is related to a reduction in the activity of vascular endothelial growth factor (VEGF). Preeclampsia occurs when there is an elevation in the levels of sFlt-1, a natural inhibitor of VEGF, and a reduction in the levels of PlGF or placental growth factor within a few weeks.[10] The symptoms of preeclampsia in mice can be efficiently eliminated by eradicating excessive sFlt-1 utilizing VEGF. In addition, the duration of pregnancy is prolonged by

Table 1 Possible Senescence Markers for Preeclampsia [18-20]

Tissue	Pathogenesis	Markers
Maternal plasma or serum	(1) The dysfunction of mitochondria (2) Inflammatory markers in the I L33/ST2 pathway	Increases mtDNA copy numbers Increases in ST2 level
Trophoblastic cell lines	(1) the regulators of the cell cycle (2) miRNA/lncRNA (3) Responses to the DNA damage (4) Regulator of the senescence (5) Changes in epigenetic	Increment of the expression of Cyclin D1 Upregulation of the Mir-376 Increase in the expression of the PARP1 Increase of activity of p53 gen The decrease in the expression of JunB Decrease expression of MDM2 Decrease of the methylation of cytosine
Placenta	(1) Responses to the DNA damage (2) The regulators of cell cycle (3) The dysfunction of the mitochondria	Increase of activity of the p53 Decrease of the hTERT expression Increment of the Telomere aggregates occurrence Stimulation of the proapoptotic BAX Increase of the Lipid peroxidation level Increase of the NOS activity Increment of the Peroxynitrite synthesis Increment of the Phosphorylated DERP1 gene

extracorporeal removal of sFlt-1 in women with early-onset preeclampsia. The findings indicate that an abnormality in the process of blood vessel formation may contribute to the development of the specific characteristics of preeclampsia. Statins inhibit the secretion of sFlt-1 from endothelial cells and trophoblasts in controlled laboratory settings. Pregnant mice exhibiting placentally derived overexpression of sFlt-1 display symptoms similar to preeclampsia. In their studies, Yung et al. examined placental samples, which are taken from the preterm, term, and second-trimester pregnancies. They discovered that early-onset preeclampsia is linked to placental pathology and the activation of the unfolded protein response (UPR) pathway and ER stress. This activation is accompanied by a downregulation of the AKT pathway, resulting in decreased cellular proliferation. These findings offer evidence for the link between the abnormal physiological processes of early-onset preeclampsia and the role of the placenta in mediating it. The authors offered compelling proof regarding the molecular distinctions between the two phenotypes of term and preterm preeclampsia.[10,11]

Furthermore, Redman et al. modified the two-stage preeclampsia model previously proposed by Roberts and Hubel, among others, to six stages. Redman suggests that the first and second stages might represent early occurrences, such as the mother's initial tolerance to the father's semen before conception or the brief interval between sexual intercourse and conception. These factors can hinder the formation of the placenta and adversely affect the development and well-being of the embryo.[11] In simple cases, the trophoblastic plugs that seal the mother's spiral arteries recede at about eight weeks pregnancy, signaling the start of stage 3, when uteroplacental circulation is established. In pre-eclampsia, the premature opening of the spiral arteries causes oxidative stress, therefore hindering implantation. Redman's model of the fourth stage in preeclamptic patients is marked by a reduction in placental growth factors, leading to a compromised ability of the trophoblast to modify the mother's spiral arteries into wider vessels with reduced resistance to blood flow.[11] Moreover, Redman notes that clinical signs of preeclampsia are noticeable in stages 5 and 6 due to increased placental and endothelial damage.[11,12]

The blastocyst in the mother's endometrium induces a decidual response that starts the placenta's development, ultimately forming the basal plate.[13] Trophoblasts can differentiate into villous cytotrophoblasts, which are going to fuse to form multinucleated syncytiotrophoblast, and invasive extravillous cytotrophoblasts (EVT). Extravillous cytotrophoblasts play a crucial role in commencing blood flow between the uterus and placenta, as well as controlling the mother's native immune system. During the first trimester of an uncomplicated pregnancy, maternal spiral arteries, veins, and lymphatic vessels of the endometrium are invaded by extravillous cytotrophoblasts (EVT). Without any neoplastic changes, EVT accumulations have also been found in lymph nodes, indicating that trophoblasts regulate immune cells.[13,14]

Defective placenta leads to a reduction in the production of the proangiogenic protein of vascular endothelial growth factor (VEGF) and placental growth factor (PLGF) and the release of harmful placental factors such as soluble fms-like tyrosine kinase 1 (sFIt1) into the mother's bloodstream, resulting in widespread dysfunction of the blood vessel lining.[11,12] The circulating sFlt1 is abundant in preeclamptic women, which makes the vessels highly constrict, thereby increasing blood pressure. Recent investigations in women diagnosed with fetal growth restriction (FGR) but without any signs of preeclampsia have shown compelling evidence of an elevated sFlt1/PLGF ratio. Glomerular endotheliosis, caused by the sFlt-1, is related to proteinuria.

Prolonged hypoxia caused by alterations in blood flow and decreased circulation leads to elevated oxidative stress in the placental tissue. Although oxidative stress occurs in the uncomplicated pregnancy's trophoblast, longer durations of oxidative stress impede trophoblast activity, exacerbating pregnancy problems.[13-15]

As the gestational age increases, nuclear aggregates or knot-like syncytial debris can be detected in the mother's circulation. The outermost layer of the villous trophoblast, known as the syncytiotrophoblast, comes into direct contact with the mother's blood. Because of the increasing syncytial aggregates, necrotic breakdown and the release of necrotic debris, and upregulation of the apoptotic cascade, preeclampsia accelerates the aging process of the syncytiotrophoblast. From the observations, the syncytiotrophoblast secretes to halt the cell cycle and undergo senescence. Beta-Galactosidase is associated with senescence.[13-15]

Cellular Senescence and Mitochondrial Dysfunction in Preeclampsia

Trophoblasts are infiltrative cells that imitate malignant cells to facilitate the expansion of the fetus. In regular pregnancies, trophoblasts maintain the telomere's length and amount of the Human Telomerase Reverse Transcriptase (hTERT), similar to malignant cells.[16] The trophoblast undergoes a physiologic hypoxic state or low oxygen tension during the first trimester, which is linked to the upregulation of HIF-1α. By maintaining telomere length and upregulating telomerase enzymes, this low oxygen tension state is in charge of modeling villous architecture and preserving cellular integrity. When the placenta becomes oxygenated at the end of the first trimester, this physiological state is changed. Normally, during uncomplicated pregnancy, the telomere's length stays unless there are some conditions, such as uncontrolled diabetes and restricted fetal growth. The alterations of telomeres may be linked to heightened oxidative stress, resulting in DNA harm, initiation of the damage response (DDR) via the p53 pathway, and facilitation of trophoblast senescence. Biron-Shental et al. initially reported the occurrence of cellular senescence in preeclampsia and fetal growth limitation in 2010. When comparing uncomplicated pregnancies to preeclampsia and IUGR pregnancies, it was found that the telomeres in the trophoblast are noticeably shorter. Additionally, there is a decrease in the expression of hTERTs and an increase in the occurrence of telomere aggregates. The absence of these placental alterations between 37 and 41 weeks gestation suggests that the placenta ages prematurely in these pregnancy complications.[16]

The placenta undergoes a slow aging process, while the theory of placental aging is supported by the presence of specific markers of cellular senescence, including p16, p21, p53, and Rb proteins, as the pregnancy approaches its end. Previous studies elucidate that the preterm placenta undergoes cellular alterations, including an increase in the expression of cyclin D1 (a regulator of the cell cycle) and PARP1 (a protein associated with DNA damage and age-related changes). In contrast, the expression of JunB (a gene that suppresses senescence) is reduced. In addition, Sharp et al. found a discrepancy in placental proteins in the syncytiotrophoblast of patients with early-onset preeclampsia. This discrepancy pertains to the signaling of the p53 gene, which induces senescence and promotes cell death, and the MDM2 gene, which suppresses the activity of p53. Another study discovered that there was an elevation in p53 signaling, cell cycle arrest, and the stimulation of proapoptotic BAX and caspase proteins in the human umbilical vein endothelial cells (HUVEC) of the preterm placental when compared to the normal placental.[17]

Possible Senescence Markers in Preeclampsia

Finding biomarkers in maternal bodily fluids to identify pregnancy complications like IUGR and preeclampsia has been a significant obstetric challenge. As shown in Table 1, several indicators of oxidative stress and mitochondrial dysfunction are potential as early indicators for pregnancy problems. In 2012, Qiu et al. reported the first instance of increased amounts of mtDNA in the blood of pregnant women with preeclampsia. This finding suggests the presence of enhanced oxidative stress and malfunctioning mitochondria.[18] Williamson, McCarthy, and Kenny conducted a recent case-control study and found that women with preeclampsia had greater levels of mitochondrial DNA (mtDNA) in their maternal plasma throughout the 15-20 weeks pregnancy compared to women with uncomplicated pregnancies.[19] Furthermore, the study showed a significant decrease in the antioxidant level of mitochondrial superoxide dismutase (mSOD) at 15 weeks gestation.[18-20]

Potential Therapeutics and Further Directions

The crucial regulation of cell cycle progression and metabolism is attributed to mitochondrial fitness. Continued oxidative stress causes a decline in mitochondrial activity, disrupting mitochondrial signaling in pregnancy complications. Pregnancy-related antioxidant supplementation, such as vitamin C and E, has not been shown to significantly reduce oxidative stress. Nevertheless, ongoing investigations into more potent antioxidants have revealed a few cytoprotective substances that target the mitochondria. Moreover, it has been demonstrated that the water-soluble amino acid ergothioneine has cytoprotective properties. Ergothioneine mainly targets mitochondria, where it can activate antioxidant pathways to scavenge reactive oxygen species, promote cellular proliferation, and facilitate cellular repair. Antioxidants offer many advantages, including the potential to target and normalize mitochondrial dynamics and functioning, thereby serving as prenatal therapeutics for

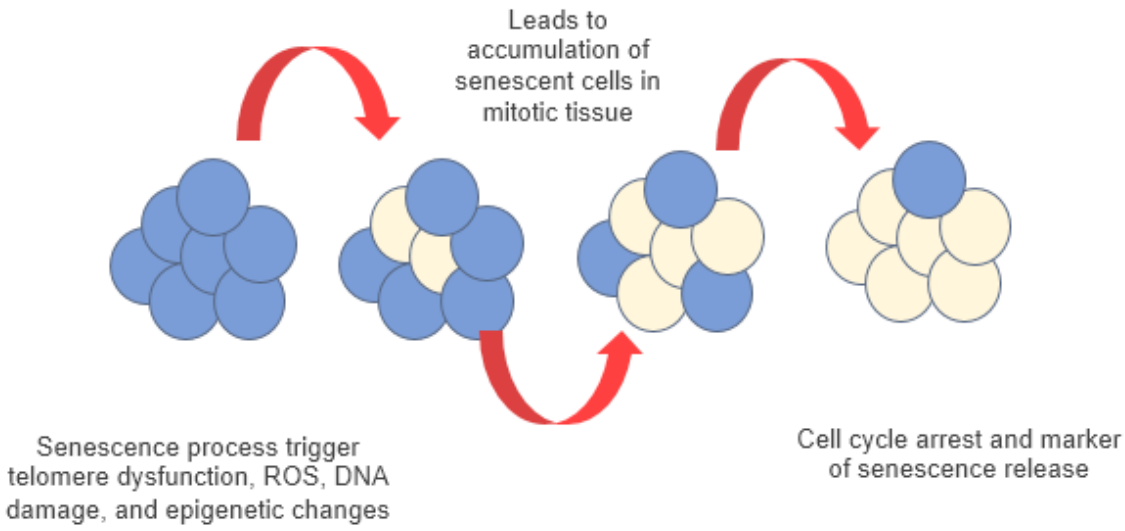

Figure 1 Stages of Placental Senescence

adverse pregnancy outcomes.[17-20]

Conclusions

This review summarizes the present comprehension of the functions performed by cellular senescence, the placental aging axis, and placental mitochondrial dysfunction in adverse pregnancy outcomes. Further research is required to explore innovative approaches to enhance outcomes, such as preeclampsia.

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