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Abstract

Preeclampsia is a complication of pregnancy primarily characterized by hypertension and proteinuria and affects other organs as well. The underlying causes are not yet fully understood. However, it is suggested that angiogenic factors of the placenta, genetic factors, a malfunctioning immune system, and oxidative stress all play a role in causing preeclampsia. Currently, the only definitive cure known for preeclampsia is delivery of the baby. Management of the condition includes taking preventative measures as well as drugs such as labetalol and MgSO4. This paper analyzes mechanisms of preeclampsia and determines the possible causes and most effective ways to manage the condition.

Introduction

Preeclampsia (PE) is a multisystem complication that occurs during pregnancy and is primarily characterized by elevated blood pressure and abnormally high levels of protein in the urine. The disorder manifests itself after the 20th week of gestation and can lead to serious complications, possibly even fatality of the mother and the baby. It can also cause long-term health conditions. The disease has a worldwide prevalence of 5-8% of pregnancies and currently ranks as one of the leading causes of maternal and perinatal morbidity (Pennington et al., 2012). In addition to hypertension and proteinuria, afflicted patients may undergo other symptoms including edema of the face and hands, headaches, dizziness, decreased urination, nausea, and vision changes. Furthermore, 10-20% of women with severe cases of PE can develop a potentially lethal condition known as the HELLP syndrome, characterized by the fundamental features of "hemolysis, elevated liver enzyme levels, and low platelets." If PE progressively worsens, it can turn into eclampsia, where the elevated blood pressure causes the mother to experience seizures and may result in a coma (Preeclampsia. 2016).

The exact etiology of PE remains unknown. The purpose of this review is to determine the possible causes of PE and the most effective therapeutic approaches available to manage the condition.

Methods

This comprehensive review was conducted based on critical analyses of data collected from various databases accessed through Touro College's online library, such as ProQuest and PubMed. The National Center for Biotechnology (NCBI) website was also a useful tool in providing additional sources. Key words and phrases used to retrieve data include "mechanisms of preeclampsia," "causes of preeclampsia," and "management of preeclampsia."

Discussion

PE can be classified into an early onset and late onset form. Women suffering from early-onset PE are diagnosed before their 34th week of pregnancy and symptoms of low birth weight and intrauterine growth restriction will manifest. Conversely, the late onset form expresses itself after the 34th week and its cause is generally associated with various maternal conditions including obesity, diabetes, and chronic kidney diseases. Regardless of the subtype, it is evident in all cases of PE that the placenta plays a central role in its pathophysiology (Lisowska et al., 2018).

In normal pregnancies, an increase in blood flow to the uterus will occur to ensure sufficient supply for the intervillous spaces and overall proper fetal development. Cytotrophoblasts invade deep inside the maternal spiral arteries to establish a vascular network and remodeling subsequently takes place to form high-capacity blood vessels. This mechanism is defective in the placentas of individuals destined to develop PE. In such cases, the cytotrophoblasts fail to entirely convert from their proliferative epithelial form into their invasive endothelial form. As a result, remodeling of the spiral arteries is greatly hindered and the restricting maternal vessels will lead to placental ischemia (Rana et al., 2019).

Another identifying feature found to be associated with the pathogenesis of this disorder is elevated levels of an antiangiogenic protein called soluble fms-like tyrosine kinase (sFLT1) in the placenta (Roberts & Bell, 2013). This was furthered studied on non-human primates. A group of animals was induced with uteroplacental ischemia (UPI) while a Sham group of animals was not. The concentration of plasma sFLT1 of both animal groups was measured over a two-week period and the results were compared. As seen in Figure 1, the UPI animals showed a significant increase in sFLT-1 over time, whereas the Sham group's sFLT1 levels remained roughly unchanged (Makris et al., 2007). This experiment shows how reduced blood flow directly increases the amount of circulating sFLT1 in the plasma.

SFLT-1 is a soluble receptor that binds to the angiogenic factors, vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), and inhibits them from interacting with their receptors, Flt1 and Flk1. When they cannot bind to their receptors, the angiogenic factors are incapable of carrying out their function of promoting the growth of new blood vessels. Therefore, the presence of sFLT1 inhibits the growth of blood vessels. In PE, the excessive amount of sFLT1 abnormally constricts the mother's blood vessels, leading to hypertension, in addition to affecting the function of various other organs. The constricted

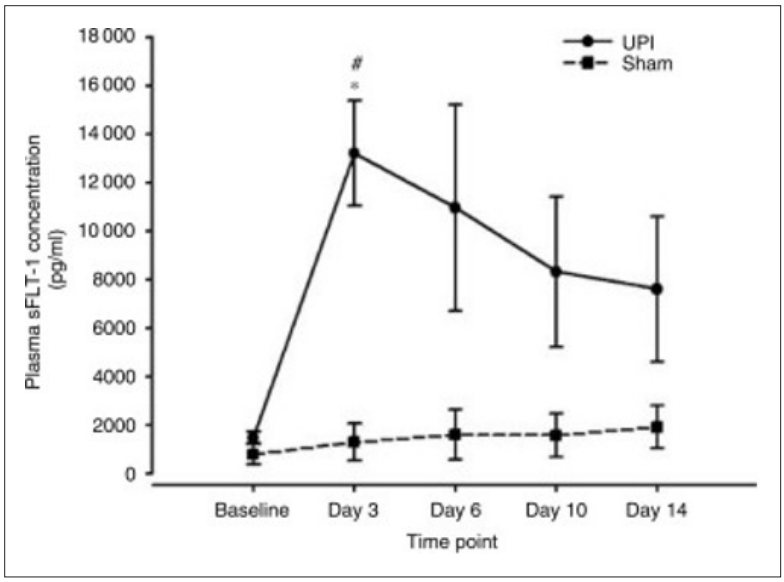

Figure 1: The concentration of plasma sFLT1 levels are significantly elevated in the UPI group in comparison to the sFLT1 of the Sham group (Makris et al., 2007).

blood vessels are also responsible for causing the kidneys to release proteins into the urine (Roberts & Bell, 2013).

Etiology of PE

The causes of placental malformation are still being researched and currently remain unclear. It is understood, however, that anything causing oxidative stress to the placenta is likely to cause PE. Oxidative stress is when there is an imbalance between reactive oxygen species (ROS) and antioxidants which disrupts metabolism and cell signaling in aerobic organisms. Several cell compartments can produce ROS, such as the mitochondria, endoplasmic reticulum, and nuclear membrane. They produce O2•– anions as a byproduct of auto-oxidation during the electron transport chain. ROS can also be produced as a result of arachidonic acid metabolism. Oxidative stress regulates the transcription factors NRF2 and FoxO which control the expression of genes that detoxify oxidizing molecules. Thus, the imbalance causes an interruption in the detoxification process and can lead to structural and physiological damage to DNA, RNA, proteins, and lipids. (Auoache et al., 2018). Oxidative stress is known to cause endothelial cell dysfunction which can contribute to PE (Duhig et al., 2016).

Risk Factors for PE

Several principle risk factors were found to be associated with the onset of PE. The presence of certain medical conditions can make a woman more prone to developing PE. Hypertension has strongly proven to be correlated with an increase in one's risk of developing PE. To be diagnosed with hypertension, there must be a "systolic blood pressure greater than or equal to 140 mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg" (Hinkosa et al., 2020). A retrospective study of the databases from two hospitals identified 362 women who had chronic hypertension that required treatment prior to their pregnancies were analyzed. The data revealed that the percentage of superimposed PE in these women was 23.2%, a percentage notably higher than that of the general population. (Lecarpentier et al., 2013).

Autoimmune diseases like systemic lupus erythematosus and antiphospholipid antibody syndrome, diabetes type 1 or 2, and chronic arterial hypertension are other conditions classified as high-risk factors for PE (Mayrink et al., 2018).

Other risk factors known to be linked with PE include nulliparity, maternal age over 35, multifetal pregnancy, prior case of PE, chronic kidney disease, prior stillbirth, and a pre-pregnancy BMI over 25. Data was extracted and pooled from 92 studies regarding the relative risk of developing PE for women with each risk factor. Pooling of the data is helpful in bringing about results that are as reliable as possible.

Genetic Factors

Currently, there are no identified genes that are directly responsible to cause the disorder. However, because clustering of PE among families is common, it is suggested that there must be a genetic etiological component involved. Women with a first relative that developed PE have a three to five-fold increased risk of getting it as well (Hansen et al., 2018). There is also research suggesting that paternal genes may be a contributing risk factor for the development of PE as well. Women who became pregnant from a man that has had a previous partner with preeclampsia were seen to be at a slightly higher risk for PE (Galaviz-Hernandez et al., 2018).

Mother's Immune Responses

PE is thought to be a disorder that may be due to malfunctioning of the mother's immune system. The syncytial surface of the placenta sheds particles, ranging from large deported multinuclear fragments to sub-cellular components, and it is suggested that these particles contain proteins that trigger an inflammatory response. In PE, the number of circulating particles present increases, indicating a relationship between excess particles and the pathology

of the disease. Thus, preeclampsia is characterized by an exaggerated inflammatory response (Palei et al., 2013).

Furthermore, complications of the maternal immunity mechanisms can be a causing factor of PE. During pregnancy, it is essential for the mother's regulatory CD4 + T cells to interact with the uterine natural killer cells in order to recognize and accept the fetal antigens and enable placental growth. Failure of this process leads to a spontaneous miscarriage, while a partial failure leads to poor placentation and dysfunction of the placental perfusion and chronic immune activation that stems from the placenta. Women with PE were found to have decreased levels of circulating regulatory CD4 + T cells. Additionally, they have increased levels of T helper 17 cells, cells that are also upregulated in various autoimmune disorders (Palei et al., 2013).

Possible Complications of PE During Pregnancy

When symptoms of PE become severe, it can lead to dangerous complications for both the mother and the fetus, including fatality. Severe PE is when one or more of the following conditions is present: blood pressure of 160 mmHg or higher for systolic and 110 mmHg diastolic on at least two occasions that are at least 6 hours apart, at least 2 g of proteinuria in a 24 urine specimen or on two urine samples collected at least 4 hours apart, oliguria of less than 500 mL in 24 hours, cerebral or visual issues, pulmonary edema, pain in the epigastric or right upper quadrant, fetal growth restriction, a persistent and severe headache, or medical issues involving acute renal insufficiency, hepatic hematoma, and HELLP syndrome (Nankali et al., 2013). It is said that 25% of PE cases are classified as severe (Minire et al., 2013).

The mother may develop HELLP syndrome, which causes mortality in 25% of affected women. This can bring about a variety of complications that can affect many different organ systems such as the central nervous system, renal system, respiratory system, and liver. Complications include stroke, cerebral edema, retinal blindness, pulmonary edema, laryngeal edema, jaundice, renal failure, liver failure, HELLP syndrome, and eclampsia. Globally, preeclampsia and eclampsia are responsible for 10-15% of all maternal deaths (Nankali et al., 2013)

As for the fetus, the baby is often deprived of receiving a sufficient amount of blood and does not get the oxygen and nutrients it needs. Development under such conditions will be hindered, and the baby will have fetal growth restriction, causing it to be very small at birth. Often, these babies will need to be hospitalized for a period following their birth. A stillbirth can happen if the placenta separates from the uterine wall, causing the mother to heavily bleed. This is more likely to happen if the mother has a more severe case of PE, including the HELLP syndrome (Preeclampsia research at the NICHD.2012). Infants whose mothers had PE during their pregnancy also have an increased risk of developing some long-term health conditions due to the lack of proper development, such as "learning disorders, cerebral palsy, epilepsy, deafness, and blindness. Later on, they may be at risk for diabetes, congestive heart failure, and hypertension. Infant death is also a possible occurrence (Preeclampsia research at the NICHD.2012).

Management Options for PE

Because of the severity of the complications that preeclampsia may cause, women should take several precautions to help lower their risk of developing the disorder. Antiplatelet drugs, primarily low dose aspirin, are useful preventative agents as they reduce the risk of PE by 19% as well as decreasing the risk of stillbirth or neonatal death by 16% (Duley et al., 2006). Aspirin is effective because it reduces platelet aggregation, but it is also a risk of in utero cerebral hemorrhage (Atallah et al., 2017). It is advised that women at high risk should begin taking this before 12 weeks until 36 weeks of gestation (English et al., 2015).

Calcium supplementation during pregnancy also appears to reduce the risk of hypertensive disorders in pregnancy, including PE. A group of 579 women were assigned as a placebo group and a group of 588 women were given calcium supplementation. When comparing the percentage of hypertensive disorders of pregnancy in the placebo and calcium groups of women, the calcium group had a significantly lower risk of hypertensive disorders, particularly after the 28th week of gestation. There seem to be no side effects associated with calcium supplementation (Belizan et al., 1991).

There is also some research suggesting that antioxidant supplementation of vitamins C and E may be useful in lowering one's risk of PE. These agents are thought to prevent ROS from inflicting oxidative damage and overall restoring the redox equilibrium. This therapy aims to ultimately prevent endothelial cell dysfunction, which is an important pathological feature of PE (Aouache R. et al., 2018). However, there are studies that show contradictory results about the effectiveness of these supplements on reducing risks of PE. To test their outcomes related to PE, women who were 9 weeks to 16 weeks pregnant were examined until delivery. 5,088 women were given daily antioxidant supplementation of vitamins C and E, whereas 5,066 women served as a placebo group. The vitamins did not have much of an effect on the risk of developing PE. Based on such findings, they do not seem to serve any significant preventative purpose (Preeclampsia

Research at the NICHD 2012).

Early and accurate detection of the disorder is important in order to provide immediate optimal management. Therefore, closely monitoring changes in pregnancy, especially for women who classify as high-risk, is recommended. Regularly assessing blood pressure can catch any hypertension which is a good indicator of PE (Mayrink et al., 2018). Consistent urinary analyses should be performed in order to check for proteinuria, another big marker of PE. Monitoring growth often is useful in identifying signs of fetal growth restriction as well (English et al., 2015).

It is certain that the only definitive cure for PE is delivery. The decision to deliver the fetus prematurely is often based on two factors, estimated fetal weight and the severity of the disorder. If the mother is experiencing "uncontrolled severe hypertension that is not responding to therapy, eclampsia, acute pulmonary edema, abruptio placentae, subcapsular hepatic hematoma, or thrombocytopenia <50,000/mm3 ", then that indicates a need for immediate delivery (Uzan et al., 2011). Nevertheless, there are various ways to help control the condition during the pregnancy. Premature birth of the fetus is almost always inevitable, since the mother will most likely be unable to survive the full pregnancy period due to her destructive conditions. However, it is ideal to allow the baby to develop for as long as possible to improve neonatal outcomes. Mainly, it is important to allow the fetal lungs to mature. Prolonging treatment for as much as possible will result in the most beneficial outcome for the fetus (Le et al., 2019).

If blood pressure reaches the level of 160/110 mmHg or higher, antihypertensive treatment is a necessity as this is considered a medical emergency. Oral antihypertensive medications such as labetalol, methyldopa, and nifedipine should be administered. If the oral therapy fails to elicit a response, intravenous medication such as a labetalol infusion or hydralazine should be given. However, the commencement of treatment may result in a drop in blood pressure that can affect uteroplacental circulation and cause fetal distress; hence, the dosage of these drugs should be titrated gradually (English et al., 2015).

Magnesium sulfate (MgSO4) is a drug that aids in preventing eclampsia. The drug should be administered to women at high risk for eclamptic seizures. It has also been shown to lower the risk of cerebral palsy in the offspring. MgSO4 does have some adverse effects and can lead to paralysis, an absence of reflexes, a lower respiratory rate, and arrhythmias. Therefore, patients will need to have their pulse, respiratory rate, and reflexes continuously monitored in the time following. In the case that toxicity does occur, it can be corrected by giving the patient calcium gluconate (English et al., 2015).

Conclusion

PE is a disorder that is not fully understood yet. Due to the limited knowledge of its precise mechanisms, it remains difficult to determine the exact etiology of the disorder. However, the reviewed research articles were all consistently in agreement that women with the disease have a common pathophysiological finding. Elevated levels of sFLT1 are present in the placenta, which suggests the disease is largely due to dysfunctional angiogenic factors. The inability of the mother's angiogenic factors to bind to their correct receptors causes her blood vessels to constrict and leads to manifestations of PE (Roberts & Bell, 2013). This seems to be the major factor behind the disorder.

PE does not have any known cures; the only way to successfully stop the disease would be to terminate the gestation period and deliver the baby. The goal would be to manage and prolong the pregnancy for as long as possible in a way that takes both the mother's and fetus' safety into account (Uzan et al., 2011). After reviewing the various treatment options available, it seems that a combination of therapeutic agents would be the most viable approach for PE. Taking low-dose aspirin is a useful protecting drug as it reduces platelet aggregation (Atallah et al., 2017). Anti-hypertensive medication is essential to control the mother's blood pressure in cases when it reaches 160/110 mmHg or higher. The use of anti-hypertensives can lead to a sudden drop in blood pressure that can cause fetal distress, so it is important to responsibly monitor women's blood pressure when they are on these medications. Additionally, MgSO4 is important for preventing or treating seizures in eclampsia (English et al., 2015). Side effects that may present include paralysis, an absence of reflexes, a lower respiratory rate, and arrhythmias. However, the drug is vastly advantageous, and monitoring the patient and regulating drug administrations will eliminate most of the harm it can cause (English et al., 2015). Knowledge of the various factors that put women at high risk for PE is also useful for preventative care. Women should have their blood pressure monitored to check for hypertension, and urinalyses monitored to look for proteinuria, two major symptoms of PE. (Mayrink et al., 2018). Taking these steps can help in early detection and management of PE.

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