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Role of Vascular Endothelial Growth Factor Receptor 2 Pathway Due to Preeclampsia:

A Review

Honors Research Project

Firdous Ali

Abstract

Preeclampsia is a pregnancy complication that is characterized mainly by hypertension in the mother. The exact pathogenesis of preeclampsia is unknown, although the disease is attributed to a number of factors such as angiogenic factor levels and endothelial dysfunction. Presently, the control program for the disease involves the delivery of the fetus and the placenta. There is a need to develop novel therapies that would control preeclampsia from the moment it is diagnosed to minimize the effects on the mother and child. VEGF is a protein involved in the pathogenesis of the condition. The defect in one of its receptors, VEGFR2, brings forwards many of the detrimental effects in preeclampsia such as endothelial dysfunction and prevention of vasodilation. This review paper summarizes ten studies over the recent years to illustrate where the current research is headed towards and what therapies are at work at the moment. Risk factors, mRNA expression, protein expression, biomarkers, current therapies, related diseases, and single polypeptide nucleotides of VEGF/VEGFR2 pathway in reference to preeclampsia are looked at to draw a pattern of commonalities and differences in this review as well.

i. Introduction

Preeclampsia is a pregnancy-specific hypertensive condition that accounts for 15% of the United States' premature births (March of Dimes, 2020). The disease is marked by endothelial cell dysfunction, reduced uterine perfusion, and protein presentation in the urine which can also usually lead to fetal growth retardation. Preeclampsia makes up 60,000 maternal deaths per year and has no cure (Ahmed & Cudmore, 2009). Evaluation of risk factors can aid in the early management of the disease, but placental delivery is the only known method of actually treating the condition. Several aspects of the body are monitored to detect the presence of

preeclampsia. Such would be platelet count, red blood cell rupturing, renal and liver abnormalities (Young et al., 2010). Although child delivery can relieve the condition, simply having preeclampsia despite being a relatively healthy individual before the onset of the disease can severely impact the mother's chances of being diagnosed with other cardiovascular diseases by double. Furthermore, preeclampsia also serves as an indicator for potential renal abnormalities after delivery(Young et al., 2010). Certain proteins have been seen to play a crucial role in elevating and lowering blood pressure to contribute to the onset of preeclampsia. One of these proteins is called the vascular endothelial growth factor (VEGF).

The vascular endothelial growth factor (VEGF) is a small protein that induces mitosis in endothelial cells as a result of a number of changes in the body including hypoxia, the presence of tumor cells, and immunomodulating agents (Neufeld et al., 1999). The morphology of its receptor includes seven immunoglobulin-like domains with one transmembrane domain, one juxtamembrane portion, one intracellular protein tyrosine kinase domain, and ends with a carboxy-terminal tail. There are three different VEGF receptors and each binds to a different variant of the VEGF molecule. For instance, the variant that binds to VEGF receptor 1, also known as Flt-1, will bind VEGF to its second immunoglobulin domain to initiate signaling (Roskoski, 2008). VEGF can also participate in accelerating cell migration, hindering programmed cell death, lymphangiogenesis, acting as a mitogen for neuronal cells, forming blood vessels from hematopoietic stem cells, but the main role of VEGF is seen in advancing angiogenesis along with vasculogenesis while also promoting blood vessel cell membrane permeability and bringing forth vasodilatory effects (Pandey et al., 2018). VEGF exerts

its effects through various signaling pathways for each role it plays in vivo. For instance, MEK-MAPK signaling is utilized for its role in cell proliferation and migration while the Src-eNOS pathway is utilized by VEGF for its accentuated role in permeabilization (Lange et al., 2016). A homodimer consisting of antiparallel polypeptide cystine-knots connected via covalent disulfide bonds makes up the structure of this mitogen. VEGFs bind to receptor tyrosine kinases (RTK), such as VEGFR1 or VEGFR2, and exerts their effects through downstream growth factor signaling (Karaman et al., 2018). However, how these pathways work to lead to endothelial dysfunction in preeclampsia has not been clearly determined.

This review brings light to recent research on the VEGF/VEGFR2 pathway and how it relates to pre-eclampsia in terms of its vasodilatory effects. The focus will be on drawing similarities and differences between research and/or current therapies. Furthermore, factors including genes, single nucleotide polymorphisms (SNPs), mRNA expression, protein expression, biomarkers, and other related proteins and receptors will be looked at to establish patterns of vulnerability to the disease. Lastly, a look at how VEGF behaves in other diseases will be noted.

ii. Findings

Treatments are a main concern for preeclampsia. Thus, one study looked at intrauterine growth restriction and how VEGF pathways can aid in vasorelaxation along with fetal growth. Although this condition is not the same as preeclampsia, it usually arises alongside it, and looking at the pathology of intrauterine growth restriction can very well give insight into how VEGFR2 promotes uterine perfusion. The findings of this study demonstrate the use of adenoviral vectors in gene therapy to mimic the effects of

VEGF. Adenoviral vectors are short-acting vectors that are most commonly used in gene therapy clinical trials. They invade cells through fiber proteins binding capsid to the coxsackie and adenovirus receptor (CAR) and are capable of triggering a mediated immune reaction between a B cell and T cell (David, 2017). Since the CAR is on various cells, the gene therapy could target the maternal uteroplacental circulation without directly having the vectors enter the placenta. Preclinical studies were done on sheep that were injected with the adenovirus vector VEGF-A in their uterine artery to examine uterine blood flow. After about 4 to 7 days, there was an increase in uterine artery blood flow, angiogenesis, VEGFR2 expression, and vascular relaxation. Furthermore, long-term results also supported these short-term results in which after 28 days of the injection, there was a 36.5% increase in uterine blood flow (David, 2017).

To examine how this potential therapy also affects fetal growth during intrauterine growth restriction (IUGR), the adenovirus VEGF-A was injected into the uterine artery of IUGR sheep. It was found that at about 3-4 weeks post-treatment, abdominal circumference quantities rose by about 20% when compared to the control and fetal growth for abdomen and head was relatively better. Weights of the lambs at birth were seen to be higher as well and the results supported that there were elevations in placental efficiency (David, 2017). Lastly, the process was repeated on guinea pigs, however, instead of injecting the adenovirus VEGF-A, a less invasive technique was applied to avoid fatal consequences. Similarly, the results for these species showed that fetal growth was increased, and abdomen to head sizes were growing efficiently with increases in birth weight and size of organs such as the brain, lungs, and liver (David, 2017).

To address preeclampsia and to move towards developing treatments, it is crucial to understand what factors or molecules in the body need to be targeted and further studied. One study looked at a protease called high temperature required factor A4 (HtrA4) and how it affects VEGF signaling during preeclampsia. Pregnancy is a physiological process that is characterized by the production of new proteins into a woman's body. Each of these proteins has a specific function, but they generally aid in the fetal growth and development process throughout the gestational period. The high-temperature requirement factor is an example of such proteins. HtrA4 is produced in the placenta and enters the mother's circulation at the onset of pregnancy. Studies suggest that the levels of HtrA4 in the maternal circulation increase significantly during the early stages of preeclampsia, or high blood pressure in pregnancy. When the levels of HtrA4 rise above normal, they cause endothelial dysfunction in human umbilical vein endothelial cells, HUVECs, thus proving that there is a relationship between HtrA4 and VEGF-A/VEGFR2 pathway (Wang et al., 2019). Findings in the study also suggest that protease HtrA4 contributes to endothelial dysfunction by damaging the kinase domain receptor, KDR (VEGFR2), which is the main receptor of VEGF-A. Consequently, it hinders the signaling of VEGF-A and the formation of blood vessels. This study confirms these findings via a western blot and immunocytochemistry analysis of in vitro cleavage of recombinant KDR by HtrA4 and a mouse aortic ring explant assay that demonstrated cessation of angiogenesis (Wang et al., 2019).

Endothelial dysfunction in pregnancy occurs when there is a limited or insufficient supply of oxygen and nutrients in the womb. VEGF-A, with the aid of VEGFR2 and other receptors, is responsible for the formation of blood vessels that supply oxygen and

nutrients. When one or both receptors are compromised, it inhibits angiogenesis. Moreover, a limited supply of blood vessels is a contributing factor to the development of blood pressure (and preeclampsia), which explains why there are increased levels of HtrA4 in the maternal bloodstream during the onset of preeclampsia (Wang et al., 2019). While it is difficult to prevent the rise in HtrA4, increasing the levels of VEGF-A so as to counter the effects of HtrA4 on KDR is nearly impossible. There is no medical treatment that has been established for this condition. However, the reduction of sFlt1 that simultaneously increases the levels of VEGFA in circulation is used as a control method (Wang et al., 2019).

The risk factors associated with preeclampsia are a history of preeclampsia in previous pregnancies or family lines, a history of high blood pressure and obesity, intrauterine fetal growth restriction, in vitro fertilization, maternal age, smoking, maternal comorbidities, protracted kidney diseases, and multiple pregnancies. This study focused on revealing management, pathogenesis, and biomarkers of the disease. The pathogenesis of preeclampsia occurs in two stages: abnormal placentation and development of the maternal syndrome (Phipps et al., 2019). In abnormal placentation, there is an insufficient circulation of blood due to limited or obscured blood vessels. Other than the previously mentioned pathogenesis of preeclampsia, specificities were noted in this study. Hyperproliferation of cells from the placenta, arteriosclerosis, decreased spiral artery diameter, and blood clots were often discovered in preeclamptics (Phipps et al., 2019). Although the reasoning for the cessation of spiral artery remodeling is unclear, it is suspected that cytotrophoblasts not undergoing the epithelial cell to endothelial cell change may be the underlying cause.

The presence or absence of antiangiogenic factors has also played a role in the development of preeclampsia. Antiangiogenic factors are based on the effects of antiangiogenic proteins that are produced by the placenta. This is considered as the primary cause of preeclampsia, although other factors stated above are given consideration during diagnoses. Furthermore, VEGFR2 was shown to not be given preference when it came to treatment strategies due to its unfavorable effects connected to the permeability of blood vessels and fluid retention (Phipps et al., 2019). There still remains a challenge in the breakthrough of a treatment program for preeclampsia. The study concludes by confirming that the existing treatment or control is still birthing of the fetus, consecutive postpartum monitoring, and evaluation for the first two weeks after delivery.

To get a better grasp of VEGFR2's role in preeclampsia, it is also necessary to look at related proteins and receptors that may or may not have a hand in elevating or inhibiting the efficacy of VEGFR2. The overproduction of one of the related receptors, sFlt-1, is stimulated by excessive VEGF levels in the trophoblasts, which is one of the leading causes of preeclampsia in pregnant women. However, there have not been any definitive measures established on the mechanisms that VEGF employs in the regulation of sFlt-1. In this particular study, an experiment was carried out to determine the mechanism used and the factors that support or control the regulation of sFlt-1 by VEGF. The experiment was conducted in vitro and involved the use of JEG3 and HTR-8/SV neo (HTR8) trophoblast cell lines as specimens. JEG3 (VEGF-GFP-JEG3, V-J) and HTR8 (VEGF-GFP-HTR8, V-H) cells were infected with lentivirus that was represented by VEGF165. VEGF overexpression caused a significant reduction of the

migration and invasion abilities of JEG3 and HTR8 cells (Xiao et al., 2018). However, it is possible to reverse the reduction through the use of a VEGF receptor inhibitor.

Additionally, the experiment included altering the concentration levels of VEGF and sFlt-1 at the start and end of the experiment with the use of an Flt-1 inhibitor (MK-2461), a KDR receptor (VEGFR2) inhibitor (XL-184), or an Flt-1 and KDR receptor (VEGFR2) inhibitor (ABT-869). The treatment and control program(s) showed different but promising results. During treatment, V-J cell migration experienced an upward trajectory as opposed to the control program(s). Results indicate that VEGF receptors, Flt-1 and KDR (VEGFR2) enable the regulation of sFlt-1 by VEGF (Xiao et al., 2018). Hence, the signaling pathway used during the regulation of sFlt-1 can be influenced by either one or both receptors at the same time.

So far, it is evident that preeclampsia is a result of a disproportion between proangiogenic proteins and antiangiogenic proteins that are produced during pregnancy and then passed into the mother's blood circulation. To further examine the relationship between VEGF and its receptors, a look at the mRNA expression levels is crucial. Evaluating proteins that contribute to the condition can open doors to management and therapies. Antiangiogenic proteins in the mother's bloodstream can cause high blood pressure, fetal stunted growth, proteinuria, and edema. Thus, studying the mRNA expression levels of these proteins was the main concern of this experiment. An example of an antiangiogenic protein is sFlt-1 that is produced in the placenta. The protein acts as a neutralizing agent against VEGF signaling and consecutively, endothelial dysfunction (Ali et al., 2019). According to this study, VEGF formulates signaling pathways for its two main receptors: VEGFR1 and VEGFR2. VEGFR1 acts as

an antiangiogenic factor due to its ability to bind itself onto VEGF and PlGF, whereas VEGFR2 is tasked with proliferating, differentiating, and migration of endothelial cells (Ali et al., 2019).

Quantitative real-time polymerase chain reaction was applied to determine mRNA expression level differences across VEGF, VEGFR1, VEGFR2, and sFlt-1 in early-onset preeclampsia, late-onset preeclampsia, and the control peripheral blood mononuclear cells. Results show that the presence of VEGF and its subsequent receptors causes a decrease in mRNA levels in comparison to an increase in sFlt-1 in maternal peripheral blood mononuclear cells. (Ali et al., 2019). The increase in sFlt-1 is due to the oxygen-deficient conditions that are a direct cause of decreased perfusion to the placenta and VEGFR2 activity.

It has been established that impaired angiogenesis of the placenta during pregnancy results in complications such as preeclampsia and fetal growth restriction. Angiogenesis is aided by the proper functioning of VEGF, which indicates an indirect relationship between the VEGF protein and preeclampsia. For VEGF to work, it requires receptors that are responsible for the binding process. These are Flt-1 and VEGFR2 (KDR). Impaired angiogenesis causes the placenta to produce a soluble variant of the Flt-1 receptor, the sFlt-1. sFlt-1 inhibits VEGF from binding successfully, thus acting as an antiangiogenic factor. Despite the progress made in the discovery of the *VEGF* and *sFlt-1* gene polymorphisms in the occurrence of preeclampsia, their protein levels are yet to be established in women of Indian origin. The following study establishes that the protein levels of the two gene polymorphisms vary based on the concentration of the receptor genotype. The experiment involved patients and controls. It was found that

high levels of *VEGF* + 936C/T genotype corresponded to low levels of VEGF-A, while *sFlt-1* + 4244G/A with the GA, AA genotype, *sFlt-1* + 4771 G/T with the GT, TT genotype, and *sFlt-1* +523 C/G with the CG, GG genotype indicated high levels of sFlt-1 in patients in comparison to controls (Arora et al., 2019).

The high levels of the *VEGF* and *sFlt-1* gene polymorphisms, irrespective of their genotypes, in patients further escalated their contribution towards the development of preeclampsia. While this stands as a generalized result of the experiment, detailed results on the homozygous and heterozygous genotypes had differing concentrations in patients and controls, wherein some instances, the levels were higher in controls as compared to patients. For instance, the *VEGF* + 936C/T gene had the CC (homozygous) genotype higher in controls and vice versa, whereas the CT genotype (heterozygous) was higher in patients (Arora et al., 2019). Most notably, patients had lower levels of VEGF-A than controls.

The type of therapeutic approach taken towards the treatment and management of preeclampsia is critical in the growth and development of a healthy baby during pregnancy. Hence, it is important to look at where therapies have thrived and the directionality of future therapies in terms of VEGF/VEGFR2. The following paper is a review of studies that discuss this topic and indicate that a balance between angiogenic factors and antiangiogenic factors is critical in healthy embryonic development. For this reason, treatment programs have to ensure that this balance is not compromised. Suitable treatment programs are geared towards being placental-targeted since the placenta acts as the root of dysfunction. Currently, the drug sulfasalazine is most promising, with studies indicating that the drug eliminates endothelial dysfunction as

well as lowering sFlt-1 levels (Jena et al., 2020). However, the reduction of the antiangiogenic factor results in an imbalance of the angiogenesis receptors and thus risks the healthy growth of the fetus.

Other drugs under consideration for the treatment of preeclampsia include Fasudil, exogenous alpha-1 antitrypsin, pravastatin, and vitamin D. These drugs have been tested to treat and control hypertension, but their potential side effects could prove to be detrimental to the mother and unborn child and therefore, calls for further studies (Jena et al., 2020). Nonetheless, there has been development of a placenta-specific drug delivery system that will enhance the efficiency of the drug towards repairing the damaged placenta alone. More studies continue to be carried out in efforts of deriving the right drug that does not pose any form of toxicity to both mother and child. In terms of where VEGFR2 falls in this, it is unclear, but it has been revealed that the receptor along with its protein kinase C-MEK signaling pathway regulates how VEGF affects VEGFR1 expression in human vascular endothelial and placental trophoblast cells (Jena et al., 2020).

The exact pathogenesis of preeclampsia is yet to be established. Similarly, there is insufficient information about genes that are specific to the development of preeclampsia. A selection of genes had to be done to identify genes that were linked to preeclampsia pathogenesis. A gene was considered pathogenic if silencing or overexpression of the gene produced phenotypes like preeclampsia and one or several polymorphisms of the gene were linked to preeclampsia. Through enrichment analysis (gene ontology (David Bioinformatics Resource) and metabolic pathways), this study aimed to determine the genes involved in the pathogenic process of preeclampsia. It

was established that VEGF, Flt-1, and KDR genes were directly involved in the onset of preeclampsia. Other genes that had potential effects on the pathogenesis of the condition are HSP90, CD247, and PAK2 (Tejera et al., 2017). However, these genes require to be undertaken through extensive experiments to determine their viability. The experimental design in array technologies is a challenge since ascertaining the difference between pathogenic and non-pathogenic genes is difficult.

Various methods were used to identify the pathogenic genes. The methods were based on the availability in web service as well as the requirement of only the name of the disease in prioritization of the gene. MetaRanker was the most effective method in detecting the genes (Tejera et al., 2017). In addition, the method allows for early detection of the genes, a very central aspect towards the discovery of the pathogenesis of preeclampsia. The consensus strategy fundamentally improved the recognition and prioritization of pathogenic genes. The integrated metabolic pathway evidently highlights the core routes followed during the pathogenic process of preeclampsia. Biological processes that are linked to blood pressure, angiogenesis, and hormonal regulation were directly associated with the development of preeclampsia. This study references recent findings of the VEGF genes as priority genes in the development and advancement of preeclampsia. The VEGF genes are VEGFA, KDR, FLT1, PGF, NRP1, VEGFB, VEGFC, FLT4, and NRP2 (Tejera et al., 2017).

VEGFR2 SNPs have been often studied, but how this receptor pathway relates to other molecules' SNPs in preeclampsia is not too common. The following study analyzed LPA gene SNPs and inflammatory markers to know whether or not there is a risk of developing preeclampsia. This was evaluated in early-onset preeclamptics,

late-onset preeclampsics, and normal pregnancies. Endothelial dysfunction is highly noted in the early onset preeclampsia pregnancies, in which these women also have a shorter gestation period in comparison to late-onset preeclampsics. It has been stated that the corruption of the VEGF/VEGFR2 pathway is responsible for endothelial dysfunction seen in the condition (Tuten et al., 2021). Thus, analyzing these SNPs can help in the understanding of why and how endothelial dysfunction occurs.

Lp(a), which is coded by the LPA gene, was assessed due to its inflammatory properties that participate in atherosclerosis. The study targets this property due to atherosclerosis's pathogenesis similarity to preeclampsia. One mechanism that Lp(a) applied to cause atherosclerosis is through the attachment between proinflammatory-oxidized phospholipids and endothelial cells (Tuten et al., 2021). Oxidized phospholipid (OxPL) interacts with lipoprotein-associated phospholipase II (Lp-PLA2) to be degraded. Moreover, OxPL binds to receptors on the cell surface to activate functions such as inflammatory gene expression, atherosclerosis, angiogenesis, and inflammatory mediators. VEGFR2 was one of the few receptors on the endothelial cells that were part of this degradation process (Tuten et al., 2021).

Although VEGF is primarily functional during pregnancy, its functions extend further to other parts of the body. To get a better grasp of the effects of VEGF/VEGFR2, one should not simply focus on its role in the uterus and placenta, but also how it functions in other diseases. Preeclampsics are not just always dealing with one medical condition and at times, they can be presented with many more incurable diseases that may have increased their risk of later developing preeclampsia or vice versa. So, this specific study looks at the role of VEGF/VEGFR2 in multiple diseases along with

preeclampsia. In the right levels, VEGF facilitates neuronal development, angiogenesis, and lymphangiogenesis (Matkar et al., 2017). In excessive levels, VEGF can enhance the development of rheumatoid arthritis and osteoarthritis, diabetes mellitus, chronic obstructive pulmonary disease (COPD), endometriosis, preeclampsia and ovarian hyperstimulation syndrome, neurodegenerative disorders such as amyotrophic lateral sclerosis, and organ fibrosis (endothelial-to-mesenchymal transition).

Each of the above disorders is associated with a specific isoform of VEGF and its contribution towards the autoimmune disease. For example, in rheumatoid arthritis and osteoarthritis, VEGF-A and VEGF-C isoforms induce complications in the diseases, while diabetes mellitus is associated with VEGF-A and VEGF-B, and VEGF-A for psoriasis. Diabetes mellitus patients also show a two-fold reduction in the circulating VEGF and its KDR receptors (Matkar et al., 2017). However, gene therapy was shown to bring those expression levels back up in those patients by decreasing oxidative stress along with endothelial cell death. In a similar manner, VEGFR2 was seen considerably reduced in the pneumocytes of the COPD patients. Additionally, in early and late-onset preeclampsia, VEGFR2 facilitated angiogenesis of the placenta, however, not much was seen in regards to uterine circulation (Matkar et al., 2017). More studies need to be conducted to determine the effects of VEGF in variants of coronary artery disease, Alzheimer's disease, and cerebral ischemia.

iii. Discussion

VEGFR2 has a considerable role in the regulation of preeclampsia. However, the exact mode of action of the receptor is an ongoing study up to this day. Research over the past few years has revealed numerous information in regards to both protein and

disease. One general pattern that can be noted from the research is the importance of identifying biomarkers for the pathogenesis of preeclampsia. Antiangiogenic and proangiogenic factors have repeatedly been stated to be the leading cause of preeclampsia, but recent studies have shown to identify other factors as well. HtrA4, sFlt-1, and Lp(a) in abnormal levels can cause severe complications during pregnancy or even after. All of these proteins either directly or indirectly target VEGFR2, to cause endothelial dysfunction, the cessation of angiogenesis, or prevent vasodilatory effects, which establishes a part of the pattern of preeclampsia's pathogenesis. sFlt-1 was mentioned to be influenced by VEGF levels and thus, VEGFR2 binding to the protein altered sFlt-1 levels to either normal or abnormal levels (Xiao et al., 2018). Nonetheless, this establishes the possibility that both sFlt-1 and VEGFR2 may be simultaneously at play when it comes to the cause of preeclampsia.

Furthermore, it was seen that expression levels across both mRNA and protein play an important role in revealing VEGFR2 regulation in the disease. The increase of sFlt-1 mRNA expression was due to a decrease in VEGFR2 mRNA levels that led to low oxygen levels and decreased placental perfusion (Ali et al., 2019). Once again, this ties the simultaneous actions of the two receptors together in preeclampsia. Another study reviewed in this paper also identified VEGFR2 genes as one of the direct causes of the condition (Tejera et al., 2017). This argument can be further strengthened by citing the protein levels examined in another study. High protein levels of sFlt-1 also promoted the pathogenesis of preeclampsia and since genotypes of the patients and controls may lead to some ambiguity, this warrants further research.

The general consensus from these studies still points towards the delivery of the child and continuous monitoring of the mother during pregnancy and after birth. However, gene therapy is seen as a promising method to aid in vasodilation and uterine perfusion in preeclampsia. VEGFR2 expression was seen to increase after application of the adenoviral vectors in the animal models which emphasizes the importance of greater research in this area of study (David, 2017). A breakthrough in this therapy could prove to alleviate a lot of complications in preeclampsia for keeping both mother and baby healthy. Hence, targeting the VEGF/VEGFR2 pathway via gene delivery is a gateway into developing more advanced forms of therapy that not only attenuate symptoms of preeclampsia, but also work to cease them in the long run.

The final study calls attention to how the VEGF/VEGFR2 pathway participates in other diseases. Diabetic patients and COPD patients were seen with very low VEGF and VEGFR2 levels, mostly in regards to inflating oxidative stress and endothelial apoptosis (Matkar et al., 2017). Both of these factors are also indicators of preeclampsia, however, it was not stated whether or not these patients also ever had preeclampsia. Therefore, future research needs to track how factors such as VEGF levels, oxidative stress, or endothelial dysfunction cooperate in patients with preeclampsia and other medical conditions, while also examining molecular pathways that are the common contributors to the pathology of both preeclampsia and the other disease. This may reveal other risk factors for the disease or may reveal what risk factors preeclampsia exposes the individual to in terms of other diseases.

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