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Abstract

Preeclampsia is a common complication of pregnancy characterized by hypertension and proteinuria. Its symptoms are well-defined, but the pathophysiology is not fully understood. This paper analyzes several of the most credible causes of this syndrome and attempts to relate these to the known risk factors. Current preeclampsia treatments are examined, and special focus is given to novel experimental treatments which offer hope of ending preeclampsia and eclampsia.

Key Words:
Preeclampsia
Eclampsia
Risk Factors
VEGF
sFlt1
Gene Therapy

Acronyms Used:
sFlt1–Soluble fms-like Tyrosine Kinase 1
HELLP–Hemolysis, Elevated Liver Enzymes, and Low Platelet count
VEGF–Vascular Endothelial Growth Factor
PlGF–Placental Growth Factor
BMI–Body Mass Index
CNS–Central Nervous System
NICU–Neonatal Intensive Care Unit
PE–Preeclampsia
APLN–Apelin

Introduction

Preeclampsia is a relatively common complication of pregnancy. Occurring in 7% of all pregnancies in the US, it is defined as an increase in blood pressure combined with proteinuria. More severe cases of preeclampsia have the potential to advance into eclampsia, which is preeclampsia with the addition of seizures. Preeclampsia and eclampsia have the ability to cause lasting harm or death to both mother and fetus, but the cause of these diseases is largely unclear (Papadakis & McPhee, 2017).

Risk factors for preeclampsia are known. Hypertension, kidney disease, family history, diabetes, and obesity are all linked to a higher incidence of preeclampsia. Preeclampsia is commonly called a disease of the first pregnancy, though women who have had preeclampsia before are also at greater risk of developing it in subsequent pregnancy. Strangely enough, cigarette smoking seems to prevent preeclampsia. There are other known risk factors as well.

Some of the pathophysiology of preeclampsia is understood. It is believed that preeclampsia develops from poor placentation and the release of soluble fms-like tyrosine kinase 1 (sFlt1) into the mother's bloodstream. However, the increase in sFlt1 levels is often not distinct enough to use as a screening tool. Additionally, the original cause of the increase is unknown.

Treatment of preeclampsia is largely based on symptoms, with the goal being the continuation of the pregnancy for as long as possible. Almost all symptoms disappear within 48 hours after delivery, so it is in the mother's best interest to give birth. Conversely, the fetus needs more time in utero to develop. The physician must balance the conflicting needs of the two patients by managing the mother's symptoms. Further understanding of the underlying causes of preeclampsia can result in more effective treatment and better outcomes for preeclamptic women and their children.

Methods

Peer-reviewed journal articles were obtained using Touro College's database and Google Scholar. The articles were critically read, analyzed, and compared. Special attention was given to retrospective studies and reviews due to the dearth of original studies in their references. This can be attributed to the fact that pregnant women tend to be apprehensive about joining clinical studies.

Discussion

Symptoms of Preeclampsia

Preeclampsia is a complication of pregnancy involving hypertension and proteinuria. It cannot be prevented. Instead, pregnant women are screened for symptoms and treated accordingly. These symptoms usually present in the third trimester, but can occur from 20 weeks' gestation. It is diagnosed when a patient presents with blood pressure of 140/90 or greater, and more than 0.3 g of proteinuria in 24 hours. Some women also have edema. Severe preeclampsia involves higher blood pressure as well as thrombocytopenia, headache, and blurred vision (Papadakis & McPhee, 2017).

Severe preeclampsia is also characterized by hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. This diagnosis was first made in 1982 and is currently found in 0.2-0.8% of pregnancies. HELLP syndrome is rarely seen in non-preeclamptic patients, though preeclampsia is about ten times as common as HELLP. Like preeclampsia, HELLP is a syndrome, a collection of symptoms whose one underlying cause is uncertain. The hemolysis aspect is a result of damaged endothelial cells in small blood vessels. Fibrin strands in the blood vessels cause red blood cells to become fragmented, often causing anemia. Microangiopathy also slows hepatic portal blood flow, damaging the liver. The same microangiopathy also exposes tissue factor on blood vessel walls which activates coagulation pathways. These blood clots lower platelet counts and can lead to further complications such as uncontrolled bleeding or placental abruption (Abildgaard & Heimdal, 2013).

If preeclampsia continues, it can develop into eclampsia, which

is defined as all of the symptoms of preeclampsia with the addition of seizures. Eclampsia is easily prevented by administration of magnesium, so it is usually only seen in patients lacking prenatal care, or in developing countries where access to this anticonvulsant is unavailable. Hyperexcitability and extreme reflex responses are typical signs that eclampsia may be developing (Papadakis & McPhee, 2017; Duley, 2009).

Preeclampsia is primarily a disease of the mother, so the fetus is not always affected. This is especially true in milder cases of preeclampsia, where the pregnancy is allowed to continue until term. However, this is not to say that the fetus is never endangered. Fetal growth restriction is a complication often correlated with preeclampsia. Because of the mother's angiopathy, blood supply to the fetus can be reduced. This does not allow the fetus to receive adequate nutrition, causing a low birth weight (Duley, 2009).

More seriously, preeclampsia often forces an early delivery because of the mother's symptoms. Preterm delivery, in this case meaning before 34 weeks' gestation, is associated with various complications. There is the immediate problem of insufficient surfactant maturity in the lungs, causing the baby to go into respiratory distress upon birth. Low birth weight often causes complications later in life, including cardiovascular problems, diabetes, and obesity. Additionally, increased risk of cerebral palsy has been associated with children of preeclamptic mothers. Although preeclampsia primarily affects the mother, the fetus is not spared of all effects (Papadakis & McPhee, 2017; Duley, 2009).

Causes of Preeclampsia

The causes of preeclampsia are poorly understood. Because preeclampsia is a syndrome, a collection of symptoms which may or may not come from one underlying cause, the pathogenesis can be different for different patients. Most people agree that preeclampsia's cause lies in the placenta due to the fact that the disease disappears upon delivery. It is hypothesized that poor placentation is a cause of preeclampsia. In normal pregnancies, cytotrophoblasts from the placenta invade the mother's myometrium and increase blood supply to the fetus. In preeclamptic placentas, insufficient invasion and remodeling of the mother's arteries occur. The placenta is therefore hypoxic, and parts of it break down and release debris into maternal circulation. This debris, containing trophoblast cells and keratin fragments, causes the inflammatory response of preeclampsia, microangiopathy and hypertension (Redman & Sargent, 2005).

Normal placentas release vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). Both are angiogenic factors which allow the placenta to build an adequate vascular network for the fetus's development. When VEGF or PlGF binds to a receptor on placental cell surfaces, increased vascularity is shown. A soluble form of this receptor, soluble fms-like tyrosine kinase-1 (sFlt1), increases in the third trimester. This receptor floats freely in the placenta and maternal serum. When sFlt1 binds to VEGF or PlGF, they are unable to create blood vessels, proving sFlt1 to be antiangiogenic, and possibly the cause of the poor placentation described above. This factor is further increased in preeclampsia, and is found to increase even before clinical signs of the syndrome are evident. It is believed that excess sFlt1 can cause preeclampsia; what is unknown is how this excess develops in the first place and what can be done to prevent it (Redman & Sargent, 2005; Levine et al., 2004).

It is believed that decreased free VEGF and PlGF in the maternal blood supply leads to the endothelial dysfunction of preeclampsia. In the kidneys, the lack of free VEGF causes glomerular endotheliosis; constantly circulating VEGF is necessary for renal function. The swelling of kidney cells then does not allow for proper filtration of the blood, causing proteinuria. Exactly how or if sFlt1 causes hypertension is unknown.

As would be expected, women with lower VEGF and PlGF levels and higher sFlt1 levels tend to have more severe symptoms of preeclampsia and eclampsia. Additionally, when sFlt1 is administered to nonpregnant rats, they develop preeclamptic symptoms. VEGF inhibitors or VEGF gene knockouts cause hypertension and proteinuria in pregnant and nonpregnant rats. Cancer patients taking VEGF-inhibitors to limit blood supply to a tumor will also often exhibit hypertension and proteinuria, further proving the role of sFlt1 in preeclampsia (Levine et al., 2004).

Preeclampsia is widely considered a disease of the nulliparous woman. In a Norwegian study examining data from over 700,000 births between 1967 and 1998, preeclampsia was found in 3.9% of first pregnancies (Skjærven et al., 2002). This is compared to a 1.7% incidence for second pregnancies, and 1.8% for third. The incongruous increase for third pregnancies is quite small and probably a statistical artifact. It is unknown exactly why preeclampsia is much more common in first pregnancies. What is known is that if a mother was preeclamptic in her first pregnancy, she is at risk for preeclampsia in later pregnancies as well. Somehow, nulliparity seems to cause preeclampsia. This Norwegian study claims that preeclampsia is a result of the mother being exposed to her partner's foreign antigens and responding inflammatorily, causing preeclampsia. In later pregnancies by the same man, preeclampsia is less likely because the partner's antigens are no longer unrecognized by her body. Giving weight to this theory, the more time that elapsed between pregnancies, the more likely the mother was to develop preeclampsia, even if she had not previously been preeclamptic. As time passed, the immune system's ability to recognize a partner's antigens decreased. Women whose second pregnancies were by different partners appear to have the same risk of preeclampsia as nulliparous women. This supports the idea that preeclampsia is partially caused by foreign antigens; a new partner supplies new antigens for which the mother is unprepared. However, since women who have changed partners often have a larger birth interval, it is very uncertain if the change in partner

actually increases the risk for preeclampsia. Interestingly, previous miscarriage seems to reduce the risk of preeclampsia in a later, successful pregnancy. This can also be connected to the idea of interbirth interval, as many women who miscarry attempt to get pregnant again very soon thereafter. Nulliparity is known to be a risk factor for preeclampsia; the reason for this is not totally clear (Skjærven et al., 2002; Sibai et al., 1995).

Risk Factors

There are many risk factors for preeclampsia, including chronic hypertension and kidney dysfunction, obesity, diabetes, previous preeclamptic pregnancies, family history of the mother or father, birth interval, age of the mother, as well as other preexisting conditions. This paper will analyze some of the more credible risk factors and attempt to explain the connection between them and the disease.

Nulliparity is the most known risk factor for preeclampsia. Whether this is due to an immune response or some other mechanism is largely unknown. What is known is that nulliparous women are more than three times more likely to develop preeclampsia than women who have previously had normotensive pregnancies (Duckitt & Harrington, 2005).

Women with chronic hypertension unrelated to their pregnancy are known to have a higher risk of developing preeclampsia and eclampsia. In one population-based study, 12.1% of preeclamptic women were found to have had hypertension before they became pregnant (Duckitt & Harrington, 2005). This is quite logical; high blood pressure before becoming pregnant leads to even higher blood pressure while pregnant. Clinically, blood pressure is used to diagnose preeclampsia. Preeclampsia is defined as systolic blood pressure of 140 mmHg or greater and/or diastolic blood pressure of 90 mmHg or greater, and at least 300 mg of proteinuria over 24 hours. Blood pressure can also be used to screen for preeclampsia. Elevated blood pressure is normal in pregnancy, but too high an elevation can be a sign that preeclampsia will develop. In one study of nearly 3000 women, the mean systolic blood pressure at 20 weeks gestation was 105.4 for healthy pregnancies, and 110.4 for those who later developed preeclampsia. This is a substantial difference, but clinically it would be difficult to gain any benefit from this statistic. Diastolic and mean blood pressure were not as useful for prediction. Not surprisingly, women who displayed significantly elevated blood pressure at 20 weeks were more likely to develop preeclampsia earlier than those whose blood pressure was not as elevated. This is a more useful diagnostic tool. Systolic blood pressure of 110 as opposed to 105 is hardly grounds to begin watching more closely for preeclampsia. Systolic blood pressure of 125 or 130 is (Sibai et al., 1995).

As with hypertension, kidney dysfunction before pregnancy is likely to lead to increased kidney dysfunction while pregnant, i.e. preeclampsia. Less research has been done on kidney dysfunction leading to preeclampsia, though. In one study of 69 pregnancies, 6.7% of women with recurring urinary tract infections developed preeclampsia, and only 2.6% of the control group did. In other words, 2 of the 39 women with renal disease developed preeclampsia, and only 1 healthy woman did. This is hardly enough evidence on which to build a treatment plan. Logically, the connection between renal disease and preeclampsia seems just as strong as that between hypertension and preeclampsia. However, not nearly as much research was done on this juxtaposition, perhaps because of the relative rarity of renal disease in women of childbearing age (Duckitt & Harrington, 2005).

Non-gestational diabetes greatly increases the risk of preeclampsia. A meta-analysis of multiple studies with a total count of 56,968 women revealed that the risk of developing preeclampsia is 3.56% greater for women who have diabetes before pregnancy. These studies are often connected to studies linking preeclampsia and obesity, which also approximately quadruples the risk of preeclampsia. Because women with diabetes and high BMI often have other health problems, it is difficult to assess exactly which of their characteristics make them more likely to develop preeclampsia (Sibai et al., 1995; Duckitt & Harrington, 2005). In a Saudi Arabian study of the effects of obesity and gestational diabetes on pregnancy, it was found that approximately 7% of women with obesity and/or gestational diabetes develop preeclampsia, compared to only 0.5% of women with neither. The combination of the two seems to increase the risk (Wahabi et al., 2014).

The connection between obesity and preeclampsia has been linked to inflammation. Obesity is inflammatory, as is preeclampsia, so it stands to reason that one inflammatory state can cause the development of an inflammatory disease. Additionally, preeclampsia often develops from hypoxic conditions in the placenta. Obesity can encourage this. Obesity is often linked with hyperglycemia, causing hemoglobin to pick up glucose and lose its affinity for oxygen. This does not allow enough oxygen to reach the placenta, leading to an inflammatory response, the release of cytokines, and subsequent endothelial dysfunction of preeclampsia (Redman & Sargent, 2005; Schmatz et al., 2010).

Previously having preeclampsia puts a woman up to seven times at risk for developing the disease in subsequent pregnancies when compared to women who have never had preeclampsia. It is assumed that whatever caused her to be susceptible in the first place will also cause later incidences of preeclampsia. A family history also puts a woman more at risk, though the mother-in-law's pregnancies do not seem to have much of an effect (Sibai et al., 1995; Duckitt & Harrington, 2005).

Treatment

Treatment options for preeclampsia are largely based on symptoms. The best treatment is delivery, but immediate delivery is

not always an option. Other treatments therefore are based on prolonging the pregnancy for as long as possible, keeping the mother's health in mind (Papadakis & McPhee, 2017).

When systolic blood pressure rises above 160 mmHg, or diastolic above 110, antihypertensive drugs are administered to bring blood pressure back down to 140/90, the threshold for preeclampsia's diagnosis. In severe preeclampsia, steps are taken to ensure that the patient will not develop eclampsia. If the mother begins to experience muscle spasms or hyperexcitability, showing that her CNS is beginning to be affected, magnesium sulfate is administered as a relaxant. Magnesium is also given to patients with eclampsia. Obviously, these women are monitored for toxicity. Calcium has been suggested as an aid in preeclampsia, but no real benefits have been proven (Papadakis & McPhee, 2017; Levine et al., 2004).

Delivery is the best option for the mother, and it is the treatment of choice from 36 weeks onward. Before that point, clinicians must decide if the fetus is ready for life outside the womb. If the fetus's lungs are not mature enough for birth, corticosteroids are administered to the mother for 48 hours, followed by induced delivery or cesarean. The steroids allow the fetus's lungs to mature more quickly. If the mother's symptoms are severe, such as in eclampsia, waiting for fetal lung maturation is not necessarily an option. Delivery must then be induced to the detriment of the fetus (Papadakis & McPhee, 2017).

Preeclampsia is a major cause of preterm delivery. Early delivery is often necessary for the mother's sake; the child suffers. Premature birth can result in respiratory distress, admittance to the NICU, low birth weight, jaundice, seizures, as well as other complications in infancy and later in life (Papadakis & McPhee, 2017). Fetal mortality is a large concern; preeclampsia is correlated with 25% of stillbirths and neonatal deaths in developing countries (Duley, 2009).

Both aspirin and nicotine appear to reduce the risk of preeclampsia. Aspirin has antihypertensive properties, so its role in decreasing the incidence of preeclampsia makes sense. In one study of healthy, nulliparous women, 4.6% of those given aspirin developed preeclampsia, compared to 6.9% of those given placebo. However, the aspirin did increase the risk of abruptio placentae, which makes the idea of treating all pregnant women with aspirin less appealing (Sibai et al., 1993). It is recommended by some for women at high risk for preeclampsia (Sibai et al., 1995).

Cigarette smoking is known to decrease the risk of preeclampsia, but doctors are hardly likely to begin advising smoking during pregnancy. One explanation for this phenomenon is that nicotine appears to play a role in reducing the amount of sFlt1 in the mother's bloodstream. This ameliorates preeclampsia's antiangiogenic effects and does not allow inflammation to cause the mother to develop hypertension and proteinuria. Even if smokers develop preeclampsia, it is usually not very severe. In a clinical trial testing aspirin's effect, 5.9% of nonsmokers developed preeclampsia, compared to 2.7% of those who quit during pregnancy, and 3.7% of those who smoked throughout. The many negative effects of cigarette smoking on both mother and child, though, far outweigh the small shielding from preeclampsia's effects (Sibai et al., 1993; Jeyabalan et al., 2008).

The current treatments for preeclampsia are less than ideal, but experimental treatments may give us some better options. It is important to note that designing preclinical and clinical trials for these treatments can be quite difficult. Animal models are often less than ideal as these animals may have very different placentas than humans. Many of these trials involve animals that do not ever develop preeclampsia. Scientists instead create situations to mimic preeclampsia's symptoms in vivo. Moving on to a clinical trial in humans will only occur after extensive testing. Nobody wants a repeat of the thalidomide disaster, so advancement in pregnancy treatment moves slowly (Sibley, 2017).

In a 2016 study of 28 rats, apelin was used to successfully ameliorate symptoms of preeclampsia. Apelin is a peptide found in the cardiovascular system. Among other effects, it reduces blood pressure in atherosclerosis and encourages angiogenesis. In this experiment, half of the rats served as control (N group), and half of these were given apelin (N+APLN group), an angiogenic factor naturally present in mammalian placentas. Preeclamptic placentas usually have lower apelin than normal. The acceptable rat model of preeclampsia was used on half the rats (PE and PE+APLN); uterine arteries were clamped to prevent adequate blood flow to the placenta, leading to the release of cytokines and debris causing hypertension and proteinuria. Half of these rats were then treated with apelin. The rats given apelin had lower blood pressure and proteinuria than the preeclamptic control, but not as low as the healthy rats. Apelin also increased fetal survival rate and birth weight. One hundred percent of N and N+APLN embryos survived, 25% of PE survived, and 50% of PE+APLN survived. Considering that fetal survival rate for humans with preeclampsia is much better than 25%, it is reasonable to believe that apelin would cause even better survival rates in humans. The effect on preeclampsia's maternal symptoms are also likely to carry over. However, as apelin was only tested on 8 preeclamptic rats, and because rat placentas differ greatly from human ones, much more research must be done before apelin is the drug of choice for preeclampsia (Sibley, 2017; Wang et al., 2017).

Researchers have also recommended mediating the effect of sFlt1 on the mother's body by somehow increasing the levels of VEGF in the placenta. One method of doing so is by injecting adenovirus vectors for VEGF into the placenta. This was done in sheep and guinea pig models, as well as in human placentas in vitro. The increase in VEGF levels mediates the inactivation of VEGF by sFlt1, resulting in an approximately normal quantity of angiogenic factors. This appears to create normal uterine blood flow and cure preeclampsia. The virus vector also does

not appear to cross the placenta and cause other complications. This treatment is extremely promising and is moving towards clinical trial in Europe (Sibley, 2017).

Conclusion

Preeclampsia is a major obstetrical complication still common in the developed world. Its causes are not fully understood, but are largely believed to develop from hypoxic conditions of the placenta. The placenta releases inflammatory factors, causing hypertension and proteinuria for the mother, as well as other side effects. Fetal effects include growth restriction and the negative effects related to premature birth. Risk factors are well-known yet poorly understood, and prophylactic treatments such as aspirin are available. Treatment for preeclampsia and eclampsia now mainly revolve around symptoms, but experiments are underway which will hopefully lead to a greater understanding and more effective treatment for this syndrome.

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