A Practical Understanding of Preeclampsia for a Nurse in a Third World Setting

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Abstract

Preeclampsia is a disease of pregnancy that affects approximately 3-5% of women with child. It is one of the primary causes of mortality in mothers and babies across the globe. The exact cause, pathogenesis, or disease progression is unknown. Therefore, there is no definition of which patients are at risk for developing preeclampsia and what can work as a preventative measure. In high socioeconomic settings where there is good healthcare, standard treatment is established to manage the symptoms and decrease the progression of preeclampsia to eclampsia. However, in more rural, third-world settings of developing countries, caring for patients with preeclampsia is not a straightforward matter. Due to decreased access to health care, low economic status, and lack of education, preeclampsia is often seen yet seldom treated among this population. The discussion below addresses several possible pathophysiological processes of preeclampsia, as well as potential risk factors. The standard treatments of care are then discussed, followed by the evaluation of studies regarding alternative treatments for preeclampsia. The importance of screening pregnant women in developing nations is included. The discussion is concluded by a summary of what caring for preeclampsia in a third-world setting might look like for a missionary nurse.

A Practical Understanding of Preeclampsia for a Nurse in a Third-World Setting

Disease: this word, simply a summation of letters, is one that makes people shiver with horror and dread. Disease causes people to evaluate themselves and look deep into their hearts to what is the meaning and significance of their lives. As Warwick Anderson sums up all too well, disease brings into focus concerns on the way we live our lives, our relationships to community, our environment, the cosmos, and challenges us to explain the purpose of suffering (Anderson, 2000). Disease brings about even more confused questioning and evaluation when it touches the lives of infants and children. For this reason, illnesses that affect infants and the young are often given much consideration, research, and resources in order to give these children a greater chance to live life. However, as sickness and disease involve the tiny intricacies of creation our human minds can never fully comprehend, many diseases have no cure, or even a definitive cause. Preeclampsia is just such a disease. Much research has been poured into searching for a cause for this disease of pregnancy, so a cure might be discovered. However, research is no closer to preventing preeclampsia than when it started.

What is Preeclampsia?

Preeclampsia is a pregnancy-specific disease process that impacts approximately 3-5% of all births. It is one of the primary causes of maternal, fetal, and neo-natal mortality, particularly in low socioeconomic settings and third-world countries (Mol et al., 2016). Traditionally, it is diagnosed when a pregnant woman presents with symptoms of hypertension and proteinuria. If preeclampsia continues untreated, patients often advance to eclampsia, experiencing severe complications. These complications often

involve seizures, liver rupture, pulmonary edema, stroke, or kidney failure (Mol et al., 2016). Preeclampsia also affects the growth of the baby, as it affects uterine perfusion. Due to hypertension involved in preeclampsia, blood flow to the fetus is altered, leading to fetal growth restriction and preterm birth, either spontaneous or through iatrogenic delivery. In addition to impacting the fetus during pregnancy, children who are born to mothers with preeclampsia can be permanently impacted as they have a high risk of bronchopulmonary dysplasia and cerebral palsy (Mol et al., 2016). These complications and others are caused by altered blood flow to the fetus during pregnancy and by preterm birth, as many preterm neonates are small for gestational age.

Diagnostic Criteria

The classic diagnostic criteria for a pregnant woman with preeclampsia were established by the International Society for the Study of Hypertension (ISSHP) in 2014. The ISSHP defined preeclampsia as de-novo, or new, hypertension that presents after 20 weeks gestation combined with protein in the urine (>300 mg/day), neurological or hematological complications, maternal organ dysfunction, renal insufficiency, uteroplacental dysfunction, liver involvement, or fetal growth restriction (Mol et al., 2016). As preeclampsia has many different presentations of the disease, the definition has been changed to no longer require proteinuria in the definition. Therefore, preeclampsia can now be split into two separate categories: proteinuric and non-proteinuric. Hypertension is defined as a systolic blood pressure that is higher than 140 mmHg, or a diastolic blood pressure greater than 90 mmHg. To be diagnosed with hypertension, the patient must meet these qualifications at two different blood pressure readings that are

taken at least 4-6 hours apart. The patient should be seated and in an upright position, or in a left lateral recumbent position (Mol et al., 2016). Whereas hypertension is very typical of preeclampsia, proteinuria is not always a clear indicator of the disease. Women with proteinuria tend to have high antenatal blood pressures, deliver at an earlier stage of gestation, and often need an operative delivery (Mol et al., 2016).

Pathophysiology of Preeclampsia

The exact pathophysiological mechanisms that produce the clinical symptoms of preeclampsia are unknown. However, there have been numerous conjectures on how the disease progresses at the tissue level. It is thought the clinical symptoms of the disease during pregnancy represent later stages of the disease progression. Therefore, the pathophysiological changes in the body most likely begin taking place long before it is realized. The pathology of preeclampsia is thought to most likely originate in the placenta during the development of the uteroplacental circulatory system. One reason for this thought is that the delivery of the fetus and the placenta at birth is the one and only cure found for the disease process (Moncrieff, 2018). Therefore, since the disease process is resolved by the delivery of the baby and the placenta, it most likely starts at the beginning stages of gestation.

Alteration in Angiogenesis

Under normal circumstances in the body of the mother, the establishment of uteroplacental circulation involves maternal spiral arteries transforming from small-diameter, high resistance arteries into low-resistance, high-volume vessels that can fully perfuse the intervillous space. This transformation begins at approximately 8-10 weeks

gestation, when cytotrophoblasts enter into the wall of the uterus and take on some of the characteristics of the cells that make up blood vessels (Moncrieff, 2018). Cytotrophoblasts do this by aiding in increasing the levels of proteins that make up endothelial and smooth muscle cells, and slightly decreasing levels of proteins that make up epithelial cells. This leads to cytotrophoblast formation that looks similar to an endothelial, or smooth muscle phenotype. This results in the 'vascular mimicry' that is seen in preeclampsia as cytotrophoblasts invade the uterine wall. As they travel through the stroma of the uterine wall, these cells cross into walls of the maternal spiral arteries and move up these blood vessels. As the cytotrophoblasts work their way up the spiral arteries, they replace the endothelial lining and some parts of the smooth muscle layer (Moncrieff, 2018). The loss of these muscle layers in the maternal spiral arteries changes the vessels from thin, small-diameter vessels into high-capacity, low-resistance arteries. Since the cytotrophoblasts remove many neuromuscular and baroreceptor components of these spiral arteries, the vessels are no longer very responsive to modulators, allowing these arteries to sustain a low-velocity, but high-volume flow to the intervillous space (Moncrieff, 2018). In this way, the mother's body naturally transitions to providing enough blood flow to the developing fetus.

In preeclampsia it is thought this transformation of the spiral arteries remains incomplete. In the pathology of preeclampsia, cytotrophoblasts are unable to fully migrate into the maternal spiral arteries. Therefore, many of the mother's blood vessels are incompletely transformed or are not transformed at all (Moncrieff, 2018). In normal uteroplacental circulatory transformation, the changes to the spiral arteries extend into the

myometrium of the arteries. In preeclampsia, however, the myometrial portion of many of the vessels is unaltered. Therefore, mothers with preeclampsia retain arteries with thick muscular walls and a highly functioning adrenergic nerve supply. These vessels remain small-diameter, high-resistance arteries that provide a low-volume, high-pressure flow to the placenta (Moncrieff, 2018). In addition, intact neurological components and baroreceptors allow the nerves of these vessels to greatly impact the blood flow to the placenta. This overall incomplete transformation of the maternal spiral arteries causes decreased perfusion to the placenta and a high blood pressure flow that is subject to vasoconstriction in response to the mother's systemic responses. This leads to placental ischemia and lack of perfusion, and therefore oxidative stress. This is thought to result in the release of cytokines and anti-angiogenic proteins into the mother's blood, which alters vascular growth and permeability (Moncrieff, 2018). In the preeclamptic mother, the high-pressure blood flow that perfuses the intervillous space leads to syncytiotrophoblast particles being released into the mother's blood. These by-products of placental stress cause the maternal signs of endothelial damage, increased vascular resistance, and increased coagulation and hemostasis (Moncrieff, 2018).

Alterations in Immune Adaptation

Yet another theory on the pathogenesis and development of preeclampsia is based on the significant and detailed immune adaptations that take place in the mother's body during pregnancy (Alrahmani & Willrich, 2018). The goal of these immune adaptations is to maintain a competent immune system in the mother in order to fight off disease, while preventing rejection of the growing fetus. This complex phenomenon is known as

maternal-placental immune tolerance. The changes that take place in the mother's body are multi-faceted. The immune response cytokine profile gradually changes from T-helper 1 to T-helper 2. The activation of T cells in general is suppressed overall, and with the help of the enzyme indoleamine-2,3-dioxygenase, the production of natural killer cells is decreased and substituted with the manufacturing of macrophages and syncytiotrophoblasts. The amount of granulocytes in the mother's blood stream increases at the same rate as the levels of acute-phase proteins. In summary, the innate immune system is enhanced in pregnancy, while components of the adaptive immune system are suppressed. The complement system is also a critical part of the innate immune system (Alrahmani & Willrich, 2018). The complement system acts to regulate tissue homeostasis. There are three separate pathways that play a part in the complementary system. These pathways are the classical, alternative, and lectin/mannose-binding pathways. Each pathway is induced by different threats to the body's homeostasis or pathogenic agent. The classic pathways are induced by an antigen-antibody immune complex or a C-reactive protein (CRP). The alternative pathway is always active to some degree at low levels, as it plays a role in the general health and immune processes of the body. Finally, the lectin/mannose-binding pathway is activated by mannose-containing bacteria (Alrahmani & Willrich, 2018). All three pathways converge into a C3 mediated loop. The activation of the enzyme C3 by C3 convertases leads to the binding and tagging of foreign cells or bacteria. This is how the complement pathways regulate the innate immune system.

One well-accepted theory regarding the pathogenesis of preeclampsia as related to the immune system is that of immune maladaptation. It is the idea that the normal immunologic changes a mother's body goes through during pregnancy are altered by a factor in the placenta that leads to an increased adaptive immune system and decreased changes in the innate immune system. This therefore would lead to an increased immune response against the fetus, which is an allograft that contains paternal antigens. The innate immune system of the mother would experience only slight alterations, leading to a heightened immune response during pregnancy. This would cause inflammation, altered angiogenesis, and increased endothelial activation that are seen in preeclampsia (Alrahmani & Willrich, 2018). Let it be understood, however, the precise pathophysiological mechanisms of preeclampsia and their effect of endothelial dysfunction and hypertension are still unclear and undergoing extensive research.

Risk Factors for Developing Preeclampsia

As there is no definitive cause for preeclampsia, treating, preventing, and identifying at-risk populations often is a complicated matter. In a study conducted in the U.S. on clinical risk factors for preeclampsia in the 21st century, two thousand six hundred thirty-seven women were included in the analysis (Pare et al., 2014). Over the process of the study, seven hundred ninety-three were excluded for the following reasons: sponsor request or decision, protocol deviation, participant missed two study visits or more, participant withdrew consent, incomplete delivery data, spontaneous or induced termination of pregnancy, or transfer of care. The women involved in the study were recruited at three different hospitals from three different areas of the country (Pare et al.,

2014). Out of the women who finished the study, one hundred sixty-five (6.2%) had a preexisting case of chronic hypertension. The rate of hypertensive disorders that developed over the progression of pregnancy were as follows: three hundred seventy-eight (14.3%) developed gestational hypertension, two hundred thirty-seven (9.0%) developed preeclampsia, one hundred ninety-four (7.4%) developed severe preeclampsia, thirty-nine (1.5%) developed a syndrome consisting of hemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome), and one patient (0.04%) progressed to eclampsia. The mean gestational delivery age of the patients who did not develop preeclampsia was 38.8 weeks (standard deviation of 2.0), while for women who did develop preeclampsia, the mean gestational age at delivery was 37.0 weeks (standard deviation of 2.7) (Pare et al., 2014). In the discussion of this study, it was found many of the previously and commonly reported risk factors for preeclampsia proved to be true. Medical conditions such as chronic hypertension and diabetes have been shown to be potential risk factors for preeclampsia. Multiple gestation, African American race, use of assisted reproductive techniques, prior cases of preeclampsia, nulliparity, and obesity were also confirmed to be independent predictors of preeclampsia and severe preeclampsia. However, in contrast to previous studies performed, the factor of advanced maternal age was not associated with an increased risk for preeclampsia. In addition to this, being overweight or obese was the most prevalent risk factor for both mild and severe preeclampsia in the patient population involved in the study (Pare et al., 2014).

Preventative Risk Factors of Preeclampsia

This study particularly highlighted risk factors that should help in affecting and guiding prevention of preeclampsia in a health care perspective. Until recently, preeclampsia has been treated from a purely pharmacological standpoint since not much is known about it. This is partly resultant to clinical prediction rules and scoring having often been limited to nonmodifiable risk factors such as medical conditions, nulliparity and race. Therefore, there was not much that could be done to prevent preeclampsia. However, the above discussed study highlights one modifiable risk factor that represented the greatest risk factor: obesity. Since it is modifiable, preventive measurements should be implemented. Given the obesity-attributable risk in the study, great efforts to prevent preeclampsia should focus on prevention of obesity in women who are pregnant or even of reproductive age. The percentage of cases of preeclampsia in the study that could be associated with obesity was 64.9% of all the cases of preeclampsia and severe preeclampsia (Pare et al., 2014). From a clinical perspective, the results of the study highlight the importance of discussing weight with women who are of reproductive age and possibly including a weight reduction component in pre-conceptional counseling for obese and overweight women. This is due to results suggesting that even a modest reduction in BMI before conception could drastically decrease the individual's risk of preeclampsia (Pare et al., 2014).

Treatment for Preeclampsia

As has been previously mentioned, much of the focus of treating preeclampsia has been on pharmacologic treatment over the years. Since preeclampsia's primary trait is

hypertension, the National High Blood Pressure Educations Program (NHBPEP) Working Group Report has focused on targeting high blood pressure treatment in preeclamptic patients. As summarized earlier, mild hypertension is a systolic blood pressure (SBP) of 140-150 mmHg or diastolic blood pressure (DBP) of 90-109 mmHg. Severe hypertension is defined as an SBP >160 mmHg or DBP of >110 mmHg (Berzan, Doyle, & Brown, 2014).

Standard Treatments of Preeclampsia

Guidelines for treatment according to the American College of Obstetricians and Gynecologists (ACOG) do not recommend antihypertensive medication for mild preeclampsia (SBP < 160 mmHg or DBP <110 mmHg). However, antihypertensive therapy is recommended for women with preeclampsia who have a sustained SBP of >160 mmHg or DBP of >110 mmHg (Berzan et al., 2014). Although this disease is one of the most common complications of pregnancy all over the world, there are a limited number of medications that are used regularly as standards of treatment.

Methyldopa and Labetalol. First-line agents for hypertension in preeclamptic patients include methyldopa and labetalol. Methyldopa is the drug of choice for hypertension in pregnant women, as its safety and efficacy have been shown through many studies. There are some concerns with side effects of depression, hepatic disturbances, and hemolytic anemia. It also may not lower blood pressures adequately or fast enough for some preeclamptic patients; therefore, methyldopa should not be used in emergent situations (Berzan et al., 2014). Labetalol is also a first line therapy. Its safety is similar to the above-mentioned medication, but labetalol may often be more efficacious

than methyldopa. However, it may be associated with possible fetal growth restriction, and when given in large doses, neonatal hypoglycemia may be seen. Labetalol then is not the drug of choice over methyldopa due to the side effects (Berzan et al., 2014). Second-line agents for hypertension in preeclamptic patients include nifedipine, verapamil, and clonidine. For emergency treatment in preeclampsia, intravenous (IV) hydralazine, labetalol, and oral nifedipine may be used (Berzan et al., 2014).

Magnesium Sulphate. Magnesium sulphate also plays a very crucial role in the management of preeclampsia and eclampsia. For more than a century, magnesium sulphate (MgSO4) has been the anticonvulsant of choice to prevent and control eclamptic fits. Historically, the total dose of magnesium sulfate used in the treatment of preeclampsia and eclampsia would be gradually increased from 2g/24 hours to as high as 54 g/24 hours with the belief the increase in titration would increase the clinical efficacy (Okusanya et al., 2015). All studies have shown convulsions are controlled well with magnesium sulphate, despite the considerable alterations in the regimen, route of administration, and total dosage used (Okusanya et al., 2015).

The goal in the administration of magnesium sulphate is to achieve physiological magnesium (Mg2+) homeostasis in the patient. A type of cation, Mg2+ is found all throughout the body. It works in the activation processes of many enzymes, including those of energy metabolism. It is critical cation in the production of ATP, therefore playing a crucial part in the neurological stability of a patient. Women who are pregnant generally maintain normal levels of Mg2+, with only minor fluctuations over the forty weeks of gestation. In preeclampsia, however, pregnancy often continues with normal

Mg2+ levels until generally the 32nd and 33rd weeks of gestation. This cation's levels decline at this stage until delivery, with hypomagnesemia at delivery seen in preeclampsia (Chiarello et al., 2018).

Magnesium sulphate is an inorganic salt that is administered for these patients. This salt contains Mg2+, oxygen, and Sulphur. Free Mg2+ concentration in maternal blood is 0.75 mmol/L and 0.83 mmol/L in fetal blood in normal pregnancies. However, in preeclamptic pregnancies, the value in maternal blood decreases to 0.66 mmol/L and increases to 1.01 mmol/L in fetal blood (Chiarello et al., 2018). The exact impact of the increased of Mg2+ levels in fetal blood is unknown at the time, as there is not a clear explanation for the accumulation of Mg2+. It is universally acknowledged the beneficial effects of Mg2+ administration are unparalleled, as they mitigate the potential and associated complications of preeclampsia. However, there is not a clear understanding as to the potential mechanisms of action of the cation. There are many suggestions as to how magnesium sulphate alters the fetoplacental vascular function. These include the magnesium sulphate impacting altered function of Mg2+ transporters, membrane receptors, inadequate generation of nitric oxide (NO), and an inflammatory and oxidative state (Chiarello et al., 2018). Parenteral administration of Mg2+ salts works primarily for the patient with severe preeclampsia to guard prophylactically against eclampsia and seizures. Although the specific mechanism of Mg2+ is not understood in preeclampsia, studies show that lower Mg2+ levels are seen in the red blood cell membranes of patients with preeclampsia in contrast to women with normal pregnancies (Chiarello et al., 2018).This consistent trend in altered Mg2+ levels in both mother and baby is considered

to be a predisposing factor in the pathogenesis and development of preeclampsia. Clinical practice dictates that maintaining a maternal plasma Mg2+ level higher than the normal range of 0.75-1.0 mmol/L is required to reduce the chance of advancing from preeclampsia to eclampsia (Chiarello et al., 2018). In addition to this, overall levels of Mg2+, calcium, creatinine, and proteins, as well as maternal bodyweight, are crucial to monitor and keep at safe levels in order to achieve a safe and effective delivery (Chiarello et al., 2018).

In planning care for a pregnant mother, antihypertensive medication and magnesium sulphate are the standards of care. However, these standards of care are those that have been determined to work in first world countries in the presence of primary health care providers. In many areas of the world where there are no primary health providers, there are great challenges in the prediction, prevention, and management of preeclampsia (Osungbade & Ige, 2011). The cost and accessibility of such medications as those which are generally prescribed for treatment of preeclampsia make treatment and management of the disease very difficult. Treatment in these countries consists of the following: prenatal care, a timely diagnosis, proper management, and a timely delivery. The impact of preeclampsia is felt significantly in low income and third world areas since medical interventions are often ineffective due to the late identification and treatment of cases of preeclampsia (Osungbade & Ige, 2011).

Screening for Preeclampsia

Prevention of this disease process requires availability of predictive measures for those at a high risk for developing the disorder. Although countless clinical and

biochemical tests have been devised for those at risk, most remain quite unrealistic for common use in developing countries. At the current time, there is no single reliable and cost-effective screening test for preeclampsia that can be recommended for use in developing countries (Osungbade & Ige, 2011).

Screening in a Third-World Country

The primary way to efficiently and accurately screen pregnant women for preeclampsia is the establishment of easily accessible, functional health care systems. In the majority of developing countries, particularly in areas like Africa and Southern Asia, there are three levels of delay that result in limited health care access (Osungbade & Ige, 2011). The first is delay in the decision to seek care. This delayed response at the patient level is often a result of insufficient information on signs and symptoms of the disease process, as well as inadequate information on where and when to seek help from a facility. Poverty, corrupt power, and the rising cost of health care lead to often fatal delays in care seeking (Osungbade & Ige, 2011). The second level is delay in reaching the health care facility. Lack of access to quality care is often one of the main obstacles to reducing maternal and neonatal mortality in low income countries. This is often in part due to the placement of the health care facilities in relation to the location of villages, distance, and lack of transport to the areas where the health care providers are located. For example, in Nigeria, up to 50% of rural women live over 5 kilometers from the nearest hospital. Most of these women have no way of reaching the hospital except by walking – even when they are in labor. Therefore, most of the pregnant population of these villages do not make it to the hospital during delivery. For a woman with

preeclampsia, this lack of treatment could progress to eclampsia, leading to death for both the mother and baby. This could all take place without the nearest health care facility knowing anything about the mother and her baby (Osungbade & Ige, 2011). Finally, the third level of delay is delay in health service provision. In many health facilities in the third world setting, health care insurance is in the teething stage, making it impossible for both the poor and the insured to obtain care during emergent situations. Identified barriers include the attitudes of many of the health service providers as well as the perceived poor quality of care. These barriers are increased by the lack of trained personnel and the extreme lack of equipment and supplies. In many cases of preeclampsia in a third world hospital, studies have shown magnesium sulphate wasn't routinely administered if it was available. Another consideration is that the use of magnesium sulphate is often limited solely to teaching hospitals. The overall lack of availability of the drug and appropriate health personnel as well as equipment to administer it frequently raises obstacles for treating preeclamptic women (Osungbade & Ige, 2011).

Using CLIP in a Rural Setting. Globally, hypertensive diseases of pregnancy, two of the top ones being preeclampsia and eclampsia, are the primary causes of maternal and neonatal mortality. Therefore, managing preeclampsia and eclampsia in less modern and first world settings is a priority when evaluating world-wide health initiatives for mothers and babies around the world (Khowaja et al., 2015). Hypertensive disorders of pregnancy (HDP), which include pre-eclampsia and eclampsia, complicate over 10 million pregnancies worldwide each year. This results in 76,000 maternal and 500,000 neonatal deaths. The large majority of these deaths (>99%) take place in low- and

middle-income countries (LMICs), particularly in South Asia and in Sub-Saharan Africa (Khowaja et al., 2015). The Community Level Interventions for Preeclampsia (CLIP) trial evaluates a package of care that could be applied at a community level in addition to being implemented through hospitals and primary health care centers. This package directly seeks to address and intervene against the three levels of delay mentioned above (Osungbade & Ige, 2011). If applied appropriately, maternal and perinatal complications and potential deaths could be reduced drastically in village communities and the third world setting. As discussed above, management of preeclampsia mainly focuses on interventions in a primary health facility. These include antihypertensive therapies, anticonvulsant therapies, and timed deliveries. However, thousands of women in LMICs are unable to reach facilities that monitor and provide treatment during delivery for those with preeclampsia. These women in hard-to-reach areas suffer disability and often lose their lives due to a lack of resources for screening and identification of HDP as well as triage and transport availability. In a first world country, these clinical processes are at the reach of almost every woman, allowing a usually safe and monitored delivery (Khowaja et al., 2015).

How CLIP Works. The goal of the CLIP trial is introducing evidence-based interventions at community levels through the availability and presence of primary health care providers. Specifically, the CLIP intervention involves three levels:

I. Community engagement

II. Provision of HDP-oriented antenatal care through household visits

III. Use of the CLIP package for women with a CLIP ‘trigger’

(Khowaja et al., 2015)

The community engagement level seeks to include all women, particularly those who are currently pregnant or could become pregnant. It also includes the decision makers of the households (husbands, father-in-laws, or brothers) and community leaders. Community engagement involves teaching these groups about preeclampsia, its origins, signs, symptoms, and potential consequences. It seeks to inform the community about potential cost for transport and treatment and what that would look like (Khowaja et al., 2015). The second step, provision of HDP-oriented antenatal care, is done through household visits to pregnant women. Community healthcare providers (cHCPs) would travel from home to home with the proper equipment, screening women for potential risk factors or symptoms of preeclampsia or other HDPs. Since the women and families will have been previously informed as to what signs and symptoms to look for, in addition to the potential complications that could arise if left untreated, this step is expected to be received with cooperation and understanding since community involvement would already be achieved (Khowaja et al., 2015). Finally, the third step aims to provide a CLIP package for women who had a CLIP 'trigger.' This CLIP package will include oral antihypertensive therapy or intramuscular magnesium sulphate. Administration of this package will be accompanied by appropriate education as to the use of these medications. Appropriate referrals to a comprehensive emergency obstetric care facility will also be provided, in addition to what transport to the facility would require (Khowaja et al., 2015). The cHCPs would regularly assess and check up on these women approximately every 4 weeks at minimum. These visits could be done either in the home, or at a primary

health care facility, if there is one close by. The cHCPs are trained specifically to screen the women for symptoms, using culture and country specific pictograms. They also take the woman's blood pressure each visit, noting trends or signs of hypertension. The cHCPs also check urine for protein at the first visit using a dipstick, and then on following visits if the patient's systolic blood pressure is over 140 mmHg. This screening process allows for consistent care and early diagnosis of preeclampsia. Women with preeclampsia can then be referred to facilities with specific care or given CLIP packets to take during pregnancy (Khowaja et al., 2015).

Alternative Treatments for Preeclampsia to Use in Third-World Setting

In addition to introducing CLIP interventions in rural and third world settings to proactively screen and manage patients with preeclampsia, there has been a significant amount of research performed on alternative therapies and treatments, other than that of antihypertensive medications and magnesium sulphate (Atallah et al., 2017).

Preventing Preeclampsia with Aspirin

Aspirin is currently the most widely prescribed medication for the prevention of cardiovascular diseases and complications. However, aspirin may also be indicated for usage during pregnancy for women who have preeclampsia. Large meta-analyses have reviewed individual patient data as well as anonymous surveys, demonstrating aspirin is often very effective in preventing preeclampsia in those patients who are at a high risk for developing the disease (Atallah et al., 2017). Aspirin has been shown to be particularly helpful in preventing preeclampsia among those patients who have a history of preeclampsia. Guidelines regarding the use of aspirin for preeclampsia vary greatly from

country to country. Types of screening, target population, and the prescribed dosage of aspirin in preventing preeclampsia are still matters of heated debate (Atallah et al., 2017).

Pathophysiology. To understand the use of aspirin for the treatment of preeclampsia, the pathophysiology of the disease must be reviewed. In this disease, the platelet TXA2 increases significantly, while prostacyclin levels drop sharply due to changes in the mother's body during pregnancy. Around the 13th week of gestation in women who are at a high risk for preeclampsia, this imbalance of platelet TXA2 and prostacyclin is visible. TXA2/PGI2 imbalance can be reversed within 2 weeks of treatment with a low dose aspirin regimen (Atallah et al., 2017). Aspirin acts by inhibiting TXA2 secretion, and thus platelet aggregation. However, aspirin doesn't alter the secretion of endothelial prostacyclin, correcting the increase of TXA2 and decrease of PG12. This correction favors maternal systemic vasodilation, resulting in decreased hypertension and increased blood flow to the uterus and therefore the fetus. More recent understanding of the impact of angiogenic factors on placental hemodynamics in women with preeclampsia has led to the study of the impact of aspirin on the secretion of these factors in the placenta (Atallah et al., 2017). In situations of decreased blood flow, and therefore hypoxic conditions for the fetus, aspirin inhibits the production of sFlt-1 in human trophoblasts. This produces proangiogenic results. The factor sFlt-1 is the common type of vascular endothelial growth factor (VEGF) seen in pregnancy. When it binds to circulating placental growth factor and other types of VEGFs, it behaves as a concentrated anti-angiogenic factor. Patients with preeclampsia or who have a history of preeclampsia have high levels of sFlt-1 in their plasma. Therefore, it is thought that sFlt-1

is responsible for the angiogenic imbalance seen in the pathophysiology of preeclamptic patients (Atallah et al., 2017). Since aspirin binds to this factor, angiogenic growth is promoted, increasing blood flow to the developing fetus and decreasing hypertension in the mother.

Controversy with the Use of Aspirin. Although numerous and continual studies have been performed on the potential use of aspirin in preeclamptic mothers, the debate continues. Even though aspirin does decrease some of the anti-angiogenic results of the factors in the patient with preeclampsia, aspirin also crosses the placental barrier and alters TXA2/PGI2 balance and platelet aggregation of the fetus (Atallah et al., 2017). After it perfuses into the placental cotyledon, aspirin transfers over into the fetal-placental circulation during the first 5 minutes. Laboratory tests performed on blood from the umbilical cord of pregnant women who are taking low-dose aspirin reveal a sharp drop in platelet TXA2. Although this acts to decrease hypertension in mothers, there have been sporadic cases reported of intracranial hemorrhage in premature infants and low-weight fetuses, in addition to early closure of the arterial canal (Atallah et al., 2017). Therefore, it is presumed that aspirin treatment may lead to a decrease in fetal platelet aggregation, resulting in an increased chance of utero cerebral hemorrhage. Low dose aspirin administration doesn’t seem to introduce a teratogenic risk in the first trimester, but it has been advised aspirin treatment should be discontinued around 36 weeks of gestation to decrease risks of hemorrhage in mothers and babies (Atallah et al., 2017).

Preventing Preeclampsia with Calcium Supplements

Pathophysiology. Yet another possible alternative treatment for preeclampsia that has been investigated is calcium. Preeclampsia is often characterized by inflammation cascades as well as endothelial activation (DeSousa et al., 2016). This results in the multi-organ disease that we see in pregnancy. A placental factor that consists of deported trophoblastic debris is increased in the blood of mothers with preeclampsia. Deported trophoblastic debris is seen in the blood of mothers in all pregnancies, but increased levels in preeclamptic mothers is suggested to be from the nature of increased cell death in the syncytiotrophoblast. In normal pregnancies, the death of syncytiotrophoblasts are more apoptosis-like, while in preeclampsia, cell death is more necrotic (DeSousa et al., 2016). Other studies point to placental factors that are related to the process of angiogenesis, such as sFlt-1, PIGF, and sEndoglin, are involved in the pathogenesis of preeclampsia. Studies show that levels Flt-1 in the maternal blood flow are directly proportional to the amount of trophoblastic debris. This trophoblastic debris from a placenta that is preeclamptic has been treated with preeclamptic sera that is dangerous and toxic. When this trophoblastic debris is phagocytosed, it leads to endothelial cell activation and increased levels of inflammatory cytokines (DeSousa et al., 2016). Both processes are seen in those with preeclampsia.

The alternative treatment to prevent or reduce the risk of preeclampsia is to provide an antenatal treatment of calcium supplementation. There is currently limited evidence of low-dose calcium supplementation reducing preeclampsia, requiring larger and higher quality trials to be performed before a definitive result is can be determined

(DeSousa et al., 2016). Calcium has been shown in these limited studies to decrease the activation of endothelial cells in the in vitro setting when the activation of these cells was caused by necrotic trophoblastic debris, preeclamptic sera, and interleukin (IL)-6. These factors all are seen in increased levels in preeclamptic patients, leading to increased activation of endothelial cells. Studies have been specifically targeted at whether the addition of a calcium supplement at clinically acceptable doses would prevent or decrease the activation of endothelial cells that were induced by toxic levels of trophoblastic debris (DeSousa et al., 2016).

Results of Studies. Results from a study which took blood samples from both preeclamptic women and normotensive pregnant women of the same gestation times were compiled, studying culture inserts into placental explant cells. The resulting endothelial cell activation was then closely monitored, after being treated by debris from trophoblasts. Results showed calcium supplementation decreased or prevented the activation of endothelial cells by the trophoblastic debris in the placenta from preeclamptic patients (DeSousa et al., 2016). When the trophoblastic debris from cells from a preeclamptic placenta were introduced, the expression of ICAM-1 by the cells was increased as well as the number of monocytes that adhered to the endothelial cells. This resulted in increased inflammation. However, when calcium was introduced to the endothelial cells, at the same time as the trophoblastic debris of preeclamptic cells, the increase in ICAM-1 and monocyte adhesion was reversed (DeSousa et al., 2016). Calcium supplementation also prevented activation of endothelial cells that was caused by increased levels of IL-1. These increased levels of IL-1 increased levels of cell-surface

endothelial ICAM-1. However, at the introduction of supplemental calcium treatment, this reactive chain was reversed. Therefore, in this vitro study, as in many others, it can be seen calcium supplements can decrease the activation process of endothelial cells in the presence of trophoblastic debris from the placenta of preeclamptic patients, as well as normal placenta that were treated with preeclamptic sera (DeSousa et al., 2016). This suggests the mechanism by which calcium acts in reducing the risk of a patient developing the disease of preeclampsia during pregnancy.

Meta-analysis of many studies looking into calcium supplementation as a potential treatment for preeclampsia show calcium treatment decreases the risk of preeclampsia by about fifty percent (DeSousa et al., 2016). This is especially true in the case of women with previous low calcium intake levels. Calcium appears to exert its mechanism of action, at least in part, by decreasing endothelial action that is caused by the toxic trophoblastic debris from preeclamptic placenta. In this way, it seems to reverse one of the direct pathways that leads to the development of increased blood pressure and inflammation seen in preeclamptic patients. Anti-inflammatory effects appear to be the result of calcium supplementation (DeSousa et al., 2016). Although the direct cause and pathogenesis of preeclampsia is unknown, calcium supplementation appears to decrease the risk or at least the exacerbation of some of the pathways that lead into preeclamptic conditions.

Conclusion

For a third-world focused nurse, standard treatments and standards of care such as magnesium sulphate may not always be readily available. However, for women who have

a history of preeclampsia in past pregnancies or who have pre-gestational hypertension, supplemental calcium or an increase in high calcium foods may potentially decrease chances of developing the disease of preeclampsia. If not completely preventing the disease, calcium may decrease the intensity of the disease as it would decrease some of the inflammatory pathways. The use of aspirin could also be potentially considered as an alternative treatment for preeclampsia.

The current interventions that have been studied and established to have the most clinical significance in diagnosing, preventing, and treating women with preeclampsia or eclampsia are diagnostics, transferring to a hospital, magnesium sulfate use, and cesarean section/labor induction (Goldenberg et al., 2014). Typically, diagnosis of preeclampsia using blood pressure screenings for high risk or hypertensive patients and screening for proteinuria have proved to be most helpful in determining which patients need further care as relates to preeclampsia. Either these patients can be transported to a hospital, or proper medical care can be brought into their area of residence to provide a timely and safe delivery through cesarean section or through induction of labor. Since the only determined cure for preeclampsia is the delivery of the baby, thereby ending this disease through the ending of the pregnancy, mothers with severe preeclampsia often need an induction of labor to ensure safety for both the mother and baby. However, this early delivery often leads to slightly preterm infants. This may necessitate the baby spending some time in the Neonatal ICU, requiring the mother and/or the baby to be sent to a nearby hospital. For preeclamptic mothers who can wait until their full gestation time is finished to deliver, magnesium sulfate can be brought in to be administered during the

delivery process. Preeclamptic mothers can also be taken to a hospital to have this treatment administered to delay the progression of preeclampsia to eclampsia, reducing both maternal and fetal mortality (Goldenberg et al., 2014). The highest priority, then, for the nurse in a third world culture providing treatment for pregnant mothers is to provide screening for this patient population. If proper screening is performed on all pregnant mothers, especially those at a high risk for preeclampsia that have a history of preeclampsia or who are obese, this will allow for early diagnosis and appropriate planning of treatment. Currently, there is not enough research completed on use of aspirin in prevention of preeclampsia to suggest that for standard of care. Although it cannot be decisively concluded whether calcium supplementation prevents preeclampsia, providing healthy nutrition for pregnant mothers, including calcium supplementation, is a standard of nursing care for this patient population. These suggestions may lead a nurse in a third world setting to better prepare for treatment of preeclampsia.

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