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Abstract

- **Introduction:** Preeclampsia during pregnancy warrants therapy with low dose aspirin. The purpose of this review is to investigate if these women are at increased future risk for cardiovascular morbidity and mortality, and if aspirin therapy prevents future cardiovascular events.
- **Research Questions**: Do women who had preeclampsia during pregnancy have increased future cardiovascular morbidity and mortality?
- Does continued aspirin use in postpartum women, who had preeclampsia during pregnancy, decrease future cardiovascular morbidity and mortality?
- **Research Methods:** Literature review was conducted utilizing CINAHL, Dynamed plus and PubMed databases.
- **Discussion**: Many studies have found that preeclampsia does increase risk of cardiovascular morbidity and mortality, but this difference is not statistically significant until later decades in life. There is also new evidence that the risks of bleeding from prophylactic aspirin therapy outweigh the benefit of decreasing cardiovascular and ischemic events. Based on this information, it is prudent to further research and study this group and stratify their risk as well as researching if there is a better modality upon which to provide prophylaxis with lower risk than benefit.

- **Keywords:** *Aspirin, Preeclampsia, Effect on endothelium, post-partum, future cardiovascular risk*

Introduction

Approximately 3-7% of pregnancies are affected by preeclampsia (Sarma, et al, 2016). These pregnancies are higher risk due to the hypertensive effects on the mother and fetus. There are recommendations for preeclamptic women to take 81 mg aspirin, daily, for prevention of negative fetal and maternal outcomes. Hypertension leads to increased cardiovascular morbidity and mortality (Sutters, 2018). Currently, there is a lack of evidence for treatment beyond the post-partum period. This review investigates if continued aspirin therapy helps to reduce future cardiovascular morbidity and mortality in patients who were diagnosed with preeclampsia during their pregnancy.

Statement of the Problem

Preeclampsia involves a hypertensive state, which increases the shear against the endothelium of blood vessels. This predisposes these women to thrombotic and ischemic events. This problem is two-fold. One, we must understand if this group is at increased future risk of cardiovascular morbidity and mortality. Two, is there a treatment that decreases this risk. This knowledge holds the potential of revealing a population in which we can intervene to produce better cardiovascular outcomes.

Research Questions

1. Do women who had preeclampsia during pregnancy have increased future cardiovascular morbidity and mortality?
2. Does continued aspirin use in postpartum women, who had preeclampsia during pregnancy, decrease future cardiovascular morbidity and mortality outcomes?

Literature Review

Preeclampsia effect on endothelium

•Chambers et al. (2001) conducted a study designed to extrapolate maternal versus placental factors contributing to the development of preeclampsia.

•Heidema et al. (2015) investigated if having history of preeclampsia versus obesity had a larger impact on the development of metabolic syndrome later in life.

- They found the incidence of developing metabolic syndrome was statistically significant in those with history of preeclampsia, compared to those who were obese (P<0.001).

•Spaanderman et al. (2005) found that formerly preeclamptic women had a 15% increase in platelet responsiveness, demonstrating endothelial dysfunction to some degree.

- They hypothesize that endothelial shear from the transient hypertension of preeclampsia increases the number of presensitized platelets, contributing to the hyperactive platelet activity of these patients.

Aspirin effect on endothelium

•Hashemi et al. (2016) utilized flow-mediated brachial artery dilation, in a triple-blind randomized control trial, to evaluate how aspirin affects endothelial function of preeclamptic patients following pregnancy.

- They found antioxidant effects of aspirin decrease oxidative injury to the endothelium, decreasing platelet activation.

•The evidence by Hashemi et al. (2016), and Spaanderman et al. (2005) demonstrate that aspirin decreases platelet responsiveness by more than one mechanism.

- Decreased endothelial shear and platelet response.

Long term cardiovascular outcomes

•Bokslag et al. (2017) and Funai et al. (2005), discovered formerly preeclamptic women are at increased future cardiovascular morbidity and mortality, starting in the 5th and 3rd decades (respectively) following delivery.

- Bokslag et al. (2017) found 42% of their formerly preeclamptic subjects met their defined criteria to require early preventative measures, compared to their counterparts (P<0.0001).
- Funai et al. (2005) had results showing in 24-36 years of follow up is when the risk of death more than doubled in women who were preeclamptic in the past.

•Grandi et al. (2017) found formerly preeclamptic women were at higher risk of developing cardiovascular disease later in life, demonstrated by a hazard ratio of 2.2, and 95% confidence interval.

•Leslie et al. (2016) conducted a well-defined meta-analysis in which the literature shows formerly preeclamptic women have a 2x increased risk of developing cardiovascular disease and mortality.

- This risk is further increased with gestation longer than 37 weeks. (RR, 0.98; 95%CI, 0.5-1.92)

•Wikstrom et al. (2005) also found statistically significant increase in future cardiovascular disease.

- Wikstrom et al. (2005) utilized IRRs and 95% CI for statistical analysis and the adjusted IRR for ischemic disease in women with hypertension during multiple pregnancies was statistically significantly higher than women who only experienced hypertension during their first pregnancy (P<0.044).

Aspirin effect on long term cardiovascular outcomes following preeclampsia

•Sarma et al. (2016) found there is a 12% decrease in cardiovascular events and 17% decrease in stroke, however, due to increased bleeding risk with aspirin therapy for primary prevention, the benefit of aspirin therapy was 0.3%, showing little benefit.

- Aspirin use for secondary prevention shows 14% decrease in all-cause mortality (HR 0.86).

•McNeil et al. (2018) found that aspirin use significantly decreased cardiovascular events (HR 0.89, 95% CI, 0.77 to 1.03). However, risk for major hemorrhagic events was also significantly higher in the aspirin group.

•The findings in these two large studies demonstrate that the risk of hemorrhagic event from aspirin therapy outweighs the benefits when used for primary prevention.

•More research is necessary to further extrapolate if preeclampsia would make this secondary prevention.

Discussion

To evaluate if preeclampsia leads to future cardiovascular risk, and if aspirin decreases that risk, is multi-fold. First, one must understand the vascular physiology of aspirin and preeclampsia. In regard to how preeclampsia affects endothelial health, the information is lacking and more studies are needed to differentiate which mechanisms are leading to endothelial dysfunction in this population. Chambers et al. (2001), Heidema et al. (2015) and Spaanderman et al. (2005) all found that preeclampsia leads to endothelial dysfunction and increased platelet activity. More research is necessary to determine the validity of these results and increase the understanding of these mechanisms at play.

Aspirin has been theorized to have mechanisms interacting with the oxidative damage to the endothelium and decreasing platelet activity following endothelial injury. Hashemi et al. (2016), and Spaanderman et al. (2005) found that aspirin works by more than one mechanism to alter endothelial physiology and improve vascular health. Again, further research is needed to validate these results.

Investigating the long term cardiovascular effects following preeclampsia is more of a challenge due to the longevity of a studied required to produce high quality results. From the available literature, only a few studies are of the quality and sample size in which to make a broad generalization to the post-preeclamptic population. Of these, it has been found that in fact, these women have increased cardiovascular morbidity and mortality, however, not until the 3rd-5th decades following delivery (Funai et al., 2005, and Bokslag et al., 2017). Many of the available information is based on retrospective studies and evaluation from a hospital database. As there is variation amongst the studies regarding inclusion and exclusion criteria, it is not always clear what other variables are present in the lives of these subjects that may predispose them to increased cardiovascular morbidity and mortality. There continues to be a need for stronger studies as it appears there is a population that can benefit from preventative therapy to decrease cardiovascular events and thus decrease healthcare costs to both the patient and the healthcare system as a whole.

When studying if aspirin is an appropriate therapy for prevention in this population, it is important to keep in mind that they are not at increased risk until later in life. Aspirin effect in an elderly population is warranted when weighing the risks versus benefits of aspirin therapy in this population. The information from Sarma et al. (2016), and McNeil et al. (2018) demonstrate long term aspirin use for primary prevention has higher risk to benefit ratio. It is important for future research to investigate if preeclampsia makes aspirin use in this population “primary” or “secondary” prevention.

There are many unknown variables that need to be considered when trying to solve this question in regard to the post-preeclamptic population. First, more information is needed to definitively determine the pathophysiology of preeclampsia. This understanding will guide researchers in evaluating future risks. Second, determination of future risk in this population. This research should include large, long-term studies with a diverse sample population. It is astute to also control for other variables that lead to cardiovascular disease.

It is upon the healthcare research community to provide sound studies and our duty as medical professionals to better serve this population. Little remains known about the pathophysiology of this group, let alone how that affects their future risk. It is our duty to provide these women with the best care possible.

Application to Clinical Practice

The clinical implications of this is important as there may be a subset that is at increased risk that could benefit from preventative measures. Understanding comes two fold in this investigation. First, determining if this population is at increased future risk and second, if aspirin is the appropriate preventive therapy for this population. The longevity required in a study of this nature has potential for high drop-out rates which will skew results. However, this information is important as there is potential to decrease burden on the healthcare system and potential for saving healthcare dollars by preventing major cardiovascular events if this population has been undertreated.

Current research remains inconclusive at this time. More studies are required to provide good evidence upon which to base practice recommendations. Determining the answers to these questions allows us as healthcare providers to better serve these patients. Not only will this knowledge and further understanding benefit the health of the patient, it has potential to decrease healthcare dollars and the burden placed on the healthcare system by preventing major cardiovascular events.

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