5-2019

Aspirin use following preeclampsia to prevent future cardiovascular outcomes

Kristi Bohlig
kristi.bohlig@und.edu

Aspirin use following preeclampsia to prevent future cardiovascular outcomes

by

Kristi Bohlig
Bachelor of Arts in Dietetics, College of St. Benedict/St. John's University
2012
Julie Solberg, PA-C
Contributing Author

Scholarly Project Literature Review—First Draft
Submitted to the Faculty
of the
University of North Dakota
in partial fulfillment of the requirements
for the degree of
Master's in Physician Assistant studies
Grand Forks, North Dakota

May 2019

Aspirin use following preeclampsia to prevent future cardiovascular outcomes

Table of Contents

Acknowledgements

First and foremost, I would like to thank my main preceptors, Dr. Rickbeil and Dr. Schrup. The information I learned, not only in practicing medicine but in the professional world of medicine is insurmountable. I cannot thank you enough for the time and effort these preceptors put into my education. I would also like to thank Dr. Phil Byrne, professor of statistics and Jessica Lind, PharmD, BCAP, for their time and input on this project. I also want to thank my advisor, Julie Solberg, PA-C, for all the advice and guidance over the past 2 years. I would like to thank Professor Daryl Sieg for his input and guidance on this scholarly project. Also thank you to all of my professors, as I would not be able to be the provider I am shaping up to be without their time and knowledge and guidance. And finally, I want to thank my husband for his unending support through this PA school journey and my other friends and family for their unending support and encouragement.

Aspirin use following preeclampsia to prevent future cardiovascular outcomes

Abstract

Introduction: Preeclampsia during pregnancy warrants therapy with low dose aspirin. The purpose of this review is to investigate whether these women are at increased future risk for cardiovascular morbidity and mortality, and if aspirin therapy should be continued following the puerperium to prevent 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 outcomes?

Research Methods: Literature review was conducted utilizing CINAHL, Dynamed plus and PubMed databases.

Discussion: It is found that further research is necessary to adequately assess if this demographic is at risk. Many studies have found that preeclampsia does increase risk of cardiovascular morbidity and mortality, but that 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.

Introduction

Preeclampsia is a diagnosis reserved for approximately 3-7% of pregnancies (Sarma et al, 2016). Preeclampsia is defined as hypertension during pregnancy, after 20 weeks, with the presence of proteinuria. Preeclampsia increases risks during pregnancy due to hypertensive effects on mother and fetus. For women with preeclampsia, there are set recommendations including the use of 81 mg aspirin, daily, for prevention of negative fetal and maternal outcomes during pregnancy. There are known harms of hypertension, to the general population. Hypertension results in increased cardiovascular morbidity and mortality (Sutters, 2018). This understanding would lead one to believe that having hypertension during pregnancy would lead to future cardiovascular risks, despite the short time frame, as these patients with preeclampsia have experienced vascular/endothelial injury. Currently, there is a lack of defined recommendations for treatment beyond the post-partum period. This review will investigate if continued treatment may help to reduce future cardiovascular risk in patients who have been diagnosed with preeclampsia.

Statement of the Problem

Hypertension during preeclampsia leads to endothelial damage, which predisposes these women to thrombotic and ischemic events. Currently, there are no set recommendations on how to treat this high-risk group of women who had preeclampsia during a pregnancy. This population, as well as healthcare providers, could be unaware of potential cardiovascular risks and ways to prevent future cardiovascular events. Understanding, first, if this population is at increased risk for future cardiovascular events, and two, if there is a treatment that decreases this risk, helps us identify a population in which we can intervene to decrease future cardiovascular morbidity and mortality.

Aspirin use following preeclampsia to prevent future cardiovascular outcomes

Research Question

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 outcomes?

Research Methods

Research was conducted using the PubMed, Dynamed Plus and CINAHL databases. Only studies published in English language are included.

The first search of CINAHL database using *preeclampsia and endothelium and damage* resulted in 11 articles. Articles were excluded if they evaluated treatment of preeclampsia or different effects of therapeutic modalities on preeclampsia. Articles were included if they specifically extrapolated the effects that preeclampsia has on the endothelium.

A search of Dynamed Plus database using the search term *Hypertensive disorders of pregnancy* resulted in one review. Under the subheadings *Postpartum management* then *prevention and screening,* under *Prevention* there is a review of aspirin therapy. However, this information provides conflicting evidence regarding when to start prophylactic aspirin therapy in pregnancy for prevention of preeclampsia.

A primary search of PubMed using *("aspirin" [MeSH Terms] OR "aspirin" [All Fields] AND ("postpartum period" [MeSH Terms] OR ("postpartum" [All Fields] AND "Period" [All Fields]) OR "postpartum period" [All Fields])* produced 120 articles. Articles were excluded if they did not include aspirin in relation to postpartum women, not for the

treatment of preeclampsia during pregnancy. Other articles were excluded as they did not address the research question.

A second search of PubMed using the search *("aspirin"[MeSH Terms] OR "aspirin"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields]) AND ("forecasting"[MeSH Terms] OR "forecasting"[All Fields] OR "future"[All Fields]) AND ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields]) AND after[All Fields] AND ("pre-eclampsia"[MeSH Terms] OR "pre-eclampsia"[All Fields] OR "preeclampsia"[All Fields])* results in 2 articles. One is included due to applicability to the literature review and research questions.

Lastly, a third search of PubMed using the search *("aspirin"[MeSH Terms] OR "aspirin"[All Fields]) AND effect[All Fields] AND ("endothelium"[MeSH Terms] OR "endothelium"[All Fields]) AND ("pre-eclampsia"[MeSH Terms] OR "pre-eclampsia"[All Fields] OR "preeclampsia"[All Fields])* results in four articles. The article included had the most clinical applicability and relevance to the stated problem and research questions.

Literature Review

The current literature available demonstrates there is an increased risk of future cardiovascular disease in women who have had preeclampsia, when compared to women who did not have preeclampsia during pregnancy. Preeclampsia is defined as hypertension during

pregnancy, after the 20th week of gestation, with the presence of proteinuria (mayoclinic.org, 2018). This review will evaluate the effect of both preeclampsia and aspirin on the endothelium, followed by long-term cardiovascular outcomes after preeclampsia, and finally will close with a review of the literature on aspirin preventing future cardiovascular morbidity and mortality in formerly preeclamptic women. Currently, there continues to be a need for further research as to whether daily aspirin therapy can decrease cardiovascular risk in this population or if the risks of continued aspirin therapy outweigh the benefits.

Preeclampsia effect on endothelium

Preeclampsia is a hypertensive disease of pregnancy that is accompanied by proteinuria and in some cases edema. Many researchers continue to investigate the mechanisms that are at fault in causing or predisposing certain women to developing preeclampsia during pregnancy, and what effects preeclampsia has on the endothelium and risk for further vascular disease processes. This can be difficult to determine as there are many theories trying to differentiate maternal versus placental mechanisms at play (Chambers, et al., 2001).

Chambers et al., (2001), conducted a study in which they investigated various placental and maternal factors that may contribute to the development of preeclampsia. In order to separate maternal from placental factors contributing to preeclampsia and effects on the endothelium, they included women who were a median of three years postpartum. Their study concluded that "vascular endothelial dysfunction is recognized to be a central disturbance in preeclampsia" (Chambers et al., 2001). These results demonstrate that it is dysfunction of the endothelium that predisposes women to developing preeclampsia.

The strengths and limitations of this study both come from its design as a Case-control study. As a case-control study, it is retrospective, and the subjects included have already been

diagnosed with the disease being studied, in this case, preeclampsia. Another limitation is the study population consists of 191 participants. Due to the relatively limited study population it will be difficult to generalize these results to the general population. Also, the subjects were chosen from hospital records from three different hospitals in London, England (Chambers et al., 2001). Again, this can be a limitation as the results may be able to be generalized to those living in London, however, due to potential influence of various environmental factors, it will be difficult to generalize these results to those living outside of the London area.

The strengths of this study also come from the fact the design is a case-control study. This study design allows the researchers to better extrapolate what risk factors are contributing to the development of preeclampsia. This is beneficial to the medical community as it can help to differentiate between the maternal or placental factors that may be causing preeclampsia.

Heidema et al., (2015), investigated history of preeclampsia versus obesity on developing metabolic syndrome. Their study also found that women with a history of preeclampsia were more inclined to develop metabolic syndrome, than their obese counterparts (Heidema et al., 2015). The difference in the incidence of metabolic syndrome in formerly preeclamptic women was statistically significant than that of the obese patients included in the study population ($P<.001$), (Heidema et al., 2015). To make connections between the development of metabolic syndrome as a result of endothelial dysfunction incurred during preeclampsia, more studies would be necessary. However, as metabolic syndrome is defined “by a cluster of traditional cardiometabolic abnormalities,” (Heidema et al., 2015), it may be reasonable to believe there is some level of endothelial dysfunction contributing to the development of metabolic syndrome and these cardiometabolic syndromes.

Aspirin use following preeclampsia to prevent future cardiovascular outcomes

Preeclampsia has a shearing effect on the endothelium as with other hypertensive disorders; however, for this population, the blood pressure typically returns to normal parameters following delivery. Chambers et al. (2001) acknowledges the endothelial injury is only transient while the blood pressure is elevated. They used flow-mediated dilatation to assess vascular endothelial function (Chambers et al., 2001). The results demonstrated that previously preeclamptic women had a statistically significantly lower brachial artery flow-mediated endothelium dilatation than the control group ($P<.001$) (Chambers et al., 2001). These results combined with those of Spaanderman, et al. (2005), who evaluated platelet responsiveness following preeclampsia, suggest that there is some level of endothelial dysfunction following preeclampsia. Spaanderman et al. (2005) found that women who formerly had preeclampsia also had a 15% increase in platelet responsiveness. Based on these findings in addition to other platelet markers, they concluded there is some element of endothelial dysfunction that is unable to accommodate the increased cardiovascular demands of pregnancy (Spaanderman et al., 2005). Endothelial shear from high blood pressure is theorized to be an underlying mechanism in hyperactive platelet activity in the preeclamptic patients in which they speculate this endothelial damage increases the number of presensitized platelets circulating in these patients (Spaanderman et al., 2005).

Heidema et al., (2015) conducted a retrospective case-control study. The benefits of this study design is that the researchers are able to differentiate which risk factors contribute to the development or progression of a disease state. The subjects were evaluated six to eighteen months postpartum as to evaluate if preeclamptic participants had more adverse cardiovascular outcomes when compared to those who had factors for metabolic syndrome. This study design

helps the researchers to develop the cases and define the specific study populations being evaluated.

Limitations are the retrospective nature of the study design. There can be some bias from Heidema et al, when evaluating the data as it is known to which group the data is coming from. The study and control groups also pose a limitation to these researchers. The study group contains 90 participants and the control group consists of 30 participants. The variation in participation number between these groups can lead to discrepancies when it comes to evaluation of the results.

Aspirin effect on endothelium

The effects of aspirin on the endothelium have been vastly studied. Hashemi et al., (2016) conducted a triple-blind randomized control trial to investigate how aspirin affects preeclamptic patients in regard to endothelial function. Their study included the use of brachial artery flow-mediated dilation analysis both during pregnancy and following delivery. The intent behind this was to evaluate these measurements after the shear stress on the endothelium had occurred. In this case, that shearing damage to the endothelium was caused by the high blood pressure of preeclampsia. The findings from Spaanderman et al, (2005), also demonstrated that the endothelial shear from preeclampsia results in hyperactive platelet activity. Therefore, one may conclude that aspirin indirectly effects the endothelium by interrupting the process of platelet activation. This poses another question of whether the endothelial shear versus the platelet activation it causes pose a greater risk of cardiovascular and circulatory morbidity. This will not be further explored as part of this review.

Hashemi et al., (2016), found that daily low dose aspirin increases flow-mediated brachial artery dilation. These results demonstrate that endothelial function in this population

with the intervention of low-dose aspirin (81mg/day) is improved (Hashemi et al., 2016). These researchers attribute the improvement to the antioxidant characteristics aspirin has on platelet function at this dose (Hashemi et al., 2016). Decreasing oxidative injury to the endothelium theoretically would decrease platelet activation that follows endothelial injury, incidentally, aspirin is therapeutic in both of these pathways as evidenced by Hashemi et al., (2016) and Spaanderman et al., (2005). As evidenced by the studies done by Hashemi et al., (2016), and Spaanderman et al., (2005), it appears that aspirin decreases cardiovascular morbidity and mortality by action in more than one pathway in the platelet activation cascade.

Spaanderman et al., (2005), conducted a trial in which 66 formerly preeclamptic patients were placed in groups that had comparable numbers for other variables contributing to cardiovascular morbidity and mortality. They then further divided the patients based on their platelet responsiveness to a low dose aspirin regimen. It does not specify whether this is a double-blind, randomized control trial or not in which case, this can be a poor study design as the researchers are aware of which participants are in which group. This kind of study design can lead to increased bias when interpreting the results as the researchers are aware of which outcomes they are looking for. Another limitation of this study is the small sample population. A sample population of 66 participants that meet very strict exclusion criteria, is very difficult to generalize to the general population.

One strength from Spaanderman et al., (2005), is that all women have the same inclusion criteria. These women were then evaluated for factors that can contribute to vascular damage. From there, their study worked to determine whether aspirin decreased platelet responsiveness in this population. The risk factors are specific and the measurement parameters are clearly stated.

Hashemi et al., (2016), conducted a triple-blind, randomized clinical trial. This is a strong study design and increases the strength of the results produced. They measured flow-mediated dilation before aspirin therapy was initiated and again following the puerperium. They utilized T-test to compare the aspirin and control groups. Hospital registries were used to find participants and inclusion and exclusion criteria were applied prior to inclusion in the study.

Limitations of the Hashemi et al., (2016) study are the small sample size. The sample population was also taken from an Iranian hospital registry so the results generated would not be able to be generalized to populations outside of Iran. Larger studies are necessary to increase the generalizability of these results.

Long term cardiovascular outcomes following preeclampsia

Bokslag et al. (2017) evaluated the future risk of developing cardiovascular disease in women who had preeclampsia during pregnancy. They reviewed current research in which they found there is increased risk for this population to develop cardiovascular disease but not until the fifth decade following preeclampsia (Bokslag et al., 2017). Their goals were to evaluate if there is an opportunity to provide preventive therapy for these patients so they do not go on to develop cardiovascular disease in the fifth decade following preeclampsia (Bokslag et al., 2017). They looked at the possibility of being able to prevent cardiovascular disease in this population. They investigated if the implementation of preventive measures within the first one to two decades following preeclampsia will decrease the risk of these women developing cardiovascular disease later in life. Following their research and statistical analysis, they found that 42% of the participants who formerly had preeclampsia met their criteria for preventive measures, which they found to be statistically significantly different from women with an uncomplicated pregnancy ($P<.0001$) (Bokslag et al., 2017). Based on the findings of Bokslag et al. (2017),

formerly preeclamptic women do not have increased risk for cardiovascular morbidity and mortality until their fifth decade post-partum. Thus, there is a need for further research to confirm these results, as this subgroup of women may be able to prevent future cardiovascular events if recognized and treated accordingly.

Bokslag et al., (2017), produced a prospective observational study to assess risk of cardiovascular disease later in life for these women. They reviewed and screened medical records to identify women who had preeclampsia, decades ago, to form the cohort. They then sent a questionnaire regarding signs and measurements such as blood pressure, lipid levels, etc., that increase risk of cardiovascular disease. They then identified a timeline of when preventive measures would be most beneficial as defined by specific risk factors for developing cardiovascular disease. In conclusion, they discovered many women are at risk for developing cardiovascular disease after having preeclampsia during their pregnancies. However, these women fall outside of the parameters to initiate preventive measures according to many various guidelines set by preventative programs. As many of these patients have not had preventive measures, it is difficult to make concrete conclusions about the efficacy of preventive measures in this population, and the ability to stave off cardiovascular disease for these patients. This group concludes that more studies need to be done to provide data on the efficacy of preventive measures in this specific population.

Funai et al. (2005) conducted a prospective cohort study for their evaluation of the long-term mortality in patients who had preeclampsia. Their goal was to evaluate the mortality risk, long-term, in women who had preeclampsia and were normotensive following their pregnancy. As part of their methods, they include the Jerusalem Perinatal Study, which includes the surveillance of patients, who met their criteria, from the three largest obstetric units in Israel. The

Jerusalem Perinatal Study evaluates hypertensive disease in pregnancy. It gives these researchers a database of women who had preeclampsia and fit into a longer-term follow up that has previously been evaluated. They discovered that preeclampsia was related to higher mortality risks (Funai et al., 2005). They then further extrapolate causes of death and make correlations based on those findings. To gather their results, they used follow-up then did statistical analysis on various components to their research. The median follow-up was 30 years. Their results show that in the 24-36 years of follow up, the risk of death more than doubled in those with preeclampsia (Funai et al., 2005). Similar to Bokslag et al., (2017), Funai et al., (2005) found that formerly preeclamptic women had increased cardiovascular morbidity and mortality, decades postpartum. The findings of these two, large, studies reveals there is possibly a subpopulation that is at risk for poor future cardiovascular outcomes. There is a need for continued investigation into this subpopulation and if these results are reproduceable as it would be prudent for the healthcare community to prevent these poor outcomes in this group.

The strengths of this study are the design and methods. They did other analysis and due to the similarity in results to their original model, they only present the first type of analysis they evaluated. The cohort selected provides a broad representation that can be compared to the total population. Also, there could not have been any bias at the time of data collection as well as being due to the use of population-based registries that only screened for preeclampsia as an identifier. They also have strong control of additional variables that could have contributed to influencing mortality in this cohort.

The authors also identify areas of weakness in their study design. They did not include other risk factors for developing cardiovascular disease, such as, obesity, diet, etc. They were also limited in the documentation of births from 1964-1976, which was predetermined by a

previous study. They did not have access to complete obstetric records of these individuals, so they are not able to ascertain if this is the woman's first pregnancy, or if it is a subsequent pregnancy, which can alter risk of preeclampsia.

Grandi et al. (2017) conducted a cohort study to evaluate risk of future cardiovascular disease in women who had hypertensive disorders during pregnancy. They used the Clinical Practice Research Datalink to identify 146748 women during their first pregnancy, to develop their cohort. From this database, they used specific diagnostic codes and blood pressure readings to further narrow the cohort to only include women who met the criteria and were between 18 weeks gestation and the puerperium. Time-variance confounders are accounted for by use of Marginal structural Cox models (MSM). Their results show, with a hazard ratio of 2.2, 95% confidence interval, that the patients in this population are at a much higher risk of developing cardiovascular disease later in life (Grandi et al., 2017). With the MSM and time-fixed analysis, they found these results are consistent.

There are multiple strengths in this article. The first is the ability to decrease the amount of residual confounding by a comprehensive database search that allowed the ability to include covariables in the search. They also utilized a clinical database. This allows them to include individuals who meet their definitions for exposure and outcomes and limits those who were not classified correctly in the database. This study design allows them to also account for women who had more than one pregnancy.

Despite the strong study design, these authors also faced some limitations. In the database used, gestational age was not readily stated which could increase the risk of them misclassifying individuals. This database also included records provided by a primary care provider. Individuals who meet criteria but are followed only by an obstetrician or a midwife

may not be included in the data. This can lead to a selection bias and will skew the results. The majority of individuals included in the cohort also only had one pregnancy despite the selection criteria being open to include those with multiple pregnancies, which would decrease the ability for this information to be generalized to multiparous women who had preeclampsia.

Hermes et al. (2010) conducted a cohort study. The goal of this study is to identify modifiable risk factors that predispose these patients to development of cardiovascular disease in the future. They used the HYPITAT study upon which to develop their cohort. The participants chosen from this study will be available for follow up by these researchers. The present study was conducted to evaluate evidence of screening women who had term preeclampsia, two and a half years after pregnancy, for cardiovascular risk.

A limitation in their evaluation is regarding the limited sample size which resulted in some statistical issues. They had to further utilize Chi-squared for comparison groups. Their statistical evaluation further includes logistic regression analysis to further extrapolate the information from the data collected. They conclude that data for this population regarding long-term risk for developing cardiovascular disease, is minimal, and they are hopeful to provide information that can be generalized to those who had term gestational hypertensive disorders of pregnancy. These authors had no conflicts of interest.

Leslie et al. (2016) did a systematic review and meta-analysis. They conducted this review to compile recommendations for reducing risk and increasing patient awareness of their future risks, in this demographic. For their systematic review, they utilized MEDLINE, Scopus, CINAHL, ISI Web of Knowledge, and Chochrane databases for their search. Inclusion criteria were defined as: English, peer reviewed, specified time frame, and relationship between hypertensive disorders of pregnancy and future risk of cardiovascular disease. The total inclusion

from the 48 qualified reviews resulted in 3,598,601 women meeting the inclusion criteria. They found that gynecology clinics were less likely to identify new-onset hypertension, than primary care clinics (22% vs 38%; P<.0001) (Leslie et al., 2016). They discovered the literature shows that women who had preeclampsia have a two times increased risk of developing cardiovascular disease and mortality. The increased risk of mortality was lower when the baby was born at 37 weeks or later (RR, 0.98; 95%CI, 0.5-1.92) (Leslie et al., 2016).

A strength of this systematic review and meta-analysis is the sample size. These findings are more likely to be generalized to other women who have hypertensive disorders while pregnant, when trying to estimate their future cardiovascular risk factors. They included all relevant studies from a vast variety of databases that were searched. Their inclusion criteria were clearly defined and allowed for accurate appropriateness when combining these results. A limitation remains in providing conclusive evidence regarding preventative therapy for the development of future cardiovascular disease. There continues to be a need for more data researching those answers.

Mannisto et al. (2013) conducted a population-based prospective cohort evaluation of long-term chronic disease risk following hypertensive disorder during pregnancy. Their goals were to evaluate women's subsequent risk of chronic diseases following hypertensive disorder during pregnancy. They specifically looked at the Northern Finland Birth Cohort of 1966. They were able to get clinical data such as blood pressure, from prenatal records. They then investigated additional diagnoses utilizing Finnish registries. For statistical analysis, they performed hazard ratios with 95% confidence intervals to compare the risk of a hypertensive vs normotensive pregnant patient.

One of the most notable strengths of this review is the outstanding sample size they were able to achieve that met their inclusion criteria. They also clearly defined exclusion criteria through each phase as it was discovered that some individuals who originally met inclusion criteria were missing important data measurements such as blood pressure. Other strengths include the control of variables even down to position of the patient when the blood pressure was taken to provide even more clarity in comparing the data. Limitations of this review include misclassification due to the evolution of diagnostic criteria for gestational hypertension over the interim. No disclosures are included by the authors.

For statistical analysis, due to the prospective nature of this study, they used Cox regression analysis to evaluate the impact hypertension had on future morbidity and mortality. They also included hazard regression and confidence intervals when evaluating their results.

Theilen et al. (2016) conducted a retrospective cohort study with the goal of evaluating if women who had hypertensive disorders when pregnant, have a higher risk of early mortality. The cohort they evaluated were women with singleton pregnancies between 1939 and 2012. They used the Utah Population Database to identify mothers who singleton pregnancies. Inclusive criteria were applied to further narrow and specify the appropriate individuals for the study. The women included were those who had a hypertensive disorder of pregnancy in a singleton pregnancy and continued to reside in Utah for one year following the birth. Specific exclusion criteria are included as well to further increase the specificity of the cohort selected. After applying inclusion and exclusion criteria, they had 2,083,331 eligible pregnancies upon which to further evaluate. They also had 123,140 normotensive women upon who to provide a comparison (Theilen et al., 2016). After discerning all-cause mortality rates, they divided the women with hypertensive disorders of pregnancy, further into subgroups and assessed mortality

rates based on individual hypertensive disorders that occurred during the pregnancies of these individuals.

This is a retrospective study which poses both strengths and weaknesses for the researchers. Additional limitations include the possibility of misclassification as well as possible selection bias. Confounding residuals can skew the interpretation of the results as well. Although there were some weaknesses identified, there are strengths to this article as well. This includes the retrospective design which allows a more longitudinal assessment of how preeclampsia effects cardiovascular and chronic health outcomes in the long term. By using a retrospective design, researchers gather the information and make associations between those who had preeclampsia and increased risk of chronic health outcomes in the decades to come, when compared to their normotensive counterparts.

Wikstrom et al. (2005) conducted a cross-sectional, population-based study. The goal of their study was to investigate if women who had gestational hypertensive disease had increased risk of developing ischemic heart disease later in life. They used the Swedish Medical Birth Register for definition of the study population. Specifically, they reviewed the period between 1973-1982. This cohort contains 403,550 women who gave birth in Sweden during this time frame. Of the main cohort, 207,054 women who were analyzed separately due to giving birth to a second child within the specified time frame (Wikstrom et al., 2005). Age, hospital and socioeconomic status were identified as possible confounders. They calculated incidence rate rations (IRRs) and 95% confidence intervals and treated age as a continuous variable. The adjusted IRR for ischemic heart disease in women with hypertension during multiple pregnancies was statistically significantly increased compared to women who only had hypertension during their first pregnancy ($P<.044$) (Wikstrom et al., 2005).

One strength of this cross-sectional population-based study was that there were very few losses to follow up due to the nationwide nature of the study. This group felt this is due to the low number of home deliveries that are performed in Sweden. With this database, they were able to evaluate both hospitalizations and deaths from ischemic heart disease, in this population. The first limitation identified is the long follow up period. They also suspect there may have been some underreporting of hypertensive disease that was thought to be milder. Another limitation identified by this research group is their inability to account for BMI and smoking habits, both contributors to the development of heart disease, as these variables were not reported to the national registry in Sweden.

Aspirin use to decrease the risk of ischemic stroke, postpartum

Tang et al. (2010) conducted a review that includes articles looking at the timeframe between pregnancy and the puerperium, in which stroke risk is increased in patients who have preeclampsia and are pregnant, or in the puerperium, and management to decrease this risk. To form conclusions and recommendations regarding management, they reviewed the epidemiology, causes, and treatment. They dissected their review of the literature and state the key issues. They found there is an increased risk of stroke during the puerperium. There is a range in the incidence of stroke during this time frame. The literature demonstrates stroke is related to 5-10% of maternal death (Tang et al., 2010). This is important as they also found hypertensive diseases of pregnancy contribute 25-45% of pregnancy-related stroke (Tang et al., 2010). This review finds that preeclampsia predisposes women to higher risk of cardiovascular diseases in later decades of life.

In this review the authors failed to identify their search methods which will decrease the strength of the review as much of the conclusions are then based on correlation and expert

clinical opinion. The credibility is decreased as bias may be included in their concluding opinions. They identify that the current management for these patients may not be as safe as once thought and more research needs to be done to provide more data. The design of such studies also needs to be strengthened to allow providers to form better conclusions about the management of these patients and decreasing future risk of cerebrovascular and cardiovascular disease.

Van Alebeek et al. (2018) aim to review data and literature on how to manage ischemic stroke in pregnancy and the puerperium, with aspirin. These authors strived to include clinically relevant data, from the limited pool of data that is available. The goals of their review are to provide a guide for the management of stroke in this population (Van Alebeek et al., 2018). They review the pathophysiology and epidemiology of preeclampsia. Then Van Alebeek et al., (2018) incorporate current knowledge on the effects of aspirin in the management and prevention of ischemic stroke in women with preeclampsia. They also include discussion about other anticoagulant and antithrombotic therapies in comparison to aspirin therapy for the management of stroke in pregnant and women in the puerperium (Van Alebeek et al., 2018).

There are scarce studies done on ischemic stroke in this population. One of the limitations to this review is the lack of primary data available. Another limitation is the lack of high-quality observational studies available to review. These reviewers could also increase the strength of their review by including their search methods and why certain articles were excluded or not. Many of their conclusions are based on their expert opinions.

Aspirin effect on long term cardiovascular outcomes following preeclampsia

Sarma et al. (2016) conducted a literature review with the goal of evaluating the use of low-dose aspirin for prevention of cardiovascular disease in men and women and low dose

aspirin for prevention of preeclampsia. They first discuss how sex differences influence the physiologic response to aspirin. Through evaluation of current literature they discovered that the platelet reaction of women is higher than men, although both sexes achieve platelet suppression with aspirin therapy (Sarma et al., 2016). They evaluated primary prevention with aspirin. Specifically, they evaluate the efficacy of aspirin for primary prevention of cardiovascular disease and stroke in women. The benefit of aspirin therapy and decreased risk of stroke or cardiovascular events was time dependent. The bleeding risks of using aspirin for primary prevention began to outweigh the benefits when evaluating 15-year outcomes. Through their review, they found, in a WHS meta-analysis, that in 100,000 patients, there is a 12% decrease in cardiovascular events and a 17% decrease in stroke, however, with further evaluation, absolute benefit of aspirin therapy was 0.3%, showing little benefit (Sarma et al., 2016). Thus, there was not a statistically significant improvement in cardiovascular events or stroke prevention when patients took aspirin prophylactically.

They then evaluate the use of aspirin therapy for secondary prevention of cardiovascular events and stroke. When used for secondary prevention, aspirin provided a 14% reduction in all-cause mortality (hazard ratio 0.86), over a follow up period of 6.5 years (Sarma et al., 2016). Their review of the literature concludes that aspirin continues to be the standard of care for secondary prevention of cardiovascular events. They also speculate that if it is possible to prevent preeclampsia, this may result in a decrease in incidence of cardiovascular disease later in life since women with preeclampsia have a higher risk of developing cardiovascular disease later in life (Sarma et al., 2016). This is an area that warrants further investigation and research.

McNeil et al., (2018), designed a randomized, double-blind, placebo-controlled study, to further investigate whether aspirin has a beneficial effect on the primary prevention of

cardiovascular disease. Their study was specifically targeted toward an elderly population. They evaluated a sample population of participants over the age of 70 who were from the US or Australia. Specific inclusion and exclusion criteria are listed in detail. Statistical analysis was done using Cox proportional-hazard ratios. During participant follow up, the results produced demonstrate that in the aspirin group, 7.8 major cardiovascular events occurred for every 1000 person-years, compared to 8.8 major cardiovascular events for every 1000 person-years in the placebo group (McNeil, et al., 2018). This was statistically insignificant (hazard ratio, 0.89; 95% CI, 0.77 to 1.03) (McNeil, et al., 2018). However, in the aspirin group, the risk for major hemorrhagic events was 8.6 per 1000 person-years, whereas the placebo group produced 6.2 hemorrhagic events per 1000 person-years (McNeil, et. al., 2018). The results produced by this study have changed the recommendations for aspirin use in the elderly population (>70 years of age), for primary prevention of cardiovascular disease.

The findings of Sarma et al (2016) and McNeil et al (2018) suggest that when used for primary prevention of cardiovascular disease, the long-term risk for bleeding or hemorrhage with aspirin therapy, outweighs the benefit of decreased cardiovascular and stroke outcomes. Further research needs to be done specifically for the post-preeclamptic population. Sarma et al. (2016), designed a study looking at women specifically, as they have historically been under represented in the sample populations of the studies in the literature. McNeil et al. (2018) also investigated an underrepresented population in these studies, the elderly. Based on the findings that increase in cardiovascular risks do not present until the third to fifth decade following preeclampsia, it is reasonable to speculate that these women would be in their seventh decade of life or beyond. Based on the information provided by these two studies, it appears that we first must identify whether preeclampsia places these women in the category of primary or secondary prevention.

Further studies are required to investigate whether there is a therapeutic intervention that decreases the future cardiovascular risk in this population.

Discussion

Preeclampsia is a condition which affects approximately 3-7% of pregnancies (Hashemi et al., 2016 and Sarma et al, 2016). This condition predisposes both mother and fetus to increased risks during the third trimester of pregnancy. It is found that these women also have increased risk for cardiovascular events or ischemic stroke into the puerperium. It remains a mystery as to the cause of preeclampsia. Many researchers continue to hypothesize and investigate the cause of preeclampsia and what predisposes these women to getting this condition during their pregnancies.

There is evidence of increased risk for thrombotic or ischemic events in these mothers during pregnancy. The current USPSTF recommendation is for these women to take 81 mg Aspirin, daily, for the second and third trimesters of their pregnancy, to decrease adverse outcomes from preeclampsia (Grade B recommendation). However, there remains a question regarding the future cardiovascular risk in this population, and if so, is there a population going untreated in which we could decrease cardiovascular morbidity and mortality later in life?

Does continued aspirin use in postpartum women, who had preeclampsia during pregnancy, decrease future cardiovascular morbidity and mortality outcomes?

To investigate what benefits aspirin may have in preventing or decreasing cardiovascular morbidity and mortality in women who formerly had preeclampsia, we first need to understand how aspirin and preeclampsia effect vascular physiology.

Evaluating the pathophysiology of preeclampsia in relation to endothelial health is difficult as there is only a small number of studies available. The information available is lacking. It has also been a challenge for researchers to differentiate whether maternal or placental

mechanisms are the cause of preeclampsia. Chambers et al, (2001) designed a study that evaluated brachial artery flow index, in women with an average time of 3 months from delivery, in order to isolate maternal mechanisms that may contribute to endothelial physiology in preeclampsia. It was also found that preeclampsia history is also a greater indicator of future development of metabolic syndrome, compared to obesity (Heidema et al., 2015). The development of metabolic syndrome in previously preeclamptic women may suggest some degree of persistent endothelial dysfunction. The Mayo clinic defines metabolic syndrome as, "a cluster of conditions—increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels." The pathophysiology that occurs during metabolic syndrome has strong connections to future cardiovascular and circulatory pathology. Spaanderman et al. (2005), also found that preeclampsia predisposes these women to have greater platelet reactivity. These conclusions demonstrate that preeclampsia has some effect on the endothelium, either directly or indirectly, as in the case with platelet reactivity. There continues to be a need for further research investigating the effect preeclampsia has on the endothelium as the discovery of these mechanisms can lead further research into the risks and benefits of preventative therapy for this population.

Spaanderman et al., (2005) also concluded that aspirin decreases platelet activity following endothelial injury. This demonstrates that aspirin indirectly affects the physiology of the endothelium by prevent the clotting cascade and platelet activity. Aspirin may also effect the endothelium by its antioxidant characteristics. This suggests that aspirin can decrease the oxidative damage imparted on the endothelium, particularly by the shear stress incurred during preeclampsia, from the high blood pressure that defines this disease (Hashemi et al., 2016). They created a randomized control trial in which endothelial dysfunction was improved, as measured

by brachial artery mediated dilation, following aspirin therapy at low doses, 81 mg (Hasemi et al., 2016). The findings of Hashemi et al (2016) and Spaanderman et al (2005) suggest that aspirin has multiple characteristics that alter endothelial physiology. Aspirin is theorized to both interact with the oxidative damage to the endothelium and decreasing the platelet activity following endothelial injury. This is important to consider when investigating whether preeclamptic women would benefit from this type of therapy to decrease future cardiovascular morbidity and mortality. However, there continues to be a need for further research investigating the effects of aspirin on the endothelium, specifically, as preeclampsia poses a shearing stress to the endothelium, and what the implications of such an injury are.

The data investigating the long-term effects on cardiovascular morbidity and mortality following preeclampsia continue to be lacking. There are a handful of various reviews available, however, this information can be weak as much of the conclusions in these literature studies are based on the expert or clinical opinion of the authors. From the available studies that have been conducted looking at this potential problem, only a few are of high quality and an appropriate sample size in which to make broad generalizations to this population. Amongst these researchers, it is found that increased cardiovascular morbidity and mortality following preeclampsia is not encountered until approximately 30 to 50 years following the diagnosis of preeclampsia (Funai et al, 2005 and Bokslag et al, 2017). Hermes et al, (2010) attempted to discern if there are risk factors for cardiovascular disease following preeclampsia, in which modification of these risk factors might possibly decrease future cardiovascular morbidity and mortality. Their sample size was quite limited and thus it is difficult to make conclusions based on their information alone. Following Chi squared regression analysis, they concluded that the increased risk to this population was minimal (Hermes et al., 2010).

It is very difficult to interpret the results of the limited number of studies available as there are a number of differences between them. The production of a sample population based on a hospital database will only provide information for the population within that country or region. It would not be astute of us as providers to apply information regarding future cardiovascular morbidity and mortality, from Sweden, to people in India.

It is also difficult to ascertain whether preeclampsia is the sole variable leading to the increased cardiovascular morbidity and mortality in this population. By thirty to fifty years following preeclampsia, these women could have been exposed to many other variables that increase risk of cardiovascular disease later in life. There is a need for more studies that target this population and also control for other variables that contribute to increases cardiovascular morbidity and mortality.

Overall, when trying to evaluate if preeclampsia predisposes women to increased future cardiovascular morbidity and mortality, there continues to be a need for stronger studies upon which to base practice recommendations. There may possibly be a significant number of patients who fit within this population, who are at increased risk, unbeknownst to the provider and/or patient, for cardiovascular events, in which we could potentially provide preventative therapies to improve their future health. Again, these studies are weakened by their reliance on expert opinions and small sample sizes. The few solid studies available demonstrate that there is, in fact, a statistically significant increase in cardiovascular risk, in the third to fifth decades following preeclampsia. This information demonstrates the need for further research so we, as providers, can appropriately care for these women for the prevention of future cardiovascular morbidity and mortality in these patients. Future studies should also include controls for other

factors that contribute to increased cardiovascular morbidity and mortality, such as, smoking, obesity, family history, physical inactivity, etc.

When investigating the effect of aspirin on future risk of ischemic stroke, following preeclampsia, the data is limited. Tang et al (2010) conducted a study in which the inclusion criteria included a very narrow time frame following preeclampsia. Their study specifically focused on the puerperium and decreasing the incidence of stroke in the first six weeks following delivery, in women who had preeclampsia. It is difficult to apply this information to women for long term treatment and prevention. They also state preeclampsia leads to a significant increase in future cardiovascular risk, (Tang et al., 2010), however, the data and statistics to support this information are not included in their commentary.

High dose aspirin for decreased risk of ischemic stroke postpartum, was also investigated by van Alebeek et al, (2018). Their data suggest that the treatment in this population is left to expert opinion and is not yet supported by clinical trials (van Alebeek et al, 2018). There is evidence to support the use of aspirin therapy following an event of an ischemic stroke in women with preeclampsia, however, this data is applied to women who are still pregnant and into the puerperium, not at preventing a longer term risk of ischemic stroke (van Alebeek et al, 2018). It is important for future studies to identify if they are investigating aspirin therapy as primary or secondary prevention of future ischemic stroke morbidity and mortality in the post preeclamptic population. Thus far, much of the information provided in regard to ischemic stroke risk related to preeclampsia, primary focuses on the second and third trimesters and into the puerperium, however, lacks investigation into longer term studies of these risks.

Finally, we also included a look at the information that evaluated the effect of aspirin therapy on long term cardiovascular morbidity and mortality, following preeclampsia. It was

discovered by Sarma et al (2016) that women are lacking in the representative samples regarding research that has been done regarding cardiovascular morbidity and mortality and therapy to reduce these statistics. They aimed to research the physiological differences amongst men and women that may contribute to why reduction in cardiovascular events is greater in men than in women (Sarma et al, 2016). Upon conclusion of their studies, their data was inconclusive regarding the use of aspirin for primary prevention of cardiovascular morbidity and mortality in this population. They also speculate that if aspirin therapy is used after the 12^{th} week of gestation, this will theoretically reduce the risk of the development of preeclampsia in high risk patients, which will in turn decrease the future cardiovascular risk in these women if preeclampsia is prevented (Sarma et al, 2016).

Investigation into aspirin effect on elderly populations is also warranted, as we previously remarked about increased cardiovascular risk following preeclampsia, not being significant until the third to fifth decades following preeclampsia. McNeil et al (2018), wanted to extrapolate the data regarding this very question. They designed a large, double blind, randomized control study in which their target population were individuals who were greater than the age of 70 years. The information from both Sarma et al (2016), and McNeil et al, (2018) demonstrate that long term aspirin use for the prevention of cardiovascular risks may in fact be more harmful than the perceived benefit it produces. McNeil et al (2018), found that there was a statistically significantly increased risk for major hemorrhage ($P<.001$), when compared to the benefit it provided, which was not found to be statistically significant. The hazard ratio for prespecified end points in this case was 0.95, by which McNeil et al (2018) conclude contradicts a major protective effect of aspirin (McNeil et al, 2018).

Aspirin use following preeclampsia to prevent future cardiovascular outcomes

Trying to evaluate if therapeutic means, specifically aspirin, in the prevention of future cardiovascular morbidity and mortality, following preeclampsia is a difficult undertaking. There are many different unknown variables that need to be considered when trying to look only at these two factors.

The first hurdle is that the scientific community is largely uncertain as to the specific pathophysiology behind preeclampsia. The first step in determining if these women are at increased risk, and if we can prevent this increased risk, is to definitively understand the underlying mechanisms of preeclampsia. This understanding would provide researchers with a target at which to investigate if it is contributing to future cardiovascular risk. Understanding the underlying pathophysiology of preeclampsia would also help to lead the scientific community toward a safe therapy, both for mother and fetus, that would decrease the incidence of preeclampsia.

The second hurdle is to determine, with certainty, as to whether this population is at risk for future increased cardiovascular morbidity and mortality. As medical professionals, it would be unwarranted to prophylactically treat these women if in fact, they do not have a greater risk for future cardiovascular morbidity and mortality. The research included in this review seems to point in the direction that this population of women have a future risk for increased cardiovascular morbidity and mortality. However, there is a need for more studies and more long term studies with large sample sizes to evaluate these women for their future risk of developing cardiovascular morbidity and mortality. It would be astute of these researchers to also control for other variables that contribute to cardiovascular disease such as smoking, obesity, increased waist circumference, family history and genetic inputs, etc. The research that is necessary to determine if these women are at increased risk would control for these variables in an effort to

extrapolate preeclampsia as the primary indicator for future increased cardiovascular morbidity and mortality.

From the data available, it suggests that these women are at risk for future increased cardiovascular morbidity and mortality. The data also suggests that using aspirin for prophylaxis may be contraindicated as its long term use increases the risk of bleeding and hemorrhage to such an extent that it does not outweigh the cardiovascular benefits. Further research is necessary to solidify the conclusions that this population is at risk for future increased cardiovascular morbidity and mortality.

Amongst the science community, there is a great deal of research that is still necessary to determine how we, as providers, would best serve our post-preeclamptic patients. There may possibly be a whole population in which we are unaware of their increased risks. The data is very limited in this population. There are also many factors that may be at play and the research that digs in and separates the different angles at which to approach this question are very limited. Among the limited amount of studies we have available, the sample sizes are often too small and limited, which prevents the application of this information to the general population at large. Many of these studies are also inconclusive which further limits the data pool amongst which to base practice and treatment practices.

The information that is currently available is only a start. There is much more work to be done in order to provide the best healthcare service to these patients. We have a duty as medical professionals to continue to investigate whether this population is at increased risk. We also have a duty to continue to investigate safe interventions to prevent and decrease the future increased risk for cardiovascular morbidity and mortality in this population.

Clinical Application

The clinical implications of this topic are important as there may be a subset of the population that is at increased risk for future cardiovascular morbidity and mortality, that are currently untreated. There are multiple parts to solving this question, that require further research. Some of these questions include the safety of aspirin for prophylaxis in this population, does preeclampsia indeed increase future cardiovascular morbidity and mortality and, is there potentially a different therapy that is beneficial for prophylaxis in this population. It would be wise to first extrapolate if preeclampsia increases future morbidity and mortality. This can be difficult due to the longevity needed to complete such a study. A study design that is this drawn out may be more prone to losing subjects to follow up, which will skew the results. This information is important because if in fact preeclampsia does increase cardiovascular morbidity and mortality in these women, appropriately treating these women could decrease the burden on the healthcare system and save healthcare dollars by preventing major cardiovascular events.

With new evidence that is leading to the evolution of aspirin recommendations for prophylaxis of cardiac or ischemic events in adults greater than 50 years old, more evidence is needed to evaluate the safety of aspirin as prophylaxis for women who were previously preeclamptic. If it turns out that preeclampsia increases future cardiovascular morbidity and mortality, it would be wise to determine if in fact, aspirin is the best prophylactic treatment for this demographic. Is there a different therapy that is more efficacious and has a lower risk of bleeding?

These are questions that we currently don't know the answers to, or the answers we have been provided with are not strong enough to stand on their own. There have been studies done, however, many are of poor design and rely on expert opinion upon which the conclusions are

made. Others have small sample sizes or the sample population is not able to be generalized to the greater population. Many of the studies done are not recent, so it may be difficult to generalize these findings to the general populations today, with the medical and health advancements that have been made.

Again, determining the answers to these questions, and providing sound evidence is important as healthcare providers may not be treating an at-risk demographic. Identifying the risks posed to this population and providing the appropriate treatment may not only benefit the health of the patient, it can decrease healthcare dollars and the burden placed on the healthcare system by potentially preventing a major cardiovascular event.

References

Bokslag, A., Teunissen, P.W., Franssen, C., van Kesteren, F., Kamp, O., Ganzevoort, W…de Groot, C.J.M. (2017). Effect of early-onset preeclampsia on cardiovascular risk in the fifth decade of life. *American Journal of Obstetrics and Gynecology*, *216*, 523.e1-523.e7. http://dx.doi.org/10.1016/j.ajog.2017.02.015

Chambers, J.C., Fusi, L., Malik, I.S., Haskard, D.O., De Suiet, M., & Kooner, J.S. (2001). Association of maternal endothelial dysfunction with preeclampsia. *Journal of American Medical Association, 285 (12)*, 1607-1612. **********DOI**********

Drost, J.T., Maas, A., van Eyck, J., & van der Schouw, Y.T. (2010). Preeclampsia as a female-specific risk factor for chronic hypertension. *Maturitas*, *67*, 321-326. http://dx.doi.org.10.1016/j.maturitas.2010.08.002

Funai, E.F., Friedlander, Y., Paltiel, O., Tiram, E., Xue, X., Deutsh, L., & Harlap, S. (2005). Long-term mortality after preeclampsia. *Epidemiology*, *16*(2), 206-215. http://dx.doi.org.10.1097/01.ede.0000152912.02042.cd

Grandi, S., Vallee-Pouliot, K., Reynier, P., Eberg, M., Platt, R.W., Arel, R…Filion, K.B. (2017). Hypertensive disorders in pregnancy and the risk of subsequent cardiovascular disease. *Paediatric and Perinatal Epidemiology*, *31*, 412-421. http://dx.doi.org.10.1111/ppe.12388

Hashemi, M., Baktash, F., Hashmat-Ghahdarijani, K., Zarean, E., & Bahrani, S. (2016). Evaluation of the effect of low-dose aspirin on endothelial dysfunction in preeclamptic patients. *Journal of Research in Medical Sciences, 21 (1)*, 131. Retrieved from: http://link.galegroup.ocm/apps/doc/A477198443/EAIM?u=ndacad_58202zund&sid=EAIM&xid=70eb2d71 on November 17, 2018.

Heidema, W.M., Scholten, R.R., Lotgering, F.K., & Spaanderman, M.E.A. (2015). History of preeclampsia is more predictive of cardiometabolic and cardiovascular risk factors than obesity. *European Journal fo Obstetrics & Gynecology and Reproductive Biology, 194,* 189-193. http://dx.doi.org/10.1016/j.ejogrb.2015.09.010

Hermes, W., Franx, A., van Pampus, M.G., Bloemenkamp, K.W., van der Post, J.A., Porath, M…de Groot, C.J. (2010). 10-Year cardiovascular event risks for women who experienced hypertensive disorders in late pregnancy: The HyRAS study. *BMC Pregnancy & Childbirth*, *10*,28. http://dx.doi.org.10.1186/1471-2393-10-28

Hermida, R.C., Ayala, D.E., & Iglesias, M. (2003). Administration time-dependent influence of aspirin on blood pressure in pregnant women. *Hypertension,* 651-656. http://doi.10.1161/01.HYP.0000047876.63997.EE

Leslie, M.S., & Briggs, L.A. (2016). Preeclampsia and the risk of future vascular disease and mortality: A review. *Journal of Midwifery and Women's Health*, *61*(3), 315-324. http://dx.doi.org.10.1111/jmwh.12469

Mannisto, T., Mendola, P., Vaarasmaki, M., Jarvelin, M-R., Hartikainen, A-L., Pouta, A., & Suvanto, E. (2013). Elevated blood pressure in pregnancy and subsequent chronic disease risk. *Circulation, 127,* 681-690. http:/doi.org.10.1161/CIRCULATIONAHA.112.128751/-/DC1

McNeil, J.J., Wolfe, R., Woods, R.L., Tonkin, A.M., Donnan, G.A., Nelson, M.R., Reid, C.M…Murray, A.M. (2018). Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *The New England Journal of Medicine, 379* (16), 1509-1518. http://doi.10.1056/NEJMoa1805819

Sarma, A., & Scott, N. (2016). Aspirin use in women: Current perspectives and future directions. *Current Atherosclerotic Report, 18*:74. http://doi.10.1007/s11883-016-0630-1

Spaanderman, M.E.A., Schippers, M., van der Graaf, F., Thijssen, H.J.M., Liem, I.H., & Peeters, L.L.H. (2006). Subclinical signs of vascular damage relate to enhanced platelet responsiveness among nonpregnant formerly preeclamptic women. *American Journal of Obstetrics & Gynecology, 194*, 855-860. http://doi.10.1016/j.ajog.2005.09.012

Sutters, M. (2018). Essential Hypertension. In M. Papadakis and S. McPhee (Eds.), Current Medical Diagnosis and Treatment, Fifty-Seventh Edition (pp. 1714-1715). United States: McGraw Hill Education.

Tang, S-C., & Jeng, J-S. (2010). Management of stroke in pregnancy and the puerperium. *Expert Review of Neurotherapeutics, 10* (2), 205-223. https://dx.doi.org.10.1586/ern.09.126

Theilen, L., Fraser, A., Hollingshaus, M.S., Schliep, K.C., Varner, M.W., Smith, K.R., & Esplin, M.S. (2016). All-cause and cause-specific mortality after hypertensive disease of pregnancy. *Obstetrics and Gynecology*, *128*(2), 238-244. http://dx.doi.org.10.1097/AOG.0000000000001534

Van Alebeek, M.E., de Heus, R., Tuladhar, A. M., & de Leeuw, F-E. (2018). Pregnancy and ischemic stroke: a practical guide to management. *Current Opinion in Neurology, 31*(1), 44-51. https://doi.org.10.1097/WCO.0000000000000522

Wikstrom, A-K., Haglund, B., Olovsson, M., & Lindeberg, S. (2005). The risk of maternal ischaemic heart disease after gestational hypertensive disease. *International Journal of Obstetrics and Gynecology*, *112*, 1486-1491. http://doi:10.1111/j.1471-0528.2005.00733.x