5-2009

Preeclampsia and Future Cardiovascular Risk

Christine Lauzon

Preeclampsia and Future Cardiovascular Risk

by

Christine S. Lauzon

Bachelor of Science in Nursing, University of North Dakota, 1997

An Independent Study

Submitted to the Graduate Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Science, Family Nurse Practitioner Specialization

Grand Forks,North Dakota

May

2009

This independent study, submitted by Christine S. Lauzon in partial fulfillment of the requirements for the Degree of Masters of Science in Nursing from the University of North Dakota, has been read by the Faculty Advisor under whom the work has been done and is hereby approved.

X Cindy M Anderson

Cindy M. Anderson
PhD, WHNP

TABLE OF CONTENTS

ABSTRACT

Several recent studies have shown that women with a history of preeclampsia or gestational hypertension are at increased risk of developing hypertension and cardiovascular disease later in life. It is unclear whether this increased risk is due to underlying conditions in the women that predispose them to preeclampsia, or to the long-term sequelae of the preeclampsia syndrome. It is clear though that cardiovascular disease is the leading cause of death in women. There is a lack of anticipatory guidance for women regarding their future risk of cardiovascular disease following pregnancy complicated by preeclampsia. Therefore, the purpose of this project was to promote a change in clinical practice by educating health care providers about this risk. A comprehensive literature review was completed to gather evidence to guide health care provider's delivery of care and counseling. Educational sessions were provided to appropriate health care personnel, with the anticipated outcome being the implementation of anticipatory guidance for women who are at increased risk. The importance of primary prevention strategies such as lifestyle modifications and early screening were stressed.

CHAPTER ONE

Introduction

Several recent studies have shown that women with a history of preeclampsia or gestational hypertension are at increased risk of developing hypertension and cardiovascular disease later in life (Bellamy, Casas, Hingorani & Williams,2007; Berends, DeGroot, Sijbrands, Sie,Benneheij & Pal,2008; Barden, 2006; Craici, Wagner, & Gerovic,2008; Kestenbaum, Seliger, Easterling,Gillen, Critchlow & Stehman-Breen,2003; Samuels-Kalow & Funai, 2007, Harskamp & Zeeman, 2007, Jonsdottir, Arngrimmson, Geirsson, Sigvaldson &Sigfusson, 1995). Preeclampsia is a disorder of pregnancy that is characterized by hypertension and proteinuria. Onset of manifestations occurs after 20 weeks of gestation, typically in the third trimester (Roberts, Pearson, Cutler & Lindheimer, 2003). Other features of preeclampsia may or may not be present, and include edema, headache, elevated liver enzymes, low platelets, and hyperreflexia (Newstead, Von Dadelszen &Magee, 2007). The occurrence of seizures indicates progression to eclampsia (Roberts et al., 2003). Hypertensive disorders of pregnancy, including preeclampsia, eclampsia, and gestational hypertension, occurs in up to 10% of pregnancies, and remains a leading cause of both fetal and maternal morbidity and mortality worldwide (Wagner, Barac, & Garovic, 2007).

It is unclear whether the increased risk of cardiovascular disease in these women is due to underlying conditions that predispose them to developing preeclampsia, or to the long-term sequelae of the preeclampsia syndrome itself. The disorder was previously considered to be a disease with no long-term sequelae, but this has been refuted by evidence from recent large

studies (Mangos, 2006). These studies suggest that preeclampsia either increases future cardiovascular risk, or that it tends to affect women who have existing cardiovascular risk factors (Mangos, 2006). Many researchers tend to favor the latter position, believing that the development of hypertension in pregnancy may actually be a precipitation of essential hypertension that would have been delayed in the absence of pregnancy (Anderson, 2007).

Statement of the Problem

This project was undertaken to synthesize evidence related to whether women with a history of preeclampsia are at higher risk of developing hypertension and cardiovascular disease than women with no history of preeclampsia. Cardiovascular disease is the leading cause of death for women (CDC, 2007). The majority of these deaths are due to coronary heart disease and stroke. Nearly two thirds of women who die suddenly have no previously recognized symptoms (Newstead et al., 2007). Many Americans are sedentary or inactive, obesity is an epidemic, and the metabolic syndrome is on the rise. Prevention is the key. The American Heart Association (2009) recommends that all women (even those at low cardiovascular risk) pursue dietary and lifestyle changes, such as smoking cessation and increased activity to reduce their cardiovascular risk.

There is a lack of anticipatory guidance for women regarding their increased risk of cardiovascular disease following hypertensive pregnancy. Advice about maintaining or improving cardiovascular health too often falls on deaf ears. Preeclampsia presents an opportunity for personalization of risk, and affords the health care provider with the chance to initiate primary prevention strategies in women at increased risk (Newstead et al., 2007).

Purpose of the Project

There is a lack of anticipatory guidance for women regarding their future risk of cardiovascular disease following preeclampsia. Therefore, the purpose of this project was to promote a change in clinical practice by educating health care providers about this risk. A comprehensive review of the literature was completed to gather evidence to guide health care providers' delivery of care and counseling. Educational sessions were provided to appropriate health care personnel, with the anticipated outcome being the implementation of anticipatory guidance for women who are at increased risk of cardiovascular disease after a history of preeclampsia. The importance of primary prevention strategies such as lifestyle modifications and early screenings will be stressed.

Conceptual/Theoretical Framework

Two conceptual frameworks guided this project; the Health Belief Model and a physiological framework. The Health Belief Model (HBM) was proposed in the 1960s as a framework for exploring why some people who are not currently sick would take actions to prevent future illness, while others do nothing to prevent future illness (Pender, Murdaugh, &Parsons, 2006). The model is viewed as potentially useful to predict individuals who will or will not use preventive measures, and suggests interventions that might increase the use of preventive measures in those who are reluctant to engage in them.

The Health Belief Model

The model asserts that variables which directly affect a person's willingness to take action include the perception of threat to their personal health, and the belief that the benefits of taking action to protect their health will outweigh the barriers that will be encountered. A

person's beliefs about their own personal susceptibility to a specific illness, as well as their beliefs about the seriousness of that illness, combine to produce the "degree of threat" of that illness (Pender et al., 2006).

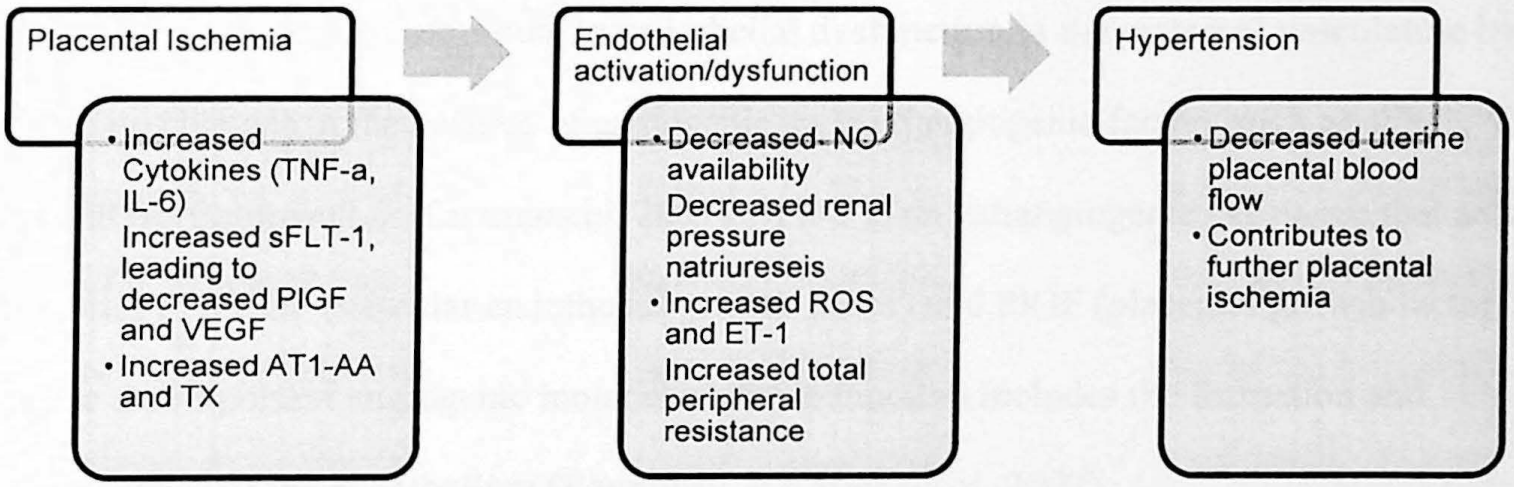
Other variables that come into play in the HBM include the perceived benefits of preventive actions, which are beliefs held by the person about the effectiveness of recommended actions in preventing the health threat. Perceived barriers are the perception that taking preventive action may result in negative aspects such as increased expense, unpleasantness of the action, inconvenience, and amount of time required.

Modifying factors in the HBM include a) demographic variables such as age, sex and race or ethnicity, b) sociopsychologic variables such as personality, social class, and peer pressure, and c) structural variables such as knowledge about the disease and prior contact with the disease (Pender et al., 2006). The HBM is mainly used as a model for disease-preventing behavior, rather than as a model for over-all health promotion. This is an appropriate model for this project, as the focus of this project is the prevention of cardiovascular disease among patients who are at high risk of developing it.

Physiologic framework: Preeclampsia

Another conceptual framework utilized in this project is the physiological framework. Preeclampsia is a pregnancy-specific syndrome characterized by new-onset hypertension and proteinuria (Roberts et al., 2003). It is a significant obstetrical complication, affecting between 5% and 8% of all pregnancies, and is an important cause of maternal and neonatal morbidity and mortality around the world (Manten et al., 2007). Many recent studies have shown new insights into the potential processes underlying the pathogenesis of hypertension in preeclampsia, although uncertainty remains regarding the mechanisms of the disorder.

The placenta plays a key role in both the pathology and the consequences of preeclampsia (Anderson, 2007). Inadequate trophoblast invasion leading to incomplete remodeling of the uterine spiral arteries is considered to be the primary cause of placental ischemia, which then results in synthesis and release of increased amounts of vasoactive factors such as soluble fms-like tyrosine kinase-1 (sFlt-1), and cytokines (Baumwell & Karamanchi, 2007). Figure 1 illustrates a model by which reduced uterine perfusion and placental ischemia may lead to endothelial and cardiovascular dysfunction during pregnancy (adapted from Gilbert et al., 2008).



(Figure1; adapted from Gilbert et al., 2008)

Animal studies

Much research has been done examining the physiological and pathological events leading to the development of preeclampsia. Animal studies have contributed greatly to our knowledge about the disorder. As shown in these animal studies, the maternal vascular endothelium is the target of many factors that are produced in preeclampsia. Nitric oxide (NO) is

2008; Roberts et al., 2003). The subsequent symptoms of preeclampsia, including hypertension and proteinuria, are experienced as part of the maternal syndrome.

Stage One- Abnormal Placentation

The only definitive cure for preeclampsia in humans is the delivery of the placenta. Furthermore, the observation that women who experience a molar pregnancy (in which a placenta develops without a fetus) frequently develop severe preeclampsia leads to the reasonable assumption that the placenta plays a central role in the pathogenesis of preeclampsia (Hladunewich, Karamanchi, &Lafayette, 2007). Examination of placentas from preeclamptic pregnancies reveals placental infarcts and sclerotic narrowing of arteries and arterioles, with diminished endovascular invasion by cytotrophoblasts and inadequate remodeling of the uterine spiral arteries (Hladunewich et al, 2007).

Placentation requires extensive angiogenesis to establish a supply of oxygen and nutrients for the fetus. It is believed that placental angiogenesis is defective in preeclampsia which may eventually lead to placental ischemia.

Stage Two- The Maternal Syndrome

The abnormal placentation that results from the failure of remodeling of the uterine spiral arteries leads to the release of secreted factors into the mother's circulation and culminates in the signs and symptoms of preeclampsia (Hladunewich et al, 2007). All of the manifestations can be attributed to glomerular endotheliosis, increased vascular permeability, and an inflammatory response that results in end-organ damage. These clinical manifestations occur after 20 weeks of gestation, and include hypertension, proteinuria and occasionally coagulopathies and eclampsia.

Significance of Clinical Problem

As cardiovascular disease is the leading cause of death in women (American Heart Association, 2009), reduction of risk is a key element in changing this trend. Many health care providers are not yet aware of the association between a history of hypertensive pregnancy and future cardiovascular disease. Such a history is considered a novel risk marker for cardiovascular disease (Newstead et al., 2007). Education must begin within the health care profession; when health care providers know the risks, it is then that a change in clinical practice may take place.

Assumptions

- Women underestimate their risk of cardiovascular disease.
- Women who are aware of their increased risk of disease may take steps to reduce this risk.
- Health care providers who are aware of this increased risk will educate their patients about risk reduction strategies.

Limitations

- It is unclear where the risk of cardiovascular disease comes from: whether it is a consequence of the long-term effects of preeclampsia or a predisposition to hypertension and cardiovascular disease among affected women. This could possibly lead to different treatment strategies if this were to be determined.
- There are no guidelines published that deal specifically with women with a history of hypertensive pregnancy. Guidelines must be used that are directed at all women, regardless of their risk level.

Summary

Women with a history of hypertensive pregnancy, and specifically women with a history of preeclampsia, are at increased risk of developing cardiovascular disease later in life. Most of these women are unaware of their increased risk, as many health care providers are not yet counseling their patients about it. Cardiovascular disease remains the leading cause of death among women. Many risk factors for cardiovascular disease are modifiable, and efforts must be made to educate patients on strategies which may be helpful in reducing risk. Effective anticipatory guidance must be implemented to help decrease this risk, and to help promote the health of women around the world.

CHAPTER TWO

Review of the Literature

Introduction

This project was undertaken to synthesize evidence related to whether women with a history of hypertensive pregnancy are at a higher risk of developing cardiovascular disease and hypertension than women with a history of normotensive pregnancy. Preeclampsia was considered in the past to be a disorder which had no lasting consequences for the women who were affected by it. There is increasing evidence to the contrary. Studies in the last several years have shown that there are clearly some long-term sequelae for these women. It is not entirely clear at this time whether the consequences are due to factors in the women that predispose them to developing preeclampsia, or whether the disorder changes the endothelial function of sufferers causing them to be more likely to develop cardiovascular dysfunction. In either case, women with a history of preeclampsia are at greater risk for development of future cardiovascular disease. Further research is underway which may answer that question in the future.

There is evidence of cardiovascular risk ; action must be taken to evaluate risk, prevent disease when possible, and treat when necessary. Clinical guidelines based on current evidence are developed to help guide health care provider's practice. These guidelines may be specific to

the individual patient, or may be taken from guidelines developed for a broader population and tailored to meet the patient's needs. This project will present guidelines that can be used to assist in the care of women with a history of hypertensive pregnancy.

Hypertension in Pregnancy

Preeclampsia is a pregnancy-specific syndrome characterized by new-onset hypertension and proteinuria (Roberts et al., 2003). It is a significant obstetrical complication, affecting between 5% and 8% of all pregnancies, and is an important cause of maternal and neonatal morbidity and mortality around the world (Manten et al., 2007). Other features of preeclampsia may or may not be present, and include edema, headache, elevated liver enzymes, low platelets, and hyperreflexia (Newstead et al., 2007). The occurrence of seizures indicates progression to eclampsia (Roberts et al., 2003).

Hypertension can present in pregnancy as preeclampsia/eclampsia, gestational hypertension, and as a continuation of chronic hypertension. Gestational hypertension is defined as new hypertension arising after midpregnancy, and is distinguished from preeclampsia by the absence of proteinuria (Roberts et al., 2003). This category is broad and includes women who later become preeclamptic and other women with increased blood pressure prior to pregnancy whose true diagnosis is masked by the tendency of blood pressure to decrease in early pregnancy. However, in most cases blood pressure normalizes in the postpartum period, at which time, the diagnosis of gestational hypertension is changed to transient hypertension of pregnancy (Roberts et al., 2003).

Chronic hypertension is defined as hypertension that predates the pregnancy. It can be assumed when elevated blood pressure is detected before 20 weeks of gestation, and can also be diagnosed in retrospect, when hypertension fails to normalize 12 weeks after delivery (Roberts, 2003). Chronic hypertension may not have been recognized prior to the pregnancy. It is an important category to consider, as women with chronic hypertension have a 25% chance of developing super-imposed preeclampsia, and outcomes for mothers and children in this instance are worse than for those suffering from de novo preeclampsia.

Cardiovascular Risk

Cardiovascular disease is the leading cause of death for women (CDC, 2007). The majority of these deaths are due to coronary heart disease and stroke. Nearly two thirds of women who die suddenly have no previously recognized symptoms (Newstead et al., 2007). Many Americans are sedentary or inactive, obesity is an epidemic, and the metabolic syndrome is on the rise. Prevention is the key. The American Heart Association (2009) recommends that all women (even those at low cardiovascular risk) pursue dietary and lifestyle changes, such as smoking cessation and increased activity.

Developmental Origins of Cardiovascular Disease

While the focus of this project was on the increased risk assumed by women with a history of hypertensive pregnancy, it is important to point out that their children may also carry increased risk of disease later in life. Barker (1990, 2004) states that early fetal and infant environment is predictive of the risk of hypertension, coronary artery disease, and type II diabetes later in life. He asserts that these diseases arise through developmental plasticity, in

response to under nutrition. Developmental plasticity refers to the quality of living things which allows them to adapt to environmental conditions by producing an alternative form of structure, physiological state, or behavior (Barker, 2004).

Anderson (2007) discussed the increased risk of cardiovascular disease that the children of preeclamptic mothers share. She states that the identification of these risks can be an opportunity to employ effective strategies for enhancing the health of women, their children, and future generations.

Preeclampsia and Increased Cardiovascular Risk

Ray, Vermeulen, Schull, and Redelmeier (2005) conducted a population-based retrospective cohort study (commonly known as the CHAMPS study) in Ontario, Canada. They studied 1.3 million women who were free from cardiovascular disease before their first delivery. Of these women, 75,380 were diagnosed with a maternal placental syndrome during their pregnancy (defined as preeclampsia, gestational hypertension, and placental abruption or infarction). The incidence of cardiovascular disease was 500 per million person-years in women with a maternal placental syndrome, compared with 200 per million in women who did not have a maternal placental syndrome (RR= 2.0, CI 95%). The risk was even higher if the maternal placental syndrome was accompanied by poor fetal growth (RR= 3.1), or in a maternal placental syndrome complicated by intrauterine fetal death (RR= 4.4).

Strengths of the study include the size of the population studied (over 1 million women). The study authors adjusted for preexisting cardiovascular disease or other potential confounders such as hypertension, diabetes, dyslipidemia, smoking, obesity, and renal disease (Ray et al., 2005). Limitations were noted by the authors, and included unmeasured potential confounders

(such as prescription drug use, or misdiagnosed hypertension) which could have biased their estimates of associated risk between maternal placental syndrome and cardiovascular disease.

Funai et al. (2005) studied 37,061 women who delivered in Jerusalem from 1964 to 1976, including 1,070 who had preeclampsia during their pregnancy. They followed them for 24-36 years following delivery, and found the relative risk of death from cardiovascular disease after preeclampsia to be 2.1. The authors controlled for the women's age, education, history of diabetes, heart disease, social class and history of low-birth weight birth.

Interestingly, this study showed that women who developed preeclampsia during one pregnancy but subsequently had a normotensive pregnancy still had excess risks of death from cardiovascular disease, although these risks did not express themselves until more than 20 years after the hypertensive pregnancy. This demonstrates that any woman with a hypertensive pregnancy is at increased risk of cardiovascular disease in the future.

Irgens, Reisater, Irgens,Lie, & Roberts (2001) conducted a population based cohort study using the Norwegian birth registry from 1967 to 1992. Six hundred thousand, two hundred seventy two women gave birth for the first time during this period, and were identified as either having preeclampsia or not, as well as whether they delivered preterm or at term.Women in this study who had preeclampsia had a 1.2-fold higher risk of death than women who did not have preeclampsia. The risk in women who had preeclampsia and a preterm delivery was 2.71-fold higher than women who did not have preeclampsia. In particular, the risk of death from cardiovascular disease among women with preeclampsia and preterm delivery was 8.12-fold higher than women who did not have preeclampsia.

This is a very important study, based on its size and the length of follow-up. It showed a significantly increased risk of death from cardiovascular disease for women who experience preeclampsia in pregnancy, especially in those who deliver early.

A study conducted by Lampinen,Ronnback, Kaaja & Groo (2006) compared 30 previously preeclamptic women who were randomly selected from a group of women with moderate to severe preeclampsia, with 21 women who had pregnancies not complicated by preeclampsia. The study was done 5 to 6 years following the index pregnancy, in order to exclude any residual effects of the disorder. The groups were similar with regards to age, BMI, and smoking, although it was noted that the study participants had higher blood pressures than the controls. The study results confirmed the presence of abnormal vasodilatation using a reproducible experimental protocol in the previously preeclamptic women. This raises the suspicion that women with a history of preeclampsia have continued endothelial dysfunction, which contributes to their risk for cardiovascular disease. However, it must be noted that this study was very small, and confounding factors such as diabetes and dyslipidemia were not controlled for. There is still no clear evidence whether the increased cardiovascular risk was due to damaged endothelium caused by preeclampsia, or to common risk factors for both cardiovascular disease and preeclampsia which contributed to the women developing it in the first place.

Kestenbaum et al.,(2003) conducted a population-based cohort study to estimate the risks for cardiovascular and thromboembolic events in women with a history of pregnancy-related hypertension. They analyzed data from all singleton births recorded in Washington State from 1987 to 1998. Mothers were classified as having gestational hypertension, preeclampsia, or chronic hypertension. Birth records were linked to subsequent hospitalizations for cardiovascular

events (acute MI or coronary artery revascularization procedure) or thromboembolic events (acute stroke, DVT, or pulmonary embolism). A total of 44,550 hypertensive pregnancies were recorded from 807,010 singleton births in the time period studied. Exclusions were made based on pre-existing conditions such as cardiac disease, diabetes, or renal disease. Furthermore, patients with pre-existing chronic hypertension were excluded, as well as patients for whom hypertension in pregnancy could not be classified. After these exclusions, 31,239 hypertensive pregnancies were classified into gestational hypertension, mild preeclampsia, and severe preeclampsia. A sample of 92,902 control mothers without pregnancy-related hypertension was matched to the hypertensive group by age, parity, and year of delivery.Mean length of follow-up was 7.8 years. During this time, there were 118 first hospitalizations for cardiovascular events among all mothers in the group. Among women without hypertension in pregnancy, the incidence density was 8.9 events/100,000 patient years compared with 25.3, 18.4, and 29.4/ 100,000 patient years for mothers with gestational hypertension, mild preeclampsia, and severe preeclampsia respectively. All forms of pregnancy-related hypertension were associated with a significantly increased risk for cardiovascular events; the magnitude of excess risk with preeclampsia was similar to that for smoking.

During the same time period, there were 172 hospitalizations for thromboembolic events. In the control group, the incidence density of thromboembolic events was 15.4/100,000 patient years. In comparison, incidence density was 21.3, 23.0, and 40.1 events/100,000 patient years for mothers with gestational hypertension, mild preeclampsia, and severe preeclampsia respectively. After adjustment for confounding factors, women with a history of severe preeclampsia had a significantly greater risk for a thromboembolic event compared with control women without hypertension in pregnancy.

Gestational hypertension, mild preeclampsia, and severe preeclampsia were found in this study to be associated with 2.8, 2.2, and 3.3 greater fold risks for cardiovascular events, respectively. Severe preeclampsia was associated with an increased long term risk for thromboembolic events. The authors feel that women with a history of hypertensive pregnancy may require more aggressive attention to co-morbid cardiovascular risk factors and may demand a lower clinical threshold to initiate diagnostic testing when cardiovascular symptoms arise.

A systematic review and meta-analysis was conducted by Bellamy et al.,(2007) looking at the association between preeclampsia and the development of cardiovascular disease or hypertension later in life. They included prospective and retrospective cohort studies which assessed women with any parity or age who developed any severity of preeclampsia. Over all, the authors identified 117 full text articles, of which 25 met all the inclusion criteria and were used.

From their analysis of these studies, Bellamy et al. found the relative risk of developing hypertension was 3.70 when compared with women who did not have preeclampsia. The relative risk (RR) of developing ischemic heart disease in women with previous preeclamptic-pregnancy was over twice that of women who had not developed preeclampsia.

Gestational age at onset of preeclampsia was shown to be associated with higher risk of ischemic heart disease: preeclampsia before 37 weeks of gestation was associated with nearly an eight-fold increased risk of ischemic heart disease. The severity of the preeclampsia also increased the risk of later heart disease, although not to the same degree as gestational age. Women with severe preeclampsia had a greater risk of later heart disease (RR= 2.25 to 3.65) compared with women with mild preeclampsia (RR=1.65 to 2.24).

Other findings of note in this systematic review include the finding that women with a history of recurrent preeclampsia (compared with women who had preeclampsia in their first pregnancy only) carry a seven-fold greater risk of developing hypertension. It was also observed that women who had early preeclampsia had the greatest risk of future cardiovascular disease, and this risk was even higher than those who had severe preeclampsia. The authors deducted from this that earlier onset of preeclampsia reflects the maternal cardiovascular phenotype, while the severity of preeclampsia may reflect more on the timeliness of antenatal observations (Bellamy et al., 2007).

As demonstrated in these studies, a history of preeclampsia is linked to significantly increased risk for cardiovascular disease, hypertension, and stroke later in life. Also demonstrated is the link between early or severe preeclampsia and even greater risk of cardiovascular pathology. Whether this is due to shared risk factors for both disorders- namely diabetes, hypertension, dyslipidemia, and obesity- or to the long-term effects of preeclampsia, it will be important to study this further in an effort to develop better prevention strategies and treatments.

Cardiovascular Risk Markers and the Development of Preeclampsia

There appears to be evidence that women with preexisting risk factors for cardiovascular disease are also at higher risk of developing preeclampsia if they become pregnant. A population-based cohort study done by Balstad- Magnussen, Vatten, Lund-Nilsen, Salveseon,

Smith, and Romundstad (2007) reported positive associations between prepregnancy serum levels of triglycerides, cholesterol, LDL, non-HDL, and blood pressure and the development of preeclampsia. The odds ratio for developing preeclampsia for a woman with a baseline systolic blood pressure of >130mmHg was 7.3, compared with women with a baseline systolic blood pressure of <111mmHg. The authors assert that this may suggest that preeclampsia and cardiovascular disease may share a common origin.

The study assessed 3,494 women giving birth in Norway, of whom 133 developed preeclampsia (3.8%). The prospective design and population base of this study make bias an unlikely explanation for the results (Balstad-Magnussen et al., 2007). A limitation of this study may be that blood lipid levels were not fasting levels, and some lipid concentrations in the blood are impacted by recent food intake. Another limitation the study authors noted is that hypertension in pregnancy may be misclassified, a limitation that is common among all of these studies.

A systematic review of controlled studies was done by Duckitt and Harrington (2005) which assessed for risk factors for preeclampsia at antenatal booking. Fifty two studies were included in the review, including 13 prospective cohort studies, 25 retrospective cohort studies and 14 case-control studies. The following factors were associated with the development of preeclampsia: a) age of >40 years=2x risk, b)preeclampsia in first pregnancy= 4x risk, c) history of preeclampsia in previous pregnancy =7x risk, d)family history of preeclampsia =3x risk, e) presence of insulin-dependent diabetes= 4x risk, f)BMI >25 carried 2x risk, while a BMI >35 carried 4x risk. In addition, the presence of chronic hypertension or renal disease also increased the risk. This review shows that the risk factors for cardiovascular disease may be similar to the risk factors for preeclampsia, which may indicate a shared risk. Of note in this study, there was

no differentiation between mild or severe preeclampsia, or between early versus later onset of the disorder. As previous studies have shown that cardiovascular risk is greatest when preeclampsia is early and/or severe, this is important information to obtain.

Mazar, Srinivas, Sammel, Andrela & Elovitz (2007) conducted a case-control study to determine whether the metabolic syndrome was associated with preeclampsia. Two hundred fifty nine women with preeclampsia were studied, along with a control group of 297. Each woman was given a metabolic score of 0, 1, or 2 or more, based on pre-pregnancy data consisting of pre-pregnancy BMI, presence of hypertension and presence of diabetes. The authors found that an initial metabolic score of 1 (compared with 0) increased the odds of developing preeclampsia by 1.67(P=.017), and an initial metabolic score of 2 or more (compared with 0) increased the odds of developing preeclampsia by 2.96 (P=.006).This study demonstrated that the metabolic score (as a surrogate measure of the metabolic syndrome) is independently associated with the development of preeclampsia. The authors assert that this finding should prompt more rigorous studies addressing all the components of the metabolic syndrome, including not only their relationship to preeclampsia risk but also to long-term cardiovascular risk in women with a history of preeclampsia.A limitation of this study is that the authors were not able to determine which metabolic component contributed to the additional risk, as each component was equally weighted. It also did not include lab data, and so triglyceride and cholesterol levels were not known. Like cardiovascular disease, preeclampsia may be the end point of many different processes of disease. The authors of this study acknowledge that the metabolic syndrome may serve as an explanation for only some cases of preeclampsia.

Preeclampsia as a Novel Risk Marker for Cardiovascular Disease

Many health care providers incorporate the use of a global risk-assessment tool, such as the Framingham tool, that take a risk marker tally approach to the assessment of cardiovascular risk (Wilson et al., 1998). Factors typically assessed for include gender, age, blood pressure, and cholesterol levels (LDL and HDL). These are then used to determine the 10 year cardiovascular disease risk estimate.

Newstead et al. (2007) assert that preeclampsia should be taken into account as a new and novel risk marker for cardiovascular disease. They state that preeclampsia and cardiovascular disease share risk markers and have a similar clinical picture and pathology, leading to the hypothesis that there is an underlying maternal disposition to vascular disease.

Samuel-Kalows & Funai (2007) hypothesize that a pre-existing disposition, most likely genetic, can be manifested as disease during the physiologic stress of pregnancy, and again in combination with other physiologic stressors later in life. As the risk of later life disease can likely be modified by lifestyle and the environment, the authors suggest that patients with a history of preeclampsia should be followed closely by primary care providers who are aware of the increased risk of cardiovascular disease. Health care providers should identify women at risk early enough so they can benefit from lifestyle and pharmacologic interventions.

Recommendations

The authors of many studies offered recommendations for the care of women with a history of preeclampsia. Bellamy et al. state: "If a history of pre-eclampsia exerts an independent risk for future cardiovascular disease it may increase the risk of cardiovascular disease in mid-

life in affected women, which would render them eligible for preventive therapies at an earlier age than usual" (2007).

Magee (2007) states that preeclampsia is a novel cardiovascular risk marker. A history of it increases both the long-term risk of developing cardiovascular disease, and the risk that it will occur earlier. However, the absolute risk in the short-term is still low. Few young women with previous preeclampsia are likely to have values of lipids, blood sugars, or blood pressure that is above intervention thresholds. Magee asserts that global risk-assessment tools have limited applicability to young women, as there may be errors in the risk estimate. A single risk factor may confer high risk in the long run, even if the 10 year risk does not appear high. The author acknowledges that there is no evidence yet to support earlier screening for cardiovascular disease or lowering thresholds for treatment. Magee states that there is a large body of evidence showing that a heart-healthy diet and lifestyle decreases cardiovascular risk, and that such advice is applicable to all women- regardless of cardiovascular risk- and is probably the most appropriate initial intervention for women with previous preeclampsia (Magee, 2007).

Newstead et al., (2007) state that clinicians need to follow evidence-based practice, and consider practice guidelines that have recommendations based on such evidence. Unfortunately, there are no published evidence-based guidelines for management of women who lack traditional cardiovascular risk markers, but who do have a history of preeclampsia. Newstead et al. reported on a national survey done of American physicians (including primary care doctors, OB/GYNs, and cardiologists): the physicians were more likely to underestimate the cardiovascular risk of women compared with men. This indicates that physician awareness of women's risk is inadequate.

Perceived personal risk has been shown to increase risk-reduction behaviors (Pender, 2006). Taking action (such as by making lifestyle changes) is associated with perceived high risk and general awareness (Newstead et al., 2007). Consequently, Newstead et al. believe that we may have a window of opportunity for the identification of women at risk following a pregnancy complicated by hypertension, and that this allows us the chance for "personalization of risk", which may lead to risk-reducing behaviors.

Samuels-Kalow & Funai (2007) and Williams (2003), state that pregnancy may be a "stress test" that might unmask pre- and subclinical illnesses that manifest later in life. Pregnancy complications and later life maternal disease may share many of the same risk factors, including a family history of cardiovascular disease, hypertension and diabetes. The authors assert that a pre-existing predisposition can be manifested as disease during the physiologic stress of pregnancy, and again in combination with other physiologic stressors later in life.

The authors recommend that women with a history of hypertensive pregnancy should be aware of their increased risk for future disease, and should follow-up with a health care provider who is also aware of the increased cardiovascular risk associated with hypertensive pregnancy. Providers can then identify women at risk early enough for them to benefit from lifestyle changes and pharmacologic interventions.

Guidelines

At this time, the most appropriate published guideline for use in caring for women with a history of hypertensive pregnancy are the Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update (Mosca, Appel & Benjamin). Recommendations for heart disease prevention are as follows:

Summary of the Review of Literature

The evidence for a link between preeclampsia and future cardiovascular disease is strong. Many studies, looking at many women, have shown conclusively that a history of hypertension in pregnancy is associated with an increased risk of future cardiovascular disease. In addition, many of these studies also show that a history of early-onset or severe preeclampsia, especially when coupled with fetal compromise, greatly increases a woman's risk of cardiovascular disease and even death.

While the evidence does not yet clearly show the direction of the association, it is clear that preeclampsia and cardiovascular disease share many of the same risk factors. Awareness of the presence of these risk factors in a pregnant woman may alert the health care provider to be aware of subtle signs of developing preeclampsia. It also offers an opportunity for education and guidance in the reduction of these risk factors when possible.

CHAPTER THREE

Methods

The purpose of this project was to promote a change in clinical practice by educating health care providers about this risk. A comprehensive literature review was completed to gather evidence to guide health care provider's delivery of care and counseling. Educational sessions were provided to appropriate health care personnel, with the anticipated outcome being the implementation of anticipatory guidance for women who are at increased risk.

Search Strategy

Electronic searches were conducted on the following databases: Pub Med, CINAHL, Medline Plus, the Cochrane database (specifically the pregnancy and childbirth group), and guidelines.gov. Inclusion criteria were articles written within the last ten years, as much of the evidence of increased cardiovascular risk has been reported through research that has been done more recently. Other inclusion criteria were articles published in English, and articles that were available through linked full text or inter-library loan. Search terms included: preeclampsia, hypertensive pregnancy, gestational hypertension, cardiovascular disease, risk of cardiovascular disease, hypertension, risk of hypertension, and combinations of all the terms above.

The MeSH database was implemented, with MeSH terms consisting of preeclampsia, cardiovascular disease, and risk. Guidelines were accessed from guidelines.gov, including guidelines for the recognition and treatment of preeclampsia, and guidelines for prevention of cardiovascular disease in women. Only one article was found in the Cochrane database which

discussed hypertension in pregnancy and future cardiovascular disease (Meher & Duley, 2005); as it was a protocol for reviewing studies it provided little new information.

Educational Project

There is a lack of anticipatory guidance for women with a history of preeclampsia. The purpose of this study was to promote a change in clinical practice by educating health care providers about the increased risk of later cardiovascular disease associated with hypertensive pregnancy. The anticipated outcome would be the implementation of appropriate surveillance and counseling for women at increased risk.

Based on conclusions from the comprehensive review of literature, an educational poster was constructed which introduced the viewer to the evidence of increased cardiovascular risk present in women with a history of preeclampsia. The problem (a lack of anticipatory guidance) and purpose of the study (to promote a change in clinical practice) were clearly stated. Study methods were outlined. Nursing implications were stated, which included the promotion of effective screening and intervention strategies, counseling women about their cardiovascular risk, and encouragement of primary prevention techniques. Clinical guidelines for the reduction of cardiovascular risk in women were presented (Appendix A).

Presentation of this educational poster was completed at the Graduate School Forum, which is open to the Graduate School students and faculty, as well as to the entire student and faculty body of the University of North Dakota. The poster was also used in the provision of an educational session that was completed for the Family Medicine Center staff, including Physicians and Nurse Practitioners who care for women. In addition, this information was

disseminated to nurses working in the Family Birthing Center at Altru Hospital, who care for women after a hypertensive pregnancy, and are in a position to offer counsel regarding the increased risk associated with such a pregnancy, as well as primary prevention strategies which are of importance to these women.

Discussion

The educational poster was presented at the Graduate School Forum in spring, 2008. In attendance were several undergraduate nursing students, graduate nursing students, College of Nursing Faculty, the Dean of the Graduate School, and many other Graduate School students and faculty. The information was presented to interested individuals in verbal form, along with the visual aid of the poster. For many people, the information presented was new to them, as they had not previously been aware of the link between preeclampsia and future cardiovascular disease. On more than one occasion, a woman who herself had a history of preeclampsia was educated on the increased risk that accompanies such a history. The importance of primary prevention strategies were emphasized to every individual who viewed the poster, including smoking cessation, weight control, avoidance of high-fat diets, and adequate physical activity.

In March of 2009, this information was presented to 4 physicians and 1 nurse practitioner who work at Altru's Family Medicine Center in Grand Forks, ND. These are practitioners who routinely care for women. Initially some were unsure how relevant the information was for them, as only one actually cares for women during pregnancy. It was explained that the information is relevant for every practitioner who cares for women, as it is the history of hypertensive pregnancy in her past that puts her at risk for cardiovascular disease now and in the future. Again, this was information that was not widely known. Two of the practitioners stated that they

had read journal articles or research studies that presented evidence of cardiovascular risk in women with such a history. The others did not recall having heard this information before. The practitioners were given references which contain evidence of the association between preeclampsia and cardiovascular disease (contained in the Reference List on the poster).

Many of the questions received in response to this education involved whether there were guidelines or recommendations regarding screenings or threshold for treatment of blood pressure or lipid levels specifically for women with a history of hypertensive pregnancy. They were informed that no specific guidelines exist at this time, and were counseled to follow existing guidelines for decreasing risk of cardiovascular disease in women (which were summarized in the poster), and to encourage their patients to follow primary prevention recommendations.

In addition to the planned educational sessions, a session was held on the Family Birthing Center with registered nurses who work in the labor and delivery and postpartum units. The information contained on the poster was verbally summarized for the nurses, and questions regarding this project were answered. Again, the information was new for many of the nurses. Most reported that they were unaware of the link between preeclampsia and future cardiovascular disease. When questioned, most of the nurses stated that they told patients that there were no known adverse outcomes associated with preeclampsia once the delivery and immediate postpartum period had passed. Most nurses stated that this was what they had read or learned in nursing school, and that they had never heard a physician counsel a woman with hypertension in pregnancy about her increased risk for cardiovascular disease. This highlights an obvious gap in education for both nurses and other health care providers.

2007;and Brenner & Rector, Chapter 44, 2007), the information has not been widely disseminated among nurses caring for women. Indeed, the results of these educational sessions point out that even physicians and nurse practitioners do not fully understand the link, and therefore have not afforded it much importance. In order for us to provide our patients with the most relevant and appropriate care and counseling, it is imperative that this information be not only taught to all health care students, but that the importance of it is emphasized.

In addition to teaching this in our nursing schools and medical schools, it is important to remember that there are many nurses, nurse practitioners, and physicians already in practice who are unaware of the link between preeclampsia and cardiovascular disease. It is crucial that this knowledge be spread to practicing health care providers. Manuscript publication can be invaluable for the dissemination of knowledge, but educational sessions may also be useful to reach a number of practitioners.

Research

Women with a history of preeclampsia are at increased risk for cardiovascular disease later in life; possible explanations include the involvement of the metabolic syndrome, diabetes, hypertension, dyslipidemia and atherosclerosis. This information prompts further research into the prevention of both preeclampsia and cardiovascular disease. Further research is needed to examine the mechanisms underlying the association between preeclampsia and future cardiovascular risk. While research into the causative factors behind preeclampsia is ongoing, it will be important to also investigate strategies to decrease risk of hypertension in pregnancy and its sequelae.

Cardiovascular disease is the leading cause of death for women in this country. Many Americans are sedentary or inactive, obesity is an epidemic, and the metabolic syndrome is on the rise. Prevention is the key. Many health care providers remain unaware of the association between future cardiovascular disease and a history of hypertensive pregnancy; hence, there is a lack of anticipatory guidance for women regarding this risk. Education must begin within the health care profession; when health care providers know the risks, then a change in clinical practice may take place. Advice about maintaining or improving cardiovascular health too often falls on deaf ears. Preeclampsia presents an opportunity for the personalization of risk, and affords the health care provider with the chance to initiate primary prevention strategies for women at increased risk.

References

American Heart Association (2009). *Heart Disease in Women.* Retrieved 4/02/09, from http:www.americanheart.org/presenter.jhtml?identifier=1200011

Anderson, C. M. (2007, January/February). Preeclampsia: Exposing future cardiovascular risk in mothers and their children. *The Journal of Obstetric, Gynecologic, and Neonatal Nurses, 36*(1), 3-8.

Balstad Magnussen, E., Vatten, L. J., Lund-Nilsen, T. I., Salvesen, K. A., Smith, G. D., & Romundstad, P. R. (2007, November 1). Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: Population based cohort study. *British Medical Journal, 335*(978-986).

Barden, A. (2006). Pre-eclampsia: contribution of maternal constitutional factors and the consequences for cardiovascular health. *Clinical and Experimental Pharmacology and Physiology, 33,* 826-830.

Barker, D. J. (1990). The fetal and infant origins of adult disease. *British Medical Journal, 301,* 1111.

Barker, D. J. (2004). Developmental origins of adult health and disease. *Journal of Epidemiology and Community Health, 58,* 114-115.

Baumwell, S., & Karumanchi, S. (2007). Pre-eclampsia: clinical manifestations and molecular mechanisms. *Nephron Clinical Practice, 106,* 72-81.

Bellamy, L., Casas, J., Hingorani, A. D., & Williams, D. J. (2007). Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *British Medical Journal, 335,* 974-986.

Berends, A., DeGroot, C., Sijbrands, E., Sie, M., Benneheij, S., & Pal, R. et al. (2008, February 7). Shared constitutional risks for maternal vascular-related pregnancy complications and future cardiovascular disease. *Hypertension:Journal of the American Heart Association, 51,* 1-8.

Brenner & Rector (2007). *Brenner and Rector's The Kidney, 8th ed.* Saunders, An Imprint of Elsevier.

Centers for Disease Control and Prevention (2007, November). *Heart Disease Facts and Statistics.* Retrieved March 17, 2008, from http://www.cdc.gov/heartdisease/facts.htm

Chelbi, S. T., & Vaiman, D. (2008). Genetic and epigenetic factors contribute to the onset of preeclampsia. *Molecular and Cellular Endocrinology, 282,* 120-129.

Craici, I., Wagner, S., & Gerovic, V. (2008). Review: Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test? *Therapeutic Advances in Cardiovascular Disease*, 2, 249-259.

Duckitt, K., & Harrington, D. (2005). Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *British Medical Journal* . Retrieved April 10, 2006, from doi:10.1136/bmj.38380.674340.EO.

Funai, E. F., Friedlander, Y., Paltiel, O., Tiram, E., Xue, X. N., & Deutsch, L. et al. (2005). Long term mortality after preeclampsia. *Epidemiology, 16,* 206-215.

Gabbe(2007). *Obstetrics: Normal and Problem Pregnancies* (5th ed.). Churchill Livingstone, An Imprint of Elsevier.

Gilbert, J. S., Ryan, M. J., LaMarca, B. B., Sedeek, M., Murphy, S. R., & Granger, J. P. (2008, February). Pathophysiology of hypertension during preeclampsia: linking placental

ischemia with endothelial dysfunction. *American Journal of Physiology Heart Circ Physiology, 294,* 541-550.

Harskamp, R. E., & Zeeman, G. G. (2007, October). Preeclampsia:At risk for remote cardiovascular disease. *The American Journal of the Medical Sciences, 334*(4), 291-295.

Hladunewich, M., Karumanchi, S. A., & Lafayette, R. (2007). Pathophysiology of the clinical manifestations of preeclampsia. *Clinical Journal of the American society of Nephrology,* 2, 543-549.

Irgens, H. U., Reisater, L., Irgens, L. M., Lie, R. T., & Roberts, J. M. (2001). Long term mortality of mothers and fathers after preeclampsia: population based cohort study. *BMJ, 357,* 1213-1217.

Jonsdottir, L. S., Arngrimsson, R., Geirsson, R. T., Sigvaldson, H., & Sigfusson, N. (1995). Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. *Acta Obstet Gynecol Scand, 74,* 772-776.

Kestenbaum, B., Seliger, S. L., Easterling, T. R., Gillen, D. L., Critchlow, C. W., & Stehman-Breen, C. O. et al. (2003). Cardiovascualr and thromboembolic events following hypertensive pregnancy. *American Journal of Kidney Diseases, 42,*

LaMarca, B. D., Gilbert, J., & Granger, J. P. (2008, February 7). Recent progress toward the understanding of the pathophysiology of hypertension during preeclampsia. *Hypertension: Journal of the American Heart Association, 51.*

Lam, C., Lim, K., & Karumanchi, S. (2005). Circualting angiogenic factors in the pathogenesis and prediction of preeclampsia. *Hypertension: The Journal of the American Heart Association, 46,* 1077-1085.

Lampinen, K., Ronnback, M., Kaaja, R. J., & Groo, P. (2006). Impaired vascular dilation in women with a history of preeclampsia. *Journal of Hypertension, 24,* 751-756.

Magee, L. A., & VonDadelszen, P. (2007, November). Pre-eclampsia and increased cardiovascular risk. Guidelines for primary prevention of cardiovascular disease are appropriate for all women. *British Medical Journal, 335,* 945-946.

Mangos, G. J. (2006). Cardiovascular disease following pre-eclampsia: understanding the mechanisms. *Journal of Hypertension, 24,* 639-641.

Manten, G., Sikkema, M., Voorbij, H., Visser, G., Bruinse, H., & Franx, A. (2007). Risk factors for cardiovascular disese in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. *Hypertension in Pregnancy, 26,* 39-50.

Mazar, R. M., Srinivas, S. K., Sammel, M. D., Andrela, C. M., & Elovitz, M. A. (2007). Metabolic score as a novel approach to assessing preeclampsia risk. *American Journal of Obstetrics and Gynecology, 197,* 411.e1-411.e5.

Meher, S., & Duley, L. (2005). Interventions for prevention of preeclampsia and its' consequences: generic protocol (Protocol).*Cochrane Database of Systematic Reviews*(2).

Mosca, L., Appel, L. J., & Benjamin, E. J. (2007, March 20). Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation, 115*(11), 1481-1501.

Newstead, J., Von Dadelszen, P., & Magee, L. (2007). Preeclampsia and future cardiovascular risk. *Expert Review of Cardiovascular Therapy, 5*(2), 283-294.

Pender, N. J., Murdaugh, C. L., & Parsons, M. A. (2006). *Health Promotion in Nursing Practice* (5th ed). Upper Saddle River, NJ: Pearson Prentice Hall.

Ray, J. G., Vermeulen, M. J., Schull, M. J., & Redelmeier, D. A. (2005, November 19). Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. *The Lancet, 366,* 1797-1803.

Roberts, J., Pearson, G., Cutler, J., & Lindheimer, M. (2003). Summary of the NHLBI Working Group on research on hypertension during pregnancy. *Hypertension: The Journal of the American heart Association, 41,* 437-445.

Samuels-Kalow, M. E., & Funai, E. F. (2007). Is pregnancy a stress test? *Contemporary OB/GYN*, 59-72.

Smith, G. C., Pell, J. P., & Walsh, D. (2001). Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet, 357,* 2002-2006.

VanPampus, M. G., & Aarnoudse, J. G. (2005, June). Long-term outcomes after preeclampsia. *Clinical Obstetrics and Gynecology, 48*(2), 489-494.

Wagner, S. J., Barac, S., & Garovic, V. D. (2007, July). Hypertensive pregnancy disorders: current concepts. *The Journal of Clinical Hypertension, 9*(7), 560-566.

Williams, D. (2003). Pregnancy: a stress test for life. *Current Opinion in Obstetrics and Gynecology, 15*, 465-471.

Wilson, P., D'Agostino, R., Levy, D., Belanger, A., Silbershatz, H., & Kannel, W. (1998). Prediction of coronary heart disease using risk factor categories. *Circulation,97,*1837-1847.