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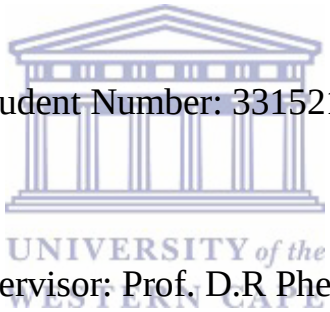

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Title of Thesis

A SYSTEMATIC REVIEW OF THE EFFECTIVENESS OF LIFESTYLE AND MEDICATION INTERVENTIONS IN THE MANAGEMENT OF HYPERTENSION IN PREGNANCY

Date: 2017

ABSTRACT

Background: Pregnancy induced hypertension is one of the causes of maternal, fetus and neonatal morbidity and mortality. It is the condition in which a pregnant woman develops hypertension because of physiological changes that result during pregnancy and both mother and fetus can be affected. According to the World Health Organization (WHO), the first target of the third United Nations Sustainable Development Goals (SDG-3) is to reduce the maternal mortality rate (MMR) to less than 10 per 100.000 live births by 2030 (WHO, 2017). This is because globally, about 350 000 women die every year from pregnancy related causes (Hogan, Foreman, & Naghavi, 2010). According to the WHO (2015), these conditions namely post-partum hemorrhage, hypertension in pregnancy, infections, unsafe abortion and other delivery-related complications cause three quarters of all maternal deaths in the World. Hence the needs to prevent or successfully treat conditions that contribute to this scourge (WHO, 2011). The two main interventions that are used to prevent or treat hypertension in pregnancy are medication and lifestyle adjustment. However, it is important to understand the intervention that is most suited to a context and its patient and compare the effects of these interventions on management of hypertension in pregnant women as a patient outcome.

Purpose: This study aimed to review the effectiveness of medication and lifestyle adjustment interventions on patient's outcome during the management of hypertension in pregnant women.

Methods: This study used a systematic review design to review the evidence of the effectiveness of medication and lifestyle interventions on hypertension in pregnancy. The five (5) steps of systematic review as explained by the Centre for reviews and Dissemination was followed. The inclusion criteria was based on the PICO strategy where Population of interest (P) is pregnant women; Intervention (I) was medications; comparative intervention (C) was

life style adjustment intervention and outcome (O) was the reduction of blood pressure. Electronic data bases such as, Google scholar, Pubmed, and Cochrane was searched for relevant evaluation studies using the relevant search terms of [(hypertension OR high blood pressure OR eclampsia OR pre-eclampsia) AND (pregnancy) AND (diet) AND (nutrition) AND (physical activity) AND (exercise)]. The investigator used; Revised - assessing the methodological quality of systematic reviews (R - AMSTAR, 2011).The elements that were included for data extraction were general information which included the date of selected study and publication year; study characteristics, participant's characteristics; intervention and setting, study design, study inclusion and exclusion criteria; outcome data/result and recommendation of study. Narrative - synthesis was done. The objective was to bring together the results of empirical research that are in a narrative form to provide an accessible combination of results from individual studies in structured narratives.

Results: The results of the study indicated that lifestyle adjustment intervention namely physical activity and diet may reduce the risk of hypertension in pregnancy. The result from this study also showed that most of the antihypertensive drugs reduce the risk of severe hypertension namely intravenous labetalol, hydralazine, nifedipine but magnesium is required to prevent the risk of developing eclampsia in women with severe preeclampsia.Low dose aspirin should be used in clinical practice to prevent pre-eclampsia.

Conclusion: The study established that antihypertensive medication is recommended for the treatment of severe hypertension. After the synthesis of articles we find that medication and lifestyle adjustment interventions are complementary in other words none is more effective than other. To prevent hypertension in pregnancy and its complication and protect the lives of the fetus it is better to use lifestyle adjustment intervention than medication intervention. But to treat severe hypertension in pregnancy in order to avoid the complications of hypertension in pregnancy it is better to use medication than lifestyle adjustment intervention.

KEY WORDS

Hypertension in pregnancy

Intervention

Lifestyle

Medication

Systematic review of reviews

DECLARATION

I Benjamin Kukatula Kutumbuka, declare that this full thesis and the work entitled "A systematic review of the effectiveness of lifestyle and medication interventions in management of hypertension in pregnancy" is my own work, that it has not been submitted for any degree or examination in any another university, and that all sources I have used or quoted have been indicated and acknowledged by complete references.

Signed:  January, 2017

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- I would like to express my sincere and deepest gratitude to my supervisor Professor Deliwe Rene Phetlhu for her knowledge, guidance and respect as she helped me through this project. Without her supervision and constant help this thesis would not have been possible.

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DEDICATION

This thesis is dedicated to my parents Mr and Mrs KUKATULA, CLAVER KUKATULA et ADELINE MAKINA for their support and encouragement. I would like to thank all my family and friend for their waiving support in the writing of this thesis. I am also thinking of my intimate friends Leka Sila, Lucretia, Pricilla, Doris Hagan, Rita and Florence.

TABLE OF CONTENTS

CHAPTER 5 CONCLUSION, RECOMMENDATION AND SUMMARY

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

AIDS	-	Acquired Immune Deficiency Syndrome
APS	-	Anti - Phospholid Syndrome
BMI	-	Body Mass Index
CRD	-	Centre for Reviews Dissemination
DIC	-	Disseminated Intravascular Coagulation
EPHPP	-	Effective Public Health Practice Project
ESRD	-	End – Stage Renal Disease
GFR	-	Glomerular Filtration Rate
HIP	-	Hypertension in Pregnancy
HELLP	-	Haemolysis Elevated Liver enzymes Low Platelet count
IUGR	-	Intra Uterine Growth Restriction
JNC	-	Joint National Committee
LDCS	-	Low Dose Calcium Supplementation
LTPA	-	Leisure Time Physical Activity
MDG	-	Millennium Development Goal
MMR	-	Maternal Mortality Rate
NCCMT	-	National Collaborating Centre for Methods and Tools

NDHSA - National Department of Health of Republic of South Africa

NOS - New castele- Ottawa Scale

PICO - Population of interest Intervention Comparative intervention Outcome

PIH - Pregnancy Induced Hypertension

PLGF - Proangiogenic Placental Growth Factor

QS - Quality Score

R-AMSTAR - Revised – Assessing the Methodological quality of Systematic Review

RCT - Randomised Controlled Trial

RT - Randomised Trial

SBP - Systolic Blood Pressure

SES - Socio Economic Status

SLE - Systematic Lupus Erythematous

SR - Systematic Review

TF - Tissue Factor

UNICEF - United Nations Children' Fund

VEGF - Vascular Endothelial Growth Factor

WHO - World Health Organisation

CHAPTER ONE

OVERVIEW OF THE STUDY

1.1 INTRODUCTION

Pregnancy induced hypertension (PIH) is a condition in which a pregnant woman develops hypertension because of physiological changes that happen during pregnancy (Pandula, 2009). PIH may pose a risk to the pregnant mother, and this risk may adversely affect the mother or the fetus or both of them (Pandula, 2009). PIH is one of causes of maternal, fetal and neonatal morbidity and mortality world – wide, affecting about 10% of all pregnancies in the world (American College of Obstetricians and Gynecologists, 2013).

According to the World Health Organization (WHO), the first target of the third United Nations Sustainable Development Goals (SDG-3) was to reduce the maternal mortality rate (MMR) to less than 10 per 100.000 live births by 2030 (WHO, 2017). This is because globally, about 350 000 women die every year from pregnancy related causes (Hogan, Foreman, & Naghavi, 2010). According to the WHO (2015), these conditions namely post-partum hemorrhage, hypertension in pregnancy, infections, unsafe abortion and other delivery-related complications cause three quarters of all maternal deaths in the World. Hence the needs to prevent or successfully treat conditions that contribute to this scourge (WHO, 2011).

Different interventions have been employed to curb this problem ranging from medication, lifestyle change, traditional and homeopathic medication (Duley, Henderson-Smart, Meher, 2007; Shirazian, Monteith, Friedman, Rebarder, 2010). In the health sector, medication and lifestyle adjustments are the two main interventions that are used to prevent or to treat hypertension in pregnancy. However, not much has been documented with regard to the efficacy of one over the other especially when access, costs and feasibility are filtered in.

This is despite the reported marked increase in the prevalence of hypertension amongst racial groups which were not previously severely affected such as blacks whose access might be challenged due to high costs of treatment (Harding, Whitrow, Lenguerrand, Maynard, Teyhan, Cruickshank & Der, 2010).

This study seeks to assess and compare the effects of medications and lifestyle interventions in the management of hypertension in pregnant women. This chapter is structured under the following sub-headings to address the suggested approach that the investigator intends to take to explore the phenomenon: Background to the study, problem statement, the purpose of the study, the significance of the study, literature review, definition of key words used, and overview of the design and methods followed.

1.2 BACKGROUND OF THE STUDY

According to the United Nations Children' Fund Sub – Saharan Africa and South Asia accounted for 86% of global maternal deaths in 2015 and in these regions the four major causes of maternal deaths were; hemorrhage, sepsis, complications of unsafe abortions and hypertension in pregnancy particularly eclampsia (UNICEF, 2015). During a normal pregnancy, the blood pressure of the expectant mother is expected to remain at a normal range (below 140/90 mmHg). However, in the case of hypertension in pregnancy, there is an elevation of blood pressure, with the systolic blood pressure becoming greater than or equal to 140 mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg (Lowe, Bowyer, Lust, Mahon, Marton, North, Paech & Said 2014; New York Department of Health, 2013). Hypertension in pregnancy is typically classified as preeclampsia, eclampsia, gestational hypertension, and chronic hypertension (WHO, 2011). According to the WHO (2010),10% of all pregnant women around the world have been associated with hypertension in pregnancy which has been reported to contribute significantly to perinatal morbidity; it is associated with severe maternal obstetric complications and most importantly is a cause of

maternal death (New York Department of Health, 2013).

According to Awoke, Awore, Alemu, and Megabiaw (2012), recent studies have demonstrated the link between certain risk factors such as obesity and hypertension amongst pregnant women. Additional factors such as null parity, older maternal age, and multiple births may also increase the risk of hypertension in pregnancy. It is also reported that the prevalence of hypertension during pregnancy has increased among African women (Hogan, Foreman & Naghave, 2010) and these racial differences are partly as a result of environmental, socioeconomic status and physiological and genetic factors (Ergul, 2000; Lopez - Jaramillo, Pradilla& Lahera, 2007).

In the black African, racial hypertension in pregnancy (HIP) has increased by 33 % in the past two decades with long-term consequences such as hypertensive heart disease; particularly in younger African women. Noteworthy, not only is HIP more pronounced in the black African population but the difference is also resistant to treatment compared to other ethnic groups (Sliwa, Oliwa, Bachellier, Bohm, Dama & Stewart, 2014).

Interestingly, it has been noted that in non-tropical regions, the rate of preeclampsia or eclampsia are highest with delivery in the winter months (Te Poel, Saftlas & Wallis 2011). According to Beltran, Wu and Laurent (2014), the factors which increased the risk of seasonal infections increased exposure to established triggers of asthma; decreased plasma levels of vitamin D; physiological responses to the cold and a wide variation in daily temperature. Possible reduced physical activity; and dietary changes during the cold or rainy seasons have been proposed to explain the association between an increased risk of preeclampsia and delivery in the months of winter in non-tropical regions and during the wet and humid weather in tropical climates.

Additionally, there are enormous differences between developed and developing countries

regarding the incidence of PIH and its contribution to maternal mortality. These differences appear to be determined by the deficient health-care systems and sanitary conditions in developing countries coupled with the fact that nutritional resources, especially of dietary minerals, are inadequate to meet the greater demand occasioned by the growth of the fetus (Opies & Seedat, 2005; WHO, 2009). Furthermore, a high proportion of women do not have access to adequate prenatal control and infections and diet deficiencies are neither detected nor corrected. This is a socioeconomic pathology which leads to a high risk of PIH and maternal mortality (WHO, 2015). It is therefore important to note that the prevalence of hypertension varies among nations and sub-populations within a nation though are generally lower among high-income populations (Opie & Seedat, 2005; WHO, 2009). This is the case even in South Africa.

The National Department of Health of South Africa (2015), reported that Acquired Immune Deficiency Syndrome (AIDS), hemorrhage and complication of hypertension in pregnancy were major challenges to maternal care in the country during 2010 -2013 reporting periods, as they accounted for 66.7% of maternal deaths (NDHSA, 2015). According to the NDHSA (2011) between 2008-2010 in South Africa (SA), HIP was part of the top three causes of maternal deaths which included non-pregnancy related infections and obstetric hemorrhage with 14% of the more than 4687 cases of maternal deaths in South Africa being as a consequence of hypertension in pregnancy. Rayner (2010) reported that the general population of South African blacks also appears to be more prone to complications of hypertension. According to Schutte, Huisman, Van Rooyen, Schutte, Malan, Reiman, De Ridder, Van der Merwe, Schwarz and Malan (2008), "the prevalence of hypertension is higher in urban black African women."

In relation to weather patterns, a study conducted by Immink (2010), to determine if the weather was the cause of seasonal variation in the prevalence of women with preeclampsia in

Tygerberg hospital in Cape Town, it was discovered that the prevalence of preeclampsia was higher in winter than in summer with a total of 13,6% being pre-eclamptic. The interpretation made by Crilly (2012) was that this phenomenon maybe the limited formation of vitamin D3 in winter.

The reduction of morbidity and mortality is the main goal of prevention and management of hypertension in pregnancy and this goal may be achieved by lifestyle modification alone or with pharmacological therapy (Joint National Committee, 2014). Different intervention modalities are used to prevent complications and causalities due to hypertension in pregnancy (American College of Obstetricians and Gynecologists, 2013) and that is true even in South Africa. In the public health sector, patients are managed with different medications and also encouraged to adapt or change their lifestyle (Imura, 2013). However, the medical interventions have an impact on the health system with escalating costs of medications and on the financial as well as the physical wellbeing of individuals.

Antihypertensive medication is strongly recommended in all women with severe hypertension (WHO, 2011). However, these drugs are reported to have a potentially negative effect on both the mother and fetus (Duley, Henderson – Smart & Meher, 2007). According to the New South Wales Department of Health (2011), the link between hypertensive drugs and the risk of neonatal death, preterm birth or small gestational age, placental abruption and caesarean section is not clear but highly probable. The probability is justified by reports that in some cases, antihypertensive therapy is stopped prior to conception and there is a recommendation to avoid angiotensin receptor blockers in late pregnancy as they are assumed to be nephrotoxic for the fetus. Despite all the potential side effects, hypertension medication are still widely recommended and seen as effective (Lowe et al., 2014; New South Wales Department of Health, 2011).

Lifestyle is defined as the way of life of an individual as demarcated by certain characteristics such as healthy diet and physical activity (WHO, 2009). A growing body of literature suggests that health habits such as maintaining normal weight, getting daily exercise, eating a diet high in fruits, vegetables, low-fat dairy products and low in sodium and taking a folic acid supplement were associated with a significantly lower incidence of self-reported hypertension among women (Hellwig, 2009). Thus, this is also recommended to hypertensive pregnant women (New York Department of Health, 2013). According to Mosca, Benjamin, Berra, Bezanson, Dolor, Lloyd-Jone and Wenger (2011), poor adherence to pharmacological treatment of hypertension is a serious challenge especially in developing countries, thus making the life style modification a pliable option to manage hypertension in pregnancy (Mosca et al., 2010). Nonetheless, the success of life style modification is not without challenges because depending on the context of the patients, acquisition of healthy food options and time for exercise may not be possible. Nutritious foods are very costly and the time for exercise is not often available. Hence all these factors need to be taken into consideration when management plans are made to deal with hypertension in pregnancy, particularly choosing the most appropriate option for pregnant women with HIP. It is important to understand the intervention that is most suited to a context and its clientele hence the need to assess and compare the effects of medications and lifestyle interventions on the management of hypertension in pregnant women as a patient outcome.

1.3 PROBLEM STATEMENT

According to the WHO, estimated 287 000 women died during pregnancy and child birth in 2010. Globally, an important cause of morbidity and death among both mothers and their babies is hypertension in pregnancy (WHO, 2012).

In South Africa, hypertension in pregnancy remains the greatest direct cause of maternal mortality and also the most predominant medical complication (NDHSA, 2011).A change of

lifestyle from a more sedentary and fat food diet to contribute to the increase of prevalence of hypertension in the black African population which is also noted among the pregnant women (Sliwa, Oji, Bachellier, Dama, Stewart, 2014). Provision of medical drugs is often a preferred route of management which is a costly endeavor for the health system and it is not without challenges to the wellbeing of the expectant mother and the fetus (Lowe et al., 2014). In addition to pharmacological drug treatment, a change in lifestyle has been identified as an important contributor to the management of hypertension in pregnancy (Mosca et al., 2011), despite challenges such as affordability which come with access to healthy food options and exercise. Nonetheless, both these interventions are credited with effectiveness in reducing HIP thus curbing the scourge of maternal mortality and morbidity. Many studies have been conducted globally to investigate the effectiveness of either hypertensive medication or life style modification interventions on pregnant women with HIP. However, there is a shortage of syntheses of studies that compare the effectiveness of these two management modalities thereby clearly outlining if there are any significant differences in the health outcomes of pregnant women with hypertension who are put on them. In conducting this comparison, the researcher believes that understanding this difference could assist health practitioners in making appropriate choices for pregnant women with HIP, based on their context which could affect adherence to either medical treatment or lifestyle modification.

1.4 PURPOSE OF THE STUDY

The purpose of this study was to review the effectiveness of medications and lifestyle adjustment interventions on patients' outcome during the management of hypertension in pregnant women.

1.5 SIGNIFICANCE OF THE STUDY

Knowledge of the effectiveness of interventions for management of hypertension in pregnancy could enable medical professionals to act appropriately and timely to avoid maternal deaths. In addition, the findings of this study may also lead to the subsequent use of these parameters by a multidisciplinary team to improve the management and prognosis of pregnancy for women who suffer from hypertension and its complications. The findings may also give direction for a suitable and cost effective intervention for a specific context or scenario.

1.6 OPERATIONAL DEFINITION OF TERMS

Hypertension: is defined by a systolic blood pressure of 140 mm Hg or more and a diastolic blood pressure of 90 mm Hg or more sustained over a long period of two to four hours on a least two occasions (Seedat & Ryner, 2011).

Gestational hypertension: hypertension after 20 weeks of pregnancy often associated with no proteinuria (Mustafa, Ahmed, Gupta & Venuta, 2012).

Preeclampsia/eclampsia: hypertension after 20 weeks with proteinuria with or without convulsions (National Department of Health of South Africa, 2015).

Chronic hypertension: hypertension before 20 weeks of pregnancy with no proteinuria, or for a period of 12 weeks after delivery (American College of Obstetricians and Gynecologists, 2015)

A pregnant woman: is a woman who has a development of one or more offspring known as an embryo or fetus in her uterus (Oxford Dictionary of Current English, 2009).

Lifestyle: a hypertensive pregnant women's way of living, in other words, her physical activity and/or diet (New York State Department of Health, 2013).

Medication: medication is a drug or other preparation for the treatment or prevention of a disease (Oxford Dictionary of Current English, 2009). In this study, medication is defined as any anti-hypertensive medications which are medicines that help lower blood pressure in pregnant women with hypertension.

Intervention: An intervention is an act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions (WHO, 2016). In this study an intervention (lifestyle and/or medication) is an act performed for, with and on behalf of a pregnant woman with pregnancy induced hypertension to reduces and maintain healthy high blood pressure levels.

1.7 RESEARCH DESIGN AND METHODS

This section provides an overview of the research design and methods with a detailed discussion presented in chapter 3.

1.7.1 Research design

This study used a systematic review design to review the evidence of the effectiveness of medications intervention and lifestyle adjustment interventions modification on hypertension in pregnancy. Systematic review is a review of a published research, and evidence relevant to a particular research question (Russell, 2009).The sections below will briefly explain what was done to accomplish the purpose of the study.

1.7.2 Steps of systematic review

According to Khan, Kunz, Kleijnen, and Antes (2011), there are five steps involved in conducting a systematic review which were adopted in the research process namely,

formulation of a focused review question, and identification of relevant publications, performing the critical appraisal, summarizing the evidence and interpreting the findings.

Step 1: Formulating a focused review question

According to the Centre for Reviews and Dissemination (CRD, 2009), formulation of a focused review question means to specify the types of population, types of interventions, comparative intervention and the types of outcomes that were of interest. In this study, the review question was posed as follows: What is the effectiveness of medication and lifestyle interventions in the management of hypertension in pregnant women. The review question was focused on the PICO strategy (Squires, Valentine, &Grimshan, 2013) as depicted in table 1 below.

TABLE 1: Components of the review question

Population of interest (P)	Pregnant women
Intervention (I)	Medication intervention
Comparative intervention (c)	Life style adjustment intervention
Outcome (O)	Reduction of blood pressure

The review was designed to meet the following objective:

- To review the published evidence on medication and lifestyle adjustment intervention on patients' outcomes during the management of hypertension in pregnant.

Step 2: Identifying relevant publications

Identifying relevant publications implies the selection of a comprehensive and unbiased set of research relevant to improve the credibility of the review (Social Science Research Unit, 2010). In this study, the following process was followed;

- **Data sources and search strategy**

Scoping review of the literature was conducted to establish what has been previously published in the field of study. The investigator searched the Cochrane institute libraries using the phrase "hypertension in pregnancy and high blood pressure in pregnancy" and systematics review that focused on intervention for management, treatment or prevention of hypertension or pre-eclampsia and eclampsia were selected. In addition, electronic databases such as Google scholar, PubMed were also used to search for relevant evaluation studies using the relevant search terms of [(hypertension OR high blood pressure OR eclampsia OR pre-eclampsia) AND (pregnancy) AND (diet) AND (nutrition) AND (physical activity) AND (exercise)]. The selection process began with reading of abstracts to identify if the paper addresses the objectives of the study followed by reading of the full article on those deemed relevant.

Inclusion criteria

The inclusion criteria for selection of papers were as follows;

1) Systematically reviewed of reviews evidence was presented;

2) The participants were pregnant women

3) The intervention described were medication and/or lifestyle modification;

4) The outcomes were synthesized and presented;

5) The reviews were moderate to good quality systematic reviews;

6) The articles were written in English and published between 2000 and 2015.

7) The article had an outcome that showed effectiveness of either medication or lifestyle on hypertension

The inclusion criteria were based on the PICO strategy.

Step 3: Performing the critical appraisal

The appraisal of the articles obtained after the elimination process was on the following: appropriateness of study design to the research objective, risk of bias and other issues related to the study. The investigator used; Revised - assessing the methodological quality of systematic reviews (R - AMSTAR, 2011) (Annexure 1) for the critical appraisal. The level of evidence was assigned for each critically appraised article as explained by Kung, Chiappelli, Cajuli, Avezova, Kossan and Maida, (2010). It was ranked as follows:

- A = Quality score (Q S) (90% -100%)

- B = Q S (80%),

- C = Q S (70%)

- D = Q S (60%)

- E = Q S (50%)

- F = Q S (40%)

Data extraction is defined as "the process by which the researcher obtains the necessary information about study characteristics and findings from the included studies" (CRD, 2009). The elements that were included for data extraction were; general information which included the date of selected study and publication year; study characteristics, participant's characteristics; intervention and setting, study design, study inclusion and exclusion criteria; outcome data/result and the study's recommendations.

- **Data synthesis**

Data synthesis involves the collation, combination and summary of the findings of individual

studies included in the systematic review. It can be done quantitatively using formal statistical technique if formal pooling of results is not appropriate through a narrative approach (CRD, 2009). In this study, a narrative approach was used because meta-analysis was not feasible.

Step 5: Interpreting the findings

Interpreting the findings is a conclusion of the study which provides a judgment on the effectiveness of a particular intervention (Khan, Kunz, Kleijnen, & Antes, 2011). According to the CRD (2009), interpreting the findings is an integral part of the review process that seeks to ensure that practitioners and policy makers who need to know about a piece of research get to know about it and can make sense of the findings. This section of the work emanated from the data analysis process, the findings and the discussions that ensued thereof. This conclusion captured the main findings of the study and the importance and relevance of the obtained findings. Interpreting the findings was the final step in the systematic review process.

1.8 RIGOUR OF THE STUDY

In research, to increase both trust and confidence in the study findings, we need to follow the required techniques and strategies (Hagan, 2014). Rigour in the systematic review includes the concepts of validity and reliability. The systematic review process and methodology does ensure the rigour of the study. Firstly, the titles and abstracts of reviews were identified and independently screened for extraction of full review for further analysis by two reviewers. Any discrepancies were resolved by a consensus. Secondly, the retrieved articles were reviewed for suitability for inclusion for full article review based on the quality of the systematic review. An evaluation sheet for the R- AMSTAR was used to assess systematic reviews. The studies that were not included the reasons for exclusion are provided.

This section specifically addresses the validity and reliability of the quality assessment tool, the AMSTAR-R.

1.8.1 Reliability of the AMSTAR-R

The reliability of an AMSTAR-R is a major criterion for assessing its validity. An instrument is said to be reliable if its measurement accurately reflects the true scores of the attribute being investigated (Polit & Beck, 2006). The reliability lies more on the consistency and stability of the instrument that was used. In the case of a systematic review, the tool must be used during the critical appraisal process.

1.8.2 Validity of the review tool

Validity is defined as the degree to which an instrument measures what it is intended to measure (Polit & Beck, 2010). The investigator used the R- AMSTAR (Appendix 1) tool for the assessment of the quality of the methodologies; this tool consists of 11 questions and content validity for measuring the methodological quality of systematic review. Every question of R-AMSTAR has a score from 1 to 4. The articles with a quality score of greater than or equal to 22 /44 were classified as eligible for assessment. The investigator conducted the critical appraisal and a second person with expertise in systematic reviews was also tasked to do the same. A consensus on quality based on the two appraisals was reached. The supervisor also appraised the process followed in this study to ensure validity.

1.8.3 Ethics considerations

In the pursuit to maintain higher ethical standards throughout this study, the proposal was submitted to the University of the Western Cape research ethics committee to ensure the study was conducted within the appropriate ethical standards. This authority gave approval for the study to be conducted (Appendix 2).The investigator maintained the highest standard

of honesty and integrity and avoided plagiarism at all costs by acknowledging all the authors whose work has been referred to.

1.9 CHAPTER SUMMARY

In this chapter, a general perception of hypertension in pregnancy was presented and the chapter also outlined the study's problem. The steps of the methodology that were followed were outlined to answer the research question and different steps of rigour that were followed for increasing trust and confidence in the study findings were discussed.

1.10 OUTLINE OF CHAPTERS

The chapters are divided as follows:

Chapter one [Overview of the study]: this chapter introduced the problem of the study, issues concerning the effectiveness of lifestyle and medication interventions in management of hypertension in pregnancy. The chapter indicated the scope of the study and explained methods used to conduct the study.

Chapter two[Literature review]: in this chapter, the relevant literature which included the notion of hypertension in pregnancy, the causes of hypertension in pregnancy, the contributory factors and complications of hypertension in pregnancy, and the intervention modalities in the care of hypertension in pregnancy, were reviewed.

Chapter three [Research design and methods]: describes the methodology of the study.

Chapter four [Summary of the findings]: the results of the study and discussion of results are outlined.

Chapter five [Conclusion, recommendation and summary]: the most important findings of the study are highlighted in this chapter. It also provided the conclusion, suggestions and

limitations relating to the main findings from the present study.

CHAPTER TWO

LITERATURE REVIEW

2.1 INTRODUCTION

Literature review is a systematic reading of the important contributions in the field of study, which further leads to the development of research questions and research objectives (Sekaran & Bougie, 2010). In this second chapter, a review of the relevant literature is presented in order to contextualize the study. This will be discussed under the following subheadings:

- The notion of hypertension in pregnancy
- Cause and contributory factors of hypertension in pregnancy
- Complications of hypertension in pregnancy
- Intervention in the management of hypertension in pregnancy

2.2 THE NOTION OF HYPERTENSION IN PREGNANCY

Hypertension, also known as high or raised blood pressure is a chronic medical in pregnancy condition in which the blood pressure in the arteries is persistently elevated. When systolic blood pressure is equal to or above 140 mmHg and /or a diastolic blood pressure equal to or above 90 mm Hg the blood pressure is considered to be raised or high (WHO, 2015).

Hypertension in pregnancy has been defined differently by different authors. According to Kumar and Sharma (2010), hypertension in pregnancy is defined as systolic blood pressure (greater than or equal to 140 mm Hg) or diastolic blood pressure (greater than or equal to 90 mm Hg) on two or more intervals. At least 6 hour intervals or a single reading of diastolic

blood pressure of more than 105 mmHg or an increase in mean arterial pressure of 20 mmH g taken at least six hours a part. According to the association of Ontario midwives (2008), hypertension in pregnancy is a diastolic blood pressure of 90 mm Hg or more based on the average of at least two observed readings.

Lowe, Bowyer, Lust, McMahon, Marton, North, Paech and Said (2014), define hypertension in pregnancy as a systolic blood pressure of 140mmHg or above and a diastolic blood pressure of 90 mmHg or above. It is necessary to confirm hypertension by repeated readings over a period, as a patient's anxiety, physical stress and apprehension can have transient elevation in blood pressure. There are four types of hypertension in pregnancy; chronic hypertension, gestational hypertension, preeclampsia/eclampsia and preeclampsia super imposed on chronic hypertension (New York State Department of Health, 2013).

2.2.1 Chronic hypertension in pregnancy

Chronic hypertension in pregnancy is hypertension diagnosed either when the blood pressure was more than 140/90 mmHg before pregnancy, or before 20 weeks of pregnancy, or for a period of 12 weeks after delivery (Chen, 2008). There are two subtypes of chronic hypertension: hypertension before 20 weeks of pregnancy and hypertension associated with diseases such as renal disease, pheochromocytoma, and Cushing syndrome. The major causes of chronic hypertension in pregnancy include chronic kidney disease such as glomerulonephritis, reflux nephropathy, adult polycystic kidney disease and renal artery stenosis; systemic disease with renal involvement such as diabetes mellitus and systematic lupus erythematous; and endocrine disorders that include pheochromocytoma, Cushing syndrome and primary hyperaldosteronism and coarctation of aorta (Naidoo, 2007). A woman with hypertension in the first half of her pregnancy, not due to any of the above conditions, has essential hypertension (Hutcheon, Lisonkova & Joseph, 2011). In recent years

in which the maternal age at child birth is increasing, advancing maternal age has emerged as another contributing factor to the increasing prevalence of chronic hypertension (Hutcheon, Lisonkova & Joseph, 2011).

Treatment of chronic hypertension in pregnancy is complex because of variations that are determined by the age of the pregnant woman, the onset of hypertension and the stage where the woman is on the continuum of pregnancy. For younger women with chronic hypertension, the use of the medications such as ACE inhibitors, angiotensin receptor blockers, rennin inhibitors and mineral corticoid receptor antagonist are not recommended unless there is the presence of protein uric, renal disease or other reasons (American College of Obstetricians, 2013). In many women with pre-existing hypertension, a medication adjustment which does not consist of steroidal inflammatory drugs is recommended postpartum because blood pressure is often unstable immediately after delivery (New South Wales Department of Health, 2011). However, women with pre-existing hypertension who did not require treatment during the pregnancy often need it post-partum and, further investigation and management of renal disease is required after six weeks of delivery (Lowe et al, 2014).

According to Moussa, Harian and Sibai, (2014), chronic hypertension in pregnancy is associated with higher rates of both adverse maternal outcomes and adverse fetal outcomes. Adverse maternal outcomes of chronic hypertension include cesarean delivery, development of postpartum hemorrhage, end organ damage, increased risk of development of gestational diabetes and increased risk of abruption placentae. For adverse perinatal outcomes, chronic hypertension is associated with fetal complications such as small gestational age, fetal growth restriction and fetal death.

2.2.2 Gestational hypertension

Gestational hypertension is hypertension that develops after 20 weeks' gestation, in labor or within 48 hours of delivery without proteinuria or any other signs of preeclampsia (New South Wales Department of Health, 2011). Some infections can increase the risk of gestational hypertension namely placental malaria and dengue infections (Te Poel, Saftlas & Wallas, 2011). There is also an association between psychiatric disorders during pregnancy and the increased risk of gestational hypertension; it is associated with job stress (Kharaghani, Geranmaye, Janan, Hantooshzade, Arbabi, Bilandi & Bagheri, 2012).

Some women (up to 25%) who are in the process of developing preeclampsia but have not yet developed proteinuria or other manifestations are included in this category of hypertension in pregnancy. However, others who are initially diagnosed in this category might be reclassified as having chronic hypertension if they manifest with persistent blood pressure elevation beyond twelve weeks postpartum (American College of Obstetricians, 2013; Lowe et Al, 2014).

Generally, if a woman with gestational hypertension has mild hypertension, treatment is not necessary whereas, the treatment of a woman with severe features is based on extrapolation of indirect evidence from management of severe preeclampsia (Moussa, Harian & Sibai, 2014). Gestational hypertension requires enhanced surveillance, even when blood pressure elevations are mild as it may also be a sign of future chronic hypertension although transient in nature (Moussa, Arian, & Sibai, 2014).

2.2.3 Pre-eclampsia

Pre-eclampsia is a multi-system disease that involves one or more organs. It is primarily defined by the occurrence of new onset hypertension plus new onset proteinuria (New South

Wales Department of Health, 2011). Pre-eclampsia is diagnosed after the 20th week of pregnancy, returning to normal within three months of giving birth with one or more of following signs:

-Proteinuria (> 30mg/mole) increase in serum or creatinine levels (90umol/L)

- Oliguria (< 80mL/4hr)

- Thrombocytopenia (< 100,000/uL)

- Evidence of micro angiopathic hemolytic anemia,

- Disseminated intravascular coagulation

- Elevated hepatic enzymes

- Severe epigastria and/or right upper quadrant pain

- Headaches

- Blurred vision,

- Pulmonary edema,

- Intra uterine growth retardation (Lowe et al., 2014).

Pre-eclampsia has two subtypes namely preeclampsia and preeclampsia with severe features. The difference between the two is based on the extent to which other organs are affected. For example, pulmonary edema, thrombocytopenia elevated liver enzymes, as well as the severity of hypertension such as systolic more than or equal 160 mmHg or diastolic more than or equal 110 mmHg (Moussa, Arian, & Sibai, 2014), pre-eclampsia can also occur without proteinuria (Lowe et al., 2014). Factors such as hydatiform mole, multiple pregnancies, fetal

triploid, or anti-phospholipid antibody syndrome predispose the woman to pre-eclampsia (New South Wales Department of Health, 2011) while abnormal placentation is reported as the primary cause (Turner, 2010). During normal pregnancy, spiral arteries lose their endothelium and most of their muscle fibers but in contrast, during preeclampsia there is a defective invasion of the spiral arteries by cytotrophoblast cells hence placental hypo perfusion is observed (Turner, 2010).

Management of pre-eclampsia decision must take the fetal risks associated with induced preterm delivery against the maternal risks into account. All in all, the gestational age plays an essential role on the management of pre-eclampsia (Turner, 2010). A woman with severe preterm preeclampsia must be transferred to a unit with neonatal and maternal care facilities prior to delivery. The time of delivery is based on both the severity of pre-eclampsia and the gestational age of the patient. If the pregnancy is less than 34 weeks, immediate management refers to delivery planned within 48 hours usually after blood pressure stabilization. Steroids are administered to accelerate fetal pulmonary maturity (Sidani &Sayyid, 2005). These signs are indicated for immediate delivery: uncontrolled severe hypertension, eclampsia, acute pulmonary edema, abruption placenta and sub capsular hepatic hematoma (Turner, 2010). The aim of hypertensive treatment in severe preeclampsia is to reduce the risk of maternal complications (Moussa, Arian & Sibai, 2014). There are currently no uniform guidelines for antihypertensive treatment of hypertension in severe preeclampsia (Turner, 2010). In South Africa, mild pre-eclampsia is treated with methyldopa in case of pre-eclampsia with severe features. Nifedipine, methyldopa, and magnesium sulphate are prescribed (National Department of Health, Republic of South Africa 2015).

Primary prevention of pre-eclampsia is based on both identification and modification of some risk factors. There are numerous risk factors namely partner related risk factors such as null parity/prim paternity; maternal specific risk factors such as maternal age, family history,

presence of certain underlying health conditions such as renal disease; exogenous factors such as smoking; pregnancy associated risk factors such as multiple pregnancies (Dekker, Sibai & 2001; Briceno-Perez, Briceno-sanabria & Vigil-De Gracia, 2009).

Some of the risk factors are not modifiable such as null parity, prim paternity, history of previous pre-eclampsia, low maternal birth weight and multiple pregnancies. They might not allow primary prevention. Secondary prevention includes life style modifications, dietary-nutritional measures and drugs; it is based on pathophysiological mechanisms. The prevention of complications must be the main objective of tertiary prevention. Furthermore, the most important part of tertiary prevention is antenatal care (Dekker, Sibai & 2001; Briceno-Perez, Briceno-sanabria & Vigil-De Gracia, 2009). These maternal complications such as eclampsia, HELLP syndrome, acute kidney injury, pulmonary edema and placental abruption are associated with severe pre-eclampsia. The delivery of the baby is the definitive treatment of pre-eclampsia (New South Wales Department of Health, 2011).

2.2.4 Eclampsia

Eclampsia can occur when a woman with preeclampsia has convulsions with no known cause. It usually occurs before labor, but some women may present with it during labor or after labor (New York Department of Health, 2013). In eclamptic women, the convulsion can occur in ante partum, intra-partum, or postpartum. A bleeding arteriovenous malformation, idiopathic seizure disorder or ruptured aneurysm can also cause seizures; a differential diagnosis is required (Moussa, Harian & Sibai, 2014). Hypertension may be absent in 16% of eclampsia patients, except for the patients who develop antepartum eclampsia or those who develop eclampsia at 32 weeks (Hart & Sibai, 2013).

In the management of eclampsia, the priority is to prevent maternal injury and to support respiratory and cardiovascular functions. Prevention of recurrent convulsions in the

management of eclampsia is the second treatment goal (Hart & Sibai, 2013). The management of associated complications such as disseminated intravascular coagulation in obstetrics (DIC), pulmonary edema is usually the next step. Pregnancy induction/delivery within 24 hours of the onset of eclampsia is recommended (Hart & Sibai, 2013).

Moreover, the primary goal of prevention of eclampsia is; to prevent women from developing preeclampsia and also to prevent the progression of preeclampsia to eclampsia (Duley, Gulmzoglu & Chou, 2011). Maternal and perinatal morbidities are higher in eclampsia patients because of prematurity, severe fetal growth restriction, abruption placental, cerebral edema, pulmonary edema, acute renal failure and disseminated intravascular coagulation (Hart & Sibai, 2013).

2.2.5 Super imposed pre-eclampsia on chronic hypertension

According to the Association of Ontario Midwifes (2012), super imposed pre-eclampsia occurs when a woman with chronic hypertension develops one or more symptoms of preeclampsia after 20 weeks of gestation. The diagnoses of pre-eclampsia super imposed are established when any of following signs are present at or after 20 weeks gestational age; resistant hypertension or new or worsening proteinuria. The strong risk factor for the development of pre-eclampsia super imposed is pre-existing hypertension (Chen, 2008).

There are two subgroups of preeclampsia super imposed namely pre-eclampsia super imposed and preeclampsia super imposed with severe features (America College of Obstetrics, 2014). Pre-eclampsia super imposed with severe features is defined by the presence of the following signs at or after 20 weeks gestational age; severe-range blood pressure despite escalation of antihypertensive therapy, thrombocytopenia, elevated liver transaminase, new onset and worsening renal insufficiency, pulmonary edema, persistent

cerebral or visual disturbances. A pregnant woman with chronic hypertension, who does not have any of the above signs, does not have preeclampsia super imposed with severe features.

According to the American College of Obstetrics and Gynecologists (2013) for ante partum management of pre-eclampsia super imposed, those medications are indicated namely corticosteroids and magnesium sulphate, for seizures prophylaxis . Timing and indications for delivery are based on gestational age, severity of disease, progression of disease, and ongoing assessment of maternal and fetal well-being gestational age of 31 weeks or older. If a woman with preeclampsia super imposed with severe features is less than thirty four 34 weeks of gestation, the management options are as follows: immediate delivery after maternal stabilization, short-term prolongation to achieve steroid benefit for the fetus or long-term prolongation to increase gestational age and improve neonatal outcome. Management of preeclampsia super imposed is based on extrapolation of indirect evidence from management of severe pre-eclampsia (Association of Ontario Midwifes, 2012; American College of Obstetrics and Gynecologists, 2013). A woman with severe chronic hypertension has a 50% risk of pre-eclampsia super imposed, while those with mild chronic hypertension have a 20% risk of pre-eclampsia super imposed (New York State Department of Health, 2013).

2.3 CAUSE AND CONTRIBUTORY FACTORS OF HYPERTENSION IN PREGNANCY.

According to Roberts, Ford, Algert, Antonsen, Chalmers, Cnattingius and Gokhale (2015), despite the etiology of hypertension in pregnancy is not known, but the risk factors that contribute to the development of hypertension in pregnancy have been well documented. It is due to an interaction between genetic and environmental factors (Sliwa & Bohm, 2014; Roberts, et Al., 2015). They can be loosely categorized into broad groups. Maternal genetic

factors, maternal obstetric factors, preexisting conditions in the mother, socio-demographic factors, this will be discussed under the following subheadings:

- Cause of hypertension in pregnancy

- Contributory factors of hypertension in pregnancy (Hutcheon, Fellow, Lisonkova, Fellow & Joseph, 2011)

2.3.1 Cause of hypertension in pregnancy

The etiology of hypertension in pregnancy is generally unknown (Sliwa & Bohm, 2014). However, both genetic and environmental factors are involved hypertension in pregnancy is observed within a family history of hypertension and it is higher and more severe when both parents are concerned; although the precise mode of heredity has not been demonstrated (Beevers & O'Brien, 2001). Many studies have demonstrated the genetic aspect of pre-eclampsia and gestational hypertension. Pre-eclampsia has a two to five-fold higher risk in first prim gravidas women with a family history of preeclampsia (Sidani &Sayyid, 2011). One of the candidate maternal susceptibility genes for gestational hypertension and preeclampsia is the angiotensinogen gene. Pre-eclampsia has also some evidence with both pathological placentation and immunological factors. In other words, it is a result of complex interactions between pregnancy – specific changes, maternal constitutional factors, fetal factors and placental factors (Zafarmand, Franx, Sabour, Van der Schouw, Grobbee, de Leeuw & Bots, 2008).

If a woman develops early onset preeclampsia, it is due to inadequate placentation but if she develops pre-eclampsia near term, it means that she had a pre-existing condition; evidently, she will develop a blended form of preeclampsia on the basis of both placental and maternal factors (Von Dadelszen, & Magee 2014). Abnormal implantation has some evidence with immunological factors. Many studies involved maternal immune response in the development

of pre-eclampsia. Because in a healthy pregnancy, there is immune tolerance of the fetus by the mother; this idea is supported by many immune associated risk factors of preeclampsia namely auto immune disease, and prim parity (Pennington, Schlitt, Jackson & Schust, 2012). In the development of essential hypertension, these mechanisms namely rennin–angiotensin system, autonomic nervous system and endothelial dysfunction can play a major role first to maintain a normal blood pressure and second to maintain balance between the cardiac output and peripheral vascular resistance. The most important endocrine system that affects the control of blood pressure is rennin angiotensin system (Beevers, Lip & Brien, 2001). In addition, one of the important roles of autonomic nervous system is to maintain a normal blood pressure because it can cause both arteriolar dilatation and arteriolar constriction if it stimulates. Hence autonomic nervous system and circulating volume together with both rennin-angiotensin and sodium can probably cause hypertension (Beevers, Lip & O'Brien, 2001).

2.3.2 Contributory factors of hypertension in pregnancy

Several factors have been identified to contribute to the development and evolution of hypertension in pregnancy and these factors include: obesity, high-levels of stress, high salt intake, age, and being of black origin (Poon, Kametas, Chelemen & Nicolaides, 2010). Genetic susceptibility has been noted for preeclampsia; the condition is more likely to develop in women >40 years of age. Suffering from obesity, diabetes mellitus, and multiple pregnancies is widely considered to be predisposing factors to hypertension in pregnancy (New York State Department of Health, 2013).

2.3.2.1 Maternal genetic factors

In a related research conducted in the United States of America, Scotland, Iceland, and Australia, it was presented that a familial predisposition to pre-eclampsia has been

consistently demonstrated and a relatively strong heritability which is estimated to be 0.54(95%CI0-0 71).The most substantial study of the respective maternal and fetal contributions to preeclampsia estimated the maternal effect to be 0.35(95%CI0, 33-0, 36) and the fetal effect to be 0.20(95%CI, 0, 11-0, 24) with maternally and paternally inherited genes assumed to act equally though fetal genetic effects" (Hill, 2011).The risk of preeclampsia increased in women who were born of a preeclampsia pregnancy. There is also increased risk of pre-eclampsia in women born of a normal pregnancy, but whose mother had preeclampsia with one her other pregnancies. Men's genetics also play a role because the men who are not born of a pre-eclampsia pregnancy are not likely to father children from a preeclampsia pregnancy (Hill, 2011). Pre-eclampsia is higher in prim gravidas than in multigravidas and is therefore considered as a disease of nulliparous. It is well known that there is an increased risk for recurrence of preeclampsia in subsequent pregnancies in women who had a previous pregnancy complicated by preeclampsia (Dildy, Belfort, & Smulian, 2007). Furthermore, the central features of pre-eclampsia are both placental ischemia and hypoxia. These are due to an alteration in the balance of angiogenic and anti-angiogenic factors that provoke hypoxia; it can cause both placental ischemia and hypoxia and in turn pre-eclampsia (Hill, 2011).

2.3.2.2 Maternal obstetric factors

According to Rana, Hacker, Most, Salahuddin, Lim, Verlohren and Karumanchi, (2012) Pregnancies with increased placental mass, especially women with twin pregnancies have the level of sFlt-1 higher than in singleton gestations. However, primary placenta pathology is not associated with the elevated level of sFlt-1, but it is due to increased placental mass as is seen in twins. Therefore, there is an increased risk of pre-eclampsia in women with twin pregnancies (Rana, et al, 2012). Women pregnant with twins carry a higher risk of morbidity and mortality for both maternal and neonatal compared to singleton gestations (Chittacharoen, Wetchapruekpitak & Suthuvoravut, 2005).

The lower risk of pre-eclampsia among multiparous women has been attributed to both smoother trophoblastic invasions after modification of maternal spiral arteries during the first pregnancy and desensitization after exposure to paternal antigens in the placenta during previous pregnancies. In this study, a long interval between the first and second pregnancy has been associated with higher incidence of pre-eclampsia (Hernandez-Diaz, Toh & Cnattingius, 2009). In multigravidas women, an interval of six years between two pregnancies increases the risk of pre-eclampsia to the level observed in prim gravidas women where the risk of pre-eclampsia is higher in those women (Mikolajczyk, Zhang, Ford & Grewal, 2008).The risk of pre-eclampsia of a new partner is similar to the risk during a first pregnancy because a new partner presents with new antigens (Skjaerven, Cox & Lie, 2002). But the risk may be attributable to a longer interval; it is also possible that the same antigens from the same partner reduce the risk of pre-eclampsia (Skjaerven, Cox & Lie, 2002).

2.3.2.3 Preexisting conditions in the mother

The risk of developing pre-eclampsia is up to 14% higher in women with Systemic Lupus Erythematous (SLE), particularly those with preexisting renal disease. The endothelial dysfunction inherent in SLE may contribute to the risk of preeclampsia because impaired endothelial repair is also linked to endothelial dysfunction in SLE. SLE is frequently seen in association with the presence of anti-phospholipid antibodies and anti-phospholipid syndrome (APS) and also in pregnancy associates with increased risk of pre-eclampsia (Scramm & Clowse, 2014).

There is an increased risk for developing preeclampsia in pregnant women with a previous diagnosis of APS and/or placental insufficiency. In the absence of APS, the association between anti-phospholipid antibodies and pre-eclampsia is uncertain. In addition, there is evidence that 10-50% of pregnant women with high concentrations of antiphospholipid

antibodies develop preeclampsia (Ruiz-Irastorza, 2010).The presence of these antibodies namely; lupus anticoagulant and cardiolipin antibodies in association with venous or arterial thrombosis and/or pregnancy complications constitute APS. In general, a woman with APS develops preeclampsia earlier and is more severe (Ruiz-Irastorza, 2010). The early onset of pre-eclampsia is caused by the risk factors linked to placental and immunology (sperm exposure, prim paternity, medical assisted pregnancy). The risk factors linked to immunology are associated with the early onset of pre-eclampsia because of maladaptation (Scioscia, Gumaa & Rademacher, 2009).

The authors reported that recurrence risk of severe preeclampsia is due to both advanced maternal age and preexisting renal disease (Mc Donald, Best & Lam, 2009). Furthermore, the highest risks for pre-eclampsia recurrence in subsequent pregnancies are found most consistently when the initial case was preterm, severe, or fetal by eclampsia, Hemolysis, Elevated Liver enzymes Low Platelets (HELLPS) syndrome or fetal growth restriction. In patients with preeclampsia, the increased possibility of disease recurrence is an important issue (Dildy, Belfort & Smulian, 2007). The result from this study demonstrated that thrombophilia is one of the potential recurrence risks of pre-eclampsia because it is associated with more than 2.5-fold increase in the risk of recurrence pre-eclampsia (Facchinetti, Marozio & Venturini, 2009). The gestational age at delivery in the first pregnancy complicated by pre-eclampsia determine the risk of recurrent pre-eclampsia in a second pregnancy. Those who are delivered earliest in the prior pregnancy have higher risk of recurrence. Another important predictor of recurrence of pre-eclampsia is pre-pregnancy Body Mass Index (BMI). The results from this study also showed that the most significant risk factors for recurrence risk of preeclampsia were gestational age at first birth and the BMI (Mostello, Kallogjeri, Tungsiripat &Let, 2008).

According to Basu, Alaupovic, Wu, Jenkins and Yu, (2012), in general, the prevalence of pre-eclampsia is higher in diabetic patients. One explanation is that the factors which are implicated as mechanisms for pre-eclampsia are also implicated in the pathogenesis of the vascular complications of diabetes namely endothelial dysfunction, imbalance between proangiogenic factors and anti-antigenic factors, lipid peroxidation, oxidative stress, systematic inflammation and dyslipidemia. Endoglin is one of only two antiangiogenic factors that are thought to constitute the prerequisite for preeclampsia. A general elevation of endoglin has been also seen in women with type 1 diabetes mellitus in their later stage of pregnancy; therefore there is higher prevalence of preeclampsia in diabetic patients (Basu, et al 2011). The risk for developing pre-eclampsia in women with preexisting diabetes mellitus is determined by the duration of the disease, glycemic control prior to 20 weeks of gestational age, presence of nephropathy as well as null parity. The diagnosis of preeclampsia in diabetic women can be based on the deterioration of hypertension, increasing proteinuria and elevated uric acid (Kourtis, 2012). The results from this study showed that the prevalence of chronic hypertension in women with type 1 diabetes mellitus is 2-11% and12 – 18% in women with type 2 diabetes mellitus (Kourtis, 2012).

A key factor in both hypertension and diabetics is insulin resistance (Kourtis, 2012). Increased insulin resistance is defined as the decreased biological response of a nutrient to a given concentration of insulin at target tissue (Catalano, 2010). Obese patients are at an increased risk for many adverse pregnancy outcomes because they are more likely have decreased insulin sensitivity. Increased risk for pre-eclampsia in obese women is 10-15% (Catalano, 2010). There are hemodynamic changes in pregnant women with obesity and it is altered arterial blood pressure hem concentration and cardio function. A pregnant woman with obesity has a 10-fold higher rate of chronic hypertension compared to normal weight women (Yogev & Catalano, 2009).

If the mother is overweight as assessed by her Body Mass Index (BMI) in early pregnancy, the risk of pregnancy induced hypertension is significantly greater. According to Yogev and Catalano, (2009), the risk of pregnancy induced hypertension in association with visceral obesity is twofold greater. There is a relationship between pregnancy, BMI and risk of preeclampsia and eclampsia, although physiologic mechanism by which maternal obesity may cause preeclampsia and eclampsia is still under investigation. However, there are several plausible mechanisms that can explain the relationship between pregnancy, BMI and pre-eclampsia/eclampsia namely; increased level of circulating markers of inflammation (C - reactive protein, tumor necrosis factor-2, interleukin-6 and -8) dyslipidemia, insulin resistance and altered endothelial function (Aliyu & Luke, 2015). These metabolic and biochemical disturbances, due to the association between obesity and oxidative stress, probably predispose women to an intrauterine environment favorable for impaired placental perfusion and endothelial dysfunction that is the defining features of pre-eclampsia (Aliyu & Luke, 2015). Research indicates that preeclampsia is strongly associated with insulin resistance, over weight and obesity (Scioscia, Gumaa & Rademacher, 2009).

An increase in Body Mass Index (BMI) from the normal range is also associated with an increased risk of pre-eclampsia. In other words, the assertion that obesity increases the risk of preeclampsia is not limited to obese and overweight women. The results from this study showed that weight loss reduces pre-eclampsia (Roberts, Bodnar, and Patrick & Powers 2010). Central obesity as a marker of visceral obesity and produces more inflammatory cytokines and contributes more to oxidative stress than peripheral obesity because visceral fat is functionally different from subcutaneous fat. Hence women with visceral obesity present with a much higher risk of developing pre-eclampsia than women with peripheral obesity (Roberts, Bodnar, and Patrick & Powers 2010). In addition, the late onset of preeclampsia is caused by the risk factors linked with maternal metabolic syndrome namely lower birth

weight, obesity, insulin resistance, diabetes mellitus, chronic hypertension and renal disease (Scioscia, Gumaa & Radecher, 2009).

Infection may contribute to the development of pre-eclampsia because it can provoke the maternal systematic inflammatory response which in turn causes endothelial dysfunction (Minassian, Thomas, Williams, Campbell& Smeeth, 2013). Several mechanisms have been proposed to explain how maternal infection might be involved in the etiology of pre-eclampsia or its manifestations. These include direct effects of infectious agents on the arterial wall, including endothelial injury or dysfunction, acute atherosis and local inflammation that might cause relative utero placental ischemia (Rustveld, Kelsey & Sharma, 2008). Maternal infections may trigger the release of pro-inflammatory cytokines into maternal circulation, which may further enhance the already heightened level of inflammation observed in women with preeclampsia resulting in endothelial cell dysfunction and oxidative stress. It can also contribute in the development of pre-eclampsia by destruction or impairment of trophoblastic cells (Rustveld, Kelsey & Sharma, 2008). During the rainy season, placental malaria and dengue infections are increased in tropical regions. These infections increase the risk of gestational hypertension and pre-eclampsia, thus increased risk of seasonal infections contribute to the increase of the incidence of hypertension in pregnancy. Therefore, there is evidence of seasonal variation in the occurrence of hypertension in pregnancy (Te Poel, Saftlas & Wallas, 2011).

There is also an association between psychiatric disorders during pregnancy and the increased risk of preeclampsia. It has been shown that pre-eclampsia and gestational hypertension is associated with job stress in working women (Kharaghani, Geranmaye, Janan, Hantooshzade, Arbabi, Bilandi & Bagheri, 2012). Increased risk of preeclampsia had a 3, 1 fold in women with depression, anxiety, or both compared to those without. The authors further reported that there is an association between depression and pre-eclampsia. This association has been

supported by two reasons; first “of all depression has over lapping risk factors with cardiovascular such as endothelial damage, vasoconstriction platelet activation and platelet aggregation which are mediated by serotonin.” Secondly, depressed patients are always stressed, stress activates the hypothalamus pituitary adrenal cortex system, which in turn increases blood levels of corticosteroids and catecholamine hormones that are produced in the adrenals glands which can provoke the increased of blood pressure (Kharaghani, Geranmaye, Janan, Hantooshzade, Arbabi, Bilandi & Bagheri, 2012).

2.3.2.4 Socio-demographic factors

The most common measure of the socioeconomic differentials in health is the association of lower socioeconomic status with fewer coping resources. Lower socioeconomic status has been associated with lower self-esteem, fewer feelings of self-worth, less optimism and a weaker sense of control, these characteristics are the moderators of the relationship between stress and health (Shoff, 2012). In addition, the most important measure of socioeconomic status used in the maternal and infant health literature is education.

The risk of chronic hypertension in low educated women is nearly double compared to highly educated women. And also, in women whose mothers had low or medium education and socially disadvantaged, the risk of chronic hypertension was increased in this study (Heshmati, Mishra & Koupil, 2013). Many studies conducted in developed countries showed that age-adjusted in mean difference in systolic blood pressure (SBP) between the highest and lowest Socio Economic Status (SES) groups was approximately 2-3 mmHg. A low SES is reported as a risk factor for hypertension in adults. This association is stronger and more consistent in women than in men (Jwa, Fujiwara, Hata, Arata, Sago & Ohya, 2013).

Marital status is often considered in studies on health, as an important factor. Many consider marital status to be one of the best predictors of health status and health behaviors. It has

more recently been found to be a significant predictor of both physical and mental health. For examining disparities in hypertension in pregnancy, marital status has been used in this study. Early onset pre-eclampsia is higher in women who are not married than others (Shoff, 2012). Because the women who are married receive partner support, both relationship quality and effectiveness of partner support are important for maternal well-being (Schetter, 2015).

The increased risk of both pre-eclampsia and eclampsia in pregnant teenagers can be attributed to biologic features of young maternal age. Socio-demographic factors can also exaggerate biological risks associated with pre-eclampsia in young maternal age. This idea is supported by the fact that the teenage mothers are more likely, than older mothers, to be nulliparous, less well educated, unmarried and less inclined to receive adequate prenatal care (Aliyu & Luke, 2015). In the last decades, a trend called advanced maternal age became more widespread for various reasons. These include late marriage, higher education and career pursuit, longer life expectancy, more effective contraceptive techniques and modern infertility treatment (Usta & Nassar, 2008). A woman who has attained the age of 35 years or older at the time of delivery, can be regarded as being of advanced maternal age. Women with advanced maternal age have an increased risk of hypertension in pregnancy (Lamminpa'a, Vehvila'inene-julkunene, Gissler & Heinonene, 2012).

Chronic hypertension complicates older pregnant women from 10 to 20% than younger pregnant women. Therefore, the risk of intra uterine growth restriction and preeclampsia is increased in older pregnant women (Usta & Nassar, 2008). Because physiologically older women's myometrial arteries collagen walls progressively replace normal muscle, this vascular change can cause intra-myometrium arteries with sclerotic lesion. The luminal expansion of the arteries may be reduced by these lesions, hence restrict blood flow to the placenta. This situation can provoke under perfusion and vascularization in turn placental

hypoxia, thus causing PIH (Zhang, Zeiter, Hatch & Berkowith, 1997; Haavadsen, Samuelsen & Eskild, 2011).

2.4 COMPLICATIONS OF HYPERTENSION IN PREGNANCY

Different severity levels of hypertension in pregnancy would affect different organs in the body leading to several complications such as abruption of the placenta, disseminated intravascular coagulation, cerebral hemorrhage, hepatic failure and acute renal failure (Naidoo, 2007; Pandula, 2009). Severe pre-eclampsia can also lead to strokes, convulsions and cerebral edema. Further liver failure can cause other disease conditions such as: epigastria or right sided upper abdominal pain and this can result from both ischemia and bleeding to the sub capsular space. Severe unrolled preeclampsia can also lead to renal failure and could be life threatening (Pandula, 2009).

Utero placental system and complication of hypertension in pregnancy; according to Yinon, Kingdom, Odutayo, Moineddin, Drewlo, Lai and Hladunewich (2010) intrauterine growth restriction (IUGR) can occasionally occur without evidence of pre-eclamptic manifestation or maternal endothelial dysfunction (Yinon et al.,). Pre-eclampsia contributes to the increase in the risk for severe perinatal outcomes because of its effect on reducing birth weight. Poor placental perfusion and hypoxia in both IUGR and preeclampsia are the consequences of inadequate trophoblast invasion and uterine spiral artery remodeling. Hence perturbations in placental development may lead to compromised pregnancy outcomes (Melchiorre, Sutherland, Liberati & Thilaganathan, 2012).

Abruptio placenta is defined as the premature separation of a normally implanted placenta (Hogberg, Rasmussen & Irgens, 2007). Poor placental perfusion or placental dysfunction is a major mechanism of abruption. The association of preeclampsia with abruption placental is dependent on the severity of pre-eclampsia (Hogberg, Rasmussen & Irgens, 2007).

Preeclampsia is an associated risk of placental abruption because preeclampsia is one of the conditions that are associated with the ischemic placental disease (Ananth, 2014). This idea is supported by the fact that there is an imbalance in circulating angiogenic factors in nulliparous women who subsequently developed hypertension and placental abruption. They have decreased levels of proangiogenic Placental Growth Factor (PLGF) and increased levels of the anti-angiogenic ratio soluble FM's-like tyrosine kinase1/PLGF. This alteration can cause both placental ischemia and pre-eclampsia (Hall, 2009). Abruption of the placenta is significantly associated with hypertension in pregnancy (Hogberg, Rasmussen & Irgens, 2007).

Complications of preeclampsia extend to involve multiple systems and organs and include the visual system. According to Errera and Dacruz, (2012), the major ophthalmic complications of both preeclampsia and eclampsia are cortical blindness, hypertensive retinopathy and exudative retinal detachment. Thus 25% of patients with severe pre-eclampsia and 50% of patients with eclampsia have visual symptoms. Blurred vision is the most common visual complaint in preeclampsia and eclampsia and in severe cases where complete blindness can occur. Blindness in pre-eclampsia and eclampsia is due to the involvement of the occipital cortex, retina or optic nerve. Hypertensive retinopathy is due to vascular narrowing that is the primary response of the retinal vasculature to systemic arterial hypertension. This response to an increased blood pressure leads to focal or diffuse vasoconstriction. Serous retinal detachments are well known causes of visual loss. This complication occurs in less than 1% of pre-eclampsia patients. They usually present with severe pre-eclampsia (blood pressure more than 160/110 mmHg) (Errera & Dacruz, 2012).

Hepatic system and complication of hypertension in pregnancy; HELLP is a severe complication of pre-eclampsia characterized by hemolysis, elevated liver enzymes and low platelet count (Haram, Svendsen & Abildgaard, 2009). Three major components are required

for diagnoses of HELLP namely hemolysis, elevated liver enzymes and low platelet count, the diagnosis is considered as partial if there are one or two elements (Haram, Svendsen & Abildgaard, 2009). The central pathogenesis of HELLP syndrome is endothelial dysfunction with resultant activation of the intravascular coagulation cascade (Nokwitz, Chaur-Dong & Repke, 2002). Many patients with HELLP syndrome have these two major signs of pre-eclampsia namely hypertension and proteinuria. Despite these two major signs of preeclampsia, the liver plays a major role in the pathogenesis of HELLP. The symptom of HELLP is primarily focused on the gastro intestinal hepatic systems (Martin, Rose & Briery, 2006). These signs are right upper quadrant or epigastric pain, severe right shoulder pain, nausea, vomiting, abdominal distention, and hypovolemic shock. Pregnant women with severe preeclampsia or HELLP syndrome should have careful screening to rule out hepatic lesion in case of development of abdominal pain (Araujo, Leao, Nobrega, & Bezerra& Pereira 2006). The risk of renal failure and pulmonary edema is increased when HELLP occur postpartum (Ghulmiyyah & Sibai, 2012).

The maternal and perinatal death rates are significantly increased when pre-eclampsia is complicated by HELLP syndrome (Nokwitz, Chaur-Dong & Repke, 2002). According to Mihu, Costin, Mihu, Seicean and Ciortea (2007) HELLP is more common in whites older than thirty five years and can be diagnosed in the absence of both pre-eclampsia and eclampsia. Most of the cases of HELLP are associated with severe preeclampsia or eclampsia. It can also recur in a subsequent pregnancy; the risk is estimated at 19-27 %. An intracranial hemorrhage associated with HELLP is a potential complication and frequently occurs during the antepartum period and may also occur after delivery (Yokota, Miyamoto, Noguchi, Oyama & Oku, 2009).

Spontaneous hepatic rupture is a complication of preeclampsia, but is frequently associated with HELLP syndrome. Pre-eclampsia, eclampsia, HELLP syndrome, hepatic infarction and

rupture are all related to hypertension in pregnancy. However, hepatic rupture is virtually exclusively associated with severe pre-eclampsia or HELLP syndrome. In other words, liver rupture is one of the most severe consequences of severe preeclampsia and HELLP (Nokwitz, Chaur-Dong & Repke 2002; Vigil-De Gracia& Ortega-Paz, 2012).The precise cause of liver rupture remains unknown but the plausible pathophysiology of liver rupture is the following sequence of events: hypertension; hypovolemic ; vasospasm; hemolysis; fibrin deposition platelet aggregation; sinusoidal obstruction; ischemia infarction necrosis; neovascularization; micro hemorrhage hematoma and rupture of hepatic capsule (Vigil-De -Gracia & Ortega-Paz, 2012).

Hematologic system and complication of hypertension in pregnancy; disseminated intravascular coagulation in obstetrics (DIC) is one of the major causes of maternal mortality and morbidity in the world. It is due to acute and massive blood loss during delivery. Severe preeclampsia is associated with DIC in around 35% of cases (Bhattacharyya, Baruah & Baruah, 2014). The plausible explanation of pathophysiology of DIC in preeclampsia is the increased release of Tissue Factor (TF) from decidua cells. In cases of hypoxia, increased release of vascular endothelial growth factor (VEGF) and TF has been seen in women with preeclampsia. Endothelial damage resulting from preeclampsia can also cause DIC (Bhattacharyya, Baruah & Baruah, 2014). Preeclampsia is characterized by coagulation abnormalities namely hypercoagulable state with intravascular coagulation and micro thrombosis in several organs (Portelinha, et al., 2008). Whereas DIC is the wide spread activation of intravascular coagulation. It is characterized by systematic activation in both fibrin formation and fibrinolysis, leading to excessive consumption of clotting factors that may result in clinical bleeding (Bangash, Mahmud & Asghar, 2012). DIC is always secondary to an underlying disorder (Levi, 2004). One of the common causes of DIC is severe preeclampsia or HELLP syndrome (Bangash, Mahmud & Asghar, 2012).

Cardiovascular system and complication of hypertension in pregnancy; the most common cardiopulmonary complication of pre-eclampsia is pulmonary edema. The incidence of pulmonary edema is significantly higher in older patients and in multigravidas (Bauer & Cleary, 2009). Pulmonary edema is a clinical diagnosis characterized by breathlessness and orthopnea along with signs of namely tachycardia, tachypnea and crackles (Dennis &Solnordal, 2012). Acute pulmonary edema is a frequent cause for admission to an intensive care unit and is a leading cause of death in women with preeclampsia (Dennis & Solnordal, 2012)

The development of pulmonary edema is usually multifactorial. It is often associated with disease severity, including the presence of HELLP and eclampsia and is also associated with excessive fluid administration (Gandhi, Powers, Nomeir, Fowele & Kitzman, 2001). It is characterized by the extravasations of fluid from the vasculature, therefore any factor that results in a reduction in colloid osmotic pressure, an increase in capillary permeability or an increase in intravascular hydrostatic pressure can predispose to the development of pulmonary edema. The underlying physiological changes in the maternal cardiovascular system is exaggerated in preeclampsia and 70%-80% of cases of pulmonary edema in the setting of pre-eclampsia develop after delivery because there is a reduction in postpartum colloid osmotic pressure caused by blood loss thus, increased capillary permeability which in turn leads to pulmonary edema (Bauer &Cleary 2009).

The kidney deserves particular attention in the pre-eclampsia complication, because of the pathologic changes that can affect this vital organ during pregnancy (Mirza & Lawrence, 2009). The key renal manifestations of preeclampsia constitute the diminished renal plasma flow in turn, decreased glomeruli filtration rate (GFR) and proteinuria. Preeclampsia is a known cause of acute renal failure in pregnancy; it can also progress to renal cortical necrosis and acute tubular necrosis in rare cases (Mirza & Lawrence, 2009).

It has been discovered that kidney disease and pre-eclampsia are caused by the same factors namely obesity, hypertension, insulin resistance and endothelial dysfunction. Therefore, there is an association between preeclampsia and subsequent renal disease (Vikse, Irgens, Skjaerven & Iversen, 2008). Subclinical kidney disease that is present before pregnancy may be exacerbated by pre-eclampsia. The clinical marker for increased risk of subsequent end-stage renal disease (ESRD) is eclampsia, but also if a preeclampsia pregnancy results in the birth of a low-birth weight or preterm infant or if preeclampsia occurs in more than one pregnancy, then the risk of ESRD is greater (Vikse, Irgens, Skjaerven & Iversen, 2008).

In addition to mortality in short and long term, the maternal morbidity associated with preeclampsia is significant. A major proportion of this morbidity is the neurological manifestation. Most of the infants born from pre-eclampsia pregnancies are born preterm and/or growth restricted and can have neurological disability as well as cardiovascular and metabolic disease later in life (Kane, Dennis, Da Silva Costa, Komman & Brennecke, 2013). The neurological manifestations of pre-eclampsia are due to impaired cerebral vaso-regulation leading to cerebral edema and (posterior) reversible encephalopathy syndrome. There is a greater incidence and severity of cerebral white matter lesions in women with prior preeclampsia and eclampsia which is associated with an increased risk of Alzheimer's disease, vascular dementia, cognitive impairment and stroke. Moreover, women with pre-eclampsia and stroke are more likely to be hemorrhagic; this condition constitutes an emergency (Kane, Dennis, Da Silva Costa, Komman & Brennecke, 2013).

2.5 INTERVENTIONS IN THE MANAGEMENT OF HYPERTENSION IN PREGNANCY

Different methods have been used to manage hypertension in pregnancy. These include medication, and lifestyle modification, traditional and homeopathic medication (Duley, DJ

Henderson-Smart, S Meher, 2007; Shirazian, Monteith, Friedman, Rebarder, 2010). Two modes are mostly used to prevent or treat hypertension in pregnancy namely; lifestyle modification and medication (Imura, 2013).

2.5.1 Medication

The goal of pharmacologic treatment should be a diastolic blood pressure less than 100-105 mm Hg and a systolic blood pressure less than 160 mm Hg. This implies that pregnant women should be started on antihypertensive therapy if the systolic blood pressure is greater than 160 mm Hg or the diastolic blood pressure is greater than 100-105 mmHg (Lowe et al., 2014). Continuing antihypertensive medication, for women with target organ damage or who require multiple antihypertensive agents for blood pressure control prior to pregnancy in order to maintain blood pressure control (JNC, 2014).

Antihypertensive is required in all women with a systolic blood pressure of greater than or equal to 160mmHg or a diastolic blood pressure greater than or equal to 110mmHg in order to reduce the risk of severe maternal morbidity (cerebral hemorrhage, liver rupture, renal insufficiency and abruption placenta) and fetal morbidity (Moussa, Arian & Sibai, 2014). In addition, hypertension emergencies are one of the significant clinical challenges. For hypertensive crisis, some investigators suggest that a diastolic blood pressure of more than 115 mmHg and/or a systolic blood pressure of more than 200 mmHg should be used to define hypertensive crisis in the management of hypertensive crisis (Norwitz, Chaur-dong &Repke, 2002).The most important first step in hypertension emergencies is to lower the blood pressure. Ideally, it should be an initial reduction of blood pressure of about 20%with systolic and diastolic pressure goals of 140 to 150 mmHg and 90 to 100 mmHg. A termination of the pregnancy is indicated if hypertension is not manageable (Norwitz, Chaur-dong & Repke, 2002).

Antihypertensive therapy for non-severe hypertension may increase the risk of small gestational age or low birth weight by decreasing blood pressure. This idea is supported by the fact that there is a physiological fall in blood pressure during the first half of pregnancy in many women with chronic hypertension. It may also cause placental abruption, caesarean section or admission to the neonatal nursery (Lowe et Al., 2014).

2.5.2 Lifestyle

Key components of a health-promoting lifestyle during pregnancy include: appropriate weight gain, information regarding balanced nutrition for maternal and infant health, and moderate exercise **(**New York State Department of Health, 2013).

The relative risk of maternal non-severe hypertension (systolic blood pressure 140-150mmHg or diastolic blood pressure 90-109mmHg) may be decreased by using anti-hypertensive therapy, but with "non – severe chronic hypertension there is insufficient evidence regarding the benefit of pharmacological treatment" (New South Wales Department of Health, 2011). Antihypertensive decreases by half the incidence of development of severe hypertension among women with mild hypertension but does not prevent preeclampsia (Lowe et al., 2014).Therefore, lifestyle (Physical activities and diet) is important for the prevention of hypertension in pregnancy (Brown, Best, Pearce, Waugh, Robson & Bell, 2013).

The candidates for lifestyle modification are women with systolic blood pressure 140 – 159 mmHg or diastolic blood pressure 90 – 99 as they are at low risk for developing cardiovascular complications during pregnancy. Several factors have been identified that contribute to the healthy lifestyle during pregnancy; appropriate weight again, safe food, moderate exercise, avoidance of alcohol and tobacco, (New York Department of Health, 2013). Moderate exercise is often part of the care plan for women with well-controlled chronic (pre-existing) hypertension, whereas aerobic exercise is not recommended for women

with pre-eclampsia. Moreover, there is insufficient evidence for a recommendation regarding optimal activity levels for women newly diagnosed with gestational hypertension. According to Wolf, Owe, Juhl and Hegaard (2013), high amounts of leisure time physical activity may increase the risk of severe pre-eclampsia.

2.5.3 Homeopathy

Homeopathy is a safe natural and effective treatment of all complaints during pregnancy. It is safe for both mother and child (Bell & Thomas, 2014). Homeopathy balances blood pressure and relieves pain and other complaints. It treats the person as a whole (British homeopathic association, 2015). However National Institutes of Health (NIH) did not support the use of homeopathy as affective treatment for any specific condition (NIH, 2015).

2.5.4 Combination of therapy

Medication may be sufficient to lower blood pressure, but in certain circumstances lifestyle change is also required (Edo, 2009). The risk of developing complications of hypertension is caused by non – compliance to prescribed medications or lifestyle (Edo, 2009).

According to Zhang, Tuomilehto, Jousilaliti, Wang, Antikainen and Hu (2012) healthy lifestyle (not smoking, normal body mass index, moderate alcohol consumption, regular physical activity, and healthy diet) is associated with the reduced risk of ischemic stroke, and hemorrhagic stroke. However, mechanisms showing that healthy lifestyles might provide more significant effects than antihypertensive treatment in reducing the risk of stroke are not clear. In contrast, single pharmacological antihypertensive treatment can lower high blood pressure but does not directly affect causes of risk factors for stroke. Therefore, in most cases, combination of therapy is used in order to give the best chances of good health as possible to the pregnant woman.

2.5.5 Limitations identified in the literature

According to Bakare, Akinyinka, Goodman, Kuyinu, Wright, Adeniran, Odusanya and Osibogun (2016), most of the patients with hypertension do not have access to antihypertensive medication. This problem is due to several factors but the main factor is financial constraints especially in African countries where health care is not free. According to Scantlebury, Schwartz, Acquah, White, Moser, and Garovic (2013), hypertension in pregnancy is also a chronic disease; this treatment can be a lifetime treatment thus it requires financial means to cater for transport cost normally incurred by patients in their quest to access health services**.** However, it has been noted that in most literature sources, the socio-economic complexities are not filtered in when the discussion about management of hypertension in pregnancy is undertaken. Considering the level of poverty in the world, especially in Africa where the majority of patients do not follow their treatments normally because of financial difficulty, it is therefore important to consider factors that may hinder interventions intended to reduce and maintain health blood pressure thus reduce maternal and infant mortality (Scantlebury, Schwartz, Acquah, White, Moser & Garovic, 2013; Bakare et Al., 2016).

According to Brinkman, Pee, Sanogo, Subran, and Bloem (2010), access to high quality nutritious foods (animal source proteins, micronutrient rich vegetables and fruits) have become a major challenge in the world especially in Africa. These are very costly therefore are not considered household priorities when the income is insufficient (Brinkman, Pee, Sanogo, Subran & Bloem, 2010). Hence lack of including this issue when advocating for lifestyle modification in the management of hypertension in pregnant women is a limitation in this field of study. Additionally, environmental conditions are very important for pregnant women to support lifestyle modification approaches. In most cases, although exercise is recommended, it is not always feasible. Walkways that allows safe walking (as an exercise);

physical spaces in the homes and access to gyms are not always accessible to these women. Therefore, lack of consideration of these aspects in most work that addresses management of hypertension in pregnancy is a limitation in this field and can impact the recommended approaches. Consequently, adherence may not be successful thus health outcomes may not be satisfactory.

2.6 CHAPTER SUMMARY

In the reviewed literature, the investigator attempted to highlight how hypertension is managed in pregnancy. The literature showed the different kinds of hypertension in pregnancy and their management and also the causes of hypertension in pregnancy. Studies have shown several factors that contribute to the development and evolution of hypertension in pregnancy and several complications of hypertension in pregnancy that affects different organs in the body. And finally, different interventions that are used to manage hypertension in pregnancy were discussed.

CHAPTER THREE

RESEARCH DESIGN AND METHODS

3.1 INTRODUCTION

This chapter contains discussions on the study's methodology. The aspects which are addressed include the research design and methods applied in conducting this study. Chapter one provided a brief orientation of the adopted steps of the systematic review approach. In this chapter, the investigator described the steps that were followed in conducting the systematic review in this study.

3.2 RESEARCH DESIGN

A research design is the guide used to systematically answer the research question or the research hypothesis (LoBiondo-wood & Haber, 2010). Burns and Grove (2009) define the research design as the overall plan for obtaining answers to the research questions guiding the study.

The investigator followed a systematic review design to assess the effects of medication and lifestyle adjustment intervention on patients' outcomes during the management of hypertension in pregnancy.

According to Hempel, Xenakis and Danz (2016) systematic review is an overview of existing evidence pertinent to a specific research question that uses systematic and explicit methods to identify, select and critically appraise relevant research and to collect, report and analyze data from the studies that are included in the review.

3.3 RESEARCH METHOD

3.3.1 Steps of systematic review

According to Khan and Kunz (2011), there are five steps involved in conducting a systematic review which was adopted in the research process. These steps include; Formulation of a focused review question; identification of relevant publications; performing the critical appraisal; summarizing the evidence and interpreting the findings.

3.3.1.1 STEP 1: Formulating a focused review question

The purpose of this study was to review the effectiveness of medications and lifestyle interventions on patients' outcome during the management of hypertension in pregnant women. The review question was specific enough to focus on applicable literature.

Review question: What is the effectiveness of medication and lifestyle interventions in the management of hypertension in pregnancy?

. **TABLE 3.1: Components of the review question**

Population of interest (P)	Pregnant women
Intervention (I)	Medication intervention
Comparative intervention (C)	Life style adjustment intervention
Outcome (O)	Reduction of blood pressure

The review was designed to meet the following objective:

- To review the published evidence on medication and lifestyle adjustment intervention on patients' outcomes during the management of hypertension in pregnancy

3.3.1.2 STEP 2: Gathering and classifying the evidence

In this step the investigator will discuss the process followed to source credible and relevant data sources, and how documentation of the search was done.

This step includes multistage and iterative processes. First the databases and additional sources must be specified. Second the study selection criteria should flow directly from the review questions and be specified a priori. Third publication status and related biases such as the type and language of their reports, the timing of their publication must also be taken into account (CRD, 2009).

3.3.1.2.1 Data sources and search strategies

The focus of this systematic review was to get evidence from existing systematic reviews in order to get a broader view of what is the dominant perspective on the topic under study

Electronic databases were used to search the literature on the topic: A systematic review of the effectiveness of medication and lifestyle interventions in the management of hypertension in pregnancy. The search included the following databases: PubMed, Google Scholar, and Cochrane Library.

Additionally the investigator went through the reference lists of retrieved articles to further select the relevant studies.

Grey literature which included theses and dissertation were also accessed. Table.3.2 depict the type of database that were used.

TABLE 3.2: Data sources

ELECTRONIC DATABASES AND TYPE OF LITERATURE :
Google Scholar, Pub med and Cochrane
These databases were used because they cover the health sciences and research studies field.
MANUAL SEARCH AND TYPE OF LITERATURE :
Grey literature: both theses and dissertations were searched.

The following key words were used in the initial search strategy:

Relevant publications using the search terms [(hypertension OR high blood pressure OR eclampsia OR pre-eclampsia) AND (pregnancy) AND (diet) AND (nutrition) AND (physical activity) AND (exercise)] AND REVIEW were searched. The investigator included all possible studies that were relevant to the review question with specific focus on outcomes, that is, the publication had to show that there was an outcome when an intervention was administered. The key words were applicable in the categories or title, and abstracts. Study selection was conducted in two stages; in the first stage the articles were screened by analyzing their titles and/or abstracts. Articles that did not meet the inclusion criteria were excluded. In the second stage of the search, the full-text articles were examined to view full details.

Inclusion criteria

The inclusion criteria for selection of papers were as follows;

1) Systematically reviewed reviews evidence was presented

2) The participants were pregnant women

3) The intervention described were medication and/or lifestyle modification

4) The outcomes were synthesized and presented

5) The reviews were moderate to good quality systematic reviews

6) The articles were written in English and published between 2000 and 2015.

7) The article had an outcome that showed effectiveness of either medication or lifestyle on hypertension.

The inclusion criteria were based on the PICO strategy (Squires, Valentine& Grimshan, 2013)

3.3.1.2.2 Documentation of the search

The search strategy was well documented to ensure transparency (see Figure 1). The record included all searches namely internet searches and hand searching. Internet search yielded results whereas no relevant documents were available during the manual search process. With regard to the internet searches, full details of the database, the search strategy and the number of records obtained by every search are included in Table 4.1.

3.3.1.3 STEP 3: Performing the critical appraisal

The next step of the systematic review involved a critical appraisal of studies included for review to evaluate their validity. This process entails checking for both the internal validity and external validity. Internal validity refers to the minimization of method error of bias and external validity refers to the generalizability of the conclusion of a trial to another population (Wright & Brand, 2007). The degree to which the internal and external validities are addressed within each study makes for judging of the quality of the study that is required to assess the methodological quality of the included studies. It involves using tools to identify those aspects of study design; data extraction processes and analysis which induce a possible risk of bias. Effective public health practice project (EPHPP) was not used because the review

included studies of diverse design intervention and population hence it was decided that the meta-analysis was scientifically unjustified. Therefore, the revised assessing the methodological quality of systematic reviews (R-AMSTAR) as an instrument was used to reduce the researcher's bias and guide the critical appraisal;

According to the National Collaborating Center for Methods and Tools (2011), the tool was developed for general use and can be used to assess the methodological quality of systematic reviews. In addition, it is suitable to be used in systematic review that tries to assess the effectiveness of an intervention, program or medication in which content and construct have been established. The instrument evaluates the following quality criteria (1) a priori design (2) duplicate study selection and data extraction (3) the use of status of population as an inclusion criteria (4) a list of included/excluded studies (5) characteristics of included studies (6) documented assessment of the scientific quality informing conclusions (7) appropriate use of methods to combine findings of studies (8) assessment of the likelihood of publication bias and documentation of conflict of interest. An independent individual with expertise in systematic reviews was involved as the second reviewer in this study to ensure reliability. A consensus between the investigator and independent reviewer on the quality of the appraised document was reached for audit purposes; completed critical appraisal instruments for each paper were submitted to the supervisor assessment of the quality of the process. The investigator reported the quality appraisal of each of the relevant studies Table 4.3.

3.3.1.3.1 Synthesis of findings

After the critical appraisal was conducted, 20 articles were finally selected for data extraction. Figure 1 below depicts the process leading the final selection of documents used in this study.

3.4 CHAPTER SUMMARY

This chapter provided an overview of the systematic review process as a research design. The following steps of the systematic review were discussed in detail:

Step 1: When formulating a focused research question the PICO strategy was used by the investigator.

Step 2: Gathering and classifying the evidence, studies were selected using the inclusion criteria, key words and sources used. Table 3.1 documents the initial search. Table 3.2 outlines the studies that were excluded and reasons for exclusion. Table 3.3 outlines the full text articles that could not be obtained. In addition, the investigator used a flowchart in order to show the number of relevant articles after every step of the search (figure 1).

Step3: Performing the critical appraisal. The critical appraisal tools used and the method of appraisal was explained in the text.

The subsequent chapters will discuss the last two steps of the systematic review which are; summarizing of evidence and interpretation of the findings.

CHAPTER FOUR

DATA EXTRACTION AND FINDINGS

4.1 INTRODUCTION

This chapter provides data extraction process, the synthesis and interpretations of the study's results. The purpose of extraction and synthesis of data was to obtain usable and useful information to report, describe, discuss and summarize the findings. The aim of this study was to review the effectiveness of medications and lifestyle interventions on patients' outcome during the management of hypertension in pregnant. In the previous chapter, the research methodology of SR was discussed. In this chapter, the fourth step (summarizing of the evidence) of the SR is discussed.

4.2 REALISATION OF THE STUDY

4.2.1 Search results

A total of 3 246 671 articles published from 2000 to 2015 were identified. After a selection, 23 articles were included in the critical appraisal. A flow chart of this process was presented fig1. These articles were independently appraised by two reviewers. After critical appraisal and consensus meeting with the second reviewer, 20 articles were retained for data extraction. Two reviewers extracted the data; in case of disagreements, a third reviewer was consulted needed. After consensus of 3 reviewers only 20 articles were extracted and then they were analyzed.

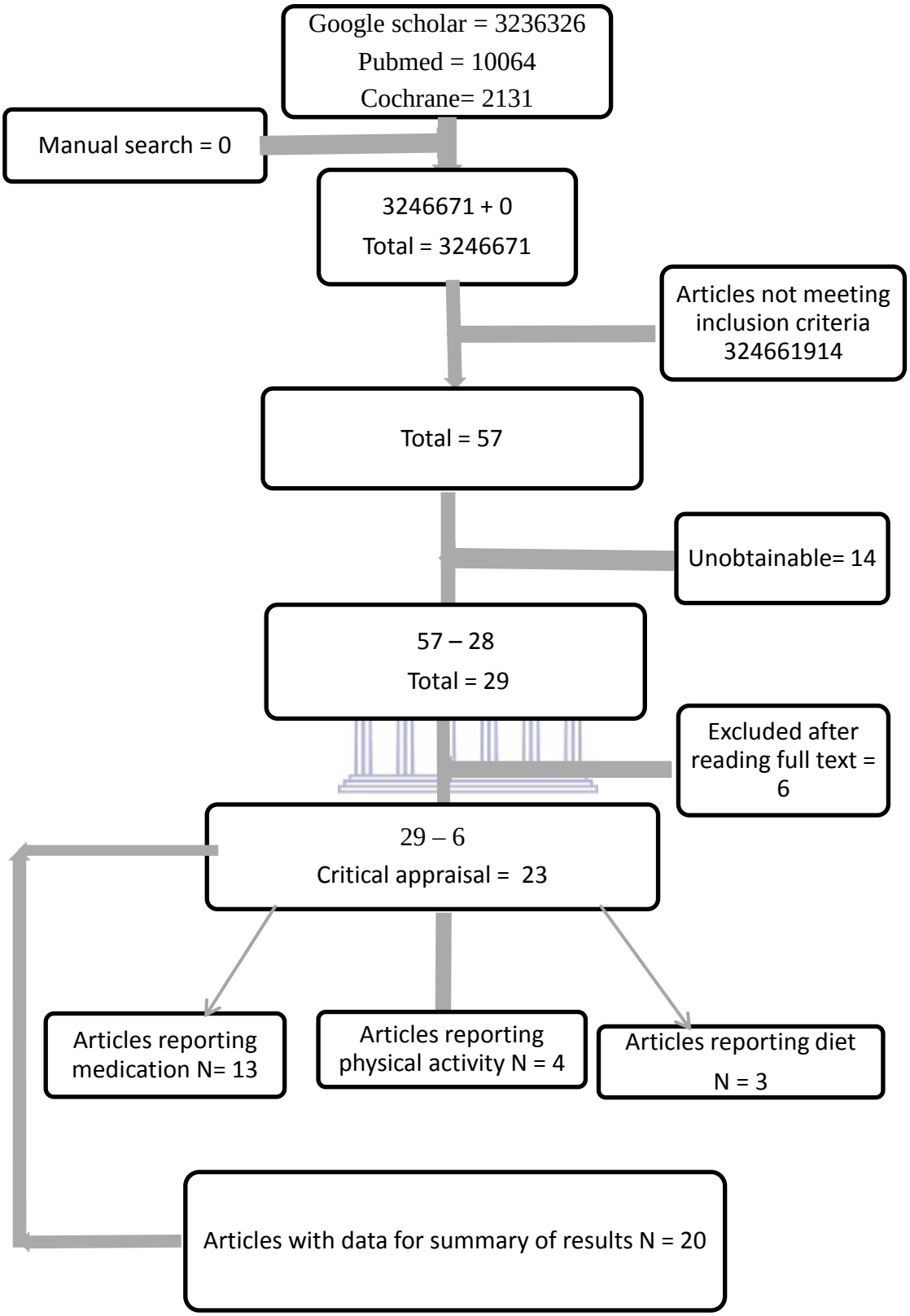


Figure 1 Flowchart of sampling

TABLE 4.1: Summary of the search

Electronic databases			
Database	**Search**	**Full text**	**For appraisal**
Google scholar	3236326	12	9
Cochrane library	10064	8	8
Pub med	281	9	7
Manual search			
Type	**Search**	**Full text**	**For appraisal**
Thesis and dissertation	0	0	0
Total	3246671	29	24

Table 4.2 indicates the articles that were excluded after analyzing their titles and/or abstracts. A flowchart was also used to show the number of relevant articles remaining at each stage .

TABLE 4.2: Excluded studies and reasons for exclusion

Reasons for exclusion	**Google scholar**	**Cochrane library**	**Pub med**	**Manual search**
Total initial search	3236326	10064	281	0
1.Irrelevant studies	3234058	10048	245	0
a. Discuss hypertension issue only	0	0	0	0
b. Language excluded	0	0	0	0

c. Old excluded	12	1	0	0
d. Research method excluded e. Discuss other topics other than hypertension	2219	0	25	0
2.Unobtainable studies	14	2	4	0
3. Duplicates	14	13	0	0
Total excluded	3236317	10056	274	0

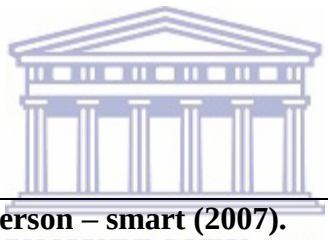
The end product of step 2 of systematic review was those articles that met this study's inclusion criteria (Table 4.1).Figure 1 depicts the process leading the final selection of documents used in this study.

4.2.2 Selection result

Table 4.3: Summary of critical appraisal

1. Dignon and Redding Lon (2013). The physical effect of exercise in pregnancy on preeclampsia, gestational diabetes, birth weight and type of delivery.	
Type of design/study	Systematic review (SR)
Aims/objective	To investigate the association between physical exercise in pregnancy and the development of hypertensive disorders, gestational diabetes, birth weight and types of delivery. This review hypothesized that modifiable behavior – physical activity – reduces the risk of these conditions.
Participant	Pregnant women
Studies	Not described
Setting	Not described
Intervention	Physical activity.
R- AMSTAR	18/44
Percentage	49 %
Rank	F
Decision	Excluded

2. Duley, Henderson-smart and Meher (2007). **Drug for treatment of very high blood pressure during pregnancy**	
Type of design/study	Systematic review of randomized trial (RT)
Aims	The aim of this review is to compare the different types of antihypertensive drugs used for women with severe hypertension during pregnancy to determine which agent has the greatest comparative benefit with the least risk.
Objective	To compare the effects of different hypertensive agents when used to rapidly lower very high blood pressure during pregnancy on: (i) substantive maternal morbidity; (ii) morbidity and mortality for the baby; (iii) side-effects for the woman.
Participant	Pregnant women with severe hypertension
Studies	24 RCT
Setting	Africa (2 RCT), Asia (150 women), America (50 women)
Intervention	Treatment of hypertension in pregnancy
R- AMSTAR	39/44
Percentage	88%
Rank	B
Decision	Included



3. Duley, Gulmezoglu and Henderson – smart (2007). **Mgso4 and other anticonvulsants for women with preeclampsia**	
Type of design/study	Systematic review of randomized trial
Aims /Objective	To assess the effects of anticonvulsants for preeclampsia on women and their children.
Participant	Any woman with preeclampsia
Studies	13 randomized control trials
Setting	America (8 RCT), Africa (2 RCT), Asia (2 RCT), Europe (1 RCT)
Intervention	Treatment of preeclampsia
R-AMSTAR	37/44
Percentage	84%
Rank	B
Decision	Included

4. Magee and Duley (2012). **Oral beta blockers for mild to moderate hypertension in pregnancy**	
Type of design/study	Systematic review of randomized trial
Aims/objective	To assess whether oral beta-blockers are over all better than placebo or no therapy for women with mild to moderate hypertension during pregnant.
Participant	Pregnant women with mild to moderate hypertension
Studies	29 randomized controlled trials
Setting	America (1 RCT), Europe (2 RCT), Asia (1 RCT).
Intervention	Treatment of hypertension in pregnancy
R-AMSTAR	37/44
Percentage	84%
Rank	B
Decision	Included

5. Rumbold et Al (2012). **Antioxidants for preventing preeclampsia**	
Type of design/study	Systematic review of randomized trial
Aims /Objective	To determine the effectiveness and safety of any antioxidant supplementation during pregnancy and the risk of developing preeclampsia.
Participant	Pregnant women at low, moderate or high risk of developing preeclampsia.
Studies	10 randomized trials
Setting	Not described
Intervention	Prevention of preeclampsia
R-AMSTAR	39/44
Percentage	88%
Rank	B
Decision	Included

6. Abalos et al (2007). **Antihypertensive drug therapy for mild to moderate hypertension in pregnancy**	
Type of design/study	systematic review
Aim	To assess the potential benefits and hazards to the women and baby with mild to moderate hypertension during pregnancy. If antihypertensive agents are overall beneficial, a secondary aim will be to assess the comparative effects of alternative agents.
Objective	To assess the effects of antihypertensive drug treatment for women with mild to moderate hypertension during pregnancy.
Participant	Pregnant woman with mild to moderate hypertension

Studies	46 randomized trials
Setting	Industrialized countries (34 RT), Middle low countries (12 RT)
Intervention	Treatment of hypertension in pregnancy
R-AMSTAR	39/44
Percentage	88%
Rank	B
Decision	Included

7. Firoz (2014). **Oral antihypertensive therapy for severe hypertension in pregnancy and postpartum.**	
Type of design/study	Systematic review
Aims /Objective	To assess the effectiveness of oral antihypertensive therapy for treatment of severe pregnancy or postpartum hypertension by reviewing relevant RCT evidence.
Participant	Pregnant women with severe hypertension or postpartum.
Studies	15 randomized controlled trial
Setting	Busy and resource-constrained setting (15 RCT)
Intervention	Treatment of hypertension in pregnancy.
R-AMSTAR	30/44
Percentage	68%
Rank	D
Decision	Included

8. Hofmeyr et Al (2004). **Calcium supplementation to prevent preeclampsia**	
Type of design/study	Systematic review of randomized trial
Aims/Objective	To assess the effects of calcium supplementation during pregnancy on hypertension in pregnancy and related maternal and child adverse outcomes.
Participant	Pregnant women
Studies	Not described
Setting	Not described
Intervention	Prevention of preeclampsia
R-AMSTAR	26/44
Percentage	59 %
Rank	E
Decision	Excluded

9. Duley et Al (2007). **Antiplatelet agents for preventing preeclampsia and its complications**	
Type of design/study	Systematic review
Aims	To identify as many of both the published and unpublished antiplatelet trials as possible and to estimate the benefits and hazards of platelet agents when used for the prevention of preeclampsia.
Objective	To assess the effectiveness and safety of antiplatelet agents for women at risk of developing preeclampsia.
Participant	Pregnant women at risk of preeclampsia
Studies	59 Randomized trials
Setting	Gestational hypertension (India 1993; India 1994; India 1999; Israel 1990).women with or without gestational hypertension (CLASP 1994; Italy 1993; UK 1992) aspirin and dipyridamole or alone versus control (EPREDA 1991; France 1985; France 1990;Russia 1993; S Africa 1988). Heparin and dipyridamole versus control (Australia 1995a), aspirin with vitamins C and E and fish oil (Venezuela 2000) hydrochloride with placebo (Japan 1999).
Intervention	Prevention of preeclampsia
R-AMSTAR	37/44
Percentage	84 %
Rank	B
Decision	Included

10. Hofmeyr, Duley and Attalla (2007). **Dietary calcium supplementation for prevention of preeclampsia and related problems.**	
Type of design/study	Systematic review
Aims /Objective	To assess the effect of calcium supplementation during pregnancy on the risk of hypertension and related maternal and foetal and neonatal adverse outcome.
Participant	Pregnant women with less than 35 weeks of gestation.
Studies	12 randomized trials from 1987 to 2006
Setting	America (12 RCT)
Intervention	Prevention of preeclampsia
R-AMSTAR	34/44
Percentage	77%
Rank	C
Decision	Included

11. Dorniak – wall (230 – 235). **The role of l-arginine in the prevention and treatment of preeclampsia.**	
Type of design/study	Systematic review
Aims/ Objective	To conduct a systematic review of the literature review and meta-analysis, to evaluate the evidence for the use of L-arginine in the prevention and treatment of preeclampsia, and the effect on clinical maternal and infant health outcomes.
Participant	Pregnant women where L-arginine was administered in prevention and treatment of preeclampsia.
Studies	America (2 RCT), Europe (3 RCT)
Setting	14 randomized trials
Intervention	Prevention and treatment of preeclampsia
R-AMSTAR	28/44
Percentage	63%
Rank	D
Decision	Included

12. Hofmeyr (2014). **Low - dose calcium supplementation for preventing preeclampsia.**	
Type of design/study	Systematic review
Aims /Objective	To review the impact of lower dose calcium supplementation on preeclampsia risk.
Participant	Woman at high risk of preeclampsia
Studies	9 randomized quasi – randomized trials
Setting	Low and high income countries.
Intervention	Prevention of preeclampsia
R-AMSTAR	29/44
Percentage	68%
Rank	D
Decision	Included

13. Magee (327: 955). **Hydralazine for treatment of severe hypertension in pregnancy meta-analysis**	
Type of design/study	Systematic review
Aims /Objective	To review outcomes in RCT comparing hydralazine against other antihypertensive for severe hypertension in pregnancy
Participant	Pregnant women with moderate to severe hypertension.
Studies	21 randomized controlled trials
Setting	Not described
Intervention	Hydralazine and treatment of hypertension in pregnancy
R-AMSTAR	31/44
Percentage	74%

Rank	C
Decision	Included

14. Henderson (695-703). Low-dose aspirin for prevention of morbidity and mortality from preeclampsia	
Type of design/study	Systematic review
Aims/objective	To systematically review benefits and harm of low dose aspirin for preventing morbidity and mortality from preeclampsia.
Participant	Pregnant women with high risk of preeclampsia.
Studies	2 large, multisite RCTs and 13 smaller RCTs, in addition to 6 RCTs and 2 observational studies.
Setting	Africa (1 RCT), America (6 RCT), Europe (12 RCT and 1 Cohort) Asia (1 RCT), Oceania (1 Case control study)
Intervention	Prevention of preeclampsia
R-AMSTAR	30/44
Percentage	68%
Rank	D
Decision	Included

15. Hypponen et Al (331-340). Vitamin D and preeclampsia	
Type of design	Systematic review
Aims/ Objective	To evaluate the role of vitamin D in the development of preeclampsia.
Participant	Pregnant women with preeclampsia
Studies	Cohort study (1st April 1991 to 31st December1992) Cases controls from the National Birth Registry of the Central Statistical
Setting	Cohort study (14,541 pregnancies resident in Avon, UK) Cases controls (the Hungarian Congenital Abnormality Registry)
Intervention	Prevention of preeclampsia
R-AMSTAR	24/44
Percentage	54 %
Rank	E
Decision	Excluded

16. Salles et Al (2012). **Antioxidants for preventing preeclampsia**	
Type of design/study	Systematic review
Aims /Objective	To investigate the efficacy of antioxidants and fetal complications among pregnant women with low, moderate or high risk of preeclampsia.
Participant	Pregnant women with low, moderate or high risk of preeclampsia.
Studies	15 randomized placebo-controlled trials.
Setting	Asia [6 Randomized placebo control trial (RPCT)], Africa (1RPCT), Europe (5 RPCT), America (6RPCT).
Intervention	Prevention of preeclampsia
R-AMSTAR	30/44
Percentage	68%
Rank	D
Decision	Included

17. Meher and Duley (2010). **Exercise or other physical activity for preventing preeclampsia and its complications**	
Type of design/study	Systematic review
Aims	To evaluate the effects of exercise or increased physical activity on prevention of preeclampsia and its complications.
Objective	To assess the effects of exercise or increased physical activity, on prevention of preeclampsia and its complications
Participant	Pregnant women at risk of preeclampsia
Studies	USA (2 RCT)
Setting	2 Randomized control trials (RCT)
Intervention	Prevention of preeclampsia.
R-AMSTAR	38/44
Percentage	86%
Rank	B
Decision	Included
18. Wolf et al (2012) **Leisure time physical activity and the risk of preeclampsia a SR**	
Type of design/study	Systematic review
Aims/ Objective	To give an overview of the literature examining the association between leisure time physical activity before and/or during pregnancy and the risk of preeclampsia.
Participant	Pregnant women at risk of preeclampsia
Studies	11 Observational studies 4 case control 7 cohort

Setting	America (4 Case-control studies, 2Cohort study) Europe (4Cohort studies)
Intervention	Prevention and treatment of preeclampsia.
R-AMSTAR	30/44
Percentage	68%
Rank	D
Decision	Included

19. Aune et Al (331-343). **Physical activity and the risk of preeclampsia**	
Type of design	Systematic review and meta-analysis
Aims/ Objective	Clarifying the possible dose-response relationship between physical activity and preeclampsia
Participant	Women with pregnancy induced hypertension OR preeclampsia OR eclampsia
Studies	15 Observational studies 11 cohorts studies and 4 Case control studies
Setting	North America (3 Case-control, 4 Cohort studies), Europe (7 Cohort studies), and Asia (1Case-control)
Intervention	Prevention of PE
R-AMSTAR	28/44
Percentage	63%
Rank	D
Decision	Included

20. Kasawara et al (2012) **Exercise and physical activity in the prevention of preeclampsia**	
Type of design	Systematic review
Aims /Objective	To evaluate the association between exercise and physical activity and the development of preeclampsia.
Participant	Pregnant women with preeclampsia
Studies	SR of 6 case-control,10 prospective cohort 1 RCT
Setting	America (6 Case-control studies, 10 Cohort studies and 1 RCT)
Intervention	Prevention of preeclampsia
R-AMSTAR	27/44
Percentage	61%
Rank	D

Decision	Included

21. Tabesh et Al (2013). **Maternal vitamin D status and risk of PE**	
Type of design	Systematic review of observational studies (OS)
Aims/ Objective	To review the current OS about the association between maternal vitamin D status and risk of PE and to perform a meta-analysis of published studies.
Participant	Pregnant women at risk of PE.
Studies	2 Cohort studies 5 Nested case control studies and 4 Case-control studies 4 cross- sectional studies
Setting	North America(2 2013Cohort Studies,4 Nested case control, 3 Case control studies, 3 Cross sectional) Europe (1 Cross sectional, 1 Nested case control, 1 Case-control)
Intervention	Prevention of PE
R-AMSTAR	29/44
Percentage	65%
Rank	D
Decision	Included

22. Shoenaker, Soedamah-muthu and Mishra (12:157). **The association between dietary factors and gestational hypertension and preeclampsia.**	
Type of design	Systematic review of observational studies
Aims/Objective	A systematic review and meta-analysis were performed to synthesize evidence from observational studies of reproductive age women on the association between dietary factors and hypertensive disorders pregnancy
Participant	Reproductive age women
Studies	23 Cohort and 15 case –control studies
Setting	Asia (1 Cohort studies,4 Case control studies) America (6 Case control Studies 9Cohort studies) Europe (11 Cohort studies,3 Case control studies) Africa (1 Cohort Study,2 Case control studies) Oceania (1 cohort study)
Intervention	Prevention of preeclampsia
R-AMSTAR	32/44
Percentage	73%
Rank	C
Decision	Included

23. Allen et Al (93:973). **Effect of diet – and lifestyle – based metabolic risk modifying interventions on PE.**	
Type of design	Systematic review of observational studies
Objective	Not described
Participant	Pregnant women at risk of obesity, hyperlipidemia /glycaemia and hypertension
Studies	6 case-control,10 prospective cohort 1 RCT
Setting	America (6 Case-control studies, 10 Cohort studies and 1 RCT)
Intervention	Prevention of PE.
R-AMSTAR	33/44
Percentage	75%
Rank	C
Decision	Included

4.2.2 Description of articles

In the initial 23 articles were appraised. Diet intervention included 11 Cohort studies, 9 Case control studies, 4 Nested case control studies and 1 Cross sectional studies, they were from America. And 1 case control study the author did not mention where it was from. Other studies were carried out in Europe namely 11 Cohort studies, 1 Cross sectional study, 4 Case control studies. 1 Cohort study and 4 Case control studies were also performed in Asia.

Physical activity intervention included 16 Cohort studies, 13 Case control studies and 3 RCT; those reviews were performed in America. But 1 cohort study the author did not mention where it was from. Other 11 Cohort studies were performed in Europe only 1 Case control study was from Asia.

Medication intervention included 36 RCT were from America, 27 RCT and 1 Cohort study were carried out in Europe , 40 RCT were from Asia, 7 RCT were from Africa only 1 Case control study were performed in Oceania. 9 quasi-randomized trials were from low and high income countries. Only 1 Cohort study included Hispanic pregnant women. 10 RT the author did not mention where it was from. After critical appraisal 20 articles were selected for data

extraction. Diet intervention included 11 Cohort studies, 9 Case control studies, 4 Nested case control studies and 1 Cross sectional studies, they were from America.

Other studies were carried out in Europe namely 11 Cohort studies, 1 Cross sectional studies, 4 Case control studies. 1 Cohort study and 4 Case control studies were also performed in Asia. Physical activity intervention included 16 Cohort studies, 13 Case control studies and 3 RCT; those reviews were performed in America.

Other 11 Cohort studies were performed in Europe only 1 Case control study was from Asia. Medication intervention included 36 RCT were from America, 27 RCT and 1 Cohort study were carried out in Europe , 40 RCT were from Asia, 7 RCT were from Africa only 1 Case control study were performed in Oceania. 9 quasi-randomized trials were from low and high income countries. Only 1 Cohort study included Hispanic pregnant women

4.2.3 Quality of articles

According to Khan, Kunz, Kleijnen and Antes (2011) the quality of study may be defined as the degree to which the design of the study and its conduct minimed the risk of bias and error. The investigator used; Revised - assessing the methodological quality of systematic reviews (R - AMSTAR, 2011).This tool consists of 11 questions and content validity for measuring the methodological quality of systematic review. Every question of R-AMSTAR has a score from one to four. The articles with a quality score greater than or equal to 22 /44 were classified as eligible for assessment of quality. In this study, the articles that were included in data extraction were those that had greater or equal to 29/44; in other words, the articles that were ranged from A to D (100% - 60%).

After appraising the articles, two physical activity articles were ranked in the D quality score (QS), one physical activity article was ranked in the C QS and the last physical activity article was ranked in the B QS. And then three diet articles were appraised; the first one was ranked

in the C QS and the second one ranked in the D QS and the third one ranked in the E QS. Physical activity and Diet had one article only that ranked in the C QS. Concerning the medication articles, seven articles ranked in the B QS, five articles ranked in the C QS and eight articles ranked in the D quality score.

Table 4.4 Quality

	Design	Search result	Search strategy	Status of publication	List of studies	Characteristics of studies	Quality of study	Conclusion	Meta-analysis	Publication bias	Conflict of interest	AMSTAR	%	Rank
P A 1	3	3	3	2	2	3	3	1	3	3	2	28/44	63	D
P A 2	3	4	4	3	4	4	3	4	3	2	4	38/44	86	B
P A 3	3	3	3	3	2	3	3	2	3	3	2	31/44	74	C
P A 4	3	3	3	4	2	3	2	0	3	3	1	27/44	61	D
DIET 1	3	2	3	4	2	3	3	1	3	3	2	29/44	65	D
DIET 2	3	4	3	3	2	3	3	2	3	3	3	32/44	73	C
PA&DIET	2	4	3	4	3	3	3	2	4	3	2	33/44	75	C
MED 1	3	4	4	3	4	4	3	4	3	2	1	37/44	84	B
MED 2	3	3	3	2	2	3	2	3	3	3	3	30/44	68	D
MED 3	3	4	4	3	4	4	3	4	3	3	4	39/44	88	B
MED 4	3	3	3	4	2	3	2	1	4	3	2	30/44	68	D
MED 5	3	3	3	3	2	3	2	2	3	3	2	29/44	65	D
MED 6	3	3	4	4	2	3	2	3	4	3	3	34/44	77	C
MED 7	3	4	4	3	4	4	3	4	4	2	4	39/44	88	B
MED 8	3	3	3	3	2	3	2	3	3	3	2	30/44	68	D
MED 9	3	4	4	3	4	4	3	4	4	2	4	39/44	88	B
MED 10	3	3	4	3	4	4	3	4	3	2	4	37/44	84	B
MED 11	3	4	4	3	4	4	3	4	1	2	4	37/44	84	B
MED 12	3	3	4	3	2	3	3	3	3	3	1	31/44	74	C
MED 13	3	1	4	3	2	3	2	1	4	3	2	28/44	63	D

Med=medication

STEP 4: Summarizing of the evidence

This section included data synthesis.

4.2.4 Data synthesis

Narrative synthesis was used because the review included studies of diverse design; therefore meta-analysis was scientifically unjustified.

According to the social science research unit (SSRU, 2010) the objective of narrative – synthesis (NS) is to bring together the results of empirical research that are in a narrative form to provide an accessible combination of results from individual studies in structured narratives or summary tables. According to SSRU (2010) conducting a narrative synthesis involves 4 main elements as depicted in figure 2:

-Developing a theory of how the intervention works, why and for whom.

-Developing a preliminary synthesis of findings of included studies (Data extraction).

-Exploring relationships within and between studies.

-Assessing the robustness of the synthesis

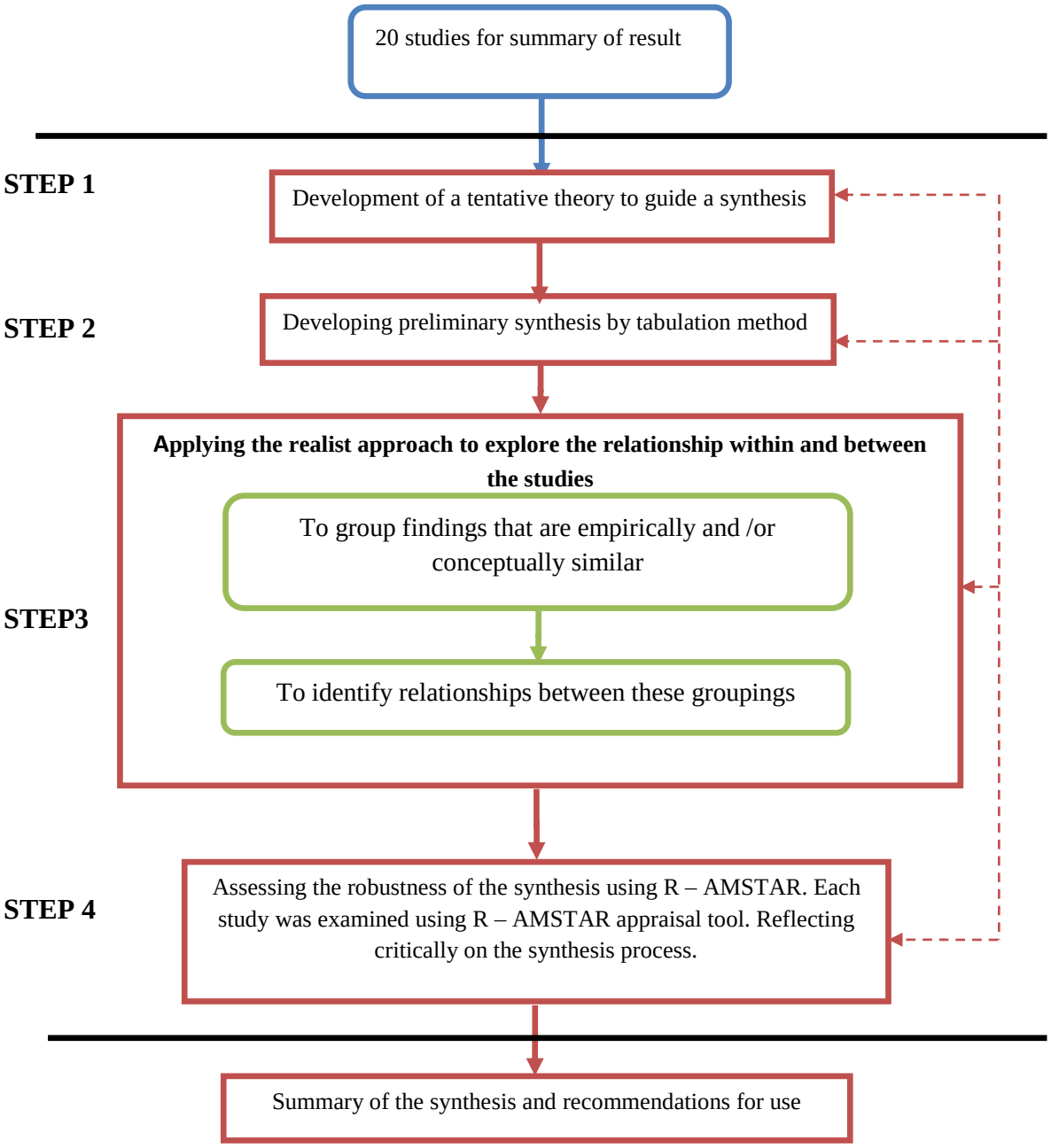


Fig 2: The analytical process of this narrative synthesis Mukumbang, Van Belle, Marcha, Van wyk (2016)

STEP1. Developing a theory of how the intervention works, why and for whom

Hypertension in pregnancy is characterized by metabolic disturbances. It includes endothelial dysfunction, inflammation, oxidative stress, insulin resistance and dyslipidemia. Oxidative stress is caused by an imbalance between pro-oxidative and antioxidants (Vitamins A, C, E, and Zinc).Oxidative stress causes complications such as endothelial cell dysfunction which in turn can cause hypertension in pregnancy (Salles, Galvao, Silva,Motta, & Pereira, 2011; Rumbold, Duley, Cowther and Haslam, 2012).

According to Rumbold, Duley, Cowther and Haslam (2012), the role of antioxidants is to prevent the destruction of proteins and enzymes by free radicals and help to maintain cell membrane integrity and also to protect proteins and enzymes from oxidation. Furthermore, serum nutrient levels (such as elevated polyunsaturated fatty acids and decreased vitamins C, E, Zinc and iron) are one of the causes of increase in inflammation. Oxidative stress and dyslipidemia in their turn provoke endothelial dysfunction involved in the etiology of hypertension in pregnancy. The antioxidants are found in foods with vitamins A, C, E Zinc and Iron, hence a diet rich in these might be important for the prevention of hypertension in pregnancy (Salles, Galvao, Silva,Motta, & Pereira, 2011) . It is widely accepted that a healthy diet; an adequate weight gain and regular exercise is required during pregnancy (New York State Department of Health, 2013).

According to Meher and Duley (2010), in many cultures, a woman remains physically active during pregnancy because maybe labor may be more difficult if a woman is not physically active during late pregnancy. Women with preeclampsia have an increased risk of cardiovascular disease because several cardiovascular risk factors (including dyslipidemia, obesity and diabetes) are also risk factors for pre-eclampsia (Aune, Saugstad, Henriksen, & Tonstad, 2014). Physical activity may reduce the risk of both blood pressure levels and

cardiovascular diseases in pregnant women because physical activity can reduce the oxidative substances and stumil vascularisation and placental growth and can also prevent the endothelial dysfunction (Kasawara, Do nascimento, Costa, Surita & Silva, 2012). According to Abalos (2007), anti-hypertensive medication may reduce the risk of severe hypertension in women with mild to moderate hypertension. To reduce the risk of severe maternal morbidity (cerebral hemorrhage, liver rupture, and renal insufficient and abruption placentae) and fetal morbidity, the anti-hypertensive medication is required for all women who have a systolic blood pressure of greater or equal to 160 mmHg or a diastolic blood pressure greater than or equal to 110 mmHg (Abalos, 2007; Lowe, Bowyer, Lust, McMahon, Marton, North, Paech & Said, 2014)

STEP2. Data extraction

The collection of data was performed by using data extraction. The objective of this stage is to obtain the necessary information about the study characteristics and findings from the primary studies to reduce the opportunities for bias (Guidelines for performing, 2007). The data was extracted by two reviewers; in case of disagreement an additional independent researcher was required. The following data was extracted from each study; author's last name and year of publication, setting (continent where the studies were conducted), reviews, study characteristics which included the period when the studies were conducted and the number of participants in that review, intervention, outcomes (conclusion), quality rating of the study and recommendations and limitations of the study.

- **Data extraction on physical activity as a lifestyle adjustment intervention**

Tables 4.1below depict the summary of the extracted data pertaining to physical activity as a lifestyle intervention.

Table 4.5 Data extraction on physical activity

ID	Author	Setting & design	Reviews	Studies 'characteristic	Intervention	Outcome/ Conclusion	Recommendations	Limitation
1	Aune(2014)	North America (3 Case-control, 4 Cohort studies), Europe (7 Cohort studies), and Asia (1Case-control)	SR of 15 Observational studies 11 cohorts studies and 4 Case control studies	Period = from 1984 to 2007 Primarily white participants	Intervention1: Physical Activity (PA) (leisure, sport and work) in high intensity (vigorous physical activity, metabolic equivalent scores at least 6) Intervention 2: low intensity (low physical activity, metabolic equivalent scores < 3) Control1: Pre pregnancy Early pregnancy combined vigorous physical activity before and during early Pregnancy, walking, Occupational physical activity Control 2: Pre-pregnancy Early pregnancy Combined low physical activity before and during early pregnancy,	**Outcome=Risk of (PE) pre-eclampsia** in the second half of pregnancy Pre-pregnancy physical activity -Low vs High ↓RR= 0.65 (CI= 0.47–0.89, X^2= 0%; n = 5). -Dose response1 ↓Hr. RR = 0.72 (CI =0.53–0.99; I2 = 0%; n = 3) vs. 20 Hr. RR=0.78 (CI =0.63–0.96; I 2 = 0%; n = 2) -A nonlinear association for PA before pregnancy & risk of preeclampsia (y, p = 0.03) Physical activity early pregnancy -Low vs High ↓RR= 0.79 (CI =0.70–0.91; I2 = 0%; n = 11). -Dose response 1 ↓Hr. RR= 0.83 (CI =0.72–0.95; I 2 = 21%; n = 7) vs. 20 Hr. RR= 0.85 (CI =0.68–1.07; I2 = 69%; n = 3) Studies of physical activity and risk of pre-eclampsia confirm an inverse association of higher levels of physical activity (both before and during early pregnancy) and lower risk of preeclampsia for women with the highest pre-pregnancy physical activity level and a ~20% RR reduction with high physical activity in early pregnancy. A stronger inverse association was observed among women who were physically active both before and during early pregnancy and for high-intensity physical	Further studies are needed to clarify whether increasing physical activity in early pregnancy reduces the risk of eclampsia among previously inactive women and to further define the dose–response association for various types and intensities of physical activity in relation to preeclampsia	physical activity level was not quantified R-AMSTAR = 28/44

ID	Author	Setting & design	Reviews	Studies 'characteristic	Intervention	Outcome/ Conclusion	Recommendations	Limitation	
					walking, and occupational physical activity.	activity in early pregnancy, In the dose–response analyses, there was evidence of nonlinear association between pre-pregnancy physical activity and preeclampsia, with the most benefit observed at levels of 5–6 hours of exercise per week ; in contrast, the association between physical activity in early pregnancy and pre-eclampsia appeared to be linear. There was evidence that walking in early pregnancy reduced the risk as well. Little evidence was found of an association between occupational physical activity and pre-eclampsia overall—although a suggestion of reduced risk was observed among cohort studies. A previous systematic review of two randomize trials of physical activity during pregnancy and PE pre-eclampsia31did not find an association (summary but there was low statistical power to detect an association). In conclusion, women with higher levels of pre-pregnancy or early pregnancy physical activity have a 20% to35% reduction in the RR of developing preeclampsia. Considering the few modifiable risk factors that have been established for preeclampsia, as well as the other health benefits of physical activity, promotion of physical activity for pregnant women may be a promising approach for reducing the risk of preeclampsia .			
2	Meher (2010)	USA (2 RCT)	SR of 2 Randomized control	N=45 women from 2002 to	Intervention: All forms of exercise or physical activity were	**Outcome=Risk of pre-eclampsia** . ↔ RR= 0.31 (CI= 0.01- 7.09)	.Need for good quality randomized trials with adequate sample size.	The sample size was too small to provide	

ID	Author	Setting & design	Reviews	Studies 'characteristic	Intervention	Outcome/ Conclusion	Recommendations	Limitation	
			trials (RCT)	2005	included, regardless of whether aerobic, or not, and whether occupational or recreational.	There is insufficient evidence for reliable conclusions about the effect of exercise on prevention of preeclampsia and its complications.		reliable Information about the effects of exercise on prevention of preeclampsia, or its complications R-AMSTAR = 38/44	
3	Wolf (2013)	America (4 Case-control studies, 2Cohort study) Europe (4Cohort studies)	SR of 11 Observational studies 4 case control 7 cohort	N=144.711 (cohort) and 44 to 244 (case-control) from 1984 to 2011	Intervention: LTPA C:Before Pregnancy, During Pregnancy, Before and During Pregnancy	<u>LTPA before pregnancy</u> (n=2) a)Strenuous to maximal LTPA ↓pre-eclampsia RR RR=0.33 (0.17–0.64) RR=0.22 (0.11–0.44) b)Moderate LTPA = ↔ RR c)High-intensity LTPA ↓PE RR (range 0.32 to 0.46) (n=3), ↔range (0.5 to 0.82) (n=9) <u>LTPA during pregnancy</u> ↔pre-eclampsia (n=5) a)Frequent LTPA ↓pre-eclampsia LTPA> 4hours(week)RR (range 0.32 to 0.60) (n=2) LTPA>13activities(month) ↓RR=0.89(0.78 -1.03) (n=1) n=1↑RR=0.92 (0.78-1.08)high amount of LTPA (at least 270 min per week) ↔ RR =1.18 (0.72–1.95) ↔ RR =0.97 (0.54–1.75)	Future studies, preferably RCTs, should be specifically designed to examine the association between LTPA and pre-eclampsia. They should include objectively assessed LTPA, validated diagnostic criteria for preeclampsia, information on LTPA before pregnancy (when feasible), the gestational timing of LTPA, the severity of PE and more detailed information on drop-outs.	First, none of the included studies used objectively Assessed LTPA. Second, score did not reflect that some studies we're not designed to investigate the association between LTPA and pre-eclampsia. Third, the present results cannot be extrapolated to women from countries other than	

ID	Author	Setting & design	Reviews	Studies 'characteristic	Intervention	Outcome/ Conclusion	Recommendations	Limitation
						↔ RR =1.32 (0.46–3.76). ↔ RR =0.62 (0.25–1.53) ↔ RR =1.23 (0.72–2.08) ↔ RR = 0.95 (0.52–1.75) ↔ RR =0.96 (0.52–1.76 ↔ RR =0.56 (0.12–2.56) High-intensity LTPA (more than 4 per week), frequent LTPA or high amounts of LTPA before and/or during pregnancy were associated with a significantly reduced risk of pre-eclampsia.		North America and Europe due to a very limited inclusion of ethnicities other than Caucasian. R-AMSTAR = 34/44
4	Kasawara (2012)	America (6 Case-control studies, 10 Cohort studies and 1 RCT)	SR of 6 case-control,10 prospective cohort 1 RCT	. N= 24.998 (Cohort), 1022 and 7.976 Controls (Case control) 41 Group and 38 Group (Randomized clinical trial)1043 Hispanic pregnant women (Prospective Cohort) and 238 black	Int: Occupational activities leisure or recreational activities and pre pregnancy physical activity C:before pregnancy, during pregnancy	<u>Occupationnel activités</u> ↔OR =1.62 (95% CI 1.09–2.42, *p* = 0.01 ;). ↔OR =1.28 (95% CI 0.92–1.77, *p*=0.13;40) <u>Exercise activity before pregnancy.</u> ↓OR =0.56 (95% CI 0.41–0.76, *p* < 0.01; 21, 31). ↔OR= 0.85 (95% CI 0.67–1.09, *p* = 0.21 ;). <u>Exercise activity during pregnancy</u> ↔OR=6.34 (95%CI 0.72–55.37,*p* = 0.09; 40) ↓OR= 0.77 (95% CI 0.64–0.91, *p* < 0.01). ↔OR= 0.99 (95% CI 0.93–1.05, *p*=0.81) The results indicate that the performance of recreational and sports PA has a protective effect on the development of PE	Occupational activity represented a risk for occurrence of PE and has to be studied and analyzed separately from the other types of PA. However, further studies with well-defined methodological designs are required to strengthen the evidence that PA and regular physical exercise during pregnancy may have a protective effect against pre-eclampsia.	The optimal intensity of recreational PA that ensures a protective effect on the development of PE could not be assessed Because of heterogeneity in study results. R-AMSTAR = 27/44

ID	Author	Setting & design	Reviews	Studies 'characteristic	Intervention	Outcome/ Conclusion	Recommendations	Limitation
				pregnant women				

PE= preeclampsia. PA=physical activity; Hr. = metabolic equivalent task (MET)-hours per week. L T PA= leisure time physical activity. I=intervention, C=Control=Relative Risk; OR= Odds Ratio; CI 95% confidence intervals; ↔=no significant effect ↓=significant protective effect ↑= Significant increase risk. P<.05

Data extraction on diet as a lifestyle adjustment intervention Table 4.6 below depict the summary of the extracted data pertaining to diet as a lifestyle adjustment intervention

Table 4.6 Data extraction on diet

ID	Author	Setting &design	Reviews	Studies 'characteristic	Intervention	Outcome/Conclusion	Recommendations	Limitation
1	Tabesh, (2013)	North America(2 2013Cohort Studies,4 Nested case control, 3	SR of 2 Cohort studies 5 Nested case control studies and 4 Case-	N=2485 From 1992 to 2012	Intervention: low serum concentration of vitamin D (< 50 mole/l, or 20 mg/ml). Control: maternal serum	↑RR= 5.00 (1.74–14.40) ↑RR=1.39 (0.59–3.55) ↑RR= 5.41 (2,02–14.50); ↑RR= 3,17 (1,56–6,46) ↑ RR= 1.35 (0.40–4.53) ↑RR= 1.35 (0,26–7.02) ↑RR=1.24 (0.58–2.66) ↑RR=1,10(0.60-2.01) n= 8 vitamin D deficiency increased risk of	There are no recommendations	Some studies included in this meta- Analysis had small sample sizes. Furthermore, some studies had evaluated serum vitamin D levels just once, whereas single measurement of serum vitamin D levels might not reflect whole body

		Case control studies, 3 Cross sectional) Europe (1 Cross sectional, 1 Nested case control, 1 Case-control)	control studies 4 cross-sectional studies		25(OH)D levels.	PE. This meta-analysis of observational studies showed a significant association between vitamin deficiency and risk of preeclampsia. Subgroup analysis indicated that the association between vitamin D deficiency and risk of preeclampsia was significant when the deficiency was defined as serum 25(OH)D concentrations of _50 mole/L (20 ng/mL); however, when the deficiency was considered as _38 mole/L (15.2 ng/mL), the association was not significant. The inverse association between vitamin D status and risk of preeclampsia was significant for both "cohort and nested case-control" and "cross-sectional and case control" studies.		vitamin D status perfectly. In addition, some studies had considered 25(OH)D levels and others considered1,25(OH)2D Concentrations as a biomarker. R-AMSTAR = 29/44
2	Tshoene ker (2014)	Asia (1 Cohort studies,4 Case control studies) America (6 Case control Studies 9Cohort studies) Europe (11 Cohort studies,3 Case control	SR of 23 Cohort and 15 case – control studies	Reproductive aged women N= 92 to 928 (Case-control) 62 to 63,226 (Cohort) From 1991 to 2014	Total energy intake, Fruit and legumes and nutrient intake	<u>Total energy</u> a)energy intake between preeclampsia cases and non-cases (87 kcal/day, 95% CI 5.99 to 168.11; I2 = 0.0%, P = 0.45) b) Pre-eclampsia with higher early second trimester energy intake↔ OR =3.7(95% CI 1.5 to 8.9, highest versus lowest quartile). c) higher energy intake and gestational hypertension ↔ OR = 1.33 (995% CI 1.17 to 1.52, per 200 kcal) d)Gestational hypertension(GH) and energy intake Weighted mean differences(WMD) -24.75(-89.01,51) 18.72% weight(W) e)PE and energy intake WMD -46.21(-13.80,106.23)81.02%W f)GH or PE and energy intake	There is a need for well-powered prospective cohort study and intervention trials in a range of populations assessing nutrition prior to and during pregnancy, examining associations with the different subtypes of HD	There was substantial Heterogeneity between studies examining differences in calcium intake between women with and without HDP, which could not be further explored by subgroup analysis because of the limited number of studies. R-AMSTAR = 32/44

		studies) Africa (1 Cohort Study,2 Case control studies) Oceania (1 cohort study)				WMD 264.60(-293.22,822.42)0.26%W <u>Fruit and legumes and nutrient intake</u> a)Magnesium intake and hypertension in pregnancy (HIP) 8 mg/day (95% CI −13.99 to −1.38; I2 = 0.0%, P = 0.41). b)Magnesium intake and GH WMD -634 (-16.12,3.44) 64.61%W c)Magnesium intake and PE WMD -9.75(-21,26,1.26) 35.39%W d)Calcium intake and HIP ↓RR= 0.60(0.38,0.95) 40.02 ↔RR= 0.97(0.23,4.13) 4.03 ↓RR= 0.63 (0.41,0.97) 44.05 ↔ RR= 0.89 (0.53,152) 30,37 ↔RR= 0.92 (0.33,2.60) 7.89 ↔RR= 0.84 (0.42,1.66}17.79 ↔RR= 0.88 (0.60,1.29) 55.95 ↔RR= 0.76 (0.57,101) 100.00 c)Calcium intake for HIP cases compared with non-cases (WMD= −39.89, 95% CI −109.52 to 29.75;I2 36.6%; P = 0.21) d)Calcium intake for preeclampsia cases compared with non-cases 56 mg/day (95% CI −120.69 to 8.06) e)Calcium for women with HIP 44 mg/day was found for (95% CI −84.31 to −3.62) f) Calcium intake in the highest (>1600 mg/day approximately) compared with the lowest (<1000 mg/day approximately) for gestational hypertension		

						↓OR = 0.63 (95% CI 0.41 to 0.97; I2 = 0.0%, P = 0.53) and HIP ↔OR = 0.76 (95% CI 0.57 to 1.01; x2 = 0.0%,p = 0.79) <u>Dietary pattern</u> a)PE and vegetables, plant foods, and vegetable oils ↓OR =(0.72, 95% CI 0.62 to 0.85), b) P E and meat, salty snacks, and sweet drinks↔ OR = 1.21 (95% CI 1.03 to 1.42) c)Diet quality and PE ↔ OR = 0.96 (95% CI 0.84 to 1.10, 5 point increase) Meta-analysis of multivariable results showed an inverse association between calcium intake and both gestational hypertension and overall HDP. Systematic review of a few studies examining foods and dietary patterns suggests a beneficial effect on preeclampsia of a diet rich in fruit and vegetable		

Data extraction on the comparison of lifestyle intervention . Table 4.3 below depict the summary of the extracted data pertaining the comparison of lifestyle adjustment interventions which include diet and physical activity

Table 4.7 Data extraction on physical activity and diet

ID	Author	Setting	Reviews	Studies 'characteristic	Intervention	Outcome/Conclusion	Recommendations	Limitation

1	Allen, (2014)		SR of 18 randomized trials	N=8712 From 1992 to 2013	I1.Diet only I2.lifestyle intervention (include both diet and physical activity with or without behavioral modification) C: modification of metabolic risks such as obesity, hyperlipidemia/ glycaemia and hypertension on the risk of preeclampsia.	<u>The interventions compared with the control group</u>. ↓ RR = 0.81 (95% CI 0.69–0.94; p = 0.006 I2 = 0%) <u>Diet intervention and PE</u> ↓RR =0.67 (95% CI 0.53–0.85; p = 0.001) <u>Mixed interventions (diet and lifestyle) and PE</u> ↔ RR=0.93 (95% CI 0.66–1.32, p = 0.68, I2 = 0%) <u>Essential fatty acids and PE</u> ↔ RR= 0.92 (95%–CI 0.71–1.18, p = 0.49, I2 = 15%). <u>After excluding women with gestational diabetes</u> ↔ RR= 0.91(95% CI 0.75–1.11, p = 0.37) or in the diet-only group ↔ RR= 0.86, (95% CI 0.45–1.64, p = 0.64). <u>after excluding intervention commenced after the first trimester</u> ↔ RR= 0.95, (95% CI 0.74–1.22, p = 0.69) Intervention based on diet only was more effective in reducing the risk of PE than the intervention based on mixed diet and physical activity	No recommendations	The findings were limited by the variation in the components; intensity, compliance, timing and delivery of complex interventions such as those based on diet and mixed type. R-AMSTAR = 33/44

Data extraction on medication as an intervention Table 4.4below depict the summary of the extracted data pertaining to medication as a medication intervention

Table 4.8 Data extraction on medication

ID	Author	Setting& Design	Reviews	Studies 'characteristic	Intervention	Outcome/ Conclusion	Recommendations	Limitation
					ASPIRIN			
1	Duley, (2007)	Gestational hypertension (India 1993; India 1994; India 1999; Israel 1990). women with or without gestational hypertension (CLASP 1994; Italy 1993; UK 1992) aspirin and dipyridamole or dipyridamole alone versus control (EPREDA 1991; France 1985; France 1990; Russia 1993;	SR of 59 Randomized trials	. N=37.560 From 1994 to 2005	Comparisons of any antiplatelet agent (such as low-dose aspirin75mg/day or less of aspirin or dipyridamole) with either placebo or no antiplatelet agent. Comparisons of one antiplatelet agent with another, and of antiplatelet with other interventions.	Pregnancy induced hypertension a)gestational hypertension ↔ RR= 0.95(95% CI 0.88 to 1.03). ↓RR =0.81, (95% CI 0.69 to 0.94) no very clear difference. b)Pre-specified subgroup ↓RR= 0.54(95%CI 0.41 to 0.70), risk difference (RD) -13% (-18.6, -8.1), number needed to treat (NNT) 8 (5, 12). ↓ RR= 0.56 (95% CI 0.40 to 0.78). Proteinuria pre-eclampsia ↓ RR =0.83(95% CI 0.77 to 0.89), RD -1.39% (-1.94,-0.24), NNT 72 (52, 119). ↓RR= 0.75(95% CI 0.66 to 0.85) ↓ RR= 0.86 (95% CI 0.79 to 0.95) Antiplatelet agents (primarily aspirin in this review) are associated with a moderate (17%) reduction in the risk of pre-eclampsia. The confidence intervals (CI) for this point estimate suggest the true effect could be a reduction of as much as 23%, or as little as 11%. For women who were	Research is needed to illuminate whether there are particular high-risk subgroups of women who might have greater benefit, whether starting treatment before12 weeks would have additional benefits without any increase in adverse effects, and whether a higher dose would be more effective.	In this aggregate data review, it is not Possible to assess the effects of antiplatelet agents for women with specific conditions or risk factors. Such an analysis would require a review based on data from Individual women. . AMSTAR = 37/44

		S Africa 1988). heparin and dipyridamole versus control (Australia 1995a), aspirin with vitamins C and E and fish oil (Venezuela 2000) hydrochloride with placebo (Japan 1999).				high risk at trial entry, antiplatelet agents are associated with a 25% reduction in the risk of preeclampsia (95% CI 34% to 15% reduction). For moderate-risk women, antiplatelet agents are associated with a 14%reduction in the risk of pre-eclampsia (95% CI 21% to 5% reduction). Based on absolute risk reduction, 72 women (95%CI 52 to 119 women) need to be treated to prevent one case of pre-eclampsia. For high risk women this drops to 19 who need to be treated to prevent one case of pre-eclampsia (95%CI 13 to 34women) and for moderate risk women it rises to 119 women (95% CI 73 to 333 women).		
2	Henderson, (2014)	Africa (1 RCT), America (6 RCT), Europe (12 RCT and 1 Cohort) Asia (1 RCT), Oceania (1 Case control study)	S R of 2 large, multisite RCTs and 13 smaller RCTs, in addition to 6 RCTs and 2 observational studies.	N=12894 From 1986 to 2013	Intervention : 50 to 150 mg of aspirin Control : placebo or no treatment group	<u>Pre-eclampsia and women at high risk</u> ↓RR= 1.43 (0.27–7.73) ↓RR= 0.07 (0.00–1.20) ↓RR= 0.19 (0.01–3.80) ↓RR= 0.13 (0.02–1.00) ↓RR= 0.20 (0.05–0.86) ↓RR= 0.43 (0.12–1.56) ↓RR= 0.11 (0.01–0.81) ↓RR= 0.72 (0.31–1.65) ↓RR=0.84 (0.37–1.95) ↓RR=0.49 (0.25–0.99) ↓RR=0.95 (0.67–1.35) ↓RR=0.90 (0.77–1.06) ↓RR=0.88 (0.75–1.03) ↓RR= 0.76 (95% CI, 0.62 to 0.95)	Research is needed to address remaining uncertainties. More primary research is needed to illuminate how preeclampsia arising from different risk factors develops and responds to aspirin. More robust and consistent tools for preeclampsia risk stratification would support future research and clinical practice	This review included only fair- to good-quality studies published in English. R-AMSTAR = 30/44

						risk reductions of 2% to 5% for preeclampsia. In conclusion, our systematic review identified benefits of low-dose aspirin for prevention of preeclampsia and Perinatal illness in women at high risk for preeclampsia. Potential rare or long-term harm could not be ruled out, but none were identified.		
					ANTIOXIDANT			
3	Rumbold (2012)		S R of 10 randomized trials	N=6533 From 1950 to 2007	1. antioxidant/s (any dosage regimen) with either placebo or no antioxidant/s. 2. Comparisons of one or more antioxidant with other antioxidant/s. 3. Comparisons of antioxidant/s with other interventions. 4. Comparisons of one or more antioxidants with other agents compared with placebo or no antioxidant/s, other antioxidants or other interventions.	<u>Pre-eclampsia</u> a) ↔RR= 0.73 (95% CI 0.51 to 1.06;) ↔RR= 0.88 (95% CI 0.75 to 1.02) a)groups Moderate/ low-risk women↔ RR= 0.85, 95% CI 0.48 to 1.51 ;) or moderate/high-risk women ↔RR= 0.56 (95% CI 0.29 to 1.11). b) treatment groups ↔RR= 1.01 (95% CI 0.86 t c)groups for women allocated vitamin C and E alone ↔ RR =0.92(95% CI 0.68 to 1.25) d)women allocated lycopene ↓RR= 0.48 (95% CI 0.24 to 0.97 ;) e) Women allocated vitamin C and E combined with aspirin and fish oil ↓RR= 0.07(95% CI 0.01 to 0.54). f) treatment groups for women allocated vitamin C alone ↔RR= 1.00(95% CI 0.21 to 4.84),	Much more information is needed to assess the effects Of antioxidants other than vitamin C and E on the risk of preeclampsia and other complications. There is also insufficient detail in the trial publications to extract data for specific risk factors, and therefore further assess the effects of antioxidants for women at different baseline risks.	There is insufficient detail in the trial publications to extract data for specific risk factors, and therefore further assess the effects of antioxidants for women at different baseline risks. Undertaking a review based on data from individual women may help to determine if the effects of antioxidants are different for women at different baseline risks. R-AMSTAR = 39/44

						↔RR= 0.73(95% CI 0.07 to 7.80 ;) ↔ RR= 0.10, 95% CI 0.01 to 1.86) <u>Severe pre-eclampsia</u> a) Antioxidant and control groups. ↔RR =1.25(95%CI 0.89 to 1.76) b) women allocated antioxidants (95% CI 0.89 to1.79). Routine use of antioxidant supplements in pregnancy should only be considered if antioxidants are shown to be associated with substantive benefits for the mother or baby, or both; none have been consistently demonstrated in this review. The point estimate for the effect of antioxidant supplements on preeclampsia was a 27% reduction in the relative risk, however, the 95% confidence interval for the true effect ranged from a 49% reduction to a 6% increase, when compared with the control group. There was no clear difference between antioxidant and control groups for the risk of other perinatal complications, including small-for-gestational-age infants and baby death.		
4	Sallies (2012)	Asia [6 Randomized placebo control trial (RPCT)] , Africa (1RPCT), Europe (5	SR of 15 randomized placebo-controlled trials.	N=21.012 From 1994 to 2011.	Comparison of antioxidant .	<u>Pre-eclampsia</u> a)antioxidants and the placebo group ↔RR = 0.1(0.01,1.86) ↔RR = 0.46(0.24,0.91) ↔RR = 1(.21,4.84) ↔RR = 0.92(0.4,2.13) ↔RR= 0.48(0.24,97) ↔RR= 1.2(.82,1.75)		

		RPCT), America (6 RPCT).				↔RR= 0.97(0.8,1.17) ↔RR= 0.24(0.06,1.01) ↔RR= 0.99(0.51,1.92) ↔RR=1.03(0.85,1.25) ↔RR=0.88(0.62,1.26) ↔RR=1.04(0.75,1.44) ↔RR=0.81(0.59,1.12) ↔RR=1.07(0.93,1.24) ↔RR=0.75(0.54,1.02) Subtotal (*I* squared=37.3%,*P*=0.072)↔RR=0.92 (95% CI: 0.821.04) <u>Severe pre-eclampsia</u> a)antioxidants and the placebo group ↔RR = 1.08(0.23,5.11) ↔RR = 1.26(0.89,1.79) ↔RR = 5.32(0.026,109.09) ↔RR = 1.04(0.82,1.31) ↔RR = 0.75(0.44,1.29) ↔RR = 0.87(0.55,1.37) Subtotal (*I*-squared= 0%, *P* = 0.508)↔RR = 1.03(95%CI: 0.87–1.22 ;). Antioxidants efficacy for preventing preeclampsia was not Observed from included studies and results from these studies are prone to have publication bias, what reduces the confidence of the findings. Only two isolated studies showed a significant reduction of preeclampsia in women treated with antioxidants compared to placebo leads us to believe that additional studies would probably not alter this result. The		

						sensitivity placebo, but important differences were present, mainly on interventions. Efficacy was also not detected for other outcomes assessed. The large number of women randomly investigated ed analysis, when including only studies that met all quality criteria, revealed a non-significant increased risk of preeclampsia, while the analysis including all studies reduced the risk, also without statistically significant differences between antioxidants and placebo.		
					CALCIUM			
5	Hofmey (2014)	Low and high income countries.	S R of 9 randomized quasi – randomized trials	N=2234 From 1987 to 2006	Lower dosages of calcium supplementation in pregnancy (<1 g daily)	<u>Pre-eclampsia</u> a)LDC(low dose calcium) with or without co-supplement ↓RR= 0.38; (95% CI 0.28–0.52) b) LDC alone ↓RR= 0.36 (95% CI 0.23–0.57]) c)LDC plus linoléique acide ↓RR= 0.23 (95% CI 0.09–0.60) d) LDC plus vitamine D ↓RR= 0.49(0.31–0.78) e) LDC plus antioxydants ↓RR = 0.24; {95% CI 0.06–1.01) In women at high risk of pre-eclampsia, without or with linoleic acid or antioxidants, report a reduction in pre-eclampsia similar to that shown in the trials.	The need for sufficiently powered trials to either confirm or refute this effect.	R-AMSTAR = 29/44

6	Hofmeyr (2007)	America (12 RCT)	SR of 12 randomized trials from 1987 to 2006	N=15528	The interventions were supplementation with at least 1 g of calcium compared with placebo	<u>Pre-eclampsia</u> a)Calcium supplementation and dietary calcium intake ↔RR= 0.09(0.01-1.48) ↔RR= 0.31(0.12-0.84) ↔RR= 0.15(0.04-0.66) ↔RR= 0.17(0.04-0.77) ↔RR= 0.21(0.07-0.58) ↔RR= 0.66(0.35-1.26) ↔RR= 0.92(0.75-1.13) ↔RR= 0.36(0.18-0.70) ↔RR= 0.14(0.02-1.02) ↔RR= 0.14(00.2-1.02) ↓RR= 0.48(0.33-0.69) b) Calcium supplementation ↔RR= 0.14(0.02-1.02) ↔RR= 0.09(0.01-1.48) ↔RR= 0.36(0.04-3.24) ↓RR= 0.31(0.12-0.84) ↓RR= 0.15(0.4-0.66) ↔RR= 0.14(0.01-2.67) ↓RR= 0.17(0.04-0.77) ↓RR= 0.21(0.07-0.58) ↓RR= 0.21(0.12-0.36) ↓RR= 0.44(0.21-0.90) ↔RR= 0.66(0.35-1.26) ↔RR= 0.94(0.77-1.16) ↔RR= 0.92(0.75-1.13) ↔RR= 0.85(0.69-1.05) ↓RR= 0.48(033-0, 69)Calcium supplementation with at least 1 g of calcium is associated with a halving of risk of preeclampsia, with the CIs putting the RR true effect anywhere	There is a need for more information about the use of health services resources and other clinical outcome should be collected. Dietary modification should also be assessed whether it has the same effect with calcium tablet, a study should be conducted to investigate any adverse effect of calcium supplementation on children exposed to it in utero. Research should also find out if calcium supplementation reduces childhood high blood pressure.	There is no information about any possible changes in the use of health care resources associated with calcium supplementation. R-AMSTAR = 34/44

						between a 31% reduction and a 67% reduction. Women with an adequate dietary intake of calcium were the only subgroup for which this was not supplementation with at least 1 g of calcium statistically significant; nevertheless, the point estimate for this subgroup of women was a 38% reduction. The greatest reduction in risk appeared to be for women at high risk and for those with low baseline dietary calcium intake. There was also a 30% reduction in the risk of gestational hypertension, with again the greatest effect being among women at high risk and those with a low calcium intake during trial entry. Although the RR of preeclampsia was reduced, this was not clearly reflected in any reduction of severe pre-eclampsia, eclampsia, or admission to intensive care. Nevertheless, the point estimates for these outcomes favor calcium supplementation and so moderate Reductions in these outcomes remain possible.		
					ANTIHYPERTENSIVE DRUGS			
7	Abalos (2007)	Industrialized countries (34 RT), Middle low countries	S R of 46 randomized trials	N= 4282 From1966 to 2006	The antihypertensive drugs used in these trials include: alpha	<u>Any antihypertensive drug versus none</u> a)Severe hypertension (19 trials, 2409women; relative risk	Large simple trials are required in order to provide reliable estimates	Simple trials were not large enough to provide reliable estimates of the benefits and

		(12 RT)			agonists, beta blockers calcium channel blockers (, vasodilators, ketanserin and glyceryl trinitrate (GTN). All drugs were given orally except glyceryl Triturate that was given trans dermally. The antihypertensive drug was compared with placebo or no antihypertensive	(RR) 0.50; (95% confidence interval (CI)0.41 to 0.61); risk difference (RD) -0.10 (-0.12 to -0.07); number needed to treat (NNT) 10 (8 to 13)) There is a halving in the risk of developing severe hypertension. b)Preeclampsia There is no evidence (RR 0.97; 95% CI 0.83 to 1.13). <u>One hypertensive drug versus another</u> a)Severe hypertension (eight trials, 493 women, RR 0.79; 95%CI 0.63 to 0.99; RD-0.08 (-0.14 to 0.02); NNT 12 (6 to 275)) Beta blockers appear to be more effective than methyldopa. b)Preeclampsia (RR 0.81; 95% CI 0.57 to1.16) there is no difference in the risk of developing proteinuria/preeclampsia. Antihypertensive drugs half the risk that a pregnant woman with mild or moderate hypertension will have one or more episodes of severe hypertension. if the reduction in severe hypertension was clinically important, you might expect to see an impact in terms of fewer preterm Births and fewer caesarean sections. There is no evidence of such an effect in this review. Beta blockers seem to be more effective than methyldopa for preventing severe hypertension,	of the benefits and adverse effect of antihypertensive treatment for mild to moderate hypertension	adverse effects of antihypertensive treatment for mild to moderate Hypertension. R-AMSTAR = 39/44

						although the comparative effects on other outcomes are unclear.		
8	Firoz (2014)	Busy and resource-constrained setting (15 RCT)	S R of 15 randomized controlled trials	N=915 From 1982 to 2011	Comparison of oral or sublingual antihypertensive with another agent.	Nifedipine a)Nifedipine capsules (10 mg orally), compared with nifedipine PA tablet(10 mg orally) were associated with more maternal hypotension (35% versus 9%; RD (risk difference) 0.26, 95% CI 0.070.46,). b)short-acting nifedipine versus intravenous hydralazine ↔RR = 1.07 (95% CI0.98–1.17). c)sublingual nifedipine versus intraveineuse hydralazine postpartum, ↔RR = 0.18 (95% CI 0.02–1.40) d) short-acting nifedipine versus intraveineuse labetalol ↔RR =1.02 (95% CI 0.95–1.09) t Labetalol and methyldopa (250 mg) ↔ RR = 0.85 (95% CI 0.54–1.33) Other antihypertensive agents Sublingual isosorbide and parenteral magnesium sulphate↔ RR= 0.14 (95% CI0.01–2.58) Based on RCTs in pregnancy and postpartum, we found that a single oral agent can adequately lower BP when compared with parenteral agents. In particular, oral nifedipine (10 mg), compared with parenteral hydralazine or labetalol, is a suitable oral agent for treatment of severe hypertension in	Future trials should focus on head to head comparisons of oral agents, particularly nifedipine, labetalol and methyldopa; one such trial is underway . Studies should also focus on early treatment of severe hypertension in the community, particularly in low- and middle-income countries.	we had a meaningful body of RCTs for the nifedipine versus other antihypertensive comparisons, but all others were under powered to find important between-group differences in outcomes given the limited number And size of trials. Second results are Limited by poor to fair study quality. R-AMSTAR = 30/44

						pregnancy or postpartum, with: similar and high treatment success rates (of at least 84%); low rates of maternal hypotension (< 2%, 3/158 women in six trials comparing nifedipine with either intravenous hydralazine or labetalol); and similar maternal and perinatal outcomes. Although there was one 10-mg nifedipine capsule versus 10-mg PA tablet trial that reported more hypotension with the capsule formulation, the absolute rates of hypotension were high in both arms of this trial (35% in the capsule arm and 9% in the 10-mg tablet arm) compared with the six other nifedipine capsule trials of similar dosage (3/158, 1.90%); also, that hypotension was not necessarily associated with adverse clinical effects (a verifier)		
9	Duley, (2007)	Africa (2 RCT), Asia (150 women), America (50 women)	S R of 24 RCT	N = 2949 From 1963 to 2006	Any comparison of one antihypertensive agent with another regardless of dose, route of administration or duration of therapy.	Labetalol versus hydralazine ↔RR= 3.00(95% CI 0.79 -11.44). Calcium channel blockers(nifedipine and isradipine) versus hydralazine Hydralazine had persistent high blood pressure (6%versus 18%). ↓ RR =0.33(95%CI 0.15 - 0.70). Ketanserin versus hydralazine Ketanserin was associated with high blood pressure(27% versus 6%;)↔RR= 4.79 (95% CI 1.95 11.73)	Future trials should measure outcomes that are important to women and their babies, rather than attempting to document relatively subtle differences in the effects on blood pressure. These outcomes should include persistent high blood pressure, need for additional antihypertensive	In this review, the data are insufficient to support the conclusion that labetalol is better than hydralazine. R-AMSTAR = 39/44

						complication of pre-eclampsia was lower with ketanserin, ↓ RR= 0.20 (95%CI 0.05 - 0.81) Labetalol versus Diaz oxide . Labetalol was associated with less hypotension ↓RR = 0.06(95% CI 0.00 - 0.99). Nitrates versus magnésium sulphate↔RR 0.14 (95% CI 0.01 - 2.58) Nimodipine versus magnésium sulphate Magnesium sulphate were associated with high levels of persistent high blood pressure (47% versus 65%) ↓RR= 0.84 (95%CI 0.76 - 0.93). The risk of eclampsia was higher with n amlodipine RR =2.24 (95%CI 1.06 - 4.73). From the data presented here it is clear that four drugs (magnesium sulphate, high dose Diaz oxide, ketanserin and nimodipine) Have serious disadvantages and so should not be used for women with very high blood pressure during pregnancy as better options are readily available. Although it is clearly of value for seizure prophylaxis in women with pre-eclampsia (Duley 2003), magnesium sulphate should not be used for control of very high blood pressure. Diaz oxide given as repeated 75mg	drugs, further episodes of severe hypertension, low blood pressure, side-effects, severe maternal morbidity (such as stroke, eclampsia, renal failure, and coagulopathy) mode of delivery, length of stay in hospital, mortality for the baby, and admission and length of stay in a special/intensive care Nursery. There should also be long-term follow up to assess possible effects on the woman's risk of cardiovascular problems after discharge from hospital, and on growth and development of the child.	

						bolus injections seems to be associated with a greater risk of dropping the blood pressure so low that treatment is required to bring it back up again, with an associated increased risk of caesarean section, when compared with labetalol. Smaller doses may not have this disadvantage, and 15 mg bolus injections are being compared with hydralazine in one study due to report results (Hennessy 2002). Ketanserin was far more likely to be associated with persistent hypertension than hydralazine. Finally, nimodipine was also associated with high levels of persistent high blood pressure, as well as an increased risk of eclampsia compared to magnesium Sulphate.		
10	Magee, (2012)	America (1 RCT), Europe (2 RCT), Asia (1 RCT).	S R of 29 randomized controlled trials	N=2500 From 1978 to 2004	Comparisons of (i) oral beta-blockers (including labetalol) with placebo or no therapy, or (ii) oral beta-blockers (including labetalol) with other antihypertensive drug therapy. We excluded single dose studies or studies that	<u>Beta-blockers with placebo/no beta blocker</u>. ↓ RR= 0.37(95% CI 0.26 to 0.53) Oral beta-blockers decrease the incidence of severe hypertension and the need for additional antihypertensive therapy. These effects would only be worthwhile if they were reflected in other more substantive benefits (such as a decrease in preeclampsia or eclampsia for the mother, and/or a decrease in preterm birth and its complications for the baby), or if they	Large, randomized placebo-controlled trials are required to determine whether, overall antihypertensive therapy (with any agent) is preferable to no treatment of mild to moderate hypertension during pregnancy.	There were insufficient data for any reliable conclusions when beta blockers was compared with methyldopa. . There is even less information about How beta-blockers compare with other agents. R-AMSTAR = 37/44

					compared beta-blockers with beta-blockers.	reduced the need for hospital admission; no such benefits have yet been clearly demonstrated. When compared with methyldopa, there are insufficient data for any reliable conclusions.		
11	Duley,(2007)	America (8 RCT), Africa (2 RCT), Asia (2 RCT), Europe (1 RCT)	S R of 13 randomized control trials	N= 12, 241 From 1989 to 2002	All randomized comparisons of an anticonvulsant, or other agents used specifically to prevent eclampsia, with placebo (or no anticonvulsant). Also, comparisons of one such drug with another. Anticonvulsant drugs which have been used for preeclampsia include magnesium sulphate, diazepam (valium), phenytoin, nimodipine, and chlormethiazole.	<u>Magnesium sulphate with placebo or no anticonvulsant</u>. ↓ RR= 0.41(95%CI 0.29 - 0.58) (risk difference) RD =0.01(95% CI -0.02 -0.01), (number needed to treat)NNT for benefit 100, (95% CI 50 – 1) For women who did not have severe preeclampsia: RR=0.44, RD -0.01(95% CI -0.01 -0.00) NNT for benefit 100(95% CI 100 to 500) <u>Magnesium sulphate versus phenytoin</u> ↓RR= 0.05(95% CI 0.00 -0.84) RD =0.009 (95% CI -0.015-0.003). NNT 111 (95% CI 67-333) magnesium reduced the risk of eclampsia. <u>Magnesium sulphate versus nimodipine</u> Magnesium reduced the risk of eclampsia. (0.8% versus 2.6%)↓ RR= 0.33 (95% CI 0.14 - 0.77) RD-0.02(95%CI -0.03-0.00) NNT for benefit with magnesium sulphate 50, (95% CI 34 -1000) Magnesium sulphate is associated with halving the risk of eclampsia, and it seems likely that	Longer term follow up of the children is required to provide reassurance that the short term safety continues into childhood.	The trials in this review included women only after admission to Hospital. R-AMSTAR = 37/44

						there is also a clinically important reduction in the risk of maternal death. There is no clear evidence that these benefits are reflected in any reduction in other measures of serious maternal morbidity.		
12	Magee (2003)		S R of 21 randomized controlled trials	N= 893 From 1991 to 2002	hydralazine compared with another short acting antihypertensive (generally via parenteral administration)	Hypertension in pregnancy a) Hydralazine was associated with a trend towards lower rates of persistent severe hypertension (median event rate 0% (range 0-20%) *v* labetalol (5% (0-60%)); relative risk ↔RR= 0.29 (0.08 - 1.04). b) Hydralazine was associated with a trend towards more severe hypertension than nifedipine or isradipine ↔RR=1.41 (0.95- 2.09). c) Hydralazine was associated with more maternal hypotension ↔RR =3.29 (1.50 -7.23).The results from this study showed that hydralazine was found to be a less effective antihypertensive than nifedipine or isradipine, and did not clearly differ from labetalol. In comparison with all other antihypertensive, was associated with more of several adverse outcomes; maternal hypotension, placental abruption, adverse effects on fetal heart rate, caesarian section. Hydralazine was more poorly tolerated than other	Definitive data from adequately powered clinical trials are needed.	In this review the limitations have not Been discussed. R-AMSTAR = 31/44

						antihypertensive. The data from this study do not support the use of hydralazine as first line for treatment of severe hypertension in pregnancy.		
13	Dorniak -wall	America (2 RCT), Europe (3 RCT)	S R of 14 randomized trials	N=884 From 2004 to 2012	L-arginine was administered alone or in combination with any other agent for the prevention or treatment of preeclampsia, eclampsia or HIP.	Pre-eclampsia a)Women at risk of pre-eclampsia ↓RR= 0.34 (95% CI: 0.21–0.55). b) women with established hypertensive disease ↓RR= 0.21 (95% CI: 0.05–0.98). The results of our systematic review indicate that L –arginine supplementation in pregnant women with either established hypertension or who are considered at risk of preeclampsia is associated with a significant reduction in the risk of PE	There is a need to evaluate protective effects of L-arginine in prevention of preeclampsia.	Data are limited with an available sample size for this outcome of only 884. Therefore, there is a need for sufficiently powered trials. R-AMSTAR = 28/44

STEP3. Exploring relationships in the data and between studies

3.1 Physical activity

WHO recommended physical activity for adults aged 18 – 64 years. Physical activity includes leisure time (for example walking, dancing , gardening, hiking, swimming), transportation (e.g. walking or cycling), occupational (i.e. work), household chores, play, games, sports or planned exercise, in the context of daily, family, and community activities. In order to improve cardiorespiratory and muscular fitness, bone health, reduce the risk of non-communicable disease and depression (WHO, 2016).

3.1.2 Leisure time physical activity (LTPA)

LTPA includes all types of activities one participates in during one's free time and is selected on the basis of personal interests and needs. Examples of LTPA include formal exercise programs and walking, hiking, gardening, playing sports, swimming, and dancing (Worlf, 2013).

3.1.2.1 before pregnancy

The review by Aune, Saugstad, Henriksen and Tonstad (2014), investigated the association between pre-pregnancy leisure time physical activity and preeclampsia. This review concludes that pre-pregnancy leisure time physical activity reduces the risk of preeclampsia. It has also explored the association between pre-pregnancy leisure time physical activity and intensity. The results from this review confirm that there was an association between pre-pregnancy leisure time physical activity and intensity of physical activity to prevent pre-eclampsia. Equally important is the review by Kasawara, Do nascimento, Costa, Surita and Silva (2012), which also supported this result, according to the it, the practice of moderate – to - heavy leisure time physical activity during the year before pregnancy reduce the risk of pre-eclampsia. According to Wolf, Owe, Juhl and Hegaard review (2013), the women who

practice strenuous to maximal leisure time physical activity a year before pregnancy have reduced the risk to develop preeclampsia compared to physically inactive women. The review has also demonstrated the association between pre-pregnancy leisure time physical activity and duration of physical activity. The result from this review showed that the women who performed pre-pregnancy leisure time physical activity four to seven hours per week had a reduction of risk of pre-eclampsia. This review has also reported that there is an association between pre-pregnancy leisure time physical activity and duration of physical activity. The review by Kasawara, Do nascimento, Costa, Surita and Silva (2014), showed that the women who practice pre-pregnancy leisure time physical activity 120 minute/week or more had a tendency to reduce the risk of pre-eclampsia, but the review by Wolf, Owe, Juhl and Hegaard (2013), reported that a high amount of leisure time physical activity (at least 270 minutes per week) has increased the risk of severe pre-eclampsia. Moreover the review by Aune, Saugstad, Henriksen and Tonstad (2014), reported that the women who performed pre-pregnancy leisure time physical activity five to six hours per week had a 40 % PE reduction risk. These reviews recommended 2 to 7 hours of LTPA, moderate - to-heavy LTPA before pregnancy, to reduce the risk of pre-eclampsia.

3.1.2.2 Leisure time physical activity during pregnancy

The review by Wolf, Owe, Juhl and Hegaard (2013), found that leisure time physical activity during pregnancy reduced the risk of pre-eclampsia. This review has also showed that, the women who performed vigorous leisure time physical activity during pregnancy had a reduction risk of severe pre-eclampsia. The review by Aune, Saugstad, Henriksen and Tonstad (2014), reported that leisure time physical activity reduced the risk of pre-eclampsia during early pregnancy; in other words, in the first trimester of pregnancy. This review has also reported on intensity of leisure time physical activity during pregnancy; the result was higher intensity of leisure time physical activity reduced the risk of pre-eclampsia in early

pregnancy. According to Wolf, Owe, Juhl and Hegaard review (2013), there was an association between leisure time physical activity during pregnancy and duration, one case control study showed that the women who performed more than 13 activities/months had a reduction of risk of pre-eclampsia and those who performed leisure time physical activity during pregnancy more than 4 hours/week. But the review by Aune Saugstad, Henriksen and Tonstad (2014), showed that one hour per day of leisure time physical activity during early pregnancy reduced the risk of pre-eclampsia. These reviews concludes that LTPA, higher intensity of LTPA, during pregnancy or during early pregnancy one hour per day or more than 4 hours per week or 13 activities per month reduced the risk of pre-eclampsia.

3.1.2.3 Leisure time physical activity before and during pregnancy

The review by Kasawara Do nascimento, Costa, Surita and Silva (2012), confirmed that the women who performed leisure time physical activity during both periods had a reduction of pre-eclampsia.

The review by Aune, Saugstad, Henriksen and Tonstad (2014) supported this result but the review by Wolf, Owe, Juhl and Hegaard (2013) did not find any association between the women who performed leisure time physical activity during two periods and those who did not perform leisure time physical activity during 2 periods. These reviews suggested that LTPA before and during pregnancy reduced the risk of pre-eclampsia.

3.1.3 Occupational-activity

The review by Aune, Saugstad, Henriksen and Tonstad (2014), there was generally no association between occupational activity and preeclampsia. However, cohort studies showed a little evidence of an association between early pregnancy occupational activity and preeclampsia. According to Kasawara Do nascimento, Costa, Surita and Silva review (2012),

concluded that the risk of PE was significantly decreased among nulliparous employed in a job that performed high levels of physical activity. These reviews indicated that high levels of occupational – activity in nulliparous during early pregnancy reduced the risk of preeclampsia.

3.2 Diet

The word diet is used when referring to specific intake of nutrition for health or weight management. A healthy diet includes eating more fruit, vegetables, legumes, nuts and grains, cutting down on salt, sugar and fats (WHO, 2016).

3.2.1 Vegetables and fruit

The review by Allen, Rogozinska, Sivarajasingam, Khan and Thangaratinam (2014), this review showed that vegetables, plant food and vegetable oils reduced the risk of pre-eclampsia. But according to Schoenaker, Soedamah-Muthu & Mishra review (2014) showed that fruit and/or vegetables may have a protective effect on pre-eclampsia, although the result was not statistically significant. These reviews recommended both fruit and vegetable to reduce the risk of pre-eclampsia.

3.2.2 Nutrient intake

Nutrition is the intake of food, considered in relation to the body's dietary needs (WHO, 2016).

- **Energy intake**

The review by Schoenaker, Soedamah-Muthu and Mishra review (2014), energy intake increased the risk of pre-eclampsia, although the result was not statistically significant. The

risk of pre-eclampsia was increased in women who had high energy intake early in the second trimester.

- **Dietary fiber intake**

The review by Allen, Rogozinska, Sivarajasingam, Khan and Thangaratinam (2014), this review concluded that dietary fiber intake was associated with a reduction in the risk for pre-eclampsia.

- **Magnesium and Calcium**

The review by Schoenaker, Soedamah-Muthu and Mishra review (2014) showed that women who had lower calcium intake were at risk to develop hypertension in pregnancy although the result was not statistically significant. Calcium intake in the highest (>1600 mg/day, approximately) compared with the lowest (<100 mg/day approximately) showed a reduction of risk of gestational hypertension. Lower magnesium intake was associated with increased risk of hypertension in pregnancy. However this result was not statistically significant (Schoenaker, Soedamah-Muthu & Mishra, 2014). These reviews recommended both magnesium and calcium intake to reduce the risk of pre-eclampsia.

3.2.3 Vitamins

Vitamins are any of a group of organic compounds which are essential for normal growth and nutrition and are required in small quantities in the diet because they cannot be synthesized by the body (Oxford Dictionary of Current English, 2009).

- **Vitamins C and E**

The review by Schoenaker, Soedamah-Muthu and Mishra (2014), does not support the use of vitamin C and E to prevent pre-eclampsia because women who supplemented with vitamin C and E were at an increased risk of developing pre-eclampsia.

- **Vitamin D**

The review by Tabesh, Salehi-Abarrgouei, Tabesh, Esmaillzadeh, (2013), demonstrated that there is an association between vitamin D deficiency and the risk of pre-eclampsia when the deficiency is defined as serum 25(OH) D [ ] of < 50 n mmlo/L (20 mg/mL). But when the deficiency was defined as <38 n mol/L (15.2ng/mL) there was no association between vitamin D deficiency and the risk of pre-eclampsia. But according to Schoenaker, Soedamah-Muthu and Mishra (2014) review reported that the result from RCT on nutrient supplementation did not show any association between vitamin D and pre-eclampsia. These reviews indicated that vitamin D may reduce the risk of pre-eclampsia.

3.3 Diet and PA

The review by Allen, Rogozinska, Sivarajasingam, Khan and Thangaratinam (2014), there was no reduction in the risk of pre-eclampsia with mixed interventions (diet, physical activity, and lifestyle).

3.4 Medications

Medication is a drug or other preparation for the treatment or prevention of disease (Oxford Dictionary of Current English, 2009).

- **Platelets**

The review by Duley, Henderson-Smart, Meher S and King (2007) reported that generally antiplatelet agent reduced the risk of pre-eclampsia by 17%but the reduction of relative risk of pre-eclampsia was more significant in women who were at high risk of pre-eclampsia than those who were at moderate risk. There was also a greater reduction risk of pre-eclampsia in the trial that used superior or equal 75 mg/day of aspirin than in the trial that used inferior or equal 75mg/day of aspirin. The review by Henderson, J. T., Whitlock, E. P., Connor, E. O., Senger, C. A., Thompson, J. H and Rowland, M. G (2014), supported this result. This review reported that 13 RCT stated that aspirin was associated with a reduction of risk by 10% to 23% for pre-eclampsia. These reviews concluded that platelets reduced the risk of preeclampsia. Superior or equal 75 mg/day of aspirin should be used to prevent preeclampsia.

- **Calcium**

The review by Hofmeyr, G. J., Duley, L and Atallah, A (2007) reported that the result from RT showed at least 1 g of calcium compared with placebo reduced the risk of both pre-eclampsia and gestational hypertension. The reduction was greater in both women at high risk and women with low dose baseline Calcium intake than others. From the Hofmeyr, G. J., Beliz , P and von Dadelszen, J. M review (2014) used low dose calcium supplementation (LDCS) <1g daily. The result showed that LDCS with or without co-supplement reduced the risk of pre-eclampsia. These reviews suggested that inferior or equal 1 g of calcium should be used to reduce the risk of pre-eclampsia.

- **Arginine and Antioxidants**

The review by Salles, Galvao, Silva, Motta and Pereira (2011) highlights that there was no statistically significant difference between women who received antioxidant treatment and women who received placebo. But from the Rumbold, Duley, Crowther and Haslam review (2012), isolated studies showed that antioxidants reduced the risk of pre-eclampsia compared

with placebo. However, antioxidant supplementation does not reduce the risk of PE and other serious complications in pregnancy.

The result from this review demonstrated that when L- arginine has been compared with placebo, it reduced the risk for pre-eclampsia. The review confirmed L-arginine may prevent or treat pre-eclampsia (Dorniak-Wall, T., Grivell, G. A., Dekker, R. M,, Hague & JM Dodd , 2014). According to these reviews antioxidant vitamins did not reduce the risk of pre-eclampsia.

- **Magnesium**

The review by Duley, Gülmezoglu, Henderson-Smart (2007), reported that magnesium compared with placebo or no anticonvulsants have been associated with a reduction of risk of eclampsia when compared with phenytoin. Magnesium was not associated with a higher risk of eclampsia. Whereas when a nitrate (isosorbides) has been compared with magnesium, there was no clear difference in the persistence of hypertension (Duley, Gülmezoglu, & Henderson-Smart, 2007).

According to this review, magnesium should be considered for women with PE for whom there is concern about the risk of eclampsia (Duley, Henderson-Smart, Meher, 2007).These reviews recommended the use of magnesium to prevent the risk of developing eclampsia in women with severe preeclampsia. But it cannot be used to treat severe hypertension in pregnancy.

- **Nimodipine**

The review by Duley, Henderson-Smart and Meher (2007), showed that magnesium was better than nimodipine to reduce the risk of eclampsia. But from the Duley, Gülmezoglu, Henderson-Smart review (2007), the risk of eclampsia was higher with nimodipine than with

magnesium but those two agents were associated with high levels of persistent high blood pressure. According to these reviews magnesium should be used to reduce the risk of eclampsia.

- **Labetalol**

The review by Firoz, Magee, Mac Donell, Payne, Gordon, Vidler and von Dadelszen (2014), reported that when short-acting nifedipine was compared with intravenous labetalol, there was no difference between these two medications in achieving the treatment of severe hypertension in pregnancy. From the Magee and Duley review (2012), labetalol was compared with placebo. The result from this review showed that labetalol has substantially reduced the incidence of severe hypertension in pregnancy and the need for additional anti-hypertensive. This review compared one hypertensive drug versus another, the review supported that labetalol was more effective in avoiding an episode of severe hypertension in pregnancy than methyldopa (Abalos, Duley, Steyn, Henderson-Smart, 2007). According to these reviews intravenous labetalol is more effective for the treatment of severe hypertension in pregnant.

- **Methyldopa**

The review by Firoz, Magee, Mac, Payne, Gordon, Vidler and von Dadelszen (2014), reported that a single trial compared oral labetalol 100mg four times daily with oral methyldopa 250 mg four times daily; there was no difference for the treatment of severe hypertension in pregnancy or post-partum. From the Abalos, Duley, Steyn, Henderson-Smart review (2007), supported this result because the author has also compared oral labetalol versus methyldopa; the data from this trial found the same result. According to these reviews both oral labetalol and oral methyldopa should be used to treat severe hypertension in pregnant.

- **Hydralazine**

The review by Firoz, Magee, Mac Donell, Payne, Gordon, Vidler and von Dadelszen (2014), compared oral/sublingual nifedine capsules (8-10 mg) with another agent (parenteral hydralazine), there was no difference between short acting nifedipine and intravenous hydralazine. From the Duley, Henderson-Smart and Meher review (2007) hydralazine was associated with more persistent severe hypertension than nifedine or isradipine. When hydralazine compared with, kentarine (oral hypertensive) was associated with a substantially higher risk of persistent hypertension than hydralazine. According to this review hydralazine was associated with a trend towards lower rates of persistent severe hypertension than labetalol (Magee, 2012). According to these reviews hydralazine should be used to treat severe hypertension in pregnancy.

4. Assessing the robustness of the synthesis

The R-AMSTAR appraisal tool was employed. The assessment of multiple systematic reviews can quantify the quality of systematic review. The tool has a merit of assessing the effectiveness of an intervention, program or medication. The attributes of the R-AMSTAR appraisal tool include11 questions:

1. Was an ‘‘a priori’’ design provided?

The research question and inclusion criteria should beestablished before the conduct of the review.

2. Was there duplicate study selection and data extraction?

There should be at least two persons who independently extracted data and a consensus procedure for disagreements should be in place.

3. Was a comprehensive literature search performed?

At least two electronic sources should be searched. The report must include years and databases used. Key words and/or MESH terms must be stated, and where feasible, the search strategy should be provided.

4. Was the status of publication used as an inclusion criterion?

The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports, based on their publication status, language etc.

5. Was a list of studies (included and excluded) provided?

A list of included and excluded studies should be provided.

6. Were the characteristics of the included studies provided?

In an aggregated form, such as a table, data from the original studies should be provided on theparticipants, interventions/exposure, and outcomes. The ranges of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

7. Was the scientific quality of the included studies assessed and documented?

A priori methods of assessment should be provided for other types of studies, alternative items will be relevant.

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

The results of the methodological rigor and scientificquality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

9. Were the methods used to combine the findings of studies appropriate?

For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity. If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration.

10. Was the likelihood of publication bias assessed?

An assessment of publication bias should include a combination of graphical aids.

11. Was the conflict of interest included?

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Overall, the studies that were included in the review met all the criteria stipulated in the R-AMSTAR appraisal tool. R-AMSTAR as an instrument was used to reduce the researcher's bias and guide the critical appraisal. The investigator reported the quality appraisal of each of the relevant studies. The level of evidence was also assigned for each critically appraised article and was ranked. The data was extracted by two reviewers; in case of disagreement an additional independent researcher was required. Based on this assessment process, we concluded that the findings obtained based on these studies could provide valuable and credible information on which sound conclusions could be drawn.

4.3 DISCUSSION OF FINDINGS

The aim of this discussion is to deliberate on the key findings of the study, thus placing the study in context (Russell, 2009). This study focused on the effectiveness of lifestyle and medication interventions in the management of hypertension in pregnancy. The purpose of this study was to review the effectiveness of medications and lifestyle interventions on patients' outcome during the management of hypertension in pregnancy.

4.3.1 Physical activity

Prevention of hypertension in pregnancy is based on factors associated with preeclampsia. Therefore the highest volume and quality of research on prevention of hypertension in pregnancy focuses on preeclampsia. The results of this study indicate that high intensity of leisure time physical activity (LTPA), frequent LTPA or high amount of LTPA before pregnancy for women who have an intention to get pregnant and LTPA during early pregnancy and LTPA before and during pregnancy, reduce the risk of preeclampsia. Additionally, high levels of occupational – activity during early pregnancy reduce the risk of pre-eclampsia (Aune, Saugstad, Henriksen & Tonstad, 2014*).*

One cohort study reported that high amounts of LTPA at least 270 minutes per week before pregnancy increases the risk of severe pre-eclampsia (Wolf, Owe, Juhl & Hegaard, 2013). Only two cohort studies confirmed that vigorous LTPA during pregnancy had a reduction of the risk of severe pre-eclampsia (Wolf, Owe, Juhl & Hegaard, 2013). This study's results support the American College of Obstetricians and Gynecology (ACOG) recommendations in terms of the amount of LTPA (Wolf, Owe, Juhl & Hegaard, 2013; Kasawara, Nascimento, Costa, Surita & Silva, 2012).

Hence the risk of pre-eclampsia is reduced only if physical activity was performed more than 4 hours per week or at least 25 times per month (Wolf, Owe, Juhl & Hegaard, 2013). The result has shown that the case control studies indicated an association between LTPA and a lower risk of pre-eclampsia more frequently than the cohort studies (Aune, Saugstad, Henriksen &Tonstad, 2014*).*

4.3.2 Diet

According to Schoenaker, Soedamah-Muthu and Mishra (2014).Fruits and vegetables may have a protective effect on pre-eclampsia; however, the result was not statistically significant.

Several mechanisms could explain the relationship between hypertension in pregnancy and dietary factors (Schoenaker, Soedamah-Muthu & Mishra, 2014). Fruits and vegetables are low in fat and calories (high calories cause hypertension through obesity) and are important sources of nutrients related to hypertension in non-pregnant women including dietary fiber, potassium, vitamins C, calcium and magnesium. These nutrients may also have a protective effect in pregnant women (Allen, Rogozinska, Sivarajasingam, Khan &Thangaratinam, 2014; Schoenaker, Soedamah-Muthu & Mishra, 2014).

According to Brantsæter, Haugen, Samuelsen, Torjusen, Trogstad, Alexander, Magnus, and Meltzer (2009), placental oxidative stress plays an important role in the manifestations of preeclampsia. Oxidative stress and lipid peroxidation accompany complications such as the occurrence of endothelial cell dysfunction in the blood vessels in women with preeclampsia and other hypertensive disorders (Brantsaeter et Al., 2009). Recently, the observation that women with preeclampsia have decreased plasma and placental concentrations of antioxidants has led to the proposal that placental under perfusion may mediate a state of oxidative stress (Scholl, Leskiw, Chen, Sims & Stein, 2005; Brantsaeter et Al., 2009).

The results from this study showed that antioxidants might be important for the prevention of lipid peroxidation and, hypothetically, for the prevention of preeclampsia. Antioxidants are loosely defined as any substance that when present in low concentrations compared with that of an oxidisable substrate, significantly delays or inhibits oxidation of that substrate(Salles, Galvao, Silva,Motta, & Pereira, 2011; Rumbold , Duley , Crowther , Haslam, 2012).

According to Rumbold, Duley, Crowther and Haslam, (2012) the role of antioxidants is to protect the proteins and enzymes from oxidation and destruction by free radicals and help to maintain cellular membrane integrity. There are 2 types of antioxidants; Free radical scavengers and extracellular enzymes; Free radical scavengers include vitamin C (ascorbate), vitamin E (tocopherols), carotenoid and glutathione. The same author also reported that their

role is to trap or decompose existing free radicals, or cellular and extracellular enzymes including glutathione peroxidase, superoxide dismutase and catalase, which are dependent on the presence of co-factors such as selenium, zinc and iron (Rumbold, Duley, Crowther & Haslam, 2012). While antioxidant enzymes are important for intracellular defenses, non-enzymatic antioxidants are the major defense mechanism in the extracellular compartment. This study's results showed that the antioxidants do not prevent preeclampsia, particularly the vitamins (Rumbold, Duley, Crowther & Haslam, 2012).

It has been hypothesized that calcium influences blood pressure by reducing the concentration of the parathyroid hormone, leading to lower levels of intracellular free calcium causing vasoconstriction and smooth muscle contractility. The results from this study showed that calcium also affects blood flow utero-placental and feto-placental by reducing resistance in the uterine and umbilical arteries. Calcium intake in the highest dose of 1600 mg/day approximately showed a reduction of risk of gestational hypertension. In populations of low calcium intake, pre-eclampsia can be reduced by calcium supplementation (Hofmeyr, Duley, Atallah, 2007; Hofmeyr, Belizan, von Dadelszen, 2014). However, most of the studies were not statistically significant. Magnesium can lower blood pressure by changing the synthesis of nitric oxide (Duley, Gülmezoglu, Henderson-Smart, 2007**)**. In addition, it was suggested that small amounts of magnesium intake can reduce prostacyclin; ratio of thromboxane and thus influence hypertension (Duley, Gülmezoglu, Henderson-Smart, 2007**).**

The result has also demonstrated an association between vitamin D deficiency and the risk of PE when the deficiency was defined as serum 25 (OH) D [ ] of < 50 mml/L (20 mg/mL). But when the deficiency was defined as < 38 n mole/L (15.2 ng /mL) there was no association between the vitamin D deficiency and the risk of PE. Low serum vitamin D levels can affect the risk of pre-eclampsia, although the mechanisms that may explain it are still unclear; but it

is biologically plausible (Tabesh, Salehi-Abarrgouei, Tabesh, Esmaillzadeh, 2013; Schoenaker, Soedamah-Muthu & Mishra 2014).

According to Tabesh, Salehi-Abarrgouei, Tabesh, and Esmaillzadeh, (2013), the renin-angiotensin system is a regulatory cascade that plays a critical role in the regulation of blood pressure, electrolyte and plasma volume homeostasis. The same author reported that vitamin D has been shown to be a potent endocrine suppressor of renin biosynthesis to regulate the renin-angiotensin system. Therefore, normal serum vitamins D levels help prevent hypertension through suppression of the renin-angiotensin system (Tabesh, Salehi-Abarrgouei, Tabesh, &Esmaillzadeh, 2013). It can also affect the arterial pressure by improving insulin and endothelial cell-dependent vasodilatation, and inhibiting anticoagulant activity. Macrophage activity and cytokine production may be modulated by vitamin D. The pathophysiological change that is observed in preeclampsia is due to abnormal endothelial function which is the basis of generalization of inflammatory activation. The transcription and function of genes associated with placental invasion, normal implantation and angiogenesis are regulated by vitamin D. Therefore, insufficient serum vitamin levels can impair the normal functioning of these processes (Tabesh, Salehi-Abarrgouei, Tabesh, Esmaillzadeh, 2013; Schoenaker, Soedamah-Muthu & Mishra 2014).

4.3.3 Medication

Pharmacological treatment is recommended for all pregnant women with severe hypertension with diastolic blood pressure values greater than 110 mm Hg. The main objective of treatment is to reduce the risk of the patients from progressing to severe hypertension, preeclampsia or eclampsia (North Sydney department of health, 2011).

This study's findings support the ACOG recommendations in terms of treatment of severe hypertension in pregnancy. The result from this study showed that most of the antihypertensive drugs reduce the risk of severe hypertension in pregnancy. Intravenous

labetalol has become popular for the treatment of severe hypertension whereas hydralazine continues to be widely used and the most commonly used calcium – channel blocker in hypertension in pregnancy is nifedipine (Lowe et Al., 2014). Magnesium is not required to treat hypertension in pregnancy but it is used to prevent the risk of developing eclampsia in women with severe preeclampsia. In other words, it is recommended for controlling seizures in women with high risk of developing eclampsia (Duley, Gulmezoglu, Henderson-Smart, 2007).

Although those antihypertensive drugs are recommended for the treatment of severe hypertension in pregnancy, they are also associated with adverse effects. Parenteral hydralazine is associated with hypotension (systolic blood pressure 90 mm Hg or less). It has recently been shown that intravenous hydralazine is associated with hypotension. This is due to a rapid uncontrolled decline in blood pressure, therefore the patients develops fetal distress hence caesarean delivery is required for these patients. Parenteral labetalol is not required in women with asthma, heart disease or congestive heart failure and may cause neonatal Brady cardiac. Nifedipine may increase the risk of maternal heart rate and with overshoot hypotension (American College of Obstetricians & Gynecology, 2015).

According to Duley, Henderson-Smart, Meher (2007), some of the antihypertensive should not be used for women with very high blood pressure (including kentanserin, nimodine, and Diaz oxide). Another antihypertensive medication was associated with high risk of eclampsia namely phenytoin. However, the antioxidant supplementations do not reduce the risk of pre-eclampsia.

According to Hofmeyr, Belizan and von Dadelszen (2014), there was a greater reduction in the risk of PE in the trial that used inferior or equal to 75 mg/ day of aspirin but also the reduction of risk was greater in women who were at high risk of pre-eclampsia than those who were at moderate risk. For calcium supplementation, at least 1g reduced the risk of both

pre-eclampsia and gestational hypertension (Hofmeyr, Duley, Atallah, 2007; Hofmeyr, Belizan, von Dadelszen, 2014). The reduction was greater in women at high risk of pre-eclampsia and gestational hypertension and women with low dose baseline calcium intake. In the medication intervention, almost all studies were randomized trials. In this study, most of the studies were from the United States of America.

After the synthesis of articles we find that medication and lifestyle intervention are complementary in other words none is more effective than other. To prevent hypertension in pregnancy and it is complication and protect the lives of the fetus it is better to use lifestyle than medication. But to treat severe hypertension in pregnancy in order to avoid the complications of hypertension in pregnancy it is better to use medication than lifestyle.

4.3.4 Summary of discussion

This study found that lifestyle namely physical activity and diet may reduce the risk of hypertension in pregnancy. The pregnant women with hypertension or women who had the intention to get pregnant, who performed high intensity of physical activity more than 4 hours per week or at least 25 times per month before pregnancy or during early pregnancy or before and during pregnancy, and a diet rich in fruits and vegetables, had a reduction of risk of hypertension in pregnancy. The results from this study also showed that most of the antihypertensive drugs reduce the risk of severe hypertension namely intravenous labetalol, hydralazine, nifedipine and magnesium and these are required to prevent the risk of developing eclampsia in women with severe preeclampsia. Despite this, they are also associated with adverse side effects

4.4 CHAPTER SUMMARY

In this chapter the results of this research were synthesized and interpreted using the data extraction and narrative synthesis. Further, the results of this research were discussed.

CHAPITRE FIVE

CONCLUSION, RECOMMENDATION AND SUMMARY

5.1 INTRODUCTION

The purpose of this chapter is to summarize the various findings of the study and its implications. As noted in the previous chapter, the findings of this study revealed that overall lifestyle namely; PA and diet reduces the risk of hypertension in pregnancy especially in the early stages of pregnancies thus reducing the risk of severe hypertension whereas anti-hypertensive therapy reduces the risk of severe hypertension in pregnant women. These findings showed the effectiveness of lifestyle (including physical activity and diet) and medication. But the comparison on the effectiveness was rather difficult to make due to the periods in pregnancy where either intervention was used. This section discusses the conclusions made from the findings of this study, the recommendations and the limitation of the study.

The main challenge remains how those two interventions (lifestyle and medication) can work together for the benefit of pregnant women with hypertension because these interventions are complementary.

5.2 OBJECTIVE OF THE STUDY

The review is designed to meet the following objective:

- To assess the effect of medication and lifestyle adjustment intervention on patients' outcomes during the management of hypertension in pregnant women.

5.3 CONCLUSION OF RESEARCH FINDINGS

5.3.1 Conclusions pertaining to lifestyle adjustment as an intervention in management of HIP.

Lifestyle intervention includes both physical activity and diet. These interventions seemed to have an effect on risk reduction to the development of severe hypertension at the later stages of pregnancy**.** The candidates for lifestyle modification are women with stage 1 blood pressure (systolic blood pressure 140 – 159mmHg or diastolic blood pressure 90 – 99) and women who have an intention to fall pregnant and during early pregnancy

5.3.1.1 Physical activity

High physical activity before pregnancy for the women who have an intention to get pregnant and during early pregnancy and before and during pregnancy more than 4 hours per week or at least 25 times per month, reduces the risk of hypertension in pregnancy. The women who are able to engage in high intensity exercise programs are those who were regular exercisers before pregnancy and who have an uncomplicated, healthy pregnancy (ACOG, 2015). A pregnant woman, before starting an exercise program, obstetrics and medical risks, must be examined. Moreover, the nutritional, cardiovascular, and musculoskeletal condition of the subject as well as fetal wellbeing should be periodically assessed during the prenatal visits in pregnant women undertaking high intensity exercise programs (ACOG,2015).

5.3.1.2 Diet

In general, a healthy diet is recommended for the pregnant women because they should have a balanced diet for maternal and infant health. A pregnant woman should have an adequate intake of vitamins and minerals because most of the vitamins and minerals are associated with hypertension namely vitamin A, D, E, C, and some minerals such as potassium, calcium and magnesium. Hence eating a diet high in fruits, vegetables and low fat dairy products may

have a protective effect on hypertension in pregnancy.

5.3.2Conclusions pertaining to medication as an intervention in management of HIP

These findings indicated that for lowering blood pressure in hypertension in pregnancy, a number of drugs have demonstrated efficacy namely; intravenous labetalol, hydralazine and nifedine. Magnesium is not required to treat hypertension; it is for controlling seizures. Low dose aspirin should be used in clinical practice to prevent PE. The relative risk of maternal non severe hypertension (systolic blood pressure 140-150mmHg or diastolic blood pressure 90-109mmHg) may be decreased by using anti-hypertensive therapy. Antihypertensive therapy is recommended in all women with severe hypertension (systolic blood pressure more than 160mm Hg or a diastolic blood pressure more than 110 mm Hg or both). However, there is no evidence that antihypertensive drugs are most effective for women with severe hypertension during pregnancy

5.3.3 Overall conclusion of the effectiveness of medication and lifestyle as intervention in management of HIP.

The study assessed the effect of medication and lifestyle intervention on patients' outcomes during the management of hypertension in pregnancy. The intention was to assess the effect of each intervention (lifestyle and medication) on pregnant women with hypertension. The findings indicate that management of hypertension in pregnancy needs several interventions not only the antihypertension therapy because there is no clear effect of antihypertensive medication on the risk of small gestation age, placental abruption, caesarean section or admission to the neonatal nursery (Lowe et al., 2014). Antihypertensive drug is recommended for the treatment of severe hypertension (Lowe et al., 2014). The antihypertensive therapy can easily cause hypotension in pregnant women with non-severe chronic hypertension; hence there is an increased risk of small for gestational age or low birth

weight by decreasing blood pressure (North Sydney department of health, 2011).Therefore in the interest of not increasing the infant mortality rate while focusing on the management of hypertension in pregnancy and saving the life of the mother, the life of the fetus must be taken into account. Additionally, the study shows that antihypertensive drugs do not prevent preeclampsia; that is why lifestyle (PA and diet) is important for the prevention of hypertension in pregnancy. The women with preeclampsia have a higher risk of recurrence and it may also be a risk factor for future cardiovascular and cerebrovascular events, so there is a need for the prevention of hypertension by initiating lifestyle interventions earlier on in the pregnancy (Brown, Best, Pearce, Waugh, Robson & Bell, 2013).However, what is more challenging is to show if the one intervention is more effective than the other as they seem to be effective at different periods of pregnancy. There were no studies found that compared the effectiveness of the two interventions and due to the period in pregnancy that the interventions were employed, it is rather difficult to conclude that one is more effective than the other. Therefore none of these interventions (medication and lifestyle) is more effective than another, they are complementary.

5.5 LIMITATIONS

One of the limitations of this study was accessing adequate reviewed articles on the topic as some articles needed were not readily available (14 articles unobtainable) and needed significant amounts of money to access. The other limitation was language restriction that is to say only studies published in English were included. Additionally; most of the articles were not from the African context, let alone the South African context which made it difficult to put the study in these contexts. This impacted on the potential significance of the study which was to use the results to improve access to health service by pregnant women thus reducing the overall mortality rates in Africa and South Africa specifically.

5.6 RECOMMENDATIONS FROM THIS STUDY

a) Recommendations for future research

- Further studies are needed to clarify whether increasing physical activity in early pregnancy reduces the risk of pre-eclampsia among previously inactive women and to further define the dose–response association for various types and intensities of physical activity in relation to preeclampsia.
- There is a need for well-powered prospective cohort studies and intervention trials in a range of populations assessing nutrition prior to and during pregnancy, examining associations with the different subtypes of PE.
- Several questions remain about the role of low-dose aspirin. Research is needed to illuminate whether there are particular high-risk subgroups of women who might have greater benefits; whether starting treatment before12 weeks would have additional benefits without an increase in adverse effects, and whether a higher dose of aspirin would be more effective.to prevent preeclampsia.
- Dietary modification should be assessed whether it has the same effect as the calcium tablet.
- Large simple trials are required in order to provide reliable estimates of the benefits and adverse effects of antihypertensive therapy for mild to moderate hypertension.
- Future trials should focus on head to head comparisons of oral agents, particularly nifedipine, labetalol and methyldopa.
- Large, randomized placebo-controlled trials are required to determine whether overall antihypertensive therapy (with any agent) is preferable to the non-treatment of mild to moderate hypertension during pregnancy.
- The challenge is to establish cost-effective and sustainable screening and subsequent management programs in the community to ensure that as many affected African

women are detected and treated in a timely manner. Because hypertensive heart disease is particularly problematic in pregnancy.

b) Recommendations for medical professionals

- The detection of nutritional deficiency especially vitamins and dietary minerals collaborate with hypertension in communities, specifically in women of childbearing age finally corrects this deficiency in the community for collective prevention of hypertension.
- Early detection of hypertension in women of childbearing age and promote lifestyle modification to prevent hypertension in women who have the intention to get pregnancy.
- Promote lifestyle modification specifically in women of childbearing age from families with a history of hypertension.

5.7 CHAPTER SUMMARY

In this chapter, this study's results and applications were summarized. Additionally, recommendations for the medical profession and for future research were tabled

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APPENDIX 1: R-AMSTAR checklist – quality assessment for systematic reviews

How to use the R-AMSTAR tool?
The tool contains 11 questions with regard to the quality of the review. These questions are in the left column. Based on the criteria mentioned in the right column, every question should be assigned a score from 1 to 4. The sum of all scores is the overall quality score of the systematic review.

AMSTAR items	*Criteria*
1. Was an "a priori" design provided? The research question and inclusion criteria should be established before the conduct of the review.	A A clearly focused (PICO-based) question B Description of inclusion criteria C Study protocol is published and/or registered in advance 3 criteria→4, 2→3, 1→2, 0→1
Explanation: A. It should be explicitly mentioned that a protocol was published or registered, for example in PROSPERO an online international prospective register of systematic reviews. C. The question contains **P**opulation, **I**ntervention/exposure, **C**omparator/control and **O**utcome.	
2. Was there duplicate study selection and data extraction? There should be at least two persons who independently extracted data and a consensus procedure for disagreements should be in place.	A At least two persons independently extracted the data, explicitly stated B Statement of consensus procedure for disagreements C Disagreements among extractors resolved properly as stated or implied 3 criteria→4, 2→3, 1→2, 0→1
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated, and where feasible, the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	A At least two electronic sources are searched B Years and databases used are mentioned C Key words and/or MESH terms are stated and where feasible the search strategy outline is provided D Searches should are supplemented by consulting current contents, reviews, textbooks, registers and by reviewing the references in the studies found E Journals are hand-searched or manual searched 4 or 5 criteria→4, 3→3, 2→2, 1 or 0→1
Explanation: E. hand-searched means identifying highly relevant journals and conducting a manual, page-by-page search of their contents looking for potentially eligible studies.	
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	A The authors state that they searched for reports regardless of their publication type. B The authors state whether or not they excluded any reports based on their publication status, language etc. C "Non-English papers were translated"or readers sufficiently trained in foreign language D No language restriction or recognition of non-English articles 3 or 4 criteria→4, 2→3, 1→2, 0→1

AMSTAR items	*Criteria*
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	A Table/list/figure of **included** studies, a reference list does not suffice B Table/list/figure of **excluded** studies either in the article or in a supplemental source C Satisfactory/sufficient statement of the reason for exclusion of the seriously considered studies D Reader is able to retrace the included and the excluded studies anywhere in the article bibliography, reference or supplemental source 4 criteria→4, 3→3, 2→2, 1→1
Explanation: "Excluded studies" refers to those studies seriously considered on the basis of title and/or abstract, but rejected after reading the body of the text.	
6. Were the characteristics of the included studies provided? In an aggregated form, such as a table, data from the original studies should be provided on the participants, interventions/exposure, and outcomes. The ranges of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	A In an aggregated form such as a table, data from the original studies are provided on the participants, interventions/exposure and outcomes B Ranges are provided of the **relevant** characteristics in the studies analyzed C The information provided appears to be complete and accurate 3 criteria→4, 2→3, 1→2, 0→1
7. Was the scientific quality of the included studies assessed and documented? ''A priori'' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo-controlled studies, or allocation concealment as inclusion criteria); for other types of studies, alternative items will be relevant.	A 'A priori' methods are provided B The scientific quality of the included studies appears to be meaningful C Discussion/recognition/awareness of level of evidence is present D Quality of evidence is rated/ranked base on characterized instruments 4 criteria→4, 3→3, 2→2, 1 or 0→1
Explanation: D. A characterized instrument is a created instrument that ranks the level of evidence, e.g. GRADE [Grading of Recommendations Assessment, Development and Evaluation].	
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	A The scientific quality is considered in the analysis and the conclusions of the review B The scientific quality is explicitly stated in formulating recommendations C Conclusions integrated/drives towards practice guidelines D Clinical consensus statement drives toward revision or confirmation of practice guidelines 4 criteria→4, 3→3, 2→2, 1 or 0→1
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I^2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).	A Statement of criteria that were used to decide that the studies analyzed were similar enough to be pooled B For the pooled results, a test is done to ensure the studies were combinable, to assess their homogeneity C a recoginition of heterogeneity or lack of thereof is present D If heterogeneity exists a 'random effects model' is used and/or the

PEROSH OSH Evidence Methods

AMSTAR items	*Criteria*
	rationale of combining is taken into consideration E If homogeneity exists, author state a rationale or a statistical test 4 or 5 criteria→4, 3→3, 2→2, 1 or 0→1
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	A Recognition of publication bias or file-drawer effect B Graphical aids (e.g. funnel plot) C Statistical tests (e.g. Egger regression test) 3 criteria→4, 2→3, 1→2, 0→1
11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	A Statement of sources of support B No conflict of interest. This is subjective and may require some deduction or searching. C An awareness/statement of support or conflict of interest in the **primary** inclusion studies 3 criteria→4, 2→3, 1→2, 0→1

Maximum quality score sum: 44

APPENDIX 2

UNIVERSITY of the WESTERN CAPE

DEPARTMENT OF RESEARCH DEVELOPMENT

10 December 2015

To Whom It May Concern

I hereby certify that the Senate Research Committee of the University of the Western Cape approved the methodology and ethics of the following research project by:
Mr B Kukatula (School of Nursing)

Research Project:	A systematic review of the effectiveness of lifestyle and medication interventions for management of hypertension in pregnancy.
Registration no:	15/7/82

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
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