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RESEARCH ARTICLE

ISSUES IN GLOBAL MATERNAL HEALTH - TRENDS IN THE MANAGEMENT OF PRE-ECLAMPSIA; A SYSTEMATIC REVIEW OF THE LITERATURE

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ABSTRACT

Aims: Pre-eclampsia (systolic blood pressure of >140 mmHg and diastolic blood pressure >90 mmHg) is a fundamentally unique condition, occurring in the post-partum as well as the pre-natal period of pregnancy. It is a progressive and acute condition, characterised by high blood pressure and proteinuria which can have deleterious impact on both the health of mother and child. Few reviews to date have examined trends in the pharmacological management of pre-eclampsia from a global perspective. The aim of this study was to highlight the pharmacological management strategies that currently operate on a global level to reduce the prevalence of pre-eclampsia.

Method: An electronic search was conducted using Cochrane, Cinahl Plus, Medline and Science Direct for randomized controlled trials investigating the treatment and management of pre-eclampsia in pregnancy in addition to searching reference lists using a predefined search strategy. The review included quasi-randomised trials, randomised controlled trials, cohort studies and programme evaluations. The primary outcome measures incorporated theeffectiveness of a range of pharmacologicalinterventions. Risk of bias and the quality of evidence of the qualitative studies selected for inclusion were assessed using the Effective Public Health Practice Project Tool. Quantitative studies were assessed using SIGN Critical Appraisal Checklist 2 for randomized controlled trials.

Results: The review identified 4,838articles of which 8 met the inclusion criteria. Eight papers were included in this review. From these eight papers, several interventions were used in the treatment and management of pre-eclampsia. Two of the eight studies (25%) investigated the efficacy of vitamins (Vitamins C and E) in the management of pre-eclampsia in pregnancy. One (12.5%) of the included study examined the effects of exercise in managing the condition while five (62.5%) investigated the efficacy of drugs/medicines.

Conclusions: Pharmacologic interventions in pre-eclampsia with anti-hypertensive medications appear to be the most efficacious pharmacological intervention used in efforts to reduce the prevalence of the condition.

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INTRODUCTION

Pre-eclampsia can be operationally defined as the elevation of systolic blood pressure of beyond 140 mmHg and diastolic blood pressure beyond 90 mmHg. The condition is characterised by high blood pressure and proteinuria in terms of its clinical symptomology (Duley, 2009). The severity of the pre-eclampsia ranges from mild to fatal, that is, 'systolic blood pressure ≥160mmHg and diastolic blood pressure ≥110 mmHg' (Taylor *et al*., 2015).

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It has been established that when the condition becomes severe, it exerts a physiological impact on the liver, kidney and the brain (ibid, 2013). Pre-eclampsia is a syndrome that has a resultant impact which is both maternal and foetal often manifesting in the development of chronic illness and developmental delay in childhood (Taylor *et al.,* 2015; Adamu *et al.,* 2010). It was historically reported that the complication of pre-eclampsia affects between 2-8% of pregnancies and increased to 5-8% of all pregnancies (Meads *et al.,* 2008). It is currently reported that complications of pre-eclampsia occur in 10-15% of all pregnancies, which is exacerbated by the predisposing conditions of renal disease, maternal diabetes and

chronic hypertension (Agrawal and Walia, 2014). The condition is characterized by endothelial dysfunction, vasoconstriction, metabolic changes and activation of the coagulation cascade in conjunction with an inflammatory response and as such it can be regarded as a multi-systemic disorder (Okpomeshine, 2014). Adegbesan-Omilabu *et al.* (2013) report that the presence of hypertension, proteinuria or both ought to be an indicator for further medical assessment to detect the presence of hyper-reflexia, oedema, changes in visual acuity, sudden weight loss and headaches. Positive diagnosis at the earliest possible stage can lead to the avoidance of blood coagulation and premature placental separation. Eclampsia also has progressive symptomology characterised by the same clinical presentations (Adegbesan-Omilabu *et al.,* 2013). Due to its severity, pre-eclampsia has remained a significant global public health threat and has been termed a major cause of perinatal morbidity and mortality occurring in both developing and developed countries (Barton and Sibai, 2008). The impact of the disease is more severe in developing countries due to its increasing incidence and prevalence as well as increasing morbidity and mortality rates associated with the disease condition (Onuh and Aisien, 2011). The condition becomes more critical with late diagnosis as evidenced by the high mortality rates related to such instances (Adegbesan-Omilabu *et al.,* 2013). The unpredictable nature of the disease and lack of understanding of its aetiology further complicates the problem (Okpomeshine, 2014). Mortality records indicate that 585,000 women die every year from complications developing as a direct result of pre-eclampsia, accounting for 10-25% of all cases globally (Kooffreh *et al.,* 2014; Taylor *et al.,* 2015). The vast majority of these are attributed to a lack of access to health care facilities, as a direct impact of health inequalities (WHO 2013).

In the UK, pre-eclampsia represents the second highest aetiological factor in maternal death (Arulkumaran *et al.,* 2011). Consequently, severe pre-eclampsia has its incidence estimated at circa 5 in 1,000 pregnancies (WHO, 2013). In 2013, about 22 deaths were attributed to pre-eclampsia. Of these 22 deaths, 20 were directly linked with suboptimal levels of care while 14 were categorised as being preventable (Duley, 2013; Agrawal and Walia, 2014). In 2014, pre-eclampsia collectively attributed to 15% of maternal deaths across the UK and the USA. The incidence of pre-eclampsia in the UK was 1 in 2000 pregnancies, whilst severe pre-eclampsia occurred in 5 of every thousand pregnancies. Furthermore, it was reported that complications of pre-eclampsia caused 44% of all deaths amongst British women (Taylor, 2015).

Pre-eclampsia has also gained recognition in developing countries due to its significantly high mortality rate (Onuh and Aisien, 2011). Nigeria remains the most populous of African countries with a population density of about 183,500,000 (Swanson, 2015). In 2014, the reported rate of pre-eclampsia was 5.6% in Nigeria, complicating over 3-5% of first pregnancies (Adegbesan-Omilabu *et al.,* 2014). Several studies have highlighted predisposing risk factors which lead to the development of pre-eclampsia (Adegbesan-Omilabu *et al.,* 2013). These include race, obesity, poor socio-economic status and nulliparity. Other predisposing factors are the experience of having a low birth weight in a previous pregnancy, longer intervals between pregnancies, change in spouse or a previous history of established eclampsia (Taylor *et al.,* 2015).

A definitive aetiology of pre-eclampsia remains a challenge to the medical profession (Taylor *et al.,* 2015), however it has been suggested that certain risk factors leading to the occurrence and the severity of pre-eclampsia could be prevented (Onuh and Aisien, 2011; Adegbesan-Omilabu *et al*, 2014). Several reports highlight high incidence and prevalence as well as mortality resulting from pre-eclampsia in low and middle income countries (Dolea and AbouZahr, 2009; McClure *et al.,* 2009; Berg *et al.,* 2009; Okonofua, 2013; Okpomeshine 2014) but there is also a reported equally increasing prevalence rate in the USA and the UK(Kooffreh *et al.,* 2014).

Aim of the Study

The aim of this study was to highlight the pharmacological management strategies that currently operate on a global level to reduce the prevalence of pre-eclampsia.

METHODS

The execution of a systematic review was rationalised as a means of illuminating the available published evidence base and of summarising key findings about the pharmacological management of pre-eclampsia (Yost *et al*., 2014; Armijo-Olivo *et al*., 2012; Van Tulder *et al*., 2003. It is hoped that the impact of this work will be the ability of decision makers to make informed decisions about the management of a condition which claims the lives of thousands of women on an annual basis globally. Operational definitions were established to standardise terminology and to ensure that interpretation bias was minimised throughout the studyVoss and Rehfuess., 2013).

Selection and Retrieval of the Published Literature

Figure 1 shows the result of the database search. A total of 4,838 papers were identified across the four database searched after using keywords (Pre-eclampsia, Maternal Health, Random Control Trials) and applying limiters such as studies published in English language, studies that had available abstracts, full texts and references, and studies published between the year 2005 till date (Cochrane Library- 29; Cinahl Plus- 106; Medline- 3661; Science direct- 1042). 103 papers were retrieved after removing duplicates and papers that were considered irrelevant. Of the 103 papers, fifteen met the inclusion criteria. By screening the reference list of the selected papers, three more papers were identified but later removed as there was no access to the publication and the full text documents were not retrievable. After screening the fifteen available papers against PICO criteria, eight papers were finally selected for this review.

Characteristics of Included Studies

Eight papers were selected for this review. Table 1 gives a summary of characteristics of papers included in this review. All selected papers were randomized controlled trials investigating the treatment and management of pre-eclampsia. RCTs were selected as it is the gold standard for clinical trials looking into the efficacy of interventions in the management of specific conditions.

RESULTS AND DISCUSSION

In relation to the overall aim of the systematic review, the most salient findings were extracted in terms of clinical significance to the pharmacological management of pre-eclampsia: Eight papers were included in this review.

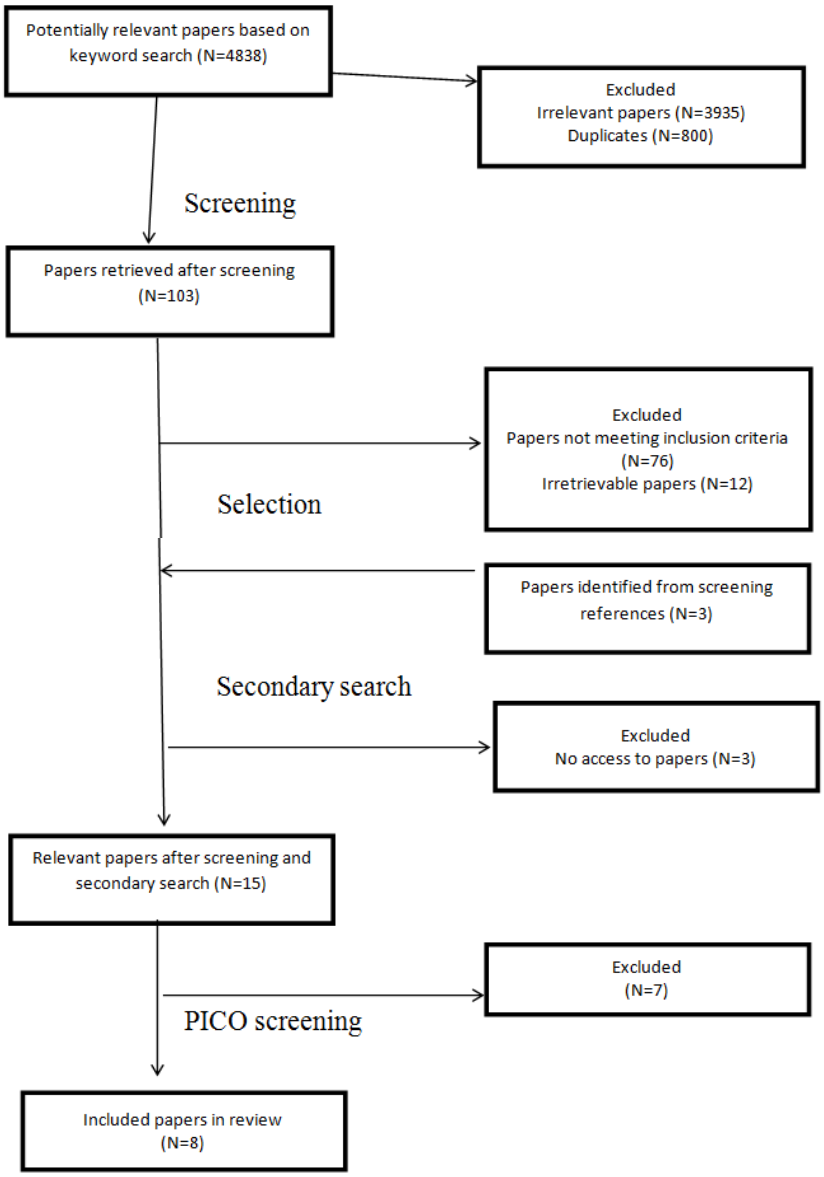

Figure 1. Database Search

From these eight papers, it was established that several interventions were used in the treatment and management of pre-eclampsia. Two of the eight studies (25%) investigated the efficacy of vitamins (Vitamins C and E) in the management of pre-eclampsia in pregnancy. One (12.5%) of the included studies examined the effects of exercise in managing the condition while five (62.5%) investigated the efficacy of drugs/medicines (hydralazine, dihydralazine; labetalol, methyldopa, magnesium sulphate, uradipil; ketanserin) in the management of pre-eclampsia. The included studies were carried out in different countries and this allowed a range of variants as to the possible interventions used in the management of pre-eclampsia across the globe. Four studies (50%) were carried out in Europe, Two (25%) in Asia, and two (25%) in South America.

Effectiveness of Anti- Hypertensives

Most of the included studies in this review utilising antihypertensive drugs as their intervention found them effective in the treatment and management of pre-eclampsia although to varying degrees based on the type of drug used and the dose at which it was administered. Of the five studies (Maia *et al.,* 2014; Wacker *et al.,* 2005; Gracia *et al.,* 2006; Dharwaldkar *et al.,* 2014; Bijvank *et al.,* 2015) that evaluated the use of drugs as interventions in the management of pre-eclampsia in pregnancy, Maiai *et al.* (2014) compared the use of intravenous magnesium sulphate for twelve and twenty four hours in women with stable severepre-eclampsia at a tertiary hospital in Brazil. They discovered that participants in the abbreviated (12 hour) magnesium sulphate therapy had less exposure to the drug but the clinical outcomes in both groups were similar as none of the women in both groups developed eclampsia. Their report was similar to findings from other studies that have investigated the use of magnesium sulphate in the management of pre-eclampsia in pregnancy (Darngawn *et al.,* 2012; Ehrenberg *et al.,* 2006; Fontenot *et al.,* 2005). Regarding safety, magnesium sulphate was safe and in this study population as no adverse occurrences was reported regarding its use. A limitation to this study was however the fact that statistically the study was not sufficiently powered to evaluate the frequency of eclampsia as evidenced in a systematic review by Duley *et al.* (2010) where it was recommended that to determine a difference in the frequency of eclampsia with short regimen of magnesium sulphate as used in the Maiai *et al.* (2012) study, a sample size of about 18000 women would have to be used.

Table 1: Characteristics of Papers Incorporated into the Study

Author(s) Year of Publication	Study Type -duration -country	Setting Sample size Age range	Intervention Dose/Duration Sample size	Follow up* Tolerance* Safety*	Quality Assessment [SIGN Critical Appraisal Checklist]	Outcomes
Maima *et al*., (2014)	*RCT* *4 months (July 1 – October 31 2011)* *Brazil*	*Instituto de Medicina Integral Professor Fernando Figueira* *120 Participants (60 in each group)*	*Magnesium Sulphate I.V 1g/hour* *Magnesium suphate 24hours [60] vs Magnesium sulphate 12 hours [60]*	- - *Safe*	+	*No woman in either group developed eclampsia*
Wacker *et al*., (2005)	*RCT* - *Germany*	*Six health centres* *42 participants*	*Urapidil ; dihydralazine* *Urapidil (12.5 – 25mg) vs Dihydralazine (5mg) Urapidil*	*Four (4) follow ups* *1 report of headache in the Urapidil group; 6 reports of adverse occurrences in the dihydralazine group.*	+	*Both drugs were effective at lowering BP.* *Urapidil showed better tolerability and controllability in patients with pre-eclampsia*
Poston *et al*., (2006)	*RCT* *2 years (August 6 2003 to June 27 2005)* *United Kingdom*	*Twenty Hospitals* *2410 participants (1199 in intervention group vs. 1205 in placebo group)*	*Vitamin C + Vitamin E* *Vitamin C (1000mg)+ Vitamin E (400 IU) vs. Placebo*	- - -	+	*Incidence of pre-eclampsia similar in both treatment and placebo group (15%[n=181] vs. 16%[n=187], 95%CI 0.80 – 1.17)*
Yeo (2009)	*RCT* *From 18 weeks of pregnancy till delivery* *USA*	*124 Participants (64 in walking group vs. 60 in stretching group)*	*Exercise – Walking; Stretching* *40 minutes duration five times a week* *Walking (64) vs. Stretching (60)*	- - -	+	*Incidence of pre-eclampsia was 14.6% (95% CI, 5.6 to 29.2) in the walking groups as against 2.6% (95% CI; 0.07 to 13.8) in the stretching group. Diastolic BP increased by 4mmHg in the walking group while there was no significant change in the stretching group.* *Systolic BP reduced by 4mmHg in the stretching group and there was no significant change in the walking group.*
Chapell *et al* (1999)	*RCT* *UK*	*283 participants (141 in intervention group vs. 142 in placebo group)*	*Vitamin C + Vitamin E* *Vitamin C (1000mg) + Vitamin E (400 IU) vs. Placebo.*	- - -	+	*Pre-eclampsia occurred in 11(8%) of the 141 women in the intervention group and 24 (17%) women in the placebo group*
Gracia *et al* (2006)	*RCT* *1 year (December 2003 – November 2004)* *Republic of Panama*	*200 participants (100 in each group)*	*I.V Hydralazine vs. I. V. Labetalol Hydralazine (5mg) vs. Labetalol (20 mg then increased up to a maximum of 300mg)*	- *Well tolerated* *Safe with few cases of tachycardia and palpitations*	+	*No significant difference observed for maternal hypotension or persistent severe hypertension.* *No increase in BP*
Dharwaldkar *et al* (2014)	RCT 2 years (2011 – 2013) India	80 participants (40 pre-eclampsia vs. 40 hypertension) Yenepoya medical college and hospital, Mangalore	Labetalol vs Methyldopa For pre-eclampsia patients (20 labetalol vs. 20 methyldopa)	1 follow-up in patients soon to deliver while patients with uncontrolled BP wee closely monitored - -	+	There was a greater drop in BP in the Labetalol group than in the methyldopa group (A drop in systolic/diastolic BP of 8.7/7.2mmHg at 48 hours and 16.8/13.2mmHg at day 5 in the labetalol group vs. 1.5/2.2mmHg at 48 hours and 8.3/6.6mmHg at day 5 in the methyldopa group)
Bijvank *et al* (2015)	RCT 2 years 9 months (March 2002 – November 2005) Netherlands	30 participants (15 in each group) University Medical Center, Rotterdam	I.V Ketanserin (15) vs I.V dihydralazine (15) Ketanserin 100mg in 50ml glucose 5% vs. dihydralazine 50mg in 50ml NaCl 0.9%	- Dihydralazine associated with some severe adverse effects	+	Dihydralazine was significantly more effective at lowering BP than ketanserin. Hypertension persisted in only 13.3% of patients in the hydralazine group as against 73.3% in the ketanserin group

Wacker *et al* (2005) carried out a prospective randomized trial comparing dihydralazine and urapidil in six clinical centers across Germany. Forty two participants took part in the trial. They reported that both drugs were effective at lowering blood pressure although urapidil showed better tolerability and controllability than dihydralazine. This is in conformity with other studies that have reported on the haemodynamic unpredictability of dihydralazine (Magee *et al*., 2003; Howart *et al*., 1997). There was one report of headache in the Urapidil group while six participants reported adverse reactions with the use of dihydralazine. Systolic and diastolic BP were reduced by approximately 20mmHg in both groups. In each group however, seven women suffered pregnancy induced hypertension alone. Pre-eclampsia was observed in thirteen patients in the urapidil group with one case being severe while fifteen participants in the dihydralazine group were observed to have developed pre-eclampsia. Though the researchers in this study reported both anti-hypertensives as effective in the management of pre-eclampsia, the evidence found in this study does not support their conclusions. More than half of participants in each group developed pre-eclampsia and this puts into question the reliability of their findings. Though the researchers in this study reported a 20mmHg in both systolic and diastolic BP in both groups, perhaps this reduction was observed in the participants who did not develop pre-eclampsia during the study period. It is probable that the few individuals without pregnancy-induced hypertension or pre-eclampsia were those individuals already taking oral antihypertensive medications before study recruitment. Nine women were already being treated with oral anti-hypertensives before recruitment and this may have allowed an overestimation of their results. Also, there is a possibility of bias being introduced to the study design as investigators were not blinded to the study protocol.

Safety and Efficacy of Pharmacological Regimen in Pregnancy

Gracia *et al* (2006) in their study carried out a randomized controlled trial investigating the safety and efficacy of labetalol and hydralazine in the management of severe hypertension in pregnancy. Two hundred participants were recruited to receive intravenous hydralazine or labetalol with the primary end point being to lower BP and maternal hypotension. They reported that there was no significant difference in both maternal hypotension and persistent sever hypertension in both groups; however, two women developed severe hypotension. Also, there were few cases of persistent severe hypertension and maternal hypotension but the cases were negligible and do not affect the conclusions of the study findings. Labetalol was found to be safer than hydralazine as palpitations (p=0.01) and tachycardia (p=0.05) were more prominent in the hydralazine group than in the labetalol group. Reports from this study were similar to findings from other randomized controlled trials that have evaluated the efficacy of hydralazine and labetalol in the management of severe hypertension in pregnancy (Bhorat *et al*., 1996; Mabie *et al*., 1987). Both medicines were reported to be safe and well tolerated as cases of tachycardia and palpitations did not exceed 10% (Gracia *et al*., 2006). A possible limitation to the Gracia *et al*. (2006) study was the possibility of bias that may have been introduced to the study protocol as the study was not blinded due to logistic and economic constraints. Dharwaldkar *et al* (2014) assessed the safety and efficacy of labetalol and methyldopa in the management of mild to moderate cases of pregnancy induced hypertension. Their study was carried out in India and the researchers recruited eighty participants from an anti-natal clinic to partake in the study. Patients were equally randomized into the labetalol group and methyldopa group, forty women in each group. Also in each group, there was an equal number of patients with gestational hypertension and pre-eclampsia. Results from their findings showed there was a greater drop in BP in the Labetalol group than in the methyldopa group. There was a drop in systolic and diastolic BP of 8.7mmHg and 7.2mmHg at 48 hours and 16.8mmHg and 13.2mmHg at day 5 in the labetalol group compared to a drop in systolic and diastolic BP of 1.5mmHg and 2.2mmHg at 48 hours and 8.3mmHg and 6.6mmHg at day 5 in the methyldopa group. Labetalol had a better effect on the control of blood pressure and also has a quick onset of action compared to methyldopa. Over a half of participants in the methyldopa group further received other antihypertensive treatment (Nifedipine and phemobarbitone) to help control their BP while only about 22.5% of women in the labetalol group received IV labetalol and phenobarbitone. The study by Dharwaldkar *et al* (2014) clearly shows that labetalol was a more effective drug in the management of pregnancy induced hypertension however their findings were in contrast to reports from other studies where it was reported that labetalol did not control hypertension in over 88% of women administered the drug within the first 24 hours (Cruickshank *et al*., 1992). Other studies have also found labetalol ineffective in the control of pregnancy induced hypertension (Lardoux *et al*., 1983; Michael., 1979). Furthermore, Dharwaldkar *et al* (2014) reported that labetalol was associated with fewer side effects than methyldopa. Safety reports of both drugs were in conformity with reports from other studies where it was also reports that adverse event with labetalol was lower than with methyldopa (Verma *et al*., 2012; El-Qarmalawi *et al*., 1995).

Effectiveness of Anti-Hypertensive Agents in Severe Pre-eclampsia

Bijvank *et al*., (2015) carried out a study to determine the definitive position of ketanserin and dihydralazine in the treatment of severe hypertension in early onset pre-eclampsia. Their study was carried out at the obstetrical care unit of the University medical center in Amsterdam. Thirty women were randomly assigned using block randomization to receive either dihydralazine or ketanserin. A finding from this study was that dihydralazine was significantly more effective at lowering blood pressure than ketanserin. However, more significant maternal side effects such as increased heart rate, tachycardia, nausea and vomiting were experienced with the use of dihydralazine. The dosing regimen was changed after some patients developed maternal hypotension and subsequently other medications were introduced when hypotension persisted. Five women in the ketanserin group and four women in the dihydralazine group received I.V magnesium sulphate. Ketanserin was associated with less severe side effects compared to dihydralazine. Severe hypertension persisted with the use of ketanserin and the study had to be stopped because of patient safety. A rescue medication, nicardipine, a calcium channel blocker had to be introduced to help control blood pressure. Ketanserin showed a better safety profile than dihydralazine but was highly ineffective among the study population involved in the Bijvank *et al*., (2015) trial.

Other studies have also reported on the inefficacy of ketanserin in the management of severe hypertension in early onset pre-

eclampsia (Duley *et al*., 2013; Hanff *et al*., 2005; Steyn and Odendaal, 2000). It is evident from these studies that ketanserin has a high failure rate and less effective than any other antihypertensive medication used in the management of hypertension in pregnancy. Based on the development of severe adverse effects with the use of dihydraliazine and the inefficacy of ketanserin in this study, Bijavank *et al*., (2015) concluded that they do not support the use of either drug in the management of severe hypertension in early onset pre-eclampsia. Furthermore, the study was not sufficiently powered to allow prolongation of the study period and had to end abruptly due to the development of adverse events. An estimated 27 participants in each group was required to obtain a study power of 90%.

The Impact of Anti- Oxidants

Two studies investigated the effects of anti-oxidants (Vitamin C and Vitamin E) in the occurrence of women at increased risk of pre-eclampsia but with contrasting results. Chappelle *et al*., (1999) carried out a randomized trial in 283 women identified at increased risk of pre-eclampsia and were randomly assigned Vitamin C at a dose of 1000mg per day and Vitamin E 400IU per day against placebo. The number of women who developed pre-eclampsia differed significantly between the control (17%) and vitamin groups (8%); adjusted odds ratio 0.39[95% CI 0.17 – 0.90, p=0.02]. Conclusions from their findings were that supplementation with vitamins C and E in women at increased risk of pre-eclampsia had great beneficial effects at reducing the development of pre-eclampsia among pregnant women. Their conclusions were in contrast to other studies that have reported no clinical benefit in supplementation with vitamins in the management of pre-eclampsia (Stratta *et al*., 1994; Gulmezoglu *et al*., 1997; Poston *et al*., 2006). A limitation to this study was that the study was not sufficiently powered to allow a true representation of the effects of vitamin supplementation in women at risk of developing eclampsia in pregnancy.

Poston *et al* (2006) in their study investigated the potential benefit of supplementation with vitamins C and E in pregnant women at risk of pre-eclampsia. Their study was a randomized placebo-controlled trial involving 2410 participants identified at being at a high risk of developing pre-eclampsia. The women were randomized into intervention (1119) groups and placebo (1205) groups. Participants in the intervention group were administered 1000mg Vitamin C and 400IU Vitamin E daily from the second trimester of pregnancy till delivery. The finding from their investigation was that the incidence of pre-eclampsia was similar in both the treatment and placebo groups; 15% in the treatment group as against 16% in the placebo group RR 0.97 [95% CI 0.80 -1.17]. Poston *et al* (2006) concluded that supplementation with vitamins C and E does not prevent pre-eclampsia in women and are against high doses of antioxidant use in pregnancy as its use has been found to be associated with a high delivery of low birth babies. Though their findings were in conformity with other studies that also reported vitamins C and E ineffective in the prevention of pre-eclampsia in pregnancy (Stratta *et al*., 1994; Gulmezoglu *et al*., 1997), it should however be stated that only 32% of participants took all of their tablets and this may have affected the result of this study. Participants were not totally compliant with their drug use as only about 80% of women took at least 50% of their tablets while 6% of women did not take either of their tablets.

Impact of Exercise as an Adjunct to Pharmacological Intervention

One study examined the effect of exercise in the prevention of pre-eclampsia among pregnant women (Yeo *et al*., 2009). The study compared a walking exercise to a stretching exercise in sedentary women at high risk of developing pre-eclampsia or in women who have previously had pre-eclampsia. 124 women partook in the trial and were randomly assigned into the walking group (64) and stretching group (60). Both groups engaged in the assigned exercise five times a week starting from 18 weeks gestation till delivery. Women in the walking group exercised an average of 36 (SD, 5.8) minutes at 18 weeks gestation, 33.7 (SD, 6.6) minutes at 28 weeks gestation, and 31.3 (SD, 11.8) minutes at the last week of the intervention. On average, participants in the walking group exercised within target heart rate range of 35% at 18 weeks gestation but below the target range at 28 weeks to (21.8% ;SD, 25%), and back to target range of 17% (SD, 25%) at the last week of the intervention. Though participants in the walking group exercised, the intensity dropped as pregnancy advanced. Participants in the stretching group engaged in stretching exercises following a 40minutes video tape. In total, walkers tracked on average 7,790 steps (SD=3,890) a day, compared to 5,355 steps (SD=3,044) a day for stretchers. Yeo *et al*, 2009 in their study discovered that walkers exercised less frequency than stretchers as pregnancy advanced and although there was no statistically significant difference in the changes in blood pressure between both groups, participants in the stretching group experienced more favorable changes in blood pressure as pregnancy advanced than those in the walking group. Perhaps, the critical factor to this difference is adherence to the study protocol. Findings from this study suggest that the type of exercise and stage of pregnancy influences adherence to exercise and impacts on the levels of risk of developing pre-eclampsia. The incidence of pre-eclampsia was 14.6% (95% CI, 5.6 to 29.2) in the walking groups as against 2.6% (95% CI; 0.07 to 13.8) in the stretching group while the incidence of gestational hypertension was 22 % (95% C.I., 8.7 to 35.2) in the walking group and 40% (95% CI, 23.2 to 55.8) in the stretching group. Yeo *et al* (2009) concluded that exercise is effective at mitigating the risk of pre-eclampsia in pregnancy. Though studies on the effects of exercise in management of pre-eclampsia is limited, results from this study is in agreement with reports from other studies that have examined the effects of exercise and the risk of pre-eclampsia (Lu and Kuo, 2003; Motivala *et al*., 2006; Narendran *et al*., 2005).

Pharmacological and Non Pharmacological Options for Intervention

Pharmacologic intervention appears to be the most effective option used in the management of pre-eclampsia, however the choice of drug is context specific in relation to individual countries and determined by the type of antihypertensive drugs licensed and available in each country. Dihydralazine appears to be the most readily available antihypertensive drug available globally, however several efforts have been made to establish an alternative for the management of severe hypertension in pregnancy (Wacker *et al*., 2006). In the United States and United Kingdom, labetalolhas emerged as the best alternative (Magee et a., 2003; Harper and Murnaghan, 1991; Mabie *et al*., 1987). Based on clinical evidence from randomized trials, the National Institute for Health and Care Excellence recommends

the use of labetalol as the first line of treatment in the management of hypertension in pregnancy; however, the agent should only be given after consideration of potential long term side effects of the drug on the mother and foetus have been factored in (NICE Clinical Guideline 107, 2010). Alternative drug treatments recommended by NICE include methyldopa and nifedipine (NICE, 2010). The two studies that compared the use of labetalol with other interventions (methyldopa and dihydralazine) established it as safe and effective at reducing blood pressure in pregnant women (Dharwaldkar *et al* (2014); Gacia *et al*., 2006). Dihydralazine was also found to be effective but concerns regarding its safety in terms of side effects limit its use as a first line antihypertensive agent in the management of hypertension in pregnancy. Methyldopa was also effective but additional agents were needed to reduce blood pressure to target range. There were contrasting reports from the two trials investing the use antioxidants (Vitamin C and E) in the management of pre-eclampsia. Poston *et al* (2006) found antioxidants ineffective in the prevention and management of pre-eclampsia while Chapelle *et al* (1999) found them effective in the management of this condition. NICE however states in the clinical guidance for the management of hypertension in pregnancy (CG 107) that there are high quality evidences available to confirm the ineffectiveness of vitamins in the prevention and treatment of pre-eclampsia and/or its complications (NICE, 2010). In addition, there is high quality evidence on the effectiveness of calcium supplements at preventing pre-eclampsia although the level of effectiveness is based on the pre-eclampsia risk status of the woman and diet. This was evidenced in a systematic review carried out by Hofmery *et al*., (2014) involving 15,730 participants where it was reported that the efficacy of supplementing with calcium is greatest in women at high risk of pre-eclampsia. There is no evidence on the effectiveness of magnesium supplementation in the management of pre-eclampsia while the available evidence on the effectiveness of folic acid supplementation in the treatment and management of pre-eclampsia is of poor quality. Few studies have reported potential benefits of folic acid use in the treatment of this condition. There is a prospective cohort study available in literature assessing the association between folic acid supplementation and pre-eclampsia (Wang *et al*., 2015). 10,041 pregnant women were recruited to per take in the study and it was found that women supplementing with folic acid had a reduced risk of pre-eclampsia (OR=0.61, 95% CI: 0.43–0.87).
Lifestyle interventions such as diet and rest have also been investigated in the management of pre-eclampsia. Though there are very limited studies evaluating the effectiveness of rest in the prevention of hypertensive disorders, a systematic review of two randomized controlled trials involving 106 pregnant participants reported that rest, in addition to nutritional supplement reduced the risk of gestational hypertension (RR 0.15; 95% CI 0.04 to 0.63) and pre-eclampsia(RR 0.13; 95% CI 0.03 to 0.51) (Meher and Duley, 2006). Weight management according to some researchers is presumed to help in the prevention of hypertension (Bacon *et al*., 2004) however, no evidence was found in literature assessing the effectiveness of weight management during pregnancy.

The prophylactic treatment with low-dose aspirin has been reported to be associated with a reduced risk of pre-eclampsia as evidenced in two systematic reviews asserting their safety and efficacy (Duley *et al*., 2007; Askie *et al*., 2007). These reviews however stated that the ratio of benefits to risk is dependent on the number needed to treat to prevent pre-eclampsia (Duley *et al*., 2007; Askie *et al*., 2007). Other pharmacological agents that have been investigated in the prevention and management of pre-eclampsia include diuretics, low molecular weight heparins, progesterone and nitrous oxide agents (Meher and Duley, 2007; Churchill *et al*., 2007). There are very few high quality studies that have examined the effects of these agents in the management of the condition. Current evidence on the use of nitric oxide agents show no efficacy on its use in the reduction of BP in pregnancy (Meher and Duley, 2007). Also, with the use of progesterone, there was no statistically significant difference in the reduction of blood pressure between then intervention and control group according to a systematic review of two trials involving 296 women (Meher and Duley, 2006b). Diuretics have been found effective in lowering blood pressure according to review by Churchill *et al*., 2007. However, there are reports of it not being beneficial in the reduction of risk of development of hypertensive diseases including pre-eclampsia. A randomized controlled trial by Mello *et al*., (2003) evaluating the efficacy of low-molecular weight heparins in eighty women with angiotensin converting enzyme DD genotype with a history of pre-eclampsia showed a clinically and statistically significant reduction in the development of pre-eclampsia; however, the evidence on the efficacy of this agent is confined to specific groups of women and as such, there is insufficient evidence to confirm the efficacy of this agent in preventing hypertensive disorders during pregnancy.

This review has highlighted some trends and interventions used in the prevention and management of pre-eclampsia in pregnancy. Pharmacological agents appears to be the most effective form of intervention however there are several limitations to the use of some antihypertensive agents. Labetalol appears to be the safest option in the choice of anti-hypertensive drug as it has been found to be both clinically safe and effective in the management of hypertensive disorders of pregnancy (Dharwaldkar *et al*., 2014; Gracia *et al*., 2006). Hydralazine, though effective has some safety issues regarding its use although when the benefit of use outweighs its risk, it is a drug of choice in countries that utilize the agent as the main antihypertensive agent of choice in pregnancy. In countries where the use of labetalol is not licensed, other agents have such as Urapidil has been investigated and found to be as equally as effective as dihydralazine and even safer in its use (Wacker *et al*., 2005).

Conclusion

Though there are risks associated with carrying out experimental studies in pregnant women, particularly with the use of pharmacological interventions, more studies however need to be carried out to evaluate the efficacy of interventions used in the management of pre-eclampsia in pregnancy. Larger sample sizes should also be used to allow sufficient study power which will help in the identification of more robust findings on interventions and the efficacy of the interventions used in the treatment and management of pre-eclampsia in pregnancy. Furthermore, due to the potential risk the use of these interventions may pose to both mother and foetus, participants should be followed up even after delivery to ensure both safety of mother and child. Pharmacologic interventions with anti-hypertensives appear to be the most efficacious intervention often used in the management of pre-eclampsia in pregnancy. Other pharmacological agents such as antioxidants may also be beneficial but their degree of efficacy fall short of

the benefits seen with the use of antihypertensive agents. Care should however be taken with the choice of anti-hypertensives as there some very efficacious agents which nevertheless can produce severe adverse effects, a typical example of this is dihydralazine. Labetalol appears to be the safest and most efficacious antihypertensive agent used in the treatment and management of pre-eclampsia in pregnancy and as such most countries embrace the use of this agent. There are some benefits with the use of non-pharmacological interventions but the evidence of efficacy regarding their use is minimal.

Ethical Approval

Formal ethical approval for this study was granted by the University of Sunderland Ethics Committee.

Conflicts of Interest

There were no potential conflicts of interest in relation to the execution of this project.

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