

Challenges in Prevention of Hypertensive Disorders of Pregnancy and Their Sequelae

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Abstract

Introduction: Globally hypertensive disorders during pregnancy (HDsP), affect around 10% pregnancies, with high chances of dangerous complications, even death during pregnancy birth and postpartum. They also cause fetal growth restriction (FGR), preterm births, low birth weight (LBW) and Perinatal deaths. Attempts need to be made to predict, prevent which presently have limitations.

Objectives: To look into challenges in prevention of HDsP, prevention of complications, mortality in mothers, babies.

Materials and Methods: Studies, reviews were looked into by available search engines to know what is being tried, challenges in prevention of HDsP, severity. Opinions were also looked into. Experiences were added.

Results: Etiology of HDsP is not yet fully understood, though literature indicates up regulation of inflammatory mediators produced by placenta. Many risk factors have been associated but many women do not have any obvious risk factor. Occurrence of HDsP one pregnancy does not predict HDsP in subsequent pregnancy but very preterm gestation at HDsP is associated with higher probability of HDsP in subsequent pregnancy. HDsP associated mortality is much higher in low income settings compared to high income. Quest for biomarkers for prediction continues. Various preventive mortalities are being tried.

Conclusion: Prevention of HDsP remains a great challenge, more so in developing countries with great need of low cost means for prevention. More research useful for global use is needed. Best of management is also a challenge and research needs to continue.

Keywords: Prevention; Hypertensive Disorders during Pregnancy; Challenges

Introduction

Hypertensive disorders during pregnancy (HDsP) affect around 10% pregnancies worldwide and continue to be one of the leading causes of maternal, Perinatal morbidity and mortality. WHO [1] reported, the incidence of HDsP seven times higher in developing countries and others reported 1.6 to 10 cases per 10,000 deliveries in developed countries and 6 to 157 cases per 10,000 deliveries in developing countries [2]. HDsP caused around 46000 maternal deaths and 1.5 - 2.0 million neonatal deaths annually and over 99% of these deaths were in less developed countries. The risk of a woman dying of pre-eclampsia/eclampsia was reported to be 300 times higher in low income countries (LIC) than that of women in high-income countries (HIC) [3]. HDsP are reported to be responsible for 7% of maternal deaths in some countries, more in others [4]. Khan [5] reported 16% of global maternal mortality due to HDsP annually. Globally

women with HDsP have been reported to have more chances of fetal growth restriction (FGR), preterm births, low birth weight (LBW) and perinatal deaths [6]. Attempts need to be made to predict and prevent HDsP and resultant mortality morbidity of mothers and babies. So, research needs to continue.

Objectives of the Study

To look into challenges in prevention of HDsP, prevention of morbidity and mortality in mothers and babies due to HDsP.

Materials and Methods

Studies, and reviews were looked into by available search engines to know the challenges in prevention of HDsP as well as morbidity mortality of mothers and babies due to HDsP. There was no criteria of inclusion. Whatever was available was looked into. Opinions were also looked into.

Results

Rudra., *et al.* [7] reported that HDsP accounted for 12% of all maternal deaths globally. In the UK, pre-eclampsia affected 6% of pregnant women and of them 2% progressed to eclampsia. Early identification of pre-eclampsia and its appropriate management before the onset of eclampsia was recognized as a way to mitigate the worst outcome for mothers and babies. However seemingly mild cases can developed eclampsia and have multiorgan failure. Sometimes convulsions occur in women with normal blood pressure. Also, a spectacular discrepancy in the incidence of HDsP and associated mortality between low and high income settings has been found [8]. Steegers., *et al.* [9] reported that maternal and neonatal complications were more common in cases of recurrent HDsP compared to the initial episode. Staff., *et al.* [10] reported that women who developed pre-eclampsia were at increased risk of cardiovascular disease in future and the association strengthened with repeat pre-eclampsia, FGR, and preterm onset of the disorder. The mechanisms behind such associations are not clear and a lot of research is needed. Association between micronutrients, medications, food, life style and HDsP has been found. Research continues. The etiology of pre-eclampsia is not yet fully understood, though the literature suggested an upregulation of inflammatory mediators produced by the placenta as a potential causal mechanism [11]. High risk factors for HDsP include nulliparity, obesity, HDsP in past pregnancy, family history of HDsP, preexisting hypertension, kidney disease, diabetes, immune disorders, multiple pregnancy and so on. Season., *et al.* [12] and Roberts., *et al.* [13] reported that the occurrence of preeclampsia in one pregnancy does not necessarily predict the occurrence of preeclampsia in subsequent pregnancies but it's development at early gestation is associated with a higher probably of its recurrence. Lecarpentier., *et al.* [14] reported that decreased urinary placental growth factor (PIGF) at mid-gestation (22 - 26 weeks of gestation) was associated with the subsequent development of preeclampsia-related adverse outcomes at less than 34 weeks of gestation. Presentation of HDsP, their occurrence, severity and deaths due to HDsP, continue to be researched.

Calcium

Disorders of Calcium metabolism, including hypocalcemia during the course of pregnancy in women who later developed preeclampsia have been consistently described, with an inverse relationship between dietary Calcium and occurrence of HDsP [15]. Studies have revealed that Calcium supplements in women with low dietary Calcium reduced the risk of HDsP, associated morbidity and mortality. The most robust randomized trials used 1.5 - 2g daily. Thirteen randomized trials revealed the potential of 1.5 to 2g Calcium carbonate supplementation every day in divided doses in reducing the risk of HDsP by 50% [16]. The reduction in risk was greatest for women at high risk of HDsP and for those with low baseline Calcium intake. However, Cormick and colleagues [17] suggested that everyday 400 - 500 mg Calcium normalized Calcium in low-intake populations too. Sibai., *et al.* [18] reported that if Calcium intake was low, Calcium supplementation reduced the risk of HDsP, but the significance of the effect was influenced by risk status. Hofmeyr., *et al.* [19] reported that Calcium commenced before pregnancy until 20 weeks gestation did not show a significant reduction in recurrence of HDsP compared

with placebo. Fetal Calcium deposition has been shown to peak at 350 mg/day in the third trimester with increased and maternal Calcium absorption to meet the demand [20]. Hence insufficient milk or Calcium intake during pregnancy, common in women with low resources can drain the bone-Calcium enormously, especially with pre-existing low bone density. Garg, *et al.* [21] reported that though chewing betel leaf with lime paste is a good source of Calcium, but could cause adverse outcome for the baby like LBW and FGR because it was taken with Areca nut. Review by Singh, *et al.* [22] revealed that twelve studies found that women receiving Calcium supplementation had half incidence of HDsP than that of women receiving placebo. The risk reduction in seven studies involving only low-risk women was 32% whereas the largest reduction (78%) was found across five studies involving only high-risk women [13]. In a trial held in South Africa [23] Calcium supplementation of 500 mg/day in early pregnancy versus placebo revealed that there was no significant effect. Researchers reported that high doses may not do good in all the women. Research continues.

Aspirin

Stegers, *et al.* [9] reported that low-dose aspirin (LDA) during pregnancy has been found to reduce the risk of preeclampsia but Aspirin given to pregnant women could cross the placenta and go to the fetal circulation. LDA enhances uterine blood flow and tissue perfusion by reducing platelet aggregation and inhibiting vasoconstriction. In a study hundred and eighty women at high risk of pre-eclampsia were prescribed 75 mg aspirin/day and significant association was found between pre-eclampsia or composite adverse outcome [24]. When platelet function was assessed with tests that measured antiplatelet effects of LDA with adherence accounted for, aspirin non-responsiveness was not identified [25]. The high degree of variable response indicated by suboptimal adherence and dosing were more pressing issues. Mone, *et al.* [26] reported that in a study LDA was more cost effective than the Fetal Medicine Foundation screen-and-treat approach for preeclampsia prevention in low-risk nulliparous women. Both strategies were compared with no interventions. Presumed rates of preeclampsia were 3.75% with no intervention and 0.45% with Aspirin use. Results revealed that routine Aspirin was preferred in terms of greater health gains and larger cost savings. It would result in an estimated cost saving of 14.9 million annually, relative to no interventions. Screen and treat approach would result in a smaller cost saving of 3.1 million. Antiplatelet agents were associated with significant reduction in the risk of preeclampsia in moderate risk women and high risk women. Subgroup analysis was conducted by LDA, 60 to 75 mg aspirin per day, higher dose Aspirin and a third category more than 75 mg Aspirin on GH showed no significant effect of higher dose of Aspirin, in nine studies with a significant effect in women receiving LDA and those receiving a higher dose of Aspirin on the incidence of HDsP compared with women receiving placebo or no treatment [27]. Of 14 studies the group taking 60 mg Aspirin every day showed a marginally significant reduction in risk of developing HDsP in eight studies [28]. The groups taking 100 mg/day and 150 mg/day Aspirin showed no significant reduction. Though higher dose groups may have been underpowered to detect a difference owing to the small numbers of studies, there were no significant differences in the incidence of potential adverse effects such as placental abruption or postpartum hemorrhage, but there was a reduction in risk of preterm births, between women receiving antiplatelet agents and those receiving placebo. Chen, *et al.* [29] suggested that Aspirin initiated in the first trimester significantly decreased uterine artery impedance in the 3rd trimester which reflected better placental perfusion.

Antioxidants

The pathogenesis of HDsP has been described as a two-stage process, reduced placental perfusion followed by the release of placental factors that triggered maternal endothelial cell dysfunction, believed to be causative factor of HDsP. Oxidative stress may be a cause of endothelial cell dysfunction. However, subgroup analysis did not identify any high-risk women that would have had benefit from the treatment. This hypothesis was supported by the observations that markers of oxidative stress were present in the maternal circulation of the affected women [30]. So, antioxidants have been proposed for prevention and treatment of HDsP. In a Cochrane review of seven trials involving over 6000 women assessed the effectiveness of antioxidants supplements during pregnancy for prevention of preeclampsia. Supplements included various combinations and doses of vitamin C, vitamin E, Selenium, Halibut liver oil containing vitamin A, fish oil, and Lycopene. Supplementation with any antioxidant during pregnancy was associated with a 39% reduction in the relative risk of HDsP

compared with no treatment or a placebo [31]. In a study there was reduction in SGA infants, with a slight increase in preterm births too [32]. One study revealed that vitamins C and E combined with Aspirin and fish oil on pre-eclampsia there was significant effect of vitamin C and E alone [9]. Lycopene was investigated in one study and was reported to reduce the risk of HDsP by 52%. Folic acid in combination with multivitamins showed a 63% reduction in the risk of developing HDsP [13].

Vitamin D

Steegers, *et al.* [9] reported that vitamin D may protect from HDsP through influences on immune modulation and vascular function. Low maternal serum 25OHD concentrations increased risk of HDsP and vitamin D supplementation lowered the risk. Patients with HDsP displayed lower vitamin D levels in response to seasonal changes. Issues with dose, timing, and duration of supplementation have not been completely addressed. While the pathogenesis of HDsP involves a number of biological processes, there are several hypotheses to suggest how vitamin D affected these processes, including its role in modulating pro-inflammatory responses and decreasing oxidative stress in PE, promoting angiogenesis through Vascular endothelial growth factor (VEGF) and gene modulation, and decreasing blood pressure through the renin-angiotensin system (RAS) [33]. A review by Purswani, *et al.* [33] reported several studies showing association between vitamin D levels and HDsP, although evidence was inconsistent. Vitamin D may prevent HDsP by its effects on immune modulation and vascular function. After clinical trials it was suggested that vitamin D had a potential role in the prevention of HDsP but probably not with vitamin D alone. In one study supplementation with multivitamins and minerals and halibut liver oil (containing 900 IU/d vitamin D) given from 20-weeks gestation reduced the odds of HDsP by 32% [15]. In the other randomized trial 400 women treated with vitamin D (1200 IU/d) and Calcium (375 mg/d) supplements or Placebo at 20 - 24 weeks pregnancy showed significant reduction in the incidence of HDsP in the treated group compared with the placebo group (6% versus 9%). While pregnant women and their neonates are highly vulnerable to vitamin D deficiency which is highly prevalent in all parts of the world. Clinical trials to date have not been able to show an independent effect of vitamin D supplementation in prevention of HDsP.

Other pharmaceutical agents

There is limited high-quality evidence on the use of nitric oxide donors in the prevention of HDsP. Existing evidence showed no reduction in HDsP following use of nitric oxide donors, nitric oxide precursors-L-arginine. Meher, *et al.* [34] reported no significant effect for either oxide donors or precursors with regard to the effects on HDsP. No significant difference in the incidence of severe pre-eclampsia between women receiving nitric oxide precursors and those receiving placebo or no treatment was found. Nahamya, *et al.* [35] reported poor-quality evidence on the use of folic acid in the risk reduction of HDsP. Stephanie, *et al.* [36] reported two studies evaluated new or worsening hypertension and showed similar results with women receiving diuretics had a lower risk of developing new hypertension or worsening of existing hypertension than women receiving placebo or no treatment but the difference was not significant. Women who received Low-molecular-weight heparin (LMWH) had a lower risk of developing pre-eclampsia than those who did not receive. The effect was similar for the development of pre-eclampsia before 34 weeks. Trial RCT provided limited evidence on the effectiveness of LMWH in the prevention of HDsP. The study showed clinically significant reduction in pre-eclampsia and its sequelae in a group of women with previous pre-eclampsia who have demonstrable thrombophilia and who have a specific genotype [24]. There is limited high-quality evidence on the use of progesterone to prevent HDsP. No evidence was identified in relation to the effectiveness of Magnesium too [37].

Diet, food and lifestyle

Liu, *et al.* [38] reported the results of the statin to ameliorate early onset pre-eclampsia T β R/TGF- β receptor TGF- β transforming growth factor- β VEGF vascular endothelial growth factor ZP zona pellucida. It did not show any significant reduction or improvement in clinical outcome. Pravastatin was not associated with reduction in birth weight or head circumference. Adverse neonatal outcomes appeared to be less common in women who received Pravastatin. There is high-quality evidence, examining the effect of Marine oil supple-

mentation using fish oils or algal oils for the prevention of HDsP. No significant difference was found in the incidence of HDsP between the women who were advised to have a low-sodium diet and the women who were advised to continue on a normal diet [9]. No evidence was identified in relation to the effectiveness of energy or protein intake. There is limited evidence that advice to adhere to a low-sodium diet prevented subsequent development of HDsP in women with weight gain and mild hypertension. No evidence was identified in relation to the effectiveness of energy or protein intake [39]. A Cochrane systematic review of one study involving 100 women investigated the effectiveness of Garlic in risk reduction for HDsP with no significant difference in the risk of developing HDsP [9]. A systematic review of two small RCTs showed potential benefit of rest over unrestricted activity in women at moderate risk of GH [15]. Abera [39] reported no identified evidence in relation to the effectiveness of bed rest for reducing the risk of HDsP. No evidence was found in relation to the effectiveness of maintaining a weight within the healthy range. One cross-sectional study and found no association between such shift work and the incidence of HDsP [40].

Management challenges in prevention of severe morbidity and mortality in relative to HDsP

According to the guidelines for the management HPSp in Zimbabwe, women with mild GH should not have received any medication. Yet in a study more than half of the women received some form of medication, may be due to insufficient knowledge. The same was proved by the fact that less than half of the respondents could clearly articulate the definition and management of GH [41]. Hydralazine was given with moderate GH as per the guidelines with cardinal signs of imminent eclampsia [42]. Urinalysis was only being done for those women who had elevated blood pressure though it should have been done for all the pregnant women, an indicator of the lack of resources low quality care. The scarcity of essential resources such as blood pressure equipment, ambulances and staff contribute to the third delay in maternal and neonatal care thus increasing the risk of maternal and neonatal mortality. The delay in receiving care for a woman with HDsP may be due to a variety of factors poorly trained or not sufficiently competent staff who lack understanding of the clinical relevance, lack of drugs, equipment, and other supplies, poor health care financing mechanisms as well as delays in referral to next level. Hospitalization with HDsP for delivery contributed to a relatively large proportion of hospitalizations with severe obstetric complications. Severe complications associated with HDsP are probably among the most difficult to predict and prevent.

Discussion

HDsP are unpredictable multifaceted disorders and can rapidly develop into life-threatening confiscations like eclampsia, HELLP. Preeclampsia kills around 76,000 women and 500,000 babies every year [43]. The mortality rates are high in low-income countries because of lack of quality maternal care. Despite extensive research during the past decade, reliable biomarkers for prediction and early detection of HDsP have not been identified. Based on the results of several randomized trials and systematic reviews published during the past 2 years, no specific medication or supplement can be recommended for prevention of preeclampsia. LDA is recommended to prevent preeclampsia in high-risk pregnant women. However, some individuals are Aspirin nonresponsive, with insufficient antiplatelet effects. The large variations in eclampsia and maternal and neonatal fatality between countries emphasize that inequality and inequity in health care persist. Alongside growing interest in improving community detection, efforts to target quality of care within healthcare facilities are key to reducing morbidity and mortality from HDsP. A significant proportion of poor outcomes may be preventable the continuum of maternal and neonatal care. Intrauterine exposure to Aspirin may have long-term protective effects on childhood blood pressure [44]. It has been demonstrated that defective placentation in pregnancy resulted in dysfunctional uteroplacental circulation and HDsP. This could lead to subsequent cardiovascular diseases for both the mother and her offspring. So, follow up becomes essential. Numerous epidemiological and experimental studies have suggested that the offspring of women with HDsP were at increased risk of cardiovascular complications later in life [9]. So, their follow up is also essential. The only current available HDsP cure is delivery of the dysfunctional placenta, which sheds excessive proinflammatory substances which affected the maternal cardiovascularity [45]. Dysregulated placental function biomarkers [46] were recommended to assess the association between ethnicity and preeclampsia in Australia's diverse multiethnic popula-

tion [47]. The risks of suboptimal outcomes from these disorders might be greater in rural remote locations. Studies in low and middle income countries suggested that improving communication was also essential [7].

Conclusion

Prevention of HDsP in developing countries remains a great challenge. There is a great need for affordable and reliable methods for prediction and prevention of these disorders. Future studies are needed to accurately predict model suitable for use in the developing countries. Best of management is also a challenge.

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