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Preeclampsia: Pathophysiology, Diagnosis and Management

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ABSTRACT

The incidence of hypertensive disorders ranges from 2-8% of all pregnancies and contribute to 9% of maternal mortality in Asia and 12% in India[20,21]. Pre-eclampsia is a pregnancy specific disease characterized by de-novo development of concurrent hypertension and proteinuria, sometimes progressing into a multiorgan cluster of varying clinical features. The pathophysiology of this multisystem disorder [pre-eclampsia], characterized by abnormal vascular response to placentation, is still unclear. Despite great polymorphism of the disease, the criteria for pre-eclampsia have not changed (systolic blood pressure >140 mmHg or diastolic blood pressure ≥ 90 mmHg and 24-hour proteinuria ≥0.3 g). The clinical features and laboratory abnormalities define and determine the severity of pre-eclampsia. The only curative treatment for pre-eclampsia is delivery. Hydralazine had been the first drug of choice for a long time; however, a meta-analysis of clinical trials reported worrisome maternal and fetal side effects with its use. Nifedipine has the advantage of being cost effective, rapid onset of action, long duration of action, oral bioavailability, easier to store and infrequent side effects. Intravenous Labetalol is effective in controlling severe hypertension, but it is not cost effective[22].

INTRODUCTION

Hypertension is the most frequently encountered medical disorder in obstetrics practice & remains a major cause of maternal, fetal & neonatal morbidity & mortality not only in the less developed but also in the industrialized countries. The incidence of hypertensive disorders ranges from 2-8% of all pregnancies and contribute to 9% of maternal mortality in Asia and 12% in India.[20,21.] It has been estimated by the WHO that worldwide approximately 45,000 women will die each year from hypertensive disorders of pregnancy. Pre-eclampsia is a pregnancy specific disease characterized by de-novo development of concurrent hypertension and proteinuria, sometimes progressing into a multiorgan cluster of varying clinical features. The conditions begins after 20 weeks of pregnancy.[5] In severe disease, there may be red blood cell breakdown, a low blood platelet count, impaired liver function, kidney dysfunction, swelling, shortness of breath due to fluid in the lungs, or visual disturbances. [4]

Pre-eclampsia may increase the risk of poor outcomes for both the mother and the baby. If left untreated, it may result in seizures at which point it is known as Eclampsia.[4] Both *Chlamydophila pneumonia and Cytomegalovirus* have been associated with pre-eclampsia and atherosclerosis and may provide a mechanistic link between pre-eclampsia and the recognized cardiovascular risk.[3] Predisposing cardiovascular or metabolic risks for endothelial dysfunction, as part of an exaggerated systemic inflammatory response, might dominate in case of late onset pre-eclampsia. Here the multifactorial pathogenesis of different pre-eclampsia phenotypes has not been fully explained, prevention and prediction are still not possible, and symptomatic clinical management are mainly directed to prevent maternal morbidity (eg: eclampsia) and mortality.[3] Expectant management of women with early onset disease to improve perinatal outcome should not preclude timely delivery- the only definitive cure.[3]

Severe pre-eclampsia is characterized by systolic blood pressure ≥160mmHg and diastolic blood pressure of ≥110mmHg. Severe pre-eclampsia requires prompt treatment to prevent cerebrovascular and cardiovascular complications such as hypertensive encephalopathy, intracerebral hemorrhage and pulmonary edema. It also presents an increased risk of complications for the foetus including prematurity, low birth weight and eventually foetal death. Antihypertensive treatment should be started in women with severe hypertension ≥160 / 110mmHg to reduce the blood pressure between 140-155mmHg systolic and 90-100mmHg

diastolic. Care should be taken not to lower the blood pressure too rapidly so as to avoid reduced renal and placental perfusion and intrauterine hypoxia leading to sudden foetal death.[11]

The optimal management of mild preeclampsia from term (less than 37 weeks' gestation) is controversial. In general, there is considerable disagreement regarding the need for hospitalization versus ambulatory management, the use of antihypertensive drugs, and the use of sedatives. A few studies have reported on the pregnancy outcome in women with mild Pregnancy-Induced Hypertension (PIH) (without proteinuria) remote from term who were randomized to either bed rest at hospital or normal activity at home.[5] By contrast, others reported that early and prolonged hospitalization for patients with mild hypertension remote from term had improved perinatal survival, reduced maternal morbidity, and was cost effective.[30]

Different drugs have been used for acute Blood Pressure (BP) control during hypertensive emergencies in pregnancy. Hydralazine had been the drug of choice for a long time; however, a meta-analysis of clinical trials reported worrisome maternal and fetal side effects with its use [18]. Mainly because of manufacturing shortages, hydralazine is unavailable in many parts of the world. Hydralazine was temporarily withdrawn from the market in the early 1990s and Methyldopa may take a few days for onset of hypotensive effect. This decline of Hydralazine has led to the arrival of Labetalol and Nifedipine for control of BP in hypertensive emergency during pregnancy. Both Nifedipine and Labetalol have demonstrated comparable efficacy and a lower risk of overshoot hypotension and fetal distress when compared with Hydralazine in randomized clinical trials.[10] To date there have been few randomized double blind trial of oral Nifedipine and intravenous Labetalol in the acute management of hypertensive emergencies of pregnancy. Currently, all three drugs have been proposed as first-line alternatives to one another.[19] The selection of these drugs is based on convenience of using the drug, local availability, and cost.[18]

PATHOPHYSIOLOGY

The exact pathogenesis of pre-eclampsia remains uncertain. Pre-eclampsia is thought to result from an abnormal placenta, the removal of which ends the disease in most cases [4]. During normal pregnancy, the placenta vascularizes to allow for the exchange of water, gases and solutes, including nutrients and wastes, between maternal and fetal circulations [8]. Abnormal

development of the placenta leads to poor placental perfusions. The placenta of women with pre-eclampsia is abnormal and characterized by poor trophoblastic invasion[8]. It is thought that this results in oxidative stress, hypoxia, and the release of factors that promote endothelial dysfunction, inflammation, and other possible reactions.[8]

The clinical manifestations of pre-eclampsia are associated with general endothelial dysfunction, including vasoconstriction and end-organ ischemia [8]. Implicit in this generalized endothelial dysfunction may be an imbalance of angiogenic and anti-angiogenic factors [4]. Both circulating and placental levels of soluble forms-like tyrosine kinase-1 (sFlt-1) are higher in women with pre-eclampsia than in women with normal pregnancy[8]. Sflt-1 is an anti-angiogenic protein that antagonizes Vascular Endothelial Growth Factor (VEGF) and Placental Growth Factor (PlGF)[3]. Soluble endoglin (sEng) has also been shown to be elevated in women with pre-eclampsia and has anti-angiogenic properties; much like sFlt-1 does.[8]

Oxidative stress may also have an important part in the pathogenesis of pre-eclampsia. The main source of Reactive Oxygen Species (ROS) is the enzyme Xanthine Oxidase (XO) and this enzyme mainly occurs in the liver[34,35]. One hypothesis is that the increased catabolism of purine from placental hypoxia results in increased Reactive oxygen species [ROS] production in the maternal liver and release into the maternal circulation that causes endothelial cell damage.[12]

Abnormalities in the maternal immune system and insufficiency of gestational immune tolerance seem to play major roles in pre-eclampsia. One of the main difference that found in pre-eclampsia is a shift toward Th_1 responses and the production of IFN-γ. It has been documented that fetal cells such as fetal erythroblasts as well as cell-free fetal DNA are increased in the maternal circulation in women who develop pre-eclampsia[19]. Above findings have given rise to the hypothesis that pre-eclampsia is a disease, by which a placental lesion such as hypoxia allows increased fetal material into the maternal circulation, that will leads to an immune response and endothelial damage, and that may results in pre-eclampsia and eclampsia.[23]

One hypothesis for vulnerability to pre-eclampsia is the maternal-fetal conflict between the maternal organism and fetus.[13] After the first trimester trophoblasts enter the spiral arteries of the mother to alter the spiral arteries and thereby gain more access to maternal nutrients.[13] It

is hypothesized that the developing embryo releases biochemical signals that results in the woman developing hypertension and pre-eclampsia so that the fetus can benefit from a greater amount of maternal circulation of nutrients due to increased blood flow to the impaired placenta[13]. This results in conflict between maternal and fetal fitness and survival because the fetus is invested in only its survival and fitness while the mother is invested in this and subsequent pregnancies.[13]

In normal early embryonic development, the outer epithelial layer contains cytotrophoblast cells, a stem cell type found in the trophoblast that later differentiate into the fetal placenta. These cells differentiate into many placental cells types, including extravillous trophoblast cells [32]. Extravillous trophoblast cells functions as to prevents maternal vasoconstriction in the spiral arteries and allow continued blood and nutrient supply to the fetus.[14]

In pre-eclampsia, abnormal expression of chromosome 19 microRNA cluster (C19MC) in placental cell lines reduces extravillous trophoblast migration[15]. It will lead to low blood flow and low nutrient supply to the fetus.[14]

CAUSES OF PRE-ECLAMPSIA

There is no definitive cause of pre-eclampsia, they are related to a number of factors. Some of these factors include [4]:

- Abnormal placentation
- Immunologic factors
- Individuals with preexisting hypertension, obesity
- Dietary factors, eg: calcium supplementation in areas where dietary calcium intake is low has been shown to reduce the risk of preeclampsia.[6]
- Environmental factors[7]

Physiological changes like alterations in the interaction between the maternal immune response and the placenta, placental injury, endothelial injury, oxidative stress, disseminated intravascular coagulation.[3,8]

MANAGEMENT OF PRE-ECLAMPSIA

Since pre-eclampsia is a disease of the placenta, it is only with delivery of the placenta that the disorder will start to resolve. Timing of the delivery can be challenging as the clinician must weigh the risk of fetal morbidity from preterm delivery with the risk of both fetal and maternal morbidity in the face of worsening pre-eclampsia[33]. In addition, treatment with intravenous magnesium is associated with a significant reduction in the risk of initial or recurrent eclampsia seizure and should be given to women with severe features of pre-eclampsia.[17]

Women presenting with new-onset hypertension should be screened for pre-eclampsia. Severe hypertension should be treated urgently and aggressively. Both Nifedipine and Labetalol are effective medications and may be used safely in breastfeeding. ACE inhibitors are also safe in breastfeeding and may be used in postpartum women [1]. Various other drugs have been used for acute blood pressure control during hypertensive emergencies in pregnancy. Hydralazine had been the drug of choice for a long time, but it is withdrawn from the market due to its worrisome maternal and fetal side effects. [1]

Severe preeclampsia requires prompt treatment to prevent cerebrovascular and cardiovascular complications such as hypertensive encephalopathy, intracerebral haemorrhage and pulmonary edema [3]. It also presents an increased risk of complications for the foetus including prematurity, low birth weight and foetal death.[27]

Antihypertensive treatment should be started in women with severe hypertension ≥160/110mmHg to reduce the blood pressure between 140-155mmHg systolic and 90-100mmHg diastolic[19]. Care should be taken not to lower the blood pressure too rapidly so as to avoid reduced renal and placental perfusion and intrauterine hypoxia leading to sudden foetal death. The most commonly used antihypertensive drugs for control of severe hypertension in preeclampsia are Nifedipine, Labetalol and Hydralazine[3]. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are contraindicated as they affect fetal development. The goal of treatment of severe hypertension in pregnancy is to prevent cardiovascular, kidney and cerebrovascular complications[33]. The target blood pressure has been proposed to be 140-160mmHg systolic and 90-105mmHg diastolic, although values are variable.[33]

Nifedipine has the advantage of being cost effective, rapid onset of action, long duration of action, oral bioavailability, easier to store and infrequent side effects. Intravenous Labetalol is effective in controlling severe hypertension. It can be given when the patient is unconscious but it is not cost effective.[22]

A recent meta-analysis demonstrated that IV Hydralazine for the control of severe hypertension in pregnancy was associated with significant maternal hypotension, placental abruption, maternal oliguria and adverse effect on foetal heart rate [2]. They conclude that they do not support the use of Hydralazine as the first line treatment. Hydralazine is not available in Indian market. Hence the aim of the present study is to compare the two most commonly used drugs in India, i.e. oral Nifedipine and IV Labetalol in terms of time taken to lower the blood pressure, dosage required, adverse effects, the maternal and perinatal morbidity and mortality, cost effectiveness and ease of administrations.[16]

A trial published in 1999 comparing oral Nifedipine with intravenous Labetalol regimens in 50 peripartum women with severe hypertension has shown that the blood pressure goal was achieved significantly more rapidly, and urine output was also higher, with Nifedipine. Nifedipine also increased the cardiac index.[9]

It is common practice to stabilise severe maternal hypertension prior to delivery by labour induction or caesarean section to avoid dangerous fluctuations or exacerbations of blood pressure during labour or anaesthesia. Hence speedy but safe blood pressure control will allow the definitive treatment of delivery of the baby to be carried with minimum delay in many cases of severe hypertension in late pregnancy[28]. While providing treatment it is necessary to assess mother's organ systems, management of severe hypertension, and prevention and treatment of eclamptic seizures[10]. Bed rest has not been found to be useful and is thus not routinely recommended.[38]

For the prevention of eclampsia in severe pre-eclampsia, intrapartum and postpartum administration of magnesium sulfate is recommended. Magnesium sulfate is also provided for the treatment of eclampsia over other anticonvulsants. Magnesium sulfate acts by interacting with N-methyl-D-aspartate (NMDA) receptor.[10]

We sought to evaluate oral Nifedipine versus intravenous Labetalol regimens in their speed, efficacy and tolerability in the acute control of severe hypertension of pregnancy. [3]

PREVENTION

Preventive measures against pre-eclampsia have been heavily studied. Because the pathophysiology of pre-eclampsia is not understood well, prevention remains a complex issue. Below are some of the currently accepted recommendations.[33]

Diet

Supplementation with a balanced protein and energy diet does not appear to reduce the risk of pre-eclampsia[24]. Further, there is no evidence that changing salt intake has an effect [25]. Drink 6-8 glasses of water a day. Avoid eating fried foods and junk food.

Vitamin C, E, and D is not included in the prevention of pre-eclampsia, because they have no effect.

In case of dietary calcium intake is low, calcium supplementation of at least 1 gram per day is provided during pregnancy. [26]

Aspirin

Taking aspirin is associated with a 1% to 5% reduction in pre-eclampsia and a 1% to 5% reduction in premature births in women at high risk[27]. World Health Organization recommends low dose aspirin for women who are at high risk of pre-eclampsia and it should be started before 20 weeks of pregnancy[28]. Benefits are less if started after 16 weeks.[23]

Physical activity

There is insufficient evidence to recommend either exercise [29]or strict bedrest[30] as preventive measures of pre-eclampsia.

Smoking cessation

It is recommended that smoking be stopped prior to, during and after pregnancy[31]. Studies suggest that marijuana use in the months prior to or during the early stages of pregnancy may interfere with the normal placental development and consequently increase the risk of preeclampsia. [32]

Low-Salt Diet and Diuretics

Many articles have been published regarding the risks and benefits of using either low-salt diet or diuretics in pregnancy. The only randomized trial of low-salt diet in pregnancy did not demonstrate any reduction in the incidence of gestational hypertension in the study group[22]. In addition, a meta-analysis of nine randomized trials comprising more than 7000 subjects regarding the use of diuretics in pregnancy revealed a decrease in the incidence of edema and hypertension but not in the incidence of preeclampsia. Thus, there is no clear evidence to suggest that prophylactic use of diuretics reduces the incidence of preeclampsia.[23]

CONCLUSION

A hypertensive disorder of pregnancy is one of the life threatening complications encountered in obstetrics. Management of hypertension during pregnancy is difficult because sudden reduction of Blood pressure leads to further complications like uteroplacental insufficiency & intrauterine fetal death. Therefore, it is necessary to provide antihypertensive agent for controlling severe hypertension in pregnancy.[17]

Present studies compare the efficacy of oral Nifedipine and IV Labetalol in reaching the therapeutic goal. From the results of various studies, we can well conclude that both the Labetalol &Nifedipine regimen are equally effective & well tolerated when used for the rapid control of blood pressure in severe hypertension in pregnancy. But Nifedipine may be preferable as it is a simple, flat dose and is an oral regimen which should be convenient to administer. Reports are showing that parallel use of Nifedipine will leads to circulatory collapse and led to a trust deficit for use of Nifedipine among health care providers, some studies says that Nifedipine is safe during late pregnancy. None of the studies had not yet reported any serious adverse effect in using Nifedipine, it is safe and efficacious. [29]

Current research focuses on the prediction of onset of pre-eclampsia or even severe preeclampsia so as to allow early management and improve the morbidity and mortality associated with this disease.[35]

REFERENCES

1. Dr.Badaldhali, etal. "A randomized trial 0f intravenous labetalol and oral nifedipine in severe pregnancy induced hypertension". 2012 Dec; 1(1): 42-46.
2. Shekhar et al, "Oral nifedipine versus intravenous labetalol on severe hypertension during pregnancy: a systemic review and metaanalysis". 26 June 2015; Volume 122: 40-47.
3. Steegers EA, Von Dadelszen P, Duvekot JJ, PijnenborgR.Pre-eclampsia Lancet, 2010, 21;376(9741);631-44
4. Al-Jameil, N; Aziz Khan, F; etal. "A brief overview of preeclampsia." Journal of clinical medicine research.(February 2014) ; 6 (1): 1-7.
5. "Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Tasks Force on Hypertension in Pregnancy" Obstet Gynecol.Nov 2013; 122 (5): 1122-31.
6. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011. ISBN 978-92-4-154833-5.
7. Jun Wu; CizaoRen; Ralph J. Delfino; Judith Chung; et al. (2009). "Association Between Local Traffic-Generated Air Pollution and Preeclampsia and Preterm Delivery in the South Coast Air Basin of California".Environmental Health Perspectives. Archived from the original on 2009-07-19.
8. Mustafa Reem; Ahmed, Sana; Gupta, etal. (2012). "A Comprehensive Review of Hypertension in Pregnancy". Journal of pregnancy.2012:1-19.
9. Bartsch, E; Medcalf, KE; Park, AL; Ray, JG; High Risk of Preeclampsia Identification, Group "Clinical risk factors for pre-eclampsia determined in early pregnancy: systemic review and metaanalysis of large cohort studies."(19 April 2016) ; BMJ.353
10. Garg, Amit X; Nevis, Immaculate F; McArthur, Eric et al. (2014). "Gestational Hypertension and Preeclampsia in Living Kidney Donors." New England Journal of Medicine. 372.
11. Drife, James O; Magowan, Brian. Clinical obstetrics and gynecology. Edinburgh; New York: Saunders. (2004).pp.367-370.
12. McMaster-Fay RA(2008)."Preeclampsia: a disease of oxidative stress resulting from the catabolism of DNA to uric acid by xanthine oxidase in the maternal liver; a hypothesis."Bioscience Hypothesis. 1:35-43.
13. Redman CW, Sargent IL."Latest Advances in Understanding Preeclampsia." Science.2005 ;308(5728): 1592-1594.
14. D, Wng W."Mini-review: Human Placental MicroRNAs and Preeclampsia." Biology of Reproduction. 2013;88(5):1-11.
15. Ouyang Y: Mouillet JF: Coyne C.B: Sadovsky Y. (2013)."Review: Placenta-specific microRNAs in exosomes- Good things come in nano-packages." Trophoblast Research.28.
16. Longo, Dn L.(2012). Harrison's principles of internal medicine. New York: McGraw Hill.pp.55-61.
17. "BBC News-Preeclampsia predicted using test during pregnancy". 2011-11-12. Archived from the original on 2011-11-18.
18. Magee LA, Cham C, Waterman EJ, Ohlsson A, etal. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis.BMJ 2003;327:955-60
19. Duley L, Henderson- Smart DJ, MeherS.Drugs for treatment of very high blood pressure during pregnancy. The Cochrane Database of Systematic Reviews 2006;3.
20. Khan KS, Daniel W, Say L, et al. WHO analysis of causes of maternal death: a systemic review. Lancet 2006;367:1066-74.
21. Kausar R. Maternal mortality in India: magnitude, causes and concerns. Lndmedica 2005-06;2(2)
22. Steegeers EAP, VanLakwijk HPJM, Jongsma HW et al: Pathophysiological implications of chronic dietary sodium restriction during pregnancy: A longitudinal prospective randomized study. Br J Obstet Gynecol 1991; 98:980.
23. Collins R, Yusuf S, Peto R: Overview of randomized trials of diuretics in pregnancy. Br Med J 1985; 290:17
24. Ota, E; Hori; Mori, R; Tobe-Gai, R; Farrar, D "Antenatal dietary education and supplementation to increase energy and protein intake." The Cochrane database of systematic reviews(2 June 2015); (6)
25. Duley L, Henderson- Smart D, Meher S." Altered dietary salt for preventing pre-eclampsia, and its complications." The Cochrane database of systemic reviews Oct 19, 2005; (4): CD005548.

26. "Preeclampsia-Eclampsia". Diagnosis and management of pre-eclampsia and eclampsia. Armenian Medical Network. 2003.
27. Duley L, Henderson-Smart DJ, MeherS, King JF (2007). "Antiplatelet agents for preventing pre-eclampsia and its complications."Cochrane Database Syst Rev.2007; (2):CD004659
28. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia.2011.
29. Meher S, Duley L (2006). Meher, Shireen, ed. "Exercise or other physical activity for preventing pre-eclampsia and its complications." Cochrane Databases of systemic reviews (2):CD005942.
30. Meher S, Duley L (2006). Meher, Shireen, ed. "Rest during pregnancy for preventing pre-eclampsia and its complications in women with normal blood pressure." Cochrane Databases of Systemic Reviews (2).
31. Whitworth, M; Dowswell, T "Routine pre-pregnancy health promotion for improving pregnancy outcomes." The Cochrane database of systemic reviews(Oct 7, 2009). (4): CD007536.
32. Albert Dekker Gustaaf, Lee Shalem Y, North Robyn A, et al. "Risk Factors for preterm birth in an International Prospective Cohort of Nulliparous Woman." PLOS ONE .7:e39154
33. Wikipedia; https: // en.wikipedia.org/wiki/pre-eclampsia.
34. Poggio ED, Braun WE, Davis C. The science of stewardship: due diligence for kidney donors and kidney function in living kidney donation -- evaluation, determinants, and implications for outcomes. Clin J Am SocNephrol 2009;4:1677-1684.
35. Garg AX, Muirhead N, Knoll G, et al. Proteinuria and reduced kidney function in living kidney donors: a systematic review, meta-analysis, and meta-regression. Kidney Int2006;70:1801-1810.

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