HYPERTENSIVE DISORDERS IN PREGNANCY

Disease of the Month: JULY 2022

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FOREWORD

With the 4th issue of Disease of the month, team DotM continues with its commitment to provide residents and students with most useful and up to date information pertinent to common ailments presenting to us as healthcare professionals.

Disease of the month has been a collaborative effort from the start. I gratefully acknowledge the contributions from our residents and student associates in compiling this issue of disease of the month. Team DotM is grateful to Executive council of RRF for its full support and recognition of efforts and contributions of the DoTM team.

For the readers interest an additional chapter has been included in this issue, which contains information provided in this handbook in the form of visual summary. I hope you will read, enjoy and gain something of substance from this issue.

All keen and aspiring medical writers are invited for DoTM's future and subsequent issues.

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In charge DotM

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INTRODUCTION AND EPIDEMIOLOGY

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INTRODUCTION:

Preeclampsia and eclampsia are two of the four types of hypertension diseases of pregnancy. Preeclampsia is a condition that develops on top of chronic hypertension, gestational hypertension, and chronic hypertension in the first place. The definition of preeclampsia, a condition that may lead to eclampsia, has changed in recent years. Although the presence of proteinuria is used to indicate preeclampsia, this is no longer the case since some individuals had severe illness prior to the beginning of proteinuria. When preeclampsia occurs beyond 20 weeks of pregnancy, it is characterized by high systolic and/or diastolic blood pressure, proteinuria, or end-organ failure, and is associated with one or more of these symptoms. Eclampsia is characterized as the sudden onset of generalized tonic-clonic seizures in a preeclamptic lady. Eclamptic seizures can occur before birth, 20 weeks after conception, during labor, and even after delivery. (2)

Because of better medical treatment, rates of the affected population in the industrialized world are low (4) Pregnancy hypertension is one of the most common and devastating causes of mortality during pregnancy.

Preeclampsia is responsible for around 12 to 25% of fetal growth restriction and small for gestational age newborns, as well as 15 to 20% of all preterm deliveries; the accompanying problems of prematurity are significant, including neonatal mortality and major long-term neonatal morbidity. (5) Eclampsia is a disease condition associated with the diagnosis of preeclampsia that may occur antepartum, during birth, and up to 6 weeks after delivery. Women with eclampsia generally present after 20 weeks of pregnancy, with the majority of cases happening after 28 weeks. Generalized tonic-clonic seizures, which normally last 60 to 90 seconds, are the distinctive physical exam finding for eclampsia. Following seizure activity, a postictal state is commonly noticed. Prior to the onset of seizure activity, patients may suffer

warning indications such as headaches, visual anomalies, stomach pain, and increased blood pressure. (6)

HISTORICAL ASPECT:

Preeclampsia-eclampsia was not properly identified as a pregnancy disease in Ancient times. Disease categorization advanced around the end of the Renaissance. In 1596, Gabelchoverus classified four varieties of epilepsy: those caused by the brain, stomach, pregnant uterus, and chilly extremities. However, the term "eclampsia" did not exist in Varandaeus' work on gynaecology until 1619. (7)

Boissier de Sauvages separated eclampsia from epilepsy in the 18th century. Along with his taxonomy of diseases, de Sauvages shared his thoughts on the etiology of convulsions. He explained that the convulsions were due to body's natural response in an attempt to remove any unwanted organism from its system. (8)

In the nineteenth century, Dr. Thomas Denman spent a lot of emphasis on labors impacted by convulsions in his book 'Introduction to the Practice of Midwifery'. Although Denman related convulsions to specific practices and attitudes connected with living in major cities and towns, he noticed that the uterus was the source of the highest danger of convulsions. According to Denman, the descending blood veins experienced increased pressure as the uterus grew during pregnancy. Such an acute elevation in pressure led in regurgitation of blood in the skull, an overflow of the cerebral arteries, and eventual convulsions. (9)

In the 1960's, multiple groups observed major differences in the physiology of the placentas for pregnancies that were affected by preeclampsia and those which were unaffected (10)

The concept suggested by Sir Roberts and his colleagues in 1989 is still driving research linked to preeclampsia-eclampsia linkage. He argued that preeclampsia reflected a state of endothelial dysfunction (10)

EPIDEMIOLOGY:

Hypertensive disorders of pregnancy have become more prevalent in recent times, hence increasing the morbidity and mortality among mothers and newborns.

- Hypertensive disorders affect as many as 10 percent of all pregnancies worldwide. (11)
- A WHO systematic assessment, notes a **maternal mortality rate** of
    - 16% in affluent countries,
    - 9% of maternal deaths in continents of Africa and Asia, and
    - 16% in Latin America and the Carribean .(12)
    - African American women in the United States have a three times greater risk of maternal death than white women.

- Women who develop pre-eclampsia after their first pregnancy have a 2-3 times higher risk of mortality in the next 35 years. Studies also demonstrate a positive linkage between pre-eclampsia and later development of cardiovascular disease and the morbidity and mortality that results from it (15)

- Preeclampsia/eclampsia is responsible for almost 25% of **stillbirths** as well as the **neonatal mortality** in underdeveloped nations. Neonatal mortality from preeclampsia is more than three times greater in the low-income nations than in the high-income ones, owing primarily to a lack of intensive care treatment for the neonates (13)
- According to studies, there is a 7-20% **risk in a future pregnancy** of recurrent preeclampsia. This risk is greater if a woman has had two prior preeclamptic pregnancies, and it is also influenced by the gestational age at which the symptoms appear. (14)
- Obesity raises the overall risk of preeclampsia by a factor of two to three. Even within the normal range, the risk of developing preeclampsia rises steadily with a rising BMI. Early and severe variants of preeclampsia, together with late or moderate disease variants, are on the rise and have been associated with high perinatal mortality and morbidity. (16)

REFERENCES:

1. Wilkerson RG, Ogunbodede AC. Hypertensive Disorders of Pregnancy. Emerg Med Clin North Am [Internet]. 2019 May 1 [cited 2022 Jun 12];37(2):301–16. Available from: https://pubmed.ncbi.nlm.nih.gov/30940374/
2. Sutton ALM, Harper LM, Tita ATN. Hypertensive Disorders in Pregnancy. Obstet Gynecol Clin North Am [Internet]. 2018 Jun 1 [cited 2022 Jun 12];45(2):333–47. Available from: https://pubmed.ncbi.nlm.nih.gov/29747734/
3. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol [Internet]. 2013 [cited 2022 Jun 12];170(1):1–7. Available from: https://pubmed.ncbi.nlm.nih.gov/23746796/
4. Hypertensive Disorders | Williams Obstetrics, 24e | AccessMedicine | McGraw Hill Medical [Internet]. [cited 2022 Jun 12]. Available from: https://accessmedicine.mhmedical.com/content.aspx?bookid=1057&sectionid=5978914
5. RL G, DJ R. Prevention of premature birth. N Engl J Med [Internet]. 1998 Apr 20 [cited 2022 Jun 12];339(5):11–5. Available from: https://pubmed.ncbi.nlm.nih.gov/9682045/
6. Hypertensive Disorders of Pregnancy - PubMed [Internet]. [cited 2022 Jun 12]. Available from: https://pubmed.ncbi.nlm.nih.gov/26926408/
7. Baker P. Pre-eclampsia: current perspectives on management [Internet]. 2003 [cited 2022 Jun 12]. Available from: https://www.taylorfrancis.com/books/mono/10.3109/9780203507544/pre-eclampsia-philip-baker-john-kingdom
8. Temkin: The falling sickness: a history of epilepsy... - Google Scholar [Internet]. [cited 2022 Jun 12]. Available from: https://scholar.google.com/scholar_lookup?title=The+falling+sickness:+A+history+of+epilepsy+from+the+Greeks+to+the+beginnings+of+modern+neurology&author=O+Temkin&publication_year=1971&
9. Denman T. An introduction to the practice of midwifery [Internet]. 1825 [cited 2022 Jun 12]. Available from: https://books.google.com/books?hl=en&lr=&id=bkhHAQAAMAAJ&oi=fnd&pg=PA17&ots=sdW8Sc76KL&sig=TwtnspCYkycncsvCiHMZ8uDTTC0
10. Bell MJ. A Historical Overview of Preeclampsia-Eclampsia. J Obstet Gynecol Neonatal Nurs [Internet]. 2010 [cited 2022 Jun 12];39(5):510. Available from: /pmc/articles/PMC2951301/
11. Magley M, Hinson MR. Eclampsia. StatPearls [Internet]. 2022 Feb 16 [cited 2022 Jun 12]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK554392/
12. Sibai BM, Mercer B, Sarinoglu C. Severe preeclampsia in the second trimester: recurrence risk and long-term prognosis. Am J Obstet Gynecol [Internet]. 1991 Nov [cited 2022 Jun 12];165(5 Pt 1):1408–12. Available from: https://pubmed.ncbi.nlm.nih.gov/1957870/
13. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol [Internet]. 2009 Jun [cited 2022 Jun 12];33(3):130–7. Available from: https://pubmed.ncbi.nlm.nih.gov/19464502/
14. Hernández-Díaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. BMJ [Internet]. 2009 Jul 4 [cited 2022 Jun 12];338(7711):34. Available from: https://pubmed.ncbi.nlm.nih.gov/19541696/
15. Chesley LC, Annitto JE, Cosgrove RA. The remote prognosis of eclamptic women. Sixth periodic report. Am J Obstet Gynecol [Internet]. 1976 Mar 1 [cited 2022 Jun 12];124(5):446–59. Available from: https://pubmed.ncbi.nlm.nih.gov/1258900/
16. Bodnar LM, Ness RB, Markovic N, Roberts JM. The risk of preeclampsia rises with increasing prepregnancy body mass index. Ann Epidemiol [Internet]. 2005 Aug [cited 2022 Jun 12];15(7):475–82. Available from: https://pubmed.ncbi.nlm.nih.gov/16029839/

CLASSIFICATION OF HYPERTENSION IN PREGNANCY

Dr.Noor Fatima, Jawad Basit, Mohammad Ebad ur Rehman

Hypertension is the most common problem occurring in the setup of pregnancy and leads to the development of complications in 10% of the pregnancies. Hypertension in pregnancy is classified into the following four types.

- CHRONIC HYPERTENSION
- PRE-ECLAMPSIA/ECLAPMSIA
- CHRONIC HYPERTENSION WITH SUPERIMPOSED PREECLAMPSIA
- GESTATIONAL HYPERTENSION

1. CHRONIC HYPERTENSION:

A high blood pressure (140/90 mm Hg) that is present before 20 weeks of gestation and continues to persist at least 12 weeks after the delivery is termed Chronic Hypertension.

Chronic hypertension can either be mild (less than 179/109 mmHg) or Severe (greater than 180/110 mmHg) (1). Since Chronic hypertension has been associated with poor outcomes for fetal growth and maternal health, a need for stringent control of blood pressure in such pregnant women is advocated. The target blood pressure is 110-140/85 mmHg. Strict monitoring of fetal growth is also warranted.

The prevalence of pregnancies with chronic hypertension is around 3-5% (3) Chronic hypertension has been associated with increasing age and obesity, both of which are increasing in the modern world. Provided the fact that most pregnancies are unplanned, the need of the hour is to educate the hypertensive women to plan their pregnancies if possible, and to be overly cautious while being pregnant to avoid perinatal morbidity and mortality. Placental dysfunction, considered to be a precursor of placental abruption, has been found to be more common in women with chronic hypertension (4) The rate of placental abruption in these patients is 1.1% compared to 0.4% in females without chronic hypertension (5)

The first line of treatment for chronic hypertension in a state of pregnancy is methyldopa, however, in the presence of certain conditions such as liver disease or headache, labetalol might be chosen. Labetalol is both an alpha and a beta-blocker. Calcium channel blockers such as nifedipine, and diuretics have been less commonly used but their usage is becoming more and more popular recently. ACE inhibitors being known teratogens are strictly contradicted. Their usage in pregnancy has been associated with renal dysgenesis and fetal hypoplasia (2)

2. PRE-ECLAMPSIA/ECLAPMSIA

Preeclampsia is defined as a blood pressure greater than 140/90 mmHg after 20 weeks of gestation which might progress to eclampsia where a women experiences seizures secondary to hypertension (6)

Preeclampsia might progress to eclampsia where a women experiences seizures secondary to hypertension (6) It has been found to be more common in women who are nulliparous, have a family history of preeclampsia, those who had hypertension in their last pregnancy and those having renal disease. Though formerly, proteinuria was considered the gold standard for diagnosis of pre-eclampsia, this is not recommended anymore. Now a days, the disease is diagnosed by new onset hypertension that occurs post 20 weeks during gestation with evidence of proteinuria or acute liver damage, Acute kidney Injury (AKI) or neurological manifestations (7) Eclampsia is due to defective autoregulation of cerebral blood flow, secondary to an enhanced permeability of the blood brain barrier in a woman with established preeclampsia (8) The treatment plan of preeclampsia/eclampsia is highlighted as follows

- The first line treatment in an eclamptic woman is the anticonvulsant agent, magnesium sulfate. A loading dose of 4-6 g should be given intravenously over a period of 15-20 minutes. Maintenance dosage of 2g/hour I/V should be given subsequently. The therapy should be continued till at-least 1 day after the last eclamptic seizure (9)
- Alternative to magnesium sulfate, diazepam or phenytoin can be given.
- Delivery is advised in severely pre-eclamptic women with a gestation age greater than 34 weeks, who have maternal or fetal instability on evidence (10)
- Since eclampsia is highly prevalent within 24 hours after delivery, so stringent blood pressure monitoring is advised postpartum.

3. CHRONIC HYPERTENSION WITH SUPERIMPOSED PREECLAMPSIA:

In a state of incessant hypertension, when a pregnant woman experiences a sudden rise in blood pressure or antihypertensive therapy needs to be modulated after 20 weeks of gestation, this is known as Superimposed Preeclampsia (sPE) (11)

It is characterized by an abrupt 2-3x increment in proteinuria, or liver dysfunction depicted by elevated ALT,AST or thrombocytopenia (6). Superimposed Preeclampsia (sPE) has been

associated with poorer fetal and maternal outcomes than preeclampsia alone (12) (13) Screening of Superimposed Preeclampsia is done in all the three trimesters (14)

- In the first trimester, it is done to identify the cohorts of pregnant women with already diagnosed chronic hypertension who are at a relatively higher risk of developing pre-eclampsia and implementing strategies to reduce this risk
- In the second and third trimester, screening is done to diagnose the disease before clinical manifestation and improve the fetal and maternal outcome and avoid complications
- Recently certain biomarkers have been identified which have been postulated to forecast appropriately those pregnant women with chronic hypertension who are at an increased risk of developing Superimposed Preeclampsia (sPE) (14)

4. GESTATIONAL HYPERTENSION:
    - Hypertension without evidence of proteinuria
    - Occurs after 20 weeks of gestation
    - May progress to preeclampsia
    - Occurs without hematological disturbances
    - Pregnancies complicated by gestational hypertension usually have good outcomes (9)
    - The cases of gestational hypertension which progress to preeclampsia generally have poorer outcomes (15)

REFERENCES:

1. Bodnar LM, Ness RB, Markovic N, Roberts JM. The risk of preeclampsia rises with increasing prepregnancy body mass index. Ann Epidemiol [Internet]. 2005 Aug [cited 2022 Jun 12];15(7):475–82. Available from: https://pubmed.ncbi.nlm.nih.gov/16029839/
2. Mammaro A, Carrara S, Cavaliere A, Ermito S, Dinatale A, Pappalardo EM, et al. Hypertensive Disorders of Pregnancy. J Prenat Med [Internet]. 2009 [cited 2022 Jun 15];3(1):1. Available from: /pmc/articles/PMC3279097/
3. Seely EW, Ecker J. Chronic hypertension in pregnancy. Circulation. 2014;129(11):1254–61.
4. Lowe SA, Brown MA, Dekker GA, Gatt S, Mclintock CK, Mcmahon LP, et al. Guidelines for the management of hypertensive disorders of pregnancy 2008. Aust New Zeal J Obstet Gynaecol. 2009 Jun;49(3):242–6.
5. Zetterström K, Lindeberg SN, Haglund B, Hanson U. The association of maternal chronic hypertension with perinatal death in male and female offspring: A record linkage study of 866 188 women. BJOG An Int J Obstet Gynaecol. 2008 Oct;115(11):1436–42.
6. Table 19, Classification of hypertension in pregnancy - The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure - NCBI Bookshelf [Internet]. [cited 2022 Jun 17]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK9629/table/A163/
7. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive Disorders of Pregnancy. Hypertension [Internet]. 2018 Jul 1 [cited 2022 Jun 17];72(1):24–43. Available from: https://www.ahajournals.org/doi/abs/10.1161/hypertensionaha.117.10803
8. Magley M, Hinson MR. Eclampsia. StatPearls [Internet]. 2022 Feb 16 [cited 2022 Jun 17]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK554392/
9. Sutton ALM, Harper LM, Tita ATN. Hypertensive Disorders in Pregnancy. Obstet Gynecol Clin North Am [Internet]. 2018 Jun 1 [cited 2022 Jun 17];45(2):333–47. Available from: https://pubmed.ncbi.nlm.nih.gov/29747734/
10. American College of Obstetricians, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol [Internet]. 2013 Nov [cited 2022 Jun 17];122(5):1122–31. Available from: https://pubmed.ncbi.nlm.nih.gov/24150027/
11. Guedes-Martins L. Superimposed Preeclampsia. Adv Exp Med Biol [Internet]. 2017 [cited 2022 Jun 17];956:409–17. Available from: https://pubmed.ncbi.nlm.nih.gov/27722963/
12. Valent AM, Defranco EA, Allison A, Salem A, Klarquist L, Gonzales K, et al. Expectant management of mild preeclampsia versus superimposed preeclampsia up to 37 weeks. Am J Obstet Gynecol. 2015 Apr 1;212(4):515.e1-515.e8.
13. Rezk M, Gamal A, Emara M. Maternal and fetal outcome in de novo preeclampsia in comparison to superimposed preeclampsia: a two-year observational study. http://dx.doi.org/103109/106419552014982329 [Internet]. 2015 May 1 [cited 2022 Jun 17];34(2):137–44. Available from: https://www.tandfonline.com/doi/abs/10.3109/10641955.2014.982329
14. Kametas NA, Nzelu D, Nicolaides KH. Chronic hypertension and superimposed preeclampsia: screening and diagnosis. Am J Obstet Gynecol [Internet]. 2022 Feb 1 [cited 2022 Jun 17];226(2S):S1182–95. Available from: https://pubmed.ncbi.nlm.nih.gov/35177217/
15. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol [Internet]. 2003 Jul 1 [cited 2022 Jun 17];102(1):181–92. Available from: https://pubmed.ncbi.nlm.nih.gov/12850627/

ETIOLOGY OF ECLAMPSIA

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INCIDENCE OF ECLAMPSIA:

Hypertensive disorders of pregnancy (HDP), which are described as a sex-specific cardiovascular illness, are one of the primary causes of maternal and foetal morbidity and death worldwide and a major danger to mother and child health (1,2). Preeclampsia is a HDP that often occurs after 20 weeks of gestation and escalates to eclampsia if left untreated (3). Preeclampsia and eclampsia are not different conditions, but rather the clinical manifestations of the same syndrome. Although preeclampsia is a significant public health threat in both developed and developing nations, causing maternal and perinatal morbidity and mortality worldwide, the impact of the disease is observed to be more severe in developing countries, where medical interventions may be ineffective due to late presentation of cases (4-9). The challenge is complicated by the persistent ambiguity of the disease's cause and its unpredictable behaviour (10). According to the WHO, preeclampsia is seven times more prevalent in underdeveloped nations (2.8% of live births) than in industrialised nations (0.4%). (10). In developing nations, the prevalence of preeclampsia varies from 1.8% to 16.7%. According to a recent comprehensive review of world mortality, Pakistan is the sixth most populous nation and has the third-highest rate of maternal, foetal, and child death (11). In Pakistan, eclampsia is responsible for 34% of maternal mortality among women referred to tertiary care institutions (12).

ETIOLOGY AND RISK FACTORS OF ECLAMPSIA:

The mechanisms responsible for the development of eclampsia are unknown. Preeclampsia/eclampsia has been linked to genetic susceptibility, immunology, endocrinology, nutrition, aberrant trophoblastic invasion, coagulation problems, vascular endothelial damage, cardiovascular maladaptation, nutritional shortages or excess, and infection. Eclampsia has also been linked to an imbalance in prostanoid synthesis and a rise in plasma antiphospholipids. In mouse models, placental ischemia seems to be connected with an increased risk of epilepsy and cerebrospinal fluid (CSF) inflammation. Identification and, if feasible, prevention of preeclampsia is a fundamental aspect of effective treatment. The National Institute for Health and Care Excellence (NICE) suggests identifying women at high risk

of preeclampsia prior to week 13 of pregnancy and initiating low-dose aspirin until week 36. Numerous illnesses and health risk behaviours are believed to contribute to preeclampsia/eclampsia:

1. Nulliparity

It has been shown that nulliparity is a risk factor, with a reported frequency 2–3 times greater than in multiparous pregnancies. Some have even proposed that preclampsia in primiparas is a distinct illness from preclampsia in multiparas. Primiparous women are much more likely to develop hypertension morbidity and chronic hypertension in later pregnancies. Recent research suggests that immunological maladaptation, increased insulin resistance, genetic susceptibility, and angiogenic imbalance are the factors behind this epidemiological phenomenon (13).

2. **Intrauterine Growth Retardation:**

After an SGA delivery, all kinds of HDP occurred more often. This supports the concept that foetal growth restriction and HDP share a pathophysiologic mechanism that may lead to foetal growth restriction in one pregnancy and PIH in a future pregnancy. In accordance with this, it is believed that foetal growth restriction and HDP originate from improper remodelling of the uterine spiral arteries, resulting in decreased placental and foetal perfusion and subsequent dysfunction of the maternal vascular endothelium. This shows that the sole difference between at least some instances of HDP and foetal growth restriction is the maternal response to a common disease (14).

3. Teen Pregnancy:

Previous research has shown that the risk of preeclampsia is higher in adolescents, particularly among girls aged 13–15 (15).

4. Patients older than 35

Older women are 1.5 times more likely to have preeclampsia than women under 35. Older women were considerably more likely to have preterm births and SGA- babies, with a risk increase of 70% for preterm deliveries before 34 weeks and 40% for both preterm deliveries before 37 weeks and SGA. Second, older women were twice as likely to need caesarean delivery. Finally, these obstetric hazards led to around a 50 percent increase in newborn asphyxia and a 40 percent increase in admissions to the neonatal critical care unit (16).

5. Obesity

Obese and overweight women are more likely to develop severe and moderate preeclampsia, as well as preeclampsia in early and late gestation (17,18). Whites and blacks have the same increased risk, but the effect may be somewhat greater for whites (19). Several communities across the globe have reported that obesity increases the risk of preeclampsia, demonstrating that this phenomenon is not exclusive to western society (20). This association is also not restricted to obese women, as rises in BMI within the normal range are also related to a higher

risk of preeclampsia (21). The assumption that fat mass is significant is bolstered by results indicating weight loss lessens the incidence of preeclampsia.

6. Antiphospholipid antibody syndrome

Antiphospholipid syndrome (APS) is characterised by recurrent thrombosis due to the existence of autoantibodies against negatively charged phospholipids or phospholipid-binding proteins in the blood. APS is linked to unfavourable pregnancy outcomes, such as preeclampsia, recurrent early pregnancy loss, foetal mortality, and intrauterine growth restriction. Approximately one-third of pregnant women with APS will develop preeclampsia (22).

7. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an uncommon autoimmune connective tissue disease with a frequency of 20 to 70 per 100000 and an incidence of 1 to 10 per 100000 person-years (23). SLE mostly affects women of reproductive age, with a female-to-male ratio of around 9:1. Pregnant women with SLE are three to five times more likely to develop pre-eclampsia, and pre-eclampsia-complicated SLE accounts for 16 to 30 percent of all SLE pregnancies. Up to 25% of SLE patients will develop pre-eclampsia, while only 5% of the general population would be affected (24). Pre-eclampsia and SLE are difficult to distinguish since the clinical signs of pre-eclampsia might match those of SLE, and the care of the two illnesses involves delivery and medicine, respectively.

Protein C and protein S deficiency, antithrombin deficiency, vascular and connective tissue disorders, gestational diabetes, lower socioeconomic status, family history of preeclampsia, previous preeclampsia and eclampsia, chronic hypertension, and renal disease are additional risk factors for eclampsia.

REFERENCES:

1. Garovic V, White W, Vaughan L, Saiki M, Parashuram S, Garcia-Valencia O et al. Incidence and Long-Term Outcomes of Hypertensive Disorders of Pregnancy. 2022.
2. Osungbade K, Ige O. Public Health Perspectives of Preeclampsia in Developing Countries: Implication for Health System Strengthening. 2022.
3. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia [Internet]. Who.int. 2022 [cited 19 June 2022]. Available from: https://www.who.int/publications/i/item/9789241548335
4. McClure EM, Saleem S, Pasha O, Goldenberg RL. Stillbirth in developing countries: a review of causes, risk factors and prevention strategies. Journal of Maternal-Fetal and Neonatal Medicine. 2009;22(3):183–190.
5. Igberase G, Ebeigbe P. Eclampsia: ten-years of experience in a rural tertiary hospital in the Niger delta, Nigeria. Journal of Obstetrics and Gynaecology. 2006;26(5):414–417.
6. Adamu YM, Salihu HM, Sathiakumar N, Alexander GR. Maternal mortality in Northern Nigeria: a population-based study. European Journal of Obstetrics Gynecology and Reproductive Biology. 2003;109(2):153–159.
7. Ikechebelu JI, Okoli CC. Review of eclampsia at the Nnamdi Azikiwe University teaching hospital, Nnewi (January 1996-December 2000) Journal of Obstetrics and Gynaecology. 2002;22(3):287–290
8. Onakewhor JUE, Gharoro EP. Changing trends in maternal mortality in a developing country. Nigerian Journal of Clinical Practice. 2008;11(2):111–120
9. Duley L. Pre-eclampsia and the hypertensive disorders of pregnancy. British Medical Bulletin. 2003;67:161–176
10. WHO. Make every mother and child count, in The world health report 2005. Geneva, Switzerland: World Health Organization; 2005
11. Bhutta ZA, Hafeez A, Rizvi A, Ali N, Khan A, Ahmad F, Bhutta S, Hazir T, Zaidi A, Jafarey SN. Reproductive, maternal, newborn, and child health in Pakistan: challenges and opportunities. Lancet. 2013 Jun 22;381(9884):2207-18. doi: 10.1016/S0140-6736(12)61999-0. Epub 2013 May 17.
12. Shah N, Khan N. Third Delay of Maternal Mortality in a Tertiary Hospital. Rawal Medical Journal. 2007;32:163-167.
13. Bdolah Y, Elchalal U, Natanson-Yaron S, Yechiam H, Bdolah-Abram T, Greenfield C, Goldman-Wohl D, Milwidsky A, Rana S, Karumanchi SA, Yagel S, Hochner-Celnikier D. Relationship between nulliparity and preeclampsia may be explained by altered circulating soluble fms-like tyrosine kinase 1. Hypertens Pregnancy. 2014 May;33(2):250-9. doi: 10.3109/10641955.2013.858745. Epub 2013 Dec 4. PMID: 24304210.
14. Rasmussen S, Irgens LM. History of fetal growth restriction is more strongly associated with severe rather than milder pregnancy-induced hypertension. Hypertension. 2008 Apr;51(4):1231-8. doi: 10.1161/HYPERTENSIONAHA.107.096248. Epub 2008 Feb 7. Erratum in: Hypertension. 2009 Jan;53(1):e11. PMID: 18259045.
15. Macedo TCC, Montagna E, Trevisan CM, Zaia V, de Oliveira R, Barbosa CP, Laganà AS, Bianco B. Prevalence of preeclampsia and eclampsia in adolescent pregnancy: A systematic review and meta-analysis of 291,247 adolescents worldwide since 1969. Eur J Obstet Gynecol Reprod Biol. 2020 May;248:177-186. doi: 10.1016/j.ejogrb.2020.03.043. Epub 2020 Mar 19. PMID: 32283429.
16. Lamminpää R, Vehviläinen-Julkunen K, Gissler M, Heinonen S. Preeclampsia complicated by advanced maternal age: a registry-based study on primiparous women in Finland 1997-2008. BMC Pregnancy Childbirth. 2012 Jun 11;12:47. doi: 10.1186/1471-2393-12-47. PMID: 22687260; PMCID: PMC3495042.
17. Mahomed K, Williams MA, Woelk GB, et al. Risk Factors For Pre-Eclampsia Among Zimbabwean Women - Maternal Arm Circumference and Other Anthropometric Measures Of Obesity. Paediatric and Perinatal Epidemiology. 1998;12:253–262. [PubMed] [Google Scholar]
18. Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world--a growing challenge. New England Journal of Medicine. 2007;356:213–5. [PubMed] [Google Scholar]
19. Hauger MS, Gibbons L, Vik T, Belizan JM. Prepregnancy weight status and the risk of adverse pregnancy outcome. Acta Obstetricia Et Gynecologica Scandinavica. 2008;87:953–959. [PubMed] [Google Scholar]
20. Grundy MA, Woodcock S, Attwood SE. The surgical management of obesity in young women: consideration of the mother's and baby's health before, during, and after pregnancy. Surgical

Endoscopy and Other Interventional Techniques. 2008;22:2107–2116. [PubMed] [Google Scholar]
21. Abodeely A, Roye GD, Harrington DT, Cioffi WG. Pregnancy outcomes after bariatric surgery: maternal, fetal, and infant implications. Surgery for Obesity and Related Diseases. 2008;4:464–471. [PubMed] [Google Scholar]
22. Clark EA, Silver RM, Branch DW. Do antiphospholipid antibodies cause preeclampsia and HELLP syndrome? Curr Rheumatol Rep. 2007 Jun;9(3):219-25. doi: 10.1007/s11926-007-0035-9. PMID: 17531175.
23. Huang PZ, Du PY, Han C, Xia J, Wang C, Li J, Xue FX. Pre-eclampsia with new-onset systemic lupus erythematosus during pregnancy: A case report. World J Clin Cases. 2019 Nov 26;7(22):3800-3806. doi: 10.12998/wjcc.v7.i22.3800.
24. Warrington JP. Placental ischemia increases seizure susceptibility and cerebrospinal fluid cytokines. Physiol Rep. 2015 Nov;3(11):e12634. doi: 10.14814/phy2.12634. Epub 2015 Nov 24.

PATHOPHYSIOLOGY

Dr Rabia, Sumia Fatima

Pathophysiology of preeclampsia and eclampsia is poorly understood. Factors may incorporate inadequately formed uterine placental spiral arterioles (which decrease uteroplacental blood flow during late pregnancy), a hereditary abnormality on chromosome 13, immunologic anomalies, and placental ischemia or infarction. Lipid peroxidation of cell membranes instigated by free radicals might add to preeclampsia.(1,2)

Clinical highlights of preeclampsia include hypertension, proteinuria, renal dysfunction, neurological anomalies, eclampsia, cardiac dysfunction, pulmonary edema, hepatic dysfunction, hematologic dysfunction, and fetal growth restriction (3)

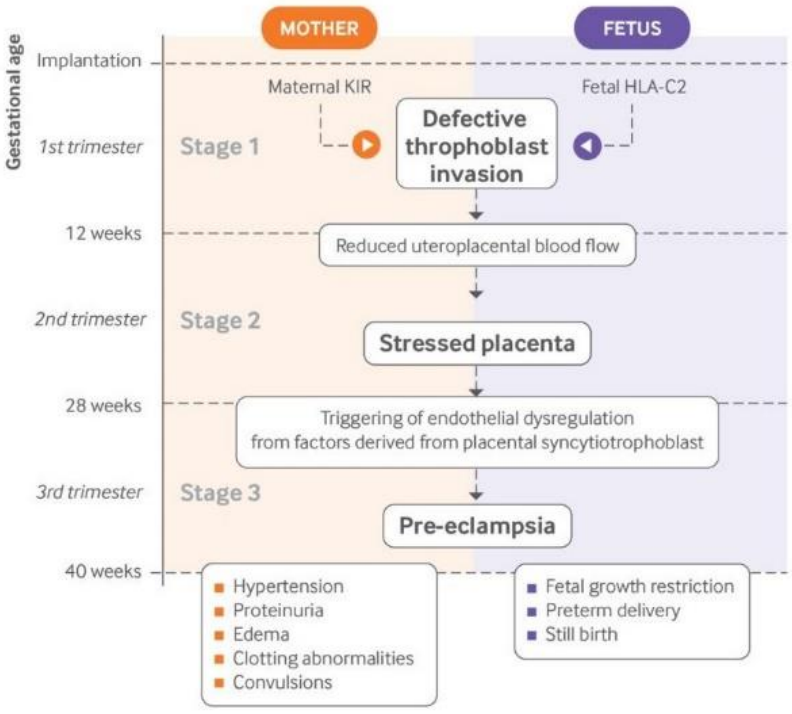


Figure 1: Pathogenesis of pre-eclampsia with the resultant impacts on mother and fetus. The failure of trophoblast uterine interactions in the first trimester prompts a stress response in the placenta. This might influence the growth and development of the villous tree, affecting

transfer of oxygen and nutrients to the fetus. The stress to the syncytiotrophoblast leads to shedding of a range of factors into the systemic circulation. These factors cause a systemic inflammatory response resulting from disruption of the homoeostatic functions of the maternal endothelium, including regulation of clotting, fluid transfer, and blood pressure (2)

During normal pregnancy, the villous cytotrophoblast invades into the inner third of the myometrium, and spiral arteries lose their endothelium and vast majority of their muscle fibers. These structural modifications are related with functional changes, such that spiral arteries become low-resistance vessels, and thus less sensitive, or even insensitive, to vasoconstrictive substances.

Abnormal Placentation

Pre-eclampsia has a complex pathophysiology, the main cause being abnormal placentation. Defective invasion of the spiral arteries by cytotrophoblast cells is observed during pre-eclampsia.

Recent studies have shown that cytotrophoblast invasion of the uterus is actually a unique differentiation pathway in which the fetal cells adopt certain attributes of the maternal endothelium they normally replace.

In pre-eclampsia, this differentiation process turns out badly, the anomalies might be related to the nitric oxide pathway, which contributes considerably to the control of vascular tone. Additionaly, inhibition of maternal synthesis of nitric oxide prevents embryo implantation.

Increased uterine arterial resistance induces higher sensitivity to vasoconstriction and thus chronic placental ischemia and oxidative stress. This chronic placental ischemia causes fetal complications, including intrauterine growth retardation and intrauterine death.

In parallel, oxidative stress induces release into the maternal circulation of substances such as free radicals, oxidized lipids, cytokines, and serum soluble vascular endothelial growth factor 1. These anomalies are responsible for endothelial dysfunction with vascular hyper permeability, thrombophilia, and hypertension, so as to compensate for the decreased flow in the uterine arteries due to peripheral vasoconstriction (5,3)

Endothelial Dysfunction

Endothelial dysfunction is responsible for the clinical signs observed in the mother, i.e., impairment of the hepatic endothelium contributing to onset of the HELLP (Hemolysis, Elevated Liver enzymes and Low Platelet count) syndrome, impairment of the cerebral endothelium inducing refractory neurological disorders, or even eclampsia. Depletion of vascular endothelial growth factor in the podocytes makes the endotheliosis more able to block the slit diaphragms in the basement membrane, adding to decreased glomerular filtration and causing proteinuria.

Finally, endothelial dysfunction promotes microangiopathic hemolytic anemia, and vascular hyper permeability associated with low serum albumin causes edema, particularly in the lower limbs or lungs. (5,4)

The crucial issue to understand is that the prime mover of pre-eclampsia is abnormal placentation. Two common theories appear to be interlinked, i.e., a genetic theory and an immunological theory (5)

Genetic Theory

Several susceptibility genes may exist for pre-eclampsia. These genes probably interact in the hemostatic and cardiovascular systems, as well as in the inflammatory response. Some have been identified, and in candidate gene studies they have provided evidence of linkage to several genes, including angiotensinogen on 1-q42–43 and eNOS on 7q36; other main important loci are 2p12, 2p25, 9p13, and 10q22.1.16

Immunological Theory

Pre-eclampsia can be seen as a debilitation of the maternal immune system that keeps it from recognizing the fetoplacental unit. Excessive production of immune cells causes secretion of tumor necrosis factor alpha which activates apoptosis of the extravillous cytotrophoblast.

The human leukocyte antigen (HLA) system also appears to play a role in the defective invasion of the spiral arteries, in that women with pre-eclampsia show reduced levels of HLA-G and HLA-E.18 During normal pregnancies, the interaction between these cells and the trophoblast is due to secretion of vascular endothelial growth factor and placental growth factor by natural killer cells.

High levels of sFl - tyrosine kinase 1 (an antagonist of vascular endothelial growth factor and placental growth factor) have been found in women with pre-eclampsia.17,18 Accordingly, assays of sFlt-1, placental growth factor, endoglin, and vascular endothelial growth factor, all of which increase 4–8 weeks before onset of the disease, may be useful predictors of pre-eclampsia.

Recent data show the protective role of heme oxygenase 1 and its metabolite, carbon monoxide, in pregnancy, and identify this as a potential target in the treatment of pre-eclampsia(3)

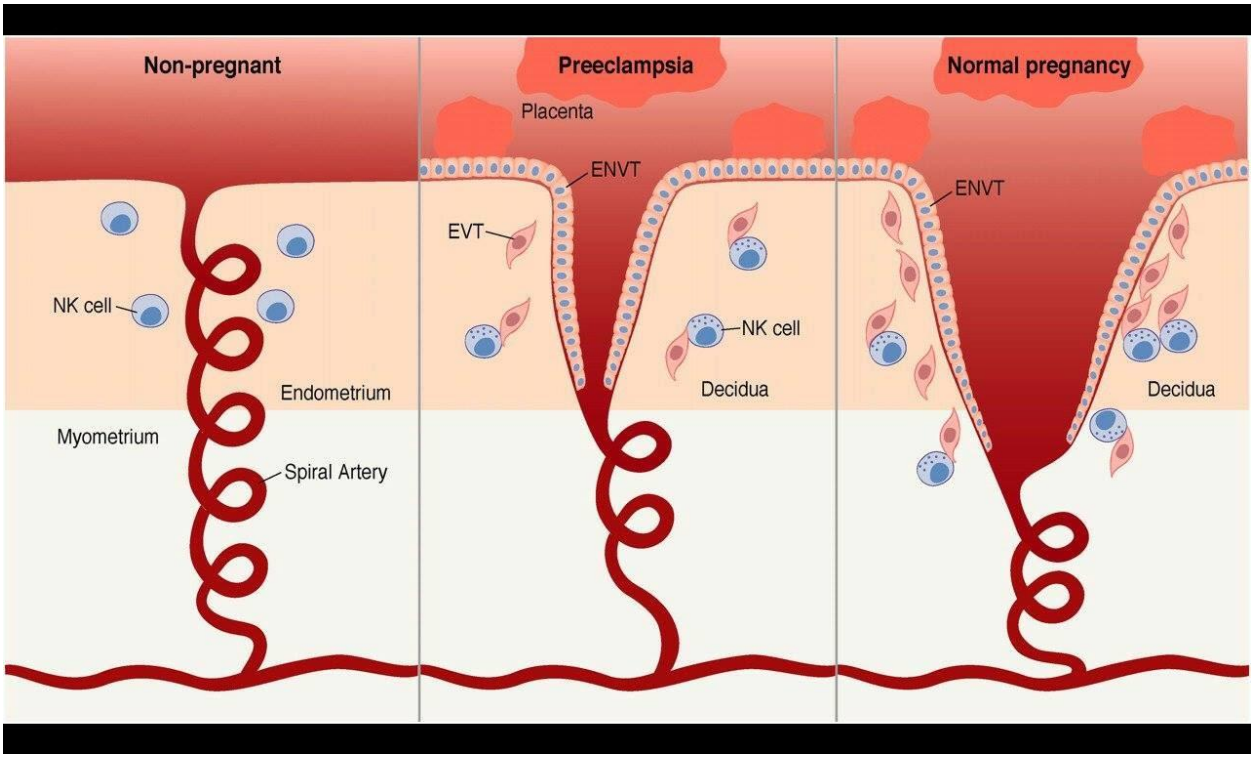


Figure 2 : Pre-eclampsia changes in arterioles (4)

Importantly, hallmarks such as endothelin-1 (ET-1), anti-angiogenic factor sFlt-1, agonistic autoantibodies to the angiotensin II type I receptor (AT1-AA) and decreased nitric oxide (NO) have been shown to play an important role in the development of PE (5)

REFERENCES

1. Khalil G, Khalil G. Preeclampsia: Pathophysiology and the Maternal-Fetal Risk. [cited 2022 Jun 5]; Available from: https://clinmedjournals.org/articles/jhm/journal-of-hypertension-and-management-jhm-3-024.php
2. Preeclampsia and Eclampsia - Gynecology and Obstetrics [Internet]. MSD Manual Professional Edition. [cited 2022 Jun 5]. Available from: https://www.msdmanuals.com/professional/gynecology-and-obstetrics/abnormalities-of-pregnancy/preeclampsia-and-eclampsia
3. Preeclampsia: Pathophysiology and Clinical Presentations [Internet]. American College of Cardiology. [cited 2022 Jun 5]. Available from: https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2020/09/30/19/20/http%3a%2f%2fwww.acc.org%2flatest-in-cardiology%2ften-points-to-remember%2f2020%2f09%2f30%2f19%2f20%2fpreeclampsia-pathophysiology-and
4. Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. BMJ. 2019 Jul 15;366:l2381.
5. Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi JM. Pre-eclampsia: pathophysiology, diagnosis, and management. Vasc Health Risk Manag. 2011;7:467–74.
6. says M. Preeclampsia and Eclampsia [Internet]. Core EM. [cited 2022 Jun 5]. Available from: https://coreem.net/core/preeclampsia-and-eclampsia/
7. Amaral LM, Wallace K, Owens M, LaMarca B. Pathophysiology and Current Clinical Management of Preeclampsia. Curr Hypertens Rep. 2017 Aug;19(8):61.

CLINICAL PRESENTATION

Dr Malik Shehryar

Hypertension (Systolic BP > 140 mmHg and Diastolic BP > 90 mmHg) affects 10% of pregnancies, many with underlying chronic hypertension, and approximately 1-2% will undergo a hypertensive crisis at some point during their lives. Hypertensive crisis includes hypertensive urgency and emergency; the American College of Obstetricians and Gynecologists describes a hypertensive emergency in pregnancy as persistent (lasting 15 min or more), acute-onset, severe hypertension, defined as systolic BP greater than 160 mmHg or diastolic BP >110 mmHg in the setting of pre-eclampsia or eclampsia. Pregnancy may be complicated by hypertensive crisis, with lower blood pressure threshold for end-organ damage than non-pregnant patients. 1 Specific hypertensive disorders of pregnancy accepted across international guidelines are the following four categories: 2

- **Chronic/pre-existing hypertension**. Hypertension discovered preconception or prior to 20 weeks' gestation.
- **Gestational hypertension**. Hypertension that appears de novo after 20 weeks' gestation and normalizes after pregnancy. It is a benign condition.
- **Preeclampsia-eclampsia**. De novo hypertension after 20 weeks' gestation accompanied by at least one of the following:
    - Proteinuria;
    - Other features of maternal organ dysfunction, including acute kidney injury (creatinine ⩾90 µmol/L; 1 mg/dL), liver involvement (elevated alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain, neurological complications (such as eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata), and hematological complications (decreased platelet count <150,000/µL, disseminated intravascular coagulation, hemolysis);

- Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth).

- **Chronic/pre-existing hypertension with superimposed preeclampsia-eclampsia**. Chronic hypertension as defined above, that develops signs and symptoms of preeclampsia or eclampsia after 20 weeks' gestation. In the absence of pre-existing proteinuria, a new onset proteinuria after 20 weeks gestation is sufficient to form diagnosis of superimposed preeclampsia.

The ESC suggests that gestational hypertension should resolve within 42 days postpartum, which is the puerperal period, and that preexisting hypertension persists beyond this period.

Symptoms of Preeclampsia

Around 3-6 percent pregnancies are affected by Preeclampsia. Although approximately 90 percent of cases present in the late preterm (≥34 to <37 weeks), term (≥37 to <42 weeks), or postpartum (≥42 weeks) period and have good maternal, fetal, and newborn outcomes, the mother and child are still at increased risk for serious morbidity or mortality. The remaining 10 percent of cases have an early presentation (<34 weeks) and carry the additional high risks associated with moderately preterm, very preterm, or extremely preterm birth. Long-term, patients with preeclampsia are at increased risk for developing cardiovascular and renal disease.

Symptoms of preeclampsia include

- visual disturbances, typically scintillations and scotoma.
- new-onset headache that is frontal, throbbing, or similar to a migraine headache.
- There could be new-onset, sudden, and constant epigastric pain with moderate to severe intensity.
- Although edema is no longer included in the diagnosis of preeclampsia, rapidly increasing or nondependent edema may be a signal of preeclampsia. Women may also report weight gain due to edema.

Symptoms of Eclampsia

Eclampsia is the presence of grand mal seizures in the patient with preeclampsia in the absence of any prior neurological disorder.

Maternal Complications

Outcomes of pregnancy complicated by hypertension, range from uneventful pregnancy in women with chronic, controlled hypertension to death in cases of preeclampsia/eclampsia.

The major adverse outcomes include

- Central nervous system (CNS) injuries such as seizures (eclampsia), hemorrhagic and ischemic strokes,
- Hepatic damage ranging from transaminase elevation, the so-called “HELLP syndrome” (hemolysis, elevated liver enzymes, and low platelets), hepatic failure,
- Renal dysfunction (spanning the gamut from a trivial reduction in glomerular filtration rate and minimal proteinuria to reversible acute renal failure or so-called acute tubular necrosis to even irreversible renal failure secondary to renal cortical necrosis) and,
- Increased frequency of cesarean delivery, preterm delivery, and abruptio placentae. 3

References:

1. Gloria T.T., James H. H., Hypertensive crisis during pregnancy and postpartum period, PubMed, 2013 Aug;37(4):280-7

2. ACOG practice bulletin no. 202: gestational hypertension and preeclampsia. *Obstet Gynecol* 2019; 133: e1–e25. [PubMed] [Google Scholar] [Ref list]

3. Reem M. et al. A Comprehensive Review of Hypertension in Pregnancy. Journal of Pregnancy. Hindawi. Volume 2012.

DIAGNOSIS

Dr Munema Khan

The diagnosis of eclampsia can be derived at via utilizing the enlisted parameters.

Urinalysis & Uric Acid Levels

Proteinuria is a hallmark of Eclampsia. A timed collection is the established standard for detection of its incidence.(>300 mg/24 h or >1 g/L). Although 24 hour measurement has been convention but 12-houred measurements are equally reliable. Recently, spot protein to creatinine ratios are becoming the norm. An albumin to creatinine ratio >35.5mg/mmol in early second trimester has been reported predictive of sub-clinical pre-eclampsia. Uric acid levels are also mild to markedly raised.

Hematologic Studies

Any or all of the following findings can be seen on a complete blood work

- Anemia → secondary to possibly microangiopatic hemolysis
- Bilirubin >1.2mg/dl
- Thrombocytopenia → might be associated with HELLP syndrome.
- Low serum haptoglobin levels
- LDH>600U/L
- Shistoytes, burr cells & echinocytes on peripheral smear.

Serum Creatinine Level

Creatinine clearance is reduced being less than 90ml/min/1.73m2. Creatinine is raised due to 1) decreased intravascular volume 2) Decreased GFR.

Liver Function Tests

20-25% of patients with eclampsia will exhibit deranged LFTS. Following findings can be present

- Aspartate aminotransferase (SGOT) level > 72 IU/L
- Total bilirubin > 1.2 mg/dL
- LDH > 600 IU/L [2]

CT Brain

CT brain imaging is not routinely indicated in eclampsia. Its utility lies in excluding concomitant causative pathology such as cerebral venous thrombosis, intracranial hemorrhage & other cerebral lesions. All of the latter can mimic the clinical presentation & merit exclusion.

However, imaging abnormalities are reported in up to 50% of patients, the characteristic findings mostly involving the occipital lobes. Comprised of cortical hypodense areas & diffuse edema. Al of the following can be observed on CT in the subset of patients.

- Cerebral edema
- Diffuse white matter low-density areas
- Patchy area of low density
- Occipital white matter edema
- Loss of normal cortical sulci
- Reduced ventricular size
- Cerebral hemorrhage
- Intraventricular hemorrhage
- Parenchymal hemorrhage (high density)
- Cerebral infarction
- Low attenuation areas
- Basal ganglia infarctions

MRI Brain

MRI brain carries the same utility as CT imaging in the diagnostic hierarchy of eclampsia. however, of note, 90% of patients will display abnormalities on MRI. Imaging studies should be reserved for patients with atypical presentation, history of trauma & refraction to magnesium sulphate therapy.

In MRI imaging, increased signal at the gray-white matter junction on T2-weighted images, cortical edema and hemorrhage are all reported. The syndrome of posterior reversible encephalopathy (PRES) has been increasingly recognized as a component of eclampsia.

Transabdominal ultrasonography

Eclampsia related complications can be detected by ultrasonography. Poor fetal growth, oligohydramnios, and/or abnormal umbilical artery Doppler velocimetry, all resultant of hypertension of eclampsia can be observed.

REFERENCE

Eclampsia. Ross M. Medscape. Available at https://emedicine.medscape.com/article/253960-overview#a14

MANAGEMENT OF ECLAMPSIA

Dr. Tayyaba Ismail, Fiza Farooq , Nida Nisar

Eclampsia is an obstetric emergency that accounts for complicating 1 in 10 of all pregnancies. (1) The eclamptic convulsions are characterized by hypertensive encephalopathy, cerebral vasospasm and mal seizure activity, the onset of which can be antepartum, intrapartum or postpartum.(2) These cases of eclamptic seizures mostly present in the third trimester of pregnancy.(1)There are no reliable tests or symptoms predicting development of eclampsia but early detection.(1) Since, it is a life threatening emergency for both mother and fetus, thus it requires proper medical management before and after delivery. It must be managed by medical and surgical therapy, supportive care and pharmacotherapy to treat seizures, control BP and ultimately deliver the infant, thus minimizing morbidity and mortality.(2,3)

MEDICAL AND SURGICAL THERAPY:

The only definitive treatment to control eclamptic seizures and high levels of BP is delivery of the fetus.(1) Inducing labor early can help manage eclampsia. Urgent delivery is required if mother presents with symptoms of progressive disease such as epigastric pain, headache, blurred vision, a high creatinine level and raised serum level of liver enzymes.(3) The mode of delivery should be based on obstetric indications but cesarean section may be necessary to prevent deteriorating maternal condition.(1) For initiating labor oxytocin and prostaglandins are infused. Further, opioids and epidural anesthesia help relieve maternal pain.(4)

PHARMACOLOGICAL TREATMENT:

Eclampsia requires treatment with intravenous anticonvulsive and antihypertensive agents.

ANTICONVULSANTS:

1. **Magnesium sulfate**
   For termination of seizures IV MgSO4 is an ideal therapy. It exerts its effect particularly as a cerebral vasorelaxant. It blocks Ca^{+2} influx by inhibiting glutamate channels thus reduces vasoconstriction. A loading dose of 4-6g (15-20 min) as a continuous IV bolus is

administered. This is followed by a maintenance dose of 1-2g per hour.(1)During this infusion maternal monitoring is really crucial since MgSO4 toxicity may result in muscle paralysis, cardiopulmonary arrest, loss of consciousness and ultimately coma, all these effects attribute to hypermagnesemia.(3,5)Calcium gluconate is administered in case toxicity is suspected.(3)

2. **Diazepam or Lorazepam:**
   Diazepam is used as an alternative if Mg is contraindicated.(1)But it is not universally approved during pregnancy because it poses greater risk of recurrent seizures and thus being related to greater maternal and neonatal mortality.(5)

3. **Phenytoin:**
   Phenytoin can also be used a drug of choice but studies indicate its likelihood to causes recurrent convulsions thus being unsafe for both mother and fetus. Hence, phenytoin is only administered if mother is unresponsive to MgSO4.(2)

ANTIHYPERTENSIVES:

Besides anticonvulsive therapy, antihypertensives are also mandatory.

1. **Labetalol:**
   Labetalol is regarded as a first line drug. It is safe to use in situations of severe pregnancy induced hypertension as it is associated with less maternal and fetal side effects. The use of labetalol is contraindicated in asthmatic mothers and alternatively oral Nifedipine is administered.(3,5)

2. **Hydralazine:**
   Hydralazine is effective in management of eclampsia and is used if patient is refractory to Labetalol or Nifedipine. Some risk factors associated with it are headache, vomiting, tachycardia and neonatal thrombocytopenia.(5)

SUPPORTIVE CARE:

Mother must be given proper supportive care that may avert any maternal injury. Following measures must be taken to ensure maternal stability: (1,2)

- Provide IV fluid therapy
- BP should be controlled
- Support respiratory and cardiovascular functions
- Establish airway potency
- Ensure maternal oxygenation

- Arterial blood gas analysis should be done
- Left lateral position of mother should be ensured

IV FLUID MANAGEMENT:

Volume expansion proves to be beneficial in treatment of eclampsia but it plays no significant role in minimizing maternal morbidity and mortality.(3) Volume expansion helps overcome volume depletion in order to ensure definite maternal and uteroplacental circulation. IV fluid therapy also helps in prevention of hypotension during vasodilator therapy. IV fluid infusion must be closely monitored since it puts mother at risk of pulmonary edema and increased resistance to antihypertensive agents.((6)The use of colloids in place of dextrose is recommended for fluid therapy because studies indicate dextrose infusion being related to birth asphyxia.(4)

POSTPARTUM MANAGEMENT:

Eclamptic mothers after labour, require close evaluation of vital signs, solid and fluid intake, urine output and symptoms for a minimum of 2 days. These patients due to high blood volume, particularly if accompanied by a renal insufficiency or placental abruption or prior chronic hypertension, are at a high risk for pulmonary oedema and an aggravation of acute hypertension postpartum. (2)

M. Sibai et al suggests the use of oral nifedipine as it enhances diuresis during postpartum time. The recommended dose of oral nifedipine is 10mg every 6 hours. (2)

If hypertension persists beyond 8 weeks, or neurological changes appear, the patient should be medically referred. (1)

PREVENTION OF ECLAMPSIA:

For people with risk factors, there are some steps that can be taken prior to and during pregnancy to reduce the chance of developing eclampsia.(2)

- Eating healthy foods that are low in salt and rich in vitamins
- Taking calcium and marine oil supplementation
- Controlling your blood pressure and blood sugar
- Maintaining a regular exercise routine
- Losing weight if you have obesity
- Taking aspirin in low dose
- Receiving treatment with antihypertensive drugs (antenatally as well as postpartum)
- Administration of Magnesium sulfate prophylactically

- Monitoring mother closely in hospital and out patient

Hence, adequate prevention is believed to be a requisite in reducing morbidity and mortality from eclampsia. Therefore, proper antenatal care must be provided to all patients under the supervision of highly skillful midwives and doctors.(4)

REFERENCES:

1. Eclampsia: Overview, Etiologic and Risk Factors for Preeclampsia/Eclampsia, Multiorgan System Effects [Internet]. [cited 2022 Jun 16]. Available from: https://emedicine.medscape.com/article/253960-overview

2. Sibai BM. Diagnosis, prevention, and management of eclampsia. Obstetrics and Gynecology. 2005 Feb;105(2):402–10.

3. Munro PT. Management of eclampsia in the accident and emergency department. Emergency Medicine Journal [Internet]. 2000 Jan 1 [cited 2022 Jun 16];17(1):7–11. Available from: https://emj.bmj.com/content/17/1/7

4. Konje JC, Obisesan KA, Odukoya OA, Ladipo OA. Presentation and management of eclampsia. Int J Gynaecol Obstet [Internet]. 1992 [cited 2022 Jun 16];38(1):31–5. Available from: https://pubmed.ncbi.nlm.nih.gov/1348987/

5. Peres GM, Mariana M, Cairrão E. Pre-eclampsia and eclampsia: An update on the pharmacological treatment applied in Portugal. Journal of Cardiovascular Development and Disease. 2018 Mar 1;5(1).

6. Lew M, Klonis E. Emergency management of eclampsia and severe pre-eclampsia. Emerg Med (Fremantle) [Internet]. 2003 Aug [cited 2022 Jun 16];15(4):361–8. Available from: https://pubmed.ncbi.nlm.nih.gov/14631704/

COMPLICATIONS

Dr. Hiba Khalid, Jawad Basit, Sajeel Saeed

Different maternal and fetal complications of preeclampsia have been explained below.

MATERNAL COMPLICATIONS:

1. Eclampsia:
   - Eclampsia is defined as the incidence of seizures in a woman who already has been diagnosed with preeclampsia. These seizures can occur anytime during the course of the pregnancy either antepartum as well as postpartum (1)
   - Majority cases of eclampsia occur after 28 weeks of gestation
   - The proposed etiology is that poor invasion of maternal endometrial tissue by the fetal cytotrophoblastic cells causes spiral artery dysfunction leading to the release of inflammatory cytokines which precipitate maternal endothelial dysfunction (2)
   - Most women recover fully from the seizures provided adequate medical treatment is provided in time
2. HELLP Syndrome:
   - One of the complications of preeclampsia is HELLP Syndrome characterized by a triad of hemolytic anemia, hepatic dysfunction causing elevated liver enzymes, and thrombocytopenia (3)
   - It occurs in less than 1% of all pregnancies, however, complicates about 10-20% of pregnancies in women who have preeclampsia (3)
   - The pathogenesis of HELLP syndrome is still a mystery.
   - At the center of the etiology of HELLP syndrome, lies endothelial dysfunction leading to platelet activation and a curtailed release of relaxing factor (4)
   - Complement activation, Nitric oxide, and genetic propensity are some of the other theories proposed to explain the sequelae of HELLP syndrome (5)(6)(7)
3. Stroke:
   - Impaired cerebral blood supply, secondary to preeclampsia can lead to stroke
   - Preeclampsia/eclampsia is considered a very strong risk factor for stroke causing a four-times increase in the incidence of stroke (8)

- Hemorrhagic stroke is the most common type of stroke associated with preeclampsia with an overall mortality of 20% (9)
- Aspirin has been the mainstay of treatment both for the treatment of preeclampsia as well as the resulting stroke and has proved to be very efficacious in randomized controlled trials (10)

4. Kidney Disease:
    - Women who have a underlying kidney disease have a higher frequency of preeclampsia (11)
    - In about 76% of preeclamptic multiparous women, glomerular endotheliosis is appreciated on a renal biopsy (12)
    - A recent study concluded preeclampsia to be an independent risk factor for Chronic Kidney Disease (CKD) (13)
    - The underlying mechanism is endothelial dysfunction, podocyte loss and sequelae causing Acute Kidney Injury (AKI) (13)
    - Renal cortical necrosis is a very rare manifestation of preecalmpsia/eclampsia even when fatality occurs secondary to hypertension (14)
5. Liver Dysfunction:
    - Abnormal liver function is noted in about 3-5% of all pregnancies (15)
    - Mainly, the hepatic abnormality is transient and is secondary to pregnancy. The pregnancy induced liver disease maybe secondary to HELLP syndrome, severe preeclampsia or acute fatty liver of pregnancy (15)
    - The most common cause of hepatic tenderness and abnormal hepatic profile in pregnancy is severe preeclampsia (15)
6. Acute Pulmonary Edema:
    - The increased capillary permeability in the presence of normal cardiac output due to preeclampsia may pose a difficulty to intubation and pose towards development of acute pulmonary edema (16)
7. Coagulopathy
    - The body promotes slight intravascular coagulation because of prognosticated hemorrhage during delivery leading to a higher chance hypercoagable states which persists till 6 weeks post-partum (17)
    - The risk of a thromboembolic event after a preeclamptic pregnancy is almost twice compared to normotensive pregnancies (18)
8. Thyroid Disease:
    - Women who have preeclampsia depict higher levels of thyroid stimulating hormones and have consequent hypothyroidism than those who do not have preeclampsia (19)
    - The degree of association is higher if preeclampsia occurs in two consequent pregnancies (19)

- Reduced thyroid vascularity triggered by high sflt-1 levels, which are commonly seen in preeclampsia is the main driving factor for higher incidence of thyroid disease in women who have had preeclampsia (19)

9. TYPE 2 Diabetes Mellitus:
    - Preeclampsia shares common risk factors with diabetes such as obesity, metabolic syndrome, hyperlipidemia, waist circumference, hip circumference etc.(20)
    - Several studies have shown a higher risk of development of T2DM in women who have had preeclampsia during their one or more pregnancies (21)
    - Studies have identified odds ratio and hazard ratio of 1.4 and 1.86 respectively for development of T2DM in women who experienced a preeclamptic pregnancy (22)(23)

FETAL AND NEONATAL COMPLICATIONS:

- Fetuses in the wombs of women who have preeclampsia often have Intrauterine Growth Restriction due to limited supply of nutrients and oxygen from the mother
- In severe preeclampsia or eclampsia, the fetus might be delivered prematurely
- 17.8% of babies born off women who are preeclamptic are Small for gestational age (SGA) compared to 5.6% babies delivered prematurely because of reasons other than preeclampsia (24)
- Regarding Respiratory Distress Syndrome (RDS), 70.6% neonates of women having preeclampsia experience it compared to 60.7% who were prematurely delivered because of other etiologies (24)
- The rate of intrauterine fetal demise in women having preeclampsia is 5.6% (25)
- Due to poor perinatal and neonatal outcomes associated with preeclampsia, Venous Doppler velocimetry must be included as part of evaluation of these fetuses right from the start (26)

REFERENCES

1. Magley M, Hinson MR. Eclampsia. StatPearls [Internet]. 2022 Feb 16 [cited 2022 Jun 19]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK554392/
2. Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi J-M. Pre-eclampsia: pathophysiology, diagnosis, and management. Vasc Health Risk Manag [Internet]. 2011 Jul [cited 2022 Jun 20];7:467. Available from: /pmc/articles/PMC3148420/
3. Kirkpatrick CA. The HELLP syndrome. Acta Clin Belg [Internet]. 2010 [cited 2022 Jun 20];65(2):91–7. Available from: https://pubmed.ncbi.nlm.nih.gov/20491358/
4. Brenner B, Lanir N, Thaler I. HELLP syndrome associated with factor V R506Q mutation. Br J Haematol [Internet]. 1996 [cited 2022 Jun 20];92(4):999–1001. Available from: https://pubmed.ncbi.nlm.nih.gov/8616100/
5. Visontai ZZ, Rigó J, Dézsi L. [The role of vascular nitric oxide (NO) in the pathomechanism of pre-eclampsia]. Orv Hetil [Internet]. 1995 Nov 1 [cited 2022 Jun 20];136(47):2547–51. Available from: https://europepmc.org/article/MED/8532319
6. Hydralazine-induced hepatitis in pregnancy - PubMed [Internet]. [cited 2022 Jun 20]. Available from: https://pubmed.ncbi.nlm.nih.gov/2898436/
7. [PDF] Is the HELLP syndrome due to inherited factors? Report of two cases. | Semantic Scholar [Internet]. [cited 2022 Jun 20]. Available from: https://www.semanticscholar.org/paper/Is-the-HELLP-syndrome-due-to-inherited-factors-of-Berti-Contino/9e947ce546123aea6a2f1aea56d4b3fbc646d7ec
8. James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. Obstet Gynecol [Internet]. 2005 [cited 2022 Jun 20];106(3):509–16. Available from: https://pubmed.ncbi.nlm.nih.gov/16135580/
9. Bushnell C, Chireau M. Preeclampsia and Stroke: Risks during and after Pregnancy. Stroke Res Treat [Internet]. 2011 [cited 2022 Jun 20];2011. Available from: /pmc/articles/PMC3034989/
10. Bateman BT, Schumacher HC, Bushnell CD, Pile-Spellman J, Simpson LL, Sacco RL, et al. Intracerebral hemorrhage in pregnancy: frequency, risk factors, and outcome. Neurology [Internet]. 2006 Aug [cited 2022 Jun 20];67(3):424–9. Available from: https://pubmed.ncbi.nlm.nih.gov/16894102/
11. Williams D, Davison J. Chronic kidney disease in pregnancy. BMJ [Internet]. 2008 Jan 26 [cited 2022 Jun 20];336(7637):211–5. Available from: https://pubmed.ncbi.nlm.nih.gov/18219043/
12. Hypertension in pregnancy: clinical-pathological correlations and remote prognosis - PubMed [Internet]. [cited 2022 Jun 20]. Available from: https://pubmed.ncbi.nlm.nih.gov/7242320/
13. Kattah A. Preeclampsia and Kidney Disease: Deciphering Cause and Effect. Curr Hypertens Rep [Internet]. 2020 Nov 1 [cited 2022 Jun 20];22(11). Available from: https://pubmed.ncbi.nlm.nih.gov/32926258/
14. Stratta P, Canavese C, Colla L, Dogliani M, Bussolino F, Bianco O, et al. Acute renal failure in preeclampsia-eclampsia. Gynecol Obstet Invest [Internet]. 1987 [cited 2022 Jun 20];24(4):225–31. Available from: https://pubmed.ncbi.nlm.nih.gov/3428711/
15. Hay JE. Liver disease in pregnancy. Hepatology [Internet]. 2008 Mar [cited 2022 Jun 20];47(3):1067–76. Available from: https://pubmed.ncbi.nlm.nih.gov/18265410/
16. Brichant JF, Brichant G, Dewandre PY, Foidart JM. [Circulatory and respiratory problems in preeclampsia]. Ann Fr Anesth Reanim [Internet]. 2010 Apr [cited 2022 Jun 20];29(4). Available from: https://pubmed.ncbi.nlm.nih.gov/20347559/
17. Williams D. Long-term complications of preeclampsia. Semin Nephrol [Internet]. 2011 Jan [cited 2022 Jun 20];31(1):111–22. Available from: https://pubmed.ncbi.nlm.nih.gov/21266269/
18. C van W, M M, A C, Y K, M W, MA R. Risk of subsequent thromboembolism for patients with pre-eclampsia. BMJ [Internet]. 2003 Apr 12 [cited 2022 Jun 20];326(7393):791–2. Available from: https://pubmed.ncbi.nlm.nih.gov/12689975/

19. Levine RJ, Vatten LJ, Horowitz GL, Qian C, Romundstad PR, Yu KF, et al. Pre-eclampsia, soluble fms-like tyrosine kinase 1, and the risk of reduced thyroid function: nested case-control and population based study. BMJ [Internet]. 2009 Dec 22 [cited 2022 Jun 20];339(7734):1355–8. Available from: https://pubmed.ncbi.nlm.nih.gov/19920004/
20. Kaaja R, Laivuori H, Laakso M, Tikkanen MJ, Ylikorkala O. Evidence of a state of increased insulin resistance in preeclampsia. Metabolism [Internet]. 1999 [cited 2022 Jun 20];48(7):892–6. Available from: https://pubmed.ncbi.nlm.nih.gov/10421232/
21. Magnussen EB, Vatten LJ, Smith GD, Romundstad PR. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. Obstet Gynecol [Internet]. 2009 Nov [cited 2022 Jun 20];114(5):961–70. Available from: https://pubmed.ncbi.nlm.nih.gov/20168095/
22. Libby G, Murphy DJ, McEwan NF, Greene SA, Forsyth JS, Chien PW, et al. Pre-eclampsia and the later development of type 2 diabetes in mothers and their children: an intergenerational study from the Walker cohort. Diabetologia [Internet]. 2007 Mar [cited 2022 Jun 20];50(3):523–30. Available from: https://pubmed.ncbi.nlm.nih.gov/17187247/
23. Carr DB, Newton KM, Utzschneider KM, Tong J, Gerchman F, Kahn SE, et al. Preeclampsia and risk of developing subsequent diabetes preeclampsia and risk of subsequent diabetes. Hypertens Pregnancy. 2009 Nov;28(4):435–47.
24. Jelin A, Cheng Y, Shaffer B, Kaimal A, Little S, Caughey A. Early-onset preeclampsia and neonatal outcomes. J Matern Fetal Neonatal Med [Internet]. 2010 [cited 2022 Jun 20];23(5):1–5. Available from: https://pubmed.ncbi.nlm.nih.gov/19670045/
25. Saadat M, Nejad SM, Habibi G, Sheikhvatan M. Maternal and neonatal outcomes in women with preeclampsia. Taiwan J Obstet Gynecol [Internet]. 2007 [cited 2022 Jun 20];46(3):255–9. Available from: https://pubmed.ncbi.nlm.nih.gov/17962105/
26. Gruslin A, Lemyre B. Pre-eclampsia: fetal assessment and neonatal outcomes. Best Pract Res Clin Obstet Gynaecol [Internet]. 2011 [cited 2022 Jun 20];25(4):491–507. Available from: https://pubmed.ncbi.nlm.nih.gov/21474384/

SCREENING AND PREVENTION

Dr Muhammad Motsim Shah Hashmi, Maryam Mansoor,

Eclampsia is one of the most severe acute complications of pregnancy, and it carries high morbidity and mortality for both the mother and baby(1). 99% of deaths that occur in developing countries are attributed towards pregnancy related complications; major ones being preeclampsia and eclampsia(2). These diseases not only cause maternal complications but also result in adverse perinatal outcomes for the fetus and newborn (3). Therefore it is very important that early detection of eclampsia should be done as it would allow early treatment and early intervention for prophylactic strategies resulting a decline in such adverse complications.

Screening:

Clinical screening for preeclampsia and eclampsia involves many parameters like:

1. Maternal history and risk factors: Two professional recommendations for screening that use a risk scoring approach are NICE guidelines by UK and ACOG guidelines by USA which are quite similar. These guidelines screen the women on the basis of accurate history and presence of any risk factors. According to these the high risk maternal factors are previous pregnancy with preeclampsia, chronic hypertension, autoimmune disease, diabetes mellitus, systemic lupus erythematosus, chronic kidney disease, multifetal gestation, thrombophilia; and whereas moderate risk factors are age greater than 40 years, inter pregnancy interval greater than 10 years, BMI at first visit greater than 35kg/m^2 and family history of preeclampsia. Under NICE scoring approach if mother has 1 high risk and 2 moderate risk factors she is considered as a high risk whereas presence of only one positive indicator is considered as high risk in ACOG guidelines; and subsequently the mother is advised for early prophylaxis(4).
2. Uterine Artery Doppler: In this procedure color flow mapping is used to identify vessels either transabdominally or transvaginally. It not only helps in screening for preeclampsia but also determines intrauterine growth restriction. Studies have indicated that its detection rate is more significant if done in second trimester but for a good prognosis and early prophylaxis it is done in first trimester(5).
3. Blood Pressure and Mean Arterial Pressure(MAP): It is seen that MAP is a better

screening test for low risk women in 1st and 2nd trimester whereas diastolic blood pressure is a better predictive tool in high risk women between 13 and 20 weeks of gestation(5).

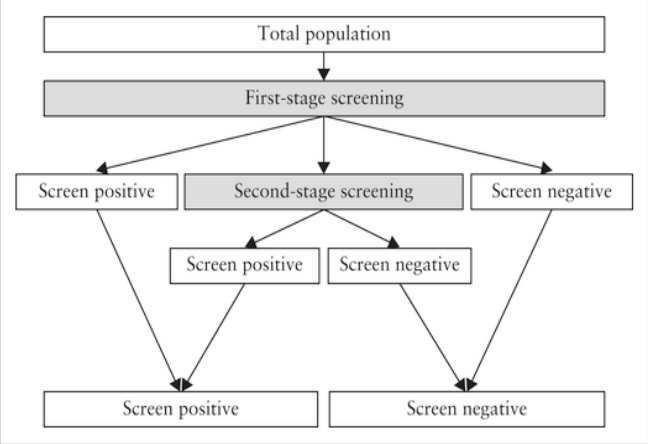


Figure 1: showing two stage screening approach

4. Biomarkers: Angiogenic factors, Pro-angiogenic markers like vascular endothelial growth factor (VEGF) and placental growth factor (PLGF) between 11-13 weeks are important screening markers. Lastly anti-angiogenic markers like serum soluble FIt-1, soluble endoglin, pregnancy associated plasma plasma protein A (PAPP-A), inhibin A and activin A, PP-13, fetal hemoglobin etc are also some of the screening options(5).
5. First trimester combined screening: Even though maternal characteristics and history are an easier and simple approach towards screening but these alone perform quite poorly as their detection rates are only 35%(6). Therefore for a better detection rate multiparametric approaches are advised like the multimarker screening model proposed by fetal medicine foundation (FMF) that has the highest detection rate.(7) This model is based on the use of maternal history and risk factors, mean arterial pressure, uterine artery pulsatility index and maternal serum levels of PLGF and PAPP-A between 11-13 weeks of gestation for screening. This screening method is superior to all other methods and can be considered as a gold standard test(8).
6. Combined screening in 2nd and 3rd trimesters: Even though combined screening in 2nd and 3rd trimester is of superior predictive value than the first trimester screening; with the detection rate being highest in 35-37 weeks because of the close proximity to events. But it is seen that late prophylactic interventions do not prove to be fruitful and therefore early screening should be done as maximum prophylactic effect seems to occur when started early.
7. Screening in 2nd trimester by using Down Syndrome Quadruple test markers: This screening approach is easier and cost-effective as screening for preeclampsia and eclampsia can be done by an already happening screening program for Down syndrome detection(9). In this screening program a combination of inhibin A, free Beta-human chorionic gonadotropin, unconjugated estriol (uE3), and alpha-fetoprotein (AFP) are used for screening for both Down syndrome and preeclampsia(10).
8. Combined screening in low resource settings: In resource limited settings where it is not possible to measure the biochemical markers and/or UTPI, the baseline screening test should be a combination of maternal factors and MAP. A combination of these two showed a detection rate of 67% for preterm preeclampsia which indicates only

this can also be a good predictive tool(4). PAPP-A is also a good alternative to PLGF and UTPI(8).

Another pragmatic practice recommendation for resource limited areas is screening in two stages as seen in the figure 1. In first stage routine screening by maternal factors and MAP in all pregnancies should be done and reserving measurements of PLGF and UTPI for only a subgroup of population in second screening stage, selected on the basis of the risk derived from maternal factors and MAP alone(11).

So in conclusion there are many screening options available from single to multiparametric approaches. But it is observed from many studies that the best and optimal screening option available is the combined screening test in 1st trimester.

Prevention:

For prevention of eclampsia our strategies are limited so our main focus is targeted towards preventing preeclampsia from progressing(12).

- Counselling: Preconception counselling holds significant importance in prevention of eclampsia. It addresses issues such as nutrition, lifestyle, early prediction of preeclampsia, benefits of prenatal visits and fetal surveillance, recurrent risks for future gestation, diagnosis of underlying predisposing factors, and potential impact on future maternal and fetal health(13).However late entry into prenatal care may occur therefore these recommendations should be given at 6 week postpartum visit to reduce the risk of eclampsia in future pregnancies. The women should be guided to keep a tight control over blood pressure, diabetes and should be advised lifestyle modifications to reduce obesity for a better prognosis in future pregnancies(14).

Prevention may be primary, secondary and tertiary. Primary prevention involves avoiding pregnancy in women at high risk for preeclampsia, modifying lifestyles or improving nutrients intake. Secondary prevention is centered on the idea of early intervention, to stop the pathophysiology from progressing into disease or severe complications. Whereas tertiary prevention is based on treatment to avoid complications(15). Some important preventive measures under primary, secondary and tertiary prevention are listed below:

- Lifestyle and nutritional measures: Bed rest, restriction of activity or regular exercise, nutritional measures such as reduced salt intake, use of protein, and antioxidants such as vitamins C and E, garlic, marine oil are advised to all mothers(12,15).
- Calcium Supplementation: It has been suggested that mothers who have a high calcium diet were least likely to develop preeclampsia and associated complications(15). Thus it was suggested that prenatal calcium supplementation should be considered in all low income country settings. Apart from dietary intake, daily 1g of calcium supplementation should be advised to mothers at a greater risk of developing eclampsia(2).
- Aspirin: There is considerable evidence from the ASPREE (Aspirin in Reducing Events in the Elderly) trial that preeclampsia and its complications can be prevented with low

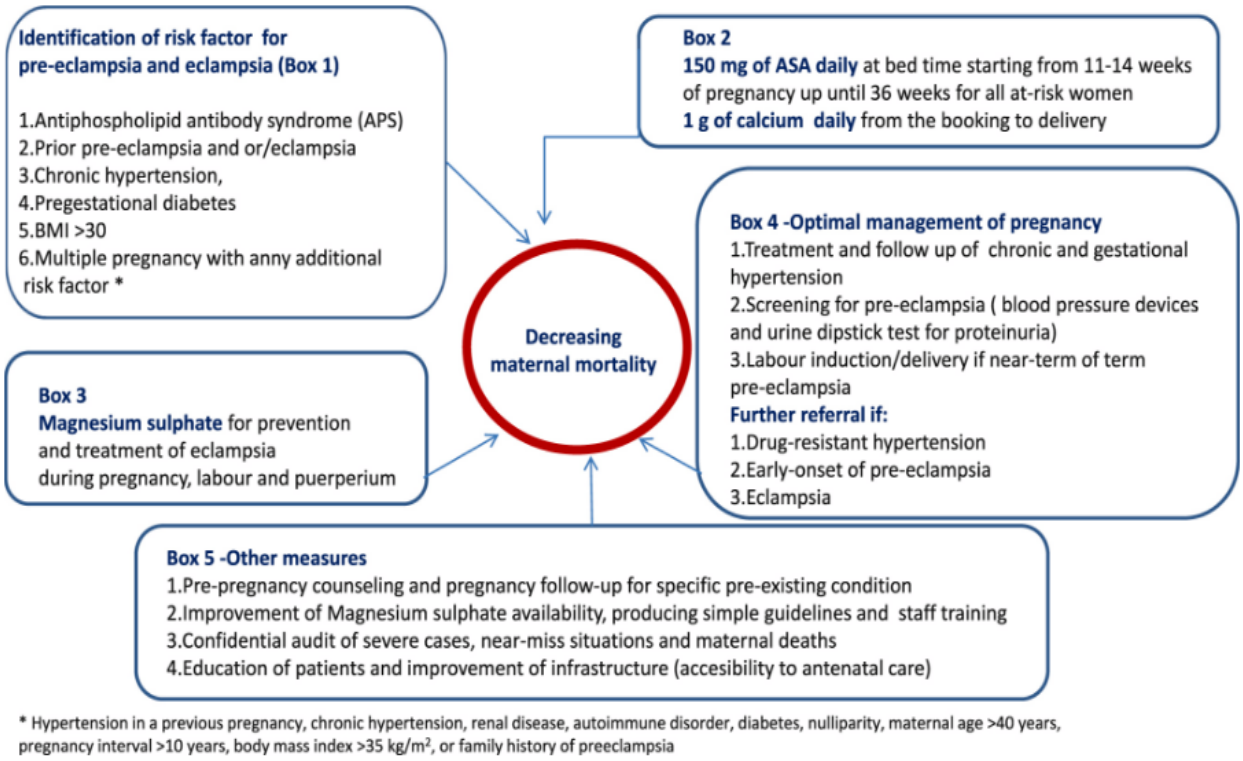
dose aspirin started in between 11-14 weeks of gestation(16). In the most recent studies it was proved that use of aspirin is only beneficial if it is started before 16 weeks of gestation and at a dose of 100-150mg per day at bedtime. It has the potential to decrease the risk of eclampsia by 70%. Aspirin is thought to prevent preeclampsia because of its negative influence on the vasoconstrictive effect of thromboxane-A2, increase in the PLGF gene expression and production and by adjustment of cytokine imbalance(17). Indications for aspirin and risk factors according to SOMANZ, NICE, USPSTF, and ACOG guidelines is given in figure 2(4). Even though use of aspirin has shown no significant complications in either mother or the fetus and is an inexpensive and simple method of prevention. Still it is seen that its universal prophylaxis has not been advised in pregnant ladies because it is suspected to reduce overall adherence rates and for the reason that unnecessary medication should generally be avoided. Therefore it is only advised in mothers that are at a high risk of preeclampsia and eclampsia(17).

SOMANZ-RANZOG	NICE 2010	USPSTF 2014	ACOG 2018
Risk factors	High-risk factors	High-risk factors	High-risk factors
Previous pregnancy with PE	Previous pregnancy with PE	Previous pregnancy with PE	Previous pregnancy with PE
Chronic hypertension	Chronic hypertension	Chronic hypertension	Chronic hypertension
Autoimmune disease	Autoimmune disease	Systemic lupus erythematosus	Systemic lupus erythematosus
Diabetes mellitus	Diabetes mellitus	Diabetes mellitus	Diabetes mellitus
Chronic kidney disease	Chronic kidney disease	Chronic kidney disease	Chronic kidney disease
Multifetal gestation		Multifetal gestation	Multifetal gestation
Nulliparity		Thrombophilia	Thrombophilia
Age >40 years	**Moderate-risk factors**	**Moderate-risk factors**	**Moderate-risk factors**
Interpregnancy interval >10 years	Nulliparity	Nulliparity	Nulliparity
BMI at first visit >35 kg/m^2	Age >40 years	Age >35 years	Age >35 years
Family history of PE	Interpregnancy interval >10 years	Interpregnancy interval >10 years	Inter-pregnancy interval >10 years
Conception by IVF	BMI at first visit >35 kg/m^2	BMI >30 kg/m^2	BMI >30 kg/m^2
	Family history of PE	Family history of PE	Family history of PE
		History of SGA or adverse outcome	History of SGA or adverse outcome
		Sociodemographic characteristics (African American race or low socioeconomic status)	Sociodemographic characteristics (African American race or low socioeconomic status)
Indication for aspirin:	**Indication for aspirin:**	**Indication for aspirin:**	**Indication for aspirin:**
Moderate- to high-risk for PE (no clear distinction of moderate and high risk)	**2 moderate or 1 high-risk factor**	**1 high-risk factor**	**1 high-risk factor**
Dose: unclear	**Dose:** 75 mg/day from 12 weeks	**Dose:** 81 mg/day optimally before 16 weeks	**Dose:** 81 mg/day optimally before 16 weeks
Until 37 weeks or until delivery	Continue daily until delivery	Continue daily until delivery	Continue daily until delivery
		Consider aspirin:	**Consider aspirin:**
		If more than one moderate risk factors	Other established medical indications

Figure 2: Risk indicators and indication for aspirin according to SOMANZ, NICE, USPSTF, and ACOG guidelines

- Magnesium Sulphate: It is the drug of choice for prevention of eclampsia and consequently reduces the chances of maternal mortality. It is more effective than diazepam and phenytoin as an anticonvulsant for treatment of eclampsia. It is not only indicated for prevention of severe preeclampsia and eclampsia but also reduces risk of cerebral palsy and neurological morbidities(18). It is usually given by intramuscular or intravenous rates. If given through intramuscular route, a 4g intravenous loading dose is given initially followed by 10g dose and then by 5g dose all intramuscularly every 4 hours in alternating buttocks. Whereas intravenously it is given as a 4g dose, followed by a maintenance infusion of 1 to 2 g/h by controlled infusion pump(19).
- Some other proposed preventive measures are: diuretics that were believed to prevent preeclampsia as they decrease the salt retention but later in many studies it was suggested that diuretics worsen hypovolemia in pregnancy and therefore they should

not be advised in routine clinical practice. Progesterone is another measure that works by increasing the expression of HLA-G protein thus it helps in improving immunological tolerance between mother and fetus, thus helping in prevention of eclampsia. Nitric oxide is associated with reduction in uterine artery resistance thus indicating that it might be useful for prevention but not enough evidence is available. Thus this is also not advised in clinical routine(15). Lastly low molecular weight heparin has also been indicated as it has the potential to recompense the balance between pro- and antiangiogenic factors. But there is still not sufficient proof available that is why this is also not practiced(17).



* Hypertension in a previous pregnancy, chronic hypertension, renal disease, autoimmune disorder, diabetes, nulliparity, maternal age >40 years, pregnancy interval >10 years, body mass index >35 kg/m², or family history of preeclampsia

Conclusion:

Thus we know that eclampsia even though a fatal disease is still preventable if proper screening and preventive measures are practiced. Figure 3 shows the summary of all those methods that can help to reduce the maternal mortality caused by preeclampsia and eclampsia as proposed by the international academy of perinatal medicine (IAPM) guidelines(18).

REFERENCES

1. Fishel Bartal M, Sibai BM. Eclampsia in the 21st century. Am J Obstet Gynecol. 2022 Feb 1;226(2):S1237–53.
2. Stefanovic V. International Academy of Perinatal Medicine (IAPM) guidelines for screening, prediction, prevention and management of pre-eclampsia to reduce maternal mortality in developing countries. J Perinat Med [Internet]. 2021 Dec 22 [cited 2022 Jun 11]; Available from: https://www.degruyter.com/document/doi/10.1515/jpm-2021-0636/html
3. Screening for Preeclampsia: Recommendation Statement [Internet]. [cited 2022 Jun 11]. Available from: https://www.aafp.org/pubs/afp/issues/2018/0115/od1.html
4. Wertaschnigg D, Reddy M, Mol BWJ, Rolnik DL, da Silva Costa F. Prenatal screening for pre-eclampsia: Frequently asked questions. Aust N Z J Obstet Gynaecol [Internet]. 2019 [cited 2022 Jun 11];59(4):477–83. Available from: https://pubmed.ncbi.nlm.nih.gov/31119729/
5. Park HJ, Shim SS, Cha DH. Combined Screening for Early Detection of Pre-Eclampsia. Int J Mol Sci [Internet]. 2015 Aug 4 [cited 2022 Jun 12];16(8):17952–74. Available from: https://pubmed.ncbi.nlm.nih.gov/26247944/
6. Tan MY, Koutoulas L, Wright D, Nicolaides KH, Poon LCY. Protocol for the prospective validation study: 'Screening programme for pre-eclampsia' (SPREE). Ultrasound Obstet Gynecol [Internet]. 2017 Aug 1 [cited 2022 Jun 12];50(2):175–9. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/uog.17467
7. Ortved D, Hawkins TLA, Johnson JA, Hyett J, Metcalfe A. Cost-effectiveness of first-trimester screening with early preventative use of aspirin in women at high risk of early-onset pre-eclampsia. Ultrasound Obstet Gynecol [Internet]. 2019 Feb 1 [cited 2022 Jun 12];53(2):239–44. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/uog.19076
8. From first-trimester screening to risk stratification of evolving pre-eclampsia in the second and third trimesters of pregnancy: a comprehensive approach [Internet]. [cited 2022 Jun 12]. Available from: https://boris.unibe.ch/136429/1/Poon_et_al-2019-Ultrasound_in_Obstetrics_%26_Gynecology.pdf
9. Wald NJ, Morris JK, Ibison J, Wu T, George LM. Screening in early pregnancy for pre-eclampsia using Down syndrome Quadruple test markers. Prenat Diagn. 2006 Jun;26(6):559–64.
10. Wald NJ, Morris JK. Multiple marker second trimester serum screening for pre-eclampsia. J Med Screen [Internet]. 2001 [cited 2022 Jun 12];8(2):65–8. Available from: https://pubmed.ncbi.nlm.nih.gov/11480445/
11. Wright D, Gallo DM, Gil Pugliese S, Casanova C, Nicolaides KH. Contingent screening for preterm pre-eclampsia. Ultrasound Obstet Gynecol [Internet]. 2016 May 1 [cited 2022 Jun 12];47(5):554–9. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/uog.15807
12. Sibai BM. Diagnosis, prevention, and management of eclampsia. Obstet Gynecol. 2005 Feb;105(2):402–10.
13. Witlin AG. Counseling for women with preeclampsia or eclampsia. Semin Perinatol. 1999;23(1):91–8.
14. Balogun OAA, Sibai BM. Counseling, Management, and Outcome in Women with Severe Preeclampsia at 23 to 28 Weeks' Gestation. Clin Obstet Gynecol. 2017;60(1):183–9.
15. Bezerra Maia e Holanda Moura S, Marques Lopes L, Murthi P, Da Silva Costa F. Prevention of Preeclampsia. J Pregnancy [Internet]. 2012 [cited 2022 Jun 12];2012. Available from: /pmc/articles/PMC3534321/
16. Poon LC, Sahota D, Li YL, Pan Y. Screening and prevention of preeclampsia. Matern Med [Internet]. 2019 Jul 1 [cited 2022 Jun 12];1(1):25–30. Available from: https://journals.lww.com/mfm/Fulltext/2019/07000/Screening_and_Prevention_of_Preeclampsia.6.aspx
17. Wertaschnigg D, Reddy M, Mol BWJ, Da Silva Costa F, Rolnik DL. Evidence-Based Prevention of Preeclampsia: Commonly Asked Questions in Clinical Practice. J Pregnancy [Internet]. 2019 [cited 2022 Jun 12];2019. Available from: /pmc/articles/PMC6699262/
18. International Academy of Perinatal Medicine (IAPM) guidelines for screening, prediction, prevention and management of pre-eclampsia to reduce maternal mortality in developing countries [Internet]. [cited 2022 Jun 11]. Available from: https://www.degruyter.com/document/doi/10.1515/jpm-2021-0636/html
19. Lu JF, Nightingale CH. Magnesium sulfate in eclampsia and pre-eclampsia. Pharmacokinetic principles. Clin Pharmacokinet. 2000;38(4):305–14.

GUIDELINES AND RECENT ADVANCES

Dr Faiza Akram, Komal Basharat

GUIDELINES FOR THE MANAGEMENT OF PRE- ECLAMPSIA AND ECLAMPSIA:[1]

In outpatient Heath Care Facility:

1.MONITORING THE PRE ECLAMPTIC WOMAN:[1]

- Making all possible efforts to reduce the blood pressure from 160/110 mm Hg to 135/85 mmHg.
- Reducing the occurrence of seizures by administering **MgSO4 regimen.**
- Maintaining an appropriate fuild balance to prevent pre eclamplsia associated complication of the lungs.i.e.pulmonary edema that can have fatal consequences.i.e.death of the mother.
- If the BP of the pregnant woman shoots above 160/110mm Hg ,physicians should consider hospitalizing the patient after informing the authorities.
- Simultaneous monitoring of the organ systems of the pre eclamptic woman should be carried out and physician should look for the appearance of the following symtoms:
    1. Proteinuria
    2. High blood pressure
    3. Papilledema
    4. Epigastric pain
    5. +ve Deep tendon reflexes
- Utilize **MEOWS** scoring as an effective tool to highlight the pregnant woman at higher risk of suffering from serious obstetric complications i.e. pre eclampsia,etc.It is of remarkable utility for both the recognized obstetricians and midwives.
- Pre eclamptic women with high SBP(systolic blood pressure) are at increased risk of suffering from stroke therefore they should be managed as soon as possible.

2.MONITORING THE FETUS:[1]

- Administer IV steroids i.e. betamethasone, dexamethasone, etc for the timely maturation of the lungs of the fetus.
- Carry out appropriate investigations i.e cardiotocography, USG, etc to ensure the timely management of pre eclampsia associated complications that might arise in the fetus.

- Perform Umblical Artery Doppler in the 3rd trimester of pregnancy .Abnormal results of the doppler indicate suspected pre eclampsia.
- If Umblical Artery Doppler fails to provide the required results, then MCA Doppler can be utilized to assess the cardiovascular distress,anemia or hypoxia in the fetus.
- It is absolutely essential to carry out a continuous CTG on the fetus while and for half an hour after administering IV hydralazine to a pregnant woman because it has the potential to cause bradycardia in the fetus because the fetal heart rate drops with the drop in maternal blood pressure.

3.PHARMACOLOGIC THERAPY:[1]

- Orally administered nifedipine is safe and has the same efficacy as the one administered via sublingual route.
- Magnesium sulphate regimen should be administered to the preeclamptic woman to prevent eclampsia and it is advisable to continue it 1 day after the delivery and 1 day after the last episode of eclampsia.
- Administer colloid expanders before antihypertensive drugs to prevent an excessive drop in blood pressure of the mother and subsequent reduced blood supply to the fetus.
- Pregnant woman at risk of suffering from pre eclampsia should be advised to restrict their fluid intake.
- Administer diuretics to the pre eclamptic woman who have developed pulmonary edema.

4.CONTRAINDICATED DRUGS AND PRACTICES:[1]

- LABETALOL in asthma.
- NIFEDIPINE with MAGNESIUM SULPHATE because interaction of the two causes muscle fatigue,drop in blood pressure of the mother and subsequent fetal hypoxia.
- NSAIDs till fluid recovery.
- Ergometrine in severe cases.
- Neglecting timely and adequate fluid management is the most definite culprit behind the development of pulmonary edema which threatens the life of the mother.

5.THE ULTIMATE TREATMENT OF ECLAMPSIA;[1]

1. Delivery
2. In case,the vitals of the mother are dropping rapidly ,carry out the following steps;

- Take measures to treat and prevent the recurrence of eclampsia.

- Administer antihypertensives.
- Ensure appropriate oxygenation of the fetus.
- administer Syntocinon (5 units)
- Induce labour by administering prostaglandins.

WHO GUIDELINES FOR THE MANAGEMENT OF ECLAMPSIA AND PRE ECLAMPSIA:

1.MgSO4 regimen:

WHO guidelines for management of eclampsia in the pre eclamptic women points out at the significance of administering magnesium sulfate regimen to prevent convulsions.i.e. eclampsia in pre eclamptic women.In a health care facility where administering a MgSO4 regimen is not possible, physicians should administer an MgSO4 loading dose and refer to the nearest tertiary health care hospital.[2]

2.Aspirin prophylaxis:

WHO guidelines also suggest the use of aspirin and appropriate anti-hypertensive drugs[3].75mg acetylsalicylic acid decreases the risk of suffering from pre eclampsia in at risk populations ,however the effect is significant in the high risk group[2].

3.Vitamin supplementation:

Vit D,E and C supplementation is strictly prohibited.However, Benjamin Brown in his review article on the vitamin supplementation pointed out at the fact that vitamin C deficient populations i.e.smokers,diabetics, etc should be guided to increase the intake of vitamin C rich diet because it does prevent the fetal membranes from disintegrating before term and has a prophylactic role against UTIs (urinary tract infections)during pregnancy[4].

4.Bed Rest:

Strict bed rest does not decrease the possibility of a woman to suffer from pre eclampsia or eclampsia.However, hospitalizing a pre eclamptic woman for monitoring and managing pre eclampsia related complications should be considered to ensure the safety of the mother and the child[2].

5.Salt intake:

,As per Cochrane Review of the 2 RCTs ,restricting salt intake does not saves a pregnant woman from suffering from pre eclampsia and pre eclampsia related complications[2]. but the WHO guidelines do suggest restricting dietry intake of salt during pregnancy [3].

6.Ca SUPPLEMENTATION:

WHO guidelines recommend calcium supplementation in the calcium deficient populations only.it prohibits calcium supplementation in the diets of the populations with adequate calcium intake[3].Calcium supplementation does decrease the risk of developing pre eclampsia by more than 50%.However ,calcium supplements should not be administered simultaneously with iron supplements because calcium decreases absorption of iron therefore it is advised to take both the supplements separately with a considerable time interval between them[2].

However Dr. Peter Von Dadelzen argued that calcium supplementation might obscure the onset of pre eclampsia making it difficult for the physicians to manage the associated complications that will most definiitely arise later[2].

7.BROADCASTING THE GUIDELINES:

WHO also points out at the importance of the collaborative effort of healthcare professionals and governmental and NGOs and community health care workers in designing and disseminating the guidelines for quality improvement in the management of complications.i.e eclampsia,etc in the pre eclamptc women[3].

8.ESSENTIAL DRUG LIST AND EQUIPMENT:

- Calcium gluconate(administered in case of Magnesium toxicity which might arise while trying to limit eclamptic seizures by administering MgSO4 to the pre eclamptic women)
- MgSO4
- Anti hypertensives i.e.labetalol,nifedipine,hydralazine or methyldopa.
- Calcium and acetylsalicylic acid formulations.
- Essential medical and surgical tools.
- Eclampsia Boxes to facilitate the quick management of pre eclamptic women[3].

9.ARE THE GUIDELINES BEING IMPLEMENTED?

Analyzing local critical indicators is also deemed essential to ensure that the guidelines suggested by WHO are being enforced in all the health care facilities[3].

AAFP GUIDELINES:

- Keeping the pre eclamptic women under close observation in ICU or HDU for 72 hours after delivery is essential to manage the subsequent complications and any episode of postpartum eclampsia because pre eclamptic women are at higher risks of suffering from an episode of eclampsia till 2 days after delivery[5].
- MgSO4 is more effective than other anticonvulsants to prevent and treat seizures[5].
- Physicians should not Induce labour by administering prostaglandins to the pre eclamptic women in the time window between 34 to 36 weeks because it might result in premature birth of the neonate with LBW and RDS and necrotizing enterocolitis adversely affecting his ability to survive after birth[5].
- Simple vaginal delivery should be carried out if possible[6].
- Caeserean section is only indicated if the patient is suffering from recurrent episodes of eclampsia despite administering MgSO4 regimen or persistently elevated BP despite administering antihypertensives before 37 weeks of pregnancy[6].
- A combination of nifedipine+labetalol or labetalol+hydralazine is recommended to control BP of the mother after delivery[5].

NICE GUIDELINES:

1.FOR PRE ECLAMPTIC WOMEN:[7]

Pregnant women during prenatal checkups if present with the following signs need to be hospitalized and managed on priority basis to save the mother and the child from fatal outcomes of pre eclampsia:

1. Blood pressure greater than 160/110mm Hg,
2. High creatinine levels
3. High ALT levels
4. Thrombocytopenia
5. Signs of an upcoming episode of eclampsia or pulmonary edema

- It is advisable to utilize fullPIERS and PREP-S models to identify pregnant women at high risk of suffering from pre eclampsia
- Take blood pressure measurements after every half an hour while trying to reduce the high blood pressure.
- When BP drops below 160/110 then decrease the frequency of measuring BP to 4 times a day.
- Carry out the following investigations and relevant tests

1. Dipstick proteinuria test when new symtoms of pre eclampsia in addition to the already existing ones appear
2. CBC, thrice a week
3. LFTs, thrice a week
4. RFTs thrice a week

- It is advisable to carry induce labour in the pre eclamptic women after 37 weeks of pregnancy.
- Replace methyldopa with any other alternative BP lowering medications is after delivery.
- Overhydration with IV fluids is strictly prohibited before administering analgesia to the pre eclamptic women
- Indications for the use of MgSO4 is not only limited to a suspicion of an upcoming episode of eclampsia .But its usage is also indicated upon the appearance of the following symtoms:
    1. headache
    2. visual disturbances
    3. GIT symtoms
    4. Oliguria
    5. resistant high blood pressure
    6. deranged creatinine levels
    7. deranged AST levels
    8. thrombocytopenia.
- Anti hypertensives of choice in pre eclampsia include labetalol,nifedipine and hydralazine.
- NICE guidelines recommend prior and simultaneous administration of crystalloids with IV hydralazine
- Corticosteroids for managing HELLP syndrome which also is one of the manifestations of pre eclampsia.

2.FOR THE MANAGEMENT OF PRE ECLAMPSIA RELATED COMPLICATIONS IN THE FETUS:[7]

Guidelines for time carrying out investigations on the fetus are:

- Frequently auscultate the fetal heart.
- Do simultaneously perform USG and CTG on the fetus when you are carrying out investigations to diagnose pre eclampsia in the pregnant woman,
- If USG turns out to be normal, then consider performing USG twice a month at regular intervals.

- If CTG turns out to be normal,then it should only be repeated when needed.
- NICE does also suggest carrying out amniocentesis which is an invasive prenatal test for the assessment of the amniotic fluid to determine the degree of maturation of lungs of the fetus.

3.TREATING HYPERTENSION IN THE LACTATING MOTHERS POSTPARTUM:[7]

- The use of diuretics and ARBs is strongly prohibited.
- Physicians should suggest anti hypertensives which are administered once daily.
- Enalapril should be utilized to lower the blood pressure after delivery but simultaneously, it is also essential to carry out RFTs and monitor the serum potassium levels of the mother and serum potassium levels of the mother need to be monitored.
- Antihypertensives administered to the lactating mothers postpartum can pass via breast milk to the child being breastfed but since the amount crossing the placental barrier is so minimal,they fail to significantly affect the blood pressure of the fetus. Despite the low concentrations of antihypertensives entering the body of the infant being breastfed,the lactating mother should be advised to keep her child under close observation and look out for the appearance of symtoms i.e. drowsiness,pallor,poor suckling reflex, lethargy,hypothermia,etc and seek medical help as early as possible.
- Pre eclamptic women are at increased risk of suffering from cardiovascular diseases in the future (hurrel)therefore NICE guidelines do suggest the pregnant women to adopt healthy dietry habits,lifestyle modifications and maintain their body weight within a favourable range for prevention purpose.

- Pre eclamptic women are also at risk of suffering from uremia after delivery but there is a very minute chance of them suffering from this pre eclampsia related postpartum complication therefore no followup is needed for this purpose.

GUIDELINES FOR THROMBOPROPHYLAXIS:

- Thrombophilia is one of the characteristic feature that pops up during gestation .It may give rise to the formation of thrombi and emboli that would subsequently narrow the vessels or clog them giving rise to GVCs one of which is pre eclampsia which is a potentially lethal condition.
- Suggestion to utilize low molecular weight heparin for the prevention of pre eclampsia is supported by limited and controversial evidence in one study[8].
- But ASA and LMWH are being increasingly used for the prevention of hypercoagulable state and subsequent pre eclampsia.

RECENT ADVANCES:

1.MODIFIED DEFINITIONS:

- **PRE ECLAMPSIA:**
  As per AAFP guidelines,
  'Proteinuria is no longer a pre requisire to define the pathology.It is now defined as persistent high blood pressure in addition to any other severe feature [5]after 20 weeks of pregnancy[9]. '
- **ECLAMPSIA:**
  'Eclampsia is defined as the complication of pre eclampsia common in the later half of pregnancy and postpartum. It is characterized by marked 60 to 90 second [6]convulsions in the pre eclamptic woman who is suffering from trophoblastic disease'

2.SCREENING:

SIGNIFICANCE[10]**:**

Pregnant women at high risk of suffering from pre eclampsia should be screened in all the 3 trimesters of pregnancy.

- 1st trimester screening is significant because it provides the physicians with the opportunity of prescribing low dose aspirin prophylaxis to the pregnant women at risk[10]
- 2nd and 3rd trimester screening points out the at risk pregnant women who should be kept under close observation to manage pre eclampsia related complications in the most effective way to ensure the safety of the mother and the child[10].

SCREENING FOR SERUM BIOMARKERS:

- Pregnant women at high risk of suffering from pre eclampsia used to be screened for term pre eclampsia by utilizing 4 biomarkers i.e. UTAPI,MAP,PIGF and sFlt1. During the 19 to 24 weeks of pregnancy[10].

CONTINGENT SCREENING:

- One of the recent advances in the screening for pre eclampsia is contingent screening .A study conducted in UK pointed out at the *efficacy* and *cost effectiveness* of CONTINGENT SCREENING .CONTINGENT SCREENING has been used in the past for down syndrome .Now introducing this screening technique for the diagnosis of pre eclampsia has further facilitated the field of obstetrics and gynaecology[10].

- The process of screening is carried in two episodes
    1. The first round utilizes history records,patient demographics,uterine artery pulsaltilty index (UTAPI) and MAP measurements.
       It serves to segregate the low risk pregnant women in whom further investigations will most definitely be futile from the high risk pregnant women in whom further investigations i.e. sflt1, plgf measurements will identify the women at risk of pre eclampsia[10].
    2. Screening 40% of the population (i.e. the high risk group)in the second episode by utilizing sFlt1 and PlGF measurements makes contingent screening a really cost effective screening tool[10].

3.ANGIOGENC BIOMARKERS:

The ratio of biomarkers i.e.soluble fms like tyrosine kinase1/placental growth growth factor is the most reliable measurement to consider while screening at risk pregnant women for preeclampsia within the first 4 weeks of pregnancy.The study suggests including elevated levels of these biomarkers while defining pre eclampsia in addition to hypertension and proteinuria[11].Moreover, these angiogenic markers do facilitate in the rapid screening for pre eclampsia providing the physician with a more wide time window to reduce fatal maternal outcomes[12].

4.EXTRACELLULAR VESICLES:

WHAT ARE EVs?

EVs are released into the maternal serum by numerous kinds of cells including those of placenta.They are composed of lipids and are spherical in shape with their diameter ranging from 10 nm to 1 um.EVs with sizes less than 200 nm are termed as exosomes and those with sizes greater than 150 nm are termed as microvesicles .Their size measurements are indicative of a number of factors.For instance, EVs greater than 1um in size constitute residual bodies of cellular destruction mechanisms.Identifying the sources of various kinds of EVs depends upon the markers present on their surface[13].

UTILITY IN THE DIAGNOSIS OF PRE ECLAMPSIA:

In the beginning of gestation period ,EV release into the maternal serum from placenta increases rapidly .

- High EV levels particularly of exosomes can be detected at approximately 6 weeks of pregnancy[13].
- A marked discrepancy in EV count per mL blood in pregnant women before and after conception is being utilized to identify the at risk pregnant women[13].

- Women who suffered from pre eclampsia had higher values of EV per ml blood and PLAP per ml blood when investigated in the beginning of pregnancy[13].

5.OPTHALMIC ARTERY DOPPLER:

I.Sapantzoglou in his prospective study analyzed and suggested taking PSV measurements(measured during 19 to 23 weeks of pregnancy)into consideration while predicting the risk of pre eclampsia in pregnant women[14].

To accomplish the feat ,the researcher carried out doppler studies on the ophthalmic arteries of pregnant women who were at high risk of suffering from pre eclampsia later in pregnancy[14].

First and second peak systolic velocities were recorded via ophthalmic artery Doppler[14].

Women in whom PSV turns out to be higher developed pre eclampsia later in pregnancy therefore the researcher suggests including PSV in addition to angiogenic biomarkers in the screening techniques utilized to predict the risk of suffering from pre eclampsia later[14].

- ***PSV is the ratio of second peak systolic velocity to the first peak systolic velocity***[14] .

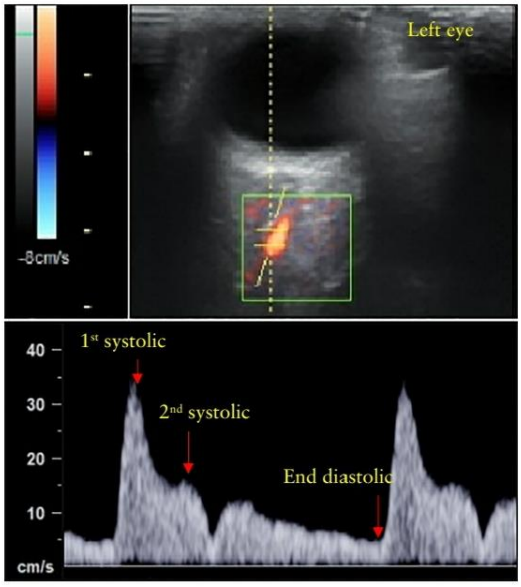


FIGURE:[14]

A. USG of left orbit showing Blood flow through ophthalmic artery.

B. Labeled Ophthalmic Artery Doppler.

REFERENCES:

[1] MANAGEMENT OF SEVERE PRE-ECLAMPSIA AND ECLAMPSIA. 2012.

[2] WHO recommendations for Prevention and treatment of pre-eclampsia and eclampsia. n.d.

[3] WHO RECOMMENDATIONS FOR PREVENTION AND TREATMENT OF PRE-ECLAMPSIA AND ECLAMPSIA Implications and Actions Background. n.d.

[4] Brown B, Wright C. Safety and efficacy of supplements in pregnancy. Nutr Rev 2020;78:813–26. https://doi.org/10.1093/nutrit/nuz101.

[5] Leeman L, Dresang LT. Hypertensive Disorders of Pregnancy. vol. 93. 2016.

[6] Leeman L, Fontaine P. Hypertensive Disorders of Pregnancy. 2008.

[7] Hypertension in pregnancy: diagnosis and management NICE guideline. 2019.

[8] Papadakis E, Pouliakis A, Aktypi A, Christoforidou A, Kotsi P, Anagnostou G, et al. Low molecular weight heparins use in pregnancy: A practice survey from Greece and a review of the literature. Thromb J 2019;17. https://doi.org/10.1186/s12959-019-0213-9.

[9] Diagnosis and Management of Preeclampsia - American Family Physician. 2004.

[10] Litwinska M, Litwinska E, Bouariu A, Syngelaki A, Wright A, Nicolaides KH. Contingent screening in stratification of pregnancy care based on risk of pre-eclampsia at 19–24 weeks' gestation. Ultrasound Obstet Gynecol 2021;58:553–60. https://doi.org/10.1002/uog.23742.

[11] Flint EJ, Cerdeira AS, Redman CW, Vatish M. The role of angiogenic factors in the management of preeclampsia. Acta Obstet Gynecol Scand 2019;98:700–7. https://doi.org/10.1111/aogs.13540.

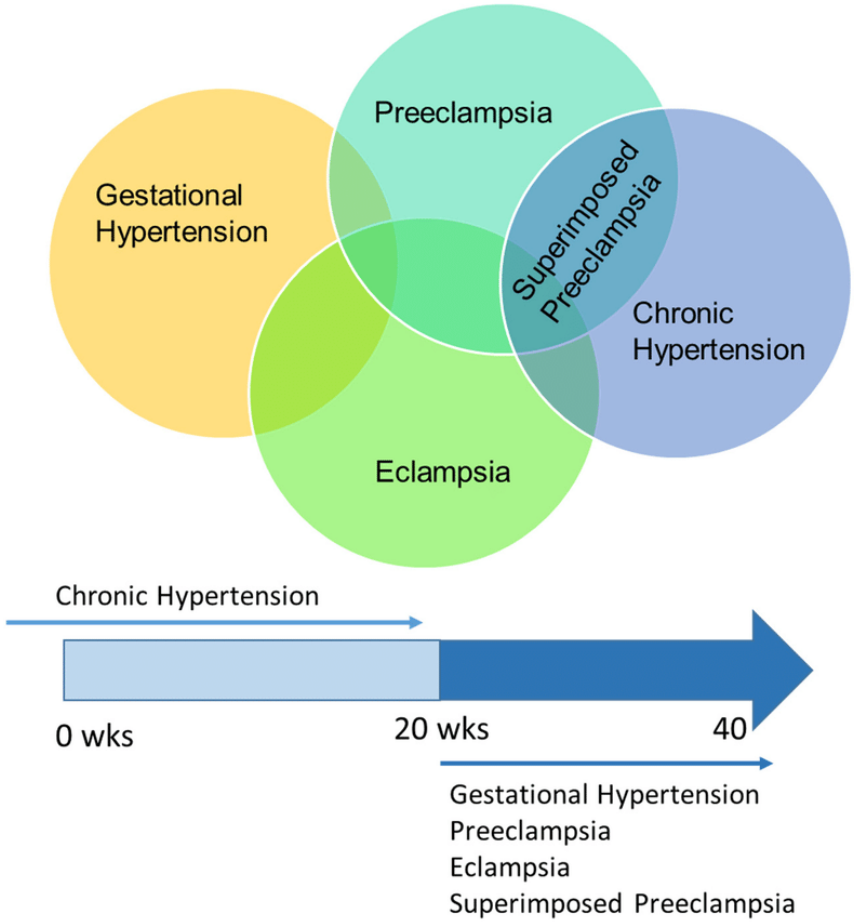
[12] Hurrell A, Duhig K, Vandermolen B, Shennan A. Recent advances in the diagnosis and management of pre-eclampsia. Fac Rev 2020;9. https://doi.org/10.12703/b/9-10.

[13] Morgan TK. Cell- and size-specific analysis of placental extracellular vesicles in maternal plasma and pre-eclampsia. Transl Res 2018;201:40–8. https://doi.org/10.1016/j.trsl.2018.08.004.

[14] Sapantzoglou I, Wright A, Arozena MG, Campos RV, Charakida M, Nicolaides KH. Ophthalmic artery Doppler in combination with other biomarkers in prediction of pre-eclampsia at 19–23 weeks' gestation. Ultrasound Obstet Gynecol 2021;57:75–83. https://doi.org/10.1002/uog.23528.

SUMMARY OF DIAGNOSIS AND MANAGEMENT OF HYPERTENSIVE DISORDERS OF PREGNANCY

Dr Ambreen Shahnaz, Zainab Idrees



CHRONIC HYPERTENSION

A high blood pressure (140/90 mm Hg) that is present before 20 weeks of gestation and continues to persist at least 12 weeks after the delivery

PREECLAMPSIA

Persistent high blood pressure in addition to any other severe feature (1)after 20 weeks of pregnancy(2)

ECLAMPSIA

Marked 60 to 90 second convulsions in the pre eclamptic woman who is suffering from trophoblastic disease

SUPERIMPOSED PREECLAMPSIA

In a state of incessant hypertension, when a pregnant woman experiences a sudden rise in blood pressure or antihypertensive therapy needs to be modulated after 20 weeks of gestation

GESTATIONAL HYPERTENSION

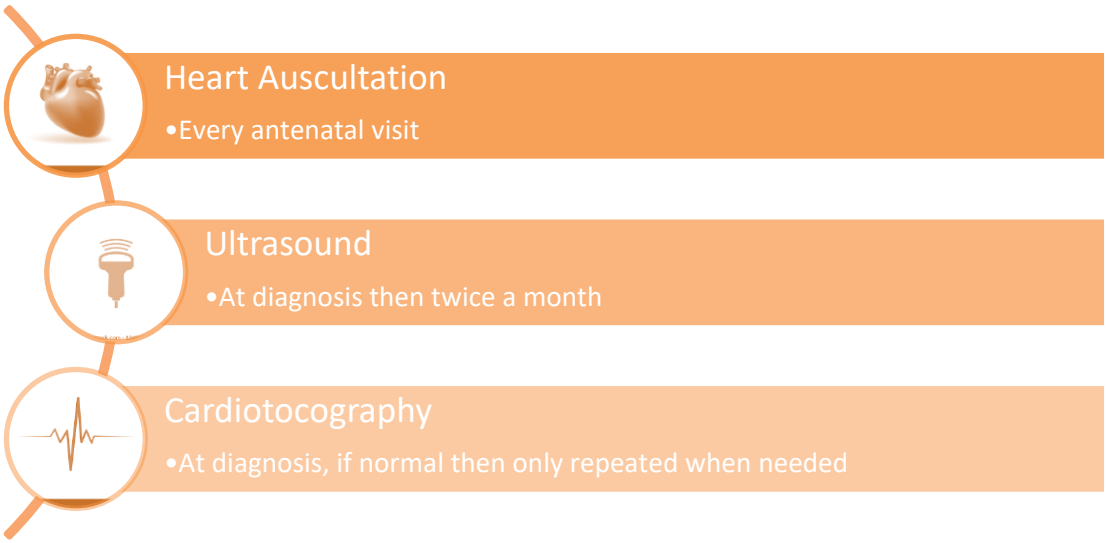
Hypertension without evidence of proteinuria. Occurs after 20 weeks of gestation. May progress to preeclampsia

Figure 1: Different Hypertensive Disorders of Pregnancy(3)

Blood Pressure	140/90 – 159/109	>160/110
Admission	Not routinely indicated, required if clinical concerns	Admit
Initial Management	**All patients with BP above 140/90 need pharmacological treatment** Anti hypertensive of choice include labetalol, nifedipine and hydralazine. *Aim for BP 0F 135/85mmHg or less.*	
Monitoring	Twice a week (48hrly if pre eclampsia)	Every 15 – 30 min

<table>
<tr><th colspan="4">Determine whether patient has Hypertension(Chronic or Gestational) or Pre eclampsia</th></tr>
<tr><td rowspan="2">Proteinuria (Dipstick)</td><td>Negative</td><td colspan="2">BP < 160/110 ---- Repeat twice a week
BP > 160/110 ---- Repeat Daily</td></tr>
<tr><td>Positive</td><td>Blood Tests
Full blood count
Liver Function
Renal function</td><td>Evidence of hemolysis
Falling Platelet Count
Albumin Creatinine Ratio (Diagnostic Threshold: 8mg/mmol)
Abnormal LFT
Worsening Renal Function</td><td>Symptoms & Signs of Preeclampsia
Severe Headache
Problem with Vision
Severe Pain just below the ribs
Vomiting
Sudden swelling of face, hands or feet</td></tr>
</table>

FETAL ASSESSMENT



DELIVERY

Do not offer planned early birth <37 weeks unless there are other medical indications (severe pre eclampsia)

After 37 weeks timing of and maternal and fetal indications for delivery should be agreed between woman and senior obstetrician

If planned early birth offer antenatal corticosteroids and magnesium sulphate if indicated (NICE Guidelines)

SCREENING FOR ECLAMPSIA (PARAMETERS)

- MATERNAL HISTORY AND RISK ASSESSMENT ON THE BASIS OF NICE AND AGOG GUIDELINES
  - GOLD STANDARD TEST
    MULTIMARKER SCREENING MODEL BY FMF
    (HIGHEST DETECTION RATE)
- UTERINE ARTERY DOPPLER THAT ALSO DETERMINES IUGR
  (DONE IN FIRST OR SECOND TRIMESTER)
  - COMBINED SCREENING IN 2ND AND 3RD TRIMESTER
    (LATE PROPHYLACTIC INTERVENTION)
- BLOOD PRESSURE AND MEAN ARTERIAL PRESSURE FOR LOW RISK WOMEN
  - 2ND TRIMESTER SCREENING BY DOWN SYNDROME QUADRUPLE TEST MARKERS.
    (EASIER AND COST EFFECTIVE)
- BIOMARKERS LIKE VEGF AND PLGF BETWEEN 11-13 WEEKS CAN BE A PREDICTIVE TOOL
  - COMBINATION OF MATERNAL FACTORS AND MAP
    (IN RESOURCE LIMITED SETTINGS)

MANAGEMENT OF ECLAMPSIA

PHARMACO-THERAPHY

- ANTICONVULSANTS:
- MgSO4 IS AN IDEAL THERAPY.
- LOADING DOSE: *4-6G AS AN IV BOLUS*
- MAINTENANCE DOSE: *1-3g/hour*
- IF THE PATIENT IS UNRESPONSIVE TO MgSO4 LORAZEPAM CAN BE USED. PHENYTOIN CAN BE A DRUG OF CHOICE BUT UNSAFE FOR MOTHER AND CHILD.
- ANTIHYPERTENSIVES:
- LABETOLOL IS REGARDED AS A FIRST-LINE AGENT. HYDRALAZINE CAN BE USED IN PATIENTS REFRACTORY TO LABETOLOL.

DELIVERY

- THE DEFINITIVE TREATMENT FOR CONTROL OF EPILEPTIC SEIZURES IS THE DELIVERY OF THE FETUS, MODE BASED ON OBSTETRIC INDICATIONS.
- (A CESARIAN SECTION MAY BE NECESSARY)

SUPPORTIVE CARE

- GIVING IV FLUIDS,
- ENSURE MATERNAL OXYGENATION
- SUPPORT RESPIRATORY AND CVS FUNCTIONS.

POSTPARTUM HTN

- A COMBINATION OF NIFEDIPINE WITH LABETALOL IS SUGGESTED IN TREATING HTN POSTPARTUM

Complications of Preeclampsia and Eclampsia

Fetal and neonatal complications

FETAL COMPLICATIONS:

Pre eclamptic women often suffer from **IUGR** and are at higher risk for **premature delivery.** 17.8% babies are small for gestational age.

Intrauterine **fetal demise** rate is 5.6%.

NEONATAL COMPLICATIONS:

Regarding **RDS** 70.6% neonates of preeclamptic women experience it.

Maternal complications

1. ***HELLP SYNDROME:***

It is triad of hemolytic anaemia, hepatic dysfunction and thrombocytopenia. The endothelial dysfunction lies at the centre of etiology.

2. ***STROKE:***

Preeclampsia is a strong risk factor and causes four times increase in the incidence of stroke. Haemorrhagic stroke is the most common type associated with it.

3. ***KIDNEY DISEASE:***

Preeclampsia is an independent risk factor for causing CKD. E underlying mechanism is endothelial dysfunction and podocyte loss.

4. ***LIVER DYSFUNCTION:***

The pregnancy induced liver disease may be secondary to HELLP syndrome or primary however the hepatic abnormality is transient.

5. ***ACUTE PULMONARY EDEMA:***

Preeclampsia increases the capillary permeability and poses risk for pulmonary edema.

6. ***COAGULOPATHY:***

The risk for the development of thromboembolic phenomenon is twice in a preeclamptic pregnancy.

7. ***THYROID DISEASE:***

Preeclamptic women have higher levels of thyroid hormones and consequent hypothyroidism. High SRTL-1 levels are the main driving factor.

8. ***TYPE 2 DIABETES MELLITUS***

Preeclampsia share common risk factors with diabetes. Odd and hazard ratios are 1.4 and 1.86 respectively.

ABBREVIATIONS USED:

BP: Blood pressure

MgSO4: Magnesium Sulphate

MEOWS: Modified Early Obstetric Warning Score

SBP: Systolic Blood Pressure

IV: Intravenous

CTG:Cardiotocography

MCA: Middle Cerebral Artery

USG: Ultrasonography

WHO: World Health Organization

RCTs:Randomized Control Trials

RFTs: Renal Function Tests

NGOs: Non Governmental Organizations

ICU: Intensive Care Unit

HDU: High Dependency Unit

CBC: Complete Blood Count

LFTs:Liver function Tests

NICE: National Institute for Health and Care Excellence

GAIN: Guidelines and Audit Implementation Network

ARBs: Angiotensin Receptor Blockers

GVCs:Gestational Vascular Complications

ASA:AcetylSalicylic Acid

LMWH: Low molecular Weight Heparin

AAFP: American Academy of Family Physicians

UTAPI:Uterine Artery Pulsatility Index

MAP:Mean Arterial Pressure

sFlt-1:soluble-Fms like tyrosine kinase1

PlGF: Placental Growth Factor

EVs: Extracellular Vesicles

PLAP: Placental Alkaline Phosphatase

PSV:Peak Systolic Velocity

PIERS:Pre-eclampsia Integrated Estimate of Risk

PREP:Prediction of Risks in Early onset Pre eclampsia

LBW: Low Birth Weight

Call for Authors
Upcoming Issue 5

Topic: Acute Gastroenteritis in Pediatric population

Interested PGTs are directed to get in contact with the DoTM team at earliest.
Contact us at: DoTM.RRF@gmail.com