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Review Article

Cardio-Renal & Neurologic Complications of Preeclampsia: Current Concepts & Clinical Implications

Tolu-Akinnawo[1], Zeth Oluwaremilekun[1], Abe Temidayo[1], Nandakumar Bangalore Vittal[2], Henry Okafor[3], Chike Nzerue[1]

[1]Department of Internal Medicine, Meharry Medical College, USA

[2]Department of Neurology, Vanderbilt University School of Medicine, USA

[3]Division of Cardiology Vanderbilt University School of Medicine, Nashville, TN, USA

***Corresponding author:** Chike Nzerue, Department of Internal Medicine, Meharry Medical College, Nashville, TN, USA

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Abstract

Preeclampsia, which afflicts 3-5% of pregnancies worldwide, has recently being recognized to be a cardio-renal syndrome, in which neurologic complications contribute to the morbidity and mortality of this syndrome. The precise pathogenesis of preeclampsia, itself, is not definitely elucidated, but an imbalance of angiogenic & anti-angiogenic factors appear at play. The acute neurologic complications of preeclampsia such as seizures, cerebral edema, stroke, and posterior reversible leukoencephalopathy syndrome (PRES) are the leading contributors to obstetric mortality and morbidity in many low to middle and some high income countries. In addition to these acute devastating complications, registry and other long-term data, over recent decades now reveal that chronic neurologic & cardiovascular complications in the mothers as well as the offspring of preeclamptic pregnancies also contribute to future morbidity. In this review, we evaluate putative biophysical mechanisms of these cardio-renal and neurologic complications in both mother & child, as well as clinical implications of these new findings. We outline a rational monitoring strategy for these late complications in preeclamptic mothers & children born from preeclamptic pregnancies. Preventive strategies, encompassing aspirin, calcium-vitamin D supplementation, exercise, pravastatin, and metformin, offer insights into mitigating preeclampsia risks. Active management, balancing antihypertensives and planned delivery, appears to yield positive outcomes. Future pathways emphasize advancements in pathogenesis research, early predictive biomarkers, personalized therapeutic approaches, and global health initiatives. The role of wearable devices, telemedicine, and continuous monitoring in maternal-fetal health surveillance is paramount. Specific attention to unraveling neurological complications and establishing long-term follow-up programs is crucial for comprehensive care.

Introduction

Preeclampsia, a complex, multi-system disease associated with hypertension after 20 weeks gestation, edema and/ or proteinuria continues to afflict about 2 to 4% of pregnancies worldwide [1,2], and neurologic complications play very significant roles in acute & long-term maternal morbidity and mortality [3]. Although it has been known that neurologic complications presage a bad outcome since proposed by Hippocrates in 400 B.C [3], the neurologic complications have garnered little attention. Autopsy studies and large case series confirm a high prevalence of neurologic complications in preeclampsia [4-7]. Furthermore there is a high burden of preeclampsia on maternal and child health in USA [8]. Significant controversies have bedeviled an understanding of the precise pathogenesis, but a gathering consensus appears to favor abnormal placentation, placental ischemia, an imbalance between angiogenic and antiangiogenic factors, which leads to endothelial dysfunction and damage in several vascular beds [9-12].

This review assesses both pre-clinical and clinical evidence supporting the occurrence of cardiorenal and neurological complications in this disorder, delving into potential biophysical mechanisms affecting both preeclamptic mothers and offspring of preeclamptic pregnancies.

The need for a rational approach to monitoring of the women and children for emergent neurological disease is discussed.

Pathogenesis of preeclampsia as a cardiorenal syndrome

In normal pregnancy, the placental remodeling with epithelial-to endothelial phenotype transformation (pseudovasculogenesis) happens seamlessly with elaboration of vasodilators such as Vascular Endothelial Growth Factors (VEGF) and others to provide oxygen & nutrients to the fetus [13-15]. This process is defective in preeclampsia leading to hypoxia and elaboration of excess vasoconstrictors like soluble fms-like tyrosine kinase 1 (sFlt-1) & soluble endoglin (sEng) [13-15].

Vascular endothelial growth factors (VEGF) play a critical role in vasculogenesis and maintenance of vascular integrity in adult tissues [13,14]. Imbalance between angiogenic and anti-angiogenic factors appears to play an integral role in triggering the preeclampsia cascade. Several studies suggest that the finding of aberrant levels sFlt-1, PlGF, and sEng levels can predict preeclampsia better than any single marker, suggesting the combined action of several angiogenic factors to produce the clinical phenotype of preeclampsia [15]. Placental dysfunction, ischemia and hypoxia with widespread endothelial dysfunction and inflammation appear to contribute to the resulting widespread vasculopathy.

Recent data support the fact that preeclampsia meets the criteria for cardiorenal syndrome- disorders of the heart and kidneys in which acute or chronic dysfunction of one organ induces dysfunction in the other [16]. Survivors and offsprings of preeclamptic pregnancies suffer a high incidence of hypertension, cardiovascular and renal disease.

This is not surprising as the occurrence of endothelial dysfunction, inflammation (endothelitis) and oxidative stress makes the kidney and heart vulnerable. Processes such as endothelial cell swelling, fenestration obliteration, and capillary space invasion contribute to the decreased glomerular filtration rate observed in preeclampsia. Glomerular swelling- endothelioses is the hallmark pathologic lesion of preeclampsia in the glomeruli. Vascular endothelial growth factors (VEGF) play a critical role in vasculogenesis and maintenance of vascular integrity in adult tissues. Imbalance between angiogenic and anti-angiogenic factors contributes to triggering the preeclampsia cascade [16-19].

Consistent with these findings, a high concentration of sFlt-1 has been suggested to play a role in podocyte effacement, adding another layer to our understanding of the renal complications associated with this condition [17].

Several studies suggest that the finding of sFlt-1, PlGF, and sEng levels can predict preeclampsia better than any single marker, converging the combined action of several angiogenic factors to produce the clinical phenotype of preeclampsia. Survivors and offspring of preeclamptic pregnancies suffer a high incidence of hypertension cardiovascular and neurologic disease [20].

However, this placenta-centric view of preeclampsia (Figure 1), has been challenged by evidence over the last few years of maternal cardiovascular dysfunction, or maladaptation, as well as evidence of two clear phenotypes of preeclampsia: early-onset and late onset preeclampsia, each with variable impact on fetal growth restriction [16-19]. The biochemical markers of endothelial dysfunction in preeclampsia such as placental growth factor/soluble fms-like tyrosine kinase -1, endoglin, aberrant VEGF levels may be seen in non-pregnant females and males with cardiovascular and kidney disorders [21,22]. Valensise et al. [23] postulated the hemodynamic differences between the early -onset phenotype, where placental insufficiency dominates the picture, where uterine artery resistance was high and maternal cardiac output (CO) was low, but systemic vascular resistance (SVR) was high, from late-onset phenotype where CO was high, but SVR & uterine artery pulsatility index were normal. In both phenotypes there is evidence of numerous, interconnecting dysfunctions of the heart, kidneys, arteries, veins and interconnecting systems driven largely by endothelial dysfunction, hypertension and vascular injury [21,22]. Interestingly, some studies show the presence of a placenta is not a sine qua non for the occurrence of preeclampsia, as cases of Bevacizumab toxicity has presented with preeclampsia and/ or a syndrome resembling PRES, in non pregnant patients [24,25].

Regardless of the operational pathophysiology, it is increasingly recognized that pre-eclampsia of both phenotypes meets the criteria for cardio-renal syndrome. Renal involvement manifests as proteinuria of variable severity which reach nephrotic range, in severe cases leading to acute tubular necrosis and acute kidney injury [26,27]. Kidney biopsy classically shows endotheliosis [28,29].

Neurological complications of preeclampsia, ranging from acute manifestations like seizures (eclampsia), Posterior Reversible Encephalopathy Syndrome (PRES)/ cerebral edema (Figure 3A-E), cerebral venous sinus thrombosis, subarachnoid hemorrhage, hemorrhagic (Fig 3A-3C) and ischemic strokes contribute significantly to mortality, particularly in the middle and some high-income countries [1,2,30]. Long-term complications, including epilepsy and vascular dementia (from periventricular white matter ischemia) are also implicated [30]. Of these complications, intracerebral hemorrhage appears to be most devastating and contributes to about 70% of mortality in some series [31].

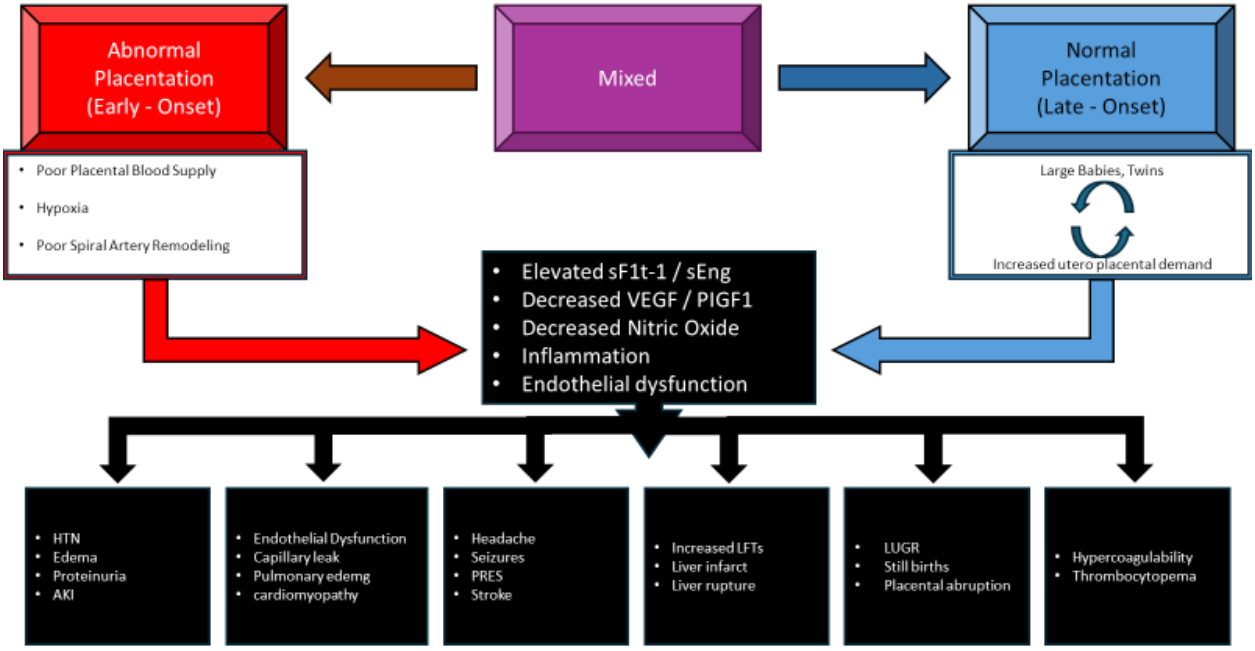

Figure 1: Illustrating pathogenesis of preeclampsia based on initiation by abnormal placentation & uteroplacental insufficiency.

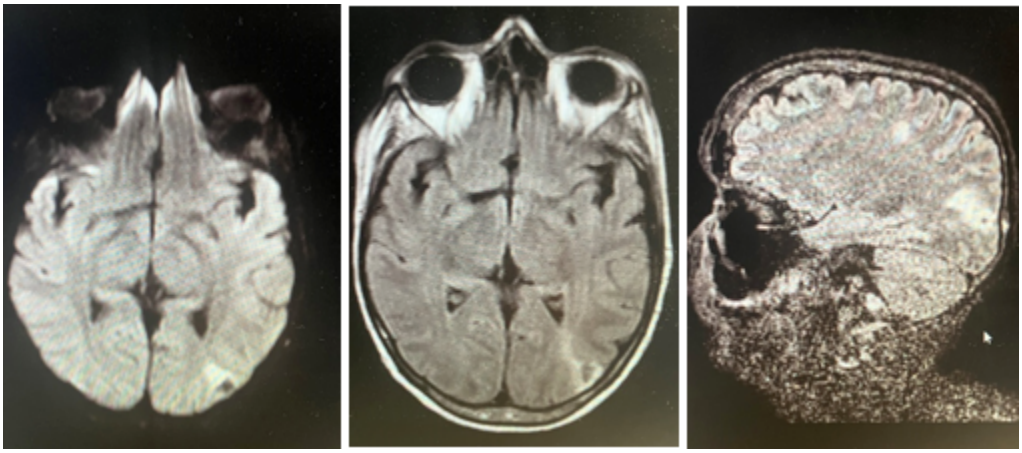

Figure 3A-3C: MRI Brain showing Left posterior parietal region hyperintense signal suggesting edema with hemorrhage (3A-Diffusion Weighted image, 3B-Axial T2-FLAIR image & 3C Sagittal FLAIR).

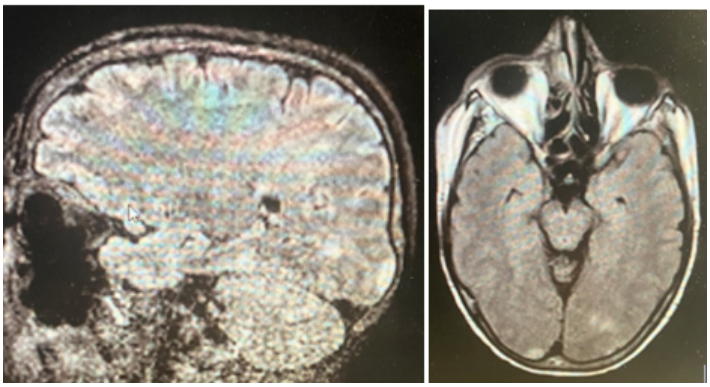

Figure 3D and 3E: MRI Brain showing Right occipital pole hyperintensity-suggesting edema due to PRES; 3D Sagital FLAIR and 3E Axial FLAIR.

MRAngiogram of head and neck was unremarkable suggesting absence of longstanding large vessel disease (not shown here). MRVenogram was normal as well (not shown here).

Biophysical effects of preeclampsia on the maternal brain

Several experimental models have been used to investigate changes in maternal brain that can explain the observed neurological complications of preeclampsia, such as genetic models based on sFlt-1 overexpression [27,32], surgical models based on reduced uterine perfusion, experimental models with altered inflammatory state [33], as well as potential role maternal inflammasomes & innate pathways [34]. These pathways have given an insight into alterations in cerebral autoregulation, blood-brain barrier integrity, excessive vasoconstrictor tone & hyperexcitability as well microvascular disease. These appear to play integral roles as shown in (Figure 2).

1. Changes in cerebral autoregulation:

The brain's ability to maintain perfusion in the face of changes in systemic blood pressure (autoregulation) is a protective mechanism against neurologic injury. Both animal [35] and human studies [36,37] show derangements in cerebral autoregulation in preeclampsia. Whether these changes are causal or casual is unclear since some studies show impairment of autoregulation [38], while other studies show paradoxically improved autoregulation in preeclampsia [39].

2. Changes in blood-brain barrier integrity:

Preeclampsia & eclampsia are associated with cerebral edema in some cases; suggesting alteration of permeability of the blood brain barrier [39-41]. The precise mechanism underlying this increased permeability is unclear, although inflammation has been blamed. Consistent with these observations, markers of inflammation such as C-reactive protein levels, Tumor Necrosis Factor –alpha (TNF-α) are elevated in Preeclampsia [42-44]. The pattern of edema seen in preeclampsia and eclampsia appears to resemble that in the posterior reversible encephalopathy syndrome (PRES) which can complicate some cases of this disorder [45-47].

Bevacizumab (a VEGF inhibitor) toxicity may also produce a preeclampsia like illness with cerebral edema, PRES and seizures [24,25,48].

3. Hyperexcitability & vasoconstriction :

Although the state of pregnancy may lower seizure threshold [49], there is clear clinical evidence in preeclampsia of hyperexcitability and sympathetic overactivity [50]. The salutary effects of magnesium sulfate in reducing seizure threshold in preeclampsia has been postulated to derive from N-methyl-D-aspartate (NMDA) antagonism and vasodilation [51,52].

4. Cerebral microvasculopathy:

Preeclampsia carries risks of stroke and cognitive decline in subsequent years after the disease [53-56]. The associations between stroke, dementia and white matter disease in later life are unclear.

The possible pathogenetic interactions that connect preeclampsia to neurologic complications are summarized in (Figure 2) below.

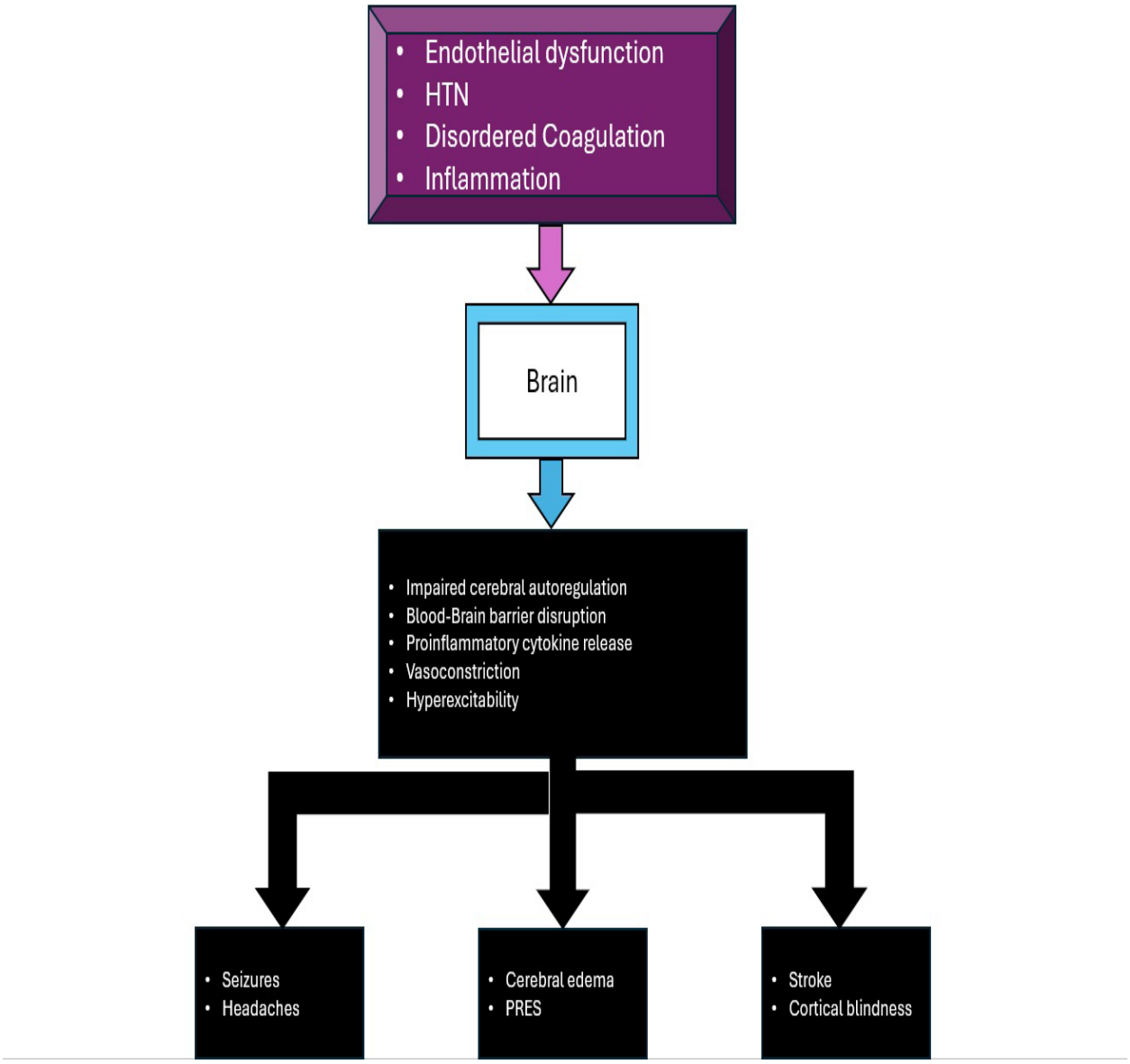

Figure 2: Showing biophysical changes that may contribute to neurological complications in preeclampsia.

Epidemiology, risk factors, and classification

Preeclampsia affects 4 million women globally [1,2]. Preeclampsia is a leading cause of maternal mortality, resulting in 70,000 maternal deaths annually. It also increases the risk of fetal death and preterm deliveries [57].

Risk factors

Table 1 highlights the risk factors for pre-eclampsia [1,2,57].

Positive risk factors

Positive risk factors	Negative risk factors
Family history of preeclampsia	Maternal Smoking
Molar pregnancies	Prolonged Sexual Cohabitation
Multiple pregnancy	
Nulliparity	
Advanced maternal age	
Maternal comorbidities such as Diabetes Mellitus, Chronic Hypertension, Obesity, Chronic Kidney Disease, Systemic Lupus Erythematosus	
Trisomy 13	
Previous Placenta abruption or intrauterine fetal growth restriction	

Table 1: Risk factors for pre-eclampsia.

In the USA the risks of hypertensive pregnancy disorders have increased predominantly among African American women, compared to Hispanic/ American Indian/ White/ Asian or Pacific-Islander women [58]. The risk of the rate of eclampsia has, however, declined in recent years due to more widespread antenatal care and the use of magnesium sulfate [59]. It is also important to note that women with preeclampsia or eclampsia have a 3-25% increased risk of severe complications in their index pregnancy, including the risk of abruptio placentae/ disseminated intravascular coagulation/ pulmonary edema/ and aspiration pneumonia [60].

Long-term maternal and fetal cardio-renal neurologic sequelae

The aftermath of preeclampsia extends into long-term health outcomes, encompassing cardio-renal and neurologic implications:

- A meta-analysis demonstrated a threefold increased risk of chronic hypertension and a twofold increased risk of cardiovascular disease (CVD) and stroke after a 10-15-year follow-up. While these patients also present with additional risk factors for CVD, the persistent impact of preeclampsia on long-term health is evident [61-65].
- Preeclampsia is associated with an increased risk of metabolic syndrome, prompting the ACOG Task Force's recommendation for periodic assessments of blood pressure, lipids, fasting blood glucose, and body mass index (BMI) in women with a history of preeclampsia or preterm delivery [64].
- Peripartum cardiomyopathy, a rare but serious complication, is linked to preeclampsia. Experimental studies in rodents suggest an antiangiogenic milieu as the primary contributor to its development. The severity of myocardial dysfunction correlates with levels of angiogenic markers, such as sFLT1 (Soluble fms-like tyrosine kinase-1) and sENG (Soluble endoglin) [65].
- Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are notable long-term complications associated with preeclampsia. A meta-analysis reveals a fourfold increased risk of microalbuminuria at a mean of 7.1 years postpartum and an eightfold increased risk in those previously diagnosed with preeclampsia [66].

Neonates born to mothers with preeclampsia face an increased risk of respiratory distress syndrome and bronchopulmonary dysplasia. While the exact mechanisms remain unclear, elevated sFLT1 has been suggested as a potential pathway, impairing angiogenesis [65].

In relation to neurocognitive follow up, it appears children born to preeclamptic mothers carry an increased risk of developing cerebral palsy, stroke, impaired neurological development, anxiety and depression [20,66-69].

The mechanisms underlying these neurological disorders in offspring of preeclamptic pregnancies are unclear, but there is evidence of microRNA dysregulation in the placental tissue of affected cases [70]. This means that preeclampsia can no longer be seen as just a pregnancy disease, considering risk for later disease in mother and child [71].

This underscores the ongoing significance of understanding the vascular dynamics that contribute to both short-term and long-term maternal and fetal outcomes in the context of preeclampsia.

Management

Prevention

The imperative to mitigate the severe short-term and long-term risks associated with preeclampsia necessitates proactive preventive measures:

a. Aspirin:

A landmark randomized study in 1985 suggested that prophylactic aspirin administration (50-162mg, daily) significantly reduces the risks of preeclampsia, fetal growth restriction (FGR), and stillbirth in at-risk women [72]. Subsequent meta-analyses support this, indicating a statistically significant but clinically modest 10% reduction in preeclampsia risk, particularly beneficial when administered to high-risk women before 16 weeks' gestation [73,74]. However, a metanalysis of 16 trials of 18,907 women showed that aspirin was more beneficial in preventing pre-term disease (relative risk, 0.62;95% CI, 0.20-0.74) than in term preeclampsia (relative risk, 0.92;95%CI, 0.7-1.21) [75]. To be effective, it appears treatment should be started before 16 weeks of pregnancy [26].

b. Calcium and Vitamin D Supplementation:

Findings from a meta-analysis encompassing 30 trials demonstrated a significantly reduced risk of preeclampsia in high-risk patients with calcium and vitamin D supplementation [76]. Calcium supplementation is effective given with or without Vitamin D [26].

c. Exercise:

A comprehensive meta-analysis of 27 trials highlighted a 25% reduction in the likelihood of gestational hypertension and preeclampsia in patients engaging in at least 260 metabolic equivalents of weekly task minutes [77].

d. Pravastatin:

As an oral statin with potential anti-inflammatory actions, pravastatin is a promising preventive measure. A trial demonstrated a 26.7% reduction in preeclampsia and preterm birth in high-risk patients taking daily pravastatin from the second trimester until delivery [78].

e. Metformin:

Another meta-analysis showed a significant reduction in gestational weight, particularly when metformin is taken between 12-18 weeks, revealing its potential in mitigating preeclampsia risk [79].

Active management

While the ultimate treatment for preeclampsia is the delivery of the placenta, the risks of preterm birth necessitate a nuanced approach.

Oral Antihypertensives

The management of preeclampsia involves careful consideration of the risks associated with antihypertensive drug treatment during pregnancy. The avoidance of aggressive treatment options aims to prevent pharmacologically induced hypotension and potential adverse fetal outcomes. This concern is particularly significant in chronic hypertensive patients or those with prior kidney problems. Antihypertensive drugs, including methyldopa, labetalol, nifedipine, and hydralazine, are considered first line [80-82]. The choice of therapy depends on the acuity and severity of hypertension, and the route of administration (oral or intravenous) is a crucial factor. Methyldopa, a centrally acting agent, exhibits a mild antihypertensive effect with a slow onset and is considered safe for long-term use, including during breastfeeding. Labetalol, a blocker of β- and α-adrenergic receptors, is known for its rapid onset of action and preservation of uteroplacental blood flow. However, caution is warranted due to potential maternal hepatotoxicity. Nifedipine, a calcium channel blocker, is generally safe and available in immediate-release oral or sustained-release tablet forms. Hydralazine, a direct vasodilator, is employed intravenously for acute severe hypertension.

Planned delivery:

The timing of active delivery initiation remains a topic of contention, involving considerations of gestational age, severity of preeclampsia, and gestational hypertension weighed against the risks of prematurity and its associated complications [83,84]. Clarifying optimal timing is paramount for achieving the delicate balance between maternal and fetal well-being.

Clinical issues in managing headaches in pregnant and postpartum women

Migraine and tension-type headaches represent the most common primary headaches globally, constituting 11.2% of the total years of life lived with disability in women aged 15 to 49 [85]. Acute headaches in pregnant or postpartum patients raise concern. In a recent retrospective study of postpartum patients requiring inpatient neurologic consultation for headaches, over 73% of cases were identified as secondary headaches, with post-dural puncture headaches (45.7%) and postpartum preeclampsia (26.1%) being the most prevalent [86].

Other headaches observed during pregnancy and the puerperium include those stemming from cervical artery dissection, reversible cerebral vasoconstriction syndrome (RCVS), ischemic stroke, subarachnoid hemorrhage, and cerebral venous thrombosis. Due to the diagnostic challenges in differentiating between primary and secondary headaches in pregnancy and postpartum, a thorough history/physical examination and a high clinical index are imperative. Red flags in the clinical history should trigger additional neuroimaging and lab testing.

Utilizing the SCAN ME features can aid in guiding patients requiring neuroimaging [30]:

- S: Sudden/Severe/Seizure
- C: Change in position
- A: Altered mentation
- N: Neurologic deficits/Nausea
- M: Medications without relief
- E: Elevated blood pressure or temperature reading

When opting for imaging, Magnetic Resonance Imaging (MRI) is the preferred choice over Computed Tomography (CT) if immediately available to minimize radiation exposure. Fetal radiation from CT is low and can be considered if MRI is unavailable, contraindicated, or clinically necessary [87]. In cases with evident "red flags," collaborative management with a neurologist is of paramount importance.

Future

The intricate landscape of preeclampsia, with its profound impact on maternal and neonatal health, demands a forward-looking approach to unravel potential future pathways, that may influence therapy. As we navigate the complexities of prevention, management, and the intricacies of its pathogenesis, several avenues beckon for further exploration.

Genomic and biomarker research:

Advancements in genomics hold promise in uncovering the genetic predispositions that render certain individuals more susceptible to preeclampsia. Identifying specific biomarkers of placental, maternal or fetal dysfunction, such as angiogenic factors sFLT1 associated with early-stage preeclampsia could revolutionize diagnostic precision and therapeutic interventions, enhancing our ability to predict, prevent, and manage the condition more effectively. Levels of sFTL1 are higher in patients with early-onset and severe disease compared to late or mild disease. Also, changes in the level of P1GF (Placenta growth factor) and sFLT1 are detected 6-10 weeks before the onset of preterm preeclampsia [88,89]. These angiogenic biomarkers also differentiate preeclampsia from similarly presenting conditions such as CKD, gestational thrombocytopenia, and chronic hypertension and can limit the use of invasive procedures such as renal biopsy [30,83-86]. Fetal RNA was also significantly higher (tenfold) in women with preeclampsia than in normal pregnancies [90-92]. A recent study confirmed that an sFlt-1: PlGF ratio of 38 or lower can be used to predict the short-term absence of preeclampsia in women in whom the syndrome is suspected clinically [93].

Precision medicine in management:

Tailoring interventions based on individual patient profiles, considering genetic makeup, comorbidities, and socio-economic factors, can pave the way for precision medicine in managing preeclampsia. Personalized treatment plans, including drug regimens, could mitigate adverse outcomes and enhance maternal and fetal well-being. Novel strategies are currently being employed to predict the disease earlier and hopefully treat preeclampsia and prolong gestation [94].

Advanced imaging techniques:

Innovations in imaging technologies, such as functional MRI and advanced ultrasound, offer an opportunity to delve deeper into the structural and functional changes within organs affected by preeclampsia. Enhanced visualization can provide critical insights into the progression of neurological and cardio-renal complications, guiding more targeted therapeutic strategies [87].

Neuroprotective interventions:

Given the significant impact of preeclampsia on neurological outcomes, the development of neuroprotective interventions becomes paramount. Exploring agents that safeguard the blood-brain barrier, mitigate hyperexcitability, and counteract vasoconstriction may hold the key to preventing severe complications like eclampsia and long-term neurological sequelae.

Longitudinal studies on maternal and fetal outcomes:

Conducting comprehensive longitudinal studies, tracking the health of mothers and their offspring over extended periods will deepen our understanding of the enduring effects of preeclampsia. Unraveling the complex interplay between angiogenic imbalance, maternal health, and fetal development can inform targeted interventions to mitigate long-term complications.

Integrated care models:

Future pathways should emphasize integrated care models seamlessly integrating obstetric care, cardiology, neurology, and nephrology. This holistic approach ensures a comprehensive understanding of the intricate connections between cardio-renal and neurologic complications of preeclampsia, leading to more cohesive and effective management strategies.

Telehealth and remote monitoring:

Leveraging telehealth and remote monitoring technologies can facilitate proactive and continuous monitoring of pregnant individuals at risk of preeclampsia. This approach enables early detection of warning signs, timely intervention, and a more patient-centric healthcare delivery model.

Patient education and empowerment:

Fostering patient education and empowerment is integral to any future pathway. Equipping individuals with knowledge about risk factors, symptoms, and the importance of regular prenatal care empowers them to participate actively in their healthcare journey,

fostering a collaborative and informed approach.

Conclusion

A lot has been learned about the pathophysiology of preeclampsia and the connection to cardio-renal and neurological complications in the past few decades. While the pathogenesis, risk factors, and long-term complications are complex, preventive measures like aspirin, calcium-vitamin D supplementation, exercise, and emerging drugs offer avenues for risk reduction. The initial belief that this syndrome resolves completely on delivery of baby and placenta has been found to be an oversimplification by occurrence of cardiac and neurological disease in mothers and children who suffer early and late cardio-renal effects. That said, there remain immediate salutary benefits for the mother with expeditious delivery, but fetal risks may be increased. Looking forward, embracing technology for continuous monitoring and predictive biomarker research holds promise. Interdisciplinary collaboration is crucial for advancing our understanding and management strategies. There is now an understanding of the two predominant phenotypes in this disease relating to how variable contributions of abnormal placentation and pre-existing maternal cardiovascular dysfunction lead to cardio-renal and neurological complications. Neurological symptoms may presage deterioration. Further clinical and biophysical research will elucidate a unifying theory on these complications and direct optimal management strategies.

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