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Preeclampsia as Risk Factor in a Diabetic Pregnancies, Management and Therapies Challenges: Review article

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ABSTRACT

Background: Preeclampsia is a serious pregnancy complication characterized by endothelial dysfunction, leading to symptoms like proteinuria and hypertension. Several other symptoms, including edema, hemostasis disruption, renal or hepatic failure, and the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet counts), depending on the systemic involvement. According to recent data, endothelial dysfunction in preeclampsia may be caused by an antiangiogenic state that is mediated by low levels of proangiogenic factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) in combination with high levels of soluble endoglin (sEng) and circulating soluble Fms-like tyrosine kinase 1 (sFlt1). The release of sFlt1 and sEng from the placenta into the mother's blood contributes to endothelial dysfunction in preeclampsia. High levels of sFlt1 have been linked to the severity of preeclampsia, suggesting a potential biomarker for the condition. Variants near the FLT1 gene in the fetal genome have been associated with an increased risk of preeclampsia, highlighting a genetic component to the disorder.

Objective: This article aimed to throw the light on preeclampsia as a risk factor in diabetic pregnancies, management and therapies challenges

Material and methods: We searched Google Scholar, Science Direct, PubMed and other online databases for Preeclampsia, Pregnancy, Gestational hypertension, sFlt1. The authors also reviewed references from pertinent literature, however only the most recent or comprehensive studies from 1985 to 2023 were included. Documents in languages other than English were disqualified due to lack of translation-related sources. Papers such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations that were not part of larger scientific studies were excluded.

Conclusion: The identification of specific risk cohorts for preeclampsia utilizing easily accessible and efficient technologies, particularly in low-resource settings, has the potential to yield improved public health outcomes for both mothers and newborns by enabling the initiation of prenatal interventions before the onset of complications. In pursuit of this objective, there has been a growing interest in exploring technologies to enhance the overall comprehension of preeclampsia and, more specifically, its predictive capabilities. These technological advancements promise to advance our understanding of preeclampsia and improve our ability to anticipate and mitigate its adverse effects.

Keywords: Preeclampsia, Pregnancy, Gestational hypertension, sFlt1.

1. Preeclampsia

A multi-system pregnancy disorder known as preeclampsia is defined by new-onset hypertension (systolic and diastolic blood pressure of at least 140 and 90 mm Hg, respectively) and proteinuria (protein excretion of at least 300 mg in a 24-hour urine collection, or a dipstick reading of at least 2+), which appear after 20 weeks of gestation in previously normotensive women [1].

Several other symptoms, including edema, hemostasis disruption, renal or hepatic failure, and the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet counts), depending on the systemic involvement, further exacerbate the clinical picture. The onset of preeclampsia can occur either early (before 34 weeks of gestation) or late (after 34 weeks of gestation). It can present with mild or severe symptoms (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg, proteinuria > 5 g/24 hours, oliguria, neurological symptoms, other clinical symptoms such as deranged liver function, thrombocytopenia < 100 000 mm^3, HELLP syndrome), and in the most severe cases, develop into eclampsia[2] .

2. Definitions for the hypertensive disorders of pregnancy

Gestational hypertension: At least two instances, separated by four hours, of new beginnings of systolic blood pressure of 140 mmHg or diastolic blood pressure of 90 mmHg in a previously normotensive person following 20 weeks of gestation [3]. And no proteinuria, there are no severe preeclampsia signs, such as thrombocytopenia, kidney dysfunction, increased liver transaminases, pulmonary oedema, or visual or cerebral problems.

- **Preeclampsia:** the systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg on two separate occasions, separated by at least four hours, following 20 weeks of gestation in a person who had previously been normotensive, or systolic blood pressure of at least 160 mmHg or diastolic blood pressure of at least 110 mmHg confirmed in a short amount of time (minutes) in order to enable prompt

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antihypertensive medication. And Proteinuria (A urine sample of at least 300 mg per 24 hours (or this quantity extrapolated calculated from a timed collection), or a urine dipstick reading of at least >2+ (if other quantitative techniques are not available), or a protein: creatinine ratio of at least 0.3 [4]. Alternatively, in the absence of proteinuria, new-onset hypertension is accompanied by the beginning of the subsequent conditions:

1. Pulmonary edema.
2. Persistent cerebral or visual symptoms.
3. Thrombocytopenia (platelet count <100,000/microL).
4. Hepatic transaminase levels were at least double the usual value, indicating impaired liver function.
5. Renal insufficiency: A doubling of the serum creatinine concentration in the absence of other renal disease, or a serum creatinine of >1.1 mg/dL [97 micromol/L].

- **Preeclampsia with severe features:**
  In a patient with preeclampsia, any of the following observations:
  1. Thrombocytopenia (platelet count <100,000/microL).
  2. 110 mmHg for the diastolic blood pressure or 160 mmHg for the systolic blood pressure (unless antihypertensive medication is started before this point).
  3. Pulmonary edema.
  4. Persistent cerebral or visual disturbances. A serum creatinine concentration >1.1 mg/dL [97 micromol/L] or a doubling of the concentration in the absence of other renal disorders is indicative of renal insufficiency.
  5. Impaired liver function as demonstrated by liver transaminase values that are at least twice as high as normal, severe, ongoing right upper quadrant or epigastric discomfort that is not relieved by medicine, or both.
- Eclampsia: Generalized seizures in a preeclamptic patient that are not attributable to any other reason.
- HELLP syndrome: Hemolysis, elevated liver enzymes, low platelet count, and maybe hypertension (HELLP is frequently seen as a subtype of preeclampsia).
- Chronic (preexisting) hypertension: Hypertension is recognized or present before gestation or before 20 weeks of gestation. Chronic hypertension also refers to hypertension that is initially identified during pregnancy and continues for at least 12 weeks after childbirth. Systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg, or both are blood pressure indicators. This diagnosis should ideally be supported by at least two high blood pressure readings that were obtained no more than four hours apart. If the patient has severe hypertension, the diagnosis can be made faster, allowing for prompt treatment [5].
- Chronic hypertension with superimposed preeclampsia: If a patient has any of the following signs of chronic hypertension:
  1. An abrupt rise in blood pressure that was previously under control or a step-up in the antihypertensive medication regimen to manage blood pressure.
  2. A sudden rise in proteinuria in a patient who already had proteinuria before or during gestation, or a new beginning of proteinuria.
- Chronic hypertension with superimposed preeclampsia with severe features: If a patient has any of the following signs of chronic hypertension with superimposed preeclampsia:
  1. Pulmonary edema.
  2. Thrombocytopenia (platelet count <100,000/microL).
  3. Either recent or worsening renal impairment.
  4. Persistent problems with the brain or vision.
  5. Antihypertensive medication being increased, a diastolic blood pressure of ≥110 mmHg or a systolic blood pressure of ≥ 160 mmHg.
  6. Impaired liver function as demonstrated by liver transaminase values that are at least twice as high as normal, pain in the right upper quadrant or epigastric discomfort that is not relieved by medicine, or both of these conditions.

* It might be difficult to make an accurate diagnosis. Given the increased dangers to the mother and fetus and neonate associated with superimposed preeclampsia, a high level of clinical suspicion is needed.

3. Eclampsia

Eclampsia is the most dangerous consequence of preeclampsia, with significant rates of morbidity and death among mothers and perinatal. Eclampsia is defined as the presence with recently developed grand mal seizures or mysterious coma in conjunction with the signs of preeclampsia. Also know is a complicated phenomenon that arises from cerebral dysrhythmia and is caused by a variety of pathophysiological factors, including aberrant trophoblastic invasion that triggers endothelial dysfunction, platelet aggregation, and vasospasm. Rarely eclampsia occurs without hypertension in 16% and proteinuria (38%). Furthermore, in wealthy nations, eclampsia is linked to a 0%–1.8% higher chance of maternal mortality. Women whose pregnancies were at or before 28 weeks of gestation had the highest chance of dying from this disease [6]. Eclamptic seizures are massive seizures lasting 60–75 seconds begins with facial deformity, eye protrusion, and mouth foaming, stop of breathing and the body becomes stiff. A widespread contraction of the muscles that starts in the face, jaws, and eyelids follows this and extends to the entire body in a pattern of forceful

contractions followed by periods of rest. In the end, the patient fell into a coma, was asleep for a varying amount of time and had no memory of the previous incidents [7].

4. HELLP syndrome

Hemolysis (H), Elevated Liver enzymes (EL) and low platelets (LP) is a dangerous pregnancy complication linked to a statistically significant rise in the morbidity and mortality of both the mother and the fetus. Also is a subtype of preeclampsia. In addition to hypertension, possible conditions include impairment of the central nervous system and/or kidney problems. Most patients, though not all, have either proteinuria (86 to 100 percent) or hypertension (82 to 88 percent). However, in some situations, the first rise in blood pressure may be slight [8]. The syndrome is seen in 10-20% of patients with severe preeclampsia and 0.5-0.9% of pregnancies. Evidence of hemolysis, elevated liver enzymes, and low platelets is used to make the diagnosis. The criteria for each of these characteristics, however differ between reports. Sibai found AST >70 IU/l, LDH of 700 IU/L and thrombocytes less than 100000/mm^3. Another study found elevated ALT and serum glutamic-oxaloacetic transaminase >40 IU/L lactate dehydrogenase >600 IU/L and thrombocytes count less than 150000/mm^3. Three classifications were defined by the Mississipi classification, with relative platelet counts of 50000/mm^3, 100000/mm^3, and 150000/mm^3 [9].

5. Epidemiology of preeclampsia

Worldwide, hypertensive disorders of pregnancy cause complications in around 5–10% of pregnancies. In Latin America and the Caribbean, hypertensive illnesses account for approximately 25% of maternal mortality, but in Africa and Asia, they only account for 9%. Researchers **Campbell and colleagues [10]** examined a group of pregnant women (n = 29,851) whose first pregnancy was registered in Aberdeen, Scotland, between 1967 and 1978 and who went on to get pregnant again over the same period (n = 6637). The classification of the women was as follows: 68.0% were normotensive, 26.3% were moderately preeclamptic, 5.6% were proteinuric preeclamptic, and 0.2% were eclamptic. Researchers discovered that preeclampsia was less common overall in second pregnancies than in first pregnancies.

6. Concepts and classification

There are two types of hypertensive problems during pregnancy: Arterial hypertension beginning at or after 20 weeks of gestation, and arterial hypertension occurring before or with symptoms before 20 weeks of gestation. The first group includes:

1. Essential chronic or secondary arterial hypertension.
2. White coat hypertension.
3. "Masked" hypertension.

The hypertension group, which appears at 20 weeks or more, includes:

1. Transient gestational hypertension.
2. Gestational hypertension.
3. Preeclampsia, which can be isolated or superposed on chronic hypertension. Within this category, arterial hypertension is characterized as a systolic blood pressure of 140 mmHg or higher and/or a diastolic blood pressure of 90 mmHg or higher [12].

When it comes to preeclampsia, one of the following conditions must coexist:

1. Proteinuria (expressed as a ratio of proteinuria to creatininuria greater than 0.3 mg/mg, as well as by a urine dipstick test result of 1+ or higher, or as 24-hour proteinuria greater than 300 mg/24 hours).
2. Maternal organ dysfunctions, such as hepatic impairment shown by an increase in transaminases and renal insufficiency defined by a creatinine level greater than 1.02 mg/dL. Two times above normal levels, or right hypochondrium pain or epigastralgia, neurological complications such as scotomas or persistent cephalgia with hyperreflexia, confusion, eclampsia, cerebrovascular accident, or amaurosis and haematological complications such as hemolysis or thrombocytopenia.
3. Uteroplacental dysfunctions include foetal development limitation and variations in the umbilical artery Doppler velocimetry, particularly when they are coupled with variations in the uterine arteries.

The categorization of preeclampsia is based on the Yorkshire Series of Severe Preeclampsia [13]. Table (1) presents an abbreviated version of the inclusion criteria. It is crucial to remember that the criteria might change quickly enough that managing women should depend more on thorough evaluation than predetermined standards.

Table (1): Classification of severity of preeclampsia (Adapted from [13].)

Category	Blood pressure	Proteinuria	Haematology	Biochemistry	Symptoms
Mild	140-149/90-99 mmHg	0.3 g/24 hrs	Normal	Normal	None
Moderate	150-159/100-109 mmHg	0.3 g/24 hrs	Normal	Normal	None
severe	60/110 mmHg or more	1 g/litre	Abnormal	Abnormal	present

* Symptoms = Severe headache, visual disturbance, nausea, vomiting, sudden facial, digital, and pedal swelling, hyperreflexia, ankle clonus. * Biochemistry = ALT >70IU/L and/or AST >70IU/L. Hematology = Platelets less or equal to 100 × 109/L.

The Australasian and American documents have been largely merged by the International Society for the Study of Hypertension in Pregnancy (ISSHP). In summary, blood pressure (BP) of 140/90 mm Hg or above and proteinuria ranging from 0.3 to 3 g/day are considered indicators of mild preeclampsia. Mild preeclampsia with one more "adverse feature," such as blood pressure between 160 and 170/ 100- and 110-mmHg, proteinuria of 3 to 5 g/day, and/or headache is referred to as severe preeclampsia. There are no grey areas in the preeclampsia dichotomy, even though it ostensibly separates women at reduced risk from those at higher risk. Pregnancy-related hypertension disorders were reclassified in 2014 by ISSHP [14]:

1. Gestational hypertension.
2. Chronic hypertension.
3. White coat hypertension
4. Preeclampsia with or without over lapping chronic hypertension.

7. Preeclampsia risk factors

Numerous risk factors have been found, the majority of which are related to immunologic and genetic variables. Risk factors can be roughly categorized as underlying medical disorders and general pregnancy-related variables [15].

General risk factors, pregnancy-related variables:

1. Primigravida
2. Maternal age >35 years.
3. Family history.
4. Multiple pregnancy.
5. Young maternal age.
6. Low socioeconomic class.
7. Others.

8. Medical disorders

1. Obesity.
2. Renal diseases.
3. Gestational diabetes.
4. Systemic lupus erythematosus.
5. Chronic hypertension.
6. Thrombophylia.
7. Vascular and connective tissue diseases.

Preeclampsia is more frequent in primigravida women, and the longer a woman waits between pregnancies, the higher her chance of developing preeclampsia, and pre-pregnancy obesity as well as women who get pregnant through donor insemination, donated eggs, or donor embryo therapy. According to Giannakou *et al*. (2018), preeclampsia was consistently linked to the presence of obesity, smoking, psychological stress, chronic renal disease, polycystic ovarian disease, and PAI-1 polymorphism [16]. At the genetic level, the development of preeclampsia has been linked to a locus in the foetal FLT1 area by a recent genome-wide association analysis, bolstering the theory that a placental isoform of sFlt-1 (Soluble fmslike tyrosine kinase-1) is involved in the pathogenesis of the illness [17]. Also, premature ovarian failure (With pregnancies resulting from ovum donation) and polycystic ovarian disease are two hormonal illnesses that primarily enhance the risk of preeclampsia because they raise the risk of cardiovascular disease even in the absence of pregnancy. Strangely, there seems to be a decrease in the risk of preeclampsia while smoking during pregnancy. Short-term vasoconstriction linked to nicotine and smoking-related carbon monoxide has been demonstrated to reduce the synthesis of preeclampsia mediators (Soluble endoglin and sFlt-1) in placental cultures and endothelial cells. Additionally, carbon monoxide has a longer-lasting hypotensive impact of 2 to 3 mmHg, which might keep certain pregnancies from reaching the 90 mmHg diastolic blood pressure threshold needed for a preeclampsia diagnosis **[18]**.

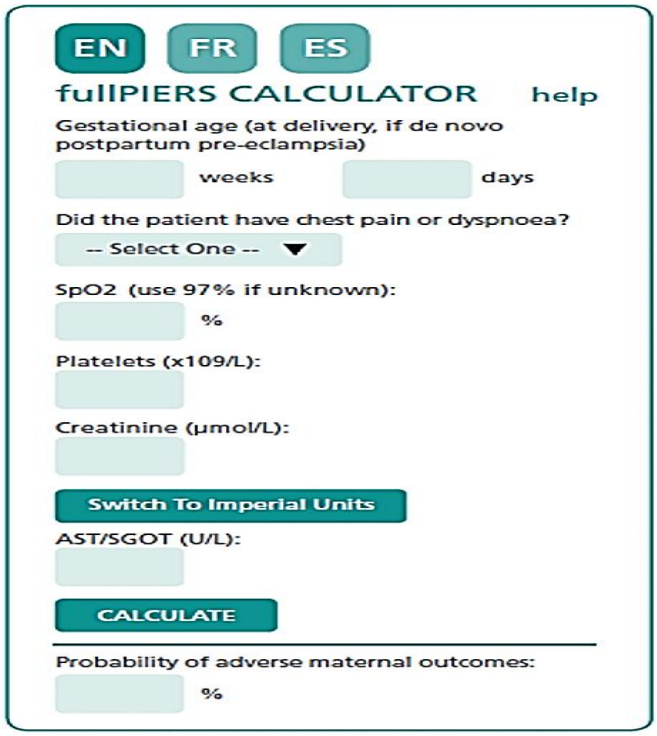

Figure (1): Risk calculator [18].

9. Diagnosis of Preeclampsia

The goal of diagnosing preeclampsia is to identify women who are at risk for negative consequences and choose the most appropriate course of treatment. After 20 weeks of pregnancy, a set of criteria is used to diagnose mild, moderate, and severe preeclampsia antepartum [15]. **Severe** preeclampsia is characterized by a blood pressure of more than 110 mm Hg (Diastolic) or 160 mm Hg (Systolic) with proteinuria of at least 5g per day. In addition, thrombocytopenia (platelet count < 100,000/uL), pulmonary oedema, or oliguria (Less than 500 mL per day) are considered indicators of severe preeclampsia. Women with severe illness may experience pulmonary edoema, hemolysis and/or thrombocytopenia, oliguria from acute renal failure, severe headaches or visual abnormalities, grand mal seizures, eclampsia, and/or oliguria from acute liver damage.

On the other hand, **moderate** preeclampsia is defined by a raised blood pressure of less than 160 mm Hg (Systolic) or 120 mm Hg (Diastolic), together with a daily proteinuria of more than 300 mg but less than 5g. Minimal or no proteinuria is present in up to 20% of females with atypical preeclampsia. Although the level of proteinuria in preeclampsia can range from little to nephrotic, neither the mother's nor the fetus's outcomes appear to be impacted by the quantity of proteinuria. Preeclampsia should not be diagnosed just on the basis of increasing hypertension but also on non-hypertensive signs. Gestational age at onset has been used to categorize preeclampsia. Women who develop the condition before 34 weeks of pregnancy have a higher probability of end-organ involvement, fetal development limitation, and a hemodynamic profile characterized by poor cardiac output and high peripheral vascular resistance compared to those who get the disease after 34 weeks of pregnancy. "The National Institute of Health and Clinical Excellence (NICE)" advises that following a diagnosis of proteinuria, retaking the test has no advantages [19]. Also, uric acid is a characteristic of preeclampsia, but its predictive power for maternal and fetal outcomes is limited. Blood testing was not useful in predicting the course of the illness. However, elevated liver transaminases, creatinine >110 mcmol/L, and a low platelet count of less than 100×10^9/L are all linked to poor maternal outcomes. Also, Aspartate transaminase and creatinine concentrations, low oxygen saturation, low platelet count, gestational age at admission, and chest pain or dyspnea were among the factors that predicted a poor outcome [20] (Table 2).

Table 2: Diagnosis of Preeclampsia [21].

eeclampsia	**Severe features**
Elevated blood pressure: In earlier normotensive females, diastolic ≥90 mm Hg or systolic ≥140 mm Hg, twice, separated by 4 hours	diastolic ≥110 or Systolic blood pressure ≥160 mm Hg
AND Proteinuria: ≥300 mg/24-hour urine collection or protein/creatinine ≥0.3 or dipstick reading =1+ OR severe features	Thrombocytopenia (<100 000 μL)
	Liver function examinations (2×normal level) Epigastric or right upper quadrant pain
	Pulmonary edema
	More than 1.1 mg/dL of serum creatinine or a doubling of creatinine in the absence of further renal disease
	signs that are new to the brain or visual

10. Pathogenesis of Preeclampsia

The characteristic features of preeclampsia include endothelial dysfunction, increased oxidative stress, placental hypoxia, and/or ischemia. Inadequate placental cytotrophoblast invasion is thought to be the origin of preeclampsia, which is then followed by extensive endothelial dysfunction in the mother.

According to recent data, endothelial dysfunction in preeclampsia may be caused by an antiangiogenic state that is mediated by low levels of proangiogenic factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) in combination with high levels of soluble endoglin (sEng) and circulating soluble Fms-like tyrosine kinase 1 (sFlt1). Additionally, sFlt-1 plays a role in decreased nitric oxide (NO). Normal pregnancy necessitates vascular changes that require NO in order to maintain the increased blood volume. In both human and animal models of preeclampsia, it has been demonstrated that a lack of NO impairs vasorelaxation. Hence, a higher bioavailability of NO may help to improve outcomes for both mothers and fetuses [22].

Vascular endothelial growth factors (VEGFs) are dimeric glycoproteins that play role in angiogenesis and vasculogenesis. Flt-1 [Vascular endothelial growth factor receptor 1(VEGFR-1)] and Kinase insert Domain Receptor (KDR) [Vascular endothelial growth factor receptor-2(VEGFR-2)] are two VEGF family receptors found on vascular endothelial cells. The products of FLT-1 produced by differential mRNA processing are Flt-1 (Fms-like tyrosine kinase 1) and soluble Flt-1 (sFlt-1). Flt-1, also called vascular endothelial growth factor receptor 1 (VEGFR-1), is a membrane-spanning receptor for PlGF and VEGF. In the bloodstream and locally in tissues, soluble Flt-1 binds to VEGF and PlGF, functioning as a scavenger to stop them from connecting with their membrane receptors on the endothelium. PIGF resembles VEGF and is highly expressed by the placenta. It also exhibits high affinity for binding to the Flt-1 receptor. Placental release of (sFlt1) and (sEng) into the mother's blood causes extensive endothelial dysfunction, which leads to systemic signs of preeclampsia such as proteinuria and hypertension. Also, Proteinuria and hypertension are side effects of anti-VEGF medication therapy for cancer patients. VEGF plays a crucial role in maintaining endothelial cell function, particularly in the fenestrated endothelium, which is present in the glomeruli, liver, and brain the three main organs impacted by preeclampsia.

However, preeclampsia has also been linked to circulating mononuclear cells as an additional source of sFlt1. Preeclamptic women have been shown to have high circulating levels of sFlt1and Levels of sFlt1 may be correlated with preeclampsia severity, and these high levels may occur before preeclampsia manifests. sFlt1 acts as a strong inhibitor of VEGF and transforming

growth factor b (TGFb) and PIGF by hooking these particles within the circulation and other targets tissues, such as the kidneys [23]. PIGF ties itself more effectively to the Flt-1 receptor by uprooting VEGF from Flt-1; other conceivable incorporate coordinate impacts of Flt-1 signaling and the build of VEGF/PIGF heterodimers. Amid pregnancy placenta discharges a large amount of PIGF and their levels increment from second trimester, and from that point, decrease (Figure 2).

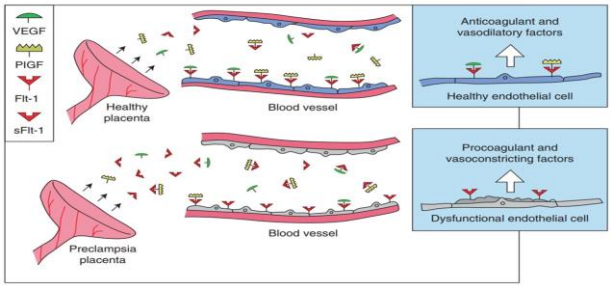

Figure 2: Vascular endothelial growth factor (VEGF) signaling and role of soluble fms-like tyrosine kinase 1 (sFlt-1) in maternal endothelial dysfunction.

Adequate placental perfusion by maternal vessels is necessary for spiral arteries to exchange waste products, nutrients, and oxygen between the foetus and the mother.

The maternal spiral arteries are invaded by invasive cytotrophoblasts of foetal origin during normal placental development. This results in the transformation of the small-caliber resistance vessels into high-caliber capacitance vessels, which can provide placental perfusion sufficient to support the developing foetus. The cytotrophoblasts undergo "pseudovasculogenesis," meaning the differentiation from an epithelial to an endothelial phenotype, during the process of vascular invasion. Cytotrophoblasts in preeclampsia do not take on the characteristics of an invasive endothelium. Rather, placental ischemia is caused by the superficial invasion of the spiral arteries, which are still small-caliber resistance vessels [22]. (Figure 3).

There is mounting evidence that VEGF, and possibly placental growth factor (PlGF), are required to maintain endothelial health in several tissues including the kidney and perhaps the placenta. In normal pregnancy, the placenta produces modest concentrations of VEGF, PlGF, and sFlt-1. In preeclampsia, excess placental sFlt-1 binds circulating VEGF and PlGF and prevents their interaction with endothelial cell-surface receptors leading to endothelial dysfunction [24].

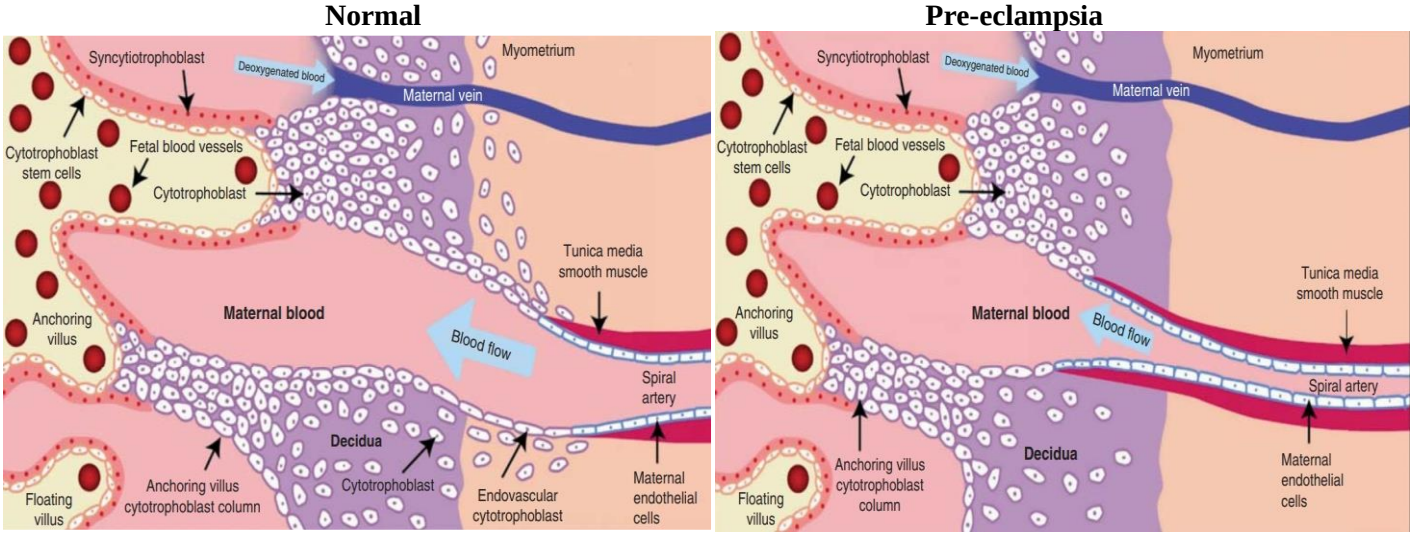

Figure 3. Spiral artery defects in preeclampsia [25].

11. Overview of Preeclampsia and Diabetes in Pregnancy

The medical condition known as gestational diabetes mellitus (GDM) is characterized by a carbohydrate intolerance that manifests or initially occurs during pregnancy and causes hyperglycemia and hyperinsulinemia. Usually, it happens during the second trimester of pregnancy. Type 2 diabetes is a risk factor for both mothers and their unborn children, however gestational diabetes normally goes away after childbirth. A higher risk is linked to the potential for type 1 or type 2 diabetes to be present but undetectable. Insulin resistance is a disease known as type 2 diabetes (T2D), which is a result of obesity, lifestyle choices, and several hereditary factors. From 4.7% in 1980 to 8.5% in 2014, T2D prevalence has increased. The incapacity of pancreatic β-cells to produce and secrete insulin, leading to autoimmune destruction, is called type 1 diabetes [26].

Until recently, pregnant women diagnosed with type 1 or type 2 diabetes were recommended to deliver in the 37th week to avoid late-term complications and developmental delays anticipated to occur with prolonged exposure to the maternal hyperglycemic state in utero. However, the interplay of preeclampsia and diabetes has potential challenges, and together, there is a greater potential for maternal- and fetal-related complications such as congenital malformations, preeclampsia, eclampsia, preterm birth, fetal demise, macrosomia, shoulder dystocia, neonatal hypoglycemia, and neonatal jaundice. However, much more work is needed in understanding the variations of preeclampsia that may be specific to pregnant women diagnosed with pregestational diabetes [27].

The diagnoses of type 1 or type 2 diabetes are established before pregnancy; a positive result for glycosuria or a fasting blood glucose of ≥140 mg/dl or a 2-hour value of ≥ 200 mg/dl on a glucose tolerance test should be followed up with a fasting glucose or glucose tolerance test. Preeclampsia is typically defined by pregnancy-specific hypertension along with proteinuria; several other signs and symptoms often accompany these diagnostic criteria. The standing blood pressure cutoff for a diagnosis of preeclampsia is 140/90 in conjunction with drawn blood pressure results of the same magnitude. A 24-hour urine should be collected and analyzed for the presence of protein and creatinine; if this test is normal, then the blood pressure change is considered gestation-related and does not require further investigation [28].

12. Therapies for Preeclampsia

Prescription medication for preeclampsia is only used to manage blood pressure symptoms and prevent seizures. Over the years, a wealth of information has been gathered about the safety and effectiveness of beta-blockers like labetalol, which is currently the top choice for managing blood pressure. With these drugs, 80% of preeclamptic patients may attain successful control. The first-line drugs Labetalol, Nifedipine, Hydralazine and Methyldopa. Labetalol, nifedipine, or methyldopa are the medications used to treat severe hypertension. However, animal studies have provided new evidence that amlodipine may be a better option than nifedipine due to its ability to induce Arrb1 (β-arrestin-1) and the subsequent downregulation of the AT1-B2 (Angiotensin II type 1 receptor and Bradykinin B2 receptor complex) receptor complex. However, further clinical research is required to confirm this conclusion. Pharmacological therapy of mild to moderate-range hypertension (systolic <160 mmHg or diastolic <110 mmHg) in the context of preeclampsia is not currently advised by ACOG (American College of Obstetrics and Gynecology)) since it may raise the risk of foetal growth restriction and does not appear to reduce the likelihood of the condition progressing. In comparison with placebo, **Rolnik *et al.*** [29] showed that high-risk female patients receiving 150 mg of aspirin had a decreased incidence of premature preeclampsia. For high-risk mothers, it is currently recommended to use aspirin to avoid preeclampsia. Low aspirin dosages lower the risk of preterm birth by 8%, fetal or neonatal mortality by 14%, and preeclampsia by 17%. The primary mechanism of aspirin's action is its inhibition of the metabolism of arachidonic acid (AA). It stops cyclooxygenase 1 and 2 (COX1, COX2) from acting irreversibly by acetylation, which stops AA from degrading into prostaglandins (such as thromboxane and prostacyclin) [30].

Labetalol, oral nifedipine, and IV hydrozine can be used as emergency treatments for preeclampsia. Studies have indicated that supplementing with calcium during pregnancy may avoid hypertensive diseases by halving the risk of preeclampsia, preterm delivery, and the infrequent occurrence of the composite result, which is defined as "death or serious morbidity. Also, A study found that the use of eculizumab suggests that it may be beneficial in treating HELLP syndrome and severe preeclampsia. Women with complement regulatory protein mutations, present in 8–18% of cases of severe preeclampsia, may benefit most from its usage. Additionally, magnesium sulphate is the preferred medication for first-line therapy of eclampsia due to its superiority over other anticonvulsant medications in this regard to keep patients with severe preeclampsia from having eclampsia convulsions [31].

13. Prevention of preeclampsia

Prenatal care would significantly prevent preeclampsia. Based on the aetiology of preeclampsia, preventive medicines have worked on endothelial activation, oxidative stress, inflammation, and vasoconstriction, individually or in combination, and focused on therapy for angiogenic imbalance. Research

backs the efficacious preventative measures of exercise, aspirin, calcium, and labour induction. So far, the data appears to support antiplatelet medicines, the majority of which are low-dose aspirins. 19 studies were included in Trivedi's systematic review, which found that low-dose aspirin had no benefit for 16550 low-risk women and reduced risk by 21% for 11687 high-risk women. Aspirin reduces the incidence of preterm preeclampsia by more than 60% when given to high-risk mothers at dosages exceeding 100 mg and started before 16 weeks of gestational age. Professional societies advise using aspirin for pregnant women who are at risk of preeclampsia since it is the only medication for which there is currently evidence of effectiveness in preventing this condition [32].

Additionally, antiplatelet medications lower the risk of premature delivery in preeclampsia and neonatal and fetal mortality. Their usage is advised by the "National Institute of Health and Clinical Excellence" for women at high risk (Previous preeclampsia, chronic renal disease, diabetes mellitus, autoimmune diseases including APS, chronic renal disease, and chronic hypertension) from 12 weeks until delivery. Nutritional supplements have been the subject of much research about their potential to prevent preeclampsia. Magnesium, calcium, folic acid, fish oil, and antioxidant vitamins are among the supplements that have been examined [33].

CONCLUSION

Preeclampsia, as previously mentioned, remains a significant contributor to both maternal mortality and severe maternal morbidity. The intricate nature of its pathophysiology poses a considerable challenge for upcoming research endeavors, as unravelling this complexity could potentially aid in developing preventive strategies and managing established cases of preeclampsia. The identification of specific risk cohorts for preeclampsia utilizing easily accessible and efficient technologies, particularly in low-resource settings, has the potential to yield improved public health outcomes for both mothers and newborns by enabling the initiation of prenatal interventions before the onset of complications. In pursuit of this objective, there has been a growing interest in exploring technologies to enhance the overall comprehension of preeclampsia and, more specifically, its predictive capabilities. These technological advancements promise to advance our understanding of preeclampsia and improve our ability to anticipate and mitigate its adverse effects.

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