



REVIEW

Pre-eclampsia: a Scoping Review of Risk Factors and Suggestions for Future Research Direction

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Abstract

Most of maternal deaths are preventable, and one-quarter of maternal deaths are due to pre-eclampsia and eclampsia. Prenatal screening is essential for detecting and managing pre-eclampsia. However, pre-eclampsia screening is solely based on maternal risk factors and has low (< 5% in the USA) detection rates. This review looks at pre-eclampsia from engineering, public health, and medical points of view. First, pre-eclampsia is defined clinically, and the biological basis of established risk factors is described. The multiple theories behind pre-eclampsia etiology should serve as the scientific basis behind established risk factors for pre-eclampsia; however, African American race does not have sufficient evidence as a risk factor. We then briefly describe predictive statistical models that have been created to improve screening detection rates, which use a combination of biophysical and biochemical biomarkers, as well as aspects of patient medical history as inputs. Lastly, technologies that aid in advancing pre-eclampsia screening worldwide are explored. The review concludes with suggestions for more robust pre-eclampsia research, which includes diversifying study sites, improving biomarker analytical tools, and for researchers to consider studying patients before they become pregnant to improve pre-eclampsia detection rates. Additionally, researchers must acknowledge the systemic racism involved in using race as a risk factor and include qualitative measures in study designs to capture the effects of racism on patients.

Lay Summary Pre-eclampsia is a pregnancy-specific hypertensive disorder that can affect almost every organ system and complicates 2–8% of pregnancies globally. Here, we focus on the biological basis of the risk factors that have been identified for the condition. African American race currently does not have sufficient evidence as a risk factor and has been poorly studied. Current clinical methods poorly predict a patient's likelihood of developing pre-eclampsia; thus, researchers have made statistical models that are briefly described in this review. Then, low-cost technologies that aid in advancing pre-eclampsia screening are discussed. The review ends with suggestions for research direction to improve pre-eclampsia screening in all settings.

Overall, we suggest that the future of pre-eclampsia screening should aim to identify those at risk before they become pregnant. We also suggest that the clinical standard of assessing patient risk solely on patient characteristics needs to be reevaluated, that study locations of pre-eclampsia research need to be expanded beyond a few high-income countries, and that low-cost technologies should be developed to increase access to prenatal screening.

Keywords Pre-eclampsia · Health disparities · Risk factors · Screening technologies · Global health · Biomarkers · Reproductive health

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Introduction

Pre-eclampsia is a pregnancy-specific hypertensive disorder that can affect almost every organ system [1]. The condition complicates 2–8% of pregnancies globally [2]. New-onset of hypertension after 20 weeks of gestation and/or protein present in the urine (proteinuria) are markers of the condition. Additionally, pre-eclampsia is diagnosed by fetal growth restriction and if proteinuria is absent, it is diagnosed by: new-onset dysfunction with the liver, brain, kidneys, red blood cells, and platelets [2–4]. One serious manifestation of pre-eclampsia is HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) and is associated with increased rates of maternal morbidity and mortality [2, 4]. Another manifestation of hypertensive disorders of pregnancy is eclampsia, which is convulsions not due to any other conditions such as epilepsy. Pre-eclampsia does not necessarily lead directly to eclampsia, as studies have shown that some patients have seizures without prior documentation of the diagnosis of hypertension or proteinuria [2]. Symptoms of pre-eclampsia will cease (in most cases) after delivery which is the only “cure” for the condition [5].

To better explain and understand the pathophysiology of pre-eclampsia, theoretical models of the condition’s causes have been developed. The most recent is the two-stage model proposed in 2019 by Anne Catherine Staff [6]. In this model, both placental and maternal factors contribute to both stages of the disease. Stage 1 represents placental dysfunction, and stage 2 represents the maternal clinical presentation of symptoms. There are three ways in which placental dysfunction for stage 1 could be caused: the first is via poor placentation (an “extrinsic cause”), the second is via normal placentation, but the placental capacity is exceeded closer to term (an “intrinsic cause”), and the third is via other factors like aging and/or senescent placentas. Stage 1 then leads to stage 2, which is the maternal clinical presentation of symptoms.

The Biological Basis of Risk Factors for Pre-eclampsia

Multiple risk factors for developing pre-eclampsia have been identified and are listed in Table 1. These risk factors are used clinically to prescribe aspirin for patients deemed high risk, as an attempt to allay systemic symptoms in advance of their development. The risk factors listed were identified by obstetricians and gynecologists in Australia and New Zealand, the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK), the American College of Obstetricians and Gynecologists (ACOG) in the United States (USA) [7], and by a World Health Organization (WHO) secondary analysis in low- and middle-income

countries (LMICs) [8]. This section will review the biological mechanisms that provide evidence of the relevance of these risk factors to pre-eclampsia.

Pregnancy-Related Risk Factors

Previous Pregnancy with Pre-eclampsia

It is not immediately clear why a previous pregnancy with pre-eclampsia is a risk factor for recurrence of pre-eclampsia in a subsequent pregnancy. This could be due to genetics (which will be discussed later), the presence of other risk factors such as obesity, or hypertensive pregnancy being a predictor of cardiovascular disease later in life [9–11].

Multifetal Gestation

Multifetal gestation requires a larger placenta, which ties into the “intrinsic cause” of the updated two-stage model of pre-eclampsia etiology [6]. The larger placenta may be larger than the uterine capacity, compressing the villi and leading to late-onset pre-eclampsia [12].

History of Small for Gestational Age or Adverse Outcome

Small for gestational age (SGA) infants are those that are born at a weight less than the tenth percentile for gestational age. This could be due to growth restriction (IUGR) or other causes. IUGR and SGA are often used interchangeably, but differ in stage of that IUGR is referring to a fetus that is growth-restricted, and SGA is referring to an infant that has a lower than expected birth weight [13]. If caused by IUGR, SGA could occur due to abnormal placentation or infection. In non-pre-eclamptic pregnancies, those with SGA have similar biomarkers and maternal symptoms to that of pre-eclamptic pregnancies [14].

Age Extremes: Advanced Patient Age and Adolescent Pregnancy

Advanced patient age is a well-known risk factor for adverse pregnancy outcomes [15, 16], with multiple theories as to why. These theories include decreased androgen levels, lower mitochondrial energy production and cytoplasmic quality, oxidative stress, and placental senescence [17, 18]. When tied together with the theorized etiology of pre-eclampsia, all these theories could lead to issues with placentation.

The WHO lists *adolescent* pregnancy as a risk factor [5], and this could be due to social factors such as partner abuse or socioeconomic status. Additionally, patients at this age may be physically immature for reasons like less menstrual cycles and/or hormone fluctuations [19, 20].

Table 1 Summary of the biological basis of risk factors for pre-eclampsia. USA United States of America, AUS Australia, NZ New Zealand, UK United Kingdom, LMICs low- and middle-income countries, USA United States of America, All: USA, AUS, NZ, UK, and LMICs

Category	Risk factor	Location	Scientific basis
<i>Pregnancy-related</i>	<i>Previous pregnancy with pre-eclampsia</i> [9]–[11]	USA, AUS, NZ, and UK	Presence of risk factors, genetics, and/or increased cardiovascular disease risk
	<i>Multifetal gestation</i> [12] [6]	USA, AUS, NZ, and UK	Placental capacity
	<i>Age “extremes”</i> [16]–[20]	USA, AUS, NZ, UK, and LMICs	Oxidative stress, lower mitochondrial energy production, decreased androgen levels, placental senescence
	<i>History of small-for-gestational age or adverse outcome</i> [14]	USA, AUS, NZ, and UK	High association with pre-eclampsia due to impaired placentation
<i>Lack of seminal fluid exposure</i>	<i>Nulliparity</i> [22, 23]	USA, AUS, NZ, and UK	Lack of immune priming
	<i>Inter-pregnancy interval > 10 years</i> [22, 23]	USA, AUS, NZ, and UK	
<i>Immunologic mismatch and absence of relaxin</i>	<i>Assisted Reproductive Technology</i> [22, 24, 28, 30, 32, 33]	USA, AUS, NZ, and UK	Lack of immune priming, absence of corpus luteum, HLA mismatching
<i>Pre-existing maternal health conditions</i>	<i>Thrombophilia</i> [35]	USA	Increased placental vascular clotting risk
	<i>Autoimmune disease</i> [35]–[37]	AUS, NZ, and UK	Dysregulation of immune cells and placental injury
	<i>Systemic lupus erythematosus</i> [35]–[37]	USA	Increased flare ups, difficulty distinguishing symptoms, and placental injury
	<i>BMI > 30 kg/m² (USA) or BMI > 35 kg/m² (all others)</i> [38, 127]–[40]	All	Inflammation, risk of hypertension; for metabolic syndrome – atherosclerotic plaques, which contain lipids that arise similarly in pre-eclampsia/preterm births
	<i>Chronic kidney disease</i> [41, 128]	USA, AUS, NZ, and UK	Issues with hormone regulation, and with kidney disease more likely to have hypertension and proteinuria
	<i>Chronic hypertension</i> [42]	All	Can be amplified during pregnancy
	<i>Diabetes mellitus</i> [49]	USA, AUS, NZ, and UK	Blood vessel and kidney damage
<i>Genetic</i>	<i>Anemia</i> [8, 50]	LMICs	Iron deficiency
	<i>Family history of pre-eclampsia</i> [51]–[55]	USA	Genetic predisposition and heritability, epigenetics
<i>Sociodemographic characteristics</i>	<i>African American race or low socioeconomic status</i> [5, 11, 66]–[57, 58, 60, 72, 129]–[65]	USA, AUS, NZ, and UK	To be determined

Lack of Seminal Fluid Exposure: Nulliparity and Long Inter-pregnancy Intervals

A well-established risk factor is a nulliparity, which refers to women who have never given birth, has not been well studied mechanistically [21]. It could be a risk factor possibly

due to a lack of immune priming of the uterine environment from a lack of seminal fluid exposure. The lack of immune priming and/or loss of short-term T cell memory also may play a role in why a long inter-pregnancy interval is a risk factor [22, 23].

Immunologic Mismatch and Absence of Relaxin: Pregnancy via Assisted Reproductive Technologies

Assisted reproductive technologies (ART) are the variety of methods developed to treat male and female fertility. Pregnancies achieved via ART are associated with a higher risk of pregnancy-related hypertensive conditions for the mother [24–27]. This could be explained also by a lack of seminal fluid exposure in the uterus depending upon the method of ART, such as that which involves artificial insemination with donor sperm [22]. Additionally, in some methods of ART like in vitro fertilization (IVF), a corpus luteum is not always present; thus, the vasodilatory hormone relaxin is not produced, or supplemented, leading to increased risk of vascular dysfunction [28]. The age of patients that undergo ART is increasing [29], which also increases risk of adverse pregnancy outcomes [15, 16]. For pregnancies achieved with oocyte donations, it has been hypothesized that an immunological reaction occurs in the recipients, leading to abnormal placentation [30]. Additionally, both HLA class I (expressed on trophoblasts) and class II (which are expressed by B lymphocytes, monocytes, macrophages, dendritic cells, and activated T lymphocytes [31]) mismatching between oocyte donor and recipient have been shown to increase the risk of pre-eclampsia development [30, 32, 33]. The number of pregnancies is a consideration when discussing ART and adverse pregnancy outcomes, but many studies have shown that singleton pregnancies are at high risk of these outcomes as well [34]. There are many theories related to why patients undergoing ART are at a higher risk of developing pre-eclampsia, but the ability to have more control over immunologic mismatching provides opportunities to allay this risk.

Pre-existing Patient Health Conditions

Pre-existing patient health conditions that are considered risk factors are thrombophilias, autoimmune disease, obesity or being overweight, chronic kidney disease, diabetes mellitus, and/or chronic hypertension.

Thrombophilias

Thrombophilias are inherited or acquired conditions that predispose an individual to thrombosis (blood clots) that could eventually block vasculature. Placental vascular lesions, specifically from cell types such as the syncytiotrophoblast, are present in all pregnancies, and the increased thrombotic risk of those with thrombophilias makes them at a higher risk for placental infarction. Therefore, the high rate of placental lesions in thrombophilias is associated with

pre-eclampsia and other conditions like miscarriage, intrauterine growth restriction (IUGR), and stillbirth [35].

Autoimmune Disease: Antiphospholipid Syndrome and Systemic Lupus Erythematosus

The UK, New Zealand, and Australia more generally list autoimmune disease as a risk factor, but are most likely referring to the antiphospholipid syndrome (APS) and/or systemic lupus erythematosus (SLE) [3]. APS is an autoimmune condition that is an acquired thrombophilia, which spans two pre-eclampsia risk factors: thrombophilias and autoimmune diseases. In pregnancy, the APS is associated with placental vascular thrombosis, decidual vasculopathy, intervillous fibrin deposition, and placental infarction. These placental pathologies may result in miscarriage, IUGR, stillbirth, and early severe pre-eclampsia [35].

SLE is an autoimmune disease that can be associated with APS. In SLE, autoantibodies are produced to ubiquitously expressed nuclear, cell, and tissue antigens. Due to the toxicity of some medications treating SLE, they are often stopped during pregnancy, leading to a higher chance of a flare-up. However, more recently, there are more medications that have been deemed acceptable for pregnancy. In addition to increased flare-ups, some symptoms and laboratory tests of flare-ups are the same as those of pre-eclampsia, delaying the management of pre-eclampsia [36]. Like APS, the placental injury seems to increase in pregnancies with SLE, likely due to hypercoagulability, hypertension, and immune-mediated vessel damage [36, 37].

Obesity

Body mass index (BMI), which is used as an indicator of obesity, is a risk factor for pre-eclampsia that has different cutoffs in different settings. In the USA, a BMI greater than 30 kg/m² is considered a risk factor, while in Australia, New Zealand, the UK, and LMICs, a BMI greater than 35 kg/m² is the cutoff to be considered a risk factor for pre-eclampsia. Obesity is considered a low-grade chronic inflammatory disease that is linked to metabolic disorders such as type 2 diabetes and insulin resistance [38]. Thus, early pregnancy modifications can become dysregulated due to pre-existing metabolic regulation problems. This could be due to multiple reasons, including increased insulin resistance and/or increased adipose tissue presence could cause increased low-density lipoprotein toxicity [39]. Increased insulin resistance affects placental growth and gene expression [39], and lipoprotein toxicity can affect endothelial cells [40].

Chronic Kidney Disease

Blood vessels and blood flow undergo large changes during pregnancy, which also occur in the kidneys. Both the fetus and placenta are in demand of an expanded cardiovascular system. Those who have pre-existing chronic kidney disease are at a higher risk of developing pre-eclampsia because they are less able to make the necessary renal adaptations for pregnancy [41].

Chronic Hypertension

Maintenance of the cardiovascular system is very important in pre-eclampsia. Preexisting cardiovascular risk factors, especially chronic hypertension, can be amplified in pregnancy and lead to pre-eclampsia due to the increase in metabolic and vascular stress on the body [42].

After developing pre-eclampsia during pregnancy, the risk for pre-eclampsia in subsequent pregnancies is increased [43], and in the long-term, cardiovascular-related morbidity, renal disease, metabolic syndrome, and neurological issues risk increases [1, 43–46]. It appears that the increased risk of these conditions is dependent upon severity of pre-eclampsia during pregnancy, prevalence of recurrent pre-eclampsia [10], and gestation age at onset [44]. In addition to an increased risk, onset of cardiovascular diseases occurs prematurely at a younger age [43]. It is not yet clear if pre-eclampsia and other adverse pregnancy outcomes causes these morbidities or if they merely “uncover” them [46, 47].

Diabetes Mellitus

Pre-existing diabetes mellitus is associated with conditions like obesity and cardiovascular stress but also can cause kidney and blood vessel damage. These conditions are closely related to worse pregnancy outcomes [48], such as pre-eclampsia and IUGR [49].

Anemia

Anemia, a risk factor in LMICs, is not well-established but could lead to pre-eclampsia due to iron deficiency, which is vital for maintaining pregnancy [8, 50].

Genetic Predisposition and Heritability

Family History of Pre-eclampsia

There has been evidence that preeclampsia could be heritable since the early 1960s, due to evidence of pre-eclampsia in family lineages, specifically mothers and daughters [51, 52]. It has been suggested that there are both maternal and

fetal contributions to the heritability [51, 53, 54]. Epigenetic modifications have been implicated in the defective invasion characteristic of trophoblasts in pre-eclampsia [55, 56].

Sociodemographic Characteristics: Racism, Not Race

Socioeconomic status is a well-established social determinant of health [57, 58], and in low-resource settings, eclampsia is a significant cause of maternal death [2]. This is largely due to inadequate access to care [5]. In addition to socioeconomic status, African American race is a sociodemographic risk factor for pre-eclampsia. African American women are three times as likely to die from pre-eclampsia than White women [59]. However, though widely thought, socioeconomic status differences, which are closely tied with a poorer health status, do not fully explain this difference [60–62]. On the contrary, studies have found that African American patients are not protected by higher socioeconomic status [61, 63].

In a recent review of pre-eclampsia in African American pregnant women, it was concluded that generally more research is needed to understand why African American patients are at a higher risk of developing pre-eclampsia [60]. Often when examining disparities in pre-eclampsia incidence, researchers conclude that due to higher prevalence of the pre-existing condition risk factors listed in Table 1, African Americans are more likely to develop pre-eclampsia. This has led several studies to more closely investigate this concept. African American (and Hispanic) patients with this pre-existing systemic lupus erythematosus are more likely to have poorer outcomes unrelated to pregnancy such as chronic renal failure. Thus, if they do become pregnant, their pregnancy-related outcomes are also more likely to be worse [64, 65], making causality difficult to establish. For patients with pre-existing chronic hypertension in the UK, it was found that those of “Black ethnicity” were at a higher risk of developing pre-eclampsia during pregnancy [66]. However, there is conflicting data on that conclusion when comparing studies that have pursued a similar research question [66, 67].

African American and Asian patients with a previous history of pre-eclampsia were found to be more likely to have recurrent pre-eclampsia compared to White patients; however, this study did not collect other demographic information besides race/ethnicity [11]. Of patients in California, USA, with gestational diabetes mellitus, African American patients were more likely to develop pre-eclampsia when compared to White, Hispanic, and Asian patients [68]. In New York, USA, Non-Hispanic Black, Hispanic, and South Asian patients, with pre-existing diabetes mellitus, were at a higher risk of developing pre-eclampsia when compared to Non-Hispanic White patients when unadjusted

and adjusted for educational attainment and other maternal characteristics [69]. A few genes related to kidney disease and thrombophilia have been shown to be mutated in African American pre-eclamptic pregnancies, but more evidence is needed [60]. These gene-based studies need to be more generalized; in one study, pregnant African Americans were compared to non-pregnant African Americans, and no other races/ethnicities were included in that study [70]. In another, the sample size is relatively small, ~ 140 people of patients that have a pre-existing mutation of a gene that predisposes people to developing thrombophilias [71]. Taken together, there is little, if any, causal evidence for why African Americans are at a higher risk of developing pre-eclampsia [72].

Biomarkers for Screening Pre-eclampsia: a Lack of Consensus Among Clinicians and Researchers

There are several biomarkers that have been identified and reviewed for being potentially clinically relevant for pre-eclampsia [73–76], and therefore will not be discussed in detail here. These include markers of oxidative stress, inflammation, and angiogenesis, the renin–angiotensin–aldosterone system, endothelial dysfunction, and placental stress. Researchers have also performed genome-wide association studies (GWAS), RNA expression, epigenetics, proteomics, exosomal, and metabolic studies. The molecules analyzed are from various bodily sources and span multiple biological functions such as angiogenesis, immune modulation, hormone production, cell proliferation, and more. These studies have been reviewed and have not found a clear marker(s) or pathways for pre-eclampsia [55, 77].

Predictive models have been created to determine the risk of developing pre-eclampsia and use logistic regression, Bayes theorem, machine learning, or other methods [78]. These models aim to predict preeclampsia early, such that the recommendation of aspirin would be made during its clinically effective period of between 12 and 28 weeks gestation. Generally, select patient characteristics, biochemical biomarkers, and/or biophysical biomarkers as used as predictors, i.e., inputs, into the models. Biochemical biomarkers include molecules like growth factors or metabolites that circulate in the peripheral blood, while biophysical biomarkers include measurements such as mean arterial pressure (MAP) and/or uterine artery pulsatility index (UtA-PI). Seventy predictive models for preeclampsia have been recently systematically reviewed by De Kat et al., and due to the vast differences of predictors chosen for each model, it is difficult to directly compare them [78]. Additionally, the studies were rarely

externally validated or calibrated, and most were done retrospectively, making it difficult to determine clinical relevance. Generally, most models used BMI, UtA-PI, blood pressure, medical history, maternal race/ethnicity, and maternal age as predictors. The biochemical biomarkers chosen for each model varied drastically though [78].

Clinicians are not fully convinced of the utility of biomarkers in pre-eclampsia. At the time of ACOG's Practice Bulletin's publication in January 2019, they were not convinced of the predictability of the statistical models, and believe they should remain investigational, along with biochemical biomarkers [2]. The International Society for the Study of Hypertension in Pregnancy (ISSHP) recommended in 2018 against the use of placental growth factor (PIGF) as rule-in or rule-out tests, which aims to distinguish pre-eclamptic and non-pre-eclamptic patients based on concentrations of some biochemical biomarkers [4]. NICE does suggest offering PIGF testing to help rule out pre-eclampsia between 20 and 35 weeks gestation [3]. Due to the uniqueness of the combination of predictors for each model created, external validation is difficult to perform, limiting clinical relevance [79].

Predictive modelling has the potential to greatly improve early prediction of a patient developing pre-eclampsia later in their pregnancy. A few models have been used in trials to detect high-risk patients that would be eligible for aspirin administration, hoping that more accurate early detection of these patients would reduce the incidence of pre-eclampsia [80, 81]. They have seen positive results that incidence was reduced, thus providing some evidence that predictive models could have a future in the clinic.

Low-Cost Technologies to Improve Access to Pre-eclampsia Screening and Diagnosis

Current clinically-accepted pre-eclampsia screening is solely based on patient characteristics, and diagnosis requires measurements taken by a clinician, for high blood pressure and/or proteinuria. Thus, access to prenatal care is essential for pre-eclampsia management, which is a large reason as to why there are more deaths in low resource settings [82]. To be most effective, the predictive models developed require sufficient medical history from medical records and for non-routine measurements such as UtA-PI and PIGF to be taken [83]. This limits their applicability to a variety of settings; thus, low-cost technologies are needed to increase access to modelling methods and prenatal screening. More generally, as telehealth and at-home diagnostics become a more common practice [84], at-home testing will help to not only make health more accessible, but to further empower patients.

In low-resource settings in LMICs, blood pressure is likely not measured during routine antenatal visits due to equipment cost and lack of trained personnel [85]. Researchers have created lower-cost blood pressure monitors for pregnancy, but few of them have been validated for pre-eclampsia diagnosis [86, 87]. In high-income countries, blood pressure testing devices are readily available, but studies have shown that measurements are lower when measured at home versus in the clinic [88]. The use of ultrasound is on the rise in LMICs, and some studies have mentioned using uterine artery Doppler measurements in LMICs [89]. Ultrasound measurements and analyses do require skilled sonographers, which could present a challenge in certain locations.

Regarding the biochemical marker that is most relevant to many predictive models, there are commercially available assays to measure PIGF which have been reviewed by Hurrell et al. [90]. The Triage PIGF test is a single-use fluorescence immunoassay and can be used at the point-of-care with a low-cost analyzer. The Triage PIGF test has a high sensitivity and is recommended to be used for patients between 20- and 34-week gestation. The other assay described measures the ratio of PIGF and an anti-angiogenic protein, soluble fms-like tyrosine kinase-1 (sFlt1). Each has its own disadvantages and advantages, and the likelihood of clinical use will be clinic specific [90]. However, as previously stated, these are not used clinically, and are currently only recommended by the UK to aid in diagnosis of pre-eclampsia [3].

Proteinuria, which does not occur in all patients with pre-eclampsia, is measured via quantitative methods such as immunoassays in high-resource settings, for non-urgent situations, or as a confirmatory test [2, 91]. In low-resource settings and for urgent situations in high-resource settings, proteinuria is measured via a dipstick that is placed into urine. Additionally, in low-resource settings, proteinuria may not be measured due to the cost of urine dipsticks [82]. These colorimetric-based urine dipstick tests are notorious for having false-positive results [2, 91, 92]. Some point-of-care diagnostics that have been developed for proteinuria include lower cost colorimetric tests, which likely will lead to similar issues as the dipstick test [86]. Others have specifically made tests for certain proteins that were found to be misfolded in severe pre-eclamptic patients [86, 93].

Low-cost technologies that could be used to provide the measurements necessary to be input into predictive models for pre-eclampsia would greatly increase access to improving detection rates for patients in a variety of settings. Low-cost tools should not only be considered for LMICs, but other settings such as at-home around the world.

Suggestions and Outlook for Pre-eclampsia Research and Screening

Diversification of Study Sites for Pre-eclampsia

A quarter of maternal deaths in the Caribbean and Latin America and one-tenth of maternal deaths in Africa and Asia are associated with hypertensive disorders of pregnancy [94]; yet most of the recommendations for pre-eclampsia come from the USA, UK, and Australia/New Zealand and other high-income countries [5]. For the predictive models reviewed by De Kat et al., 76% of them were from the USA, Australia, and the UK [73]. A diversification of study sites for all aspects of pre-eclampsia screening and risk factor analysis is needed. Researchers and clinicians in LMICs should be empowered to not only screen for pre-eclampsia, but to be able to study genetic biomarkers. For example, Brazil has begun to perform country-specific and region-specific analyses on risk factors and genetic biomarkers [77, 95]. This need has also been recognized by researchers from a consortium of seven Latin American countries, the Red Iberoamericana de alteraciones Vasculares Asociadas a TRastornos del Embarazo (RIVA-TREM). The consortium makes several suggestions such as the need for clinical guidelines for Latin America, multicenter studies, collaborations, and to seek local risk factors and biomarkers [96]. As shown in this review, some risk factors are specific to different populations, but one study did show that risk factors in 878,680 Latin American and Caribbean women were similar to those in North American and European women [97]. Similarly, many of the risk factors identified by the USA, UK, and Australia were found to be risk factors of patients in sub-Saharan Africa in a systematic review of pre-eclampsia and eclampsia in sub-Saharan Africa [98]. While there are clear differences between regions, such as nutrition environmental threats, and access to care, most risk factors are similar. This is likely due to worldwide trends of morbidity and mortality shifting towards non-communicable diseases, which most risk factors for pre-eclampsia are classified as.

A Need for Improved Biomarker Analytical Tools

Since pre-eclampsia's etiology is not fully elucidated, it is difficult to know if the plethora of possible biomarkers identified cause dysfunctional placentation or vice versa [99], making them hard to be accepted clinically. Therefore, future studies need to refine further the many biochemical biomarkers identified since causality cannot be established from the current plethora of information available. One contributing

factor to this are issues with obtaining consistent measurements of potential biomarkers. For example, to draw conclusions on the clinical relevance of deported trophoblasts, there are discrepancies between studies due to differences in isolation and detection methods of the trophoblasts. There is a lack of antibody specificity, low concentration of deported trophoblasts in the maternal peripheral circulation, and lack of continuity with the presence of circulating deported trophoblasts [100]. More generally, when utilizing placental lysates, which are used to study placental biomarkers, analytical methods do not distinguish between which cell types express the molecules of interest. Secondly, the quantification of circulating biomarkers depends on assays such as an ELISA to capture the analyte, which may not distinguish between the bound and free forms of molecules in circulation [75]. Lastly, the classification of pre-eclampsia (e.g., preterm vs early-onset) highly varies throughout the literature, and this complicates systematic reviews and drawing parallels between distinct datasets. As machine learning and other models continue to improve, it is important to consider sample origin to make accurate predictions. In vitro models of pre-eclampsia for predictive purposes are an area also in need of more attention. Trophoblast cell invasion has shown to be hindered when treated with sera from human pre-eclamptic patients, indicating the potential for in vitro predictive models [101–103].

Platforms to simplify the analysis of biomolecules should be developed to ease the cost burden of performing genetic-based and protein-based studies on patient populations. Genetic analyses require complex equipment, but also careful extraction of the nucleic acids. Point-of-care devices such as microfluidic devices and lateral flow assays should be implemented into study designs for laboratory sample analysis to expand the access of these studies. Additionally, those developing the assays should have collaborators in the location in which they hope to work, to truly understand the challenges outside of their home setting [104]. Lower cost single-cell sequencing platforms would also be beneficial for studies involving placental lysates and other sample types, to increase the granularity of biomarker data. To better validate biomarker research overall, more specific assays must be developed, and studies should aim to be prospective versus retrospective to better understand pre-eclampsia at a molecular level.

In addition to blood and placental lysates, alternative biological samples, such as follicular fluid, should be considered when performing pre-eclampsia biomarker studies, which allows for insight into the oocyte microenvironment. Follicular fluid can be obtained from in vitro fertilization patients, and its RNA expression has been studied previously for understanding oocyte quality [105]. This would allow for patients to be studied before they are pregnant,

which could better indicate causality in pre-eclampsia etiology theories [106].

Risk Factors for Pre-eclampsia—a Need for Specificity and Evidence

African Americans are thought to be at a higher risk of developing pre-eclampsia due to a higher prevalence of pre-existing conditions [107]. However, few studies show evidence of this. Studies have highlighted the importance of evaluating psychosocial factors for various outcomes in pregnancy or postpartum [108–111], which is where differences may truly lie between races and ethnicities, since inequities can affect all aspects of health [112]. Institutionalized racism is a fundamental cause of health inequities, yet that concept is often not considered in research articles [113]. Race is not biological; it is a social construct. Researchers should more carefully examine causalities not erroneously to indicate associations that may not exist [114]. Future studies should consider stress, institutionalized racism, and quality of healthcare received when studying African American pregnancies complicated with pre-eclampsia [63].

Increasing disparities in maternal mortality between African American and White mothers were recently highlighted in an article by Amy Roeder of the Harvard T.H. Chan School of Public Health, which discussed the concept of weathering. Weathering is described as a way that health is corroded due to social disadvantage, that was first described by Arline Geronimus [115]. This could be due to stressful situations that leave one in a constant state of fight-or-flight, such as working multiple minimum wage jobs to maintain livelihood [116] and/or institutionalized racism, which affects African Americans and other minority populations regardless of socioeconomic status. Thus, these social factors impart stress on the body that may lead to adverse health outcomes earlier in life, including the risk factors of pre-eclampsia, which African Americans are at a higher risk of having [60]. Additionally, African Americans are at a higher risk of these morbidities such as obesity due to social factors like inaccessibility to healthy food options, further adding to stress [117]. Stress can also be passed down generationally, and studies have shown that cardiovascular disease risk can be inherited due to similar stressors present in one's life [118]. Elevated levels of stress can affect the placental pathophysiology seen in pre-eclampsia [18]. Additionally, Roeder highlights the systemic racism present in healthcare, which led to near-death experiences and maternal deaths. The concept of transgenerational racism affecting the body epigenetically and peoples' telomere lengths has also been explored as a biological impact of racism [119].

People of Southeast Asian descent have also been identified as being at a higher risk for developing pre-eclampsia,

but are not recognized as a risk factor by major societies of obstetricians and gynecologists [83, 120, 121]. Interestingly, the studies that were performed in the USA found that Southeast Asian people not born in the USA were at a higher risk than USA-born people of the same ethnicity. This highlights not only the importance of thorough groupings of individuals included in studies, but again the importance of psychosocial factors in pregnancy such as immigration status. A predictive model did find that people of South Asian descent are at a higher risk of developing pre-eclampsia [83]. However, the authors use white race as a reference population, among other factors such as nulliparity. This demonstrates another potentially harmful aspect of race in research practice, since using one race as a reference population limits the generalizability of the research to other locations, especially in those where that race is not as prevalent.

When it comes to obesity, BMI is a highly debated metric to define the condition [122–124]. BMI is a Eurocentric measurement that has been shown to be inaccurate for various non-Caucasian populations such as those of recent African, Polynesian, and Asian descent [125]. Excess weight may not be what is the cause of comorbidities associated with obesity, but excess body fat [123]. However, more research is needed to understand the implications of this fat's role in morbidity. This debate has implications in pre-eclampsia screening as well, since BMI is often a predictor included in predictive models for the condition.

Pre-conception Analyses: an Unmet Need

The largest gap in terms of the focus of pre-eclampsia screening efforts is that the focus is on patients after they become pregnant, not beforehand. Even as prediction tools have improved detection rates, once a patient is pregnant, only delivery may “cure” pre-eclampsia. Previous history of pre-eclampsia has been shown to be predictive of an increased cardiovascular risk later in life, and at a younger age [1, 43–47]. If patients were aware of their risk of developing pre-eclampsia before becoming pregnant, knowing the post-pregnancy risks as well, they would be empowered to decide if they would like to become pregnant or seek other options. Additionally, pre-conception studies could improve research around the etiology of pre-eclampsia, which remains highly theoretical. In one study by Foo et al. discovered a different etiology than placental dysfunction via studying patients prospectively before and after they became pregnant [126]. This highlights the significance of studying patients pre-conception in the understanding of pre-eclampsia.

Conclusions

Pregnancy could be considered a stress test for the body, and the stress of pre-eclampsia may accelerate the presentation of cardiovascular-related morbidities. Pre-eclampsia is a complex condition with multiple theorized causality pathways, making the condition challenging to study and define. When screening for the risk of developing pre-eclampsia to prescribe aspirin to high-risk patients, physicians use risk factors that involve patient medical history, family medical history, sexual history, and maternal demographic characteristics. Not only does this method have low detection rates, these risk factors, especially obesity and race, need to be analyzed more closely to establish a true association. Additionally, the study locations of pre-eclampsia research need to be expanded beyond a few high-income countries to include more LMICs since hypertensive disorders of pregnancy are a worldwide cause of maternal mortality. Potential biomarker analyses need to be better regulated, and low-cost technologies have the chance to increase access to patient sample-based research for pre-eclampsia. Lastly, pre-conception prospective studies for pre-eclampsia are critical to establishing causality for the “disease of theories.” Expertise from multiple fields is vital for the advancement of pre-eclampsia screening, research, diagnosis, and management.

Search Strategy and Selection Criteria

Data from this review were identified by searches of PubMed and references from relevant articles using the following keywords, alone or in combination: “pre-eclampsia,” “risk factor,” “LMICs,” “clinical definitions,” “diabetes,” “obesity,” “chronic kidney disease,” “thrombophilias,” “autoimmune disease,” “hypertension,” “anemia,” “point of care,” “etiology,” “pathophysiology,” “immunology,” “screening,” “African American,” “Asian,” “Hispanic,” “blood pressure,” “machine learning,” “predictive models,” “seminal fluid exposure,” “assisted reproductive technologies,” “placental implantation,” or “COVID-19.” Only articles published in English were included. Abstracts and reports from meetings were excluded.

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Declarations

Conflict of Interest The authors declare no competing interests.

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This article refers to “women” and “mothers” as biological sex but recognizes that multiple genders may experience what was discussed.

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