Pregnancy Hypertension 15 (2019) 23–31

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

Preeclampsia: Disease biology and burden, its management strategies with reference to India

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ARTICLE INFO

Keywords:
Preeclampsia
Etiology of preeclampsia
Incidence of preeclampsia
Risk factors predisposing women to preeclampsia
Prevention and management of preeclampsia
Preeclampsia predicting diagnostic markers

ABSTRACT

Preeclampsia is the cause of significant maternal and fetal mortality and morbidity. It is characterized by new-onset hypertension and proteinuria after 20 weeks of gestation. Preeclamptic women and children born from preeclamptic pregnancies are at greater risk to develop severe cardiovascular complications and metabolic syndromes later in life. The incidence of preeclampsia is estimated to be seven times higher in developing countries as compared to the developed countries. This review summarizes the pathophysiology of preeclampsia, emerging new hypothesis of its origin, risk factors that make women susceptible to developing preeclampsia and the potential of various biomarkers being studied to predict preeclampsia. The health care of developing countries is continuously challenged by substantial burden of maternal and fetal mortality. India despite being a fast developing country, is still far behind in achieving the required maternal mortality rates as per Millennium Development Goals set by the World Health Organization. Further, this review discusses the prevalence of preeclampsia in India, health facilities to manage preeclampsia, current guidelines and protocols followed and government policies to combat this complication in Indian condition.

1. Introduction

Preeclampsia, a pregnancy disorder, is defined as a systemic syndrome characterized by new-onset of hypertension (blood pressure – systolic > 140 mm Hg, diastolic > 90 mm Hg on two occasions at least 4 h apart, or in severe cases systolic blood pressure > 160 mm Hg and diastolic blood pressure > 110 mm Hg) and proteinuria (protein [mg]/creatinine [mg] ratio of > 0.3 or protein > 5 g in a 24 h urine sample, or > 3 g in two samples taken 6 h apart from a patient on bed rest) after 20 weeks of gestational age in pregnant women, which resolves before the end of 6th week postpartum [1]. In the absence of proteinuria, preeclampsia presents with hypertension associated with any features of end organ damage [1]. Eclampsia is characterized by onset of seizures in pregnant women with preeclampsia. In cases of severe preeclampsia, additional symptoms like oligouria, headache, cerebral or visual disturbances, shortness of breath with reduced oxygen saturation or pulmonary edema, epigastric/right upper-quadrant pain, thrombocytopenia, renal function compromise, hemolysis, impaired liver function of unclear etiology, vomiting, reduced fetal movements after 20 weeks of pregnancy are also present [1]. Preeclampsia-eclampsia rank second to hemorrhage as a specific, direct cause of maternal mortality [2]. In the mother, preeclampsia later in life can cause development of cardiovascular diseases such as chronic hypertension, ischemic heart disease, and stroke [3–5]. Children born from preeclamptic pregnancies often suffer from Intra Uterine Growth Restriction (IUGR) and are Small for Gestational Age (SGA) [6,7]. Preeclampsia also increases the risk of stroke, coronary heart disease and metabolic syndrome during adult life in the children born from preeclamptic pregnancies [8–10].

The health care in developing countries is continuously challenged by substantial burden of maternal and fetal mortality. In India as well as worldwide, 7–8% of maternal deaths are directly associated with hypertensive disorders of pregnancy [2,11]. Preeclampsia is the most commonly occurring hypertensive disorder of pregnancy [12,13]. As per the report of India's third National Family Health Survey (NFHS-3, 2005-06), which was based on self-reported symptoms suggestive of preeclampsia and eclampsia by women who had a live birth in the five years preceding the survey, the incidence of preeclampsia and eclampsia in India might be higher (~28% and 7.4–11.3% respectively) as compared to its incidence worldwide [14,15]. The number of preterm births reported in India is the highest in the world [16]; and hypertensive disorders of pregnancy (preeclampsia – 36%, chronic

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https://doi.org/10.1016/j.preghy.2018.10.011
Received 13 July 2018; Received in revised form 29 October 2018; Accepted 31 October 2018
Available online 02 November 2018

hypertension – 5%, eclampsia – 4.8%, gestational hypertension – 4.8%) are the most common risk factors of the preterm births reported in India [17]. India is recently working on reducing maternal and fetal mortality through efforts in providing institutional deliveries, early detection of pregnancy related disorders, supplementation of pregnant women with calcium and providing quality antenatal care to pregnant women with special focus on preeclampsia.

This review elaborates on the pathophysiology of preeclampsia, emerging new hypothesis of its origin, its diagnosis, various risk factors and potential of biomarkers for early diagnosis of preeclampsia. The prevalence of preeclampsia in India, health facilities to manage preeclampsia, current protocols and guidelines followed, and government policies of India to combat preeclampsia have also been discussed.

2. Etiology of preeclampsia and theories of its origin

Removal of placenta leads to resolution of symptoms of preeclampsia in most of the cases, and thus its management mainly relies on delivery. Clinical symptoms and laboratory abnormalities related to preeclampsia usually regress after delivery, but the risk of complications persists for some time following delivery [18], and some women can even develop preeclampsia/eclampsia postpartum. Incidence of preeclampsia increases in cases of hydatiform moles. Additionally, multiple pregnancy increases the chances of developing preeclampsia. These clinical observations provide irrefutable evidence of placental origin of preeclampsia, but the underlying cause of preeclampsia eludes researchers. Theories elaborating the mechanisms of development of preeclampsia include uteroplacental origin, angiogenic origin, immunogenic origin and genetic predisposition (Fig. 1). The two stages in which preeclampsia develops are – (i) initial stage: during which placental perfusion deficiency, endothelial dysfunction, defective implantation, oxidative stress or high placental mass (as present in multifetal pregnancies/vesicular mole) generate an unidentified signal; (ii) later stage: where this unidentified signal leads to aberrant maternal response (which is the clinical manifestation of preeclampsia characterized by hypertension and proteinuria) due to her genetic predisposition, which is further influenced by physiological and metabolic changes during pregnancy [19,20].

i) Utero-placental origin of preeclampsia: Placental biopsies and cesarean hysterectomy specimens from preeclamptic women in their early pregnancy show shallow invasion of trophoblasts and failure to remodel maternal spiral arteries leading to less placental perfusion which later give rise to maternal symptoms of preeclampsia [21]. An animal model that indirectly tests this theory involves administration of doxycycline (a matrix metalloproteinase inhibitor, thus reducing trophoblast invasion and spiral artery remodeling) to pregnant Sprague-Dawley rats [22]. This study reported reduced trophoblast invasion and spiral artery remodeling which led to reduced placental perfusion and development of hypertension in the pregnant rats. The causes of impaired placentation in women which develop preeclampsia is not completely understood, but may be in part due to faulty differentiation of extravillous trophoblast (EVT) with poor invasive properties and in part due to changes in maternal decidual tissues, which regulate cytokines/growth factors-mediated trophoblast behavior. A recent study shows that human endometrial stromal cells from women with previous severe preeclamptic pregnancy fail to decidualize *in vitro* [23]. Further, expression of prolactin and insulin-like growth factor binding protein (both decidualization markers) were greatly reduced or completely absent in tissue sections of decidua from women suffering from severe preeclampsia. The culture medium of decidual cells isolated from women with severe preeclampsia also fail to promote cytotrophoblast invasion [23]. The differentiation defect of cytotrophoblasts may be due to reduced/inhibited maternal synthesis of nitric oxide which contributes to endothelial dysfunction or prevent implantation [24,25]. Further, impaired trophoblast invasion and poor placental perfusion is known to increase due to increased oxidative stress, hypoxic environment, endothelial dysfunction and aberrant maternal systemic inflammatory response [26]. The oxidative stress generated further induces release of free radicals, oxidized lipids, pro-inflammatory cytokines and serum soluble vascular endothelial growth factor (VEGF)

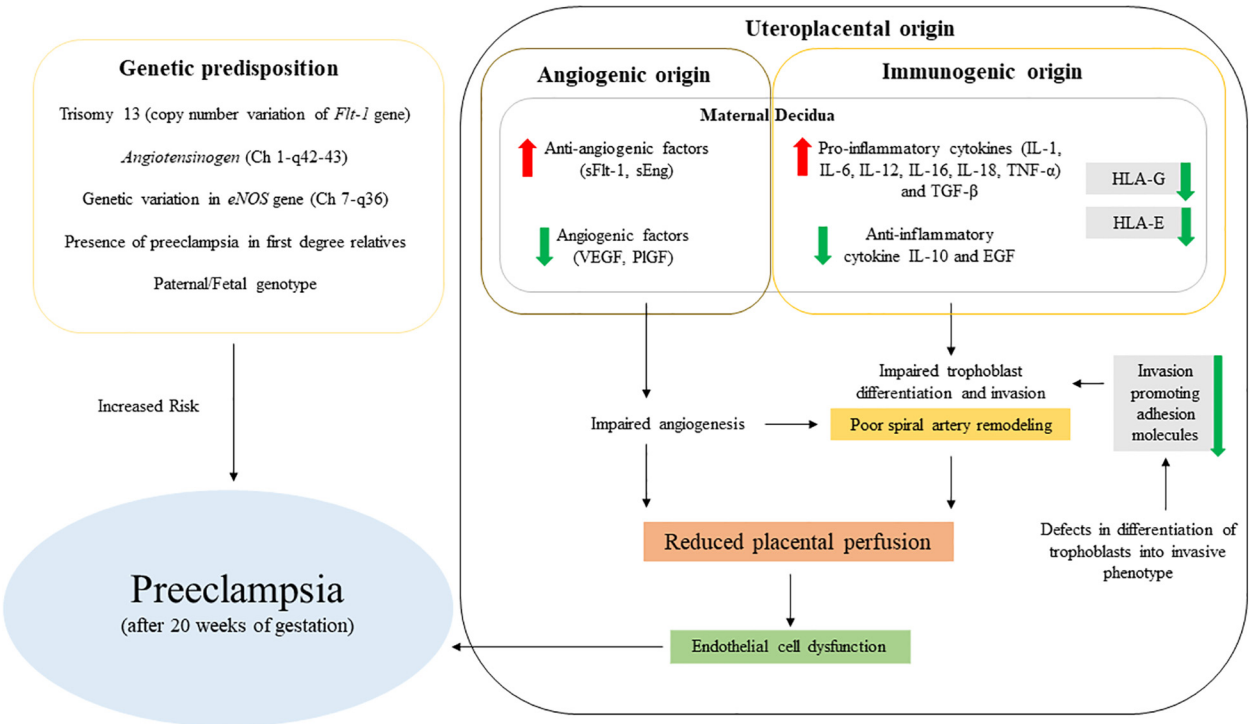

Fig. 1. Theories of origin of preeclampsia. Preeclampsia is a systemic disorder characterized by new-onset of hypertension and proteinuria after 20 weeks of gestational age in pregnant women. Theories elaborating the mechanisms of development of preeclampsia include uteroplacental origin, angiogenic origin, immunogenic origin and genetic predisposition.

[27]. Placental hypoxia due to poor placental perfusion leads to increased expression of soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) in pregnant rats [28,29].

Preeclampsia is associated with increased expression of pro-inflammatory cytokines like tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, IL-12 & IL-18, and decreased production of anti-inflammatory cytokine IL-10 [30–32]. Higher levels of transforming growth factor (TGF)-β and sFlt-1 are observed in early onset preeclampsia (EOPE), whereas VEGF, epidermal growth factor (EGF) and placental growth factor (PLGF) are decreased [33,34]. Invasive cytotrophoblasts express VEGF-A, VEGF-C, PLGF, vascular endothelial growth factor receptor (VEGFR)-1 and VEGFR-3 in early gestation, and VEGF-A, PLGF and VEGFR-1 at term [35]. The interactions among these molecules is critical for invasion and pseudovasculogenesis (the process by which cytotrophobasts switch their adhesion molecules to mimic that of vascular cells) [35]. Further, the expression of invasion promoting adhesion molecules are altered in women with preeclampsia. Trophoblast cells from placentas of preeclamptic women show lower attachment to fibronectin and vitronectin which may be reflecting the decreased expression of extracellular matrix (ECM) interacting adhesion molecules [36].

ii) Angiogenic origin of preeclampsia: The plasma from women with preeclampsia impairs the ability of pre-constricted vessels (from women with normal pregnancy) to relax, thus mimicking vessels from preeclamptic women [37]. Further, the endothelial cell dysfunction during preeclampsia due to ischemic placenta is attributed to alteration in balance of the circulating angiogenic and anti-angiogenic growth factors which can cause hypertension and proteinuria. These observations led researchers to investigate the role of circulating factors like VEGF, TNF, lipid peroxidases and syncytiotrophoblast micro-fragments during pregnancy. The circulating levels of angiogenesis regulators like VEGF and PLGF are reduced during preeclampsia and may be responsible for many of the clinical symptoms of preeclampsia [38,39]. Both VEGF and PLGF promote angiogenesis by binding to VEGFR2 and VEGFR1 (alternately known as Flt-1) respectively, whereas soluble Flt-1 (sFlt-1) inhibits angiogenesis [40]. In both early and late-onset preeclampsia an increase in the sFlt-1/PLGF ratio and increased circulating levels of sFlt-1 are observed [41,42]. The expression of sFlt-1 and sEng (anti-angiogenic factors) are reported to be increased before the clinical onset of preeclampsia [42]. Overexpression of circulating sFlt-1 in pregnant rats or placenta of pregnant mice can cause the hypertension, proteinuria and renal damage characteristic of preeclampsia [43,44], and pregnant rodents exposed to high circulating levels of sFlt-1 also elicit severe preeclampsia-like symptoms [45,46]. Additionally, increased circulating levels and placental expression of sEng or CD105 (inhibitor of capillary formation) are associated with preeclampsia and correlate with disease severity [42,47]. In pregnant rats, overexpression of sEng also increases blood pressure and proteinuria, but it is not to the same extent as overexpression of sFlt-1. The increase in blood pressure and proteinuria is most severe with simultaneous overexpression of sFlt-1 and sEng [47].

iii) Immunogenic origin of preeclampsia: Impairment of the maternal immune system to recognize the feto-placental unit may act as a trigger for preeclampsia by inducing defects in vascular remodeling, hypertension and proteinuria. Women with preeclampsia show reduced levels of histocompatibility antigen (HLA)-G and -E [48]. Preeclampsia has been postulated to be a continuation of the immune-mediated inflammatory changes as observed in pregnancy, and it can be hypothesized that women who respond vigorously to paternal HLA antigens are more susceptible to develop endothelial injury that precedes preeclampsia [49]. The importance of immune response to paternal antigens is supported by the increased risk to preeclampsia observed after a change in partner and short initial coitus-to-conception interval [50,51]. Several immune-associated risk factors like pre-existing autoimmune disease, autoimmune antibodies to angiotensin II type I (AT_1) receptors and phospholipids etc. in the pregnant woman also increases the probability of developing preeclampsia [51,52]. Injection of anti-AT_1-receptor antibodies in pregnant mice and rat induces symptoms of preeclampsia including hypertension, proteinuria, defects in vascular remodeling and increases HIF-1α expression [53,54]. In preeclampsia, the balance of circulating T helper (Th) cells is shifted from the Th2 bias of normal pregnancy towards Th1, which is marked by increased secretion of IL-12 and IL-18 and reduction in IL-10 secretion [31]. It is suggested that TNF-α and IFN-γ elicit enhanced inflammatory response towards trophoblasts due to deficiency of anti-inflammatory action of IL-10 leading to apoptosis and reduced invasion of trophoblast cells [55]. This is supported by observed symptoms of preeclampsia in IL-10 knockout mice exposed to hypoxic environment [56]. Additionally, IL-10 inhibition by passive immunization during early gestation in pregnant baboons leads to increased blood pressure [57]. A recent study demonstrated that pregnancy conceived through oocyte donation have an increased risk of preeclampsia, which suggests that immunological tolerance between the fetus and the mother might be playing crucial role in pathogenesis of preeclampsia [58].

***iv) Genetic predisposition leading to preeclampsia*:** Family history of hypertension, pre-existing hypertension before pregnancy increase the risk of developing preeclampsia [51]. The BPH/5 mouse strain (which is mildly hypertensive) develops multiple preeclampsia-like symptoms, including late gestational hypertension, proteinuria, endothelial dysfunction, poor placental development and abnormal maternal uterine arteries [59]. Although both genetic and environmental factors increase the risk of preeclampsia [60], the presence of preeclampsia in first degree relatives increases a woman's risk of preeclampsia by 2–4 fold [61]. Genetic factors might be playing an important role for generating angiogenic imbalance found in women with preeclampsia. No causal mutations in PLGF, sFlt-1, and sEng genes associated with preeclampsia have been so far identified [62]. However, women with trisomy 13 fetuses have a higher incidence of preeclampsia [63], and the Flt-1 gene is located on chromosome 13. This suggests that gene dosage or copy number variation may contribute to the development of preeclampsia. There is some evidence to suggest that in addition to maternal genotype, paternal or fetal genotype may also contribute to the risk of preeclampsia. The risk of fathering a preeclamptic pregnancy is increased among males who fathered a preeclamptic pregnancy with a different partner [64]. Also, men who are born from a pregnancy complicated by preeclampsia are at a higher risk of fathering a preeclamptic pregnancy [65]. Several susceptibility genes may exist for preeclampsia which may be interacting with the hemostatic & cardiovascular systems, as well as inflammatory response. Evidence of linkage of angiotensinogen (Ch 1-q42-43) and eNOS (Ch 7-q36) to increased incidence of preeclampsia have been reported in candidate gene studies [60,62]. The genetic variations in the NOS3 gene increases the risk for preeclampsia [66].

3. Emerging hypothesis of the origin of preeclampsia

The idea that the imbalance in secretion of angiogenic factors, anti-angiogenic factors, and cytokines during preeclampsia ('accelerators') may be due to the failure of the endogenous protective pathways ('the braking system') led to the proposed "accelerator and brake hypothesis" [67]. Thus, to cure preeclampsia, it is hypothesized that the strategy should be centered on identifying cytoprotective pathways. The haemoxygenase (HO)/carbon monoxide (CO) system and cystathionine-γ-lyase (CSE), which produces hydrogen sulphide (H_2S), are two protective pathways that inhibit sFlt-1 and sEng release and act as the break system [68,69]. Additionally, nitric oxide synthase (NOS) is another protective pathway, as it is observed that loss of endothelial NOS3 activity contributes to endothelial dysfunction [25]. In pregnant mice and rats, administration of NOS3-inhibiting agents led to inhibition of NO production and mimicked all the symptoms of preeclampsia [70]. These gaseous signaling molecules (NO, CO and H_2S; gasotransmitters) can act as vasodilators [71–73].There is evidence of NO, CO and H_2S

producing enzyme systems regulating placental blood vessel tone and thus promote placental vasodilation [70,74–77]. Thus, therapies that up-regulate these endogenous cytoprotective pathways might benefit women predisposed to develop preeclampsia.

4. Identification of maternal risk factors that predispose women to preeclampsia

There are multitude of diseases, environmental and genetic factors that predispose women to preeclampsia. In absence of an effective diagnostic marker, clinical risk can assist in identifying women at risk to develop preeclampsia and aid in its effective management. Primigravida and new male partner increase the risk of incidence of preeclampsia by 3–5%, whereas the risk increases by 13–18% in the second pregnancy for women who developed preeclampsia during the first pregnancy [52,78–80]. The risk of incidence of preeclampsia increases, if the pregnant women had a history of diseases such as chronic hypertension, renal disease, pre-gestational diabetes, systemic lupus erythematosus, rheumatoid arthritis, migraine and thrombophilia [52]. Women younger than 18 years and older than 35 years have potentially high risk of developing preeclampsia during pregnancy [52]. History of preeclampsia in a first-degree relative of the pregnant woman also correlates to increased risk of incidence of preeclampsia [52]. According to PREeclampsia COmmunity Guidelines (PRECOG, published in 2005), assessment of the risk should be performed before 20 weeks of pregnancy and women with known previous preeclampsia, multiple pregnancy, or the above mentioned diseases should be referred for evaluation by specialists [81].

5. Early detection of preeclampsia

The diagnosis of preeclampsia remains a challenge as it relies on the emergence of non-specific symptoms which vary from woman to woman. Various biomolecules with reported potential to be developed as clinical diagnostic markers are summarized in Table 1. The most widely studied and promising markers being developed are VEGF and PlGF and their antagonist sFlt-1 and sEng. During pregnancy, sFlt-1 levels remain stable until 29–33 weeks, and then rise steadily until delivery [41]. While levels of PlGF rise progressively starting from the first trimester, reaching its peak around 29–33 weeks, and decline there after [41]. In preeclampsia, maternal circulating sFlt-1 levels are significantly increased more than one month before the onset of the early detectable clinical symptoms [41]. In the case of PlGF, significant lower concentrations in women who later develop preeclampsia are seen from the beginning of the second trimester. While individually sFlt-1 and PlGF failed to be good predictors of preeclampsia, but sFlt-1/PlGF ratio lower than 38 has been reported to be negative predictor of preeclampsia with 100% accuracy [82,83]. The sFlt-1/PlGF ratio greater than 85 (for early onset preeclampsia, EOPE) or 110 (for late onset preeclampsia, LOPE) are indicative of high risk of developing preeclampsia or placenta-related disorders, and these women should be closely monitored [82,83]. However, the positive predictive value of the sFlt-1/PlGF ratio is only 18–20% [82,83].

Another candidate with potential diagnostic value is pregnancy associated plasma protein-A (PAPP-A), which is synthesized by trophoblast and reported to be decreased in plasma in women with preeclampsia [84]. Combining serum levels of PAPP-A along with uterine artery Doppler studies might prove to be better diagnosis marker to predict preeclampsia [85]. During normal pregnancy, placental protein 13 (PP-13) gradually increases and is also proposed as promising candidate biomarker for preeclampsia. Abnormally low serum levels of PP-13 in the first trimester are observed in women who later develop preeclampsia and Fetal Growth Restriction (FGR) [86]. Similar to PAPP-A, combining serum PP-13 levels along with uterine artery Doppler studies improve the predictive ability of this test. Various other molecules like sex hormone-binding globulin (SHBG), apolipoprotein E (ApoE), inhibin A, activin A, free β-human chorionic gonadotropin (β-hCG), sEng, disintegrin, and metalloproteinase domain-containing protein 12 (ADAM12) etc, have been studied as potential biomarkers for predicting/diagnosis of preeclampsia but failed to show consistent results (Table 1) [87–95]. A combination of most promising biomarkers with clinical parameters may improve prediction and diagnosis of preeclampsia as well as its management through development of predictive models [96]. Hence, additional research inputs are required to find ideal biomarkers that can improve risk prediction in association with clinical factors.

6. Geographical prevalence of preeclampsia in India

WHO estimates that the incidence of preeclampsia is seven times higher in developing nations (2.8% of live births) as compared to the developed countries (0.4% of live births) [97]. A WHO secondary analysis in low- and middle-income countries reported the incidence of preeclampsia to be in the range of 2–15% in India, and India has an average of 4.5% reported preeclampsia cases as per data collected from individual institutions during this study [98]. In one of the independent study from India, follow-up of 1802 pregnant women revealed that 3.38% patients developed preeclamsia/eclamsia [99]. However, there is lack of studies on geographical prevalence of preeclampsia in various states of India. India's third National Family Health Survey (NFHS-3, 2005-06) had reported the prevalence of preeclampsia based on self-reported symptoms suggestive of preeclampsia by women who had a live birth in the five years preceding the survey [14,100]. Eastern and northeastern states of India were reported to have highest incidence of preeclampsia. Whereas, states like Andhra Pradesh, Haryana, Himachal Pradesh and Karnataka had lowest incidence of preeclampsia (Table 2). The NFHS-4 (2015-16) has not reported on state-wise prevalence or total prevalence of preeclampsia in India [101]. But, the NFHS-4 reports that among women that had a live birth in five years preceding the survey, 16.5% of pregnant women experienced convulsions without

Table 1
Potential biomarkers for early detection of preeclampsia.

Biomarker	Plasma concentration in preeclampsia	Category	Reference
Sex hormone-binding globulin (SHBG)	decrease	Metabolic	[93]
ApolipoproteinE (Apo-E)	increase	Metabolic	[90]
Activin A	increase	Endocrine	[87]
Inhibin A	increase	Endocrine	[87]
β-human chorionic gonadotropin (β-hCG)	decrease	Endocrine	[85,88]
Disintegrin and metalloproteinase domain containing protein 12 (ADAM12)	increase	Protease	[92]
Placental protein 13 (PP-13)	decrease	Immunological	[86,91]
Pregnancy associated plasma protein A (PAPP-A)	decrease	Immunological	[84,85,88]
Soluble endoglin (sEng)	increase	Anti-angiogenic	[29,42,47,68,95]
Soluble fms-like tyrosine kinase 1 (sFlt-1)	increase	Anti-angiogenic	[44,68,82,83,94]
Placental growh factor (PlGF)	decrease	Pro-angiogenic	[39,43,94]
Vascular endothelial growth factor (VEGF)	decrease	Pro-angiogenic	[35,89]

Table 2
Self-reported prevalence of symptoms suggestive of preeclampsia during pregnancy among women aged 15–49 years with reported live births in the five years preceding the NFHS-3 (2005-06).

State	Symptoms suggestive of preeclampsia (% of total live births)		
	Urban	Rural	Total
Andhra Pradesh	23.3	19.8	21.0
Arunachal Pradesh	41.9	37.6	38.7
Assam	25.8	30.1	29.6
Bihar	34.2	35.4	35.3
Chhattisgarh	28.5	25.3	25.9
Delhi	31.3	16.2	30.1
Goa	38.7	39.7	39.1
Gujrat	36.6	34.4	35.3
Haryana	23.7	16.6	18.5
Himachal Pradesh	29.9	22.8	23.5
Jammu & Kashmir	32.6	36.0	35.3
Jharkhand	37.2	42.4	41.4
Karnataka	23.5	17.4	19.8
Kerala	46.2	49.5	48.4
Madhya Pradesh	39.1	33.2	34.6
Maharashtra	31.0	20.7	25.5
Manipur	26.4	30.1	29.0
Meghalaya	48.6	40.8	42.2
Mizoram	50.0	48.4	49.2
Nagaland	35.3	34.0	34.3
Orissa	25.7	26.5	26.4
Punjab	29.9	24.1	26.3
Rajasthan	39.6	25.0	28.2
Sikkim	38.0	41.6	41.0
Tamil Nadu	22.5	24.6	23.7
Tripura	48.8	49.5	49.4
Uttar Pradesh	24.4	25.9	25.6
Uttarakhand	46.3	40.7	42.1
West Bengal	31.0	25.5	26.7

fever, 10.9% had difficulty with vision during daytime, and 31.8% experienced swelling of legs, hands or face, which are symptoms that may be indicative of preeclampsia.

7. Health facilities and government policies in India to manage preeclampsia

The national level health care system is guided by the Union Ministry of Health and Family Welfare (MoHFW), further each state has a state run Department of Health and Family Welfare, headed by the State Minister. The healthcare infrastructure in India consists of primary, secondary, and tertiary health care setups [102]. Both public and private health care providers are working to provide medical care at these levels. At the primary level of health care, Community Health Centers (CHCs), Primary Health Centers (PHCs), and Sub-centers (SCs) are established by the government [102]. The PHC serve as the first point of care in the Indian public health system. Each PHC is staffed by one doctor and three to five staff nurses [103]. Auxiliary nurse midwife (ANM), is a village health worker and acts as a first contact person to avail health services in rural India. Health services including screening, management, and referral for pregnancy and newborn complications is provided by ANMs. Secondary health care of the Indian healthcare system run by the government consists of Sub-divisional Hospitals, District Hospitals, and Mobile Medical Units, which provide assistance by a specialist to patients referred from the primary healthcare [102]. Public-Private Partnership (PPP) in health care is also being encouraged by the government, these PPP run at secondary and tertiary healthcare levels and aim to deliver public health care services through the combined efforts of public, private and other organizations by contributing to the core competency of the healthcare system. At the tertiary healthcare setups, specialized preventive care is given to the patients usually on referral from primary and secondary health care centers. Tertiary health care setups include medical colleges, advanced medical research institutes and super-specialty hospitals. Both secondary and tertiary healthcare setups have well equipped laboratories and highly trained medical staff [102]. The National Rural Health Mission (NRHM) was launched in 2005 by Government of India to extend the reach of healthcare system to rural areas and improve the existing healthcare system. Under NRHM, the MoHFW has instituted local women in every village as accredited social health activists (ASHA) who motivate women to give birth in hospitals, bring infants to immunization clinics, treat basic illness and give first aid, encourage family planning and keep demographic records.

Various yojna's (plans) have been launched by the government of India to achieve Millennium Development Goals, and many of these yojna's focus on reducing maternal and fetal mortality and improving their health. Under Janani Suraksha Yojna (JSY) [104] by MoHFW, increased institutional deliveries have been reported since its launch. JSY is a centrally sponsored scheme, which integrates cash assistance with delivery and post-delivery care. Under the JSY, eligible pregnant women are entitled for cash assistance irrespective of the age of mother and number of children for giving birth in a government or accredited private health facility. The scheme also provides performance based incentives to women health volunteers known as ASHA for promoting institutional delivery among pregnant women. The government launched Janani Shishu Suraksha Karyakaram (JSSK) in 2011 [105] to ensure free health services like delivery, C-section, diagnostics, food during hospital stay, transport between facilities, provision of blood and medication to pregnant women and sick neonates for reducing maternal and infant mortality. The NFHS-4 (2015-16) reported ~79% institutional deliveries for the births in the 5 years before the survey [101]. The government of India, in order to bring down the maternal mortality rates introduced Pradhan Mantri Surakshit Maitritva Abhiyaan (PMSMA) [106] in 2016 to provide quality antenatal checkups to pregnant women in public health facilities as well as public-private partner institutions by ensuring that all basic laboratory investigations (like hemoglobin levels, urine albumin, rapid malaria test, blood grouping, dipstick hematuria, ultrasound, complete blood count, erythrocyte sedimentation rate, Venereal Disease Research Laboratory test and blood pressure) are done before the beneficiary is examined by the Obstetrician & Gynecologist/Medical Officer. Identification and treatment of high risk factors during pregnancy by quality antenatal checkups aims to assist in reducing maternal mortality rates by identifying women at greater risks to develop pregnancy related complications like preeclampsia, IUGR etc. and providing timely intervention. Additionally, PMSMA aims at creating awareness among pregnant women about care during pregnancy, danger signs during pregnancy, birth preparedness and complication readiness. It also provides contact details to be used in case of need, family planning, requirement of nutritional supplementation including iron-folic acid consumption & calcium, institutional delivery, entitlements under JSK & JSSK, and postnatal care.

8. Current protocols/guidelines/clinical practices for prevention and management of preeclampsia in India and gaps

Micronutrient (iron, calcium) and antioxidant deficiencies (vitamin C and E) may be probable contributors to the development of preeclampsia/eclampsia. It is reported that iron (Fe, anaemic women) and calcium (Ca) deficiencies increase the risk of preeclampsia in women [107–109]. Elimination of these micronutrients and antioxidant deficiencies in pregnant women in developing nations could help reduce the risk of preeclampsia. It has been proven that in women with low dietary calcium intake, calcium supplementation during placentation halves the risk of preeclampsia [107–109]. For prevention of preeclampsia, the MoHFW India issued guidelines in 2014, which advise on use of calcium supplementation during pregnancy as primary preventive strategy to reduce the risk of hypertensive disorders like

preeclampsia in pregnant women [110]. Proper antenatal care and timed delivery are of the utmost importance for tertiary prevention of preeclampsia [111]. Keeping the importance of proper antenatal care to pregnant women in mind; PMSMA introduced in 2016 in India, aims at providing quality antenatal care, identifying and treating pregnant women with high risk factors that can lead to development of pregnancy related disorders [106].

Management of preeclampsia depends on the stage to which pregnancy has progressed. Irrespective of the severity of preeclampsia, there is no advantage in continuing the pregnancy when preeclampsia is discovered after 36–37 weeks of pregnancy [112–114]. If severe preeclampsia is discovered before 24 weeks of pregnancy, interruption of pregnancy is advisable in view of the high risk of maternal complications and poor neonatal prognosis [115–117]. As per the WHO guidelines, at 24–34 weeks and 34–37 weeks of gestation, management depends on the severity of preeclampsia. Expectant management is recommended in case of mild preeclampsia, but severe preeclampsia or presence of signs like uncontrolled severe hypertension (non-responsive to dual therapy), acute pulmonary edema, sub-capsular hepatic hematoma, thrombocytopenia, abruption placentae or eclampsia indicate the need of immediate delivery [107].

Expectant management of preeclampsia focuses on reducing the risk of maternal and neo-natal complications by administration of anti-hypertensive (like nifedipine/methyldopa/labetalol/dihydralazine etc as a single agent or a combination of two) and anti-convulsants (like magnesium sulfate or alternately phenytoin) to manage hypertension and convulsions. Anti-hypertensive drugs reduce the maternal complications like cerebral hemorrhage, eclampsia and acute pulmonary edema [118] and anti-convulsants reduce the maternal and neonatal complications of eclampsia [119]. Taking gestational age into account, the use of betamethasone (a corticosteroid, two injections of 12 mg 24 h apart) helps in fetal pulmonary maturation and reduces the risk of hyaline membrane disease, intraventricular hemorrhage and neonatal mortality [120].

9. Ignorance of patients and risks

Antenatal care non-attendance is an additional significant risk factor of preeclampsia [52], which may be due to inadequate management during pregnancy to prevent development of the condition. Delay in decision to seek care in case of obstetric emergencies as a result of inadequate information on when to seek help and sometimes where to seek help is a challenge in the management of pregnancy related complications like preeclampsia in developing nations [121,122]. This is worsened by lack of decision making power with women, poverty and the rising cost of healthcare [123,124]. Additionally, socio-demographic (e.g. level of education and marital status) and cultural underpinnings of maternal health-seeking behavior have also been documented [125]. Social factors have been recognized to influence up to 27% of maternal deaths [126].

Preeclampsia and eclampsia carry a high fatality rate for the mother and/or the infant. Ignorance of patients to pregnancy complications and the associated risk of maternal and fetal mortality can also lead to casual behavior of the patient and their family, which in rural areas in developing countries leads patients to seek advice from alternative or orthodox medical practitioners leading to referral delays. These delays have been documented to account for 46.4% of preeclampsia cases [127,128]. Due to lack of access to health care and pregnancy-related health information, pregnant women in rural India generally rely heavily on information and misconceptions about pregnancy gleaned from elder women, friends, and mothers-in-law [129]. Doctors and para-medical staff are only consulted during complications. Further, pregnant women face personal, societal, and structural level barriers, including feelings of shame and embarrassment, and fear of repercussion for discussing their pregnancies with their doctors [129]. In spite of these shortcomings, remarkable decline in Maternal Mortality Ratio (MMR) has been recorded in India; 22% reduction in maternal deaths since 2013 [130]. According to NFHS-4 (2015-16) of India, only 51.2% pregnant women came for 4 or more antenatal care visits out of the women who had a live birth in past five years, and only 64.8% received information about pregnancy complications. Improving the knowledge of patients about pregnancy complications can improve healthcare seeking behaviors, which might aid in timely diagnosis and treatment of preeclampsia [131].

10. Postnatal follow-up and issues

Clinical symptoms and laboratory abnormalities related to preeclampsia usually regress in the hours after delivery, but the risk of complications persists for some time following delivery [18]. Examination of retrospective records and prospective cases of 39,050 births, 101 cases had postpartum eclampsia (0.26% of birth). Interestingly, 51.58% cases were diagnosed with pre-delivery hypertensive disorders and 48.52% were *de novo* [132]. Further, the National Eclampsia Registry (NER) [133], India has reported high index (13%) of postpartum eclampsia. Post-delivery (till 72 h), hemodynamic transition is occurring in the mother which needs close neurological monitoring of signs like headaches, phosphene signals, tinnitus and brisk tendon reflexes for early detection of eclampsia [134]. Women who had preeclampsia, can become hypertensive again in the postnatal week, thereby making hemodynamic monitoring essential [135]. Frequent blood pressure measurements should be made to enable adjustment of anti-hypertensive treatment [135]. Anti-hypertensive drug like methyldopa should be avoided postpartum due to the risk of postnatal depression. Women with gestational hypertension or preeclampsia, are usually able to stop all anti-hypertensives within six weeks postpartum. Three months after delivery, screening for renal or hypertensive disease should be done; as this examination may unmask previously undiagnosed systemic disease or kidney diseases or thrombophilia [136].

Approximately 20% of women who develop preeclampsia during pregnancy develop hypertension or microalbuminuria later in life [137]. Further, the risk of developing cardiovascular and cerebrovascular disease doubles in women who suffered from preeclampsia and gestational hypertension as compared with age-matched controls [138]. An epidemiological study (with a media follow-up duration of 30 years) provides evidence that preeclampsia is a marker of increased mortality from cardiovascular disease [137]. Accordingly, long-term monitoring of cardiovascular, renal and metabolic risk factors should be recommended to patients after severe preeclampsia [136]. Additionally, the risk of preeclampsia in subsequent pregnancy needs to be discussed with the patients, and counselling should be given for importance of pre-conception check-up and the necessary care required in case of a subsequent pregnancy.

11. Future roadmap

Despite the efforts of Indian government in improving Indian public health system by introducing various national schemes/programs, India is still far away from the target of Millennium Development Goals. Improving healthcare system or introduction of various schemes without proper implementation is a major challenge in achieving desired results. A recent study on community health worker knowledge and management of preeclampsia in rural Karnataka state of India sheds light on the knowledge gaps and common misconceptions among the healthcare providers like ASHA, ANMs and staff nurses [139]. Community health workers are essential in identifying obstetric emergencies, thus a sound knowledge of pregnancy complications is needed for early diagnosis. Though the National guidelines authorize ANMs and nurses to administer $MgSO_4$ to women suffering from convulsions/eclampsia; majority of the ANMs interviewed in the study had never administered $MgSO_4$ themselves. This highlights a gap in knowledge and the implementation of guidelines [139]. The above reported

observations indicate that there is a need to update training and regular assessment of knowledge, competence and confidence of community health workers regarding the identification and treatment of hypertensive disorders of pregnancy. Awareness of the pregnant women themselves along with their family members might also aid in improving healthcare seeking behaviors and timely diagnosis and treatment of pregnancy related complications. Further, clinical risk factors need to be incorporated during antenatal check-ups to help in identification of women at a higher risk to develop preeclampsia. Identification of women at higher risk will aid in early detection of preeclampsia and its effective management. To aid the government and policy makers to understand the shortcomings and advantage of the various schemes being implemented by the government, better record keeping by primary health centers is also essential. Currently, there is no proper data available regarding the effect of various government schemes on pregnancy complications like preeclampsia, IUGR etc even in NFHS surveys. Additionally, research related to identifying markers that can predict preeclampsia needs to be strengthened.

Conflict of interest

Authors declare that no conflict of interest exists.

Funding sources

This work is funded by Science and Engineering Research Board, Department of Science and Technology, India (J. C. Bose Fellowship, grant no-SB/S2/JCB-040/2015); Department of Biotechnology, Government of India (project number – BT/ PR12312/MED/30/1424/2014) granted to SKG. SKG would also like to acknowledge National Institute of Immunology, New Delhi, India for financial support. The views expressed herein are of authors and funding agencies have no role in data collection and manuscript preparation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2018.10.011.

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