

Pre-eclampsia in India: Cutting-edge Insights and Cost-effective Strategies to Save Lives

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Abstract

The landscape of maternal health in India has undergone a transformative shift over the preceding decades, transitioning from a state of crisis to one of measured progress. The Maternal Mortality Ratio (MMR), a primary indicator of a nation's healthcare efficacy and reproductive safety, declined from 130 per 100,000 live births in 2014-16 to 97 per 100,000 in 2018-20, and further estimates suggest a figure near 88 by 2023. While India successfully achieved the National Health Policy target of an MMR below 100 by 2020, the journey toward the United Nations Sustainable Development Goal of fewer than 70 deaths per 100,000 live births by 2030 remains contingent upon addressing the leading causes of maternal death.

Among these, hypertensive disorders of pregnancy (HDP), and pre-eclampsia in particular, have emerged as critical determinants of maternal and perinatal outcomes. Complicating approximately 5% to 10% of pregnancies in India, pre-eclampsia is a multi-systemic disorder characterized by new-onset hypertension and often proteinuria after 20 weeks of gestation. The persistence of eclampsia in 0.5% to 1.8% of deliveries underscores the ongoing challenge of early detection and effective management within a diverse and often resource-constrained healthcare ecosystem.

1. Introduction

Epidemiological Heterogeneity and the Urban-Rural Divide

The prevalence of hypertensive disorders among pregnant women in India, aged 15–49, stands at approximately 11% according to the fifth National Family Health Survey (NFHS-5). This national average, however, obscures the significant regional variations that characterize the Indian subcontinent. Northern and rural states, including Bihar and Madhya Pradesh, report rates of stillbirth and pre-eclampsia that are three to four times higher than those observed in southern states such as Kerala and Tamil Nadu. These disparities are largely driven by differences in health system readiness, access to tertiary care, and the presence of specialized obstetric teams. In states like Kerala, Maharashtra, and Tamil Nadu, pregnancy-related hypertensive disorders have become a significant threat, contributing to nearly 20% of maternal deaths, primarily because deaths from other causes like obstetric hemorrhage have been more effectively managed through high institutional delivery rates and robust blood-bank support.

Institutional births in India have seen a substantial rise, increasing from 79% in 2015-16 to 89% in 2019-21, with rural areas achieving an impressive 87% institutional delivery rate. Despite this progress, the

quality and content of Antenatal Care (ANC) remain suboptimal. While 70% of pregnant women now have an ANC visit in their first trimester, only 59% receive the recommended four or more visits, and a mere 10% reach the eight-visit model currently advocated by the World Health Organization. This gap in care is particularly critical for

pre-eclampsia, where the opportunity for early risk stratification and prophylactic intervention, such as the initiation of low-dose aspirin, typically occurs before the 16th week of gestation.

Maternal Mortality and Delivery Indicators by Region (NFHS-5)

Indicator	National Average	High-Performing States (e.g., Kerala)	Low-Performing Regions (e.g., Bihar/UP)
Maternal Mortality Ratio (MMR)	88 - 97	30	>130 (Historical)
Institutional Births (%)	88.6	100.0	~80 - 85
First Trimester ANC Visit (%)	70.0	>80.0	Variable
4+ ANC Visits (%)	58.5	High	Low
Hypertensive Disorder Prev. (%)	11.0	Higher Relative Burden	Higher Absolute Mortality

The age distribution of maternal deaths further highlights the vulnerability of certain cohorts. Data from 2018-20 reveals that 32% of maternal deaths occur in the 20-24 age group, while 30% occur among those aged 25-29. Adolescent pregnancies (ages 15-19) account for 6% of maternal deaths, a figure that remains concerning given the physiological and social risks associated with early childbearing. Pre-eclampsia risk is significantly elevated in these younger cohorts, with women under 20 years of age facing a 3.87 times higher risk than their older counterparts.

Biological Mechanisms and Molecular Pathogenesis

The pathophysiology of pre-eclampsia is fundamentally rooted in defective trophoblastic invasion of the maternal spiral arteries. Under normal physiological conditions, extravillous trophoblasts invade the uterine spiral arteries, transforming them from high-resistance, low-capacity vessels into high-capacity, low-resistance conduits capable of meeting the metabolic demands of the growing fetus. In pre-eclamptic pregnancies, this invasion is shallow and incomplete, leading to placental ischemia and hypoxia. The stressed placenta subsequently releases various anti-angiogenic factors into the maternal circulation, most notably soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng). These factors antagonize pro-angiogenic proteins such as Placental Growth Factor (PlGF) and Vascular Endothelial Growth Factor (VEGF), triggering widespread maternal endothelial dysfunction.

Recent molecular research in Indian cohorts has shed light on the role of specific angiogenic markers. Placental analysis reveals a marked downregulation of VEGFA mRNA in pre-eclamptic pregnancies compared to uncomplicated ones, with a true fold change of -8.95 in severe cases and an even more

drastic -13.33 in those complicated by HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome. This deficit in pro-angiogenic signaling is a primary driver of the systemic vascular inflammation observed in the mother. Furthermore, the human leukocyte antigen-G (HLA-G), a non-classical class I HLA molecule, plays a critical role in maternal immune tolerance by preventing fetal tissue destruction by maternal immune cells. Meta-analyses of Indian studies indicate that soluble HLA-G (sHLA-G) levels are significantly lower in pre-eclamptic women during both the first and third trimesters, suggesting that impaired immunomodulation is a key precursor to the clinical manifestation of the disorder.

Expression of Angiogenic and Molecular Markers in Pre-eclampsia

Marker	Normal Pregnancy	Pre-eclampsia (PE)	Severe PE / HELLP
PlGF	High (Peaks 28-32 wks)	Low (2-3x decrease)	Very Low
sFlt-1	Low	High	Very High
VEGFA mRNA	Baseline	-2.186 Fold Change	-8.95 to -13.3 Fold
sHLA-G (Trimester 1)	Higher	Lower (SMD: -0.84)	Lower
sHLA-G (Trimester 3)	Higher	Lower (SMD: -0.39)	Lower

In addition to angiogenic factors, mitochondrial dysfunction and oxidative stress within the trophoblasts have been implicated. Swollen mitochondria and increased levels of placental debris circulating in the maternal blood exacerbate endothelial damage. Modern genomic studies also suggest a significant epigenetic component. DNA methylation changes in gene-specific regions are associated with both early and late-onset pre-eclampsia, affecting genes involved in placental development and lipid regulation. These findings provide a biological rationale for why certain women, despite lacking traditional risk factors, develop severe forms of the disease.

Genetic Predisposition and Hereditary Risk Factors

The genetic architecture of pre-eclampsia is complex and involves multiple susceptibility loci. Indian women with a family history of pre-eclampsia or chronic hypertension are at a substantially higher risk, reflecting an inherited predisposition to vascular and endothelial sensitivity. Studies have identified a 4-fold increase in the angiotensin II type 1 (AT1) receptor in the decidua of pre-eclamptic women, coupled with the presence of agonistic autoantibodies that target these receptors, leading to hypertension and proteinuria.

Specific genetic variants have been scrutinized for their association with the disorder in Indian populations. For instance, the Vascular Endothelial Growth Factor A (VEGF-A) variant rs699947 is significantly linked to risk; individuals carrying the AC or AA genotypes exhibit higher susceptibility compared to those with the CC genotype. Interestingly, while global studies have linked variations in the APOL1 gene to increased risk among Black women, the focus in India has been on variants associated with prothrombin and factor V Leiden. However, meta-analyses in certain Indian cohorts have not always found statistically significant associations with these specific thrombophilic variants, suggesting that the genetic drivers of pre-eclampsia in South Asia may be distinct from those in Western or African populations.

Genetic Risk Profiles and Odds Ratios in Indian Cohorts

Genetic Variant / Risk Factor	Observed Association	Odds Ratio (OR) / Significance
Nulliparity	Strong	$\text{OR} = 3.18 - 6.33$
Family History of PE	Strong	Significant Predictor
VEGF-A rs699947 (AA)	High Risk	$\text{OR} = 12.44$
VEGF-A rs699947 (AC)	Moderate Risk	$\text{OR} = 2.76$

Genetic Variant / Risk Factor	Observed Association	Odds Ratio (OR) / Significance
Age < 20 years	High Risk	$\text{OR} = 3.87$
Household Income < ₹4000	Socioeconomic Risk	$\text{OR} = 6.81$

The intersection of genetics and ethnicity is further illustrated by the variation in blood pressure polygenic risk scores (BP-PRS). Women whose genetic makeup predisposes them to higher baseline blood pressure values are significantly more likely to develop severe and recurrent forms of pre-eclampsia. This genetic background, when combined with environmental triggers like high salt intake and obesity, creates a "perfect storm" for the development of hypertensive disorders.

Sociodemographic and Behavioral Determinants

Beyond biological and genetic factors, the social ecology of India plays a profound role in the prevalence and severity of pre-eclampsia. Low socioeconomic status (SES), rural residence, and limited education are consistently identified as major risk factors. The rigid social structures, including the caste system, often limit access to healthcare resources and employment opportunities, which in turn affects nutritional status and health-seeking behavior.

Nutritional factors are particularly salient. Diets high in salt and visible fats are significantly linked to HDP risk in India. Conversely, low protein intake (less than 65 g/day) increases the risk of pre-eclampsia by 3.61 times. Tobacco consumption is another critical behavioral determinant. NFHS-5 data indicates that 5.3% of pregnant women in India consume tobacco, and the prevalence of hypertension among this group is a staggering 24.3%. Tobacco use is higher among rural pregnant individuals (8.7%) compared to urban counterparts (6.9%), further widening the health equity gap.

Risk Factors for Hypertension Among Pregnant Tobacco Consumers

Factor	Prevalence / Risk Impact
Tobacco Consumption (National)	5.3% of pregnant women
Hypertension in Tobacco Users	24.3%
Rural Tobacco Use	8.7%
Urban Tobacco Use	6.9%
Independent Risk Status	Independent of SES and age

Obesity and high body mass index (BMI) are rising challenges in the Indian context. Women with a BMI ≥ 25 are six times more likely to develop pre-eclampsia than those with a normal BMI. This risk is not confined to urban areas; even in rural settings, the "dual burden" of malnutrition means that

overweight and anemia often coexist, complicating the clinical picture of pregnancy. Furthermore, psychological stressors, including marital discord, domestic violence, and prenatal depression, have been identified as socio-ecological risk factors that uniquely increase HDP burden in the Indian microsystem.

Cultural Barriers and the "Three Delays" Model

Cultural norms and beliefs significantly influence maternal health outcomes by shaping health-seeking behaviors. In rural India, practices such as "pregnancy secrecy"—the custom of hiding a pregnancy during the early months to avoid the "evil eye"—often lead to delays in initiating antenatal care. This delay is particularly dangerous for pre-eclampsia, as it prevents early screening and the timely administration of low-dose aspirin, which must be started before 16 weeks to be maximally effective.

The "Three Delays" model provides a framework for understanding maternal mortality in India:

1. **Delay in Deciding to Seek Care:** Often caused by a lack of knowledge regarding warning signs like severe headache, blurred vision, or epigastric pain. Only 21% of pregnant women in India currently utilize the full spectrum of recommended prenatal services.
2. **Delay in Reaching the Healthcare Facility:** Geographical barriers, poor road infrastructure, and a lack of reliable transport (ambulances) in rural and hilly terrains are persistent obstacles.
3. **Delay in Receiving Adequate Treatment:** Once at a facility, delays may occur due to a lack of trained obstetricians, non-availability of life-saving medications like Magnesium Sulfate (MgSO_4), or slow laboratory processing.

Furthermore, gender stereotypes and low female autonomy mean that the decision to seek care often rests with male heads of household or older family members, who may not prioritize clinical interventions over traditional practices. Reliance on traditional birth attendants (TBAs) remains high in remote areas, where eclampsia may be misattributed to supernatural forces rather than a medical emergency.

Cutting-edge Diagnostics: Novel Biomarkers and PoC Technology

Early identification of pre-eclampsia remains a primary goal of antenatal care. While traditional screening relies on maternal history and clinical factors, these methods have modest sensitivity, especially in nulliparous women who have no prior pregnancy history to guide risk assessment. Emerging approaches incorporate biochemical markers and ultrasound parameters, such as Uterine Artery Doppler velocimetry, to enhance predictive accuracy. An elevated pulsatility index (PI) in the first or second trimester is a moderate-sensitivity, high-specificity (0.88) marker for predicting early-onset pre-eclampsia.

A significant breakthrough in the Indian context is the development of a low-cost, fiber-optic biosensor by a multi-institute team led by the Indian Institute of Technology Madras (IIT Madras). This point-of-care (PoC) platform, unveiled in 2025, utilizes fiber-optic sensor technology to detect the Placental Growth Factor (PlGF) biomarker at femtomolar levels. The biosensor requires only a 30-microliter drop of blood and provides results within 30 minutes, making it ideal for use in resource-limited rural clinics where access to traditional laboratory infrastructure is minimal.

Comparison of Diagnostic Technologies for Pre-eclampsia

Technology	Mechanism	Detection Level	Time to Result	Key Benefit
Standard ELISA	Biochemical Assay	Picomolar	4-6 Hours	Established accuracy
Visual Urine Strip	Proteinuria Dipstick	>300 mg/24h	Immediate	Low cost; no power
IIT-M Biosensor	Fiber-Optic FAB	P-Femtomolar	<30 Minutes	PoC;

Technology	Mechanism	Detection Level	Time to Result	Key Benefit
				Super-sensitive
Intignus PoC	Lateral Flow Assay	sENG / PlGF	Minutes	Designed for frontline
Uterine Artery Doppler	Sonography	Elevated PI	Real-time	Detects poor perfusion

In tandem with these technological advancements, startups like Intignus Biotech are developing lateral flow assays to detect sENG and PlGF biomarkers. These tools empower frontline health workers, such as ASHA (Accredited Social Health Activist) workers, to stratify pregnant women into high-risk and low-risk groups. High-risk women can then be prioritized for early aspirin prophylaxis and more frequent monitoring, significantly improving the chances of a positive outcome.

Cost-Effective Management Strategies for Low-Resource Settings

Cost-effectiveness is a paramount consideration for large-scale health policy in a country of India's scale. Analysis of various diagnostic devices for low- and middle-income countries (LMICs) suggests that the most cost-effective combination is a semi-automatic blood pressure measurement device and a visually read urine strip test, with a combined per-use cost of approximately \$0.2004. This approach yields an incremental cost-effectiveness ratio of \$93.6 per DALY (Disability-Adjusted Life Year) gained.

When access to treatment is limited, it is often more cost-effective to improve treatment availability rather than solely increasing the sensitivity of diagnostic tools. For managing established pre-eclampsia and eclampsia, the use of oral antihypertensives like Nifedipine and Labetalol is highly effective for lowering blood pressure into the non-severe range. Magnesium Sulfate remains the sole agent of choice for preventing and treating eclamptic seizures; however, its availability at the primary health center (PHC) level in India remains inconsistent, leading to untreated seizures during the "Golden Hour" of transport.

Clinical Implementation of Preventive Pharmacotherapy

Medication	Target Group	Recommended Dosing	Effectiveness
Low-Dose Aspirin	High-Risk women	75 - 150 mg/day (before 16 wks)	Reduces PE risk
Calcium Suppl.	Low dietary intake	1.5 - 2.0 g/day	47-65% Risk reduction
Magnesium Sulfate	Severe PE / Eclampsia	Loading + Maintenance	Prevents seizures
Vitamin D	Insufficiency	Corrective dosing (Optimal TBD)	Modifiable risk

The role of calcium supplementation is particularly critical in India, where baseline dietary calcium intake is often below 600 mg/day, significantly lower than the 1,000 mg/day seen in high-income countries. WHO and FOGSI guidelines recommend at least 1 g/day (ideally up to 2 g/day) of calcium for women in low-intake populations. This intervention alone can reduce the risk of pre-eclampsia by up to 65% in high-risk pregnancies. Furthermore, emerging evidence supports the use of prophylactic negative pressure wound therapy (sNPWT), such as the PICO system, for women with a BMI ≥ 30 undergoing C-sections to reduce surgical site infections and improve postpartum recovery.

The CLIP Trial and the Power of Community-Level Interventions

The Community-Level Interventions for Preeclampsia (CLIP) trials, which included clusters in North Karnataka, India, have provided some of the most compelling evidence for task-shifting and digital health support in managing maternal health. These trials utilized validated-for-pregnancy, semi-automated blood pressure devices and the "PIERS on the Move" (POTM) digital platform to empower community health workers to identify and manage pre-eclampsia in women's homes.

The results of the CLIP trials demonstrated that providing at least eight antenatal contacts through digital-health-supported CHWs cost-effectively reduced the burden of mortality:

- Maternal mortality was reduced by 60%.
- Fetal mortality was reduced by 60%.
- Neonatal mortality was reduced by 40%.

A critical lesson from the CLIP trial is the importance of local terminology and community education. Many rural Indian languages lack a direct term for "pre-eclampsia," leading to significant misperceptions. Interventions must therefore begin with culturally appropriate education that demystifies the medical condition and emphasizes the importance of routine blood pressure checks even in the absence of felt symptoms. The use of mHealth platforms to send appointment reminders and educational content has shown promise in improving ANC attendance and health literacy among women in low SES areas.

Post-Operative and Postpartum Vigilance

The resolution of pre-eclampsia is traditionally thought to occur with the delivery of the placenta; however, clinical reality in India shows that a significant portion of maternal morbidity and mortality occurs in the postpartum period. Postpartum pre-eclampsia can manifest several days after delivery, and without continued monitoring, these women are at high risk for eclamptic seizures, stroke, or heart

failure. Expert masterclasses, such as those conducted by Prof. Ajit Virkud in Mumbai, emphasize that delivery is only the beginning of the recovery phase, and high-risk women must be monitored for at least 48 hours following birth.

Management of the "closed surgical incision" after C-sections in high-risk patients (those with obesity or diabetes) is another emerging focus. Surgical site infections (SSIs) are a major cause of delayed recovery and increased financial burden for Indian families. The prophylactic use of single-use negative pressure wound therapy (sNPWT) has been shown to reduce SSIs by 50% in women with a BMI ≥ 30 , facilitating earlier mother-baby bonding and prompt discharge from the hospital.

Future Directions and Policy Imperatives

To further reduce the burden of pre-eclampsia and achieve the SDG 2030 targets, India must focus on three strategic pillars: innovation, integration, and infrastructure.

1. **Scaling Point-of-Care Diagnostics:** The rapid commercialization of PlGF biosensors and lateral flow assays is essential. These tools should be integrated into the standard kit for ASHA workers and primary health centers, moving the focus of screening from the hospital to the community.
2. **Universalizing Prophylaxis:** Given the high prevalence of calcium deficiency in India, universal calcium supplementation during pregnancy should be strictly enforced and monitored for compliance. Low-dose aspirin must be made available and promoted for all high-risk women at their first ANC visit.
3. **Strengthening Referral and Transport:** The "Golden Hour" for eclampsia management can only be secured by improving rural ambulance networks and ensuring that every first point of contact (even at the sub-center level) has the training and the supply of Magnesium Sulfate to initiate life-saving treatment before referral.
4. **Addressing Socio-Ecological Barriers:** Policies must move beyond clinical care to address the root causes of health inequity. This includes promoting women's education, addressing non-nutritional causes of anemia (such as environmental hygiene), and using mHealth to bridge the literacy and autonomy gaps that currently prevent women from seeking timely care.

The progress India has made in maternal mortality reduction is commendable, yet the "silent killer" of pre-eclampsia remains a major hurdle. By leveraging cutting-edge molecular insights, deploying cost-effective diagnostic technologies, and strengthening community-based care models, India can set a global example for how to save maternal and neonatal lives in a complex, resource-diverse environment. The goal of an MMR below 70 is not merely a statistical target but a promise of safety and health for the millions of women who embark on the journey of motherhood each year.

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