



**Commodity and service  
delivery innovations for  
detection and management  
of pre-eclampsia**  
Landscape report

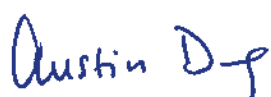


# Foreword

The global community continues to drive progress and innovation in the area of maternal and newborn health. Yet far too many mothers are dying from conditions that are both preventable and treatable. Pre-eclampsia is the second leading cause of maternal mortality in Sierra Leone and one of those conditions that cause us to lose far too many mothers and imperil far too many babies. In Sierra Leone, we are working to prevent mortality from various causes, and we continue to improve how we tackle pre-eclampsia as a major cause of morbidity and mortality. Specifically, we are building the capacity of our health professionals through pre-service and in-service training of staff; establishing high dependency units (HDUs) in hospitals for the optimal management of severe cases; and increasing antenatal attendance (now at 87%) and quality so that women with pre-eclampsia are identified early and the appropriate care is provided. But all these approaches require access to high-quality products. As we work to reduce our maternal mortality ratio from 443 per 100,000 live births to 70 per 100,000 live births, the acknowledged Sustainable Development Goal (SDG), we need partnership with the global community to ensure that every mother has adequate antenatal care and delivers with a skilled birth attendant. This document helps drive that partnership.

This landscape analysis of tools and solutions to address pre-eclampsia is critical for partners like us in Sierra Leone and other low- and middle-income countries. It helps us identify the highest priority interventions that should be available in every health center and hospital, and in the hands of every midwife and doctor, and the processes for ensuring that there is reliable access to those products. Unitaids work to prepare this landscape analysis and act upon its contents will help solve problems in countries with limited resources, where difficult health system decisions must be made. We need to ensure that every woman is identified early in pregnancy if she has an increased risk of pre-eclampsia. We need to measure blood pressure at each antenatal visit and provide interventions like low-dose aspirin and low-dose calcium to mothers at high risk. We need to track women carefully during pregnancy and provide them with specialized care around the time of birth to ensure that pre-eclampsia is appropriately treated with magnesium sulfate, antihypertensives, and attended delivery.

I know that many other countries are facing the same foe and fighting the same fight. Having a document like this supports various country Ministries of Health efforts to prioritize action and achieve results. As in many areas of maternal and newborn health, we know the solutions, and we need to direct our effort to the work of implementing those solutions. As we work to achieve the targets of the Every Woman / Every Newborn – Everywhere action plan, and accelerate progress towards those targets, this document helps us to hold ourselves and our partners accountable. I congratulate Unitaids on the production of this document and call on maternal and newborn health advocates around the world to consider these interventions as we work together to produce a safer, healthier and happier environment for our mothers and newborns.



**Dr. Austin H. Demby**

Minister of Health

Republic of Sierra Leone

© World Health Organization 2024 (acting as the host Organization for the Secretariat of Unitaid)

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area of its authorities, or concerning the delimitations of its frontiers or boundaries. The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. All reasonable precautions have been taken to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind either expressed or implied. The responsibility and use of the material lie with the reader. In no event shall Unitaid or the World Health Organization be liable for damages arising from its use.

Suggested citation: Commodity and service delivery innovations for detection and management of pre-eclampsia landscape report. Geneva: Unitaid. 2024.

# Contents

<b>1. Introduction</b>	<b>1</b>
<b>2. Global burden of hypertensive disorders of pregnancy and effect on maternal and newborn outcomes</b>	<b>3</b>
<b>3. Key initiatives and efforts in pre-eclampsia and eclampsia</b>	<b>8</b>
<b>4. Current and promising tools and interventions as well as key gaps</b>	<b>11</b>
4.1 Diagnostics for risk assessment and onset of pre-eclampsia	12
4.2 Prevention medicines and dietary supplements	25
4.3 Therapeutics, including candidate repurposed medicines	28
4.4 Evidence-informed practices for screening, prevention and management (including timed delivery)	36
4.5 Models to support early and continuous antenatal care for early detection of hypertension, management of pre-eclampsia risk, triage and appropriate referral	38
4.6 Market information for equitable access to pre-eclampsia / eclampsia commodities	40
<b>5. Cross-cutting access barriers to addressing pre-eclampsia and eclampsia</b>	<b>42</b>
<b>6. Potential opportunities</b>	<b>46</b>
<b>7. Conclusion</b>	<b>53</b>
<b>Appendix A: Key informants</b>	<b>54</b>
<b>Appendix B: References</b>	<b>55</b>

# Acknowledgements

This report was prepared by Suzanne Fournier and Charlotte Warren of Cambridge Economic Policy Associates Ltd in collaboration with Kelsey Barrett at Unitaid. The WHO Maternal Health Unit led by Allisyn Moran provided valuable guidance throughout conceptualization, development and review, as well as facilitated input collection from the WHO Human Reproduction Programme, including Özge Tunçalp. We wish to thank the many reviewers that provided helpful feedback which strengthened the landscape, including Jeff Smith and Dale Halliday (Unitaid), A. Metin Gulmezoglu (Concept Foundation), Andrew Shennan and his team (Kings College London), Ashley Muteti (Zuri Nzilani Foundation), Manu Vatish (Bill & Melinda Gates Foundation), and Justus Hofmeyr (University of the Witwatersrand). Graphics and layout supported by ACW.

# Abbreviations

<b>AfCTA</b>	African Continental Free Trade Area	<b>NIHR</b>	National Institute of Health and Care Research (UK)
<b>Africa CDC</b>	Africa Centres for Disease Control and Prevention	<b>NMRA</b>	National Medicines Regulatory Authority
<b>AI</b>	artificial intelligence	<b>PAPP-A</b>	pregnancy associated plasma protein A
<b>AIM</b>	Accelerating Innovation for Mothers	<b>PE/E</b>	pre-eclampsia and eclampsia
<b>ANC</b>	antenatal care	<b>PEARLS</b>	Preventing PE: Evaluating AspiRin Low-dose Regimens Following Risk Screening
<b>APPM</b>	African Pooled Procurement Mechanism	<b>PI</b>	Pharma Initiative
<b>BP</b>	blood pressure	<b>PIERS</b>	pre-eclampsia integrated estimate of risk
<b>EML</b>	Essential Medicines List	<b>PIGF</b>	placental growth factor
<b>ENAP</b>	Every Newborn Action Plan	<b>POC</b>	point-of-care
<b>EPMM</b>	ending preventable maternal mortality	<b>POCUS</b>	point-of-care ultrasound
<b>FCDO</b>	Foreign and Commonwealth Development Office, United Kingdom (UK)	<b>PrCr</b>	protein to creatinine
<b>FDA</b>	U.S. Food and Drug Administration	<b>PPH</b>	postpartum hemorrhage
<b>FIGO</b>	International Federation of Gynaecologists and Obstetricians	<b>PQ</b>	Prequalification (WHO program)
<b>FMF</b>	Fetal Medicine Foundation	<b>QA</b>	quality assurance
<b>G-ANC</b>	group antenatal care	<b>R&amp;D</b>	research and development
<b>GA</b>	gestational age	<b>RCOG</b>	Royal College of Obstetricians and Gynaecologists
<b>GlyFn</b>	glycosylated fibronectin	<b>RHSC</b>	Reproductive Health Supplies Coalition
<b>HDP</b>	hypertensive disorders of pregnancy	<b>sFlt-1</b>	serum FMS-like tyrosine kinase-1
<b>HELLP</b>	hemorrhage, elevated liver enzymes, and low platelet (syndrome)	<b>SDG</b>	Sustainable Development Goal
<b>ICD</b>	International Classification of Diseases	<b>SRA</b>	stringent regulatory authority
<b>IUGR</b>	intrauterine growth restriction	<b>SSA</b>	sub-Saharan Africa
<b>LMICs</b>	low- and middle-income countries	<b>TPP</b>	Target Product Profile
<b>MgSO<sub>4</sub></b>	magnesium sulfate	<b>UAPI</b>	uterine artery pulsatility index
<b>MAP</b>	mean arterial pressure	<b>UAD</b>	uterine artery doppler
<b>MNH</b>	maternal and newborn health	<b>UNCoLSC</b>	United Nations Commission on Life-Saving Commodities
<b>NCD</b>	noncommunicable disease	<b>USAID</b>	United States Agency for International Development
<b>NICE</b>	National Institute for Health and Care Excellence (UK)	<b>USP</b>	United States Pharmacopeia
		<b>WHO</b>	World Health Organization

# Executive summary

Every day, over 800 women die due to complications in pregnancy and childbirth. Nearly all these deaths occur in low- and middle-income countries (LMICs). Pre-eclampsia and eclampsia (PE/E) are leading causes of maternal and perinatal morbidity and mortality worldwide. PE complicates between 3% to 10% of pregnancies globally and is responsible for over 76,000 maternal deaths and 500,000 perinatal deaths annually, including 200,000 stillbirths. The incidence of PE has increased by 11% in the past 30 years, concomitant with a rise in non-communicable diseases (NCDs) including diabetes, obesity and hypertension which are risk factors for PE.

Although the underlying causes of PE are not fully understood, PE is predominantly caused by endothelial dysfunction due to placental factors, which can progress to life threatening multi-organ damage and death. PE is characterized by the presence of elevated blood pressure, proteinuria (protein in urine) and/or maternal end organ dysfunction (often kidney or liver dysfunction) presenting after 20 weeks' gestation. PE occurs as preterm PE (20-35 weeks), term PE (36-40 weeks) or postpartum PE (48 hours after childbirth to 6 weeks).

The cornerstone of a comprehensive approach to care for pregnant women with, or at risk for PE is high quality antenatal, intrapartum and postpartum care in line with WHO guidelines. This includes appropriate clinical and laboratory assessments and ongoing communication, both between a woman and her health care provider and among a comprehensive team of well-equipped health care providers. A major challenge for prevention and early detection of PE is that women may not attend for their first antenatal care (ANC) contact during the first trimester. This delays identification of risk and the opportunity to intervene early with evidence-based interventions to minimize further pregnancy-related complications, avoid unnecessary preterm birth and maximize positive health outcomes for a woman and her baby.

In recent years, there have been advances in updating the diagnostic criteria for PE. There is also a growing interest amongst researchers in identifying critical knowledge gaps related to the underlying pathophysiology of PE and

understanding the range of genetic and environmental risk factors that may serve as possible avenues of prediction and prevention. Alongside enhancing existing technologies and interventions, there are more opportunities to improve the detection and management of PE/E.

Under its Programmatic Priority on Women's and Children's Health: *Improve access to better tools for safe pregnancy and birth for women and newborns*, Unitaaid sought to conduct a technology landscape of tools and interventions for the diagnosis and management of PE/E, with a focus on care in LMICs. This landscape provides a comprehensive overview of the status of available and pipeline innovations for addressing PE/E and mitigating impact on fetal growth restriction and preterm birth, with analysis of key opportunities to accelerate efforts to address PE/E.

## There are several key developments to improve prevention, diagnosis and management of PE/E in high burden settings

One of the most transformative shifts in PE risk identification and management has been the introduction of **blood biomarker-based testing**. Several biomarkers hold potential as predictive markers for PE and/or of progression to severe PE.

- Two key biomarkers are **placental growth factor (PlGF)**, a protein which is decreased in women both at the time of PE diagnosis, and early in pregnancy prior to PE onset; and **serum FMS-like tyrosine kinase 1 (sFlt-1)** which is elevated in women with PE > 20 weeks' gestation. sFlt-1 has also been identified as a candidate therapeutic target. A further biomarker **glycosylated fibronectin (GlyFn)** is a glycoprotein involved in cell adhesion and migration. PlGF, sFlt-1 and select few other biomarkers, are now recommended by professional organizations like the International Federation of Gynaecology and Obstetrics (FIGO) and the International Society for the Study of Hypertension in Pregnancy (ISSHP) as a "rule out" tool to inform clinical decisions and the timing of delivery.



- A small number of **point-of-care (POC) or near-POC** assays have been commercialized and adapted for low-resource contexts, with more under development measuring PIGF, sFlt-1 and GlyFn. There is a growing body of evidence to validate these diagnostics in LMIC settings, integrate within clinical algorithms, and evaluate performance in ‘real world’ clinical settings. Improvements to **urine protein biomarker diagnostics** also continue, based on identification of misfolded proteins in urine which bind to Congo Red Dye (congoophilia). Although this is inexpensive and easy to perform, evidence to date indicates lower sensitivity and specificity compared to blood-based biomarkers. More extensive research and in larger populations, including for different use cases, is required.

New evidence and research and development (R&D) are also underway to improve existing prevention and screening interventions founded on quality, comprehensive ANC. Developments include the following:

- **Blood pressure (BP)** measurement with a device validated for use with pregnant populations and used routinely at each ANC contact, is the cornerstone of diagnosis and monitoring of women at risk of PE. Availability of validated BP devices in ANC clinics is a key gap, with need for training on accurate measurement and interpretation. The CRADLE VSA device, a semi-automatic digital BP device which incorporates a traffic light warning system to support interpretation by health care workers (including those with minimal training), is an example of a key innovation that has been commercialized (currently in more than 15 LMICs, but with need to increase demand and availability, including the infrastructure of procurement pathways for large scale distribution). New innovations such as the smartphone application **OptiBP** have shown self-monitoring of BP to be feasible and acceptable to women with hypertension and their clinicians, with high potential for scalability and empowering women with information on their health status, although this has not yet been validated in pregnancy. OptiBP is included in the *WHO compendium of innovative health technologies for low resource settings* 2024.
- **Low-dose aspirin** is one of the few available preventative interventions for women at risk of PE and is currently recommended by WHO before 20 weeks’ gestation. A new randomized trial, PEARLS (Preventing pre-eclampsia: Evaluating AspiRin Low-dose regimens following risk Screening), conducted in Ghana, Kenya and South Africa, will compare the effects of 75 mg and 150 mg daily aspirin, answering key questions on safety of a higher and potentially more efficacious dose. Results from the formative research are expected in early 2025, and results from the main trial are expected in early 2027.
- **Calcium supplementation** is recommended by WHO for pregnant women in populations with low dietary calcium intake to reduce risk of PE. However, despite evidence of

its safety and effectiveness, calcium supplementation is not always integrated into routine ANC. One alternative for populations with low calcium intake could be to legislate the fortification of staple foods, similar to practices in the UK. This approach would benefit the entire population, increasing the likelihood of reaching most pregnant people. Additionally, consistent messaging by health care workers about the benefits of calcium, alongside early identification of women who would benefit, could also enhance uptake.

- **Ultrasound** prior to 24 weeks’ gestation is recommended by WHO to estimate gestational age and detect any abnormalities. Subsequent ultrasound scans can detect intrauterine growth restriction (IUGR), a fetal manifestation of PE. Affordable point-of-care ultrasound (POCUS) is becoming increasingly popular in LMICs. POCUS technology can be enhanced with AI tools to support less skilled health care workers perform accurate scans, however even with AI support, training and mentoring are needed to interpret findings and make clinical decisions. The use of one AI-POCUS platform will be validated as part of the PEARLS trial.

Through the AIM project (Concept Foundation and Burnet Institute), four **Target Product Profiles (TPPs)** have been developed for PE and preterm labor. These TPPs are designed to stimulate interest, innovation, and investment by outlining the desired characteristics of products for: 1) PE prevention, 2) PE treatment, 3) preterm labor prevention, and 4) preterm labor management. Additionally, the WHO plans to release a TPP focused on ultrasound in 2024.

Other significant developments include new evidence in LMICs on the benefits of timed delivery and induction of labor for women with severe PE to improve newborn outcomes and reduce severe hypertension. Clinical support tools, predictive models and algorithms are gaining traction in routine clinical care, helping clinicians determine which women can be safely monitored at home and which require hospitalization. These advancements benefit both women and health care facilities by improving patient outcomes and reducing strain on resources.

**Key barriers** to addressing PE/E include inconsistent availability of recommended commodities and insufficient investment in R&D for new interventions. Consequently, there are limited preventive and therapeutic options, and diagnostic tools and devices are insufficiently adapted for low resource settings. Affordability of new diagnostics and devices remains a key issue, particularly as financing for PE/E is predominantly led by governments with limited health budgets. Low-dose aspirin is one of the few prevention interventions for PE. However, delayed first ANC contact, inconsistent BP monitoring, and gaps in the quality of ANC often prevent women at risk from starting low-dose aspirin before 20 weeks, when it would have maximal impact.

Additionally, supply chain weaknesses result in stock-outs of maternal health medicines including magnesium sulfate ( $\text{MgSO}_4$ ), used to prevent and manage eclampsia. The production of antihypertensive medications methyldopa and nifedipine, which are recommended for use during pregnancy, has decreased, and labetalol is not licensed in South America. Addressing the skills gaps among health care workers and optimizing the strained health workforce through task sharing are also critical needs.

## Potential opportunities to improve pre-eclampsia risk detection and management

There are several opportunities to address PE/E, firstly through improving the quality and uptake of ANC. Approaches such as Networks of Care, midwifery models of care, group ANC, and women's groups have been shown to increase quality and continuity of ANC. Expanding routine and accurate BP measurement with a validated device, provision of low-dose aspirin for women at risk of developing PE, and calcium supplementation, are more feasible when ANC platforms are robust. Demand generation for quality BP devices, for example using matching funds to spur domestic financing, mobilizing national professional associations of doctors and midwives, and engaging communities to drive awareness and uptake could improve comprehensiveness of ANC. The CRADLE-V study in Sierra Leone will generate evidence on 'real-world' scale up of the CRADLE VSA BP device, which can inform wider efforts to introduce validated BP devices into ANC and expand screening for hypertension. Home-based BP monitoring is recommended by WHO and innovative software is under development to make this accessible to women in LMICs.

Making blood-based biomarker assays (s-Flt-1, PlGF, GlyFn) affordable and accessible for LMICs is a key priority area, and other urine biomarkers under development could be promising. There may be opportunities to support market entry of high priority POC biomarker assays, for example through funding country introduction (e.g., local piloting, generating demand from health care workers and women, adapting national guidelines, sensitizing decision-makers, supporting regulatory processes and updating procurement and supply chain management). Market shaping interventions to improve affordability and access could also be explored in the medium to longer term.

Consensus is required on the minimum interventions in each pregnancy trimester which accommodate most settings, including the interventions outlined above, among others. Another area requiring consensus is on the optimal timing of delivery for women triaged as 'high risk.' While WHO recommends women with PE deliver at 37 weeks' gestation, PE is a progressive condition and the health of the woman and her fetus will deteriorate, even with expectant management. The CRADLE 4 study found that delivery from 34 weeks for women with PE reduces hypertension and stillbirths. This requires wide review and discussion, and further studies are needed to inform clinical practice. Countries need support to implement evidence-based labor induction protocols at levels of the health system with adequate maternal and newborn health (MNH) care, including caesarean section and newborn intensive care.

Several lower cost POCUS devices have been tested in low-resource settings (e.g., Butterfly iQ+, Philips Lumify) and AI technology validated for use by less skilled health care workers to use POCUS is on the horizon. There are opportunities to advance POCUS through generating evidence of use along the pregnancy care continuum in different settings, including information sharing between stakeholder groups (e.g., industry, funders, researchers) to advance product development.

Supply security and quality of antihypertensives,  $\text{MgSO}_4$  and other MNH medicines is a neglected area supported by few partners and initiatives. Addressing supply security for quality assured PE products should be pursued jointly with products for other priority MNH products (e.g., postpartum hemorrhage (PPH), gentamicin for possible serious bacterial infection in newborns). Local or regional manufacturing of maternal health products and supporting WHO pre-qualification (PQ) would support sustainability.

Finally, a small number of promising preventive and therapeutic products to improve the management of women at risk of PE or to treat PE are undergoing clinical trials and are estimated to be at least two to five years away. These therapeutics target elevated sFlt-1 and may be applicable in high burden contexts.

These high-priority opportunities to address PE/E could be advanced through an approach aligned with the [Roadmap to combat postpartum haemorrhage](#), fostering cooperation among diverse stakeholders committed to bridging the gap in access to quality and lifesaving interventions for women and children in low-resource settings.

# 1. Introduction

Every day, over 800 women die due to complications in pregnancy and childbirth. Nearly all these deaths occur in low- and middle-income countries (LMICs). In the first five years of the Sustainable Development Goals (SDGs), the global annual rate of maternal mortality reduction nearly plateaued – falling only marginally from 227 per 100,000 live births to 223 from 2015 to 2020.

Hypertensive disorders of pregnancy (HDP) are a leading cause of maternal and newborn death, and pre-eclampsia (PE) is a significant driver of this burden. PE complicates 3% to 10% of pregnancies worldwide and is responsible for 76,000 maternal deaths and 500,000 perinatal deaths annually, including 200,000 stillbirths. PE is a progressive pregnancy condition characterized by the onset of high blood pressure (BP) and proteinuria and/or new onset maternal end organ dysfunction, presenting after 20 weeks' gestation. In LMIC settings, hypertension and proteinuria are the most widely used markers of PE. If not appropriately managed, PE can progress to eclampsia – convulsions or seizures before, during and after delivery. Management of women with PE aims at minimizing further pregnancy-related complications, avoiding unnecessary preterm birth, and implementing interventions to maximize maternal and newborn survival.

Greater efforts are needed to address the burden of PE/E in LMICs through respectful, high quality maternal and newborn care. The World Health Organization (WHO) recommends screening for PE risk at every antenatal care (ANC) contact. Much of this screening is simple, involving accurate BP measurement, maternal medical history and characteristics and monitoring for clinical symptoms. However, clinical signs of PE are often missed, and validated BP devices may not be available. Additionally, diagnostic tools to aid in identifying onset of PE are inconsistently available in health facilities

or limited to certain levels of the health system. Though screening using new biomarker tests is now the standard of care in many high-income countries, efforts to introduce these protocols to low-resource settings are still nascent. After a PE diagnosis, the condition can initially be managed with antihypertensives to lower blood pressure, but delays in identification and the need for increased vigilance often hinder appropriate management, placing both women and newborns at risk of severe complications.

Over the last decade, there has been underinvestment in R&D for medicines and technologies for pregnancy-specific conditions, and this is particularly true for PE and its complications. Many medicines used for pregnancy-related conditions, such as low-dose aspirin, methyldopa, nifedipine and beta-blockers were repurposed from other indications for non-pregnant adults. There is an urgent need to enhance deployment of underutilized, new, and emerging interventions for the prevention, diagnosis, and management of PE.

To better understand these challenges and identify potential opportunities, this report provides an overview of health products and interventions currently available and under development for the diagnosis and management of pre-eclampsia and eclampsia (PE/E). This information is intended to contribute to advancing the SDGs for maternal and child health.

## Methodology and scope

This report was prepared between February and May 2024 based on a comprehensive review of various sources, including peer-reviewed published literature, grey literature, organizational websites, global and national guidelines, as well as consultations with subject matter experts in maternal health, HDP and PE/E from international and national organizations, academia and industry. A limitation of this report is that some products may have been omitted due to a lack of publicly available information, or where information on pricing and key specifications were either not yet fully determined or considered proprietary information by manufacturers.

The aim of this landscape report is to provide a comprehensive overview of the status of available and pipeline innovations for addressing HDP, including PE/E, and for mitigating the impact of PE/E on fetal growth restriction and preterm birth in LMIC settings, where the burden of PE/E and placenta-related conditions is highest. It also offers an analysis of potential opportunities to accelerate efforts to address PE/E. While the report's suggestions are not exhaustive, they aim to inform global discourse, guide agenda setting, and encourage stronger collaboration and coordination among stakeholders, ultimately leading to a reduced burden of disease.



## 2. Global burden of hypertensive disorders of pregnancy and effect on maternal and newborn outcomes

Progress in reducing maternal mortality stalled over the first five years of the Sustainable Development Goals (SDGs), with 810 maternal deaths occurring every day.<sup>1</sup> Hypertensive disorders of pregnancy (HDP) are one of the most common medical problems arising during pregnancy and include chronic hypertension, gestational hypertension and pre-eclampsia. HDPs are the second most prominent cause of maternal death worldwide after postpartum hemorrhage (PPH), accounting for 14% of deaths globally. The number of pregnant women with HDP has been increasing over the past 30 years, with regional differences in the burden of disease. Currently pre-eclampsia and eclampsia (PE/E) is the leading cause of maternal mortality in the Latin America and Caribbean region.<sup>1-5</sup>

## Pre-eclampsia and eclampsia

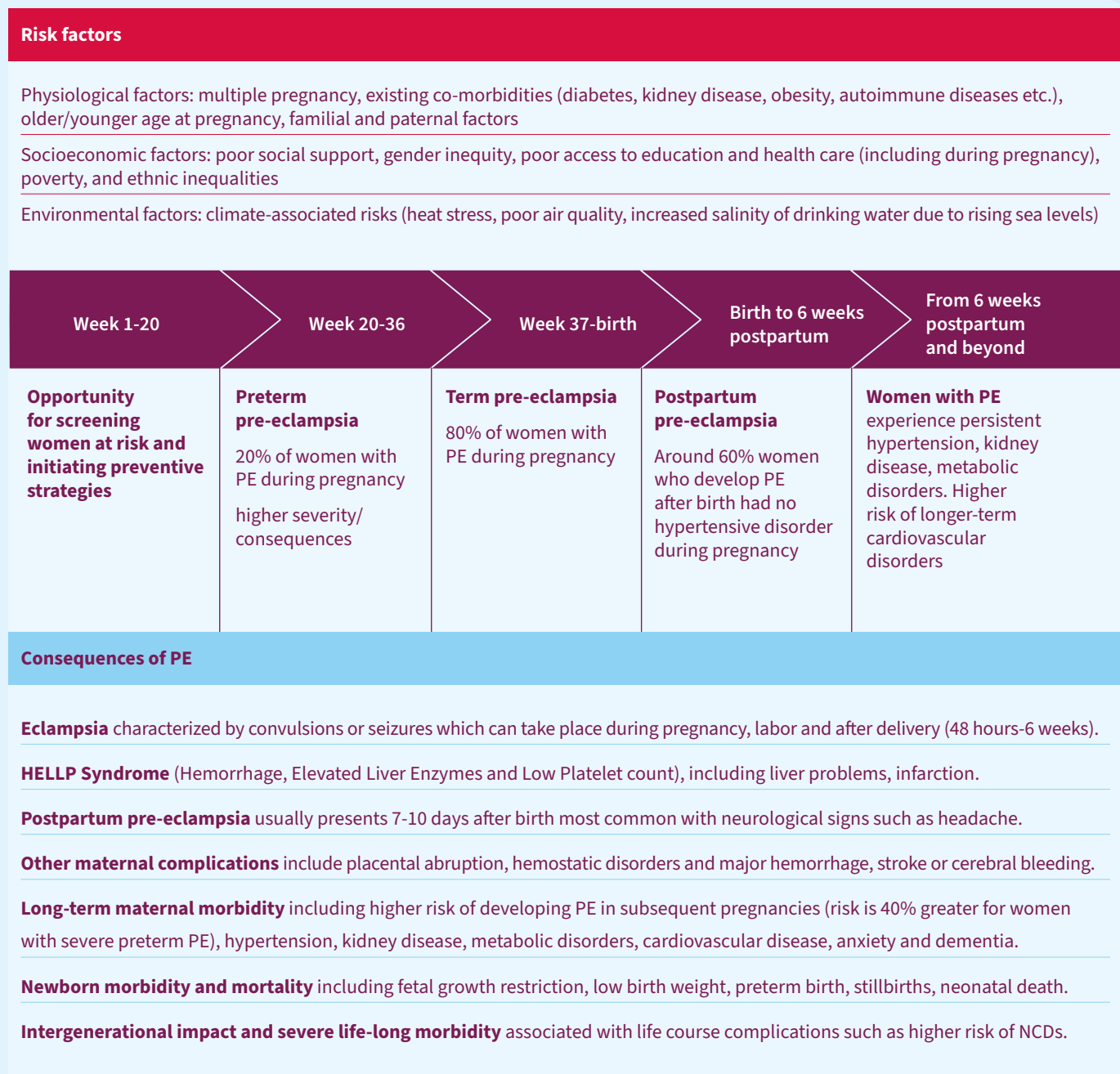
PE is a progressive pregnancy condition - a multiorgan disease process that is now recognized as a placental disorder. PE is generally defined as the onset of high blood pressure (BP) any time after 20 weeks' gestation accompanied by proteinuria and/or maternal end-organ dysfunction. The International Classification of Diseases 11<sup>th</sup> Revision (ICD-11) defines PE as characterized by ***systolic BP greater than 140 mmHg and/or diastolic BP greater or equal to 90 mmHg on two occasions 4 hours or more apart in the presence of either proteinuria or other new onset maternal organ dysfunction characterized by one thrombocytopenia, elevated serum creatinine or liver transaminases, or neurological conditions or fetal growth restriction.***<sup>6</sup> Most leading organizations that develop clinical guidelines (International Federation of Gynecology and Obstetrics (FIGO), International Society for the Study of Hypertension in Pregnancy (ISSHP), American College of Obstetricians and Gynecologists (ACOG), UK National Institute for Health and Care Excellence (NICE)) are largely consistent with this definition. PE can progress rapidly and unpredictably, and if not promptly identified and managed, it can develop into eclampsia.<sup>6</sup> Eclampsia is characterized by convulsions or seizures which can take place before, during or after delivery.<sup>2,7-9</sup> In addition to the clinical signs of PE and eclampsia outlined above, women often experience anxiety, epigastric pain, severe headache, blurred vision, proteinuria, and oedema during pregnancy, labor and puerperium. One major complication of PE and eclampsia is the development of HELLP syndrome (hemorrhage, elevated liver enzymes, and low platelet count) resulting in serious liver problems, including infarction, hemorrhage, and rupture. Maternal end organ dysfunction may present as maternal hematological / biochemical dysfunction, neurological symptoms, stroke or cerebral bleeding, angiogenic biomarker imbalance, or uteroplacental dysfunction, leading to fetal growth restriction, abruption, or stillbirth.<sup>7</sup>

PE can be associated with fetal growth restriction, resulting in babies born with low birth weight. It is the cause of up to 20% of the 13 million preterm births and 15% of the 30 million infants affected by intrauterine growth restriction (IUGR) each year.<sup>10</sup> PE has intergenerational impacts on both women and her children. Women who survive PE are at risk of severe long-term health issues, including hypertension, kidney disease, metabolic disorders, cardiovascular disease, anxiety

and dementia. Likewise, infants born too small or too soon have a higher risk of developing non-communicable diseases (NCDs) later in life, highlighting the need for long-term follow up of both women and children born to mothers with PE.<sup>10-12</sup> For example, one study found that 15% of women who experienced PE had developed acute kidney injury. Of those who underwent repeat creatinine tests, 16% had not regained normal kidney function at follow up, indicating potential long-term kidney health issues.<sup>13</sup> There are limited data available from LMICs on long term effects of PE on women's health. However, a study in Nigeria that followed over 400 women who had experienced PE for one year found that a significant proportion continued to suffer from hypertension, kidney disease, or metabolic disorders.<sup>14-16</sup>

The management of women with PE focuses on minimizing further pregnancy-related complications, avoiding unnecessary preterm birth and implementing interventions to maximize maternal and infant survival. For women with PE experiencing severe hypertension, antihypertensive medicines can reduce the risk of severe complications, including stroke and heart failure. Magnesium sulfate (MgSO<sub>4</sub>) is administered to prevent and manage eclampsia (seizures).<sup>17-21</sup>

While the majority (80%) of PE cases occur after 37 weeks of pregnancy (late-onset or term PE), early-onset or 'preterm PE' (from 20 weeks to 37 weeks' gestation) is less common but has more severe consequences. These include severe maternal morbidity and death, as well as preterm birth, fetal growth restriction, low birth weight and stillbirth or neonatal death (figure 2.1). Recent evidence suggests that planned early delivery for preterm PE, from around 34 weeks' gestation, may result in better outcomes for the newborn due to the progressive deterioration of the placenta.<sup>19,22</sup> While the current definitive treatment for PE and its consequences is the delivery of the fetus and the placenta, some women may also develop postpartum PE, characterized by new-onset hypertension occurring between 48 hours' and 6 weeks' after birth, most commonly 7 to 10 days postpartum.<sup>7</sup> It has been reported that 60% of women who develop postpartum PE do not experience PE during pregnancy.<sup>20</sup> There is limited awareness of postpartum PE, though risk factors include older maternal age, maternal obesity, black race and cesarean delivery.<sup>21-24</sup>

**Figure 2.1:** Onset of PE, risk factors and health consequences



## Risk factors for pre-eclampsia and eclampsia

Known risk factors for PE/E include pre-existing NCDs including co-morbidities such as diabetes, kidney disease, obesity, and autoimmune diseases (systemic lupus erythematosus, anti-phospholipid syndrome), multiple pregnancy, as well as familial factors (e.g., mother or sister who experienced PE) and paternal factors such as a higher risk with the first pregnancy with a specific partner.<sup>19,25,26</sup> Women with pre-pregnancy diabetes have a 20% higher risk of developing PE, and those with existing kidney disease a 40% higher risk. Additionally, women who have experienced PE have a 14% to 16% higher risk of developing PE in subsequent pregnancies, and a 40% higher risk if they experienced severe preterm PE or HELLP Syndrome.<sup>7,14,27</sup> PE is increasingly recognized as a state of angiogenic imbalance characterized by elevated sFlt-1 and/or low concentrations of placental growth factor (PlGF). The identification of these biomarkers has opened promising opportunities to identify women at risk of PE, to manage their pregnancies and plan for delivery accordingly.<sup>28,29</sup> Social factors compound the risk of PE/E, including gender inequality, lack of social support, poverty, poor access to

education for girls, older or younger age at pregnancy and not attending ANC. Pregnant adolescents are at high risk of PE but often do not receive preventive measures and are more likely to face discrimination and stigma when seeking medical care. The impact of HDP on different ethnic and racial minority women remains poorly understood, although clear differences exist between global regions and populations. Efforts are underway to identify variations in disease presentation and progression across various countries.

Climate change has unfavorable effects on PE/E and preterm birth.<sup>30</sup> Extreme heat and poor air quality are associated with an increased risk of PE, IUGR, stillbirth, perinatal mortality, and other adverse pregnancy outcomes, especially among women in lower socio-economic groups.<sup>30–34</sup> Emerging risk factors for eclampsia in LMICs include outdoor exposure to traffic pollution and indoor air pollution from traditional fuels and cooking stoves.<sup>35</sup> Coastal flooding and rising sea levels, which increase drinking water salinity, also contribute to increased risks of HDP.<sup>36</sup> More research is needed to fully understand these relationships.





## Relevant global landscape and policy goals: challenges and successes

The overarching effort to improve maternal health is guided by the SDGs and the Global Strategy for Women's, Children's, and Adolescents' Health (2016-2030), supported by several targeted initiatives, most notably Ending Preventable Maternal Mortality (EPMM) and Every Newborn Action Plan (ENAP). EPMM and ENAP have established coverage targets for scaling up MNH interventions, with shared milestones to support country-level implementation and progress towards these goals, including a target that 90% of women receive at least four ANC visits. An EPMM-ENAP joint country implementation tracking tool supports monitoring of this progress.

Since 2015, WHO has released and updated numerous guidelines, frameworks, and tools aimed at improving care for women and newborns. Central to these efforts is the Maternal and Newborn Health Quality of Care Framework, which emphasizes both the provision and experience of care, covering eight key domains including communication and respectful maternal and newborn care. WHO recommendations on (1) **ANC for a positive pregnancy experience**, (2) **Intrapartum care for a positive childbirth experience**, and (3) **Maternal and newborn care for a positive postnatal experience**, are foundational guidelines, with additional regular updates by WHO to address more specific complications of pregnancy and childbirth, such as the prevention and treatment of PE.

In February 2024, WHO published materials to support program reviews for Maternal, Newborn, Child and Adolescent Health (MNCAH). These resources are designed to assist in planning, managing, and implementing national and subnational program reviews and workshops for MNCAH. This includes addressing bottlenecks around MNH complications including HDPs, preterm birth and associated poor health outcomes.<sup>37</sup>

In line with the growing understanding of the origins of PE, and building on the ICD-11 definition, several international institutions revised the clinical definition and diagnostic criteria

for PE since 2018 to define PE as gestational hypertension accompanied by one or more of the following: new onset conditions after 20 weeks' gestation, and either proteinuria, or other maternal health organ dysfunction, including utero placental dysfunction such as FGR, abnormal umbilical Doppler findings, or stillbirth. Other institutions (ISSHP, Society of Obstetricians and Gynaecologists of Canada (SOGC), International Society of Ultrasound in Obstetrics & Gynecology (ISUOG)) have now incorporated angiogenic and antiangiogenic markers for uteroplacental dysfunction.<sup>7,17</sup>

The current stalling of progress toward EPMM has led many experts to call for a paradigm shift in maternal health, particularly during the perinatal period and beyond. During the routine six-week postnatal check-up, BP is rarely measured, with the focus often on the baby's immunization with limited follow up for women who have experienced severe morbidities such as PE/E. Many women who experienced PE/E continue to have persistent hypertension, kidney disease and other metabolic disorders, putting them at increased risk for cardiovascular disease later in life. However, studies show that when interventions to optimize BP control are implemented during the postpartum period in women with HDP, their long-term BP outcomes noticeably improve.<sup>14</sup>

Addressing maternal morbidity and mortality requires a broad, multipronged approach, including promotion of social development and gender equality at national level, universal health coverage (UHC) and strong health systems. Framing the recent WHO pregnancy related guidelines as part of a positive experience for women supports respectful maternal and newborn care while also enhancing self-care and autonomy in decision-making. Moreover, pregnancy, childbirth and the postnatal period should not be viewed as isolated events but as integral components of a woman's life, necessitating a more holistic, human-centered approach to care.

# 3. Key initiatives and efforts in pre-eclampsia and eclampsia

Under the umbrella of the SDGs and the Global Strategy for Women's, Children's, and Adolescents' Health (2016-2030), EPMM and ENAP collaborate closely. However, fragmentation and coordination challenges within the MNH ecosystem, including funding for scaling up known MNH interventions, have hindered progress. Funding for critical MNH issues, such as HDP and preterm birth, has stagnated in recent years, highlighting the need for a more unified global approach to MNH to achieve the SDGs.<sup>38</sup>

Governments are the primary financiers and implementers of MNH programs, including for procurement and supply chain management of medical devices and products, and face increasing fiscal constraints and operational bottlenecks to provision of quality maternal care. Although many governments developed ENAP/EPMM acceleration plans, full execution of those plans remains challenging.

Key stakeholders leading and supporting HDP-related initiatives include funders, researchers, policymakers, civil society, program implementers, health care workers,

coalitions, networks as well as industry partners. Given that PE/E is a leading cause of maternal morbidity and mortality in both high- and LMICs, there are some synergies across stakeholders, particularly in R&D, and in implementation research for new interventions. However, the development and deployment of affordable solutions for LMICs lag significantly behind advances in high-income settings.

While not an exhaustive list, stakeholders from across the health and development landscape engaged in addressing PE/E include those listed on the following two pages.

“

**There are few upstream R&D funders dedicated to PE/E, and overall, R&D targeting MNH conditions constitutes a small fraction of global R&D efforts.**

### Research and development

Many groundbreaking R&D trials, such as for blood and urine biomarkers, have taken decades to come to fruition. These efforts have been primarily led by academic institutions in the Global North, although with an increasing number of partnerships in LMICs. The product development and pharmaceutical industry, along with non-governmental organizations also play a critical role in upstream innovation and R&D by supporting product development, testing, and commercialization. TPP<sup>39</sup> have been developed to guide product developers and funders on the minimal characteristics and desired attributes of medical products—including devices, diagnostics, tests and therapeutics—focused on PE prevention and treatment, preterm labor prevention and management, and monitoring maternal and fetal well-being in any health care setting. WHO will release a further TPP on obstetric ultrasound in 2024.

Industry partners involved in PE/E include Revvity (formerly PerkinElmer) with their PIGF POC reader, ThermoFisher Scientific (PIGF and sFLt-1 assays), Aucheer (POC sFLt1/PIGF assay), MOMMDIAGNOSTICS (POC sFLt1/PIGF assay), Comanche Biopharma (investigational siRNA therapeutic CBP-4888 for treatment of sFLt-1-mediated PE). Other players include Lepzi and Diabetomics. Additionally, further investment is needed in developing safer labor induction methods. Downstream funders for PE are critical for promoting the introduction and scaling up of access to PE products and interventions, particularly in resource-constrained environments where a decline in donor funding and competing health priorities further limit the resources available for PE/E.

There are few upstream R&D funders dedicated to PE/E, and overall, R&D targeting MNH conditions constitutes a small fraction of global R&D efforts. The public sector remains the primary funder of PE/E basic research and product development. Between 2018 and 2021, the US National Institutes of Health (NIH) was the largest funder of basic PE/E research (US\$47 million), followed by the Canadian Institute of Health Research (US\$2.9 million). The UK's National

Institute of Health and Care Research (NIHR) and Foreign and Commonwealth Development Office (FCDO) also support global maternal health research. USAID has been a significant funder of PE/E through a variety of global implementation and research projects over the last two decades, alongside WHO, UNFPA, UNICEF and the Global Financing Facility. Among foundations, the Gates Foundation has been a key investor, supporting the development and implementation of regional and global policies and financing that expand the use of product innovations and interventions. These efforts aim to address underlying biological drivers of risk and mortality, improve data on MNH-specific conditions, and strengthen the broader MNH ecosystem to drive progress. Other foundations engaged in PE/E include Merck for Mothers (U.S.-based), MSD for Mothers (global), and the McArthur Foundation which previously supported the introduction of MgSO<sub>4</sub> to several LMICs between 2008 to 2018. The Foundation for the National Institutes of Health Biomarkers Consortium in the USA, supported by the Gates Foundation, Merck for Mothers, and others, is a newly established public-private partnership focused on achieving U.S. Food and Drug Administration (FDA) validation of the PIGF and PAPP-A (Pregnancy Associated Plasma Protein – A) biomarkers and stimulating innovation in PE/E.<sup>40</sup>

Examples of nonprofit patient-led organizations include the Preeclampsia Foundation in the USA, Action on pre-eclampsia in the UK and the Zuri Nzilani Foundation (ZNF) in Kenya, which work to raise public and professional awareness of HDP, improve care, and alleviate or prevent the physical and emotional suffering caused by hypertensive disorders. These organizations offer health care worker training and provide targeted research funding, though many face financial and resource constraints that limit their ability to fully carry out activities. In 2017, the first World Pre-eclampsia Day was launched on May 22 by a network of patient advocacy groups, researchers and implementers, and has continued annually since then.

## Normative guidance, regulatory, advocacy, and accountability

International institutions involved in normative guidance, regulation, advocacy, and accountability include WHO, UN agencies, donors, implementing partners and professional organizations. WHO is currently mapping clinical recommendations developed by key clinical institutions over the past five years, with the goal of streamlining existing and newer evidence-based research. In 2023, WHO convened a summit on PPH to facilitate knowledge exchange and

promote greater alignment among governments, global agencies, donors, researchers, program managers and civil society to accelerate progress on PPH. This effort culminated in the publication of the *Roadmap to Combat Postpartum Haemorrhage between 2023 and 2030*.<sup>41</sup> There are discussions about enhancing the impact of the opportunities for PE/E outlined in this landscape report through a coordinated effort in alignment with the PPH Roadmap.

## Coalitions and networks

MNH coalitions and networks bring together civil society, non-governmental organizations and other nonprofits, academic institutions, as well as donors and UN agency representatives. These groups drive collaboration, alignment, and the dissemination of updated guidelines and information. They include coalitions such as the Partnership

for Maternal, Newborn and Child Health, the Maternal Health Caucus of the Reproductive Health Supplies Coalition (RHSC), the Healthy Newborn Network, the national White Ribbon Alliances, Family Planning 2030, and dedicated initiatives, such as AlignMNH, which serves as the secretariat for the International Maternal Newborn Health Conference, amongst others.

## Global health supply chain for maternal commodities

Several global initiatives are actively addressing maternal health supply chain challenges. The **Maternal Health Caucus of the RHSC** provides a forum for the maternal health community to collaborate, establish a common understanding of supply-related issues and leverage existing approaches to overcome bottlenecks that threaten commodity security. Several coalition members, including CHAI, MSD for Mothers, R4D and Concept Foundation, are working to address market challenges and improve access to PE and other MNH products. RHSC is collaborating with manufacturers and supporting in-country procurement practices, including support to national medicines regulatory authorities (NMRAs), particularly in relation to maternal health medicines and devices. Information presented in this landscape draws from this work, including an analysis on manufacturing capacity and demand for maternal health commodities in sub-Saharan Africa (SSA).

**The UNFPA Supplies Match Fund** (Match Fund) is an innovative financing mechanism designed to encourage governments to maximize domestic financing

for maternal health commodities and transition to the procurement of QA commodities. The fund supports the purchase of contraceptives and six priority maternal health medicines, including MgSO<sub>4</sub> and calcium gluconate. It currently operates on a 2:1 matching basis, with a US\$ 2 million ceiling per country, conditional upon an annual increase in domestic allocation for reproductive health commodities (whether through concessional financing or public funds). Five countries to date have used the Match Fund to procure PE/E medicines, specifically MgSO<sub>4</sub> and/or calcium gluconate.

The **USAID Global Health Supply Chain (GHSP) program** encompasses eight complementary projects, one of which is the GHSP-PSM (Procurement and Supply Management) project.<sup>42</sup> This project supports USAID priority countries to strengthen national supply chains to ensure the availability of QA MNH commodities. It focuses on procurement, last mile delivery, in-country technical assistance, capacity building, quality assurance and service delivery among other critical aspects of supply chain management.

# 4. Current and promising tools and interventions as well as key gaps

This section reviews current and promising tools and interventions to address PE/E and key issues to consider for their use in high-burden contexts.

A comprehensive database on investigational candidates for PE/E has been created by the Accelerating Innovation for Mothers (AIM) project, led by the Concept Foundation in partnership with Policy Cures Research and the Burnet Institute. The AIM database identified 15 high- and medium-potential candidates for prevention and/or treatment of PE. These are included in this landscape analysis, along with additional products identified through this review.

The landscape of medical products for PE/E is organized into four sections based on the opportunities to intervene:

- Diagnostics for risk assessment and onset of PE
- Prevention medicines and dietary supplements for women identified as high-risk
- Therapeutics for the management of HDP and PE/E
- Evidence-informed practices for screening, prevention and management (including timed delivery)

These opportunities are then followed by an exploration of models that support quality, comprehensive ANC and an overview of key market issues concerning PE/E commodities.

## 4.1 Diagnostics for risk assessment and onset of pre-eclampsia

### Standard of care for detection of PE risk and onset of PE

Over the past decade, significant efforts have been made to develop tools for predicting the risk of PE among pregnant women and to improve risk stratification. Until recently, accurately and reliably predicting PE risk in the first trimester remained elusive. Advancements have now made it possible to use maternal factors – such as family and individual medical history – alongside BP, PlGF and uterine artery pulsatility index (UAPI), measured around 11-13 weeks' gestation, to identify women at risk of developing PE.<sup>43,44</sup> This early screening is often used comprehensively in high-income countries (HICs), though PlGF screening and UAPI have limited availability in low-resource settings.

Despite these limitations, the measurement of UAPI through Doppler ultrasound at 16-22 weeks combined with medical and obstetric history can help identify high-risk pregnancies in these settings.<sup>43,45</sup> Early identification of risk is crucial for initiating preventive interventions such as low-dose aspirin (ideally before 16 weeks' gestation as may have more limited benefit if taken before 20 weeks), and calcium supplementation in populations with low dietary intake. FIGO recommends several management strategies for women at risk of PE, including providing guidance on PE symptoms and when to seek care, home BP monitoring, regular clinical assessment to monitor HDP and PE risk (including biomarker analysis) and uterine artery Doppler ultrasound or UAPI.<sup>9,45</sup> Biomarker analysis and UAPI remain less accessible in LMIC settings.

## Encouraging early ANC attendance is a critical component of detection and management of PE risk in low-resource settings

These screening interventions, combined with additional biomarkers and clinical symptoms, are also recommended for diagnosing PE from 20 weeks' gestation onward. Diagnostic algorithms have been developed to assist in risk triage based on symptoms, maternal factors and biomarkers. This risk stratification informs clinical care, including BP monitoring, prescribing antihypertensives, regular antenatal and fetal monitoring, which all support decision-making on the timing of delivery and postpartum monitoring.

Between 2018 and 2021, six recommendations were updated in the WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia. These include new evidence around use of antihypertensives for non-severe and severe hypertension, use of antiplatelet agents (low-dose aspirin)

and induction of labor for severe PE. The guidelines have not yet incorporated newer blood-based biomarkers. WHO is undertaking a scoping review of clinical guidelines published from 2014 to 2024 developed by major organizations including NICE, ACOG, FIGO, ISSHP and others. The objective is to identify content related to PE diagnostics and to highlight areas of convergence and differences in content and recommendations.

The products and tools covered in this landscape that support early detection of PE risk, onset of PE and risk stratification include: i) Urine-based diagnostic tests; ii) blood-based biomarker tests; iii) BP measurement devices; iv) diagnostic algorithms and decision-making software; and v) POC ultrasound.

### Urine-based diagnostic tests

The onset of hypertension plus elevated protein in urine (proteinuria) beyond 20 weeks' gestation have historically been the primary clinical indicators for PE in low-resource settings together with other clinical signs and symptoms. There are several urine-based tests widely available and under investigation to support PE diagnosis.

**Urinary dipstick test for proteinuria.** This test is commonly used and is recommended in WHO and country ANC guidelines. These are easy to obtain, easy to use, and relatively inexpensive. Some urinary test strips are specific to proteinuria, and others are multiparameter (e.g., include protein, glucose) to provide other useful information for pregnancy care.<sup>46</sup>

## Key barriers

**Varied performance:** While the urinary dipstick test for proteinuria is the standard in low-resource settings, a key drawback is that proteinuria is not reliably seen in all women with PE, and programs report wide variation in the sensitivity and specificity in urine dipsticks used in LMICs.<sup>46–48</sup> One of the causes of poor performance is that protein-only dipsticks cannot adjust for daily fluctuation in body hydration which can lead to both over- and underestimation of protein levels.

**Supply security – particularly in peripheral facilities:** While relatively inexpensive, the dipstick test is not necessarily widely available in facilities, with resource constraints being a factor. To stretch available supply, health care workers may cut up a test strip to be used for multiple women, further compromising performance.

Given proteinuria tests are deeply embedded in country ANC guidelines, a potential option to improve the quality of this diagnostic is to assess the performance of various dipstick products used in LMIC markets to help inform procurement decisions. However, given not all LMIC settings are using urinary dipstick tests, further analysis is needed to understand the added value of potential performance data, and where it would be most impactful.

### Other marketed and investigational proteinuria tests

Other options for diagnosis of proteinuria include the Protein-to-Creatinine ratio (PrCr) test or the urinary Albumin-to-Creatinine ratio (ACR), which are recommended by some health guidelines, including the UK National Institute for Health and Care Excellence, if urinary dipstick screening is positive.<sup>49</sup> Currently, these tests require a laboratory setting using chemistry analysis which is not feasible in low-resource settings. While multiparameter urine dipsticks available in LMICs often test for both protein and creatine, they do not return results in a format that allows health care workers to determine the PrCr ratio. A urine dipstick test designed specifically for determining the PrCr ratio was developed by LifeAssay and PATH, which uses a visually read colorimetric

scale and grid to interpret results. Real-world performance of the PrCr dipstick has not been promising and is now considered a low priority (table 4.1).<sup>50</sup>

### Other marketed and investigational urine tests

Women with PE have elevated levels of misfolded urine proteins, which bind to Congo Red dye (congoophilia). Some rapid tests under development are using congoophilia as the basis for detection (table 4.1). This is an area with potential for further development, including testing in diverse populations and for different use cases. As with the PrCr ratio test, ensuring health care workers — and potentially in future women themselves or community health workers — can accurately and reliably interpret the results will be important to ensure relevance for LMICs. The patents for the Congo Red Dot (CRD) Paper Test are held by Yale University, which has licensed the rights to GestVision for commercialization in the United States and to Shuwen Biotech in China. Both companies also hold various intellectual property rights in additional countries. Furthermore, a small number of other urine biomarkers are under investigation, though none are currently considered a priority for advancement by subject matter experts.



**Table 4.1:** Urine biomarker diagnostics tested in LMICs and investigational urine biomarkers

Urine-based test	Description	Manufacturer and cost details
<b>CapCord test (Congophilia)</b>	<p>Simple, non-invasive, POC paper test that measures urine congophilia.</p> <p>Results available in 3 minutes, though considered somewhat difficult to interpret by health care workers in LMIC settings.</p> <p>Initial performance indicated 80% sensitivity and 89% specificity. More recent data are mixed, finding low sensitivity in detecting HDP or PE.<sup>51,52</sup> There is also an absence of data in SSA.</p>	<p>Patent held by Shuwen Biotech. Partnered with PerkinElmer to commercialize outside China, including India and South America.</p> <p>Pursuing FDA approval as a PE diagnostic aid (2022) CE Marked.</p> <p>Cost ~US\$20.</p> <p>An electronic reader to improve usability is reportedly being developed by the manufacturer.</p>
<b>GestAssured rapid test (Congophilia)</b>	<p>Lateral flow test that detects urine congophilia. A positive result is indicated by the presence of red color in the results window.</p> <p>Beta prototype testing was conducted in Bangladesh and Mexico<sup>53</sup> involving use of a visual chromatic aid to score test results on a 6-point scale based on intensity of color.</p> <p>When using a higher cut-off depicted by a more intense red color, sensitivity ranged from 30.8-66.7% and specificity ranged from 97.8%-100%. Specificity declined at a lower cut-off.<sup>51,54</sup></p>	<p>Patent held by GestVision.</p> <p>Multi-center US clinical study underway to evaluate the GestAssured rapid test.</p>
<b>LifeAssay Diagnostics Test-it™ PrCr dipstick test</b>	<p>Paper based dipstick where results are based on a visually read colorimetric scale that indicates whether the PrCr ratio is considered normal or abnormal.</p> <p>Real world performance in LMIC study sites was not promising, particularly among women with a low level of proteinuria. The need for health care workers to calculate the PrCr ratio was also viewed as complex.<sup>50</sup></p> <p>Exploration for other clinical use cases, such as triage among high-risk populations could be warranted but not currently considered high priority.</p>	<p>LifeAssay Diagnostics (developed with PATH).</p> <p>CE marked and registered with regulatory authorities in Ghana and South Africa.</p> <p>US\$0.10 per strip (comparable to protein dipsticks).</p> <p>Optional device to support results interpretation by LifeAssay (additional cost).</p>
<b>Investigational urine biomarkers</b>		
<b>Urinary Adipsin</b>	<p>High sensitivity (70%) and specificity (&gt;90%) in initial testing.</p> <p>Developed by PATH through proof of concept to usability evaluation.</p>	<p>Development discontinued due to variability in results and lack of commercially available antibodies.</p>
<b>Complement C5a and C5b-9 (also possible therapeutic candidate)</b>	<p>C5a and soluble C5b-9 are elevated in severe PE and could be used to differentiate PE from other HDP.</p> <p>Complement C5 inhibitor eculizumab for treatment of HELLP.</p>	<p>N/A. Continued research is needed to identify the initiator(s) of activation, the pathways involved and the key component(s) in the pathophysiology.<sup>55</sup></p>



## Blood-based biomarker tests

Several blood-based biomarker diagnostics are available to screen for and detect PE and support clinical decision-making. Their high predictive value is a major driver for cost-effectiveness within clinical protocols.<sup>56</sup> Many of these biomarkers are associated with the development of blood vessels (angiogenesis) in the placenta. Two angiogenic biomarkers have the strongest evidence as markers for the prediction, diagnosis and risk stratification of PE: **Placental Growth Factor (PLGF)** – which is suppressed in women who develop PE, and **serum FMS-like tyrosine kinase 1 (sFlt1)**, which is elevated in women with PE.<sup>57</sup>

It is now understood that sFlt-1 blocks other proteins needed for placental development, such as PLGF. Therefore sFlt-1 serves both as a biomarker for indication of PE and a candidate therapeutic target (discussed further under PE candidate therapies). Other angiogenic biomarkers linked to PE that are in various national guidelines are Pregnancy Associated Plasma Protein A (PAPP-A) and Vascular Endothelial Growth Factor (VEGF).<sup>58</sup> Additionally, Glycosylated fibronectin (GlyFn), a glycoprotein involved in cell adhesion and migration, has been identified as a biomarker for PE.<sup>59</sup>

These biomarkers have several potential use cases as follows:

**First trimester screening:** Low levels of PLGF are already apparent towards the end of the first trimester. FIGO recommends PLGF testing starting from 11-13 weeks where available to aid in identification of women at risk of developing PE. For now, this use case is less relevant to low-resource settings given later ANC attendance, and cost-effectiveness considerations.

**Second and third trimester screening (20-37 weeks):** For women with symptoms of suspected preterm PE, screening using PLGF and sFlt-1 (and the ratio of sFlt-1/ PLGF) can support clinical decision-making and patient management. These biomarkers can help to “**rule out**” or also “**rule in**” PE– the risk of PE developing within the next 7-14 days.<sup>60</sup> These biomarkers can thus provide valuable information for clinical and admission/discharge decisions, with implications for health system and household costs. Evidence to date demonstrates that there is no maternal or perinatal benefit associated with routinely repeating PLGF testing in all women who receive an initial test.<sup>61</sup> However, stratified analysis of the PARROT-2 trial suggests that there may be a benefit in repeating the test in women who had an initial normal result but **re-present** with new symptoms or signs of PE.<sup>62</sup> Other biomarkers are also being investigated as potential alternatives or adjunctive tools.

Available blood-based biomarker diagnostics are listed in table 4.2 including PLGF, sFlt-1, the sFlt-1/PLGF ratio, and GlyFn. A few products are currently considered suitable for low-resource settings, particularly POC or near-POC tests. However, most of the commercially available assays require laboratory infrastructure and are designed to be used in conjunction with high throughput analyzers. Where available, quantitative cutoff values indicative of the likelihood of developing PE are indicated.

Several cost-effective analyses (economic modelling) conducted in high-income countries have demonstrated significant reductions in the prevalence of preterm PE and substantial cost savings associated with a policy of population-wide first-trimester high-risk screening, including use of biomarkers and prevention of preterm PE through the prescription of low-dose aspirin from 16 weeks.<sup>56,63,64</sup>

However, NICE has concluded that the evidence is inconclusive on cost-effectiveness of first trimester screening, and therefore, it is not recommended in current practice. The NIHR are currently funding a large trial of first trimester screening, known as the STARSHIP study. For pregnancies beyond 20 weeks’ gestation, the UK NICE considers the Elecsys Triage tests and DELFIA Xpress PLGF 1-2-3 cost-effective for “**ruling out**” or “**ruling in**” preterm pre-eclampsia.<sup>29</sup>

### **Developments in blood-based biomarker test for LMIC contexts**

A small number of blood-based biomarker tests are currently being investigated in LMIC contexts. So far, promising evidence has emerged from Mozambique, with emerging evidence in Sierra Leone, on the value of PLGF testing for women with suspected PE beyond 20 weeks’ gestation in

low-resource settings. Further research is underway, including studies supported by the UK NIHR and the Gates Foundation, to validate several blood-based biomarker tests in Brazil, India, Sierra Leone and Zambia (PAPAGAIIO study). These include the Quidel Triage PIGF assay, the RONIA PIGF POC test, the LEPZI® Quanti PLGF Test and the Lumella Glycosylated Fibronectin (GlyFn) assay (refer to table 4.2). While many tests provide the time to results, this typically refers to the time once the sample is on the analyzer. The testing process can take longer—sometimes more than 24 hours—depending on the laboratory setup and technical skills.

- In Mozambique, introduction of PIGF screening for women identified as at-risk of PE, as part of a core set of PE interventions, was found to reduce number of women with eclampsia by 19% (with improvements for higher risk gestational age of 20 to 32<sup>66</sup> weeks) and reduce the need for MgSO<sub>4</sub>. A small reduction in stillbirths and neonatal mortality rates was also detected (pre-publication data – yet to be verified). These trials utilized the Quidel

Triage PIGF assay (originally developed by Alere and now supplied by Quidel-Ortho), which is reportedly being introduced in five Mozambiquan provinces with support from CHAI.<sup>65</sup> The Quidel assay is a small benchtop analyzer that requires a small volume of blood plasma provided on a single-use cassette for analysis; blood samples must be processed in a centrifuge before analysis.

- In Sierra Leone, the RONIA PIGF POC assay, distributed by Revvity (formerly PerkinElmer), along with the LEPZI® Quanti PLGF Test and the Lumella GlyFn assay, are being evaluated through a prospective observational cohort study. The research aims to determine the impact of integrating PIGF into clinical management pathways, including planned early delivery. The RONIA device is compact, portable, and uses a single-use cassette for analysis of whole blood (finger prick). The total time to result using the RONIA Platform is approximately 30 minutes. The device can be connected to an electricity supply, and the battery holds a charge sufficient for three tests.

## Key barriers

**Awareness and demand:** Blood-based biomarker screening is relatively new, with limited, but growing, investment to assess performance in low-resource settings and optimize use within clinical pathways. There is a need for awareness raising and demand generation in low-resource settings, as these tests are still largely unknown or unavailable in most high-burden countries.

**Infrastructure requirements:** Most commercially available assays require laboratory infrastructure and refrigeration with reliable electricity supply. In contrast, the tests under investigation in LMICs are POC or near-POC and a mix of whole blood and serum-based tests. Serum-based tests require centrifuge capacity, potentially limiting their impact in more rural areas.

**Cost:** The cost of some devices and cartridges per test is currently prohibitive for large-scale use and would require market interventions to improve affordability. Additionally, the cartridge packs for certain devices, such as the Quidel Triage PIGF assay and the Elecsys immunoassay sFlt-1/PIGF ratio, must be used within six weeks of opening. Refer to table 4.2 for available cost information.

**Clinical considerations:** Although PIGF tests are similar, the quantitative thresholds used to guide clinical decisions are not directly interchangeable due to differences in the assays. Manufacturers advise that laboratories establish their own reference ranges, which should consider thresholds that provide clinically relevant information across various gestational ages. Second, PIGF levels may vary by population, suggesting that reference ranges might need to be determined in different population groups/geographies. This is an important area of research, but definitive data is awaited. These factors must be considered when introducing blood-based biomarker screening into national PE/E programs.

**Table 4.2:** Blood-based biomarkers and candidate biomarkers, including products adapted to LMICs

Blood biomarker	Description	Available product details
<b>Placental Growth Factor (PLGF)</b>	<p>Low concentrations of PLGF precede the clinical onset of PE and may predate the clinical syndrome by 10 weeks.</p> <p>Indicated where available for screening of women at risk of PE from around 11-13 weeks' gestation.</p> <p>Indicated for use in suspected preterm PE between 20- and 37-weeks' gestation to "rule in" OR "rule out" PE for next 7-14 days.</p> <p>Once PLGF levels reach the lower cutoff (&lt;12pg/ml), further prognostic information on disease progression is not possible.</p>	<p><b>Adapted to low-resource contexts:</b></p> <p>Quidel Triage® PLGF assay (QuidelOrtho—originally developed by Alere). ~US\$23/cartridge + US\$2,500 for 'bedside' analyzer. Serum assay requires centrifuge capacity for sample preparation.</p> <p>Ronia POC Reader &amp; PLGF kit (Revvity). €15-20/cartridge + US\$5,000 device. Whole blood sample (finger prick). Marketed as no maintenance required.</p> <p>Portable LEPZI® Quanti PLGF Test. Test result in 10 minutes. £12.50 per box of 25 tests + £50 device.</p> <p>Laboratory assays:</p> <p>DELFIAXpress PLGF 1-2-3 test 66 (Revvity, formerly PerkinElmer). Result in 30 minutes. Indicated for use in 2<sup>nd</sup> and 3<sup>rd</sup> trimester. "Rule out" PE threshold is PLGF &gt;150pg/ml; "Rule in" PE threshold is PLGF &lt; 50 pg/ml.</p> <p>Elecsys immunoassay sFlt-1/PLGF ratio (Roche). Indicated for use in women 24-37 weeks. "Rule out" threshold if ratio is ≤ 38. "Rule in" PE if ratio is &gt;38 and &lt; 85 indicates 20% risk over next 7 days, and &gt; 85 indicates 56% risk.</p> <p>[Above 3 assays all perform similarly in prediction for need to deliver in 14 days (UK COMPARE study)]</p> <p>Triage PLGF assay (Quidel). Result in 45 minutes. Indicated for 20-36<sup>6</sup> weeks' gestation. "Rule out" PE for next 14 days if PLGF ≥ 100 pg/ml. "Rule in" if PLGF &gt; 12 and &lt; 100 pg/ml (abnormal) and &lt; 12pg/ml highly abnormal (UK PELICAN study).<sup>66,67</sup></p> <p>BRAHMS PLGF plus Kryptor (ThermoFisher).</p> <p>PLGF ELISA (DRG Diagnostics).</p>
<b>serum FMS-like tyrosine kinase 1 (sFlt-1)</b>	<p>Used as a standalone biomarker or as sFlt-1/PLGF ratio.</p> <p>Indicated for use in suspected preterm PE from 20-37 weeks' gestation.</p> <p>Recently recommended by US FDA.</p>	<p><b>Laboratory assays:</b></p> <p>DELFIAXpress sFlt-1 serum test (PerkinElmer).</p> <p>BRAHMS sFlt-1 Kryptor assay (ThermoFisher Scientific).</p>
<b>sFlt-1/ PLGF ratio</b>	<p>In women who develop PE, the sFlt-1 to PLGF ratio is higher than in normal pregnancy.</p> <p>Indicated for short-term prediction of PE within the next 7 days in women with suspected PE and is intended to be used in conjunction with other clinical information.</p> <p>Results dependent on different assays, used with varying affinity for different PLGF isomers (PLGF 1-4).</p> <p>The timing of results may vary. Once the test is on the analyzer can take between 15-45 minutes. However, can be more than 24 hours depending on the laboratory.</p>	<p><b>Laboratory assays:</b></p> <p>Elecsys immunoassay sFlt-1/PLGF ratio (Roche Diagnostics). Indicated for short-term prediction of PE (24 -36+6 weeks) where a ratio &lt; 38 rules out PE for the next 7 days and ratio &gt; 38 rules in PE within next 4 weeks. Other cut offs for different weeks' gestation.</p> <p>DELFIAXpress PLGF 1-2-3 test / DELFIAXpress sFlt-1 kit (PerkinElmer). Used standalone or together for ratio test.</p> <p>BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor (ThermoFisher Scientific). Used standalone or together for ratio test. Indicated to confirm/preclude PE &gt; 20 weeks' gestation. Ratio &gt; 85 is suggestive of PE.</p> <p>Atellica IM Analyzer for sFlt-1 and PLGF. The Atellica IM PLGF assay is used in combination with the Atellica® IM sFlt-1 assay to determine the sFlt-1/PLGF ratio.</p>

**Table 4.2:** Blood-based biomarkers and candidate biomarkers, including products adapted to LMICs (continued)

Blood biomarker	Description	Available product details
<b>Glycosylated fibronectin (GlyFn)</b>	<p>GlyFn levels are elevated in PE.</p> <p>Indicated for use in suspected PE between 13 to 37 weeks' gestation.</p> <p>May have improved sensitivity and specificity compared to standard care.</p>	<p><b>Adapted to low-resource contexts:</b></p> <p>Lumella GlyFn POC test (Diabetomics Inc. USA). Whole blood (finger prick). Requires test cartridge and reader. Test results displayed in 10 minutes. Price understood to be in the range of affordability for LMICs (£50 per unit).</p> <p>Tests have long shelf life (&gt; 2 years).</p> <p>Can be stored and test run at room temperature.</p> <p>Validated in a LMIC setting for PE diagnosis and may be a useful adjunctive tool for early identification, appropriate triage and improved outcomes.<sup>68</sup></p>
<b>Pregnancy Associated Plasma Protein A (PAPP-A)</b>	<p>PAPP-A is suppressed in PE when measured in the first trimester.</p> <p>Considered a less robust indicator of PE than PlGF alone. Inferior to PlGF when used in first trimester screening.<sup>69</sup></p>	<p><b>Laboratory assays:</b></p> <p>DELFI and AutoDELFI PAPP-A Kits (PerkinElmer, Revvity).</p>
<b>Investigational biomarkers for screening</b>		
<b><i>Cis</i> P-tau<sup>70</sup></b>	<p><i>Cis</i> P-tau identified as circulating etiological driver and its stereo-specific antibody is valuable for early PE diagnosis and treatment.</p> <p>Antibody treatment (mAb) to <i>Cis</i> P-tau is already in clinical trials for its role in pre-clinical Alzheimer's and after vascular or traumatic brain injury.</p>	No products yet identified.

## Blood pressure measurement devices and software

The WHO recommends that every pregnant woman should have their BP checked at each ANC contact, immediately after childbirth and six hours later, followed by daily BP for five days and then regularly until six weeks postpartum. All BP devices used in ANC and maternity units should be validated for use in pregnant women. The 2020 WHO technical specifications for BP measuring devices (i.e., semi-automated/automated non-invasive devices with an upper arm cuff) provide guidance for governments, manufacturers, health care organizations and other stakeholders on implementing recommendations to ensure accurate BP measurement and to make informed decisions about procuring BP devices.<sup>71</sup> This is critical as current estimates suggest that 75–80% of automated BP devices marketed globally (around 3,500 unique models) for non-pregnant populations lack evidence of being adequately clinically validated for accuracy.<sup>72,73</sup>

The International Organization of Standards (ISO) specifies the requirements and methods for the clinical investigation of equipment used for the intermittent non-invasive automated estimation of arterial BP using a cuff. The British and Irish Hypertension Society and American Medical Association also work to maintain lists of validated BP measurement devices.<sup>74</sup> A 2019 study supported by RHSC found very little regulation or national policy guidance on procurement of BP devices in India, Mexico and Uganda.<sup>75,76</sup> This lack of regulation highlights the need for more robust policies to ensure the use of accurate and reliable BP devices in maternal health care settings.

**Stride BP** is a joint initiative of the European Society of Hypertension, the International Society of Hypertension, and the World Hypertension League, which provides a list of validated devices for BP measurement including in pregnancy/PE. The Stride BP Validated Devices Lists include only BP measuring devices adequately validated and approved by the Stride BP Scientific Advisory Board, making them recommended for clinical use.<sup>77</sup> In May 2024, according to Stride BP, there were three validated upper arm-devices available on the market for clinical-based measurement: the Dinamap ProCare 400, the Microlife VSA (BP3GP1-1L), and the Welch Allen Vital Signs. Additionally, several other devices are validated for home use or non-clinician use. These and other BP devices and innovative software are listed below.

- **Dinamap ProCare 400:** An automated oscillometric device designed for bedside patient monitoring. The Dinamap ProCare 400 provides non-invasive measurement of systolic BP, diastolic BP, mean arterial pressure, pulse rate, temperature and oxygen saturation. The BP measurement technology used in this device has been validated in two clinical studies involving pregnancy populations, adhering

to recognized standard protocols, and is published in peer-reviewed publications.<sup>78,79</sup>

- **Microlife VSA (BP3GP1-1L)** An automated oscillometric device with manual inflation that also includes a Shock Index. The Microlife WatchBP Home A, WatchBP Home BT, and WatchBP Home S are also validated by STRIDE BP, are capable of detecting atrial fibrillation, and have features such as automated duplicate or more measurements, automated storage of multiple readings and PC connectivity.
- **Welch Allen Vital Signs:** An automated oscillometric device. This is a digital mobile BP measurement device which can be mounted on a model stand or attached to wall for use in a clinical setting. The cost is approximately US\$600 or above.
- **Omron devices:** Several Omron devices validated by STRIDE BP are available for home use, providing simple and quick BP and pulse rate. Features include automated oscillometrics, with validated cuff sizes (22-42 cm), automated duplicate or more measurements, automated storage of multiple readings, and some with Smartphone Bluetooth connectivity. The **Omron HEM-SOLAR** uses solar energy to recharge. The cost is about US\$30.
- **Microlife 3AS1-2/ CRADLE vital sign alert (VSA):** Not available on the open market, this handheld, upper arm, semi-automated BP device has been successfully validated for use in both non-pregnant pregnant and pregnant populations, including those with PE. It is designed for easy use by untrained workers, featuring a traffic light system to alert health workers to abnormal results. The device costs US\$19 and meets WHO requirements for automated BP devices suitable low-resource settings.<sup>80</sup> It has received positive feedback from diverse health care cadres, including in motivating women to attend pregnancy care, although some users have reported technical difficulties in charging the device.<sup>81</sup> The CRADLE VSA continues to be used in research trials and large-scale implementation, and is currently used in more than 15 LMICs, including a national rollout in Sierra Leone.<sup>82,83</sup> The ongoing CRADLE-5 trial in Sierra Leone will determine whether ‘real-world’ scale-up of the CRADLE VSA device combined with a focused education package can be sustainably adopted and reduce maternal and fetal mortality and severe maternal adverse outcomes.<sup>84</sup> The CRADLE device is also being used within the PEARLS aspirin trials.
- **LifeSource One-Step Monitor:** This device measures BP accurately with automatic inflation and rechargeable batteries. Priced higher than other POC BP monitors at

US\$174–178, the LifeSource One-Step Monitor still needs to be evaluated in pregnant populations.

### Investigational software for BP measurement

- **OptiBP** is a Smart Phone application (runs on Android OS 8.1) designed to record BP. It operates by using image data generated from volumetric blood flow changes detected as light passes through the fingertip. The smart phone camera records photoplethysmographic (PPG) optical pulse waves, which are derived from blood volume changes in the

fingertips. Studies have validated BP measurements taken with OptiBP against standard BP cuffs in both pregnant and non-pregnant populations. In its current format, the OptiBP algorithm requires a one-time baseline BP measurement obtained from a traditional cuff for calibration. After this initial calibration, the app can estimate blood pressure. Study results are promising,<sup>85,86</sup> however, further research is required with different populations and to determine how the app can be incorporated within existing maternal health care settings. A feasibility study in Indonesia suggests that self-monitoring of BP to be feasible and acceptable to women with hypertension and their clinicians.<sup>87</sup>

## Key barriers

**Device availability in the ANC clinic and provider competencies:** BP is one of the most important indicators for assessing the risk of PE, yet many women attending antenatal or postnatal care do not always have their BP measured. The appropriate BP device may be missing or broken, or in use elsewhere in the facility. Health workers may also not be trained to accurately measure and interpret BP.

**Need for validation for use in pregnant populations:** It is crucial that BP devices used in health care settings are validated for use in PE, and failure to do so can lead to under- or overestimate BP readings. Although it is recommended that all BP devices used in health facilities should be checked at least annually against a calibrated device, a systematic review examining 28 different BP measurement devices found several ambulatory devices had both major and minor violations of standard validation protocols.<sup>88</sup>

**Weak demand:** insufficient demand for devices validated specifically among pregnant populations is another challenge. Despite initiatives such as the Stride BP Validated Devices Lists, validated devices are not adequately prioritized in procurement.

**Misconceptions related to BP and interventions during pregnancy:** Insights from the OptiBP trial indicate an insufficient understanding of the concept of BP among pregnant women along with misconceptions about the effects of iron and folic acid supplementation on BP. This suggests a need to communicate basic health education to accompany the introduction of OptiBP and improvements in BP monitoring. It also suggests that other innovations in pregnancy care should similarly assess the risk of any unintended consequences.

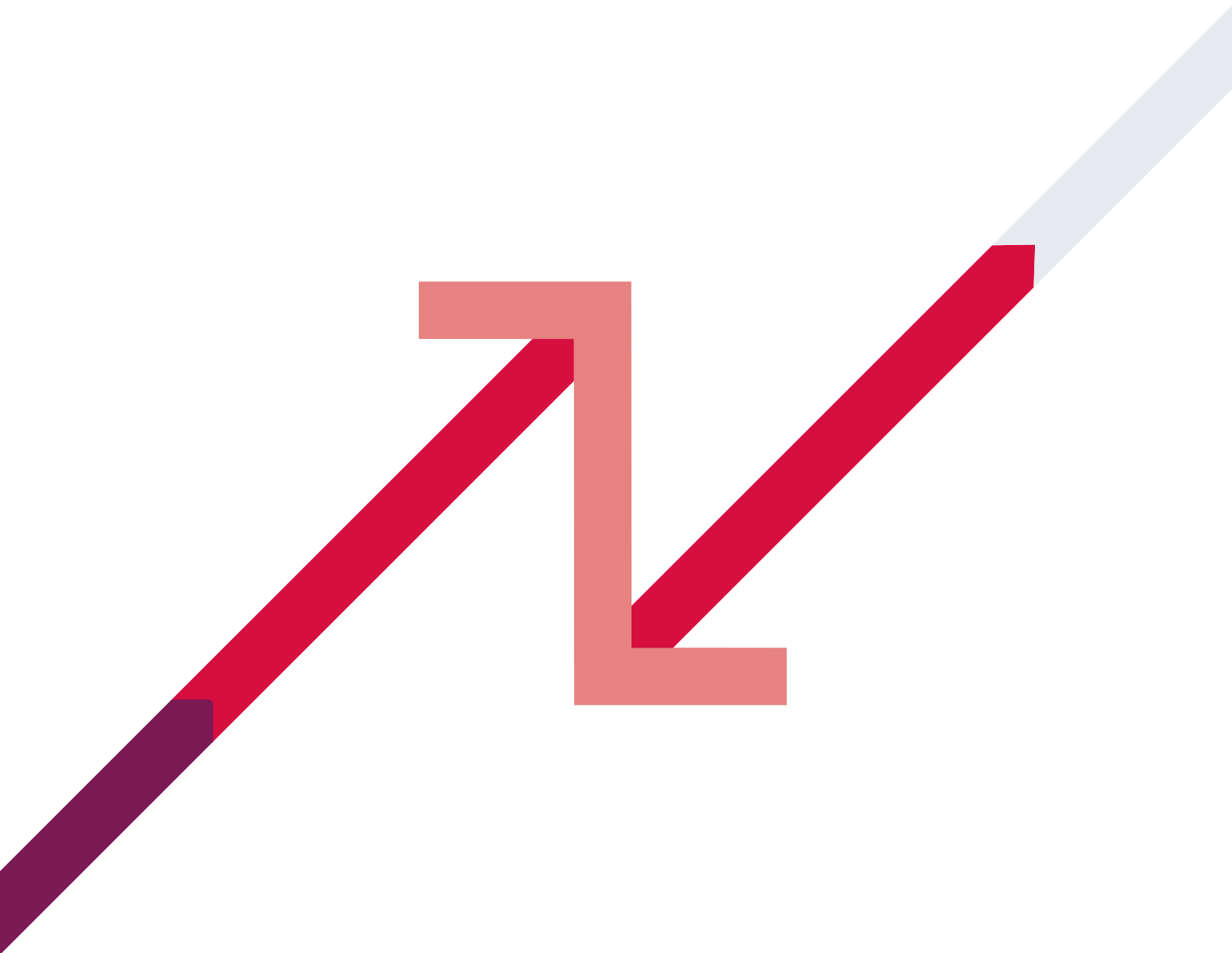
“

**A feasibility study in Indonesia suggests that self-monitoring of BP to be feasible and acceptable to women with hypertension and their clinicians.**

## Diagnostic algorithms and decision-making software

**Clinical support tools, predictive models and algorithms** are increasingly being integrated into routine clinical care to identify pregnancies at high-risk of PE. Several risk assessment tools and predictive applications for PE, as well as diagnostic algorithms, have been validated or are undergoing validation in LMICs.<sup>89</sup> While some user facing digital apps—such as virtual midwife and obstetrician, Bliss4Midwives<sup>90</sup>, and a smart wristwatch for BP monitoring — have only been piloted and not validated, there are examples of more widely used or adapted tools across various settings, detailed in table 4.3. These algorithms and predictive models are often utilized in academic PE trial settings, with some evidence of broader clinical adoption in LMICs.

Diagnostic algorithms are considered superior to a checklist-based system that relies solely on maternal risk factors. For example, according to the Fetal Medicine Foundation (FMF), the UK NICE checklist detects only 30% of all PE cases, and 40% of preterm PE cases, with a 10% screen-positive rate.<sup>90</sup> The FMF developed a first trimester algorithm that combines demographics, medical history, biomarkers and biophysical risk factors to estimate a woman's individual risk of developing PE, achieving a detection rate of up to 90%.<sup>44</sup> The Tommy's App was developed to assess a woman's risk of developing PE. The Preeclampsia Integrated Estimate of Risk (PIERS) risk prediction model was developed with the aim of identifying the risk of fatal or life-threatening complications in women with PE (>20 weeks' gestation). All three examples in table 4.3 have been academically researched though and are not yet widely used.



**Table 4.3:** Examples of key risk assessment and diagnostic algorithms

Algorithm	Description	Use examples
<b>Tommy's National Centre for Maternity Improvement<sup>91</sup></b>	<p>An online clinical decision support tool developed as an app to assess women's risk of developing PE.</p> <p>Uses Mean Arterial Pressure (MAP), PlGF, UPTI, PAPP-A resulting in &gt;90% detection.</p>	<p>The PEARL Trial led by Concept Foundation plan to adapt and use a modified version for risk screening in Ghana, Kenya and South Africa.</p> <p>There will be a validation exercise before the trial starts but likely to include medical history, MAP and measure BP using the CRADLE VSA BP device.</p>
<b>Fetal Medicine Foundation (FMF) Screening tool for women in their first trimester<sup>44</sup> to calculate PE risk</b>	<p>The FMF combined screening identifies up to 90% of women with preterm PE &lt;37 weeks, and 41% of women with term PE ≥37 weeks, with a 10% screen-positive rate.</p> <p>Uses a combination of demographics (e.g., age, weight), medical history (e.g., chronic hypertension, previous PE), biomarkers (PlGF/sFlt-1), and biophysical (BP, uterine artery Doppler) risk factors to estimate a woman's individual risk of developing PE.</p>	<p>Adopted by FIGO.</p> <p>Efficacy as a first-trimester screening algorithm for PE was established in the ASPRE multi center RCT<sup>92</sup>. This combined maternal history, MAP, uterine artery pulsatility index (UA-PI), maternal serum PAPP-A and PlGF.</p>
<b>The PIERS risk prediction model (Preeclampsia Integrated Estimate of Risk Score)</b>	<p>The PIERS model is used later in pregnancy as a diagnostic tool for women at increased risk of adverse outcomes up to 7 days before complications arise. This allows for timely adjustments in care, clinical trial design, and biomedical investigations related to PE.</p> <p>Assesses maternal signs/symptoms and laboratory findings to generate a valid and reliable algorithm for predicting maternal and perinatal outcomes in women with PE.</p>	<p>Awaiting new analysis from King's College London.</p>
<b>Investigational algorithms</b>		
<b>M-PREG diagnostic tool (MirZyme)</b>	<p>Small scale clinical results reported to provide PE diagnosis with &gt;90% specificity and sensitivity.</p> <p>Based on biomarkers alone.</p> <p>Cloud-based.</p>	<p>Patented. MirZyme has in its pipeline a series of patented products that have proven effective in a range of preclinical and clinical studies.</p>



## Point of care ultrasound

WHO recommends a single ultrasound scan before 24 weeks of pregnancy to estimate gestational age (GA), improve detection of fetal anomalies and multiple pregnancies, reduce the need for induction of labor due to post-term pregnancy, and enhance a woman's pregnancy experience.<sup>47,93</sup> Assessing GA is also crucial for assessing risk of PE and determining the appropriate course of action for the mother and fetus. Fetal Doppler ultrasound is commonly used to examine the fetal and uterine blood vessels and to predict the likelihood of developing PE. It is performed during the 10–12-week mark for high-risk pregnancies. Between 31- and 40-weeks' gestation, ultrasound is used to analyze risks of IUGR in the fetus.

Point of care ultrasound (POCUS) products are typically small, handheld wireless ultrasound probes that connect into a smartphone or tablet for real-time imaging and connectivity. POCUS has become increasingly popular in LMICs due to its affordability, user-friendliness, adaptability to challenging health system contexts and acceptable to women and their families and health care workers.<sup>94</sup>

A recent landscape assessment identified several available POCUS costing under US\$10,000 (table 4.4).<sup>95</sup> Three of these devices are also available on a subscription basis. Of the 14 POCUS devices identified, ten employ convex probes, commonly used for obstetrics due to the width of the field of view; three use linear probes, which may also be useful for

non-obstetric applications, and one device uses a dual probe (convex and linear). The ability of these devices to calculate gestational age is indicated.

POCUS technology is being enhanced with **artificial intelligence (AI)-enabled software** to support less experienced health care workers to perform accurate ultrasound scans. The AI-enabled software is designed to obtain GA from videos of the fetal head, automatically measuring the fetal trans-cerebellar diameter and head circumference. AI-assistance can be device agnostic, offering increased potential for scalability. The Bill & Melinda Gates Foundation is a key funder in the development of POCUS and AI technology.

One AI firm is Intelligent Ultrasound, which has developed the ScanNav FetalCheck software to support lower-skilled users to measure GA with minimal training. The software can be paired with a variety of ultrasound machines. The use of AI-POCUS will be validated as part of the PEARLS Trial on the use of low-dose aspirin to prevent PE in Kenya, Ghana and South Africa. The Butterfly iQ Ultrasound System is a handheld, whole-body single-probe portable ultrasound system designed for use by trained health-care professionals. It was recently listed in the WHO compendium of innovative health technologies for low resource settings 2024.<sup>96</sup> A WHO TPP on obstetric ultrasound is forthcoming in 2024 to guide further developments in this field.

“

**POCUS has become increasingly popular in LMICs due to its affordability, user-friendliness, adaptability to challenging health system contexts and acceptable to women and their families and health care workers.**

**Table 4.4:** Low-cost point of care ultrasound (POCUS) devices

Device	Probe type	Calculation of GA	Certification	Cost (US\$)
<b>Butterfly iQ+</b>	Linear	Yes	FDA/CE	Device: \$2,399 Subscription: \$199–420/year
<b>Philips Lumify C5-2</b>	Convex	Yes	FDA/CE	Device: \$7,000–10,000 Subscription: \$2,388/year
<b>Clarias C3 HD</b>	Convex	Yes	FDA/CE	Device: \$4,900
<b>GE Vscan Extend</b>	Convex	No	FDA/CE	Device: \$4,995
<b>GE Vscan Air</b>	Convex & Linear	No	FDA/CE	Device: \$4,495
<b>Konted C10T</b>	Convex	Yes	No FDA	Device: \$800–1,400
<b>Konted Gen4</b>	Convex	Yes	No FDA	Device: \$700–1,800
<b>Biim 12-4</b>	Linear	No	FDA/CE	Device: \$5,000
<b>Vave</b>	Linear	No	FDA	Device: \$1,795 Subscription: \$1,188/year
<b>SonoQue C3</b>	Convex	Yes	FDA/CE	Device: \$1,350
<b>Healcerion Sonon300C</b>	Convex	Yes	FDA	Device: \$2,995
<b>Telemed MicrUS Pro-C60S</b>	Convex	No	No FDA	Device: \$4,000–4,700
<b>ALT Cerbero</b>	Convex	Yes	No FDA	Not available
<b>Healson U20C</b>	Convex	Yes	No FDA	Not available

## Key barriers

**Affordability:** Cost is a key barrier to the use of POCUS, with many devices having been introduced in research settings to determine their performance in real-world settings and generate evidence for wider use, including cost-effectiveness. Out-of-pocket costs are barriers to patients, as health services commonly charge for ultrasound.

**Integration in health systems, including provider training:** There is a need to train health care workers/ technicians in ultrasound, practice, quality assurance and referral guidelines including strong capacity to triage and manage complications safely and appropriately.<sup>97</sup> AI-enabled POCUS may offer potential to mitigate a lack of ultrasound technicians in LMICs to support scalability. Ensuring equipment maintenance capability and budgeting for ongoing costs is critical for sustainability of POCUS introduction and scale.

## 4.2 Prevention medicines and dietary supplements

This section describes the limited prevention products available for women identified as being at risk of developing PE later in pregnancy, as well as investigational prevention candidates. The WHO standard of care for women identified as being at moderate or high risk of PE includes prophylaxis with low-dose aspirin (75 mg daily) from around 16 weeks’

gestation until delivery. WHO also recommends daily calcium supplementation for pregnant women in populations with low dietary calcium intake to reduce the risk of PE. These preventive measures should be provided alongside regular BP monitoring and information on PE symptoms, including guidance on when to seek care.

## Medicines

**Low-dose aspirin.** WHO recommends low-dose aspirin be provided daily to women between 11-14 weeks’ and 36 weeks’ gestation to prevent preterm PE, and preterm birth induced fetal growth restriction and shorten the length of stay of the newborn in neonatal intensive care units. A 2019 Cochrane review provided high-certainty evidence that low-dose aspirin reduced the risk of small-for-gestational age infants in pregnant women with or at risk of PE, compared to placebo.<sup>98</sup> Low-dose aspirin is considered safe when used between 12-36 weeks in pregnancy and is a widely available and affordable oral medication, costing between US\$0.01 and US\$0.28 per tablet.

The recommended dose of aspirin for PE prevention varies across different guidelines from WHO and professional organizations, ranging from 75 to 162 mg daily. The optimum dose of low-dose aspirin has not yet reached consensus, and there are ongoing questions whether higher and more efficacious doses might increase risk of obstetric hemorrhage. A new randomized trial, PEARLS (Preventing Pre-eclampsia: Evaluating AspiRin Low-dose Regimens Following Risk Screening) is being conducted in Ghana, Kenya and South Africa to compare the effects of 75 mg and 150 mg daily aspirin. Results from the formative research are expected in early 2025, and results from the main trial are expected in early 2027.

## Key barriers

**Delayed identification of women at risk:** The primary challenge to preventive therapy with low-dose aspirin is identifying women early enough in pregnancy to maximize its benefits. In settings where ANC commences after 20 weeks' gestation (which is common in LMICs), WHO still advises low-dose aspirin to be initiated as soon as ANC starts but acknowledges that most of the supporting evidence-base comes from trials in high-income countries where low-dose aspirin was started at 12 weeks' gestation.

**Varied formulations available:** Availability of low-dose aspirin in ANC clinics can be highly variable. While various dosages of low-dose aspirin are widely available in public and private sectors, access to the appropriate dosage can be inconsistent. In some cases, higher dose tablets (e.g., 500mg) need to be broken up into smaller doses, which can complicate dosing accuracy.

## Dietary supplements

A maternal diet rich in vegetables, fruit, whole grains, fish and shellfish and monounsaturated oils, are essential for a healthy pregnancy. While micronutrients play a significant role in placental endothelial function, oxidative stress and expression of angiogenic factors, there is insufficient data to support the routine supplementation of vitamins C, E D for the prevention or treatment of PE. Further research is recommended in this area.<sup>99</sup>

**Calcium supplementation** is recommended by WHO for pregnant women in populations with low dietary calcium intake to reduce risk of PE.<sup>100</sup> The suggested daily dose is 1500-2000mg elemental calcium, divided into three doses, at an estimated cost of US\$11.50 per pregnancy. Although there is no clear evidence on the timing of initiation of calcium supplementation, WHO advises that women commence supplementation at the first ANC contact to improve adherence to the regimen.<sup>101</sup>

A recent publication describes two independent, individually randomized, parallel-group, double-blind, noninferiority trials where low-dose calcium supplementation (500 mg) was compared with high-dose calcium supplementation (1500mg) in nulliparous pregnant women in India and Tanzania.<sup>102</sup> These trials found low-dose calcium supplementation was non-inferior to a high dose of calcium supplementation with respect to the risk of PE and preterm birth in populations with low calcium dietary intake. Despite the evidence supporting safety and effectiveness, calcium supplementation is still rarely integrated into routine ANC.

One alternative for low dietary calcium intake populations would be to legislate fortification of staple foods with calcium, as has been done in the UK. This approach could benefit the entire population and increase the likelihood of reaching most pregnant people. Consistent messaging by providers about benefits and risks of calcium, coupled with efforts to encourage early ANC could improve uptake in populations with low calcium intake.<sup>101</sup>

## Key barriers

**Inclusion of calcium in national guidelines:** In a global survey of 31 countries on HDP prevention, 65% of countries reported including calcium supplementation during pregnancy within national guidelines, and 71% reported inclusion in public pre-service and in-service training.<sup>103</sup> However, the conditional recommendation focused on low dietary intake of calcium can be confusing for decision makers. Moreover, the definition of low dietary intake is not universal. Additionally, health system challenges arise as calcium supplementation often falls under nutrition departments not health, leading to potential coordination and accountability gaps.

**Supply value chain:** Calcium supplements are bulky, which create perceived challenges in manufacturing and supply chain distribution.

**Demand and adherence:** Women describe limited knowledge about calcium supplements and PE. Reported user challenges of calcium supplementation include side effects, working schedules, being away from home and already taking other supplements.

## Investigational candidates for prevention of PE

Several investigational medicines and dietary supplements for prevention of PE have been identified. The large-scale impact of these products is still unknown, and results are

unlikely in the foreseeable future. High- and medium-priority candidates, as identified by the AIM Project and this landscape, are listed in table 4.5.

**Table 4.5:** High- and medium-priority candidates for prevention of PE

Candidate	Evidence / trial status	Next research steps / priority level (if available)
<b>Vaginal progesterone</b>	A systematic review and metanalysis of 11 RCTs evaluating 11,640 women found that vaginal progesterone started in the first trimester reduced the risk of any HDP by 29%, and PE by 39%, compared to a placebo. <sup>104</sup>	Further trials are suggested, including i) to assess long-term safety of in-utero exposure to progesterone, and ii) whether low-dose aspirin or progesterone, or both, are effective in reducing HDP (including PE) and preterm birth.
<b>Esomeprazol</b>	Phase III	AIM high priority.  Phase II placebo-controlled trial ongoing (ESPRESSO trial involves 7 hospitals in Australia, 500 women at risk of PE taking 40mg daily from 16 weeks'). Anticipated trial outcomes in 2025-26.
<b>L-Arginine</b>	Phase III	AIM high priority. Ideally identify opportunities to commence trial in 1-3 LMICs.
<b>Chloroquine/ Hydroxychloroquine</b>	Phase II	AIM high priority. Waiting for ongoing trial outcomes. Phase II trial currently recruiting.
<b>Metformin (also, candidate for PE treatment)</b>	Phase II	AIM high priority. Waiting for ongoing trial outcomes.
<b>Probiotic Lactobacilli</b>	Phase III	Deprioritized as evidence for efficacy not strong
<b>Vitamin D</b>	Phase III  Women with low Vitamin D are at increased risk of PE.	Need to revisit evidence base. Some are concerned about the quality of some small studies having heterogenous populations. One of the four studies in the Cochrane review has since been retracted.
<b>Omega-3 Fatty acids</b>	Phase III	Evidence base needs to be revisited.
<b>Daltaparin</b>	Phase III	Deprioritize. Requires self-injection which may reduce priority compared to other oral therapies.
<b>Selenium</b>	Phase II	No promising trial evidence.

### 4.3 Therapeutics, including candidate repurposed medicines

This section covers the following: i) **anti-hypertensives**, which are used to manage high BP in pregnant women to prevent serious consequences, including progression to severe hypertension, PE/E, stroke, and other complications that can negatively affect the fetus and newborn; ii) **Magnesium sulfate (MgSO<sub>4</sub>)**, which is administered to women with severe PE to prevent eclampsia, and is the first line treatment for eclamptic seizure, and; iii) **repurposed medicines** which are drugs indicated for other conditions that show potential in treating HPD and/or PE/E.

#### Anti-hypertensive medicines used in pregnancy and postpartum

Hypertension in pregnancy is defined as BP measuring  $\geq 140/90$  mmHg, based on the average of at least two measurements taken at least 15 minutes apart, using the same arm. Severe hypertension is defined as BP reading  $> 160/110$  mmHg. Undetected hypertension in pregnant and postpartum women can result in severe maternal complications, making timely access to antihypertensives critical for adequately controlling BP and preventing stroke.

WHO recommends that every health facility should have antihypertensive drugs available in the antenatal, labor, and maternity units. Four antihypertensive drugs are safe for use in pregnant women and effective in lowering the risk of developing severe hypertension<sup>105</sup> and include **oral Nifedipine, Methyldopa, and Labetalol**, as well as **intravenous Labetalol, and intravenous Hydralazine**.

However, the WHO Essential Medicines List (EML) 2023 includes only methyldopa and hydralazine as antihypertensives, and lists nifedipine as a tocolytic to be used for treatment for preterm birth prevention rather than the management of severe hypertension in pregnancy (table 4.6). This contradicts WHO and other professional bodies, such as ACOG, SGO, FIGO, ISSHP, which recommend the use of nifedipine for treatment of severe hypertension in pregnancy. Furthermore, although nifedipine immediate-release tablets are recommended for the treatment of severe hypertension in pregnancy, slow-release tablets are often the only form available, complicating treatment.<sup>106,107</sup>

Labetalol, which is not listed on the WHO EML, and not licensed in any South American countries,<sup>106,108</sup> is the preferred first choice in

most obstetric societies. Methyldopa, nifedipine and labetalol are considered viable initial options for treating severe hypertension in low-resource settings, though their availability varies; for instance, nifedipine and methyldopa may be available in rural areas and labetalol in urban areas. However, some pharmaceutical companies have stopped producing nifedipine and methyldopa, making them difficult to find in some countries.

Clinical considerations for selecting an antihypertensive include assessing contraindications, such as poorly controlled asthma, which labetalol may exacerbate. Methyldopa is associated with an increased risk of postpartum depression. Although labetalol may also decrease proteinuria, PE and fetal/newborn death, its use is also linked with hypoglycemia in newborns.<sup>108</sup>

A recent meta review (2022) aimed at identifying the most effective antihypertensives found that all commonly prescribed antihypertensives decrease the incidence of severe hypertension compared with placebo or no therapy. The review indicated labetalol may also reduce proteinuria/PE and fetal/newborn death.<sup>108</sup> The authors concluded that new trials to demonstrate the efficacy of other antihypertensives for preventing severe hypertension during pregnancy would require prohibitively large sample sizes. As a result, it is unlikely that additional antihypertensives will be repurposed for use during pregnancy in the near to medium term.

#### Postpartum anti-hypertensives

Two additional drugs, **Amlodipine and Enalapril**, are commonly used for women in the extended postpartum period and are included on WHO EML (refer to Table 4.6). Monitoring of BP in the first two weeks after birth is important, as postpartum PE is most likely to occur 7-10 days after birth.<sup>109</sup> Moreover, close follow-up of women who experienced PE in pregnancy is essential. In one study all types of HDP—chronic hypertension, gestational hypertension and preeclampsia—demonstrated abnormal BP requiring antihypertensive medicines up to 42 days postpartum. Many women will continue to experience hypertension one year after birth, highlighting the need for consistent follow-up and management throughout their lives.<sup>21,109</sup>

**Table 4.6** Antihypertensive medicines used to control hypertension in pregnant and postpartum women

Medicine	WHO formulation and indication	Typically, available formulation	Treatment guideline
<b>Alpha Methyldopa (Centrally acting <math>\alpha</math>2-adrenergic agonist)</b>	250mg tablet for acute management of severe hypertension in pregnancy only.	250mg and 500mg tablets	750mg oral with a repeat dose after 3h until BP goal achieved. Max dose: 3g in 24 hours.
<b>Nifedipine (Calcium channel blocker)</b>	Immediate release capsule 10 mg for anti-oxytotic (tocolytics).	5mg and 10mg immediate release (capsule), 10mg, 20mg and 30mg modified.  Release (retard tablet) and 20mg or 30mg extended release (XR) formulations.	5-10mg immediate-release capsule oral with a repeat dose after 30 minutes if response is inadequate until BP goal achieved.  Max dose in acute treatment setting: 30mg.
<b>Labetalol (<math>\beta</math>-blockers)</b>	Not listed.	200mg tablet and ampoule	Oral: 200mg. Repeat dose after 1 hour until BP goal achieved. Max dose: 1200mg in 24 hours.  IV: 10mg IV and, if the response is inadequate after 10 mins, then 20mg IV.  Max total dose: 300 mg.
<b>Hydralazine (Direct vasodilator)</b>	Powder for injection; 20mg (hydrochloride) in 2mL ampoule for acute management of severe hypertension in pregnancy only.	Ampoule	5mg-10mg by slow IV injection repeated after 20-30 minutes until BP goal achieved. Repeat hourly as needed or give 12.5mg IM every two hours as needed.  Max dose: 20mg in 24 hours.
<b>Amlodipine (Calcium channel blocker)</b>		Tablet: 5mg (as maleate, mesylate or besylate).	10 mgs /day orally.
<b>Enalapril (Ace inhibitor)</b>		Oral liquid: 1 mg/mL (as hydrogen maleate).  Tablet: 2.5 mg; 5 mg; 10 mg (as hydrogen maleate).	10 mgs /day orally

## Magnesium sulfate

Decades after the discovery of magnesium sulfate ( $\text{MgSO}_4$ ) to prevent and treat eclampsia, no new drugs have been developed for treatment of PE and eclamptic seizures. Advancement in screening tools and early identification of women at risk of PE offers opportunity to appropriately manage risk earlier, potentially leading to improved outcomes for both woman and baby. This could also reduce the need for  $\text{MgSO}_4$ .

Magnesium sulfate is inexpensive, heat stable (between 0-30 degrees Celsius), and has a shelf life between 24 to 36 months. It has been proven globally as an effective first line prophylaxis and treatment for eclampsia. It is also recommended for fetal protection against neurological complications when administered to women at risk of preterm birth before 32 weeks' gestation to prevent cerebral palsy in the baby.<sup>110</sup>

$\text{MgSO}_4$  is formulated as an injection with a concentration of 500mg/mL, available in 2mL and 10 mL ampoules.  $\text{MgSO}_4$  is administered via intramuscular and or intravenous routes to manage severe PE/E.  $\text{MgSO}_4$  must be diluted to a solution of less than 20%. Common diluents are 5% glucose solution and 0.9% sodium chloride solution. To create a 20% solution, 10 mL of  $\text{MgSO}_4$  is diluted with 15 mL of diluent. When administering  $\text{MgSO}_4$  intravenously, an infusion pump should be used if available.<sup>111</sup>

Although the pharmacokinetic basis for the optimal dose and concentration of  $\text{MgSO}_4$  has never been clearly established<sup>112</sup>, there are currently two regimes for administering  $\text{MgSO}_4$ : the Pritchard and Zuspan regimens. A review of 28 studies investigating the pharmacokinetic properties of  $\text{MgSO}_4$  found that “the minimum effective serum magnesium concentration for eclampsia prophylaxis is lower than the generally accepted therapeutic level.”<sup>112</sup> Additionally, a study in Nigeria demonstrated that the Pritchard regimen is effective in achieving therapeutic serum magnesium levels.<sup>113</sup>

Merck for Mothers is currently supporting WHO to conduct the clinical trial, “Simplified Treatment for Eclampsia Prevention using Magnesium sulfate: A Two-stage, Phase III, Non-Inferiority trial” (The STEP-Mag Trial). Stage 1 of the trial has been completed, including an interim analysis and application of Stop/Go criteria for Stage 2.

- The Pritchard regimen involves two loading doses of 4g of  $\text{MgSO}_4$  administered intravenously over five to ten minutes, immediately followed by an intramuscular dose of 10g, divided into 5g in each buttock. A maintenance dose of 5g intramuscularly is then injected into alternate buttocks every four hours.
- The Zuspan regimen involves a single loading dose of 4g, administered by slow intravenous infusion over five to ten minutes, followed by an hourly maintenance infusion of 1-2g by a controlled infusion pump.

In some LMICs a “modified” Pritchard regimen, or sometimes called the Dhaka regimen, includes a ‘loading dose’ of 10gs intramuscularly, typically administered at a primary health care (PHC) facility. The woman is then referred to a referral hospital for continued monitoring. Studies in Pakistan and India have demonstrated that a single dose of  $\text{MgSO}_4$  can be as effective in preventing eclampsia.<sup>114</sup>

**Maternal toxicity** is rare when  $\text{MgSO}_4$  is administered carefully, with close monitoring of tendon reflexes, respiratory rate, urine output, BP and pulse. In the event of  $\text{MgSO}_4$  toxicity, the antidote is **Calcium Gluconate Injection**: 100 mg/mL in a 10 mL ampoule, administered slowly via IV. This antidote is listed in the WHO EML 2023.

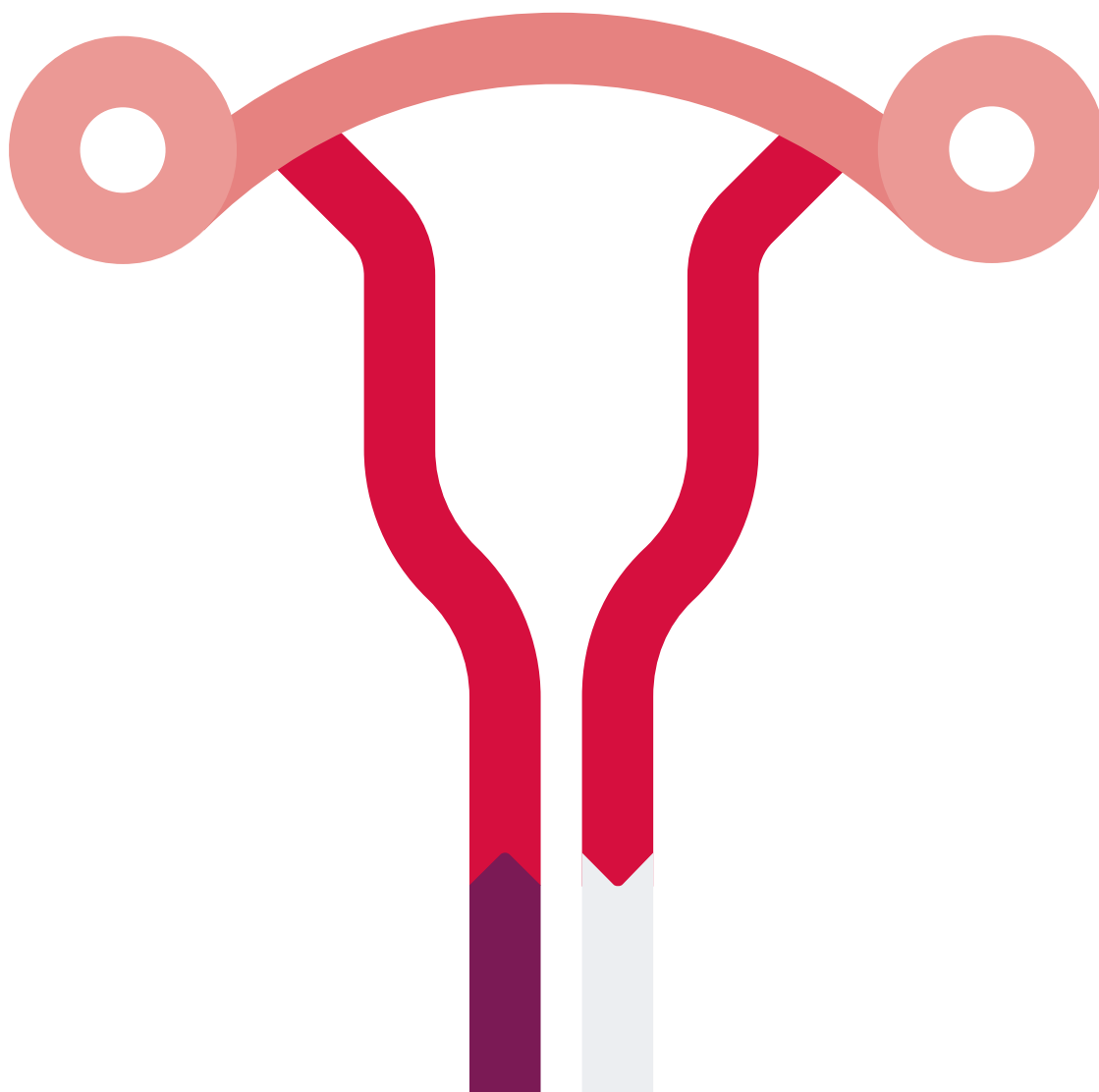
Opportunities to address challenges regarding antihypertensives and  $\text{MgSO}_4$  are shown below (box 4.1) and expanded upon in Section 6.



### Box 4.1: Opportunities for investment in antihypertensives and MgSO<sub>4</sub>

The following potential solutions for PE/E could be taken as part of a comprehensive approach to improve the supply security of key MNH commodities:

- Expand use of anti-hypertensives for maternal health included on EM Lists.
- Improve stock management between central, sub-national and health facility levels to improve availability of essential medicines.
- Strengthen implementation of national guidelines at facility level including skills updates.
- Support procurement of quality medicines. The UNFPA Supplies Matching Fund is an example of a model incentivizing procurement of QA maternal health commodities.
- Expand local manufacturing, with support for QA.



## Key barriers for antihypertensives and MgSO<sub>4</sub>:

- **WHO recommended antihypertensives are not always included on national essential medicines lists (EML).** Or if they are on the National EML list, these medicines have been repurposed for prevention and management of PE/E (Methyldopa and Nifedipine) and the formulation may be different to what is required. WHO EML lists Nifedipine as a tocolytic and not as an antihypertensive, but WHO guidelines recommend Nifedipine as an antihypertensive, potentially creating confusion for countries developing normative guidelines. Labetalol is not listed on the EML.
- A 2022 survey by USAID MOMENTUM of 31 countries reported that MgSO<sub>4</sub> is included in the EML of all surveyed countries, but the four WHO-recommended antihypertensives are in the national EML to a lesser extent: (nifedipine (97% of countries), Methyldopa (81% of countries), Hydralazine (77% of countries) and Labetalol (71% of countries). While either Methyldopa or Nifedipine are effective oral antihypertensives, the apparent lack of IV Hydralazine for reducing severe hypertension rapidly (such as in a woman with severe PE/eclampsia) is concerning.
- **Acute shortages at sub-national level due to supply chain weaknesses, drug expiry/low demand and market availability in some contexts.** Most procurement and supply chain management of PE/E commodities, as with maternal health medicines more generally, is financed and implemented by governments, with need for supply strengthening especially to lower levels of the health system.
  - The USAID MOMENTUM survey found that MgSO<sub>4</sub> was regularly available in 58% of countries in the private sector and 45% of countries in the public sector. MgSO<sub>4</sub> and antihypertensives were more likely to be available at the central level, indicating uncoordinated supply chain and logistics contribute to shortages at lower levels of the health system. Analysis of HDP products in Ghana reported that expiry of MgSO<sub>4</sub> and calcium gluconate due to low demand contributed to stockouts.
  - Market availability of antihypertensives is also variable: Labetalol is not licensed in many South American countries and the extent of local manufacturing of Methyldopa or Nifedipine in LMICs is unclear.
- There is limited information on manufacturing, availability and cost of calcium gluconate, the antidote to MgSO<sub>4</sub>. Considering availability of these products jointly could help reduce health care worker hesitancy around using MgSO<sub>4</sub>.
- Limited data on the availability, cost and affordability of antihypertensive for HDP. Antihypertensives are often not included as part of basic emergency obstetric care.
- **Gaps in health care worker competence and confidence, health system capability, and knowledge translation** were identified as key drivers of poor referral practices for PE/E.<sup>115</sup> Health care workers globally have concerns around the complexity of administering MgSO<sub>4</sub>, which requires providers to identify, calculate and prepare the correct dosage and avoid potential toxicity.
- Variability in local dosage regimens and MgSO<sub>4</sub> formulation available cause confusion. Regular clinical updates, including simulated training through mentoring, would encourage providers to use MgSO<sub>4</sub> more appropriately.

- Many national task-sharing policies do not allow health care workers at PHC level to prescribe antihypertensive, however this is where most women first seek care, and those at risk are first detected.
- In several countries, guidelines recommend the administration of only a loading dose of MgSO<sub>4</sub> administered IM by PHC workers prior to referral which is considered less complicated. However, if the health system capacity is low and essential equipment and supplies are missing, this undermines health care worker's confidence.
- Sometimes MgSO<sub>4</sub> is produced in non-standard concentrations. Often both 25% and 50% (and sometimes 33%) are provided in varying supply batches, creating confusion among health care workers on calculating correct dosage. Although this is now less frequent, it contributes to gaps in health care worker confidence.
- Antihypertensives may only be available in doses to treat NCDs.
- Knowledge translation in the form of dissemination of research and recommendations and consistent use of appropriate policies and clinical guidelines on use of antihypertensives and MgSO<sub>4</sub> is also a gap influencing poor health care worker behaviors in managing PE/E. For example, health care workers may advise women to stop taking antihypertensives due to their belief that once the baby/placenta is born the high BP will go away. Women also stop taking antihypertensives after delivery due to a fear of lifelong dependency (and cost), thereby posing future dangers in poorly controlled BP.
- **Procurement of non-quality-assured MgSO<sub>4</sub>, antihypertensives** and other maternal health medicines more widely is a concern. A survey of the quality of medicines for the United Nations Commission of Life Saving Commodities (UNCoLSC) in 2015 indicated an 11% failure rate for MgSO<sub>4</sub> injection (the highest failure rate was 64% for oxytocin for prevention and management of PPH). A recent systematic review that included the UNCoLSC study among others similarly reported pervasive issues of poor quality across all recommended medicines for PE including MgSO<sub>4</sub> and antihypertensives (nifedipine, methyldopa, enalapril, amlodipine) across several LMICs.<sup>116</sup>
- National procurement of maternal health products may be influenced by several factors, including cost, quality, preference for local manufacturers, or for referring to national regulatory bodies rather than WHO PQ or stringent regulatory authority (SRA). The UNFPA Supplies Match Fund is a model that could provide lessons for incentivizing government procurement of quality assured essential maternal health products.
  - Hypertensives are not generally perceived as essential maternal health medicines among those responsible for procurement.
- **Limited interest among pharmaceuticals to invest in maternal health medicines.** There is limited knowledge and structural investment in LMIC markets that makes it challenging for pharmaceutical companies to bring innovative MH medicines for pregnancy specific conditions into those markets.<sup>117</sup> Medicines such as MgSO<sub>4</sub> are inexpensive and the profit margin low and manufacturing companies have little incentive to make them (discussed further in Section 4.6).

## Repurposed and investigational candidates for treatment of PE

A shortlist of candidate therapies for the treatment of PE has been identified (table 4.7). Among these, two candidates target elevated levels of sFlt-1 and are in various stages of fundraising for clinical trials. The first, CBP-4888 (Comanche Biopharma) is a small interfering RNA (siRNA) that is delivered subcutaneously. The second is MZe786 (MirZyme), an oral active pill that neutralizes sFlt-1. Both manufacturers have

committed to ensuring their products would not be cost prohibitive. Additionally, some studies have reported that pravastatin may have a positive influence on BP and reduce the risk of adverse pregnancy outcomes, although clinical trials are still ongoing.<sup>118</sup> Other candidate therapies identified by the [Accelerating Innovation for Mothers \(AIM\)](#) project include sulfasalazine and metformin (table 4.7).



**Table 4.7:** High and medium priority candidates for treatment of PE

Candidate	Evidence / trial status	Next research steps / priority level (if available)
<b>Investigational siRNA therapeutic (CBP-4888) targeting sFlt-1 (Comanche Biopharma)</b>	<p>CBP-4888 is a fixed-dose combination of two small interfering ribonucleic acid (siRNAs) duplex oligonucleotides targeting soluble fms-like tyrosine kinase-1 (sFlt-1) mRNA isoforms in the placenta.</p> <p>Sub-cutaneous injection.</p> <p>Completed a Phase 1 healthy volunteer study in women of child-bearing age.</p>	<p>Fundraising completed early 2024 for clinical trial.</p> <p>Received US FDA Fast Track Designation for the Treatment of sFlt-1 mediated pre-term preeclampsia. Studies to potentially include a LMIC-context (pending funding).</p>
<b>MZe786 therapeutic (MirZyme)</b>	<p>Oral active pill to neutralize sFlt-1 taken daily from 20 weeks until delivery by women at risk of PE.</p>	<p>Fundraising for clinical trial.</p> <p>Fast tracked for development by the UK Medicines Health and Regulatory Authority. In 2022 awarded the Innovative Licensing and Access Pathway to accelerate the time to market and facilitate patient access.</p>
<b>Metformin (also, a candidate for PE prevention)</b>	<p>Phase II</p>	<p>AIM high priority.</p> <p>Extended-release metformin appears to prolong women's gestation specifically for women with early onset PE.<sup>119</sup></p> <p>Used for controlling diabetes in general population and considered to have potential to prevent both gestational diabetes and pregnancy hypertensive disorders in obese pregnant women.</p> <p>Waiting on ongoing trial outcomes (South Africa).</p>
<b>Sulforaphane</b>	<p>Phase III</p>	<p>Waiting for ongoing trial outcomes. Trial currently underway (Melbourne) of 180 women with early-onset pre-eclampsia, 2 hospitals.</p>
<b>Pravastatin</b>	<p>Phase III</p>	<p>Three trials are still in progress.</p>
<b>Rosuvastatin</b>	<p>Phase II</p>	<p>Waiting for ongoing trial outcomes.</p>
<b>Vitamin B3</b>	<p>Phase II</p>	<p>No promising trial evidence. Trial registered in 2018, but no results published.</p>
<b>Sulfasalazine</b>	<p>Phase I</p>	<p>No promising trial evidence. May be promising, but not highest priority.</p>
<b>Cis P-tau</b>	<p>Monoclonal antibody (mAb) to <i>Cis</i> P-tau is already in clinical trials for its role in pre-clinical Alzheimer's and after vascular or traumatic brain injury.</p>	<p>No information available.</p>

#### 4.4 Evidence-informed practices for screening, prevention and management (including timed delivery)

Evidence from the literature and consultations with subject matter experts indicate most clinical protocols for PE combine HDP screening, PE prevention and clinical management (Figure 4.1). Clinical protocols used in studies in LMIC settings are often simplified from those of national guidelines in high-income countries, tailored to local availability of diagnostics and the need to maximize the efficient use of scarce health resources.

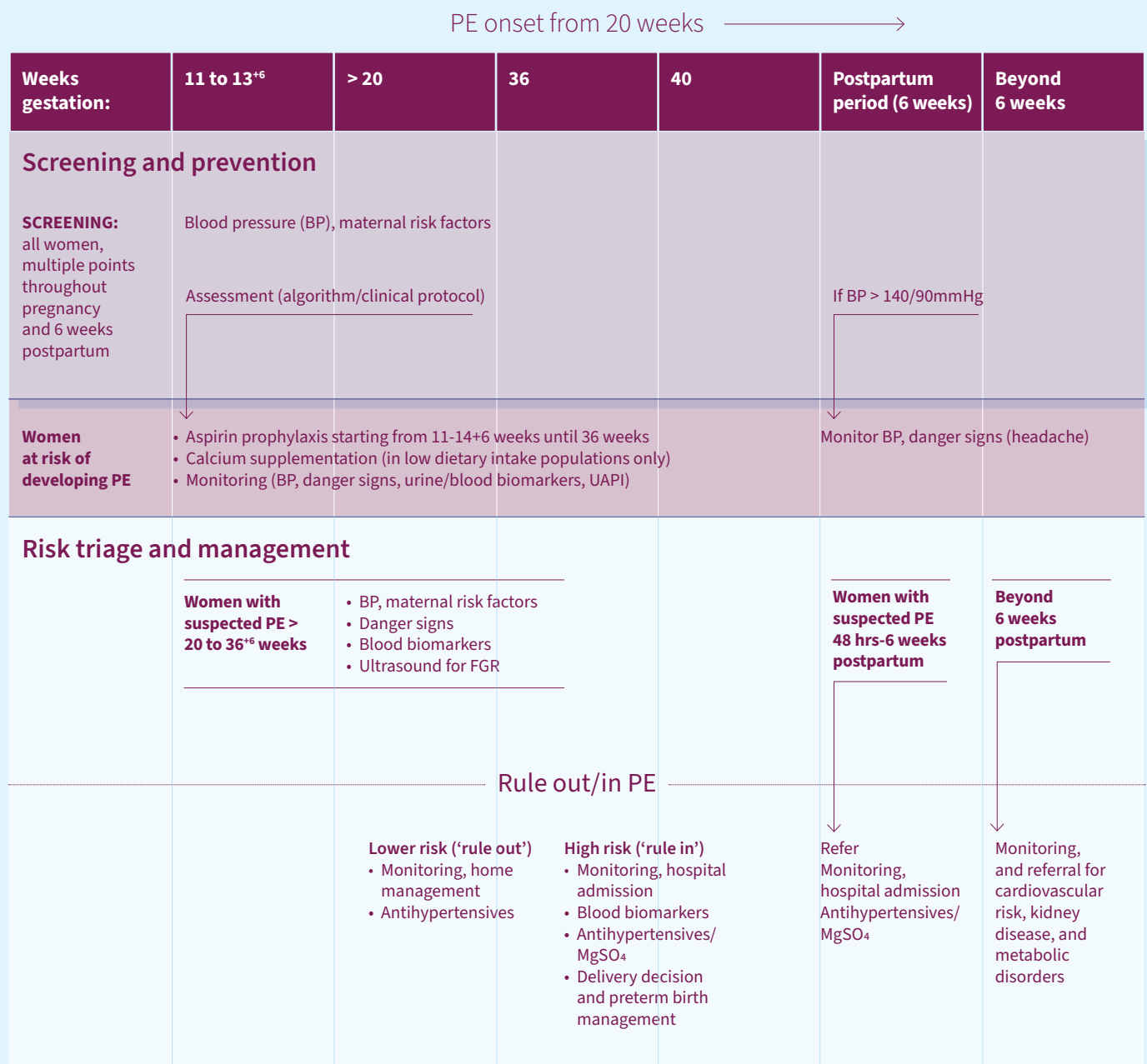
- **Key components for screening** include at a minimum, medical and family history, BP measurement, and, where available, blood-based biomarkers such as PlGF. Women identified as at risk are counseled to start low-dose aspirin prophylaxis and counselled on danger signs of HDP and PE, with ongoing monitoring throughout pregnancy.
- **Risk triage and management** of women with suspected PE beyond 20 week's gestation would ideally take advantage of new blood-based biomarkers to help “rule out” imminent risk of PE.<sup>9,29,66,120</sup> This would enable more effective triage, with only women deemed at risk of PE admitted to hospital, while also allowing for planning for preterm birth (e.g., antenatal corticosteroids for the fetus) within the next two weeks.

It is well recognized that the management of PE/E ultimately revolves around decision-making regarding the timing of delivery to protect both the mother and the newborn. This decision-making process should involve the woman, her family, and the care team, and it acknowledges the importance of ensuring that the woman is treated at a higher, more equipped level of the health care system. WHO recommends expectant management—vigilant observation of the mother and baby, with ongoing assessment and awaiting the spontaneous onset of labor in the absence of complications—between 34–37 weeks' gestation for all women with PE.<sup>120</sup>

For women with PE who do not have an indication for immediate delivery, newer evidence from the CRADLE-4 study in India and Zambia supports initiating delivery (through induction of labor, unless there are contraindications to vaginal birth) between 34<sup>+0</sup> and 36<sup>+6</sup> weeks' gestation for both maternal and perinatal benefit.<sup>19</sup> At study sites across the two countries, this approach resulted in a significant reduction in maternal hypertension and stillbirths compared with usual care (expectant management). It also reduced the length of maternal stay in the hospital.

“

It is well recognized that the management of PE/E ultimately revolves around decision-making regarding the timing of delivery to protect both the mother and the newborn.

**Figure 4.1:** Evidence-informed practices for detection and management of pre-eclampsia

## 4.5 Models to support early and continuous antenatal care for early detection of hypertension, management of pre-eclampsia risk, triage and appropriate referral

This section highlights promising approaches to support the delivery of quality ANC and promoting health-seeking behaviors throughout the continuum from pregnancy to the postnatal period. These approaches facilitate the early identification of pregnant women at risk of HDP and enable timely detection of suspected PE and referral to more advanced levels of care. Innovative service delivery models, including self-care, that encourage early contact

with the health system and provide a positive experience are crucial for improving the uptake of ANC services.

Models and approaches described in this section cover (i) **task sharing among the health care workforce**, and (ii) **primary health care and self-care platforms** including Group antenatal (G-ANC) and postnatal care, networks of care, community health workers, participatory women's groups and self-care interventions.

### Task sharing among the health care workforce

Task shifting and task sharing involve the strategic redistribution of tasks among health workforce teams and personnel to address shortages and improve service delivery. The WHO 2012 recommendations on *Optimizing health worker roles to improve access to key maternal and newborn interventions through task shifting*, describe when and where specific health worker cadres – from community health care workers to physicians – can administer PE/E interventions such as low-dose aspirin for women at high-risk of PE, antihypertensives for severe hypertension in pregnancy, and the loading/maintenance

dose of MgSO<sub>4</sub>.<sup>121</sup> Most LMICs have a robust midwifery workforce, with midwives, including nurses with midwifery skills, serving as primary providers of woman-centered care. Midwives are a critical cadre in the fight against PE/E and a well-trained and well-resourced midwife can promptly diagnose and initiate timely treatment. India has recently started a direct entry midwifery program with first graduates expected in 2024. There is need to optimize the available health workforce to deliver PE/E interventions, supported by appropriate training, skills updates, supervision and commodity supply strengthening.

### Primary health care and self-care platforms

PHC is the cornerstone of any health system aimed at achieving UHC and health-related SDGs. PHC is estimated to provide around 90% of the health services an individual might need during their lifetime. Delivering quality, continuous care requires systematic coordination among service delivery sites, and increasingly is recognized to include community level interventions.

In LMICs, many women receive ANC through a combination of formal and informal networks of health care workers.

This includes community health workers linked to a PHC facility, with clusters of PHC facilities formally linked to a hospital. These networks rely on a functioning referral system, the distribution of essential medicines and supplies, and a competent workforce. Informal networks may involve groups of health care workers communicating through chatbots such as WhatsApp for supportive supervision, mentoring, information and psycho-social support, as well as managing commodity distribution within the network.

## Group antenatal and postnatal care

G-ANC is a rapidly expanding alternative ANC delivery model, with some evidence that G-ANC reduces incidence of preterm birth and improves women's overall ANC experience.<sup>122–125</sup> The Global Group Antenatal Care Collaborative was established in 2016 to coordinate research and learning on G-ANC, aiming to improve ANC delivery and outcomes at-scale in LMICs. The collaboration recognizes that G-ANC concepts must be adapted to local contexts and priorities to ensure ownership, sustainability and scalability.<sup>123</sup>

The key components of G-ANC include clinical assessment and care for all routine ANC services, participatory and

facilitated learning and peer support. Findings from Kenya and Nigeria suggest women participating in G-ANC were more likely to give birth in a facility, receive quality ANC and attend a higher frequency of ANC visits.<sup>125</sup> Ongoing research is exploring whether G-ANC results in earlier entry into care for women. Health care workers have also expressed appreciation for the opportunity to provide more holistic woman-centered care. Further research is ongoing on the perspectives of health care workers with respect to workload, task shifting and the structural changes needed to support the sustainability of G-ANC as much of the evidence come from pilot feasibility settings.<sup>126</sup> G-ANC aligns well with



the self-care movement, fostering partnership between pregnant women and the health system, especially for those starting care in the first trimester. Extending G-ANC into

the postnatal period could also ensure women continue to monitor their BP after birth and receive support with their newborns.

## Networks of care

The Networks of Care (NOC) approach is a health system strategy designed to enhance the quality and continuity of care, ultimately improving outcomes for MNH. NOCs focus on building connections between people and services and strengthening the functional aspects of health systems. They can be found in both the public and private sectors and can include collaboration among doctors and nurses at the same

hospital, between facilities at different levels of care, and from the home to the hospital. The [Network for Improving Quality of Care for Maternal, Newborn and Child Health](#) has four strategic objectives: leadership, action, learning and accountability. This initiative is led by WHO, UNICEF and UNFPA who are supporting over 10 countries in collaboration with other partners.

## Community health workers

Evidence suggests that focusing solely on community-level interventions for HDP without enhancing health facilities is unlikely to yield significant improvements in maternal and perinatal outcomes. The Community-Level Interventions for pre-eclampsia (CLIP) Trials demonstrated CHWs were able to reach thousands of women at home and record their BP and test urine for protein, however the trial did not have a sizeable impact on HDP outcomes. In a meta-analysis of the three

countries involved in the CLIP Trial – Mozambique, Pakistan, and India– involving 60,000 pregnancies, only 1% of women were eligible for methyldopa for HDP, 1% were treated with a loading dose of MgSO<sub>4</sub> and only 6% were referred for emergency obstetric care.<sup>83</sup> The trials indicated that while community-level interventions addressing HDP can be successfully implemented, at least eight antenatal care contacts were required to improve maternal and perinatal health.

## Participatory women's groups

Women's self-help groups and/or support groups have long been recognized as key platforms for disseminating health information and providing peer support, encouraging healthy behaviors during pregnancy including early and routine ANC attendance and advice to women at risk of pregnancy complications. Evidence from some rural settings has shown that pregnant women involved in women-led participatory groups are more likely to seek ANC, access institutional delivery, have trained birth attendance and practice hygienic care – with community health workers playing a key role in

improving health system access.<sup>127–129</sup> The pathways to improved health outcomes through these groups are complex, and may involve creation of an “enabling environment” that empowers women to be informed about services and access quality care. WHO's 2014 guidance,<sup>130</sup> recommends the use of facilitated participatory learning and action cycles with women's groups to improve MNH, particularly in rural settings with low access to health services. WHO emphasizes that any intervention aimed at increasing access to health services should be paired with strategies to enhance the quality of those services.

## Self-care interventions

The WHO defines self-care as “the ability of individuals, families, and communities to promote health, prevent disease, maintain health and cope with illness and disability with or without the support of a health care worker.”<sup>131</sup> Self-care interventions promote choice, self-efficacy and autonomy and can empower pregnant women with the information needed to make informed decisions on where and when to seek health care during pregnancy and childbirth.<sup>132</sup>

Self-care interventions for PE/E include home-based BP monitoring, which is routinely practiced in high-income settings. In 2013, WHO recommended its use for appropriate patients where affordability is not a barrier.<sup>133</sup> Although the current cost of BP devices can be prohibitive, decentralizing BP measurement closer to the community could be a feasible solution, and smartphone applications would be game changing in this regard. Evidence from Indonesia on women's

use of the Opti-BP device suggests that self-monitoring of BP is both feasible and acceptable to women with hypertension and their clinicians.<sup>87</sup> In future, low-cost screening tests using urine or blood biomarkers could be made available to

women deemed at high risk of PE, either distributed through the health care system or self-purchased. These tools would enable earlier identification of PE onset, and further empower women with information about their health.

## 4.6 Market information for equitable access to pre-eclampsia / eclampsia commodities

There is limited information on the market size for maternal health products, particularly for PE in LMICs. The following analyses use MgSO<sub>4</sub> as a tracer to analyze the market for PE/E commodities.

### Available market size information for eclampsia products

Earlier work by RHSC estimated that the market size for MgSO<sub>4</sub> in sub-Saharan Africa (SSA) ranges from 361,000 to 1 million cases annually - based on the assumption that 1% to 2.8% of all pregnancies result in severe PE and eclampsia.<sup>134</sup> Adjusting for current population and fertility levels, this estimate increases to between 400,000 and 1.14 million cases of severe PE and eclampsia annually in SSA.

Analysis supported by RHSC on the demand for maternal health products in six countries in SSA found that South Africa was the only country with easily accessible and collated government tender award data. Since South Africa sources all its MgSO<sub>4</sub> locally, these data may provide the closest estimate of national demand, though they should be interpreted cautiously. Based on government procurement data, annual demand for MgSO<sub>4</sub> (50% injection, 2 ml) in South Africa was estimated at 2,284,576 units of the 2 ml product. In contrast, procurement information from the other countries in the sample was found to be incomplete or unreliable due to various caveats.

Demand for PE diagnostics is expected to grow, particularly with the availability of new blood-based tests. This growth is anticipated to be largest in high-income countries, where affordability is less of a barrier and ANC is more accessible. Depending on the outcome of studies integrating blood-based biomarker screening into clinical algorithms, it is possible that some women suspected of having PE, but testing below the action threshold, may require a repeated biomarker test several weeks later (if presenting with new symptoms), which would increase the number of tests required. Resource constraints underscore the need for robust evidence to guide inclusion of these new diagnostics into clinical algorithms.

### Supply security, including regional manufacturing in sub-Saharan Africa

In SSA, where the burden of PE/E is highest, the supply of MgSO<sub>4</sub> appears to be dominated by a few international manufacturers, underscoring the risks associated with a lack of supply diversification for MgSO<sub>4</sub>. However, there is a small but potentially growing number of local manufacturing firms

which could offer opportunities for increasing supply security in the region.

A market landscape of maternal health commodities in eight countries in SSA identified the MgSO<sub>4</sub> market is currently supplied primarily by one manufacturer from the United Kingdom, one from China and two from India.<sup>135</sup> The number of MgSO<sub>4</sub> products registered with the NMRAs varies significantly: South Africa, Tanzania and Zimbabwe each have only one registered manufacturer, while Ethiopia has ten registered brands. Notably, South Africa sources all its MgSO<sub>4</sub> domestically.

In the African context, MgSO<sub>4</sub> has been identified as a priority product for pooled procurement by regional economic communities such as SADC as well as the African Continental Free Trade Area (AfCFTA)-anchored Pharmaceutical Initiative (Pharma Initiative) pilot pooled procurement mechanism. This initiative, which began as a pilot pooled procurement mechanism, has now transitioned to the African Pooled Procurement Mechanism (APPM) under the Africa CDC. The pilot's initial focus was on Sexual, Reproductive, Maternal, Neonatal and Child Health (SRMNCH) to showcase a proof of concept in ten African countries: Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Mauritius, Rwanda, Seychelles and Sudan. The pilot initiative developed a dashboard to track the product pricing by country, including country vendor pricing the total cost by volume and the different procurement channels.

Another valuable resource for PE commodities is the **USAID Global Health Supply Chain - Procurement and Supply Management project (GHSP-PSM)** which has developed a manual for Procurement & Supply of Quality-Assured Maternal Newborn and Child Health (MNCH) Commodities.<sup>111</sup> The manual is divided into three modules: **Module I** describes general QA for procurement as per WHO's Model Quality Assurance System.<sup>(107)</sup> **Module II** sets out an approach to assuring the quality of MNCH products that resource-limited procurement agencies may implement when assessing products for prequalification and procurement. **Module III** provides useful technical information on priority MNCH products, including the PE medicines MgSO<sub>4</sub>, methyldopa and hydralazine. Module III is particularly valuable for national government procurement agencies, as it provides essential technical specifications for each product. It also includes examples of available

WHO PQ and SRA-approved products, along with details such as marketing authorization holder, manufacturing site registration number, packaging and presentation, shelf life and storage conditions.<sup>111</sup>

## Regional manufacturing in Africa

The expansion of local manufacturing of health products, particularly in the African region, has been identified as a priority for enhancing global health security, increasing sustainable access to affordable health solutions and providing tailored solutions for regional needs. This would also contribute to the achievement of climate targets by reducing carbon emissions in the supply chain. This section provides a brief overview of available information on regional manufacturing of MgSO<sub>4</sub> in SSA and local production of QA products, along with estimates of market size.

An analysis conducted by United States Pharmacopeia (USP) and funded by RHSC identified that regional production of MgSO<sub>4</sub> in SSA is currently led by four manufacturers: Humanwell Pharma in Ethiopia, Laboratory and Allied Health in Kenya, Juhel in Nigeria and Adcock Ingram in South Africa.<sup>135</sup>

Two of these manufacturers are actively pursuing the WHO PQ process. There are also indications that local manufacturing for MgSO<sub>4</sub> is expanding: a second manufacturer in Kenya has submitted a dossier to the Kenyan Pharmacy and Poisons Board (PPB), and three others in Ghana and Nigeria are planning to begin MgSO<sub>4</sub> production.

Insufficient demand data in the SSA region makes it challenging to compare manufacturing capacity to national or regional demand. The majority of MgSO<sub>4</sub> and antihypertensives are financed domestically, and all four local MgSO<sub>4</sub> manufacturers identified in SSA in USP's analysis sell exclusively to the public health system. Consequently, the MgSO<sub>4</sub> market, and local manufacturing capacity, are highly dependent on government demand. The absence of a regional manufacturer with WHO PQ status currently limits

procurement by UN agencies, though this could change should any of the African manufacturers successfully obtain WHO PQ. USAID's Global Health Supply Chain Program recommends that medicines not yet on WHO PQ, such as hydralazine and methyldopa, should try to meet other recognized pharmacopeia specifications such as those of the International Pharmacopeia, European Pharmacopeia, and US Pharmacopeia, depending on the procurement agency's quality assurance policy.<sup>111</sup>

None of the manufacturers surveyed by USP reported supplying their products to other countries in the region, even though they hold NMRA authorization for other products in their portfolio in these countries. The median plant utilization rate was 40%, indicating untapped potential to increase production capacity. For MgSO<sub>4</sub> and other maternal health commodities, the key factors limiting output are **access to affordable financing and competition from imports**.

Additional barriers to expanding sales to neighboring countries include the unpredictability of country regulatory frameworks, registration delays, transportation infrastructure and absence of a regional procurement mechanism.

Opportunities identified by partners to strengthen African manufacturing of maternal health products include:

- **Strengthening the regulatory environment:** including ensuring NMRAs are maintained and have accurate records of licensed products and supporting regional harmonization of regulatory processes. Such efforts will encourage manufacturers to expand their markets.
- **Investing in coordination and technical support for regional manufacturing:** including through strategically diversifying the manufacturing footprint across the region and strengthening capacity, such as providing support for obtaining WHO PQ.
- **Increasing the share of procurement from local manufacturers and strengthening market intelligence:** including exploring tools such as volume guarantees to build confidence in the market, as well as increasing transparency in procurement to facilitate accurate demand forecasting.

# 5. Cross-cutting access barriers to addressing pre-eclampsia and eclampsia

Access barriers relevant to PE/E in high-burden countries share commonalities with other maternal and newborn complications, many of which overlap with those identified in the Global PPH Roadmap.<sup>41</sup> These include: social inequities that limit access to quality care, as well as challenges related to women's rights and social status, gaps in national policy and leadership, procurement and supply chain weaknesses and issues related to health care workers.

These cross-cutting barriers are summarized in Table 5.1 across five dimensions of market health: (i) innovation and availability; (ii) quality; (iii) affordability; (iv) demand and adoption and (v) supply and delivery and expanded upon further below.

**Table 5.1:** Cross-cutting access barriers for pre-eclampsia and eclampsia prevention and management

Innovation and availability	Quality	Affordability	Supply and delivery	Demand and adoption
Low profit incentive for investing in maternal health products	BP devices in use are not validated for pregnancy and poorly maintained	Most PE/E products procured by governments who face competing budget demands and declining donor funds. Even low-cost PE/E products can be unfunded	Procurement and supply management weaknesses lead to acute shortages of PE/E commodities at sub-national level	Late first ANC visit (~25 weeks) hinders early detection of PE, initiation of prevention, and GA assessment
Higher cost and complexity of maternal health R&D	MgSO <sub>4</sub> often expired due to low use (24-36 mo. shelf life)	High cost of BP devices, newer PE biomarker diagnostics, and ultrasound	Key devices for diagnosis often not available at ANC (e.g., BP devices, urine protein dipstick, ultrasound)	Providers do not always measure BP during ANC or associate clinical signs with PE
Low donor investment in maternal health R&D	Evidence of low-quality medicines: aspirin, calcium supplement, antihypertensives and MgSO <sub>4</sub> procured by public health system	Out-of-pocket and lost wages are a barrier to ANC, referral, hospital care/tests for women with suspected PE	Out-of-date EMLs do not include WHO recommended low dose aspirin, calcium supplementation or antihypertensives	Lack of skilled providers in: <ul style="list-style-type: none"> <li>• Accurate BP measurement, preventive measures, (low dose aspirin, calcium);</li> <li>• Management of PE;</li> <li>• Use of antihypertensives</li> <li>• Administration of MgSO<sub>4</sub>, with hesitancy to use MgSO<sub>4</sub> due to concerns of overdose</li> </ul>
Only a few products developed in the last decade are being adapted to LMICs	Local manufacturing of MgSO <sub>4</sub> in Africa does not have WHO PQ/SRA		Laboratory facilities not equipped for confirmatory PE tests	Lack of task-sharing policies
Incomplete understanding of the etiology of PE/E	Weak regulatory systems and capacity of national regulatory authorities		Limited tracking of use of PE medicines and coverage	Referral network weaknesses for maternal care

**Innovation and availability.** One major factor slowing MNH progress globally, is the under investment in R&D, resulting in limited innovation in products to predict, prevent and treat PE/E. Analysis by Policy Cures Research's G-FINDER project, which tracks investment in global health R&D by governments, non-profits, foundations and industry, found that basic R&D totaled US\$101 million from 2018 to 2021, of which US\$20.7 million was in 2021.<sup>40</sup> Basic research funding has remained relatively constant and represents nearly three-fifths of total R&D funding, whilst funding for diagnostics declined over

2020-21. The AIM project identified several barriers to R&D investment, including the perceived lower profitability of maternal health products, additional costs and regulatory requirements for involving pregnant women in research and associated liability concerns, along with fragmented LMIC markets.<sup>136</sup> The more recent introduction of biomarker assays (e.g., PIGF, sFlt-1 and GlyFn) in high-income countries is a promising development, though few companies are investing in adapting this technology for LMIC contexts.

“

**We need new medicines (and devices and diagnostics) for preventing and treating pre-eclampsia, preterm labor and birth, and impaired fetal growth urgently... If we start investing now, we may have potential solutions in 10–15 years.**

AIM Project (R&D Blueprint for Accelerating Innovation for Mothers)

**Quality assured medicines and tools.** Ensuring quality assured medicines and BP devices validated for use in pregnancy is a priority. Quality BP devices tailored to low-resource settings (e.g., Cradle VSA) need to be more widely available and replace less accurate devices that have not been validated, are not robust, require continuous electricity to function, or are harder for lower skilled health care workers to interpret. A recent systematic review of medicines for HDP led by Monash Institute identified widespread issues of poor quality across all recommended medicines used to prevent or treat HDP and PE. These quality concerns have implications for the effectiveness and safety of these products and can influence health care worker decisions to use these medicines.<sup>116</sup> There are four manufacturers of MgSO<sub>4</sub> based in SSA, and none have WHO PQ or SRA approval, although two are reportedly pursuing WHO PQ. The recent development of the four TPPs are however a useful resource.

**Affordability.** Most products and devices needed for prevention, detection and management of PE are procured by governments who face competing budget pressures, often resulting in stock outs at health facilities and ANC clinics. In this context, newer PE diagnostics and ultrasound are particularly unaffordable for most LMIC health budgets. Women and households also bear a high cost for accessing health services, including routine ANC, seeking higher level care for suspected PE, and hospitalization for severe PE where timed birth through labor induction is required.

**Supply and delivery.** A recent WHO-commissioned survey on maternal health commodities obtained responses from 130 stakeholders across WHO regions on the availability and barriers to PE/E medicines, devices and diagnostics. Respondents cited **costs, uncoordinated supply chain, logistical challenges and limited health care workers with adequate skills and training as key barriers for use of PE/E products.** BP monitoring is a cornerstone of screening and management of HDP and PE. While every ANC clinic should be equipped with a BP measurement device, they are often missing or broken, in use elsewhere in the facility. Scarce supplies can result in providers trying to “stretch” urine proteinuria test strips by cutting them into multiple strips. Across 31 countries surveyed by the USAID MOMENTUM project, MgSO<sub>4</sub> was only regularly available in 58% of countries in the private sector and 45% of countries in the public sector. Products may also not be available in the required dosage for use in pregnancy or PE management.

This includes low-dose aspirin, which are frequently available in larger doses than the 75-150 mg recommended and need to be broken up for daily use.

**Demand and adoption.** Alarming, women with PE/E describe multiple contacts with the health system before receiving the necessary life-saving care.<sup>137</sup> BP measurement can be skipped entirely in busy clinics and data from the recent CRADLE-4 study on PE in Zambia and India found women did not have quantitative assessment of proteinuria performed.<sup>19</sup> Further, although pregnant women who are at a high-risk of developing PE risk can receive preventive care, in many LMICs the mean gestational age for the first ANC contact is 25 weeks – well beyond when preventive management is recommended to start. In settings where ANC is started later than 20 weeks in pregnancy, WHO still advises low-dose aspirin is initiated as soon as ANC starts but notes that most of the evidence-base is from trials that initiated low-dose aspirin at 12 weeks’ gestation.<sup>98</sup> A systematic review suggested that low-dose aspirin would still have benefit if initiated prior to 16 weeks. Late ANC also makes gestational age assessment more challenging, which informs PE clinical care for both mother and baby (e.g., timed delivery, corticosteroids for where there is a likelihood of preterm birth). Uptake of calcium supplementation is also inconsistent even in populations with low dietary calcium intake.

Analysis of PE/E services in five LMICs reported the following demand and adoption-related challenges in PE/E identification and management: poor knowledge and skills amongst health care workers, including early detection at the PHC level, along with health systems-related gaps (e.g., lack of task sharing policy, weak referral policies, lack of access and use of antihypertensives and lack of postpartum monitoring).<sup>138</sup> Magnesium sulfate, while effective, requires providers to prepare the dose from a 50% solution which can be challenging to calculate, with hesitation due to concerns of overdose (although rare). Revising national guidelines and clinical protocols can help health care workers on how to approach pregnant women and identify potential risk factors before serious complications occur.<sup>139</sup> Several country programs have attempted to task share through training mid-level and community-based workers in detecting hypertension and initiating treatment (as per clinical protocols). Obtaining buy-in for task sharing among national professional associations has proven important in these settings.

## 6. Potential opportunities

This section highlights several opportunities to accelerate the identification and management of PE and HDP. A key priority is aligning stakeholders on the gaps and opportunities in PE/E, with the goal of establishing a common agenda for late-stage products, approaches and service delivery interventions tailored to different LMIC contexts. This could be achieved through convening both maternal *and* newborn health stakeholders, in recognition of the impact of PE/E on both maternal and perinatal morbidity and mortality. The agenda could also consider the broader consequences of HDP and PE/E, including preterm birth, fetal growth restriction and stillbirths. Such an initiative could build on the current PPH Roadmap to align and coordinate partners and promote monitoring and accountability to drive progress.

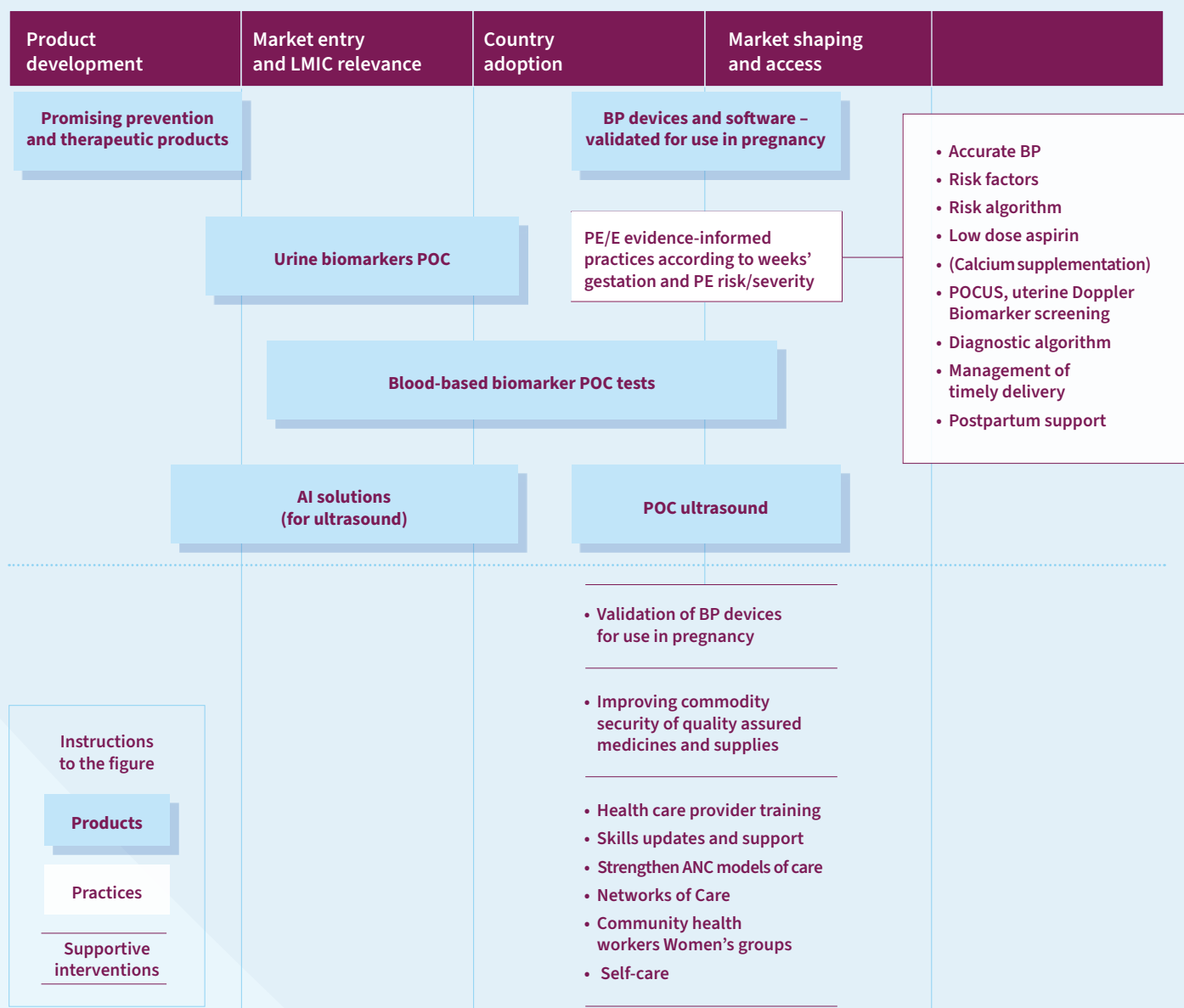
Though this landscape report identifies a growing number of opportunities to improve the prevention, detection and management of PE/E, there is an equally pressing need to build demand for investment in maternal health R&D and for the implementation of promising solutions. This is essential to ensure a viable market for future preventive and therapeutic products. The process of developing this landscape has identified several priorities that could serve as a starting point for a common agenda

for PE/E. These priorities are informed by the evidence-base and expert opinion on key opportunities to accelerate global progress on PE/E. While these priorities are not exhaustive and are presented for consideration rather than as a commitment to funding, they are intended to offer guidance for strategic focus. Opportunities are organized according to prevention, management, and crosscutting priorities (box 6.1), and by their position along the value chain for products/ solutions (figure 6.1).



**Box 6.1:** Preventive, management and cross-cutting opportunities for addressing pre-eclampsia and eclampsia

Identification of PE risk and preventive interventions during ANC (from 11 weeks and at each ANC contact)	Management of women with suspected PE (from 20-36 <sup>+6</sup> weeks)	Cross-cutting needs
<ul style="list-style-type: none"> <li>• Priority interventions and products include validated BP devices/software, low-dose aspirin and calcium supplementation for women at risk, POC ultrasound (at least once before 24 weeks' gestation) and uterine artery Doppler where available.</li> <li>• Capacity strengthening of health care workers to screen for maternal risk, including clinical signs and familial history and accurate BP measurement.</li> <li>• Efforts are required to raise awareness among health care workers and communities about ANC benefits, especially starting in the first trimester, while addressing cultural and health system barriers limiting access.</li> <li>• Models to facilitate early and repeat ANC contact such as G-ANC and participatory women's groups should be explored, as well as supporting women's agency over their access to health services, including through self-care innovations.</li> </ul>	<ul style="list-style-type: none"> <li>• New blood-based biomarkers offer significant opportunity to improve triage of women with suspected PE and guide clinical decisions on management and timing of delivery to improve outcomes for a woman and her baby. These interventions build on the evidence-based preventive practices above.</li> <li>• Diagnostic algorithms adapted for low-resource contexts can integrate these biomarkers, along with other factors, to support evidence-based clinical decisions.</li> <li>• There are several promising preventive and treatment therapies in the pipeline, as well as urine-based biomarker tests that could add value for different use cases.</li> </ul>	<ul style="list-style-type: none"> <li>• Advocacy around promotion of underutilized commodities, technologies and medicines for prevention and treatment, including existing products: aspirin, calcium supplementation, antihypertensives, MgSO<sub>4</sub>.</li> <li>• Utilization of TPPs to guide product R&amp;D, alongside greater investment in maternal health R&amp;D for priority conditions like HDP and investment to scale solutions tailored for LMICs.</li> <li>• Health system strengthening, including for laboratories, procurement and supply chain management, along with increased collaboration to reinforce health systems investments are critical for sustainability.</li> <li>• Development of postnatal follow up strategies to reduce long term morbidity. These could include POC tests, enabling community-based and more accessible support.</li> </ul>

**Figure 6.1:** Opportunities to advance pre-eclampsia and eclampsia – focused on low-resource settings

## Product development

### **Accelerate development of promising preventive and treatment therapies, relevant and affordable for LMICs**

Preventive and therapeutic products aimed at improving the management of women at risk of PE or treating PE are estimated to be at least 2-5 years away, with a small number of investigational candidates currently undergoing clinical trials. Two patent holders, Comanche and MirZyme, are developing therapies which target elevated sFlt-1 and have indicated that these products would be made accessible in high-burden contexts. The AIM project and WHO have developed TPPs for prevention and treatment of PE, in accordance with WHO's procedures. These TPPs serve as benchmarks

against which late-stage candidates can be assessed and prioritized.

For promising candidates, there is a need to accelerate the generation of evidence in LMIC-settings so that trials are not solely conducted in high-income settings, which could delay access where products are most needed. Although new products are several years away, a clear roadmap for supporting access in LMICs could be developed. This roadmap would identify actions that each stakeholder can take according to their comparative advantage and should include considerations for pricing in LMICs, recognizing the diversity of countries in this category and varying levels of health spending.

## Market entry and low- and middle-income country relevance

### **Accelerate access to blood-based biomarker assays (e.g., PlGF and sFlt-1) which are affordable for LMICs, ideally point of care**

The most promising advancement for screening and triaging women with suspected PE is the use of blood-based biomarker testing. Several products have emerging evidence of effectiveness in both high- and low-resource settings. These include the near-POC Quidel PlGF assay, the Ronia POC PlGF assay, the Lepzi POC PlGF, and the Lumella POC GlyFn assay. PlGF has been incorporated into the Fetal Medicine Foundation algorithm for high-risk screening. Additionally, there is data suggesting that combining PlGF and GlyFn biomarkers could potentially replace the need for ultrasound Doppler. Prospective studies might investigate this further, particularly as novel POC PlGF and GlyFn tests suitable for LMIC settings have been developed.

Additional blood-based biomarker products are reportedly being assessed with promising results in LMICs. The Quidel product is currently available on the market and has shown emerging real-world evidence in Mozambique. However, its high price point (US\$2,500 per device and \$US23 per test cartridge) poses a barrier to widespread use. The Ronia PlGF assay is also showing promise, although in smaller studies conducted to date.

Combining some PlGF and sFlt-1 assays may have a better performance than using either PlGF, or sFlt-1 assays alone. Although, the current lack of an sFlt-1 assay for low resource contexts, combined with promising results from other blood-

based biomarkers tests suitable for LMICs, suggests there are adequate options to pursue at this time. However, if therapeutics to target elevated sFlt-1 are estimated to be 2-5 years away, there could be significant benefits to having a POC sFlt-1 test available. Such a test could also optimize suitability for treatment, dosage, and repeat courses of therapy, if needed. Currently, all sFlt-1 tests are performed on laboratory analyzers, which limits their applicability in LMIC settings.

Given that PlGF assays have been tested in a limited number of LMIC settings, gaining additional country experience could be invaluable for expanding the evidence base for PlGF screening and understanding the health system requirements in different contexts. This expanded evidence base would also help build demand for PlGF screening. This would also be informed by WHO's planned review of diagnostic guidelines. Research in this area would also contribute to identifying which tests are most suitable for various levels of care and generate evidence to inform their cost-effectiveness.

There are opportunities to support market entry of POC assays by funding country introduction, including local piloting, adapting national guidelines, sensitizing decision-makers, supporting regulatory processes and updating procurement and supply chain management aspects. Market shaping interventions to address the cost of these assays could also be explored in the medium to longer term, such as investigating interventions such as pooled procurement and other strategies to improve access in LMICs.

## Country adoption, market shaping and access

### Accelerate access to validated blood pressure devices and software, and point of care ultrasound

Blood pressure measurement is the mainstay of detecting HDP and PE, as well as monitoring their progression. A significant effort is needed to ensure that validated BP devices, appropriate for low-resource contexts, are made widely available and routinely used for all women during every ANC contact. Low-cost devices, such as the CRADLE VSA, specifically designed for use by lower-skilled workers need to be scaled up. Innovative financing solutions such as ‘matching funds’ initiatives could be used to encourage their purchase by governments, potentially as part of broader national MNH initiatives.

As a supporting intervention, there is a need to produce updated validation data on affordable BP devices currently available in LMIC markets to inform procurement decisions. This should be coupled with efforts to raise awareness among procurement officials about the importance of purchasing validated devices that meet WHO criteria. Supporting health care workers to accurately measure and interpret BP is also needed. Accountability for quality ANC can be strengthened through closer scrutiny of data on the proportion of women who have BP measured during ANC, and this could help reinforce supply-side interventions through influencing health care worker behaviors.

Several lower cost POCUS devices, such as Butterfly iQ+ and Lumify (Philips), have been tested in low-resource settings, and the integration of AI technology validated for use by lower skilled health workers during ANC is on the horizon. There are opportunities to advance POCUS by generating evidence on its effectiveness within clinical care across different settings. Fostering information sharing between stakeholder groups including industry, funders and researchers, could also help advance product development. Most POCUS devices are already designed to be rechargeable, rugged and long lasting, making them climate-friendly solutions.

### Consensus on interventions for identifying and managing hypertensive disorders of pregnancy and pre-eclampsia and eclampsia

Consensus is needed on the minimum interventions in each trimester that can be accommodated during ANC and for managing HDP and PE/E in most settings. These include (Box 6.2):

Additional evidence-based interventions that could be applied in select settings include the use of POCUS and encouraging

early ANC attendance to identify women at risk earlier in their pregnancies. Emerging evidence from Mozambique offers a ‘proof of concept’ for a screening and management strategy that includes initial screening followed by blood-based biomarker testing (PIGF), patient education for high-risk women, a structured clinical algorithm for health care workers and referral and transfer to higher level of care if necessary.

Another area requiring consensus is the optimal timing of delivery for women triaged as ‘high risk’ due to PE. While WHO currently recommends women with PE deliver at 37 weeks’ gestation, PE is a progressive condition and the health of the woman, and her fetus may continue to deteriorate despite management efforts. The findings from the CRADLE 4 study - that delivery from 34 weeks for women with PE reduces hypertension and stillbirths – warrants review and consideration of whether additional studies are needed to refine clinical practice guidelines.

Optimization of immediate postnatal care and longer-term follow up also require consideration, particularly given the strong association identified between PE and cardiovascular disease in recent years. Other NCDs, including kidney and metabolic disease, also require attention to support women’s health over the longer term. Research around pregnancy and hypertension is actively being pursued by several academic institutions.

Effective implementation of these preliminary core components for HDP and PE/E (box 6.1), would need to consider health care and health system management interventions. These interventions are designed to build health care worker confidence and competence in managing women triaged into the ‘high risk’ PE category. This includes decision-making on timed delivery, where modifying health care practices on early delivery can be particularly challenging behaviors to change, even where clinically indicated.

The scoping review underway by WHO to identify convergences and gaps in PE diagnostic guidelines across eleven of the main clinical organizations will inform further priorities in this area. These could include consensus building on global guidelines and recommendations or additional evidence generation needs. There is general agreement across these organizations (FIGO ISSHP NICE, ACOG, SOMANZ etc.) on two key components of the definition of PE as hypertension and proteinuria after 20 weeks’ gestation. Several organizations have updated their guidelines (since 2020) following reviews of the emerging evidence and now include “and/or maternal end organ dysfunction” which is in line with the ICD-11 definition of PE. Most organizations’

**Box 6.2:** Preliminary list of core components for HDP and PE/E

1. Identifying women's risk factors
2. Using a validated BP measurement device at each ANC contact
3. Risk assessment/ first trimester screening algorithm/ clinical decision support tool (e.g., the FMF screening tool, Tommy's App)
4. Ultrasound and uterine doppler
5. Low-dose aspirin for women at high-risk from 12 weeks to 36 weeks, with Calcium supplementation for women with low dietary intake
6. Urine biomarkers for proteinuria > 20 weeks in women with hypertension
7. Blood-based biomarker screening (ideally point-of-care) for women > 20 weeks' presenting with symptoms of PE for triage to the appropriate clinical care pathway
8. Use of a diagnostic algorithm (e.g., the PIERS App)
9. Management of delivery < 37 weeks' gestation for highest risk women, with interventions for the preterm baby
10. Optimize postnatal monitoring and support to women to manage the long-term effects of HPD and PE/E

“

**A significant effort is needed to ensure that validated BP devices, appropriate for low-resource contexts, are made widely available and routinely used for all women during every ANC contact.**

guidelines state that at least two recordings of BP with a validated BP device and proteinuria measurement are required to suspect PE. Guidelines then recommend that clinicians conduct other confirmatory tests and history taking to confirm PE and subsequent management.

There is still no agreement on use of biomarkers, but where organizations do include blood biomarkers in their revised guidelines, these are recommended to strengthen clinical assessment and are not routine on every woman nor as a

standalone test. There are also general discrepancies across guidelines around ultrasound to measure fetal growth restriction, abnormal fetal Doppler and oligohydramnios. Finally, there is a need to improve data on the burden of HDP and PE/E in LMICs, including on postpartum PE. As the burden of HDP is rising, data will help to prioritize the deployment of interventions, track progress, and ensure HDP and PE/E are adequately prioritized by the health system and its financing strategies.

**Supply security for quality-assured pre-eclampsia/ eclampsia medicines and products, including regional manufacturing**

Addressing supply security for quality assured PE medicines and products could be pursued in conjunction with other priority maternal health conditions, such as PPH, and ideally extend to include newborn care commodities. For PE/E, this should encompass MgSO<sub>4</sub> and calcium gluconate, locally recommended antihypertensives, low-dose aspirin, calcium supplements, and potentially antenatal corticosteroids.

There is ongoing work to strengthen local and regional manufacturing of maternal health products in SSA, where the highest burden of preventable maternal deaths occurs. Ensuring that maternal health products are of high quality is of paramount importance as there are pervasive issues of sub-standard medicines across all recommended medicines

for HDP. This contributes to poor patient outcomes and can demotivate health providers from using them.

While none of the current SSA-based manufacturers for MgSO<sub>4</sub> have WHO PQ or SRA approval, two are reportedly pursuing WHO-PQ. Technical support for managing WHO PQ processes has been identified as an area for capacity strengthening. Achieving WHO PQ would also create opportunities for UN and donor procurement from local manufacturers. Harmonizing regulatory processes at the regional level would help unlock new markets for local manufacturers.

At the country level, key opportunities include addressing gaps in EML registration for antihypertensives, strengthening post-market surveillance of product quality and sensitizing key stakeholders involved in the procurement of MH products of the issue of quality (e.g., procurement officials, NMRA staff).



# 7. Conclusion

The stalling progress on maternal health targets within the SDGs signals an urgent need to accelerate access to practices and innovations that address PE/E – one of the leading causes of preventable maternal and perinatal mortality and morbidity. The expanding number and diversity of stakeholders working to address PE/E reflects the high burden of this condition and priority it holds, alongside emerging evidence on solutions to aid in prevention, diagnosis and management.

New developments in diagnostics for PE, particularly those adapted for LMICs, along with evidence on optimal timing of delivery, are poised to become key tools to inform clinical care for PE to optimize outcomes for a woman and her baby. However, effectively leveraging these solutions will require their integration into overstretched health systems. This necessitates the need for evidence on models suited to low-resource settings, improved access to underutilized priority commodities, and a step change in affordable access to product innovations for PE/E and care during pregnancy.

Quality and respectful ANC is the cornerstone of pregnancy care yet too many women do not receive the basic components of ANC – including accurate BP

measurement and thorough history taking – crucial for early identification of PE risk, mitigating progression and detecting danger signs. There remains significant scope to improve women's positive pregnancy, intrapartum and postpartum experience through quality, comprehensive ANC. This will be increasingly critical in settings facing a growing burden of NCDs, including hypertension, kidney disease and cardiovascular disease.

Through integrating solutions for PE/E with broader commitments to improving access, affordability and quality of pregnancy and postpartum care, we can make a substantial impact on the health and wellbeing of both mothers and their babies.

# Key informants

The following stakeholders shared their perspectives to inform this landscape review.

Name	Organization
Agnes Chidanyika	UNFPA Supplies
Allisyn Moran	WHO (MNCAH+A)
Andrew Shennan	Kings College London
Andrew Storey	Clinton Health Access Initiative (CHAI)
Anyada Portela	WHO (MNCAH+A)
Asif Ahmed	MirZyme
Beatriz Manriquez Rocha	Clinton Health Access Initiative
Becky Barney	PATH
Catharine Taylor	Merck for Mothers
Deborah Armbruster	USAID - MCHN/MNH Global Health
Edgardo Abalos	Rosarino Center for Perinatal Studies (CREP)
Emily Gerth-Guyette	PATH
Emily Moore	GestVision Inc
Emma Foster	UNFPA Supplies
Jane Sandall	Kings College London
Jeff Jacobs	Merck for Mothers
Jill Durocher	Gynuity Health Projects
Joshua Vogel	Burnet Institute
Manu Vatish	Bill & Melinda Gates Foundation
Marleen Temmerman	Aga Khan University
A. Metin Gülmezoglu	Concept Foundation
Oluwaseun Aladesanmi	Clinton Health Access Initiative
Özge Tuncalp	WHO (RHR/HRP)
Patricia Coffey	PATH
Peter von Dadelszen	Kings College London
Subhasri Balakrishnan	World Health Organization
Telle Ukonaho	Rewity
Valerie Thomas	Comanche



# References

1. WHO UU et al. Trends in maternal mortality 2000-2020: estimates by WHO, UNICEF, UNFPA, World Bank Group and UNDESA/Population Division. Published online 2023.
2. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: A WHO systematic analysis. *Lancet Glob Health*. 2014;2(6):323-333. doi:10.1016/S2214-109X(14)70227-X
3. Giachini FR, Galaviz-Hernandez C, Damiano AE, et al. Vascular Dysfunction in Mother and Offspring During Preeclampsia: Contributions from Latin-American Countries. *Curr Hypertens Rep*. 2017;19(10):1-22. doi:10.1007/S11906-017-0781-7/METRICS
4. Kassebaum NJ, Barber RM, Bhutta ZA, et al. Global, regional, and national levels of maternal mortality, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*. 2016;388(10053):1775-1812. doi:10.1016/S0140-6736(16)31470-2
5. Fu R, Li Y, Li X, Jiang W. Hypertensive Disorders in Pregnancy: Global Burden From 1990 to 2019, Current Research Hotspots and Emerging Trends. *Curr Probl Cardiol*. 2023;48(12). doi: 10.1016/J.CPCARDIOL.2023.101982
6. WHO. ICD-11 for Mortality and Morbidity Statistics. (2024), Eclampsia in Pregnancy code JA25.0.
7. Magee LA, Brown MA, Hall DR, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens*. 2022; 27:148-169. doi: 10.1016/J.PREGHY.2021.09.008
8. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol*. 2013;170(1):1-7. doi: 10.1016/J.EJOGRB.2013.05.005
9. Poon LC, Magee LA, Verlohren S, et al. A literature review and best practice advice for second and third trimester risk stratification, monitoring, and management of pre-eclampsia: Compiled by the Pregnancy and Non-Communicable Diseases Committee of FIGO (the International Federation of Gynecology and Obstetrics). *Int J Gynaecol Obstet*. 2021; 154 Suppl 1(Suppl 1):3-31. doi: 10.1002/IJGO.13763
10. Abalos E, Cuesta C, Carroli G, et al. pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG*. 2014;121 Suppl 1:14-24. doi:10.1111/1471-0528.12629
11. Ashorn P, Ashorn U, Muthiani Y, et al. Small vulnerable newborns-big potential for impact. *Lancet*. 2023;401(10389):1692-1706. doi: 10.1016/S0140-6736(23)00354-9
12. Kua KL, Rhoads E, Slaven JE, et al. Decreased vascular reactivity associated with increased IL-8 in 6-month-old infants of mothers with pre-eclampsia. *Pediatric Research* 2024. Published online March 20, 2024:1-7. doi:10.1038/s41390-024-03132-4
13. Conti-Ramsden FI, Nathan HL, De Greeff A, et al. Pregnancy-Related Acute Kidney Injury in Preeclampsia: Risk Factors and Renal Outcomes. *Hypertension*. 2019;74(5):1144-1151. doi:10.1161/HYPERTENSIONAHA.119.13089
14. Fox R, Kitt J, Leeson P, Aye CYL, Lewandowski AJ. Preeclampsia: Risk Factors, Diagnosis, Management, and the Cardiovascular Impact on the Offspring. *Journal of Clinical Medicine* 2019, Vol 8, Page 1625. 2019;8(10):1625. doi:10.3390/JCM8101625
15. Ishaku SM, Olanrewaju TO, Browne JL, et al. Prevalence and determinants of chronic kidney disease in women with hypertensive disorders in pregnancy in Nigeria: a cohort study. *BMC Nephrol*. 2021; 22(1): 1-10. doi: 10.1186/S12882-021-02419-6/TABLES/4
16. Ishaku SM, Karima T, Oboirien KA, et al. Metabolic syndrome following hypertensive disorders in pregnancy in a low-resource setting: A cohort study. *Pregnancy Hypertens*. 2021;25:129-135. doi: 10.1016/J.PREGHY.2021.05.018
17. Magee LA, Smith GN, Bloch C, et al. Guideline No. 426: Hypertensive Disorders of Pregnancy: Diagnosis, Prediction, Prevention, and Management. *Journal of Obstetrics and Gynaecology Canada*. 2022;44(5):547-571.e1. doi: 10.1016/J.JOGC.2022.03.002
18. Sibai B, Dekker G, Kupferminc M. pre-eclampsia. *The Lancet*. 2005;365(9461):785-799. doi:10.1016/S0140-6736(05)17987-2
19. Beardmore-Gray A, Vousden N, Silverio SA, et al. Planned early delivery for late preterm pre-eclampsia in a low- and middle-income setting: a feasibility study. *Reprod Health*. 2021;18(1). doi:10.1186/S12978-021-01159-Y
20. Steegers EAP, Von Dadelszen P, Duvekot JJ, Pijnenborg R. pre-eclampsia. *Lancet*. 2010;376(9741):631-644. doi:10.1016/S0140-6736(10)60279-6
21. Hauspurg A, Jeyabalan A. Postpartum preeclampsia or eclampsia: defining its place and management among the hypertensive disorders of pregnancy. *Am J Obstet Gynecol*. 2022;226(2S): S1211-S1221. doi: 10.1016/J.AJOG.2020.10.027
22. Sibai BM. Etiology and management of postpartum hypertension-preeclampsia. *Am J Obstet Gynecol*. 2012;206(6):470-475. doi: 10.1016/j.ajog.2011.09.002
23. John B, Dorairajan G, Chinnakali P, Mondal N. Factors Associated with Perinatal Mortality in Adult Pregnant Women with Hypertensive Disorders: A Case-Control Study. *J Obstet Gynaecol India*. 2023;73(Suppl 1):11-18. doi:10.1007/S13224-023-01782-8
24. Al-Safi Z, Imudia AN, Filetti LC, Hobson DT, Bahado-Singh RO, Awonuga AO. Delayed postpartum preeclampsia and eclampsia: demographics,

- clinical course, and complications. *Obstetrics and gynecology*. 2011;118(5):1102-1107. doi:10.1097/AOG.0B013E318231934C
25. Laine K, Murzakanova G, Sole KB, Pay AD, Heradstveit S, Räisänen S. Prevalence and risk of pre-eclampsia and gestational hypertension in twin pregnancies: a population-based register study. *BMJ Open*. 2019;9(7): e029908. doi:10.1136/BMJOPEN-2019-029908
  26. Khan B, Yar RA, Khakwani A Khan, et al. Preeclampsia Incidence and Its Maternal and Neonatal Outcomes With Associated Risk Factors. *Cureus*. 2022; 14(11). doi: 10.7759/CUREUS.31143
  27. Brown MA, Magee LA, Kenny LC, et al. International Society for the Study of hypertension in pregnancy (ISSHP). The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens*. 2018; 13:291-310. doi: 10.1016/j.preghy.2018.05.004
  28. Hurrell A, Beardmore-Gray A, Duhig K, Webster L, Chappell LC, Shennan AH. Placental growth factor in suspected preterm pre-eclampsia: a review of the evidence and practicalities of implementation. *BJOG*. 2020;127(13):1590-1597. doi:10.1111/1471-0528.16425
  29. NICE. Overview | PLGF-based testing to help diagnose suspected preterm pre-eclampsia | Guidance | NICE. *NICE Guidelines*.
  30. Poursafa P, Keikha M, Kelishadi R. Systematic review on adverse birth outcomes of climate change. *J Res Med Sci*. 2015; 20(4): 397. doi: 10.4103/1735-1995.158283
  31. Mandakh Y, Rittner R, Flanagan E, et al. Maternal Exposure to Ambient Air Pollution and Risk of Preeclampsia: A Population-Based Cohort Study in Scania, Sweden. *International Journal of Environmental Research and Public Health* 2020, Vol 17, Page 1744. 2020;17(5):1744. doi:10.3390/IJERPH17051744
  32. Shankar K, Hwang K, Westcott JL, et al. Associations between ambient temperature and pregnancy outcomes from three south Asian sites of the Global Network Maternal Newborn Health Registry: A retrospective cohort study. *BJOG*. 2023;130(S3):124-133. doi:10.1111/1471-0528.17616
  33. Shashar S, Kloog I, Erez O, et al. Temperature and preeclampsia: Epidemiological evidence that perturbation in maternal heat homeostasis affects pregnancy outcome. *PLoS One*. 2020;15(5). doi: 10.1371/JOURNAL.PONE.0232877
  34. Chersich MF, Pham MD, Areal A, et al. Associations between high temperatures in pregnancy and risk of preterm birth, low birth weight, and stillbirths: systematic review and meta-analysis. *BMJ*. 2020;371. doi:10.1136/BMJ.M3811
  35. Robbins T, Kuhrt K, Vousden N, Seed P, Shennan A. Household air pollution and incidence of eclampsia in eight low- and middle-income countries. *International Journal of Gynaecology and Obstetrics*. 2023;160(2):449. doi:10.1002/IJGO.14484
  36. Pinchoff J, Shamsudduha M, Hossain SMI, Shohag AAM, Warren CE. Spatio-temporal patterns of pre-eclampsia and eclampsia in relation to drinking water salinity at the district level in Bangladesh from 2016 to 2018. *Popul Environ*. 2019;41(2):235-251. doi:10.1007/S11111-019-00331-8/TABLES/2
  37. WHO. Facilitators' guide for conducting national and subnational programme reviews for maternal, newborn, child and adolescent health. 2024. Accessed August 16, 2024. <https://www.who.int/publications/i/item/9789240088900>
  38. Chapman Nick, Doubell Anna., Goldstien Maya, et al. *G-FINDER-Sexual and Reproductive Health Research and Development: Understanding the Spectrum*.; 2020.
  39. McDougall ARA, Hastie R, Goldstein M, et al. Systematic evaluation of the pre-eclampsia drugs, dietary supplements and biologicals pipeline using target product profiles. *BMC Med*. 2022;20(1):1-12. doi:10.1186/S12916-022-02582-Z/TABLES/3
  40. Policy Cures Research. *2023-SRH-Research and Development: Beyond Spillovers*.; 2023.
  41. WHO. *A Roadmap to Combat Postpartum Haemorrhage between 2023 and 2030*.; 2023. Accessed August 16, 2024. <https://www.who.int/publications/i/item/9789240081802>
  42. USAID. *Updated Manual for Procurement and Supply of Quality-Assured Maternal, Newborn and Child Health Commodities | USAID Global Health Supply Chain Program*.; 2022. Accessed August 16, 2024. <https://www.ghsupplychain.org/procurement-and-supply-quality-assured-maternal-newborn-and-child-health-commodities>
  43. Poon LC, McIntyre HD, Hyett JA, da Fonseca EB, Hod M. The first-trimester of pregnancy - A window of opportunity for prediction and prevention of pregnancy complications and future life. *Diabetes Res Clin Pract*. 2018;145:20-30. doi: 10.1016/J.DIABRES.2018.05.002
  44. Tan MY, Syngelaki A, Poon LC, et al. Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol*. 2018;52(2):186-195. doi:10.1002/UOG.19112
  45. Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database of Systematic Reviews*. 2017;2017(6). doi: 10.1002/14651858.CD007529.PUB4/MEDIA/CDSR/CD007529/IMAGE\_T/TCDD007529-CMP-001-21.XXX
  46. Teeuw HM, Amoakoh HB, Ellis CA, Lindsley K, Browne JL. Diagnostic accuracy of urine dipstick tests for proteinuria in pregnant women suspected of preeclampsia: A systematic review and meta-analysis. *Pregnancy Hypertens*. 2022; 27:123-130. doi: 10.1016/J.PREGHY.2021.12.015
  47. WHO. *WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience*.; 2016. Accessed August 16, 2024. <https://iris.who.int/bitstream/handle/10665/250796/9789241549912-eng.pdf;sequence=1>
  48. Henderson JT, Thompson JH, Burda BU, Cantor A. Preeclampsia Screening: Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2017;317(16):1668-1683. doi:10.1001/JAMA.2016.18315
  49. NICE. Overview | Hypertension in pregnancy: diagnosis and management | Guidance | NICE. NICE.
  50. Gerth-Guyette E, Adu-Gyasi D, Tawiah Agyemang C, et al. Evaluation of a protein-to-creatinine dipstick diagnostic test for proteinuria screening in selected antenatal care clinics in three Districts in the Bono-East Region of Ghana. *Pregnancy Hypertens*. 2022; 30:21-30. doi: 10.1016/J.PREGHY.2022.07.004
  51. Khaliq OP, Phoswa WN, Moodley J. The effectiveness of the Congo Red Dot paper test in hypertensive disorders of pregnancy: A systematic review and meta-analysis. *Frontiers in Reproductive Health*. 2023; 5:1120937. doi:10.3389/FRPH.2023.1120937/BIBTEX
  52. Wong STK, Sahota DS, Wong NKL, et al. A point-of care urine test to predict preeclampsia development in Asian women with suspected preeclampsia. *Pregnancy Hypertens*. 2023; 32:28-34. doi: 10.1016/J.PREGHY.2023.03.003

53. Bracken H, Buhimschi IA, Rahman A, et al. Congo red test for identification of preeclampsia: Results of a prospective diagnostic case-control study in Bangladesh and Mexico. *EClinicalMedicine*. 2021; 31:100678. doi: 10.1016/J.ECLINM.2020.100678
54. Tuntivararut P, Raungrongmorakot K, Chaiyasit N, Yuenyongdechawat N, Chaemsaitong P. Urine Congo red test for the detection of preeclampsia in pregnant women presenting with suspected preeclampsia. *Journal of Maternal-Fetal and Neonatal Medicine*. 2024;37(1). doi:10.1080/14767058.2024.2332787
55. Amari Chinchilla K, Vijayan M, Taveras Garcia B, Jim B. Complement-Mediated Disorders in Pregnancy. *Adv Chronic Kidney Dis*. 2020;27(2):155-164. doi: 10.1053/j.ackd.2020.01.002
56. Zakiyah N, Postma MJ, Baker PN, van Asselt ADI. Pre-eclampsia Diagnosis and Treatment Options: A Review of Published Economic Assessments. *Pharmacoeconomics*. 2015; 33(10):1069-1082. doi: 10.1007/S40273-015-0291-X/TABLES/5
57. Duhig KE, Myers JE, Gale C, et al. Placental growth factor measurements in the assessment of women with suspected Preeclampsia: A stratified analysis of the PARROT trial. *Pregnancy Hypertens*. 2021; 23:41-47. doi: 10.1016/j.preghy.2020.10.005
58. Adu-Bonsaffoh K, Antwi DA, Gyan B, Obed SA. Endothelial dysfunction in the pathogenesis of pre-eclampsia in Ghanaian women. *BMC Physiol*. 2017;17(1). doi:10.1186/S12899-017-0029-4
59. Sokratous N, Bednorz M, Wright A, Nicolaides KH, Kametas NA. Prediction using serum glycosylated fibronectin of imminent pre-eclampsia in women with new-onset hypertension. *Ultrasound in Obstetrics and Gynecology*. 2023;62(5):653-659. doi:10.1002/uog.27458
60. Cerdeira AS, Karumanchi SA. Serial placental growth factor-based testing in pre-eclampsia. *The Lancet*. 2024;403(10427):588-589. doi:10.1016/S0140-6736(23)02578-3
61. Hurrell A, Webster L, Sparkes J, et al. Repeat placental growth factor-based testing in women with suspected preterm pre-eclampsia (PARROT-2): a multicentre, parallel-group, superiority, randomised controlled trial. *Lancet*. 2024;403(10427):619-631. doi:10.1016/S0140-6736(23)02357-7
62. Hurrell A, Webster L, Sparkes J, et al. Repeat Placental Growth Factor-Based Testing in Women With Suspected Preterm Preeclampsia: A Stratified Analysis of the PARROT-2 Trial. *Hypertension*. 2024;81(7):1561-1573. doi:10.1161/HYPERTENSIONAHA.123.22411
63. Ortved D, Hawkins TLA, Johnson JA, Hyett J, Metcalfe A. Cost-effectiveness of first-trimester screening with early preventative use of aspirin in women at high risk of early-onset pre-eclampsia. *Ultrasound in Obstetrics & Gynecology*. 2019;53(2):239-244. doi:10.1002/UOG.19076
64. Park F, Deeming S, Bennett N, Hyett J. Cost-effectiveness analysis of a model of first-trimester prediction and prevention of preterm pre-eclampsia compared with usual care. *Ultrasound in Obstetrics & Gynecology*. 2021;58(5):688-697. doi:10.1002/UOG.22193
65. Manriquez Rocha B, Mbofana F, Loquiha O, et al. Early diagnosis of preeclampsia using placental growth factor: An operational pilot study in Maputo, Mozambique. *Pregnancy Hypertens*. 2018; 11:26-31. doi: 10.1016/J.PREGHY.2017.12.005
66. Giblin L, McCarthy FP, Gill C, et al. Rule-in thresholds for DELFIA Xpress PLGF 1-2-3 test for suspected pre-eclampsia. *Pregnancy Hypertens*. 2020; 21:35-37. doi: 10.1016/J.PREGHY.2020.04.005
67. Redman C. Diagnostic and predictive accuracy of placental growth factor in suspected pre-eclampsia. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*. 2014;4(3):241. doi: 10.1016/J.PREGHY.2014.04.008
68. Nagalla SR, Janaki V, Vijayalakshmi AR, et al. Glycosylated fibronectin point-of-care test for diagnosis of pre-eclampsia in a low-resource setting: a prospective Southeast Asian population study. *BJOG*. 2020;127(13):1687-1694. doi:10.1111/1471-0528.16323
69. Mazer Zumaeta A, Wright A, Syngelaki A, Maritsa VA, Da Silva AB, Nicolaides KH. Screening for pre-eclampsia at 11-13 weeks' gestation: use of pregnancy-associated plasma protein-A, placental growth factor or both. *Ultrasound in Obstetrics & Gynecology*. 2020;56(3):400-407. doi:10.1002/UOG.22093
70. Jash S, Banerjee S, Cheng S, et al. Cis P-tau is a central circulating and placental etiologic driver and therapeutic target of preeclampsia. *Nature Communications* 2023 14:1. 2023;14(1):1-18. doi:10.1038/s41467-023-41144-6
71. John O, Campbell NRC, Brady TM, et al. The 2020 "WHO Technical Specifications for Automated Non-Invasive Blood Pressure Measuring Devices With Cuff." *Hypertension*. 2021;77(3):806-812. doi: 10.1161/HYPERTENSIONAHA.120.16625/ASSET/27F5F90D-A86A-40E4-AE09-F588275DEAF3/ASSETS/GRAPHIC/HYPERTENSIONAHA.120.16625.FIG01.JPG
72. Picone DS, Campbell NRC, Schutte AE, et al. Validation Status of Blood Pressure Measuring Devices Sold Globally. *JAMA*. 2022;327(7):680-681. doi: 10.1001/JAMA.2021.24464
73. Sharman JE, Ordunez P, Brady T, et al. The urgency to regulate validation of automated blood pressure measuring devices: a policy statement and call to action from the world hypertension league. *Journal of Human Hypertension* 2022 37:2. 2022;37(2):155-159. doi:10.1038/s41371-022-00747-0
74. Cohen JB, Padwal RS, Gutkin M, et al. History and justification of a national blood pressure measurement validated Device Listing. *Hypertension*. 2019;73(2):258-264. doi: 10.1161/HYPERTENSIONAHA.118.11990/ASSET/56F10901-1DBC-4619-A0DE-4B0B47D05CD4/ASSETS/IMAGES/LARGE/258FIG01.JPG
75. Gynuity. *Antihypertensive Medicines and Blood Pressure Devices: A Landscape Assessment of Access to Essential Supplies for Treatment of Hypertensive Disorders of Pregnancy in Three Countries: Antihypertensive Medicines and Blood Pressure Devices*; 2019.
76. Bracken H, Bousiégué M, Frye Laura. *Antihypertensive Medicines and Blood Pressure Devices. A Landscape Assessment of Access to Essential Supplies for Treatment of HDPs in Three Countries*; 2019.
77. Stergiou GS, O'Brien E, Myers M, Palatini P, Parati G. STRIDE BP: An international initiative for accurate blood pressure measurement. *J Hypertens*. 2020;38(3):395-399. doi:10.1097/HJH.0000000000002289
78. De Greeff A, Ghosh D, Anthony J, Shennan A. Accuracy Assessment of the Dinamap ProCare 400 in Pregnancy and Preeclampsia. *Hypertens Pregnancy*. 2010;29(2):198-205. doi:10.3109/10641950902968650
79. Brothwell S, Dutton M, Ferro C, Stringer S, Cockwell P. Optimising the accuracy of blood pressure monitoring in chronic kidney disease: The utility of BpTRU. *BMC Nephrol*. 2013;14(1):1-11. doi:10.1186/1471-2369-14-218/TABLES/2
80. Nathan HL, De Greeff A, Hezelgrave NL, Chappell LC, Shennan AH. An accurate semiautomated oscillometric blood pressure device for use in pregnancy (including pre-eclampsia) in a low-income and middle-income country population: The Microlife 3AS1-2. *Blood Press Monit*.

- 2015;20(1):52-55. doi:10.1097/MBP.0000000000000086
81. Bright S, Moses F, Ridout A, et al. Scale-up of a novel vital signs alert device to improve maternity care in Sierra Leone: a mixed methods evaluation of adoption. *Reprod Health*. 2023;20(1):1-11. doi:10.1186/S12978-022-01551-2/TABLES/2
  82. Nathan HL, Boene H, Munguambe K, et al. The CRADLE vital signs alert: qualitative evaluation of a novel device designed for use in pregnancy by healthcare workers in low-resource settings. *Reprod Health*. 2018;15(1):5. doi:10.1186/S12978-017-0450-Y/TABLES/3
  83. von Dadelszen P, Bhutta ZA, Sharma S, et al. The Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised trials in Mozambique, Pakistan, and India: an individual participant-level meta-analysis. *The Lancet*. 2020;396(10250):553-563. doi:10.1016/S0140-6736(20)31128-4
  84. Ridout AE, Moses FL, Herm-Singh S, et al. CRADLE-5: a stepped-wedge type 2 hybrid implementation-effectiveness cluster randomised controlled trial to evaluate the real-world scale-up of the CRADLE Vital Signs Alert intervention into routine maternity care in Sierra Leone—study protocol. *Trials*. 2023;24(1):1-14. doi:10.1186/S13063-023-07587-4/FIGURES/3
  85. Festo C, Vannevel V, Ali H, et al. Accuracy of a smartphone application for blood pressure estimation in Bangladesh, South Africa, and Tanzania. *npj Digital Medicine* 2023 6:1. 2023;6(1):1-9. doi:10.1038/s41746-023-00804-z
  86. Schoettker P, Degott J, Hofmann G, et al. Blood pressure measurements with the OptiBP smartphone app validated against reference auscultatory measurements. *Scientific Reports* 2020 10:1. 2020;10(1):1-12. doi:10.1038/s41598-020-74955-4
  87. Peeling L, Tucker KL, Fletcher B, et al. Perceptions and experiences of blood pressure self-monitoring during hypertensive pregnancy: A qualitative analysis of women's and clinicians' experiences in the OPTIMUM-BP trial. *Pregnancy Hypertens*. 2022; 30:113-123. doi: 10.1016/J.PREGHY.2022.09.006
  88. Bello NA, Woolley JJ, Cleary KL, et al. Accuracy of blood pressure measurement devices in pregnancy: A systematic review of validation studies. *Hypertension*. 2018;71(2):326-335. doi: 10.1161/HYPERTENSIONAHA.117.10295/SUPPL\_FILE/HYP\_HYPE201710295\_SUPPL1.PDF
  89. WHO. WHO compendium of innovative health technologies for low-resource settings, 2016- 2017. Accessed August 18, 2024. <https://www.who.int/publications/i/item/9789241514699>
  90. Noël L, Coutinho CM, Thilaganathan B. Preventing Stillbirth: A Review of Screening and Prevention Strategies. *Maternal-Fetal Medicine*. 2022;4(3):218-228. doi:10.1097/FM9.0000000000000160
  91. Carter J, Anumba D, Brigante L, et al. The Tommy's Clinical Decision Tool, a device for reducing the clinical impact of placental dysfunction and preterm birth: protocol for a mixed-methods early implementation evaluation study. *BMC Pregnancy Childbirth*. 2022;22(1):1-14. doi:10.1186/S12884-022-04867-W/TABLES/5
  92. Rolnik DL, Wright D, Poon LCY, et al. ASPRE trial: performance of screening for preterm pre-eclampsia. *Ultrasound in Obstetrics and Gynecology*. 2017;50(4):492-495. doi:10.1002/uog.18816
  93. WHO. Imaging ultrasound before 24 weeks of pregnancy: 2022 update to the WHO antenatal care recommendations for a positive pregnancy experience. 2022. Accessed August 18, 2024. <https://www.who.int/publications/i/item/9789240051461>
  94. Koech A, Musitia PM, Mwashigadi GM, et al. Acceptability and Feasibility of a Low-Cost Device for Gestational Age Assessment in a Low-Resource Setting: Qualitative Study. *JMIR Hum Factors*. 2022;9(4). doi:10.2196/34823
  95. Ranger BJ, Bradburn E, Chen Q, Kim M, Noble JA, Papageorgiou AT. Portable ultrasound devices for obstetric care in resource-constrained environments: mapping the landscape. *Gates Open Res*. 2023; 7:133. doi:10.12688/gatesopenres.15088.1
  96. WHO. WHO compendium of innovative health technologies for low-resource settings 2024. 2024. Accessed August 30, 2024. <https://www.who.int/publications/b/74255>
  97. Noguchi L, Bucagu M, Tunçalp Ö. Strengthening antenatal care services for all: implementing imaging ultrasound before 24 weeks of pregnancy. *BMJ Glob Health*. 2023;8(5): e011170. doi:10.1136/BMJGH-2022-011170
  98. Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database of Systematic Reviews*. 2019;2019(10). doi: 10.1002/14651858.CD004659. PUB3/MEDIA/CDSR/CD004659/IMAGE\_T/TCD004659-AFIG-FIG22.PNG
  99. Achamrah N, Ditisheim A. Nutritional approach to preeclampsia prevention. *Curr Opin Clin Nutr Metab Care*. 2018;21(3):168-173. doi:10.1097/MCO.0000000000000462
  100. World Health Organization. Calcium supplementation before pregnancy for the prevention of pre-eclampsia and its complications. Published online 2020:48. Accessed August 30, 2024. <https://apps.who.int/iris/bitstream/handle/10665/331787/9789240003118-eng.pdf?ua=1>
  101. Cormick G, Moraa H, Zahroh RI, et al. Factors affecting the implementation of calcium supplementation strategies during pregnancy to prevent pre-eclampsia: a mixed-methods systematic review. *BMJ Open*. 2023;13(12): e070677. doi:10.1136/BMJOPEN-2022-070677
  102. Dwarkanath P, Muhihi A, Sudfeld CR, et al. Two Randomized Trials of Low-Dose Calcium Supplementation in Pregnancy. *New England Journal of Medicine*. 2024;390(2):143-153. doi: 10.1056/NEJM0A2307212/ SUPPL\_FILE/NEJM0A2307212\_DATA-SHARING.PDF
  103. Country M, Leadership G. NATIONAL PROGRAMS FOR THE PREVENTION AND MANAGEMENT OF POSTPARTUM HEMORRHAGE AND HYPERTENSIVE DISORDERS OF PREGNANCY A Global Survey MOMENTUM Country and Global Leadership National Programs for the Prevention and Management of PPH and HDP: A Global Survey 2022. Accessed August 30, 2024. [www.usaidmomentum.org](http://www.usaidmomentum.org).
  104. Melo P, Devall A, Shennan AH, et al. Vaginal micronised progesterone for the prevention of hypertensive disorders of pregnancy: A systematic review and meta-analysis. *BJOG*. 2024;131(6):727-739. doi:10.1111/1471-0528.17705
  105. Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database of Systematic Reviews*. 2018;2018(10). doi: 10.1002/14651858.CD002252.PUB4/MEDIA/CDSR/CD002252/URN:X-WILEY:14651858:MEDIA:CD002252:CD002252-CMP-001-02
  106. Easterling T, Mundle S, Bracken H, et al. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. *The Lancet*. 2019;394(10203):1011-1021. doi:10.1016/S0140-6736(19)31282-6
  107. WHO. WHO EML 23rd List (2023). 2023. Accessed August 18, 2024. <http://apps.who.int/bookorders>.

108. Bone JN, Sandhu A, Abalos ED, et al. Oral Antihypertensives for Nonsevere Pregnancy Hypertension: Systematic Review, Network Meta- and Trial Sequential Analyses. *Hypertension*. 2022;79(3):614-628. doi: 10.1161/HYPERTENSIONAHA.121.18415/SUPPL\_FILE/HYP\_HYPE-2021-18415\_SUPP1.PDF
109. Palatnik A, Mukhtarova N, Hetzel SJ, Hoppe KK. Blood pressure changes in gestational hypertension, preeclampsia, and chronic hypertension from preconception to 42-day postpartum. *Pregnancy Hypertens*. 2023; 31:25-31. doi: 10.1016/J.PREGHY.2022.11.009
110. WHO. WHO recommendations on interventions to improve preterm birth outcomes. 2022. Accessed August 18, 2024. <https://www.who.int/publications/i/item/9789241508988>
111. USAID. *Module Iii: Technical Information for Life-Saving MNCH Products Technical Information for Life-Saving MNCH Products*; 2022.
112. Okusanya BO, Oladapo OT, Long Q, et al. Clinical pharmacokinetic properties of magnesium sulphate in women with pre-eclampsia and eclampsia. *BJOG*. 2016; 123(3):356-366. doi: 10.1111/1471-0528.13753
113. Brookfield K, Galadanci H, Du L, et al. Magnesium sulfate pharmacokinetics after intramuscular dosing in women with preeclampsia. *AJOG global reports*. 2021;1(4). doi: 10.1016/J.XAGR.2021.100018
114. Padda J, Khalid K, Colaco LB, et al. Efficacy of Magnesium Sulfate on Maternal Mortality in Eclampsia. *Cureus*. 2021;13(8). doi:10.7759/CUREUS.17322
115. Eddy KE, Vogel JP, Zahroh RI, Bohren MA. Factors affecting use of magnesium sulphate for pre-eclampsia or eclampsia: a qualitative evidence synthesis. *BJOG*. 2022;129(3):379-391. doi:10.1111/1471-0528.16913
116. Maharjan P, Ponganam MP, Lambert P, Vogel JP, McIntosh M, McDougall A. The quality of medicines for the prevention and management of hypertensive disorders of pregnancy: A systematic review. *PLOS Global Public Health*. 2024;4(2): e0002962. doi: 10.1371/JOURNAL.PGPH.0002962
117. Concept Foundation. *Medicines for Pregnancy-Specific Conditions Research, Development and Market Analysis Accelerating Innovation for Mothers*. 2022.
118. Sakowicz A, Braleswska M, Rybak-Krzyszowska M, Grzesiak M, Pietrucha T. New Ideas for the Prevention and Treatment of Preeclampsia and Their Molecular Inspirations. *International Journal of Molecular Sciences* 2023, Vol 24, Page 12100. 2023;24(15):12100. doi:10.3390/IJMS241512100
119. Cluver CA, Hiscock R, Decloedt EH, et al. Use of metformin to prolong gestation in preterm pre-eclampsia: randomised, double blind, placebo controlled trial. *BMJ*. 2021; 374:2103. doi:10.1136/BMJ.N2103
120. World Health Organization. WHO Recommendations: Policy of interventionist versus expectant management of severe pre-eclampsia before term. *World Health Organization*. Published online 2018:1-38. Accessed August 18, 2024. <https://www.who.int/publications/i/item/9789241550444>
121. World Health Organization. Optimizing health worker roles to improve access to key maternal and newborn health interventions through task shifting. *World Health Organization*. Published online 2012:1-98. Accessed August 18, 2024. <http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:health+worker+roles+to+improve+access+to+key+maternal+and+newborn+health+interventions+through+task+shifting#0%5Cnhttp://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Optimizing+health>
122. McNeil DA, Vekved M, Dolan SM, Siever J, Horn S, Tough SC. A qualitative study of the experience of Centering Pregnancy group prenatal care for physicians. *BMC Pregnancy Childbirth*. 2013;13(Suppl 1): S6-S6. doi:10.1186/1471-2393-13-S1-S6
123. Grenier L, Lori JR, Darney BG, et al. Building a Global Evidence Base to Guide Policy and Implementation for Group Antenatal Care in Low- and Middle-Income Countries: Key Principles and Research Framework Recommendations from the Global Group Antenatal Care Collaborative. *J Midwifery Womens Health*. 2020;65(5):694-699. doi:10.1111/JMWH.13143
124. Musabyimana A, Lundeen T, Butrick E, et al. Before and after implementation of group antenatal care in Rwanda: A qualitative study of women's experiences. *Reprod Health*. 2019;16(1):1-9. doi:10.1186/s12978-019-0750-5
125. Grenier L, Suhowatsky S, Kabue MM, et al. Impact of group antenatal care (G-ANC) versus individual antenatal care (ANC) on quality of care, ANC attendance and facility-based delivery: A pragmatic cluster-randomized controlled trial in Kenya and Nigeria. *PLoS One*. 2019;14(10): e0222177. doi: 10.1371/JOURNAL.PONE.0222177
126. Lazar J, Boned-Rico L, Olander EK, McCourt C. A systematic review of providers' experiences of facilitating group antenatal care. *Reprod Health*. 2021;18(1):1-21. doi:10.1186/S12978-021-01200-0/FIGURES/2
127. Hazra A, Atmavilas Y, Hay K, et al. Effects of health behaviour change intervention through women's self-help groups on maternal and newborn health practices and related inequalities in rural India: A quasi-experimental study. *EclinicalMedicine*. 2019;18. doi: 10.1016/J.ECLINM.2019.10.011
128. Prost A, Colbourn T, Seward N, et al. Women's groups practising participatory learning and action to improve maternal and newborn health in low-resource settings: A systematic review and meta-analysis. *The Lancet*. 2013;381(9879). doi:10.1016/S0140-6736(13)60685-6
129. Azad K, Barnett S, Banerjee B, et al. Effect of scaling up women's groups on birth outcomes in three rural districts in Bangladesh: a cluster-randomised controlled trial. *The Lancet*. 2010;375(9721):1193-1202. doi:10.1016/S0140-6736(10)60142-0
130. World Health Organization. WHO recommendation on community mobilization through facilitated participatory learning and action cycles with women's groups for maternal and newborn health. WHO. Published online 2014:32. Accessed August 18, 2024. [http://apps.who.int/iris/bitstream/10665/127939/1/9789241507271\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/127939/1/9789241507271_eng.pdf?ua=1)
131. Narasimhan M, Allotey P, Hardon A. Self care interventions to advance health and wellbeing: a conceptual framework to inform normative guidance. *BMJ*. 2019;365. doi: 10.1136/BMJ.L688
132. Muthelo L, Mbombi MO, Bopape MA, et al. Reflections on Digital Maternal and Child Health Support for Mothers and Community Health Workers in Rural Areas of Limpopo Province, South Africa. *International Journal of Environmental Research and Public Health* 2023, Vol 20, Page 1842. 2023;20(3):1842. doi:10.3390/IJERPH20031842
133. WHO Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care. Published online 2020.
134. RHSC. Business Case: Investing in Production of High-Quality Magnesium Sulfate for Low-Resource Setting. 2014. Accessed August 30, 2024. <https://www.conceptfoundation.org/publications/business-case-investing-in-production-of-high-quality-magnesium-sulfate-for-low-resource-settings/>



135. U.S. Pharmacopeial Convention. *Manufacturing Landscape Assessment for Maternal Health Supplies in Sub-Saharan Africa: Regionalization.*; 2024.
136. Concept Foundation. Medicines for Pregnancy Specific Conditions: Research, Development and Market Analysis. AIM Project.
137. Dempsey A, Sripad P, Sultana K, Kirk K, Hossain SMI, Warren C. Pathways to service access for pre-eclampsia and eclampsia in rural Bangladesh: Exploring women's care-seeking. *PLoS One*. 2021;16(2): e0245371. doi: 10.1371/JOURNAL.PONE.0245371
138. Warren CE, Hossain SMI, Ishaku S, Armbruster D, Hillman E. A primary health care model for managing pre-eclampsia and eclampsia in low- And middle- income countries. *Reprod Health*. 2020;17(1):1-7. doi:10.1186/S12978-020-0897-0/FIGURES/1
139. Meazaw MW, Chojenta C, Muluneh MD, Loxton D. Systematic and meta-analysis of factors associated with preeclampsia and eclampsia in sub-Saharan Africa. *PLoS One*. 2020;15(8). doi: 10.1371/JOURNAL.





**Unitaid Secretariat**

Unitaid — Global Health Campus  
Chemin du Pommier 40, fifth floor  
1218 Grand-Saconnex  
Geneva, Switzerland  
**[unitaid.org](https://unitaid.org)**

© Unitaid 2024