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PREECLAMPSIA: PLACENTAL PATHOPHYSIOLOGY, PREDICTIVE BIOMARKERS, MATERNAL-FETAL OUTCOMES, AND EVIDENCE-BASED MANAGEMENT IN CONTEMPORARY OBSTETRICS AND GYNECOLOGY

Otaboyeva Xilolaxon Abdulla qizi

Asia International University

ABSTRACT

Background: Preeclampsia is a multisystem hypertensive disorder of pregnancy affecting 2–8% of all pregnancies globally and remaining a leading cause of maternal and perinatal mortality and morbidity worldwide. Characterized by new-onset hypertension (systolic blood pressure ≥ 140 mmHg or diastolic ≥ 90 mmHg) after 20 weeks of gestation with evidence of systemic organ involvement—including proteinuria, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or new-onset headache—preeclampsia is responsible for approximately 70,000 maternal deaths and 500,000 perinatal deaths annually. Its underlying pathophysiology centers on defective placental implantation and impaired trophoblast invasion, resulting in placental ischemia, antiangiogenic factor imbalance, and systemic endothelial dysfunction that produces the clinical syndrome.

Objective: To provide a comprehensive, evidence-based review of the pathophysiology, first-trimester risk stratification, biomarker-based prediction, maternal-fetal complications, pharmacological prevention with low-dose aspirin, and acute and definitive management of preeclampsia within the framework of contemporary obstetric and gynecological practice, synthesizing evidence from eight primary peer-reviewed sources.

Methods: A systematic review of eight primary sources was conducted, including prospective cohort studies, large randomized controlled trials, meta-analyses, and authoritative clinical practice guidelines published between 2001 and 2024.

Results: Defective deep placentation—failure of extravillous trophoblast (EVT) remodeling of spiral arteries beyond the decidual segment—is the central pathogenic mechanism, producing a high-resistance, low-flow uteroplacental circulation. Placental hypoxia and oxidative stress increase soluble fms-like tyrosine kinase-1 (sFlt-1) secretion and reduce placental growth factor (PlGF), with sFlt-1/PlGF ratio > 38 predicting preeclampsia onset with 80% sensitivity and 95% specificity within 4 weeks. First-trimester combined screening (uterine artery Doppler pulsatility index, MAP, PAPP-A, PlGF) identifies 90% of early-onset preeclampsia at a 10% false-positive rate. Low-dose aspirin (150 mg/day from 11–14 weeks until 36 weeks) reduces preterm preeclampsia by 62% in high-risk women (ASPRE trial). Magnesium sulfate prevents eclamptic seizures in severe preeclampsia with a number needed to treat of 50.

Conclusion: The paradigm shift from reactive management of established preeclampsia to proactive first-trimester risk stratification and aspirin prophylaxis has transformed the preventive potential of obstetric care. Integration of the Fetal Medicine Foundation (FMF) competing-risks algorithm into routine antenatal practice offers the most validated pathway for identifying high-risk pregnancies that benefit from early aspirin prophylaxis and intensified surveillance.

Keywords

preeclampsia, placental implantation, trophoblast invasion, sFlt-1, PlGF, uterine artery Doppler, low-dose aspirin, ASPRE trial, magnesium sulfate, HELLP syndrome, fetal growth restriction, antihypertensive therapy, gestational hypertension

1. INTRODUCTION

Preeclampsia is a pregnancy-specific, multisystem hypertensive disorder that remains one of the foremost challenges in contemporary obstetrics, accounting for a disproportionate burden of maternal and perinatal morbidity and mortality worldwide despite decades of intensive research [1]. Defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) as new-onset hypertension—systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg—at or after 20 weeks of gestation, with evidence of systemic organ dysfunction manifesting as proteinuria (≥ 0.3 g/24 hours or protein/creatinine ratio ≥ 30 mg/mmol), thrombocytopenia (platelet count < 150 × 10⁹/L), renal insufficiency (serum creatinine > 90 µmol/L), impaired liver function (elevated transaminases ≥ 2× upper limit of normal), pulmonary edema, or new-onset headache or visual disturbance, preeclampsia affects 2–8% of all pregnancies globally—translating to approximately 8.5 million affected pregnancies annually [1].

The global mortality burden of preeclampsia and its complications—eclampsia (tonic-clonic seizures), HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets), and abruptio placentae—is concentrated in low- and middle-income countries (LMICs), where limited access to antihypertensive therapy, magnesium sulfate for seizure prophylaxis, antenatal surveillance, and skilled obstetric care produces case fatality rates of 1–2% compared to < 0.1% in high-income settings [2]. In Uzbekistan and Central Asia, hypertensive disorders of pregnancy—including gestational hypertension, preeclampsia, eclampsia, and chronic hypertension—collectively account for 15–20% of all maternal deaths, making them the leading single cause of maternal mortality after obstetric hemorrhage, and underscoring the critical importance of evidence-based prevention, early diagnosis, and timely management in the regional obstetric context [2].

The pathophysiological understanding of preeclampsia has been fundamentally transformed over the past two decades by the "two-stage model": Stage 1 consists of impaired placentation during the first trimester, in which defective extravillous trophoblast (EVT) invasion of maternal spiral arteries produces a high-resistance uteroplacental circulation and chronic placental ischemia; Stage 2 comprises the release of vasoactive, antiangiogenic, and pro-inflammatory factors from the ischemic placenta into the maternal circulation, producing the systemic endothelial dysfunction that generates the clinical syndrome [3]. The central molecular mediators of this placenta-to-maternal systemic transition—sFlt-1 (soluble fms-like tyrosine kinase-1), a circulating decoy receptor that sequesters vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), reducing their bioavailability and impairing endothelial function—were identified by Maynard et al. in a landmark 2003 paper and have since been developed into validated clinical biomarkers for preeclampsia prediction and diagnosis [3].

The recognition that Stage 1 placental pathology begins in the first trimester—months before the clinical syndrome manifests—has created the scientific foundation for first-trimester risk stratification and prophylactic intervention [4]. The Fetal Medicine Foundation (FMF) competing-risks algorithm, combining maternal risk factors with biophysical (uterine artery Doppler pulsatility index, mean arterial pressure) and biochemical (PlGF, PAPP-A)

measurements at 11–14 weeks of gestation, achieves detection rates of 90% for early-onset preeclampsia (< 34 weeks) at a 10% false-positive rate—a dramatic improvement over the risk factor-based screening endorsed by NICE and ACOG guidelines, which detect only 30–40% of cases [4]. The ASPRE trial's demonstration that aspirin 150 mg/day from 11–14 to 36 weeks reduces preterm preeclampsia by 62% in FMF-identified high-risk women has established first-trimester screening-directed aspirin prophylaxis as the most important preventive advance in obstetrics of the past decade [5].

This review systematically synthesizes evidence from eight primary sources to provide a comprehensive account of preeclampsia pathophysiology, first-trimester screening and prediction, biomarker-based diagnosis, maternal and fetal complications, pharmacological prevention and management (antihypertensive therapy, magnesium sulfate), and the definitive treatment strategy of timely delivery, with particular attention to the clinical implications for obstetric practice in Uzbekistan and the Central Asian region.

2. MATERIALS AND METHODS

2.1 Literature Search Strategy

A systematic literature search was performed between January and February 2025 using PubMed/MEDLINE, EMBASE, Cochrane Library, and Web of Science. The following MeSH terms and free-text keywords were applied individually and in Boolean combinations: "preeclampsia pathophysiology," "placental implantation trophoblast invasion," "sFlt-1 PlGF preeclampsia," "uterine artery Doppler preeclampsia," "first trimester preeclampsia screening," "low-dose aspirin preeclampsia prevention," "ASPRE trial aspirin," "HELLP syndrome management," "magnesium sulfate eclampsia," "antihypertensive therapy pregnancy," "fetal growth restriction preeclampsia," and "preeclampsia postpartum cardiovascular risk." Searches were not restricted by date, but publications from 2000 onward were prioritized. Guidelines from ISSHP, NICE, ACOG, and FIGO were identified through direct institutional website searches.

2.2 Eligibility Criteria

Sources were included if they: (i) were published in peer-reviewed obstetrics, gynecology, or maternal-fetal medicine journals with an impact factor ≥ 4.0 (including American Journal of Obstetrics and Gynecology, BJOG, Ultrasound in Obstetrics and Gynecology, NEJM, and Lancet), or constituted authoritative clinical practice guidelines from ISSHP, NICE, ACOG, FIGO, or the FMF; (ii) enrolled pregnant women ≥ 18 years presenting for antenatal care or hospital management of hypertensive pregnancy disorders, or reported mechanistic studies with direct clinical translation; and (iii) reported quantitative data on screening performance (sensitivity, specificity, positive predictive value), biomarker diagnostic accuracy, clinical outcome rates, or treatment efficacy with defined statistical methods. Case reports, editorials, and studies restricted to animal models were excluded. Eight primary sources providing complementary coverage of all review topics were selected.

2.3 Data Extraction and Synthesis

From each included source, the following data were extracted: study design and population size, gestational age at study entry, diagnostic criteria applied for preeclampsia classification, screening or biomarker methodology, primary clinical outcomes (preeclampsia incidence, maternal mortality, perinatal mortality, gestational age at delivery, neonatal intensive care unit admission), and effect size estimates with 95% confidence intervals. For randomized controlled trials, the Cochrane Risk of Bias Tool (RoB 2.0) was applied. For observational

studies, the Newcastle-Ottawa Scale (NOS) was used. Screening performance metrics were extracted directly from primary sources without recalculation. Characteristics of all eight included sources are summarized in Table 1.

Table 1. Primary sources included in this review: design, population, and key contributions to preeclampsia evidence base

Ref.	First Author / Source	Study Type	Population	Primary Focus	Key Contribution
[1]	Brown et al. (ISSHP)	Clinical Guideline	Global consensus	PE classification	ISSHP 2018 definition
[2]	Poon et al. (FIGO)	Clinical Guideline	Antenatal care	PE prevention	FIGO 2019 PE initiative
[3]	Maynard et al.	Original Research	PE vs normal Preg.	sFlt-1 / PlGF mechanism	Antiangiogenic theory
[4]	Akolekar et al.	Prospective Cohort	n=58,884 singleton	1st trimester screening	FMF competing-risks model
[5]	Rolnik et al. (ASPRE)	RCT (NEJM)	n=1,776 high-risk	Aspirin 150 mg vs placebo	62% preterm PE reduction
[6]	Magee et al. (CHIPS)	RCT (NEJM)	n=987 non-severe HTN	Tight vs less-tight BP control	Antihypertensive targets
[7]	Altman et al. (Magpie)	RCT (Lancet)	n=10,141 PE women	$MgSO_4$ vs placebo	Eclampsia prevention NNT=50
[8]	Bellamy et al.	Meta-analysis (BMJ)	n=3,488,160 women	PE & cardiovascular risk	Long-term CV outcomes

PE = preeclampsia; ISSHP = International Society for the Study of Hypertension in Pregnancy; FIGO = International Federation of Gynecology and Obstetrics; FMF = Fetal Medicine Foundation; RCT = randomized controlled trial; sFlt-1 = soluble fms-like tyrosine kinase-1; PlGF = placental growth factor; $MgSO_4$ = magnesium sulfate; NNT = number needed to treat; CV = cardiovascular; HTN = hypertension; ASPRE = Aspirin for Evidence-Based Preeclampsia Prevention; CHIPS = Control of Hypertension In Pregnancy Study.

3. RESULTS

3.1 Classification and Epidemiology of Hypertensive Disorders of Pregnancy

The ISSHP 2018 classification, authored by Brown et al. and endorsed by FIGO and WHO, provides the current international standard for categorizing hypertensive disorders of pregnancy (HDP) into four groups with distinct pathophysiology, management implications, and prognosis [1]. Chronic hypertension—SBP ≥ 140 mmHg or DBP ≥ 90 mmHg present before 20 weeks of gestation or diagnosed before pregnancy—affects 1–5% of pregnant women and carries a 25% risk of superimposed preeclampsia. Gestational hypertension—new-onset hypertension after 20 weeks without systemic features—complicates 5–6% of pregnancies but may progress to preeclampsia in 15–25% of cases, mandating continued surveillance. Preeclampsia—hypertension after 20 weeks with evidence of systemic organ dysfunction as defined above—is further classified as early-onset (< 34 weeks, 10% of cases, associated with severe placental dysfunction and highest maternal-fetal risk) and late-onset (≥ 34 weeks, 90% of cases, associated with milder placental disease but representing the largest absolute burden) [1].

Global preeclampsia prevalence estimates range from 2% to 8%, with higher rates in LMICs reflecting a combination of greater baseline risk factor prevalence (nulliparity, multiple gestation, pre-existing hypertension, diabetes, chronic kidney disease, obesity, antiphospholipid syndrome) and reduced access to effective preventive interventions [2]. In sub-Saharan Africa and South Asia, preeclampsia accounts for 9–26% of all maternal deaths. In Central Asia and Uzbekistan, national perinatal registry data indicate preeclampsia and related hypertensive disorders complicate approximately 5–7% of deliveries, with eclampsia rates of 0.5–1.0 per 1,000 births—substantially above the rates of < 0.05 per 1,000 achievable with optimal magnesium sulfate utilization—reflecting gaps in both prevention and acute management that evidence-based clinical protocols can address [2]. The FIGO 2019 initiative on preeclampsia, authored by Poon et al., provides a global implementation framework for universal first-trimester screening and aspirin prophylaxis that is directly applicable to the Central Asian context [2].

3.2 Pathophysiology: Defective Placentation and the Two-Stage Model

The central pathogenic event in preeclampsia—particularly early-onset, severe disease—is defective deep placentation: the failure of extravillous trophoblast (EVT) cells to adequately invade and remodel the maternal spiral arteries beyond the decidual into the myometrial segments during the first and early second trimesters (8–18 weeks of gestation) [3]. In normal pregnancy, EVT invasion transforms spiral arteries from high-resistance, vasoconstricted muscular vessels (mean diameter 200–300 μm) into low-resistance, high-flow uteroplacental vessels (mean diameter 1,000–2,000 μm) incapable of vasoconstriction—a remodeling process driven by EVT secretion of metalloproteinases (MMP-2, MMP-9) that degrade the vascular smooth muscle and elastic tissue, and by HLA-G-mediated suppression of maternal NK cell cytotoxicity that prevents immunological rejection of the invading trophoblast [3]. In preeclampsia, EVT invasion is limited to the decidual segment alone, leaving the myometrial spiral artery segments unremodeled—narrow, vasoconstricted, and vasoreactive—producing the characteristic high-resistance uteroplacental waveform on Doppler velocimetry (absent or reversed end-diastolic flow in severe cases) and generating chronic placental ischemia.

The ischemic preeclamptic placenta responds with a dramatic shift in its angiogenic factor secretion profile that constitutes the molecular bridge between Stage 1 (placental pathology) and Stage 2 (maternal systemic disease) [3]. Maynard et al. demonstrated in a landmark study that preeclamptic placentas overexpress sFlt-1—a splice variant of the VEGF receptor Flt-1 that lacks the transmembrane and cytoplasmic domains and is secreted into the maternal circulation—at levels 4–8-fold higher than normal pregnancies from 5–6 weeks before clinical disease onset. Circulating sFlt-1 acts as a decoy receptor, binding free VEGF and PlGF

with high affinity (Kd ≈ 10 pM) and preventing their interaction with endothelial cell-surface receptors, thereby impairing endothelium-dependent vasodilation (VEGF-mediated NO production), reducing endothelial cell survival and proliferation, and disrupting glomerular endothelial fenestration (glomerular endotheliosis—the pathognomonic renal lesion of preeclampsia) [3]. Simultaneously, placental secretion of PlGF is reduced to 20–30% of normal levels—a finding detectable as early as 11–14 weeks of gestation and exploited in first-trimester screening algorithms—while endoglin (soluble co-receptor for TGF-β signaling) is elevated, contributing to impaired endothelial NO and prostacyclin production and augmenting sFlt-1's antiangiogenic effects.

The systemic endothelial dysfunction produced by the antiangiogenic milieu explains the clinical multiorgan phenotype of preeclampsia through organ-specific endothelial pathology: cerebrovascular endothelial dysfunction and autoregulatory failure produce the headache, visual disturbance, and eclamptic seizures; hepatic sinusoidal endothelial damage causes periportal hemorrhage and necrosis (elevated transaminases, subcapsular hematoma); platelet consumption at sites of endothelial damage produces thrombocytopenia; glomerular endotheliosis causes proteinuria and renal impairment; and pulmonary endothelial leakage produces pulmonary edema [1]. The temporal evolution of sFlt-1 and PlGF levels—rising sFlt-1 and falling PlGF detectable weeks before clinical hypertension—provides the rational basis for the biomarker-based monitoring and prediction strategies that have become central to contemporary preeclampsia management [3].

3.3 First-Trimester Screening: The FMF Competing-Risks Algorithm

The Fetal Medicine Foundation competing-risks model for first-trimester preeclampsia screening, developed and prospectively validated by Akolekar and colleagues in a cohort of 58,884 singleton pregnancies, integrates maternal risk factors with biophysical and biochemical measurements obtained at the 11–14 week scan to estimate individual woman-specific risks for early-onset (< 34 weeks) and preterm (< 37 weeks) preeclampsia [4]. The algorithm combines: (i) maternal history factors (prior preeclampsia, nulliparity, interpregnancy interval > 10 years, body mass index, ethnic origin, conception method, pre-existing hypertension, diabetes, and autoimmune conditions) converted into a prior risk estimate through a Bayes' theorem competing-risks model; (ii) mean arterial pressure (MAP) measured at the 11–14 week visit, the biophysical marker with the highest individual screening performance (area under ROC curve 0.75 for preterm PE); (iii) uterine artery Doppler pulsatility index (UtA-PI), reflecting the completeness of early first-trimester trophoblast invasion and spiral artery remodeling (AUROC 0.78 for preterm PE); (iv) serum PlGF concentration (AUROC 0.83 for preterm PE—the highest-performing single marker); and (v) serum PAPP-A (pregnancy-associated plasma protein A) concentration [4].

When all five components are combined in the FMF competing-risks algorithm, the resulting screening performance for early-onset preeclampsia (< 34 weeks) is: detection rate 90% at a 10% false-positive rate (screen-positive cut-off: 1-in-100 risk), compared to 30–40% detection rates achieved by conventional risk factor-based screening (NICE or ACOG criteria) at the same false-positive rate [4]. For preterm preeclampsia (< 37 weeks), combined first-trimester screening achieves a detection rate of 75% at 10% false-positive rate. The clinical implementation of this algorithm requires standardized measurement of UtA-PI by color Doppler at the 11–14 week scan, calibrated automated blood pressure measurement devices for MAP, and quantitative PlGF and PAPP-A assays on validated immunoassay platforms (DELFIA Xpress, BRAHMS KRYPTOR, Roche Elecsys) with gestational age and maternal characteristic-adjusted multiple of the median (MoM) normalization [4]. Women identified as high-risk (risk ≥ 1:100

for preterm PE) by the FMF algorithm constitute the target population for low-dose aspirin prophylaxis, whose efficacy was established in the ASPRE trial [5].

3.4 Low-Dose Aspirin Prophylaxis: The ASPRE Trial

The Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial, published in the New England Journal of Medicine in 2017 by Rolnik and colleagues, is the definitive randomized controlled trial establishing the efficacy of low-dose aspirin for preeclampsia prevention in first-trimester-screened high-risk women [5]. The trial enrolled 1,776 women identified as high-risk for preterm preeclampsia by the FMF algorithm at 11–14 weeks (risk ≥ 1:100), randomizing them 1:1 to aspirin 150 mg daily or matched placebo from 11–14 weeks until 36 weeks of gestation. The primary outcome was delivery with preeclampsia at less than 37 weeks of gestation. Preterm preeclampsia occurred in 1.6% of women in the aspirin group versus 4.3% in the placebo group—a relative risk of 0.38 (95% CI 0.20–0.74; $p = 0.004$), corresponding to a 62% reduction in preterm preeclampsia with aspirin [5]. The number needed to treat (NNT) to prevent one case of preterm preeclampsia was 37. There was no significant reduction in term preeclampsia (≥ 37 weeks), consistent with the hypothesis that late-onset preeclampsia has a distinct, less severe placental pathology less responsive to aspirin's antiplatelet mechanism.

The mechanism of aspirin's preeclampsia prophylaxis involves selective inhibition of platelet thromboxane A_2 (TXA_2) synthesis through irreversible acetylation of cyclooxygenase-1 (COX-1), reducing the TXA_2/prostacyclin (PGI_2) ratio that is shifted toward vasoconstriction and platelet aggregation in preeclamptic pregnancies [5]. The dose of 150 mg (rather than the 60–81 mg historically used in older trials) was selected based on pharmacokinetic modeling demonstrating that complete platelet COX-1 suppression requires ≥ 100 mg daily in pregnancy, as increased plasma volume and accelerated drug clearance reduce drug bioavailability compared to non-pregnant adults. The evening administration specified in the ASPRE protocol was based on evidence that uteroplacental blood flow resistance peaks at night and that aspirin taken at bedtime produces maximal morning plasma levels coinciding with this high-resistance period, optimizing pharmacodynamic effect [5]. Meta-analyses of updated aspirin prevention trials incorporating the ASPRE data confirm that aspirin initiated before 16 weeks (particularly before 11–14 weeks as in the ASPRE screening paradigm) is significantly more effective than aspirin initiated after 16 weeks, emphasizing the importance of first-trimester screening identification and early prophylaxis initiation.

3.5 Antihypertensive Management: The CHIPS Trial

The management of non-severe hypertension in pregnancy (SBP 140–159 mmHg, DBP 90–109 mmHg)—whether arising from gestational hypertension, preeclampsia, or chronic hypertension—requires careful titration to balance the risk of maternal end-organ damage from sustained hypertension against the risk of uteroplacental hypoperfusion from excessive blood pressure reduction [6]. The CHIPS (Control of Hypertension In Pregnancy Study) trial, published in NEJM in 2015 by Magee and colleagues, randomized 987 women with non-severe, non-proteinuric chronic or gestational hypertension between 14–33+6 weeks to either "less-tight" control (target DBP 100 mmHg) or "tight" control (target DBP 85 mmHg) [6]. The primary outcome—composite of pregnancy loss or high-level neonatal care for more than 48 hours—did not differ significantly between groups (31.4% tight vs. 30.7% less-tight; adjusted OR 1.02, 95% CI 0.77–1.35). However, tight control significantly reduced the risk of severe maternal hypertension (defined as SBP ≥ 160 or DBP ≥ 110 mmHg) by 27.5% (40.6% tight vs. 27.5% less-tight; $p < 0.001$) without increasing the risk of fetal growth restriction, establishing the clinical safety of treating to a DBP target of 85 mmHg [6].

First-line antihypertensive agents recommended for use in pregnancy by international guidelines (ISSHP 2018, NICE 2019, ACOG 2020) based on established safety and efficacy data include: labetalol (non-selective beta/alpha-1 blocker), nifedipine (dihydropyridine calcium channel blocker, preferred oral agent for acute hypertension), and methyldopa (central alpha-2 agonist, the most extensively safety-profiled agent with the longest post-marketing experience in pregnancy) [1]. Hydralazine (arteriolar vasodilator) is the traditional intravenous agent for acute severe hypertension in the delivery suite but has been largely superseded by intravenous labetalol (bolus 20–40 mg, repeat every 10 minutes to maximum 220 mg) and oral immediate-release nifedipine (10–20 mg, repeat every 20 minutes) due to equivalent efficacy with a more favorable maternal side-effect profile [6]. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are absolutely contraindicated throughout pregnancy due to their teratogenicity (renal tubular dysgenesis, oligohydramnios, neonatal renal failure—the "ACEi fetopathy") and must be discontinued before conception or immediately upon pregnancy diagnosis in women prescribed these agents for chronic hypertension.

3.6 Magnesium Sulfate for Eclampsia Prevention: The Magpie Trial

Magnesium sulfate ($MgSO_4$) is the definitive pharmacological agent for both treatment of eclamptic seizures and prophylaxis against eclampsia in women with severe preeclampsia, with a body of evidence that is unique in obstetric pharmacology for its scale and consistency [7]. The Magpie Trial (MAgnesium sulPhatE for Prevention of Eclampsia), published in The Lancet in 2002 by Altman and colleagues, is the largest trial ever conducted in preeclamptic women, enrolling 10,141 women with preeclampsia from 33 countries in a placebo-controlled, double-blind design comparing $MgSO_4$ (4 g loading dose over 15–20 minutes followed by 1 g/hour maintenance infusion for 24 hours) to matched placebo [7]. $MgSO_4$ reduced the risk of eclampsia by 58% compared to placebo (eclampsia rate: 0.8% $MgSO_4$ vs. 1.9% placebo; RR 0.42, 95% CI 0.29–0.60; $p < 0.0001$), with consistent efficacy across all subgroups including women in LMICs. The number needed to treat to prevent one eclamptic seizure was 50 overall (NNT = 36 in women with severe features). There was no significant effect of $MgSO_4$ on maternal mortality, though the trial was underpowered for this endpoint [7].

Magnesium sulfate's anticonvulsant mechanism in eclampsia is distinct from its use as a uterine relaxant (tocolysis) and operates primarily through antagonism of N-methyl-D-aspartate (NMDA) glutamate receptors in the central nervous system—reducing cortical excitability and raising the seizure threshold—and through reversal of cerebral vasospasm via both direct smooth muscle relaxation (competing with calcium at voltage-gated channels) and endothelium-dependent vasodilatation through magnesium-stimulated prostacyclin synthesis [7]. Clinical monitoring during $MgSO_4$ infusion requires assessment of deep tendon reflexes (loss of patellar reflex is the first sign of toxicity, occurring at serum $Mg^{2+} \approx 5–7$ mmol/L), respiratory rate (respiratory depression at $\approx$ 7–10 mmol/L), and urine output (oliguria reduces magnesium excretion and accelerates accumulation to toxic levels). Calcium gluconate (1 g IV over 10 minutes) is the antidote for $MgSO_4$ toxicity and must be immediately available at the bedside of all women receiving magnesium infusion [7]. Despite the unequivocal evidence from the Magpie Trial, $MgSO_4$ utilization for severe preeclampsia remains below 30% in many LMIC settings due to supply chain challenges, provider knowledge gaps, and fear of toxicity—a care quality gap with directly preventable maternal mortality consequences [2].

3.7 Maternal-Fetal Complications and Long-Term Cardiovascular Risk

Preeclampsia produces a spectrum of acute maternal complications whose severity determines the urgency of delivery—the only definitive treatment [1]. HELLP syndrome—the most dangerous complication, occurring in 10–20% of severe preeclampsia cases—is

characterized by hemolysis (peripheral blood smear showing schistocytes and burr cells, LDH > 600 IU/L), elevated liver enzymes (AST and/or ALT > 70 IU/L), and low platelets (< 100 × 10^9/L), and carries maternal mortality rates of 1–3% in high-income settings and up to 30% in resource-limited settings without intensive care. Complications include hepatic rupture (subcapsular hematoma causing acute abdomen), disseminated intravascular coagulation (DIC), acute pulmonary edema, acute renal failure, placental abruption (occurring in 10–15% of severe cases and associated with 50% of fetal deaths in preeclampsia), and stroke (the leading cause of preeclampsia-associated maternal death in high-income countries) [1]. Delivery is indicated immediately for severe preeclampsia with eclampsia, HELLP syndrome, uncontrolled severe hypertension despite maximal antihypertensive therapy, pulmonary edema, or non-reassuring fetal status—regardless of gestational age.

Fetal and neonatal complications of preeclampsia reflect the consequences of uteroplacental insufficiency (fetal growth restriction, oligohydramnios, fetal hypoxia, stillbirth) and the sequelae of iatrogenic preterm delivery necessitated by the maternal condition [5]. Fetal growth restriction (FGR, defined as estimated fetal weight < 10th percentile for gestational age with evidence of placental insufficiency) complicates 30–40% of early-onset preeclampsia and is associated with a 3–5-fold increase in perinatal mortality, perinatal hypoxic-ischemic encephalopathy, necrotizing enterocolitis, and intraventricular hemorrhage compared to appropriately grown fetuses. Antenatal fetal surveillance in preeclamptic pregnancies includes weekly or twice-weekly cardiotocography (CTG), umbilical artery Doppler velocimetry (absent or reversed end-diastolic flow indicating severe placental insufficiency and mandating delivery or intensive monitoring), middle cerebral artery Doppler (brain-sparing redistribution), and ductus venosus Doppler (reflecting fetal cardiac decompensation—a-wave reversal indicating imminent fetal demise) [4].

The long-term cardiovascular consequences of preeclampsia represent a critically important but underappreciated dimension of the condition's total burden [8]. Bellamy and colleagues conducted a systematic meta-analysis of 25 studies encompassing 3,488,160 women, demonstrating that women with a history of preeclampsia have substantially elevated lifetime risks of major cardiovascular events compared to women with normotensive pregnancies: the risk of hypertension is increased 3.70-fold (95% CI 2.70–5.05), ischemic heart disease 2.16-fold (95% CI 1.86–2.52), stroke 1.81-fold (95% CI 1.45–2.27), and venous thromboembolism 1.87-fold (95% CI 1.28–2.72) over follow-up periods of 5–30 years [8]. These elevated risks are independent of conventional cardiovascular risk factors—including hypertension, obesity, and dyslipidemia measured at study entry—suggesting that preeclampsia either reveals pre-existing susceptibility to endothelial dysfunction or causes durable vascular injury that persists after placental delivery. Women with early-onset or recurrent preeclampsia carry the highest long-term cardiovascular risk, with absolute 10-year risks of ischemic heart disease exceeding the thresholds for statin prophylaxis in many risk scoring systems. Current ISSHP and ACOG guidelines recommend formal cardiovascular risk assessment in all women with a history of preeclampsia at their 6–12 week postpartum visit and annually thereafter [1, 8].

4. DISCUSSION

The evidence reviewed in this article documents a paradigm shift in preeclampsia management over the past two decades—from a condition managed reactively upon clinical presentation to one that can now be predicted in the first trimester with high sensitivity, prevented in high-risk women with aspirin prophylaxis, and monitored with validated biomarker algorithms that stratify severity and guide management decisions [4, 5]. The FMF competing-

risks algorithm represents the most clinically validated and methodologically robust approach to first-trimester preeclampsia risk stratification, achieving detection rates that are more than twice those of the conventional risk factor-based approaches still recommended by NICE and ACOG guidelines at equivalent false-positive rates. The widespread implementation of combined first-trimester screening in Uzbekistan and Central Asian obstetric settings would require investment in UtA-PI Doppler training for sonographers, validated PlGF and PAPP-A immunoassay platforms, and clinical informatics tools for algorithm-based risk calculation—but would deliver the dual benefit of identifying high-risk women for aspirin prophylaxis while simultaneously providing Down syndrome and other chromosomal aneuploidy screening through the same 11–14 week scan visit [4].

The ASPRE trial's demonstration of 62% reduction in preterm preeclampsia with aspirin 150 mg from 11–14 weeks has created a clear, actionable evidence-based pathway for preeclampsia prevention in FMF-identified high-risk pregnancies [5]. The clinical and public health significance of this finding is amplified by the concentration of preterm preeclampsia's burden: while term preeclampsia is more frequent by volume, preterm preeclampsia (< 37 weeks) accounts for the overwhelming majority of severe maternal complications (eclampsia, HELLP, stroke), perinatal deaths, and long-term neonatal morbidity from extreme prematurity. Preventing preterm preeclampsia through aspirin thus simultaneously addresses maternal safety, perinatal survival, and the long-term developmental outcomes of children born extremely preterm. The cost-effectiveness analysis from the ASPRE trial estimated that screening-directed aspirin prophylaxis prevents one case of preterm preeclampsia per 37 screened women (NNT = 37) at a cost of approximately USD 250 per prevented case—a health economic argument that is compelling even in resource-constrained healthcare systems [5].

The CHIPS trial's key clinical message—that targeting a diastolic blood pressure of 85 mmHg is safe for the fetus (no increase in growth restriction or perinatal loss) while significantly reducing maternal severe hypertension episodes compared to the traditionally permissive 100 mmHg target—has been incorporated into the 2018 ISSHP guidelines and represents an important evidence-based upgrade of blood pressure management practice in pregnancy [6]. The implication for clinical practice is that obstetricians and midwives should no longer delay antihypertensive treatment until blood pressure reaches the "severe" threshold (SBP ≥ 160 or DBP ≥ 110 mmHg), but should initiate or escalate antihypertensive therapy in women with sustained non-severe hypertension (SBP ≥ 140 or DBP ≥ 90 mmHg) to reach the 85 mmHg diastolic target. This shift from a passive "wait for severe hypertension" approach to an active "treat to target" strategy parallels similar evidence-based transitions in other specialties (cardiovascular medicine, nephrology) and should similarly improve maternal outcomes by reducing the frequency of hypertensive emergencies requiring emergency delivery.

The Magpie Trial's definitive evidence for magnesium sulfate's efficacy in eclampsia prevention establishes an absolute standard of care for women with severe preeclampsia that is difficult to ethically justify withholding, yet consistently underprovided in LMIC settings including parts of Central Asia [7]. The barriers to $MgSO_4$ utilization in these settings—supply chain unreliability, provider concerns about toxicity, absence of monitoring protocols, and absence of calcium gluconate antidote—are all modifiable through targeted quality improvement interventions. The WHO's recommendation that $MgSO_4$ be included on the essential medicines list and that its administration be within the competency of all skilled birth attendants (including midwives, not only physicians) provides the policy framework for addressing this gap. Implementation of standardized $MgSO_4$ administration protocols with embedded safety checklists (reflexes, respiratory rate, urine output monitoring frequency specified) in all facilities

providing obstetric care in Uzbekistan would represent a high-impact, low-cost patient safety intervention with direct mortality reduction potential [2].

The long-term cardiovascular risk legacy of preeclampsia documented by Bellamy et al. has clinical implications that extend far beyond the obstetric unit into primary care and cardiology [8]. The 2–3-fold elevated lifetime risks of hypertension, ischemic heart disease, and stroke in women with prior preeclampsia are of comparable magnitude to the cardiovascular risk conferred by smoking or type 2 diabetes, yet preeclampsia history is rarely systematically captured or acted upon in post-reproductive primary care. The integration of preeclampsia history into cardiovascular risk calculators—included in the Framingham Risk Score recalibration proposals and the American Heart Association/American College of Cardiology 2019 Cardiovascular Risk Guideline as a "risk-enhancing factor" mandating earlier statin and antihypertensive consideration—represents an important translational advance, but requires active communication between obstetric providers (who know the pregnancy history) and primary care providers (who will manage the long-term cardiovascular risk) through robust medical record documentation and structured postpartum care pathways [8].

Emerging research frontiers in preeclampsia include: liquid biopsy approaches (circulating cell-free fetal DNA and placenta-derived extracellular vesicles as first-trimester biomarkers of placental dysfunction, with potential to enhance FMF algorithm performance); therapeutic interventions targeting the sFlt-1 excess (extracorporeal apheresis of sFlt-1 from maternal plasma, which reduced sFlt-1 by 20–40% and prolonged pregnancy by a mean of 15 days in pilot RCTs, potentially bridging to viability in extremely early-onset cases); low-molecular-weight heparin (LMWH) as an adjunct to aspirin for women with antiphospholipid syndrome or thrombophilias where the thromboinflammatory mechanism of defective trophoblast invasion may be amenable to anticoagulant intervention; and statins (particularly pravastatin), which have shown promising preclinical anti-sFlt-1 and placental angiogenesis-promoting effects and are undergoing evaluation in phase II clinical trials [3]. The convergence of multiomics placental profiling, machine learning-enhanced biomarker algorithms, and precision pharmacological prevention strategies holds genuine promise for further reducing the global burden of preeclampsia over the next decade.

5. CONCLUSION

This systematic review has established that preeclampsia—one of the most consequential and complex disorders in obstetric medicine—is now approachable through a coherent evidence-based framework spanning from first-trimester pathological risk assessment to biomarker-driven diagnosis, targeted pharmacological prevention, evidence-based management of acute hypertension and seizure prophylaxis, and structured long-term cardiovascular risk management. The central mechanistic insight of defective trophoblast invasion producing antiangiogenic factor imbalance (elevated sFlt-1, reduced PlGF) provides a unified pathophysiological explanation for both the clinical syndrome and the evidence base supporting targeted preventive and diagnostic interventions. The sFlt-1/PlGF ratio, validated against clinical outcomes in prospective multicenter studies, represents the most mature clinical biomarker in obstetric medicine and should be integrated into antenatal monitoring protocols for women at risk of or developing preeclampsia.

The ASPRE trial's demonstration of 62% reduction in preterm preeclampsia through first-trimester screening-directed aspirin 150 mg prophylaxis represents the most important advance in preeclampsia prevention since the Magpie Trial established magnesium sulfate's role in

eclampsia prevention. Together, these evidence-based interventions—universal first-trimester combined screening with the FMF competing-risks algorithm, aspirin prophylaxis from 11–14 weeks in high-risk women, antihypertensive treatment to the 85 mmHg diastolic target informed by the CHIPS trial, and magnesium sulfate for all severe preeclampsia—constitute a prevention and management bundle whose coordinated implementation in Uzbekistan's obstetric services would substantially reduce both the maternal and perinatal mortality burden attributable to hypertensive disorders of pregnancy.

The recognition that preeclampsia is not simply an obstetric condition but a lifelong cardiovascular risk marker—with 2–3-fold elevated risks of hypertension, ischemic heart disease, and stroke persisting decades after delivery—mandates a paradigm shift in how women's health services conceptualize and document reproductive history. Structured postpartum cardiovascular risk assessment at 6–12 weeks following preeclamptic pregnancies, with clear communication to primary care providers and annual cardiovascular risk monitoring thereafter, represents an achievable and cost-effective extension of preeclampsia's clinical management that will prevent cardiovascular deaths in a population whose risk is currently largely unrecognized and unaddressed in routine primary care.

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