



FIRST TRIMESTER SCREENING AND PREVENTION FOR PREECLAMPSIA AND FETAL GROWTH RESTRICTION: PERSPECTIVE IN BULGARIA

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ABSTRACT

Preeclampsia (PE) and fetal growth restriction (FGR) are major contributors to maternal and perinatal morbidity and mortality worldwide. In Bulgaria, the burden of these conditions is compounded by delayed diagnosis and limited access to comprehensive early screening. First-trimester screening enables the identification of high-risk pregnancies through maternal risk factors, biomarkers, and Doppler ultrasonography. Preventive strategies, particularly the timely administration of low-dose aspirin, have proven effective in reducing the incidence of early-onset PE and FGR. This review summarizes current evidence on the pathophysiology, screening models, and prevention strategies for PE and FGR, with emphasis on their implementation in Bulgarian clinical practice. Recommendations are provided for enhancing maternal care through national policies and expanded screening programs.

Keywords: preeclampsia, first trimester screening, fetal growth restriction, gestational age, pregnancy,

INTRODUCTION

Primary prevention and early evaluation of preeclampsia (PE) and fetal growth restriction (FGR) are gaining increasing importance for pregnant women in Bulgaria and their future children. PE affects approximately 2%–15% of all pregnancies and remains a leading global cause of both maternal and fetal complications. In the later stages of pregnancy (≥ 20 weeks of gestation), PE may present with hypertension accompanied by proteinuria, progressive edema not attributable to anemia, thrombocytopenia or other hematologic disorders, renal insufficiency, hepatic involvement, pulmonary edema, or neurological dysfunction [1].

First-trimester screening for PE and FGR offers a critical opportunity to identify pregnancies at elevated risk and initiate timely interventions. Early management is essential to prevent the development of severe forms of PE, which may involve multi-organ dysfunction, impaired placental perfusion, intrauterine growth restriction, and preterm birth. Implementing risk assessment and management strategies in the first trimester has the potential to reduce maternal and fetal morbidity and mortality in Bulgaria and improve overall maternal-infant health outcomes [2].

Prevention and early detection of PE and FGR in early pregnancy are associated with improved maternal and neonatal outcomes. First-trimester screening, performed before 14 weeks of gestation, typically includes an evaluation of maternal risk factors, biochemical markers, and fetal anatomical indicators via ultrasound [3]. Multiple studies have demonstrated that the early identification of high-risk pregnancies enables healthcare providers to recommend the use of low-dose aspirin,

thereby reducing the incidence of early-onset PE (gestational age <34 weeks) and FGR [4–6].

It is important to distinguish between early-onset and late-onset preeclampsia, with the latter occurring after 34 weeks of gestation, as these two forms often differ in their underlying pathophysiology, prevention strategies, and therapeutic approaches.

Given their impact on perinatal outcomes, PE and FGR should be prioritized in prenatal care. Both conditions can be screened for during the first trimester, between 11 and 14 weeks of gestation [3]. Risk stratification is typically based on biomarkers such as placental growth factor (PIGF), uterine artery Doppler indices, and maternal characteristics including age, BMI, blood pressure, and medical history [7]. Improving awareness, accessibility, and implementation of these early screening methods in Bulgaria is necessary to reduce pregnancy complications, lower healthcare costs, and improve outcomes for mothers and newborns.

Although the exact etiology of preeclampsia remains unclear, several theories have been proposed. The widely accepted two-stage model posits that shallow trophoblast invasion and inadequate uteroplacental perfusion occur during early placentation (Stage I) [8]. This impaired circulation results in systemic endothelial dysfunction, which underlies the clinical manifestations of PE. The interval between these stages provides a valuable window for early prediction and subclinical intervention.

The administration of low-dose aspirin from the first trimester is recommended to reduce the risk of vascular complications in pregnancy, including PE and FGR. Evidence suggests that prophylaxis should begin before 16 weeks of gestation and may continue until 36 weeks [9]. Although early intervention is beneficial, some cases of PE may still occur, highlighting the complexity of the condition and the need for continued surveillance throughout pregnancy. Given the significant contribution of PE to maternal and fetal morbidity and mortality, understanding its epidemiology, risk factors, and economic burden is of critical importance [10].

First-trimester screening and prevention represent some of the most cost-effective approaches in obstetric care [11]. Therefore, the development of accurate predictive models and timely interventions is essential, especially considering the two-stage pathogenesis of PE. Dur-

ing early pregnancy, inadequate trophoblast invasion may result in improper placental development and compromised blood supply to the placenta [12]. As this stage is typically asymptomatic, it is the ideal period for screening.

This review aims to synthesize current data and recent research developments on the pathogenesis, diagnostic markers, prevention, and treatment of severe PE and FGR. The primary objective is to evaluate established screening protocols and promote their integration into routine obstetric practice in Bulgaria.

MATERIALS AND METHODS

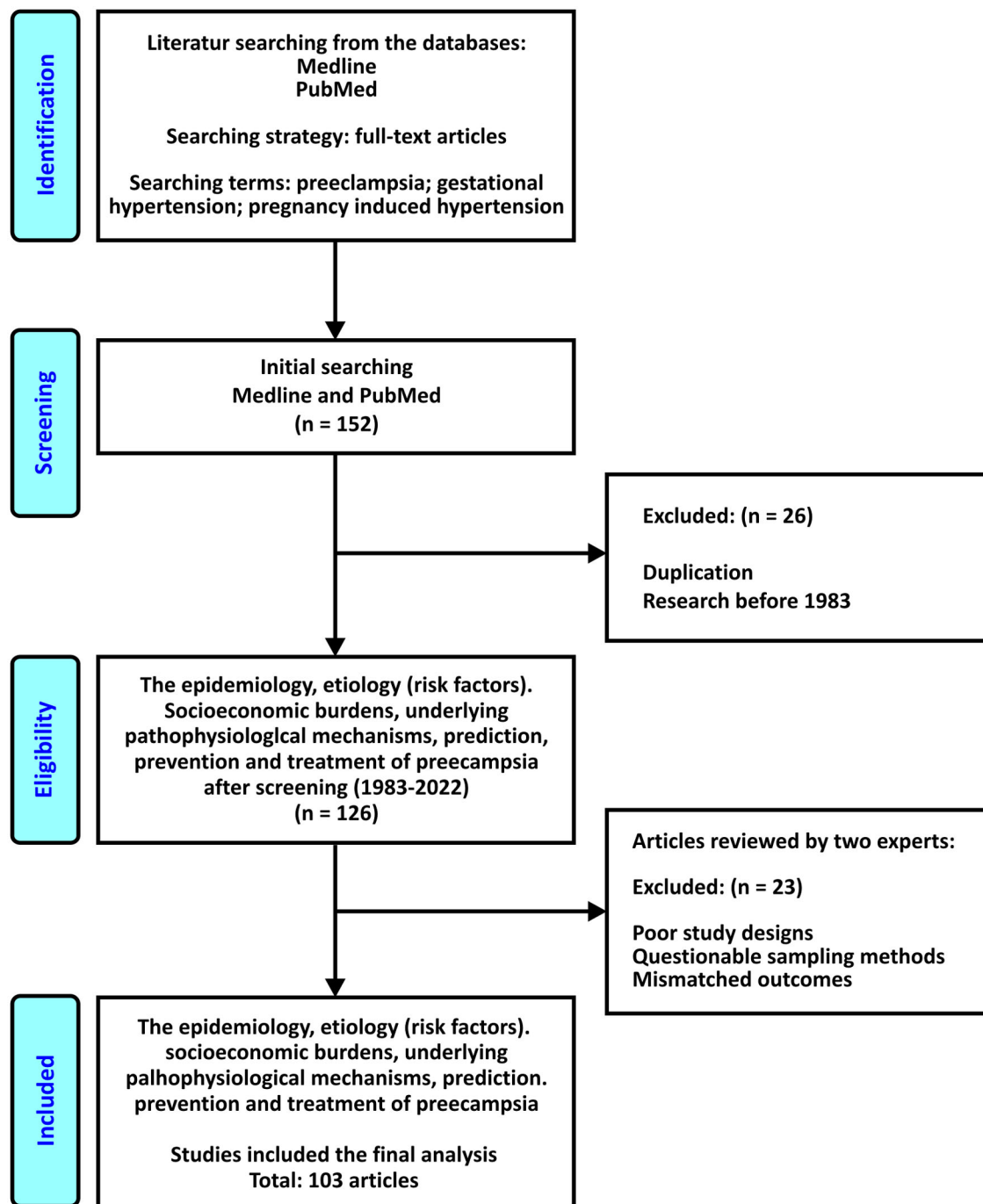
Using criteria such as epidemiology, risk factors, socio-economic impact, pathophysiology, early prediction, prevention, and treatment of various diseases, a systematic review was conducted. The databases Medline and PubMed were searched using the keywords: preeclampsia, fetal growth restriction, and first-trimester screening. To ensure comprehensiveness, only full-text articles and journals were included. Where applicable, studies published before 1983 were excluded to maintain relevance and reflect contemporary medical practices.

Out of 152 initially identified papers, 126 met the inclusion criteria for studies published between 1983 and 2024. This review analyzes the outcomes with the aim of increasing awareness among healthcare providers regarding the risks of preeclampsia and FGR during early pregnancy, and it evaluates strategies applicable to the Bulgarian healthcare context for early detection and management of these conditions.

Two independent researchers reviewed the Bulgarian literature on first-trimester screening and the FIRSTLINE preventive strategies, focusing on demographic data, study design, and reported outcomes. Studies with inappropriate design, flawed sampling methods, or unreliable results were excluded. The reviewers assessed discrepancies between studies and reached consensus through discussion.

A systematic process was followed, including search term identification, database screening, article selection, and final inclusion based on predefined eligibility criteria. Ultimately, out of the 152 initially retrieved papers, 103 were selected for inclusion in the final review.

Fig. 1. Flowchart of database searching, screening, and inclusion of the references selected from the literature.



RESULTS

The outcomes of preeclampsia and FGR in the Bulgarian population remain suboptimal—for women, newborns, the healthcare system, and society as a whole. Reducing maternal and fetal risks requires the implementation of preventive measures for preeclampsia and FGR beginning in the first trimester of pregnancy. The Bulgarian Society of Obstetrics and Gynecology has recommended a prediction model that incorporates established risk factors. This model systematically includes high-risk indicators such as a history of preeclampsia in previous

pregnancies, chronic hypertension, autoimmune disorders, renal disease, diabetes mellitus, and multifetal gestation. Additional moderate risk factors include nulliparity or multiparity, maternal age over 35 years, maternal weight greater than 90 kg, and a history of spontaneous abortion. Risk factors for incident diabetes, relevant to Bulgarian screening and prevention efforts, include a prior medical history of the condition and persistent hypertension. These predictive models support healthcare providers in refining early intervention strategies aimed at reducing the incidence of preeclampsia and FGR among pregnant women.

Table 1. A comparison between different screening models of preeclampsia.

Organization	NICE (National Institute for Health and Care Excellence)	ACOG (American College of Obstetricians and Gynecologists)	ISSHP (International Society for the Study of Hypertension)	FMF (Fetal Medicine Foundation)
Screening method	Based on number of risk factors	Based on number of risk factors	Based on number of risk factors	Bayes theorem: to combine the a priori risk from maternal characteristics and results of various biomarkers
	High-risk factors:	High-risk factors:	High-risk factors:	- MAP (mean arterial pressure)
	Previous pregnancy with preeclampsia	Previous pregnancy with preeclampsia	Previous pregnancy with preeclampsia	- UtA-PI - (uterine artery pulsatility index)
	Chronic hypertension	Chronic hypertension	Chronic hypertension	- PAPP-A (serum pregnancy - associated plasma protein A)
	Autoimmune disease	Autoimmune disease	Autoimmune disease	
	Diabetes mellitus	Diabetes mellitus	Diabetes mellitus	
		Multifetal pregnancy	Renal disease	
		Renal disease	Initial BMI $\geq 30 \text{ kg/m}^2$	
	Moderate-risk factors:	Moderate-risk factors:	Moderate-risk factors:	
	Nullparity	Nullparity	Nullparity	
	Age ≥ 40 y/o	Age ≥ 35 y/o	Age ≥ 35 y/o	
	Interpregnancy interval ≥ 10 years	Interpregnancy interval ≥ 10 years	Family history of preeclampsia	
	Initial BMI $\geq 35 \text{ kg/m}^2$	Initial BMI $\geq 30 \text{ kg/m}^2$	<6m sexual relationship before pregnancy	
	Family history of preeclampsia	Family history of preeclampsia	Connective tissue disorder	
	Multifetal pregnancy	History of SGA or adverse outcomes		
		Socioeconomic features		
Detection rate	Preterm: 41%	Preterm: 5%	Not documented	8.2%, 64.0%, 71.8%, and 75.8% at 5%, 10%, 15% and 20% fixed FPRs
	Term: 34%	Term: 2%		
False positive rate	Preterm: 10%	Preterm: 0.2 %	Not documented	
	Term: 10%	Term: 0.2 %		

Maternal and neonatal outcomes in Bulgaria are strongly influenced by first-trimester assessment and prevention of PE and FGR. Risk assessment based on maternal history and characteristics can be individualized and dynamic when applying Bayes' theorem [12]. The Fetal Medicine Foundation (FMF) performs both internal and external validation of its prediction model. A comprehensive checklist is used to evaluate all relevant risk variables, including maternal factors such as mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and serum pregnancy-associated plasma protein A (PAPP-A).

The optimal timeframe for PE screening is between 11 and 13 weeks of gestation, as part of the combined first-trimester screening. Preventive measures for high-risk preeclampsia should begin as soon as risk is identified.

Large-scale studies have assessed the prognostic value of biomarkers such as soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), and their ratio in predicting preeclampsia [10]. One evaluation included 33 eligible trials encompassing 9,426 participants. Plasma PlGF—and particularly the sFlt-1/PlGF ratio—demonstrated reasonable predictive accuracy, with receiver operating characteristic (ROC) values ranging from 0.68 to 0.87 for adverse maternal and perinatal outcomes, including preterm birth and FGR.

Several prediction models for gestational hypertension and preeclampsia have been developed based on data from high-income countries. Among 40 reviewed studies, 28 integrated maternal clinical features with biomarkers—most commonly PAPP-A and PlGF. However, only five of these studies addressed the applicability of such models in low- and middle-income country (LMIC) contexts. This review assesses whether external validation is needed before implementing predictive models in Bulgaria, where access to biomarker testing may be limited.

Preventive Measures

Prevention of preeclampsia and FGR is typically categorized as primary, secondary, or tertiary prevention [13]. Primary prevention aims to avoid pregnancies in individuals at high risk of these conditions, often through lifestyle interventions [14]. However, achieving primary prevention remains challenging. In Bulgaria, secondary prevention has emerged as the primary area of focus, targeting the early detection and management of preeclampsia and FGR. Tertiary prevention centers on minimizing complications from established disease.

Combining aspirin prophylaxis with lifestyle modifications, nutritional supplementation, and routine prenatal monitoring may enhance the effectiveness of both primary and secondary prevention strategies. Recommended interventions include rest, moderate exercise, a low-sodium diet, antioxidants, and 150 mg of aspirin daily [3]. Unfortunately, not all of these strategies have demonstrated consistent efficacy.

This study reviewed the effects of various agents and interventions, including heparin, enoxaparin,

dalteparin, nadroparin, aspirin, pravastatin, nitric oxide, yoga, and micronutrients such as L-arginine, folic acid, vitamins E and C, phytonutrients, lycopene, vitamin D, and calcium [15]. Evidence suggests that low-molecular-weight heparin (enoxaparin), yoga, L-arginine, folic acid, and vitamin D with calcium may reduce the incidence of preeclampsia and FGR. These findings highlight the necessity for first-trimester screening and individualized treatment strategies to improve maternal and fetal outcomes in Bulgaria.

Low-Dose Aspirin

Evidence supports recommending daily low-dose aspirin for Bulgarian women identified as high risk for preeclampsia, beginning in the first trimester. Aspirin exerts antithrombotic effects by irreversibly inhibiting cyclooxygenase-1 (COX-1), thereby reducing the synthesis of thromboxane A2 (TXA2) while preserving prostacyclin (PGI2) function [16]. A daily dose of 150 mg selectively inhibits TXA2 without impairing PGI2 activity.

Although the role of aspirin in primary prevention within obstetrics and cardiovascular medicine remains somewhat controversial [17], its benefits—particularly when initiated early—are supported by substantial evidence. Clinicians must carefully weigh the potential benefits against risks such as gastrointestinal bleeding, intracranial hemorrhage, and bleeding in susceptible individuals.

Since the initial recognition of aspirin's preventive potential in 1978, numerous studies have evaluated its effectiveness. Recent meta-analyses show that aspirin is most effective when initiated before 16 weeks of gestation—prior to placentation [18]. The ASPRE trial demonstrated that timely initiation of aspirin prophylaxis, coupled with high adherence, can reduce the risk of early-onset preeclampsia by 76%–90%.

A meta-analysis of 18,907 participants across eight studies found that aspirin significantly reduced the risk of preterm preeclampsia (relative risk: 0.62; 95% CI: 0.45–0.87), although no significant effect was found for term preeclampsia [19]. The greatest benefit was observed in women who began aspirin therapy at or before 16 weeks and received a dose of at least 100 mg daily (RR: 0.33; 95% CI: 0.19–0.57). Therefore, initiating aspirin early in pregnancy at an adequate dose is critical for reducing preterm preeclampsia risk.

The Bulgarian Association of Obstetrics and Gynecology recommends initiating low-dose aspirin therapy (150 mg daily) between 12 and 16 weeks of gestation and continuing until 35 weeks [20]. Although low-dose aspirin rarely causes bleeding complications, some women may experience gastrointestinal discomfort.

An integrated screening and prevention program—including first-trimester risk assessment and low-dose aspirin prophylaxis—remains essential to improving maternal and neonatal outcomes in Bulgaria by reducing the incidence of preeclampsia and fetal growth restriction.

Table 2. Recommendations for administration of low-dose aspirin in women at risk of future preeclampsia.

Organization	ACOG 2018	USPSTF 2021	NICE 2019	ISSHP 2018	FIGO 2019
Indication	Recommend in high-risk patients	Recommend in patients with ≥ 1 high-risk factors or 2 moderate-risk factors	Recommend in high-risk patients	Recommended in high-risk patients	Recommended in high-risk patients or when the risk is $\geq 1/100$
	Considered in patients with 1 or more moderate risk factors	Considered in patients with ≥ 1 moderate risk factors	Considered in patients with 1 or more moderate risk factors		
Timing	Initiate between GA 12 and 28 weeks (best before GA 16 weeks) and use until delivery	Initiate \geq GA 12 weeks	Initiate \geq GA 12 weeks and use until delivery	Initiate \leq GA 20 weeks (best before GA 16 weeks)	Initiate between GA 11 and 14 weeks and use until GA 36 weeks, delivery or preeclampsia
Dosage	81 mg/day	81 mg/day	75-150 mg/day	75-162mg/day	150 mg/day

DISCUSSION

The present systematic review of first-trimester screening and prevention strategies for PE and FGR in Bulgarian women highlights key aspects including epidemiology, risk factors, screening models, and prevention strategies. Given the significant maternal and neonatal morbidity and mortality associated with PE and FGR, early identification and intervention are essential.

The first trimester is considered the most effective period for risk assessment and diagnosis of PE and FGR, as confirmed by this review. In the context of the two-stage hypothesis of preeclampsia, particular emphasis is placed on early trophoblast development and placentation. This underscores the importance of integrating maternal characteristics with clinical history to efficiently screen high-risk individuals. Expert evaluations further indicate that predictive algorithms can more accurately identify women at elevated risk for these complications.

Predictive Models and Risk Assessment

Many existing predictive models are based on data derived from industrialized countries and may not be directly applicable to the Bulgarian population or healthcare system. While current models often combine maternal characteristics with biomarkers effectively, there is limited research tailored to the Bulgarian context. Future predictive models should consider incorporating additional risk factors such as socioeconomic status, access to healthcare, and genetic predispositions. Advanced risk assessment methods, including the application of Bayes' theorem, may also allow for more individualized screening and intervention approaches.

Preventive Strategies

Managing preeclampsia and FGR remains a clinical challenge, underscoring the need for effective prevention strategies. Categorizing prevention into primary, secondary, and tertiary levels helps clarify the scope of possible interventions. Although primary prevention (e.g., avoiding high-risk pregnancies) is difficult to implement, secondary prevention—such as early screening and timely initiation of low-dose aspirin—shows considerable promise [15]. Aspirin, when administered early in pregnancy, has been shown to reduce the incidence of early-onset PE in specific high-risk groups, according to international guidelines.

Recent studies also suggest that lifestyle modifications and nutritional supplementation may enhance the effects of pharmacologic prevention, highlighting the potential of a combined preventive approach.

Implications for Future Research and Policy

The findings of this review have substantial implications for both healthcare policy and research in Bulgaria. Currently, there is a lack of local studies evaluating the appropriateness of screening and intervention strategies specific to the Bulgarian population. Policymakers should base recommendations on locally derived data, thereby adapting international guidelines to meet the specific needs of Bulgarian women [21].

Enhancing public health efforts to increase awareness of early disease detection—among both healthcare providers and the general population—could improve maternal health literacy and participation in screening programs. This, in turn, may lead to better maternal and neonatal outcomes and reduce the healthcare and societal burdens imposed by PE and FGR [22].

This systematic review suggests that Bulgaria needs to improve first-trimester screening and prevention rates for PE and FGR. By optimizing predictive models, implementing effective prevention measures, and continually reviewing current clinical practices, healthcare professionals can significantly reduce the adverse outcomes associated with these conditions [23].

Ultimately, bridging gaps in knowledge and clinical practice is fundamental to improving maternal and fetal health outcomes within the Bulgarian healthcare system.

In the Bulgarian context, several studies and professional guidelines emphasize the urgent need to incorporate first-trimester screening for preeclampsia and FGR into routine prenatal care. According to the Bulgarian Society of Obstetrics and Gynecology, risk stratification models should be adapted to local demographic and healthcare realities, taking into account regional disparities in maternal outcomes and limited access to certain biomarkers [24]. A recent national report by the Ministry of Health confirms that hypertensive disorders, including preeclampsia, remain among the leading causes of maternal complications, with preeclampsia-related morbidity showing limited improvement over the past decade [25]. These local adaptations aim to translate the predictive power of models developed in high-income settings into the context of the Bulgarian healthcare system, where national-level data are still limited. This approach aligns with global efforts to restructure prenatal care toward early screening and prevention, as originally advocated by Nicolaides in his “Turning the Pyramid of Prenatal Care” concept [26]. Incorporating uterine artery Doppler, mean arterial pressure, serum PAPP-A, and PIGF at 11–13 weeks has shown strong predictive accuracy in international studies [27], and its local validation is crucial for successful implementation. Taken together, these findings strongly support the urgent need to integrate first-trimester screening and evidence-based preventive measures into national prenatal care policies in Bulgaria to reduce the burden of preeclampsia and FGR.

A retrospective cohort study involving over 9,000 pregnant women found that maternal serum markers (PAPP-A and PIGF), mean arterial pressure (MAP), and uterine artery pulsatility index (UtA PI) were significant independent predictors of PE in Bulgaria [1]. Additionally, a prospective cohort study assessed ophthalmic artery Doppler parameters in 200 Bulgarian women between 19 and 23 weeks’ gestation and demonstrated that the PSV2/PSV1 ratio effectively distinguished high-risk pregnancies, suggesting its potential as an early diagnostic tool for PE [28].

These findings support the argument that a multifaceted screening approach—employing biochemical, biophysical, and vascular assessments—should be adop-

ted across Bulgarian prenatal care to enable early risk identification and timely prevention of PE and FGR.

CONCLUSION

Screening and prevention programs for preeclampsia and fetal growth restriction are of critical importance in Bulgaria, and this study supports the implementation of global advancements aimed at improving maternal and fetal health. Preeclampsia is a common pregnancy-related disorder associated with substantial morbidity and mortality for both mother and fetus. It presents with a range of systemic symptoms—most notably hypertension—that make the condition complex and necessitate careful monitoring and management.

Non-invasive first-trimester screening is essential, with particular emphasis on maternal characteristics, first- and second-trimester ultrasonography (especially assessment of uterine artery blood flow), and biochemical markers such as PIGF and PAPP-A. These assessments should be accompanied by evaluations of the risk for other pregnancy complications, including fetal aneuploidy. Early identification of at-risk individuals enables healthcare providers to implement timely risk management and initiate preventive therapies that may reduce the severity of preeclampsia and its associated complications.

The early detection and prevention of preeclampsia and fetal growth restriction is not only a medical priority but also a moral imperative, as it contributes directly to improving maternal and neonatal health outcomes. High-quality healthcare delivery must therefore rely on evidence-based methods and timely interventions to effectively manage these critical conditions.

In order to improve maternal and neonatal health outcomes, several key policy measures should be prioritized at the national level. First, it is essential that Bulgarian health authorities adopt and finance structured first-trimester screening programs for preeclampsia (PE) and fetal growth restriction (FGR) as part of routine public healthcare services. These programs should be based on evidence-based models and tailored to local clinical settings. Second, efforts must be made to validate and adapt international screening algorithms, such as the Fetal Medicine Foundation (FMF) model, to the Bulgarian population through locally generated epidemiological and clinical data. Third, continuous professional development programs for obstetricians, maternal–fetal medicine specialists, and midwives should incorporate updated protocols on early screening, risk assessment, and preventive interventions. Finally, targeted public health campaigns are needed to increase awareness among pregnant women about the importance of early antenatal care and the benefits of individualized, risk-based pregnancy monitoring. These coordinated policy actions are critical to ensure equitable access to preventive care and to align

Bulgaria with global standards in obstetric practice.

Implementing these strategies nationally will close current practice gaps, reduce maternal and neonatal morbidity, and align Bulgarian prenatal care with international standards.

Abbreviation list:

BMI – body mass index

COX-1 – cyclooxygenase 1

FGR – fetal growth restriction

FMF – Fetal Medicine Foundation

GA – gestational age

MAP – mean arterial pressure

PAPP-A – serum pregnancy-associated plasma protein A

PE – preeclampsia

PGI2 – prostacyclin

PIGF – Placental growth factor

sFlt-1 – soluble fms-like tyrosine kinase-1

TXA2 – thromboxane A2

UtA-PI – uterine artery pulsatility index

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