(REVIEW ARTICLE)

Ultrasound and biochemical first trimester markers as predictive factors for intrauterine growth restriction: Systematic review

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Abstract

Background: Intrauterine growth restriction (IUGR) is important cause of perinatal morbidity and mortality. Early identification of pregnancies at risks enables timely interventions and improved outcomes. First trimester ultrasound and biochemical markers (pregnancy-associated plasma protein-A (PAPP-A)) and uterine artery Doppler indicators, show a potential as predictive tools for IUGR, but evidence is different. In this study we aimed to systematically review and evaluate the predictive value of ultrasound and biochemical markers in the first trimester to detect intrauterine growth restriction.

Methods: A literature search was conducted in major databases, which include PubMed and Scopus, for studies published between 2005 and 2024. Inclusion criteria comprised original research studies which evaluate first trimester markers (PAPP-A, Plage, β-chg., and uterine artery Doppler indicators) in relation to IUGR outcomes. Data were extracted on study design, population characteristics, predictive methods, and outcomes.

Results: Eight studies met the inclusion criteria. All included studies examined PAPP-A levels, with the majority reporting lower levels in pregnancies complicated by IUGR. Several studies include uterine artery Doppler and PlGF as part of combined predictive models, which improved sensitivity. The detection rates for IUGR using integrated approaches are more than 70% in several studies. Variations in marker thresholds, definitions of IUGR, and study designs limited generalizability.

Conclusion: First trimester biochemical and ultrasound markers, mainly PAPP-A and uterine artery Doppler indicators, show potential in predicting IUGR. Integrative screening models in combination with maternal characteristics, serum biomarkers, and Doppler ultrasound produce higher predictive value.

Keywords: Intrauterine Growth Restriction; First Trimester Screening; Papp-A; Uterine Artery Doppler; Placental Growth Factor; Fetal Growth Restriction; Prenatal Prediction; Biochemical Markers

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1. Introduction

Intrauterine growth restriction (IUGR) is one of the most significant contributors to perinatal morbidity and mortality, mainly in resource-limited settings. IUGR is defined as the failure of a fetus to achieve its predetermined growth and is commonly measured by an estimated fetal weight or birth weight below the 10th percentile for gestational age. This definition includes constitutionally small fetuses and misses growth restricted fetuses above this threshold, which complicates clinical diagnosis and risk stratification (Shrivastava et al. 2020).

The pathophysiology of IUGR is most commonly caused by impaired placental development. Deficiencies in uteroplacental circulation during the early stages of pregnancy compromise nutrient and oxygen delivery to the fetus, which result in poor fetal growth parameters (Hong et al. 2023). This pathogenesis indicates the need for early detection tools capable of identifying pregnancies at risk before clinical manifestations appear.

The first trimester gives a critical window for risk assessment and gives opportunity for preventative strategies. Pregnancy-associated plasma protein-A (PAPP-A) and beta-human chorionic gonadotropin (β-chg.) have been widely studied. Several studies show that low PAPP-A levels during the first trimester are associated with increased risk of IUGR and other adverse outcomes (Abdollahi et al. 2011). Ultrasound-based assessments [uterine artery Doppler velocimetry and nuchal translucency (NT)] are investigated for their predictive utility in fetal growth disorders. Increased uterine artery resistance, measured by elevated plasticity index (PI), was associated with impaired placentation and fetal underdevelopment (Wang et al. 2017).

An integrated methods combines ultrasound and biochemical markers give higher predictive accuracy than alone methods. A recent study shows that combining uterine artery Doppler indicators, maternal mean arterial pressure (MAP), and serum biomarkers like PAPP-A and placental growth factor (Plage) provided better detection rates for IUGR, mainly in early-onset cases (Pinnatisect et al. 2022). Our review aims to discuss available evidence on the use of first-trimester ultrasound and biochemical markers for predicting intrauterine growth restriction.

2. Methodology

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search was performed using PubMed, Scopus, ScienceDirect, and Google Scholar databases to identify original research articles published between 2005 and 2024. Keywords and medical subject headings (MESH) include; first trimester, ultrasound, biochemical markers, PAPP-A, β-chg., uterine artery Doppler, intrauterine growth restriction, and fetal growth restriction.

We include original research articles published in English; investigated the predictive value of first trimester biochemical and/or ultrasound markers for IUGR or FGR; involved singleton pregnancies; and provided quantitative results relating to screening or diagnostic performance. We exclude reviews, editorials, case reports, conference abstracts, and non-human studies.

Two independent reviewers screened titles and abstracts. Full texts of eligible articles were retrieved and assessed for inclusion criteria. Data were extracted with a standardized form that included citation, study design, population characteristics, predictive markers or methods used, study aim, methodology, and outcomes. Discrepancies in study selection or data extraction were resolved through discussion with a third reviewer. A qualitative synthesis was performed, data were grouped based on marker type (biochemical, ultrasound, or combined models) and summarized descriptively. Eight studies met the inclusion criteria and were included in the final analysis (Ismail et al., 2024; Springer et al., 2023; He et al., 2020; Poon et al., 2018; Benítez et al., 2017; Yu et al., 2017; Falcon et al., 2006; Spencer et al., 2005) (Fig 1) (Table 1).
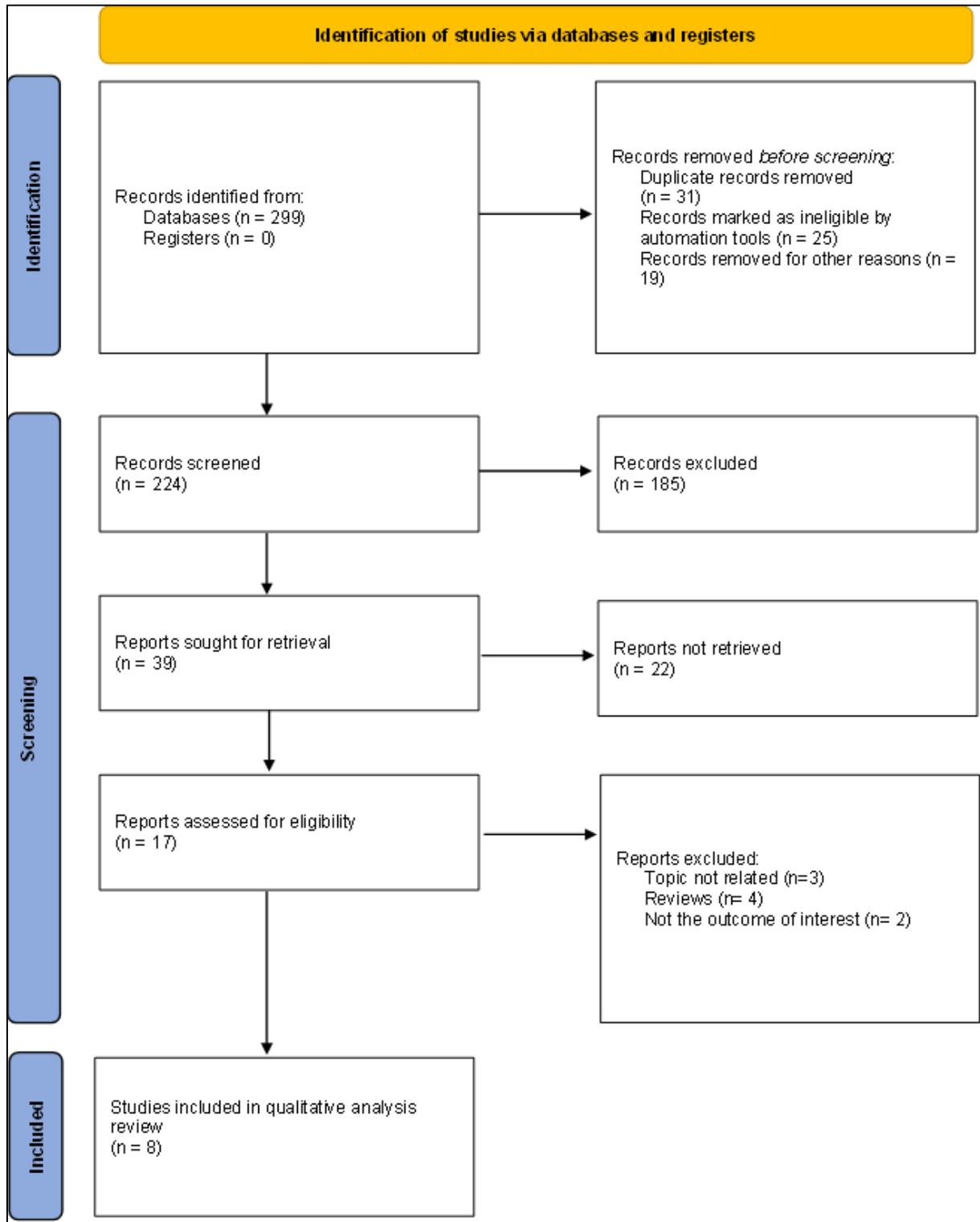
Figure 1 PRISMA consort chart

3. Results

Eight original studies were included in this systematic review (Table 1). These studies examined different first-trimester biochemical markers and ultrasound parameters for their predictive value in detecting intrauterine growth restriction (IUGR) or fetal growth restriction (FGR). The sample sizes ranged from 124 to 58,606 participants, including low and high-risk pregnancies in multiple regions and healthcare settings.

Table 1 Summary of Studies on First Trimester Markers and IUGR/FGR Prediction

Citation	Study Design	Population Characteristics	Predictive Factors / Method Used	Study Aim	Methodology
Ismail et al., 2024	Randomized clinical cross-sectional	124 pregnant women at high risk of FGR at Zagazig University Hospital	Homocysteine, PAPP-A, uterine & umbilical artery Doppler	To evaluate combined efficiency of biochemical and Doppler markers in predicting FGR	Clinical assessment, biochemical assays, and Doppler ultrasound from 2017–2021
Springer et al., 2023	Retrospective cohort	1930 singleton pregnancies, Vienna and Munich	PAPP-A, free β-chg., NT, uterine artery PI	Association between first-trimester markers and FGR (<3rd percentile)	Multivariate logistic regression on screening and outcomes
He et al., 2020	Prospective study	1796 unselected singleton pregnancies in Shanghai	PAPP-A, Uterine artery PI, RI, notching,	Early diagnosis of FGR using uterine artery Doppler and PAPP-A	First-trimester Doppler and biochemical analysis, with follow-up outcomes
Poon et al., 2018	Prospective multicenter cohort	58606 singleton pregnancies at 11–13 weeks' gestation	Maternal characteristics, PAPP-A, Plage, MAP, uterine artery PI	To assess performance of screening for FGR using maternal characteristics and biomarkers	Bayesian approach for combining variables; evaluation of detection rate for FGR <3rd percentile
Benítez et al., 2017	Retrospective cohort	16788 singleton pregnancies (2009–2016)	PAPP-A, β-chg., CRL, NT	To investigate associations of first trimester markers with IUGR	Statistical analysis including multivariate modeling
Yu et al., 2017	Nested case-control within prospective cohort	200 normal vs. 462 preeclampsia and 350 FGR cases	PAPP-A, β-chg., ADAM12, PP13, uterine artery PI	Prediction of preeclampsia and FGR using serum and Doppler markers	Serum analyte measurement and Doppler analysis at 11–24 weeks
Falcon et al., 2006	Observational study	77 fetuses with trisomy 21 and 232 chromosomally normal fetuses	Tricuspid regurgitation, NT, free β-chg., PAPP-A	To evaluate screening performance combining tricuspid regurgitation with NT and biochemical markers	CVS-confirmed karyotypes; pulsed wave Doppler; two-stage risk screening model
Spencer et al., 2005	Cohort	4390 singleton pregnancies in the UK	PAPP-A, free β-chg., uterine artery Doppler	Predict adverse pregnancy outcomes including FGR and preeclampsia	First and second trimester screening with Doppler follow-up

All included studies examined serum levels of pregnancy-associated plasma protein A (PAPP-A), and some show significant lower levels in pregnancies that later developed IUGR or FGR compared to controls (Ismail et al., 2024; He et

al., 2020; Yu et al., 2017; Spencer et al., 2005). Other studies included free β-human chorionic gonadotropin (β-HCG) as a marker, and findings on its predictive value were inconsistent (Benítez et al., 2017; Spencer et al., 2005).

Ultrasound based assessments, mainly uterine artery Doppler indicators (the plasticity index), were used and found to be significantly elevated in pregnancies complicated by FGR (He et al., 2020; Poon et al., 2018; Yu et al., 2017). The integration of maternal characteristics, mean arterial pressure (MAP), PAPP-A, and uterine artery plasticity index had higher detection rates for FGR according to multivariable prediction models (Poon et al., 2018).

Studies include ADAM12 and placenta protein 13 (PP13) in combination with Doppler indicators showed improved screening effect (Yu et al., 2017). One study explored the value of tricuspid regurgitation combined with biochemical markers and nuchal translucency (NT), which provide additional predictive value mainly for chromosomal anomalies but with application for FGR screening strategies (Falcon et al., 2006).

There is a variability in study design and populations, but most studies concluded that combining biochemical and ultrasound markers generate better accuracy than single marker methods (Table 2). Detection rates for FGR differ depending on the marker combination and cutoff thresholds used, with some studies show a detection rates above 70% at a 10% false positive rate (Yu et al., 2017; Poon et al., 2018).

Table 2 Study Demographics, Findings, and Outcomes

Citation	Demographic Characteristics	Main Findings	Outcomes
Ismail et al., 2024	124 pregnant women at high risk of FGR; Egypt	Low PAPP-A and abnormal uterine/umbilical Doppler linked with FGR	Combination of markers improved prediction accuracy of FGR
He et al., 2020	1796 singleton pregnancies; Shanghai, China	Abnormal uterine artery Doppler and low PAPP-A associated with FGR	Early screening enabled potential intervention planning
Springer et al., 2023	1930 singleton pregnancies; Austria and Germany	Significant association between low first trimester markers and FGR (<3rd percentile)	Supports use of combined markers for early FGR prediction
Benítez et al., 2017	16788 singleton pregnancies; retrospective data (2009–2016)	Lower PAPP-A and β-HCG correlated with IUGR	Routine use of biochemical markers can enhance screening efficiency
Yu et al., 2017	462 preeclampsia, 350 FGR cases vs. 200 controls; China	Low PAPP-A and ADAM12 + high uterine PI linked with FGR and preeclampsia	Combination approach had high detection rate with 10% FPR
Falcon et al., 2006	77 trisomy 21 vs. 232 normal foetuses; UK	Tricuspid regurgitation and NT with biochemical markers improved trisomy detection	Two-stage screening model improved detection with fewer false positives
Spencer et al., 2005	4390 singleton pregnancies; UK	Lower PAPP-A and high uterine PI in FGR and preeclampsia cases	Combined Doppler and biochemical markers improved early prediction
Poon et al., 2018	58606 singleton pregnancies at 11–13 weeks; multicentre	Combined markers significantly improved screening for FGR <3rd percentile	High detection rate using Bayesian model combining markers

4. Discussion

This systematic review aimed to evaluate the predictive value of first trimester ultrasound and biochemical markers for IUGR. The findings from the included studies show that PAPP-A, placental growth factor (Plage), uterine artery Doppler indicators, and additional biochemical and imaging parameters had a good predictive value for IUGR and small for gestational age (SGA) outcomes.

Several studies show the role of PAPP-A as a key biochemical marker in early pregnancy screening. Low maternal serum levels of PAPP-A measured in the first trimester were associated with an increased risk of adverse fetal outcomes, IUGR and low birth weight. In a prospective study, low PAPP-A levels were shown to correlate with IUGR, and the authors suggested a threshold of 0.4 MoM for elevated risk (Papamichail et al., 2022). Another study shows that pregnant women with PAPP-A levels below 0.75 MoM had increased likelihood of delivering SGA neonates (Hosseini et al., 2020). These findings support the incorporation of PAPP-A as a reliable screening biomarker in routine prenatal assessments.

The combination of PAPP-A with uterine artery Doppler measurements improves predictive accuracy. The addition of Doppler indicators, and plasticity index (PI), improve the identification of pregnancies at risk for IUGR when combined with low PAPP-A values (Lesmes et al., 2015). This integrated model shows better sensitivity and specificity compared to biochemical or ultrasound parameters alone. A study using ophthalmic artery Doppler indicators in the first trimester show that some maternal vascular patterns were associated with fetal growth restriction (Gurgel Alves et al., 2018).

Plage and soluble fts-like tyrosine kinase-1 (sFlt-1) were also examined as placental biomarkers. In a cohort study, reduced Plage concentrations measured at 35–37 weeks were predictive of SGA neonates, and the same predictive value was not observed with sFlt-1 (Fadigas et al., 2015). This indicates the specificity of Plage as a marker of placental function. Poon et al. (2015) found that Plage, when measured during the second trimester in combination with maternal factors and mean arterial pressure (MAP), give high predictive value for both preeclampsia and fetal growth restriction (Poon et al., 2015).

Another noteworthy study examined fetal umbilical vein flow combined with maternal hemodynamic parameters to distinguish between constitutional and pathologic FGR (Ferretti et al., 2022). This differentiation is important as it influences decisions and timing of delivery. This advanced biophysical methods, though not yet widely available, but show a good result for future individualized screening methods. A systematic review and meta-analysis show that low PAPP-A levels in the first trimester were associated with both SGA and adverse perinatal outcomes in many populations (Morris et al., 2017). It must be acknowledged that variability in gestational age at testing, differing cutoffs for biomarkers, and inconsistent definitions of IUGR in studies limit direct comparison and synthesis. Most studies report improved predictive power with multimodal approaches, but some others considered the cost-effectiveness of implementing these strategies in low-resource settings.

List of abbreviations

- AFP, Alpha-Fetoprotein;
- β-HCG, Beta Human Chorionic Gonadotropin;
- CRL, Crown-Rump Length;
- FGR, Fetal Growth Restriction;
- IUGR, Intrauterine Growth Restriction;
- MAP, Mean Arterial Pressure;
- MoM, Multiples of the Median;
- NT, Nuchal Translucency;
- PAPP-A, Pregnancy-Associated Plasma Protein-A;
- PI, Pulpability Index;
- Plage, Placental Growth Factor;
- SGA, Small for Gestational Age;
- SFlT-1, Soluble fts-like Tyrosine Kinase-1;
- UAD, Uterine Artery Doppler.

5. Conclusion

The findings from this review indicate the utility of first-trimester markers (PAPP-A, Plage, and uterine artery Doppler) in predicting IUGR. Their integration into early pregnancy screening protocols has the role to identify high-risk pregnancies before clinical symptoms arise, allowing for timely intervention, and improved perinatal outcomes. There is a need for further research to standardize marker thresholds, explore combinations with biomarkers, and evaluate the impact of predictive models in different populations.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclsoed.

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