

Pregnancy-associated plasma protein-A beyond the first trimester: Predictive value for adverse pregnancy outcomes (Review)

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Received July 31, 2026; Accepted October 9, 2026

DOI: 10.3892/etm.2026.13348

Abstract. Pregnancy-associated plasma protein-A (PAPP-A) is a placentally-derived metalloproteinase that serves a key role in trophoblast invasion and fetal growth through the regulation of insulin-like growth factor bioavailability. Since its introduction into first-trimester aneuploidy screening, low maternal serum PAPP-A concentrations have been consistently associated with adverse pregnancy outcomes, including preeclampsia, preterm birth, fetal growth restriction, low birth weight and stillbirth. Although the clinical importance of reduced first-trimester PAPP-A concentrations is well established, the predictive value of PAPP-A measurements beyond the first trimester, particularly during the second trimester, remains less clearly defined. The present review summarizes the current research regarding the association between maternal serum PAPP-A concentrations throughout pregnancy and adverse obstetric outcomes, with a particular emphasis on second-trimester findings. Available evidence suggests that persistently low maternal serum PAPP-A concentrations from the first into the second trimester are

associated with placental dysfunction-related complications. However, despite statistically significant associations, the predictive performance of PAPP-A as a standalone biomarker remains limited. Future prospective studies are required to determine whether incorporating second-trimester PAPP-A into multimarker prediction models can improve risk stratification, clinical decision-making and pregnancy outcomes.

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Abbreviations: AC, abdominal circumference; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; FGR, fetal growth restriction; NICHD, National Institute of Child Health and Human Development; nuMoM2b, Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be; NPV, negative predictive value; PAPP-A, pregnancy-associated plasma protein-A; PE, preeclampsia; PlGF, placental growth factor; PP13, placental protein 13; PPV, positive predictive value; SGA, small-for-gestational-age; WHO, World Health Organization

Key words: PAPP-A, PE, preterm birth, FGR, low birth weight, stillbirth

1. Introduction

Pregnancy-associated plasma protein (PAPP)-A was originally discovered in 1974 by Lin *et al* (1) in the serum of pregnant women, along with other pregnancy-associated plasma proteins, including PAPP-B, PAPP-C and PAPP-D. PAPP-C corresponds with β -pregnancy-specific glycoprotein SP1, while PAPP-D refers to human placental lactogen (2). PAPP-A is primarily synthesized by placental trophoblast cells and released into the maternal circulation throughout pregnancy. Functioning as a metalloproteinase, PAPP-A cleaves insulin-like growth factor (IGF)-binding proteins (IGFBPs), particularly IGFBP-4, and, to a lesser extent, IGFBP-2 and IGFBP-5, thereby increasing the local bioavailability of IGFs. Through this mechanism, PAPP-A serves an important role in placental development, trophoblast invasion and fetal growth (3). Using highly sensitive immunoassays, PAPP-A is also detectable in the circulation of healthy

non-pregnant women and men at very low concentrations (4,5). During pregnancy, maternal serum PAPP-A concentrations increase exponentially, reaching ~100-fold those observed in non-pregnant individuals during the first trimester and ~10,000-fold by the third trimester, before peaking at term (6). Following delivery, maternal PAPP-A concentrations decline rapidly over the subsequent days to weeks, returning to baseline values (7). PAPP-A concentrations are ~100-fold lower in fetal blood and ~1,000-fold lower in amniotic fluid than in maternal serum (8).

In 1990, low first-trimester maternal serum PAPP-A concentrations were first recognized as a marker associated with an increased risk of fetal Down syndrome, leading to the incorporation of PAPP-A into first-trimester aneuploidy screening protocols (3). Since then, numerous studies have consistently demonstrated that reduced first-trimester PAPP-A concentrations are associated with adverse pregnancy outcomes, including preeclampsia (PE), preterm birth (PTB), fetal growth restriction (FGR) and stillbirth (9).

Despite the well-established role of first-trimester PAPP-A, substantially less is known about the clinical significance of PAPP-A measurements during the second trimester. Among the available evidence, the National Institute of Child Health and Human Development (NICHD) Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b) provides notable prospective data on placental biomarkers measured during both the first and second trimesters, and their associations with adverse pregnancy outcomes (10).

The present review aims to summarize the current evidence regarding the predictive value of maternal serum PAPP-A concentrations measured during the second trimester for adverse pregnancy outcomes and to discuss their potential role in contemporary obstetric risk assessment.

2. Evidence from large prospective cohort studies evaluating second-trimester PAPP-A

A total of 10,038 eligible nulliparous pregnant women were recruited into the nuMoM2b cohort between October 2010 and September 2013. A nested case-control analysis was subsequently performed within this cohort that included 800 pregnancies complicated by PTB (466 spontaneous, 330 medically indicated and 4 unclassified cases), 568 cases of PE, 406 small-for-gestational-age (SGA) births and 49 stillbirths. These groups were compared with 911 control participants who delivered at term without pregnancy complications (10).

To identify novel biomarkers associated with adverse pregnancy outcomes, concentrations of placental-derived proteins were measured in maternal serum during the first two trimesters of pregnancy. Blood samples were collected at two scheduled study visits, at 6-13 and 16-21 weeks of gestation, and the levels of nine biomarkers were analyzed. PAPP-A was among the biomarkers evaluated, and the corresponding findings are summarized in Table I (10). In the study, 'lower' PAPP-A levels did not refer to a single predefined clinical cut-off, such as <0.4 multiples of the median (MoM). Rather, PAPP-A concentrations were evaluated according to their distribution in the study population and their associations with adverse pregnancy outcomes. Therefore, the term 'lower PAPP-A concentrations' is used in the present review to describe comparatively

reduced concentrations associated with these outcomes rather than a specific diagnostic threshold (10). The study demonstrated that lower maternal serum PAPP-A concentrations at both study visits were consistently associated with placental dysfunction-related outcomes, particularly medically indicated PTB, PE, SGA births and stillbirth, whereas no clear association was observed with spontaneous PTB. Although lower maternal serum PAPP-A concentrations were associated with medically indicated PTB, no significant association was observed with overall PTB, which was the primary outcome of the study.

Despite the limited predictive value of the biomarkers studied, further investigation of novel placental proteins in diverse patient populations may yield clinically meaningful biomarkers for patients at greatest risk of placental dysfunction-related adverse outcomes. The ratio between first- and second-visit maternal serum PAPP-A concentrations may offer improved discriminatory performance for identifying pregnancies at increased risk of adverse pregnancy outcomes (10).

Taken together, these findings suggest that maternal serum PAPP-A concentrations measured during the first and second trimesters primarily reflect placental dysfunction rather than PTB itself, supporting their potential role in multi-biomarker prediction models for placental-mediated pregnancy complications.

3. PAPP-A and PE

PE is one of the leading causes of maternal and perinatal morbidity and mortality worldwide, affecting 2-8% of pregnancies and accounting for >50,000 maternal deaths annually (11). PE is classically defined by new-onset hypertension and proteinuria after 20 weeks of gestation. Despite well-established diagnostic criteria, the clinical presentation of PE remains highly heterogeneous, making early diagnosis challenging. Early pregnancy biomarkers may improve risk stratification by identifying women at increased risk of PE, thereby facilitating closer surveillance and the timely implementation of preventive interventions (11).

Several prediction models incorporating maternal characteristics, medical history, biochemical markers and ultrasound parameters have been developed to estimate the risk of developing PE. Overall, these models are stronger at predicting early-onset PE (<34 weeks) than late-onset disease, reflecting the distinct pathophysiological mechanisms underlying these two clinical entities. However, the implementation of these prediction models varies considerably across healthcare systems. In the United States, uterine artery Doppler studies are not routinely performed, and serum biomarkers are not routinely available, especially now that cell-free DNA testing has largely replaced traditional serum-based aneuploidy screening such as measurements of PAPP-A (12).

The Fetal Medicine Foundation developed a first-trimester risk calculator for PE that integrates maternal characteristics (medical and obstetric history), biophysical parameters (mean arterial pressure and uterine artery pulsatility index) and biochemical markers. Among the biochemical markers, placental growth factor (PlGF) is the preferred biomarker, whereas PAPP-A may be used when PlGF is unavailable, although this approach is associated with lower detection rates for preterm PE (12).

Table I. Median (25th, 75th percentiles) PAPP-A values by pregnancy outcome group and study visit.

Group	PAPP-A, U/ml					
	Visit 1			Visit 2		
	n	Median	Q1-Q3	n	Median	Q1-Q3
No adverse pregnancy outcome (n=911)	866	1,012	485-1,973	839	9,418	5,530-14,615
PTB (n=800)	768	819	328-1,661	713	9,165	4,986-16,029
SPB (n=466)	449	926	406-1,846	418	9,463	5,578-16,703
IPB (n=330)	315	692	249-1,430	291	7,660	4,077-15,443
PE (n=568)	540	776	335-1,604	514	8,232	4,350-14,907
PE or gestational hypertension with preterm birth (n=630)	599	774	322-1,629	571	8,292	4,417-14,918
SGA (n=406)	386	801	327-1,418	370	8,459	4,833-14,099
Stillbirth (n=49)	49	781	287-1,430	42	7,516	4,035-15,416

Data derived from a previous study (10). Values are presented as median (Q1-Q3). PAPP-A, pregnancy-associated plasma protein A; PTB, preterm birth; SPB, spontaneous preterm birth; IPB, indicated preterm birth; PE, preeclampsia; SGA, small-for-gestational-age.

While first-trimester prediction models have been more extensively studied and validated, fewer studies have directly compared PAPP-A measurements obtained during the first and second trimesters. A case-control study performed in Iran between 2010 and 2011 included 1,500 pregnant women and measured maternal serum PAPP-A and placental protein 13 (PP13) concentrations during both the first (11-13 weeks) and second (24-28 weeks) trimesters (13). PAPP-A concentrations were markedly lower in women who subsequently developed PE at both time points. For PAPP-A alone, the reported area under the receiver operating characteristic curve was 0.793 in the first trimester and 0.809 in the second trimester, indicating broadly comparable discriminatory performance, with only a modest numerical increase in the second trimester. At the reported cut-off values, first-trimester PAPP-A had a sensitivity of ~60% and specificity of ~78%, whereas second-trimester PAPP-A had a sensitivity and specificity of ~71% each (13).

Notably, the study also evaluated combinations of PAPP-A and PP13 within and across trimesters. Combining the two biomarkers improved predictive performance compared with either marker alone, while the model incorporating both PAPP-A and PP13 measurements from both the first and second trimesters achieved the highest overall discrimination. These findings suggest that the principal potential benefit of second-trimester assessment may lie not in replacing first-trimester PAPP-A measurement, but in providing additional longitudinal information when incorporated into multimarker models (13). Nevertheless, these results were derived from a single study population and require external validation before conclusions can be drawn regarding the incremental clinical value of repeated PAPP-A measurements.

Consistent with these findings, a review by Grill *et al* (14) summarized evidence from multiple studies reporting decreased maternal PAPP-A concentrations in women with PE across the first, second and third trimesters. However, the review also highlighted variability in the predictive performance of individual

biomarkers, underscoring the need for larger, well-designed studies before their implementation in routine clinical prediction.

Taken together, the available evidence suggests that low maternal serum PAPP-A concentrations are associated with an increased risk of PE. However, direct comparisons between first- and second-trimester PAPP-A remain limited, and the available evidence does not demonstrate a substantial improvement in prediction from second-trimester PAPP-A when used as an isolated biomarker. Rather, its potential incremental value may lie in serial assessment and its incorporation into multimarker prediction models. Further large-scale prospective studies are required to determine whether the addition of second-trimester PAPP-A to established first-trimester screening algorithms provides clinically meaningful improvement in the prediction of PE.

4. PAPP-A and PTB

PTB, defined as birth before 37 completed weeks of gestation, is commonly categorized as spontaneous or medically indicated; the latter may be associated with pregnancy complications related to placental dysfunction, including PE and impaired fetal growth (10).

PAPP-A has been investigated as a potential biomarker of PTB as it is produced by the placenta and may reflect placental development and function. Several reports have described an increased risk of preterm delivery in women with reduced maternal serum PAPP-A levels (15-20). However, most of the available evidence derives from PAPP-A measurements obtained during the first trimester, when PAPP-A is routinely assessed as part of aneuploidy screening. Furthermore, numerous studies did not distinguish between spontaneous and medically indicated PTB. Only a limited number of studies have specifically evaluated first-trimester PAPP-A concentrations in relation to idiopathic or spontaneous preterm labor (16-20) (Table II).

Table II. Studies evaluating maternal serum PAPP-A concentrations in relation to preterm birth according to gestational age at measurement.

First author, year	No. of participants	PAPP-A concentration/ cut-off	Outcome	Interpretation	(Refs.)
Goetzinger <i>et al</i> , 2010	2,028	222: <10th centile (0.59) 2,006: >10th centile	196 preterm birth in those with PAPP-A <10th centile, 128 PTB <35 weeks, 68 PTB <32 weeks	PAPP-A <10th centile not significantly predictive of PTB <35 weeks	(15)
Kirkegaard <i>et al</i> , 2010	9,540	PAPP-A <0.3 MoM	5.5% PTB	PAPP-A, 0.3 MoM has a strong association with PTB	(16)
Dane <i>et al</i> , 2013	868	<0.35 MoM	3.4 % PTB	Significantly related to early PTB	(17)
Pummara <i>et al</i> , 2016	3,160	PAPP-A levels: 1.37 MoM at term, 1.27 MoM <37 weeks, 0.97 MoM <34 weeks and 0.80 MoM <32 weeks	8.4% PTB	Significant association of low PAPP-A with PTB	(18)
Pakniat <i>et al</i> , 2019	994	PAPP-A <1.1+/-0.69	7.74% PTB	Significantly related to PTB	(19)
Swiercz <i>et al</i> , 2024	1,164	PAPP-A <0.4 MoM	7.2% <37 weeks 2.5% <35 weeks	Low PAPP-A levels are significantly associated with PTB <35 weeks	(20)
Parry <i>et al</i> , 2022	10,038 nulliparous women; nested case-control analysis including 800 preterm births	PAPP-A measured at 6-13 and 16-21 weeks of gestation; lower PAPP-A concentrations	Preterm birth, including spontaneous and medically indicated preterm birth	Lower PAPP-A concentrations were associated with medically indicated preterm birth, but not with overall preterm birth; no clear association was observed with spontaneous preterm birth.	(10)

PAPP-A, pregnancy-associated plasma protein A; PTB, preterm birth; MoM, multiples of the median.

Evidence regarding PAPP-A measured during the second trimester is substantially more limited but is not entirely absent. In the prospective NICHD nuMoM2b cohort, maternal serum concentrations of PAPP-A and other placental proteins were measured at both 6-13 and 16-21 weeks of gestation. Thus, unlike most of the aforementioned studies, the study provides direct evidence, including a second-trimester PAPP-A measurement. Lower PAPP-A concentrations were associated with medically indicated PTB, as well as with PE and SGA birth, which are common placental-mediated causes of medically indicated preterm delivery. By contrast, decreased PAPP-A concentrations were not associated with overall PTB, the primary outcome, and no clear association was observed with spontaneous PTB (10). These findings suggest that PAPP-A may be more closely associated with placental dysfunction underlying medically indicated preterm delivery than to spontaneous PTB itself.

Taken together, although first-trimester PAPP-A remains the most extensively studied time point, emerging data indicate that second-trimester PAPP-A may provide additional information regarding placental dysfunction associated with medically indicated PTB. Nevertheless, the number of studies evaluating second-trimester PAPP-A specifically in relation to PTB remains limited, particularly for spontaneous PTB. Whether second-trimester PAPP-A provides incremental predictive value beyond first-trimester measurements remains uncertain and requires further investigation. At present, therefore, second-trimester PAPP-A should be considered an emerging marker of placental dysfunction rather than an established standalone predictor of PTB.

Moreover, in twin pregnancies, the association between maternal serum PAPP-A and PTB has also been investigated, although findings have been inconsistent (21). Differences in

study populations, gestational age at sampling and definitions of PTB may partly explain the variability between studies. Notably, evidence specifically evaluating second-trimester PAPP-A concentrations in relation to PTB in multiple pregnancies remains particularly limited.

Overall, current evidence suggests an association between low PAPP-A concentrations and placental-mediated adverse pregnancy outcomes, including medically indicated PTB. However, the predictive value of PAPP-A for spontaneous PTB appears less consistent. Further prospective studies are needed to clarify the clinical significance of second-trimester PAPP-A measurements, to determine whether longitudinal changes between the first and second trimesters improve risk discrimination, and to assess whether PAPP-A can contribute meaningfully to multimarker models for the prediction of PTB.

5. PAPP-A and low birth weight

Most studies investigating the association between maternal serum PAPP-A concentrations and neonatal birth weight have focused on measurements obtained during the first trimester. First-trimester prediction of impaired fetal growth has been evaluated using maternal characteristics together with biochemical and ultrasound markers, including PAPP-A, free β -human chorionic gonadotrophin and nuchal translucency (22-24). Reduced first-trimester PAPP-A concentrations have been associated with lower subsequent birth weight and an increased risk of delivering an SGA neonate (22-24). However, as the present review focuses on PAPP-A beyond the first trimester, the substantially more limited evidence regarding measurements obtained during the second trimester is of particular relevance.

PIGF is another placentally-derived biomarker that has been extensively investigated in relation to placental dysfunction and impaired fetal growth. Both reduced PAPP-A and reduced PIGF concentrations have been associated with an increased risk of SGA birth. Notably, PIGF and PAPP-A have also been evaluated as part of second-trimester biochemical screening for SGA at 19-24 weeks of gestation (25). In addition, second-trimester PIGF has been incorporated into multimarker prediction models together with maternal characteristics, estimated fetal weight (EFW) and uterine artery pulsatility index (26). These findings highlight the importance of considering PAPP-A within a broader multimarker framework and indicate that, for second-trimester assessment of placenta-related fetal growth complications, PIGF and biophysical markers represent important comparators.

Evidence specifically evaluating second-trimester PAPP-A in relation to neonatal birth weight is considerably more limited. A study performed at the Department of Obstetrics and Gynecology of the Institute of Mother and Child and Warsaw Medical University between January 2010 and March 2012 included 150 healthy pregnant women and evaluated maternal serum PAPP-A concentrations during the first, second and third trimesters (27). The clinical and biochemical characteristics of the study population are summarized in Table III.

The study therefore provides longitudinal evidence relevant to the focus of the present review. Maternal PAPP-A concentrations were positively significantly associated with neonatal birth weight across all three trimesters: First trimester ($\beta=31.6$; $P<0.001$), second trimester ($\beta=10.6$; $P<0.05$) and third

Table III. Clinical and biochemical characteristics of pregnant smokers and non-smokers in the study by Chełchowska *et al* (27).

Characteristic	Non-smoking	Smoking
Number	70	80
Age, years	29.5 $\pm$ 0.6	30.6 $\pm$ 0.5
Ethnic origin: White (%)	100	100
GA, weeks		
1st trimester	12.6 $\pm$ 0.10	12.4 $\pm$ 0.10
2nd trimester	21.8 $\pm$ 1.5	21.6 $\pm$ 1.5
3rd trimester	31.4 $\pm$ 1.4	31.5 $\pm$ 1.3
Birth	38.9 $\pm$ 0.1	38.7 $\pm$ 0.2
Birth weight, g	3.529 $\pm$ 52	3.167 $\pm$ 55
Birth body length, cm	55.4 $\pm$ 0.2	54.4 $\pm$ 0.3
Head circumference, cm	34.5 $\pm$ 0.1	33.7 $\pm$ 0.1
First-trimester PAPP-A, MoM	1.20 (0.68-2.31)	0.76 (0.53-2.07)
PAPP-A 2, MoM	1.21 (0.92-2.34)	0.75 (0.58-1.99)
PAPP-A 3, MoM	1.28 (1.05-2.78)	0.85 (0.61-2.05)

PAPP-A, pregnancy-associated plasma protein A; GA, gestational-age; MoM, multiples of the median.

trimester ($\beta=4.6$; $P<0.001$). Notable associations between PAPP-A concentrations and neonatal body length and head circumference were also observed during the second and third trimesters (27).

The same study also evaluated the influence of maternal tobacco smoking on PAPP-A concentrations. Maternal serum PAPP-A concentrations were consistently lower among smokers than among non-smokers throughout pregnancy ($P<0.001$), and the magnitude of this effect was associated with smoking intensity (27). This association may partly reflect smoking-related placental dysfunction. PAPP-A regulates IGF bioavailability through proteolytic cleavage of IGF-binding proteins, particularly IGFBP-4 and IGFBP-5 (3), providing a biologically plausible link between altered PAPP-A concentrations, placental function and fetal growth.

Overall, the available evidence indicates that maternal PAPP-A concentrations remain associated with neonatal growth parameters when measured during the second trimester. However, the evidence base for second-trimester PAPP-A is substantially smaller than that for first-trimester PAPP-A, and current data do not establish that second-trimester PAPP-A alone provides clinically meaningful incremental prediction of low birth weight or SGA. By contrast, second-trimester PIGF has been evaluated within larger multimarker prediction models incorporating maternal characteristics, fetal biometry and uterine artery Doppler. Further prospective studies directly comparing second-trimester PAPP-A with PIGF and evaluating their combined predictive performance are needed to determine whether serial PAPP-A measurements provide additional value

in the prediction of placenta-mediated fetal growth complications.

6. PAPP-A and FGR

FGR refers to a condition in which the fetus does not achieve its expected growth potential as a result of underlying pathological factors, most commonly related to placental dysfunction. Globally, FGR is a major contributor to stillbirth, neonatal death, and both short- and long-term morbidity (28).

It is important to distinguish FGR from SGA as the two terms are not synonymous. SGA generally refers to a fetus with an EFW or abdominal circumference (AC) below the 10th percentile for gestational age; however, not all fetuses below this threshold are pathologically growth-restricted, as some may be constitutionally small. Conversely, a fetus may fail to achieve its individual growth potential despite having an EFW above the 10th percentile. Definitions of FGR also differ between professional societies. The Society for Maternal-Fetal Medicine defines FGR as an ultrasonographic EFW or AC below the 10th percentile for gestational age. By contrast, the International Society of Ultrasound in Obstetrics and Gynecology distinguishes SGA from FGR and recommends a multiparametric approach based on the international Delphi consensus criteria, incorporating fetal size, growth trajectory and Doppler findings (29,30).

According to the Delphi consensus, early-onset FGR (<32 weeks) is defined by an EFW or AC below the 3rd centile or absent end-diastolic flow in the umbilical artery, or by an EFW/AC below the 10th centile in combination with abnormal uterine and/or umbilical artery Doppler findings. Late-onset FGR ($\geq$ 32 weeks) is defined by an EFW or AC below the 3rd centile or by the presence of at least two of the following criteria: EFW/AC below the 10th centile, crossing of more than two growth quartiles, or an abnormal cerebroplacental ratio or umbilical artery Doppler. Although these diagnostic frameworks have limitations and remain subject to ongoing discussion, the multiparametric approach aims to distinguish pathological growth restriction from constitutional smallness more accurately than fetal size below the 10th percentile alone (30,31).

Given the important contribution of FGR to adverse perinatal outcomes, early identification of affected fetuses is essential. Several studies have investigated PAPP-A concentrations during early gestation and the early second trimester for the identification of fetuses at risk of growth restriction (22-25,32). However, the available evidence remains limited, particularly regarding PAPP-A assessment during the second trimester. A prospective cohort study performed at the Department of Obstetrics and Gynecology, Dhaka Medical College Hospital, Dhaka, Bangladesh, between January and December 2020 included 186 pregnant women to assess the predictive utility of PAPP-A concentrations for FGR (32). Participants were stratified into two groups according to gestational age at sampling: Group A consisted of 93 women in the first trimester (6-12 weeks), whereas Group B included 93 women in the early second trimester (13-20 weeks). Table IV presents the predictive performance of low PAPP-A concentrations for the identification of FGR in both groups. In Group A, the positive predictive value (PPV) was 70.59% and the negative predictive value (NPV) was

Table IV. Predictive performance of low PAPP-A levels for IUGR in Group A and Group B.

A, Group A (6-12 weeks)

PAPP-A levels	IUGR cases	Normal fetal growth	Total
Low	12 (TP)	5 (FP)	17
Normal	5 (FN)	71 (TN)	76
Total	17	76	93

B, Group B (13-20 weeks)

IUGR PAPP-A levels	Normal fetal cases	growth	Total
Low	13 (TP)	5 (FP)	18
Normal	6 (FN)	69 (TN)	75
Total	19	74	93

Data derived from a previous study (32). PAPP-A, pregnancy-associated plasma protein A; IUGR, intrauterine growth restriction; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

93.42%. In Group B, the PPV and NPV were 72.22 and 92%, respectively, indicating comparable predictive values within this study cohort during the second trimester (32). During follow-up, FGR was observed in 18.3 and 20.4% of fetuses in Groups A and B, respectively. The majority of FGR cases were associated with reduced PAPP-A concentrations in early pregnancy, with PPVs of 70.59 and 72.22% in the two groups, respectively. Based on the data presented in Table IV, the sensitivity and specificity of low PAPP-A concentrations were 70.59 and 93.42%, respectively, in Group A, and 68.42 and 93.24%, respectively, in Group B (32).

However, these findings should be interpreted with caution. The study was performed at a single tertiary center and included a relatively small cohort of 186 women, limiting the generalizability of its findings to broader obstetric populations. In addition, PPVs and NPVs are influenced by the prevalence of the outcome in the population studied; therefore, the relatively high PPV and NPV reported in this cohort may not be reproduced in unselected screening populations with a different baseline prevalence of FGR. Estimates derived from relatively small, single-center studies may also be influenced by population characteristics, case selection, assay methodology and sample size. Furthermore, the study was performed during the COVID-19 pandemic, which may further limit its external validity. Consequently, although these findings support an association between low PAPP-A concentrations and FGR, they should not be interpreted as establishing PAPP-A as an effective standalone screening biomarker in the general obstetric population. Larger, multicenter prospective studies are required to validate its predictive performance across populations with different baseline risks.

7. PAPP-A and stillbirth

The definitions of stillbirth and fetal death vary internationally. According to the World Health Organization (WHO), stillbirth is defined as the birth of a baby with no signs of life following fetal death before complete expulsion or extraction from the mother, occurring at or after 22 completed weeks of gestation. For international comparison of stillbirth rates, the WHO recommends using a threshold of 28 completed weeks of gestation. In the United States, the National Center for Health Statistics defines fetal death from ≥ 20 weeks of gestation (33).

Most of the available evidence linking low maternal serum PAPP-A concentrations with stillbirth is derived from measurements obtained during the first trimester. Low first-trimester PAPP-A has been associated particularly with stillbirth related to placental dysfunction, including pregnancies complicated by FGR, PE or placental abruption (34,35). A prospective cohort study performed at the University Clinic for Obstetrics and Gynecology in Skopje reported that very low first-trimester PAPP-A values (0.05-0.20 MoM) were associated with adverse pregnancy outcomes, including stillbirth and preterm placental abruption; however, second-trimester PAPP-A concentrations were not evaluated (34). Thus, although these findings support an association between low PAPP-A and subsequent stillbirth risk, they do not provide evidence regarding the predictive value of PAPP-A measured later in pregnancy.

Similarly, a systematic review and meta-analysis evaluating first- and second-trimester tests for the prediction of stillbirth reported that low first-trimester PAPP-A and an elevated second-trimester uterine artery pulsatility index were associated with stillbirth related to placental dysfunction (35). Notably, the PAPP-A measurements contributing to this association were obtained during the first trimester; therefore, these findings should not be interpreted as evidence for the predictive performance of second-trimester PAPP-A. Moreover, no individual first- or second-trimester test demonstrated sufficient predictive accuracy for stillbirth as a single outcome (35).

Evidence specifically evaluating maternal serum PAPP-A measured during the second trimester in relation to stillbirth is considerably more limited. The prospective NICHD nuMoM2b study provides relevant longitudinal evidence as placental proteins, including PAPP-A, were measured at both 6-13 and 16-21 weeks of gestation (10). The study included 49 stillbirths and demonstrated associations between lower PAPP-A concentrations and placental dysfunction-related adverse pregnancy outcomes. However, the discriminatory performance of individual placental analytes was modest, and the relatively small number of stillbirths limits conclusions regarding the independent predictive value of second-trimester PAPP-A specifically for stillbirth (10).

Taken together, current evidence supports an association between low PAPP-A and stillbirth, particularly when stillbirth is related to placental dysfunction. However, this evidence is predominantly based on first-trimester PAPP-A measurements. Data specifically addressing second-trimester PAPP-A remain sparse, and there is currently insufficient evidence to support its use as a standalone predictor of stillbirth. Future prospective studies with serial PAPP-A measurements across gestation and adequate numbers of stillbirth outcomes are required to determine whether second-trimester concentrations or longitudinal

changes in PAPP-A provide incremental predictive information beyond first-trimester assessment and established biophysical markers.

8. Discussion and conclusion

The research summarized in the present review reinforces the concept that PAPP-A is primarily a biomarker of placental function rather than a disease-specific marker. Reduced maternal serum PAPP-A concentrations reflect impaired placentation and altered trophoblast function, mechanisms that contribute to a spectrum of adverse pregnancy outcomes, including PE, FGR, medically indicated PTB and stillbirth.

Although first-trimester PAPP-A has been extensively studied, the principal focus of the present review is its potential value beyond the first trimester. The available evidence indicates that PAPP-A concentrations measured during the second trimester, as well as longitudinal changes between the first and second trimesters, may provide information regarding ongoing placental dysfunction. However, the evidence base is considerably smaller and more heterogeneous than that available for first-trimester PAPP-A. The nuMoM2b study is particularly relevant in this context as PAPP-A was assessed at both 6-13 and 16-21 weeks of gestation. Lower PAPP-A concentrations were associated predominantly with placental dysfunction-related outcomes, including medically indicated PTB, PE, SGA birth and stillbirth, whereas the association with spontaneous PTB was less evident (10). These findings support the interpretation of second-trimester PAPP-A as a marker of placental health rather than as a specific predictor of an individual pregnancy complication.

Notably, PAPP-A should be considered in the context of other placental biomarkers, particularly PIGF. Both PAPP-A and PIGF reflect aspects of placental development and function, but their clinical trajectories have differed substantially. PAPP-A remains predominantly associated with first-trimester aneuploidy screening and subsequent risk stratification, whereas PIGF has been investigated and clinically implemented beyond the first trimester, particularly in the assessment of placental dysfunction and PE. PIGF-based testing, either alone or in combination with soluble fms-like tyrosine kinase-1, has demonstrated clinical utility in the second and third trimesters, especially for the assessment of women with suspected PE. Thus, PIGF provides an important contemporary benchmark against which the potential clinical value of second-trimester PAPP-A should be considered (36).

This distinction is also relevant to prediction. Evidence from second- and third-trimester studies indicates that PIGF-based models incorporating maternal characteristics and other biophysical or biochemical markers can improve risk stratification for PE. PIGF has also been evaluated in second-trimester multimarker models for SGA/FGR, together with maternal characteristics, fetal biometry and uterine artery Doppler parameters. By contrast, evidence demonstrating an independent incremental predictive contribution of second-trimester PAPP-A remains limited. Therefore, although both biomarkers are biologically related to placental dysfunction, the current evidence supporting their use beyond the first trimester is substantially stronger for PIGF than for PAPP-A (25,26,36).

With respect to fetal growth, available longitudinal evidence indicates that maternal PAPP-A concentrations remain associated with neonatal anthropometric parameters when measured during the second trimester. However, an association with an outcome should not be equated with clinically useful prediction. The evidence currently available does not demonstrate that second-trimester PAPP-A alone provides sufficient incremental predictive value for low birth weight, SGA or FGR to support its use as an independent screening tool. In this setting, PIGF and established biophysical parameters, including fetal biometry and uterine artery Doppler, represent important comparators and potential components of integrated prediction models.

Similarly, the evidence regarding PTB and stillbirth illustrates the limitations of interpreting PAPP-A as an isolated predictor. For PTB, second-trimester PAPP-A appears to be more closely associated with medically indicated preterm delivery related to placental dysfunction than with spontaneous PTB. For stillbirth, most of the existing evidence is based on first-trimester PAPP-A measurements, and evidence specifically evaluating second-trimester PAPP-A remains sparse. These observations further support the interpretation of PAPP-A as a nonspecific marker of impaired placental function rather than as a standalone predictor of individual adverse outcomes.

Despite statistically significant associations, the clinical utility of maternal serum PAPP-A as a standalone screening tool therefore remains limited. Its sensitivity and specificity are insufficient to justify altered surveillance or intervention in unselected populations on the basis of PAPP-A alone. The apparently favorable predictive values reported in certain smaller single-center studies should also be interpreted cautiously. PPVs and NPVs depend on the prevalence of the outcome in the population studied and may differ substantially between selected or higher-risk cohorts and unselected screening populations. Moreover, estimates derived from relatively small cohorts may be influenced by population characteristics, case selection, assay methodology and sample size. Consequently, high predictive values observed in individual studies should not be considered evidence of equivalent screening performance at the population level without external validation in large, diverse prospective cohorts.

The comparison with PIGF also highlights an important direction for future research. Rather than evaluating second-trimester PAPP-A as an isolated replacement for established biomarkers, future studies should determine whether serial PAPP-A measurements provide incremental information when incorporated into contemporary multimarker models that include PIGF, maternal characteristics, fetal biometry, uterine artery Doppler, and, where appropriate, other angiogenic markers. Direct head-to-head comparisons of PAPP-A and PIGF at comparable gestational ages would be particularly valuable in determining whether PAPP-A contributes independent predictive information beyond established placental biomarkers.

Finally, changes in prenatal screening practices, particularly the widespread adoption of cell-free DNA testing, have reduced the routine availability of PAPP-A measurements in certain healthcare systems. This further emphasizes that any proposed role for PAPP-A beyond the first trimester would need to demonstrate clinically meaningful incremental value over biomarkers and biophysical parameters already available in contemporary obstetric practice. At present, the evidence

supports second-trimester PAPP-A primarily as a marker of placental dysfunction with potential value within integrated longitudinal prediction models, rather than as an established standalone clinical test.

In conclusion, PAPP-A is a well-established marker of placental function with consistent associations with a range of adverse pregnancy outcomes, particularly those related to impaired placentation. Low first-trimester maternal serum PAPP-A levels are reliably associated with PE, FGR and medically indicated PTB, while emerging evidence suggests that second-trimester measurements and longitudinal changes may provide additional insight into placental health. However, the predictive value of PAPP-A alone remains modest, and its use as a standalone screening tool is not justified in routine clinical practice. Future research should focus on determining whether serial second-trimester PAPP-A measurements provide incremental predictive value when incorporated into contemporary multimarker models that include established placental biomarkers such as PIGF, together with maternal characteristics, fetal biometry and Doppler parameters, and whether such integrated approaches can meaningfully improve maternal and perinatal outcomes.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

MK and SS conceived the study. MK, IT, AV and SS designed the study, and drafted, reviewed and edited the manuscript. MK, IT and AV wrote the manuscript. MK, and IT analyzed the literature. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content

produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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