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Review Article

Unveiling the role of pregnancy associated plasma protein-A in idiopathic preterm labour: a review

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ABSTRACT

Idiopathic preterm birth (IPTB) is birth before 37 weeks in the absence of any identifiable cause for preterm labour. Prediction and prevention of preterm birth can significantly reduce the burden of morbidity and mortality associated with under-five mortality across the world. Pregnancy-associated plasma protein-A (PAPP-A), a glycoprotein secreted by the placenta, which plays an important role in early placenta development through regulation of the IGF system, has emerged as an excellent biomarker for the prediction of preterm birth. This narrative review aims to understand the possible mechanism by which it is linked to preterm birth and its potential as a predictive biomarker for idiopathic preterm birth.

Keywords: Pregnancy associated plasma protein-A, Pregnancy outcome, Preterm birth, Adverse pregnancy outcome

INTRODUCTION

Birth between 20 0/7 weeks and 36 6/7 weeks of gestation is termed as preterm birth.[1] According to World Health Organisation (WHO) estimates, approximately 13.4 million preterm births occurred in 2020 alone, accounting for 4-16% of live births.[2] Despite the availability of quality delivery and neonatal care facilities, preterm birth is the leading cause of neonatal and under-five mortality across the globe, with an estimated 900,000 deaths in the year 2019.[3] There has been a continuous effort to understand the etiology of preterm birth to formulate standardized protocols for risk assessment, intervention, and timely referral to centers for delivery and neonatal care. The etiology of preterm birth is multifactorial, and various environmental, placental, genetic, and immunological factors play an important role.

Preventive measures like improved nutrition, smoking cessation, and progesterone therapy have been implemented wherever necessary to reduce the risk of preterm birth. Recently few studies have shown a possible association between idiopathic preterm births and pregnancy-associated plasma protein-A (PAPP-A). This literature review has been done to explore the role of PAPP-A as a potential biomarker for preterm birth.

PAPP-A: AN OVERVIEW

PAPP-A, part of the pappalysin family, is a metalloproteinase secreted from syncytiotrophoblast cells of the human placenta.[4] PAPP-A is an important regulatory enzyme of the insulin-like growth factor (IGF) system. PAPP-A has been extensively studied for its role as a screening for Down's syndrome and is now an essential part of first-trimester or second-trimester screening for chromosomal anomalies in pregnant women. Its role in the pathophysiology of preeclampsia and fetal growth restriction has also been established.[5-7]

However, its role in idiopathic preterm birth is still under research, and recently, few studies have been done to find its association with preterm birth. Since PAPP-A estimation is a routine for first-trimester screening done between 11-13+6 weeks of gestation, no additional testing is required, and the same values can be used for risk stratification for preterm birth.

PAPP-A AND PRETERM BIRTH

Pathophysiology and mechanism

PAPP-A is an important glycoprotein of placental origin which modulated the insulin like growth factor system (IGF) system (IGF I and II). IGF plays a key role in early trophoblastic invasion and hence early placental development, vascularization, and fetal growth. IGF activity is inhibited by insulin-like growth factor binding proteins (IGFBPs). Due to proteolytic action on IGFBP 2, 4, and 5, PAPP-A helps in the release of IGF, which in turn helps in early placentation and angiogenesis. Low levels of PAPP-A will lead to reduced availability of active or free IGF in circulation, leading to placental insufficiency and vascular damage. This placental insufficiency can lead to low-grade placental inflammation. Release of inflammatory markers like cytokines, matrix metalloproteinase (MMP), and prostaglandins may thus cause the start of uterine contractions and thus preterm labor and birth.[8]

EVIDENCE FROM PREVIOUS STUDIES

The placenta and various placental factors and hormones are essential for pregnancy, its maintenance, and delivery. Since PAPP-A is also secreted from the placenta, its role as a predictor for preterm birth is an area of interest for several researchers. Earlier studies done to investigate the association between PAPP-A and pregnancy outcomes have established its relationship with preeclampsia and growth restriction. Various studies have mentioned preterm birth in women with low PAPP-A levels; however, these studies have not mentioned whether the preterm births were due to idiopathic or iatrogenic causes. We found only six studies where flow first-trimester PAPP-A levels were studied in relation to idiopathic preterm labor (Table 1).

Table 1: Studies showing association of PAPP-A levels with idiopathic preterm birth.

Study	No. of participants	PAPP-A levels	Outcome	Interpretation
Goetzinger et al[9]	2028	222: <10th centile (0.59) 2006: >10th centile	196 preterm birth in those with PAPP-A <10th centile, 128 PTB <35 weeks, 68 PTB <32 weeks	PAPPA <10th centile not significantly predictive of PTV <35 weeks
Kiekegaard et al[10]	9540	PAPP-A <0.3 MoM	5.5% PTB	PAPP-A,0.3 MOM has a strong association with PTB
Dane et al[11]	868	<0.35 MoM	3.4% PTB	Significantly related to early preterm birth
Pummara et al[12]	3160	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% PTBs	Significant association of low PAPP-A with PTB
Pakniat et al[13]	994	PAPP-A<1.1±0.69	77 (7.74%) PTB	Significantly related to PTB
Swiercz et al[14]	1164	PAPP-A <0.4 MOM	84 <37 weeks (7.21%, 30 <35 weeks (2.57%)	Low PAPP-A levels are significantly associated with PTB <35 weeks

The results of these studies are also variable for delivery <37 weeks of gestation; however, the results are significantly associated with preterm birth at <35 weeks in most of the studies.

Different cut-off values have been suggested, and hence, there is still no clarity under which cut-off level of PAPP-A (MoM) antenatal women should be stratified as high risk for preterm birth.

From the available data, it can be inferred that though PAPP-A levels done in early pregnancy can be a useful predictor of preterm birth, more research is required to find a cut-off value below which a woman can be stratified at risk of preterm birth.

DISCUSSION

Birth before 37 weeks of gestation without any apparent cause is termed idiopathic preterm birth (IPTB). Preterm birth cases can again be divided into extreme preterm birth when it occurs before 28 weeks, early preterm birth 28-34 weeks, and late preterm between 34 to 36 0/6 weeks. Preterm birth is one of the leading causes of morbidity and mortality in under five age group, accounting for nearly 4-6% of the under-five deaths across the globe. Those who survive are at risk of long-term disabilities. Premature birth not only increases the threat to the baby, it also is a cause of tremendous distress to the parents, family, and treating medical team. Despite of advancement in the medical field, introduction of antenatal corticosteroids, neuroprotection, availability of quality antenatal and

delivery services, better neonatal care and availability of neonatal intensive care units almost 9 out of 10 preterm babies survive in high income countries whereas only1 in 10 babies can make it in low-income countries.[15] To reduce this gap implementation of strategies for prevention, early identification, and risk stratification is of utmost importance. Various strategies for prevention of preterm birth are available where risk can be identified by detailed history examination and ultrasound. However, for idiopathic preterm births where there is no identifiable cause, planning a preventive strategy is challenging. PAPP-A, which is a part of routine first and second trimester screening for chromosomal anomalies during pregnancy, seems to be a promising biomarker for prediction and risk stratification for reducing the burden of IPTB. No extra visit to the health care facility is required, and there is no extra out-of-pocket expenditure, making it excellent for screening. Data from the previous studies remain promising. However, there is a lack of uniformity and standardization in the method used and the cut-off values used for the same. Hence, more well-structured research studies are required to estimate the cut-off values to be used.

CONCLUSION

PAPP-A plays a key role in the regulation of the IGF system and hence is a determinant of early placenta growth and vascularization. Though mostly used for prenatal screening of chromosomal anomalies, PAPP-A has emerged as an excellent biomarker for the prediction of IPTB alone or in combination with other biomarkers. More research is required to fully elucidate its true potential for prediction for IPTB and as a possible target for therapeutic intervention in the management and prevention of IPBD.

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