



Original Article

## Second-Trimester Maternal Serum Alpha-Fetoprotein as a Predictor of Persistent Placenta Previa and Placenta Accreta Spectrum: A Prospective Observational Study

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### ABSTRACT

**Background:** Pregnancies with a low-lying placenta or placenta previa at 15–20 weeks may either resolve or persist; a subset is complicated by placenta accreta spectrum (PAS). Early risk stratification remains clinically important.

**Objective:** To examine whether second-trimester maternal serum alpha-fetoprotein (MSAFP) is associated with persistent placenta previa and PAS.

**Materials and Methods:** In this hospital-based prospective observational study, 180 women with singleton pregnancies and second-trimester sonographic evidence of low placentation were enrolled. MSAFP was measured at 15–20 weeks, expressed as multiples of the median (MoM), and related to follow-up placental outcomes. Logistic regression and receiver operating characteristic analysis were performed.

**Results:** Placenta previa persisted in 113 women (62.8%) and PAS was identified in 40 (22.2%). Persistence occurred in 93/116 (80.2%) women with AFP >1.25 MoM compared with 20/64 (31.3%) at ≤1.25 MoM (OR 8.90; 95% CI 4.42–17.88). PAS occurred in 31/75 (41.3%) women with AFP >1.50 MoM versus 9/105 (8.6%) at ≤1.50 MoM (OR 7.52; 95% CI 3.30–17.12). AFP remained associated with both outcomes after adjustment (adjusted OR 4.72 and 4.44, respectively). Areas under the curve were 0.783 and 0.780.

**Conclusion:** Higher MSAFP in the second trimester was associated with subsequent persistence of previa and with PAS in this tertiary-care cohort. MSAFP may assist risk stratification alongside ultrasound and obstetric history; the findings require external validation.

**Keywords:** alpha-fetoprotein; placenta previa; placenta accreta spectrum; pregnancy; second trimester; prospective study.

### INTRODUCTION

Placenta previa and low-lying placentation remain clinically important causes of antepartum haemorrhage, operative delivery and perinatal morbidity. Although many placentas identified near the internal cervical os in the second trimester subsequently appear to move away as the uterus enlarges, persistence carries a higher risk of bleeding and emergency obstetric intervention.<sup>1</sup>

Placenta accreta spectrum (PAS) adds a further risk of severe haemorrhage and complex surgery, particularly after previous caesarean delivery. Ultrasound provides the principal assessment of placental position and invasion, but early second-trimester findings may not fully determine which pregnancies will progress to persistent previa or PAS.<sup>2,3</sup>

Maternal serum alpha-fetoprotein (MSAFP) is a fetal protein measurable in maternal blood during pregnancy. Levels are interpreted as multiples of the median (MoM) to account for gestational age. Elevated MSAFP has been associated with

persistent placenta previa and abnormally adherent placentation, possibly reflecting disruption of the fetomaternal placental interface. Such a marker could complement, rather than replace, serial ultrasonography.<sup>4,5,6</sup>

Placental localization during the second trimester should be interpreted in relation to the gestational age at which the examination is performed. The lower uterine segment continues to develop as pregnancy advances, and the apparent distance between the placental edge and the internal cervical os often increases without any physical movement of the placenta. Consequently, an early diagnosis of low-lying placenta does not necessarily indicate that the placenta will remain low at delivery. The probability of persistence also varies with the extent of internal os coverage and the gestational age at initial detection. These observations explain why risk assessment based on a single early scan may be uncertain.<sup>7</sup>

Serial ultrasound remains central to placental assessment when a low-lying placenta is identified in the second trimester. Transvaginal ultrasonography allows the placental edge to be localized in relation to the internal cervical os and helps guide subsequent reassessment. The possibility of persistent low placentation must be considered alongside the original ultrasound findings and the obstetric history. A biochemical marker obtained in the same period would therefore be most useful as an adjunct to serial imaging, rather than as a replacement for it.<sup>8</sup>

Placenta accreta spectrum represents a related disorder in which the normal decidual interface is deficient, allowing abnormal adherence or invasion of placental tissue into the underlying myometrium. Changes at this placental-uterine interface are relevant to abnormal vascularity and the risk of significant haemorrhage at delivery. Previous uterine surgery and coexisting placenta previa remain important clinical considerations. Assessment of suspected invasive placentation continues to depend primarily on imaging and obstetric history, while serum biomarkers are being investigated for their additional prognostic value.<sup>9</sup>

The clinical interest in MSAFP is based on its relationship to the maternal-fetal interface. Alpha-fetoprotein originates predominantly from fetal tissues, while only a proportion enters the maternal circulation. Maternal serum concentrations change with gestation and may also be influenced by fetal and maternal characteristics; reporting the result in multiples of the median allows comparisons between women sampled at different stages of the screening window. Where placental integrity or vascular architecture is disturbed, increased passage of fetal proteins may occur. This proposed pathway offers a plausible explanation for the associations described between raised MSAFP, persistent previa and placental adherence, although it does not establish a causal mechanism.<sup>4,5,6</sup>

Our study assessed second-trimester MSAFP levels in women with ultrasound-diagnosed placenta previa or low-lying placenta and examined their relationship with persistence of placental position and subsequent PAS in a tertiary obstetric setting.

## **MATERIALS AND METHODS**

### **Study design and participants**

A hospital-based prospective observational study was undertaken in the Department of Obstetrics and Gynaecology, J.L.N. Medical College and Associated Group of Hospitals, Ajmer, Rajasthan, India. The cohort comprised 180 women with singleton pregnancies and ultrasonographic diagnosis of low-lying placenta or placenta previa at 15–20 weeks of gestation. Women with multiple pregnancies, major fetal anomalies, fetal demise, placental abruption or specified chronic conditions were excluded according to the study protocol. Participants provided written informed consent, and the study was conducted following institutional ethics approval.

### **Assessment and follow-up**

Baseline information included age, parity, prior caesarean delivery, placental type and position, and relevant clinical variables. Maternal venous blood was obtained during recruitment for serum AFP estimation by immunoassay, and the result was expressed in MoM after adjustment for gestational age. Repeat ultrasound was performed during the third trimester, usually around 32 weeks, or earlier if clinically indicated. Placental persistence or resolution was recorded, and PAS was assessed from available imaging and operative findings. Maternal and neonatal outcomes were obtained from hospital records.

### **Statistical analysis**

Categorical findings were expressed as numbers and percentages. Associations were assessed using chi-square or Fisher exact tests as appropriate, with odds ratios (OR) and 95% confidence intervals (CI). Multivariable logistic regression and receiver operating characteristic (ROC) analyses were performed for placental persistence and PAS. A *p* value <0.05 was treated as statistically significant. The analyses were performed in SPSS version 25.

## **RESULTS**

### **Study profile and placental outcomes**

A total of 180 women were included. Most participants were aged 25–30 years (52.2%), and 62 (34.4%) had a previous caesarean section. At enrolment, low-lying placenta was the most frequent sonographic category (37.8%). Persistence of placenta previa was reported in 113 women (62.8%); PAS was identified in 40 (22.2%) (Table 1).

**Table 1. Baseline characteristics and outcomes of the cohort (N=180)**

| Characteristic          | Category          | n (%)      |
|-------------------------|-------------------|------------|
| Maternal age            | <25 years         | 29 (16.1)  |
|                         | 25–30 years       | 94 (52.2)  |
|                         | >30 years         | 57 (31.7)  |
| Parity                  | Primigravida      | 63 (35.0)  |
|                         | Para 1            | 61 (33.9)  |
|                         | Para $\geq 2$     | 56 (31.1)  |
| Previous caesarean      | Yes               | 62 (34.4)  |
| Placenta at 15–20 weeks | Low-lying         | 68 (37.8)  |
|                         | Marginal previa   | 52 (28.9)  |
|                         | Partial previa    | 32 (17.8)  |
|                         | Complete previa   | 28 (15.6)  |
| Primary outcome         | Persistent previa | 113 (62.8) |
| Secondary outcome       | PAS identified    | 40 (22.2)  |

#### Association between MSAFP and adverse placentation

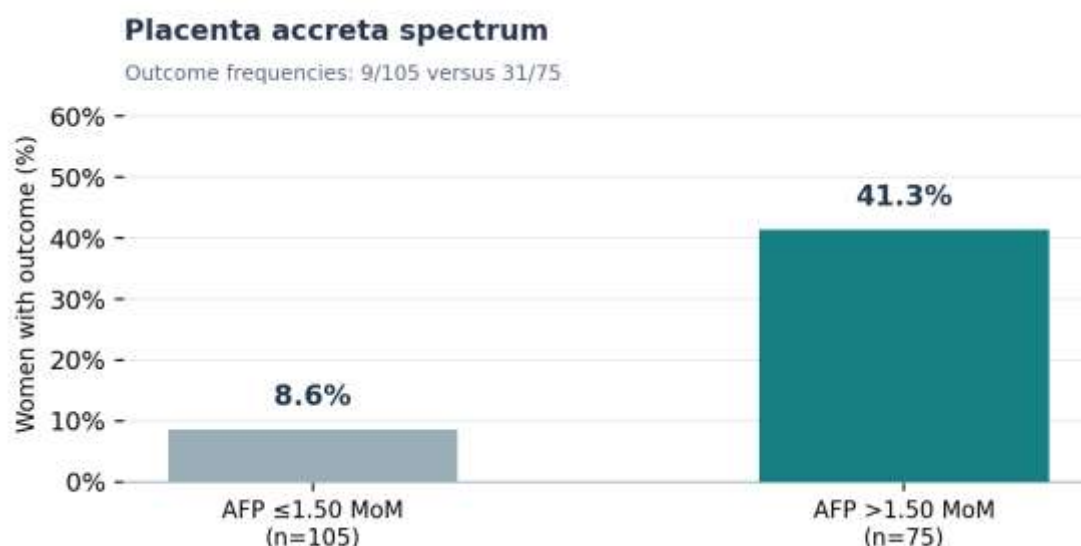
Persistent placenta previa occurred in 80.2% of women with AFP >1.25 MoM, compared with 31.3% in the lower AFP category (OR 8.90; 95% CI 4.42–17.88;  $p < 0.001$ ). PAS was present in 41.3% of women with AFP >1.50 MoM and 8.6% with values  $\leq 1.50$  MoM (OR 7.52; 95% CI 3.30–17.12;  $p < 0.001$ ). Group-specific frequencies are given in Table 2 and Figures 1–2.

**Table 2. MSAFP categories and subsequent placental outcomes**

| Outcome           | AFP group       | Outcome n/N (%) | OR (95% CI)       | p value |
|-------------------|-----------------|-----------------|-------------------|---------|
| Persistent previa | $\leq 1.25$ MoM | 20/64 (31.3)    | 1.00 (Ref.)       | —       |
|                   | >1.25 MoM       | 93/116 (80.2)   | 8.90 (4.42–17.88) | <0.001  |
| PAS               | $\leq 1.50$ MoM | 9/105 (8.6)     | 1.00 (Ref.)       | —       |
|                   | >1.50 MoM       | 31/75 (41.3)    | 7.52 (3.30–17.12) | <0.001  |



**Figure 1. Proportion with persistent placenta previa according to MSAFP >1.25 MoM.**



**Figure 2. Proportion with placenta accreta spectrum according to MSAFP >1.50 MoM.**

### Adjusted associations and diagnostic performance

In the multivariable analysis, AFP >1.25 MoM remained associated with persistent previa after adjustment for the model covariates (adjusted OR 4.72; 95% CI 2.12–10.51;  $p < 0.001$ ). AFP >1.50 MoM was likewise associated with PAS (adjusted OR 4.44; 95% CI 1.59–12.44;  $p = 0.005$ ). The ROC areas were 0.783 for persistence and 0.780 for PAS (Tables 3–4).

**Table 3. Adjusted associations with placental persistence and PAS**

| Outcome           | Predictor              | Adjusted OR (95% CI) | p value |
|-------------------|------------------------|----------------------|---------|
| Persistent previa | AFP >1.25 MoM          | 4.72 (2.12–10.51)    | <0.001  |
|                   | Anterior placenta      | 2.29 (1.08–4.84)     | 0.031   |
|                   | Previous caesarean     | 1.80 (0.83–3.88)     | 0.134   |
|                   | Placenta severity      | 1.64 (1.10–2.46)     | 0.016   |
|                   | Age >30 years          | 1.11 (0.51–2.41)     | 0.784   |
| PAS               | AFP >1.50 MoM          | 4.44 (1.59–12.44)    | 0.005   |
|                   | Previous caesarean     | 3.19 (1.16–8.72)     | 0.024   |
|                   | ≥2 previous caesareans | 8.56 (2.20–33.31)    | 0.002   |
|                   | Persistent previa      | 2.72 (0.80–9.27)     | 0.109   |

**Table 4. Reported discrimination of second-trimester MSAFP**

| Outcome                    | AUC   | Cut-off (MoM) | Sensitivity | Specificity |
|----------------------------|-------|---------------|-------------|-------------|
| Persistent placenta previa | 0.783 | 1.36          | 73.5%       | 79.1%       |
| Placenta accreta spectrum  | 0.780 | 1.44          | 85.0%       | 65.0%       |

### Maternal and neonatal outcomes

Persistent placenta previa was associated with more caesarean deliveries, postpartum haemorrhage and blood transfusions than resolved previa. PAS was associated with hysterectomy and a higher reported frequency of neonatal intensive care admission (Table 5). The study design does not establish that higher AFP itself caused these outcomes.

**Table 5. Selected clinical outcomes by placental status**

| Clinical outcome   | Higher-risk group, n/N (%) | Comparator group, n/N (%) | p value |
|--------------------|----------------------------|---------------------------|---------|
| Caesarean delivery | Persistent: 109/113 (96.5) | Resolved: 28/67 (41.8)    | <0.001  |

| Clinical outcome        | Higher-risk group, n/N (%) | Comparator group, n/N (%) | p value |
|-------------------------|----------------------------|---------------------------|---------|
| Postpartum haemorrhage  | Persistent: 42/113 (37.2)  | Resolved: 11/67 (16.4)    | 0.004   |
| Blood transfusion       | Persistent: 51/113 (45.1)  | Resolved: 11/67 (16.4)    | <0.001  |
| Hysterectomy            | PAS: 7/40 (17.5)           | No PAS: 0/140 (0.0)       | <0.001  |
| Neonatal intensive care | PAS: 16/40 (40.0)          | No PAS: 32/140 (22.9)     | 0.042   |

## DISCUSSION

This prospective cohort of women with second-trimester low-lying placenta or placenta previa showed a marked relationship between higher MSAFP and subsequent abnormal placentation. The associations remained evident in the reported adjusted models, and the ROC findings indicated moderate-to-good discrimination for both persistence of previa and PAS. The observations suggest that MSAFP may offer prognostic information beyond placental location alone.

Earlier observational work found that the likelihood of persistent placenta previa rose across increasing mid-trimester MSAFP values. Subsequent studies of pregnancies complicated by previa reported associations between elevated maternal serum biomarkers, including AFP, and abnormally adherent placenta. The direction of association in our cohort is concordant with this literature, although the magnitude of effects and absolute event rates differ across populations.<sup>4,5,6</sup> A biologically plausible explanation is increased transfer of fetal proteins into maternal circulation at sites of abnormal placental attachment or disruption. However, AFP elevation is not specific for placental adherence; fetal conditions and other placental disorders may also affect maternal concentrations. Ultrasound, clinical history and assessment of prior uterine surgery therefore remain indispensable when interpreting an elevated AFP result.<sup>10,11</sup>

The observed rate of placental persistence (62.8%) was substantially higher than the proportion described in some earlier second-trimester cohorts. This discrepancy is important because the present sample was selected in a tertiary-care setting and may not represent the natural history of all low-lying placentas identified during routine screening. The reported PAS prevalence (22.2%) also limits extrapolation of predictive values to lower-risk antenatal populations.<sup>4</sup>

Persistence of previa was accompanied by higher rates of caesarean delivery, postpartum haemorrhage and transfusion. PAS was linked to hysterectomy and neonatal intensive care use. These outcomes underline the importance of identifying women who may need specialist imaging, blood-product availability and coordinated delivery planning. MSAFP should be investigated as an adjunct to established pathways rather than as a stand-alone diagnostic or management test.<sup>3,12</sup>

## Study limitations

The study was conducted at a single referral centre with a selected cohort and relatively few PAS events. PAS was not confirmed histopathologically in every case. An independent assessment of added predictive value beyond ultrasound-based models was not available. External prospective validation and evaluation of AFP within combined risk models are necessary before these study-specific cut-offs can be recommended for routine use.

## CONCLUSION

Among women with low-lying placenta or placenta previa identified at 15–20 weeks, elevated second-trimester MSAFP was associated with persistence of placenta previa and with placenta accreta spectrum. The associations persisted in the reported adjusted analyses, and AFP showed useful, though not definitive, discrimination for both outcomes. Integration with ultrasonography and prior obstetric history may improve early risk assessment, subject to validation in larger and more representative populations.

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