RESEARCH LETTER

Second-trimester maternal serum markers and placenta accreta

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Placenta accreta is a life-threatening obstetrical complication associated with massive postpartum haemorrhage. The placental trophoblast invades the endometrium beyond Nitabuch's layer because of a defect in the decidua basalis, which normally separates the anchoring placental villi and the myometrium. The exact pathogenesis is unknown. Given the significant morbidity associated with placenta accreta, accurate diagnosis is essential as it allows both the patient and the medical team to be prepared for the potential complications during delivery. Imaging tools, such as ultrasound and even MRI can be used for prenatal assessment of possible placenta accreta, but their effectiveness is controversial as sensitivity ranges from 33% to 93% and specificity from 71% to 100%.[1–3] Second-trimester maternal serum markers used in Down syndrome (DS) screening have been studied but in small series.[4–6] The objective of this study was to investigate the relationship between second-trimester maternal serum markers used in Down syndrome screening and placenta accreta in a series of 69 cases.

This retrospective case–control study was conducted over the period 2000 to 2009. Cases consisted of patients who presented with placenta accreta at delivery. Placenta accreta was diagnosed according to the following clinical and/or histological criteria: (1) partial or total impossibility of manual removal of the placenta with no cleavage plane between all or part of the placenta and uterus, (2) prenatal diagnosis of placenta accreta confirmed by the failure of gentle attempts to remove it during the third stage of labour, (3) evidence of gross placental invasion at the time of surgery, and (4) histological confirmation of accreta on a hysterectomy specimen.[7] Patient details were recorded from two data bases: (1) patients previously included in the study group entitled the French Collaborative Conservative Treatment of Placenta Accreta Study Group[7] and (2) patients from a reference centre (Robert Debré Hospital) who underwent surgical treatment (i.e., caesarean-hysterectomy) and histological examination of the placenta. Maternal serum marker values were retrieved from several laboratory data files (ABA laboratories). Pregnancy dating was based on first-trimester ultrasound crown-rump length measurement. The final database consisted of 69 patients who underwent routine second-trimester maternal Down syndrome screening (34 patients in the group who received conservative treatment and 35 in the group who received surgical treatment). The control group consisted of 552 serum samples (1:8 ratio) matched by maternal age, randomly selected from the routine second-trimester maternal serum screening databases. Markers were hCGβ and alpha-fetoprotein (AFP) (Dualkit, AutoDelfia, Life cycle software, PerkinElmer, Turku, Finland). Results were expressed in multiples of median (MoM) corrected for maternal weight and smoking status. Twin pregnancies were excluded. Informed consent for biochemical testing was obtained for each patient prior to blood sampling as part of routine antenatal care. The Mann–Whitney test was used for MoM comparisons. $P < 0.05$ was considered as significant.

Median maternal age was 33 years (range from 21 to 43 years). As shown in Table 1, significantly higher values ($P < 0.0001$) were observed for both AFP and hCGβ MoM values (1.23 and 1.50, respectively) in the placenta accreta group. No significant difference was observed between conservative treatment and surgical treatment patients (1.18 vs 1.35 for AFP and 1.45 vs 1.86 for hCGβ, respectively). Receiver operating characteristic curves for AFP, hCGβ, or both markers were computed (Figure 1) to choose optimal cut-offs depending on health priorities and available resources. However, there are too few data to provide with reliable values of sensitivity and false–positive rate for different cut-off points. Another approach using an MoM cut-off of 2.5 allowed the

Table 1 **Median MoM values (ranges) of second-trimester maternal serum AFP and hCGβ in control cases versus in patients presenting an accreta placenta at delivery**

	AFP MoM	hCGβ MoM
Control group ($n=552$)	0.99	1.00
	(0.40–2.71)	(0.31–6.45)
Placenta accreta group ($n=69$)	1.23***	1.50***
	(0.50–18.35)	(0.37–6.33)

AFP, alpha-fetoprotein; MoM, multiples of median.
***$P<0.0001$.

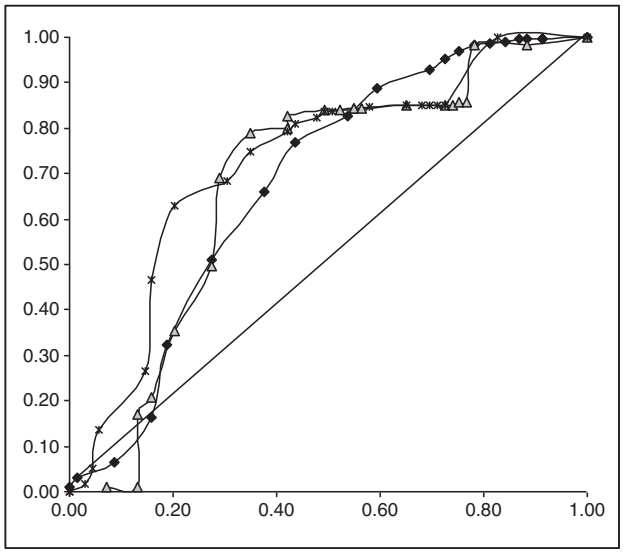

Figure 1 **Receiver operating characteristic curves (sensitivity vs 1-specificity) of maternal serum AFP (full black diamonds), hCGβ (grey triangles) or both (stars)**

following three groups of patients to be distinguished: (1) patients at high risk of placenta accreta with AFP or hCG >2.5 MoM, odds ratios were 9.7 and 8, respectively and when both markers were >2.5 MoM, the odds ratio increased to 32.2; 2) patients at very low risk when both AFP and hCG were <1 MoM, the odds ratio being 0.54; and 3) patients with intermediate risk.

Although until recently placenta accreta was considered a fairly rare event, its annual incidence appears to have increased from 1/2510 before 1994 to 1/533 in 2002. Several risk factors have been associated with placenta accreta, including placenta previa, previous caesarean delivery, uterine surgery, previous uterine curettage, advanced maternal age, multiparity and high gravidity.[8] Failure to diagnose placenta accreta prenatally places the mother at increased risk of life-threatening haemorrhage[9] and surgical complications, including injury to the ureter and urinary bladder.

As prenatal Down syndrome screening is widely performed on the basis of second-trimester or first-trimester maternal serum markers, we aimed to correlate the markers with placenta accreta. Correlation between markers and pregnancy outcome and/or fetal pathology such as preeclampsia, chromosomal anomalies, fetal death, small for gestational age and prematurity has been studied,[10] but few studies report an association with placental implantation. In a study of 11 cases, Zelop *et al.*[4] suggested that there is a direct relationship between the extent of invasion and the elevation of AFP. Kupferminc *et al.*[5] observed that AFP was elevated in 9 out of 20 patients with placenta accreta/percreta/increta. In their study of 28 patients of 35 years and older, with placenta praevia, Hung *et al.*[6] observed that for a cut-off of 2.5 MoM for both AFP and hCGβ, the odds ratios were 8.3 and 3.9, respectively. In our much larger study based on 69 cases, we observed that both markers are significantly higher (1.50 MoM vs 1 MoM for hCGβ and 1.23 MoM for AFP) when pregnancy is complicated by placenta accreta. Different strategies can be used for clinical practice: focusing on patients at higher risk of placenta accreta for example when both markers are >2.5 MoM, or conversely targeting patients at lower risk (AFP and hCGβ both <1 MoM). These higher values of both hCGβ and AFP can probably be explained by the abnormal vascularisation observed in placenta accreta, which modifies the passage of placental markers into the maternal circulation. No data in the literature supports any evidence of abnormal AFP values in women with other risk factors for accrete such as multiparity or prior uterine surgery or caesarean section.

We must acknowledge several weaknesses in our study. Because of its retrospective design, most of the other clinical factors associated with placenta accreta were not available in our databases (previous placenta accreta or placenta praevia, previous caesarean delivery, uterine surgery, or uterine curettage, multiparity and gravidity), thus preventing multivariate modelling. In addition, because first-trimester maternal Down syndrome screening has been performed in France only since 2010, it was not possible to study first-trimester markers.

In conclusion, second-trimester maternal serum markers hCGβ and AFP may help to improve prenatal detection of placenta accreta. Serum markers may provide with additional useful information in a restricted group of patients at high risk for accreta. Further prospective evaluation including first-trimester and/or second-trimester maternal markers as well as other clinical factors is required to confirm these preliminary findings.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Given the significant morbidity and mortality associated with placenta accreta, accurate diagnosis of this abnormal placentation prior to delivery is essential as it enables optimal care and planned management during the perinatal period.

WHAT DOES THIS STUDY ADD?

- As maternal serum markers are routinely measured in Down syndrome screening, we evaluated the utility of second-trimester AFP and hCGβ in the case of placenta accreta.

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ANNEXE

ABA Study Group: This is an association of the French laboratories authorised by the Ministry of Health to carry out Down syndrome screening: Angers (V Moal, H Puissant); Biomnis Bordeaux (I Fischer, E Ruedas,); Le Havre (F Artur, D Thibaud); Biomnis Lyon (C Sault, A Galland); Marseille (C Giorgetti, Caparros); Nancy-AtoutBio (C Baillet, M Teboul, Y Germain); Nice (D Delpech); Nîmes (F Bebin, M Cabrol); Paris Antoine Béclère (Joëlle Taieb, C Benattar), Paris Cerba (I Lacroix); Biomnis Paris (L Druart, C Hamberger); Paris Robert Debré (I Czerkiewicz, S Dreux, F Muller, C Nguyen); Poitiers (C Millet, MP Bounaud); Saint-Etienne (B Tisseur, P Guiardiola, P Antoine, G Belot); Toulouse (F Fortenfant).

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