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Ahmed Abd El Salam

*Departments of Obstetrics & Gynecology, Faculty of Medicine, Al-Azhar University, Egypt,*  
ahmednasrabdelsalam@gmail.com

Fareed Hassan

*Departments of Obstetrics & Gynecology, Faculty of Medicine, Al-Azhar University, Egypt,*  
fareedhassan70@yahoo.com

Mofeed Mohammed

*Departments of Obstetrics & Gynecology, Faculty of Medicine, Al-Azhar University, Egypt,*  
mohammedmofeed93@yahoo.com

Wael Hablas

*Departments of Clinical Pathology\*, Faculty of Medicine, Al-Azhar University, Egypt,*  
hablas.wael@yahoo.com

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## Use of Maternal Serum Alpha-Fetoprotein Measurement in the Diagnosis of Placental Accretion Compared with 2D and 3D Ultrasound

Ahmed Nasr Abd El Salam<sup>1,\*</sup> M.Sc, Fareed Ebrahim Hassan<sup>1</sup> MD and Mofeed Fawzy Mohammed<sup>1</sup> MD and Wael Refaat Hablas<sup>2</sup> MD.

### \*Corresponding Author:

Ahmed Nasr Abd El Salam

[ahmednasrabdelsalam@gmail.com](mailto:ahmednasrabdelsalam@gmail.com)

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<sup>1</sup>Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University Cairo, Egypt.

<sup>2</sup>Clinical Pathology Department, Faculty of Medicine, Al-Azhar University Cairo, Egypt.

### ABSTRACT

**Background:** The accretion of the placenta has now been identified as a major cause of maternal morbidity and mortality. The condition is defined as the placenta adhering abnormally to the uterus.

**Aim of the work:** To assess the effectiveness of greyscale ultrasonography and 3D power Doppler in detecting placenta accreta vs maternal serum alpha-fetoprotein levels in women who had previous caesarean sections.

**Patients and methods:** After 36 weeks of pregnancy, 100 patients with previous caesarean sections were classified into two groups: cases with placenta previa and controls with upper segment implanted placenta. Ultrasound was used on each group. Maternal serum levels of alpha-fetoprotein are determined using greyscale ultrasound and 3D power Doppler. The status of the placenta is assessed intra-operatively by the surgeon.

**Results:** At the time of Cesarean delivery, 30 patients had placenta accreta and its variations (including increta and percreta). When we compared greyscale ultrasound to 3D power Doppler and MS-AFP, we discovered that MS-AFP had the highest sensitivity, at 88.9%, followed by greyscale ultrasound at 77.8% and 3D power Doppler at 66.7 percent. However, with a specificity of 33.3 percent, MS-AFP was the least specific, followed by greyscale ultrasonography with a specificity of 66.7 percent., and 3D power Doppler with a specificity of 83.3 percent.

**Conclusion:** MS-AFP could be used in conjunction with 2D and 3D ultrasonography to diagnose placenta accreta in the prenatal period. It could also be used as a screening test for placenta accreta diagnosis.

**Keywords:** Serum Alpha-Fetoprotein; 2D, 3D ultrasound; placenta accrete.

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### INTRODUCTION

Due to a deficiency in the decidua basalis, the placental trophoblast develops deeply in the endometrium behind the Nitabuch's layer, causing placenta accreta.<sup>1</sup> When the chorionic villi penetrate the myometrium abnormally, placenta accreta develops. Placenta accreta (chorionic villi in touch with the myometrium), placenta increta (chorionic villi invade the myometrium), and placenta percreta (chorionic villi invade the myometrium) are the three classes based on histology (chorionic villi penetrate the uterine serosa). The reported incidence of placenta accreta is 1 per 2500 deliveries.<sup>2</sup>

Risk factors of placenta accreta include placenta previa, repeated cesarean deliveries, multiparity, history of abortion, and prior curettage. The growing trend of cesarean sections correlates with an increase in the incidence of placenta accrete.<sup>3</sup> According to a

large prospective observational study, the risk of placenta accreta was 0.03 percent for women having their first caesarean delivery if there was no placenta previa, remained 1 percent for women having up to their fifth caesarean delivery, and increased to 4.7 percent for women having their sixth caesarean delivery. In the case of a placenta previa, the risk of placenta accreta was 3% at the first caesarean delivery and escalated to 40% or more after the third caesarean delivery.<sup>4</sup>

Unfortunately this life threatening obstetrical condition may be diagnosed at the time of delivery, often resulting in emergency treatment with a greater risk of morbidity. In contrast, a prenatal diagnosis would allow for a planned approach with the possibility of treatment under more controlled conditions, and could also reduce the blood loss associated with placenta accreta during delivery.<sup>5</sup> Because of its wide availability and great accuracy

(sensitivity of 93 percent and specificity of 79 percent), gray-scale ultrasonography has become the gold standard for identifying placenta accreta. <sup>6</sup> 3D strength Doppler may be useful as a supplement to ultrasound in the diagnosis or exclusion of placenta accrete during pregnancy. <sup>7</sup>

Placenta accreta has been related to elevated maternal blood alpha-fetoprotein, and it's been suggested that there's a link between the magnitude of invasion and this analyte's rise. <sup>8</sup> Preterm birth, intrauterine growth restriction (IUGR), preeclampsia, and placental separation have all been linked to an increase in maternal serum alpha-fetoprotein (MSAFP). <sup>9</sup>

These lesions allow alpha-fetoprotein to leak from the high-concentration foetal circulation to the low-concentration maternal circulation, resulting in an increase in maternal serum AFP. It has also been linked to uterine deformity in women. <sup>10</sup> The goal of this study was to assess the effectiveness of grayscale ultrasonography and 3D power Doppler in detecting placenta accreta vs maternal serum alpha-fetoprotein levels in women who had previous caesarean sections.

#### PATIENTS AND METHODS

This was case control study conducted at outpatient clinic and obstetrics and gynecology unit in El Hussein Hospital, Said Galal Hospital and Suez General Hospital from the period marsh 2019 to marsh 2021 after the approval of the ethical committee.

100 patients with previous cesarean sections after 36 weeks gestation age divided into 2 groups: Study group: 50 candidates with previous cesarean sections with placenta previa, and Control group: 50 candidates with previous cesarean sections with upper segment implanted placenta.

Inclusion criteria: Women in the third trimester (34-40 week), associated placenta previa in the study group only, single living baby, and all women were delivered by cesarean section.

Exclusion criteria: The presence of causes of elevated maternal serum level of alpha-fetoprotein such as: Open neural tube, abdominal wall defects, placental anomalies such as chorioangioma, and multiple pregnancy, maternal uterine malformation, fetal demise, and fetal echogenic bowel.

All Patients were subjected to:

Informed written consent was done taken from each patient enrolled in the study.

History taking including maternal age, parity and previous uterine scar. The gestational age was calculated by first day of last menstrual period or using ultrasound for those who were not sure of their dates.

Complete general and obstetric examination was done.

Grey-scale trans-abdominal ultrasound: For evaluation of both; (A) Fetal biometry, fetal well being, congenital anomalies, amniotic fluid, placental site and grading and any abnormalities. (B) 1- Any vascular lacunae (irregular vascular gaps) within the placenta that give it a "Swiss cheese" appearance, lack of normal hypoechoic retroplacental zone, blood vessels or placental tissue bridging the uterine-placental boundary, myometrial-bladder interface, or crossing uterine serosa.

Maternal blood samples were taken to determine the level of maternal serum alpha-fetoprotein weekly from 34th week till labor.

The surgeons were asked to assess the condition of the placenta intra-operative, whether it is accreta, increta or percreta or not and whether it was focal, partial or total whenever it was adherent placenta. Any bladder invasion in case of placenta percreta was reported, as well as operative procedure.

All ultrasound examinations were done by senior sonographers. All measurements were done few days before termination and operations were performed by senior surgeons.

Statistical analysis:

SPSS (Statistical Package for Social Sciences) version 22 for Windows® was used to code, process, and analyse the obtained data (IBM SPSS Inc, Chicago, IL, USA). The Shapiro Walk test was used to determine if the data had a normal distribution. Frequencies and relative percentages were used to depict qualitative data. To calculate the difference between two or more sets of qualitative variables, use the Chi square test (2). The mean and standard deviation (SD) were used to express quantitative data (Standard deviation). To compare two independent groups of normally distributed variables, the independent samples t-test was used (parametric data). Significant was defined as a P value of less than 0.05.

#### RESULTS

	Study group (n=50)	Control group (n=50)	P value
Age (years)	32.0 ± 3.3	30.3 ± 4.0	0.08 NS
Parity	3.3 ± 1.0	2.8 ± 0.9	0.06 NS
Para 2	13 (26.7%)	22 (43.3%)	0.3 NS
Para 3	18 (36.7%)	18 (36.7%)	
Para 4	10 (20.0%)	9(16.7%)	
Para 5	9 (16.7%)	1 (3.3%)	
No of previous CS	2.9 ± 1.0	2.5 ± 0.6	

NS: non significant

**Table 1:** Demographic data of the study and control groups

There were no significant statistical differences between the two groups as regard the Age, number of previous cesarean section and parity (Table 1).

	Condition of placenta intraoperative				P value
	Adherent (n=30)		Non-adherent (n=20)		
	N	%	N	%	
<b>Age mean ± SD</b>	31.9 ± 3.7		32.0 ± 3.1		0.9 NS
<b>Parity</b>					
<b>Para 2</b>	8	27.8	5	25.0	0.5
<b>Para 3</b>	10	33.3	8	41.7	NS
<b>Para 4</b>	8	27.8	2	8.3	
<b>Para 5</b>	4	11.1	5	25.0	
<b>No of previous CS</b>	3.2 ± 1.0		2.5 ± 0.7		0.02 S

S: Significant

**Table 2:** Demographic data of adherent placenta and non adherent placenta in study group:

There was significant statistical difference between number of cesarean and adherence (Table 2).

Type of adherence		
<b>Accreta</b>	179.3 ± 67.1	0.5
<b>Increta</b>	127.3 ± 82.6	NS
<b>Percreta</b>	177.7 ± 86.4	
<b>Bladder invasion</b>		
<b>Yes</b>	177.7 ± 86.4	0.4
<b>No</b>	134.7 ± 73.6	NS
<b>Operation done</b>		
<b>CS</b>	85.1 ± 50.4	0.006
<b>CS + hysterectomy</b>	168.8 ± 68.1	HS
<b>CS + hysterectomy + bladder repair</b>	177.7 ± 86.4	

**Table 3:** Relation of MS-AFP to type on invasion, bladder invasion and type of operation done among patients with placenta previa:

There was no significant statistical difference between adherence degree of placenta, bladder invasion and MS-AFP. But high significant statistical relation with operation done (Table 3).

	Condition of placenta intraoperative				P value
	Adherent (n=30)		Non-adherent (n=20)		
	N	%	N	%	
<b>2D US</b>					
<b>Present</b>	23	77.8	7	33.3	0.02
<b>Absent</b>	7	22.2	13	66.7	S
<b>3D Power Doppler</b>					
<b>Present</b>	20	66.7	3	16.7	0.01
<b>Absent</b>	10	33.3	17	83.3	S

**Table 4:** Diagnostic efficiency of 2D ultrasound and 3D power Doppler among patients in the study group:

There was significant statistical relation between adherence of placenta intraoperative and Diagnostic efficiency of 2D ultrasound and 3D power Doppler (Table 4).

	Condition of placenta intraoperative				P value
	Adherent (n=30)		Non-adherent (n=20)		
	N	%	N	%	
<b>Criteria of accreta by 2D US</b>					
<b>Present</b>	23	77.8	7	33.3	0.02
<b>Absent</b>	7	22.2	13	66.7	S
<b>Criteria of accreta by 3D power Doppler</b>					
<b>Present</b>	20	66.7	3	16.7	0.01
<b>Absent</b>	10	33.3	17	83.3	S
<b>MS-AFP</b>					
<b>&gt;2.5 MoM</b>	27	88.9	13	66.7	<0.001
<b>&lt;2.5 MoM</b>	3	11.1	7	33.3	HS

**Table 5:** Comparing Diagnostic efficiency of 2D Ultrasound, 3D ultrasound and MS-AFP:

There was significant statistical relation between adherence of placenta intraoperative and diagnostic efficiency of 2D ultrasound and 3D ultrasound. Highly significant statistical difference between adherence of placenta intraoperative and diagnostic efficiency of MS-AFP (Table 5).

	Sensitivity	Specificity	Positive predictive value	Negative Predictive value
MS-AFP	88.9 %	33.3 %	66.7 %	66.7 %
Greyscale ultrasound	77.8 %	66.7 %	77.8 %	66.7 %
3D power Doppler	66.7 %	83.3 %	85.7 %	62.5 %

**Table 6:** Sensitivity, Specificity, positive predictive value, and negative predictive value of 2D ultrasound, 3D power Doppler and MS-AFP in diagnosis of placenta accrete:

When the three groups were compared, the MS-AFP Greyscale ultrasound, with 77.8% sensitivity, and 3D power Doppler, with 66.7 percent sensitivity, were found to be the most sensitive, with 88.9% sensitivity. However, with a specificity of 33.3 percent, MS-AFP was the least specific, followed by greyscale ultrasonography with a specificity of 66.7 percent., and 3D power Doppler with a specificity of 83.3 percent (Table 6).

## DISCUSSION

In this study the mean age of placenta previa patients (study group) was  $32.0 \pm 3.3$  years while that of upper segment implanted placenta (control group) was  $30.3 \pm 4.0$  years. Moreover the number of previous cesarean sections in the study group was  $2.9 \pm 1.0$  CS, while the control group was  $2.5 \pm 0.6$  CS. While the mean number of parity for the study group was  $3.3 \pm 1.0$  and that of the control group  $2.8 \pm 0.9$ .

Also, the mean age of the adherent placenta previa was  $31.9 \pm 3.7$  while the mean age of non-adherent placenta previa was  $32.0 \pm 3.1$ . Which showed no significance between the two groups. Also the parity between two groups showed no significance. However the mean number of CS in the adherent placenta previa was  $3.2 \pm 1.0$  while the mean number of previous CS in the non-adherent placenta previa was  $2.5 \pm 0.7$  which shows significant between both groups, which proves that previous CS is a risk factor for adherent placenta.

Assessment of placenta intra-operatively among the group with placenta previa showed 30 (60 %) patients with adherent placentas and 20 (40 %) patients with non-adherent placentas. On the other hand none of the patients of the control group showed adherent placenta, which proves that placenta previa is the main risk factor for adherent placenta.

The final pathological analysis of the 30 patients with adherent placenta revealed 20 cases of placenta accreta, 5 cases of placenta increta and 5 cases of placenta percreta. All of these patients underwent CS hysterectomy. The 5 patients with placenta percreta, the placenta invaded the bladder and had primary bladder repair during the operation.

In 20 of the 50 patients, the conclusive diagnosis of placenta previa without accreta was made. Due to uncontrollable bleeding from the implantation site following placental separation, two of these patients underwent caesarean hysterectomy.

The mean value of MS-AFP of the cases of placenta previa was  $139.0 \pm 74.4$  IU/ml where abnormal elevations ( $>2.5$  MoM) were found in 40 out of the 50 patients with mean gestational age of  $36.9 \pm 0.8$  weeks while the control group showed mean value of  $41.9 \pm 19.2$  ng/ml where only two of the patients showed abnormal elevations, with mean gestational age of  $37.2 \pm 0.6$  weeks with high significance.

On analyzing MS-AFP within the placenta previa patients we found out that the mean value of MS-AFP of cases of adherent placenta previa was  $170.4 \pm 70.6$  IU/ml were abnormal elevations ( $>2.5$  MoM) were found in 27 out of the 30 patients of placenta accreta, with sensitivity of 88.9 %, while the mean value of MS-AFP of cases of non adherent placenta previa was  $56.2 \pm 39.4$  IU/ml were 13 out of the 20 patients showed abnormal elevations ( $>2.5$  MoM) with a low specificity of 33.3 % but with high significance.

So we could conclude that placenta previa is associated with higher levels MS-AFP than patients with upper segment implanted placenta, and patients with placenta accreta are associated with even higher elevations of MS-AFP with high sensitivity but with low specificity. The mean value of MS-AFP according to the type of placenta accreta was  $179.3 \pm 67.1$  IU/ml for placenta accreta,  $127.3 \pm 82.6$  IU/ml for placenta increta and  $177.7 \pm 86.4$  IU/ml for placenta percreta, which showed no significance between the 3 groups. Bahadue et al.<sup>11</sup> found a link between higher MS-AFP levels and a higher risk of persisting placenta previa, which is similar to our findings. A MSAFP score of less than 1 MoM is linked to a lower probability of previa persistence until birth.

Furthermore, Zelop et al.<sup>12</sup> discovered elevated MS-AFP levels (between 2.3 and 5.5 MoMs) in 45 percent of 11 women with placenta accreta, whereas none of the controls with placenta previa without accreta did. Although these studies are small, they suggest that women with elevated MSAFP levels with no other obvious cause should be considered at increased risk of placenta accreta. It's also been suggested that in women with placenta accreta, abnormalities in the placental-uterine interface cause foetal alpha-fetoprotein to seep into the maternal blood, resulting in higher MS-AFP levels.<sup>12</sup>

Similarly, Belfort et al.<sup>13</sup> found that increased maternal blood alpha-fetoprotein has been linked to placenta accreta, and that there is a clear link between the amount of invasion and the elevation of this analyte. Similarly, Mosbeh et al.<sup>14</sup> discovered that a maternal blood alpha-fetoprotein level of  $>2.5$  MoM is linked to placenta accreta. In addition, Matsuzaki et al.<sup>15</sup> showed that 9 of the 20 (45 percent) women with placenta accreta had increased MS-AFP levels (between 2.7 and 40.3 multiples of the median [MoM]), whereas the controls all had MS-AFP levels within normal limits (less than 2.0 MoM).



Regarding ultrasonographic diagnosis, when we compared greyscale ultrasound to 3D Doppler in the diagnosis of placenta accreta within patients with placenta previa. Intraoperative 30 (60 %) of patients in the study group showed placenta accreta while 20 (40 %) of the patients did not show placenta accrete. With greyscale ultrasound 23 patients (77.8%) showed at least one criterion for placenta accreta, while 7 patients did not show evidence of placenta accrete for the 30 patient confirmed intraoperative as accreta. While with 3D power Doppler 20 patients (66.7%) showed at least one criterion for placenta accreta, while 10 patients did not show evidence of placenta accrete for the 30 patient confirmed intraoperative as accreta.

Comparing the results of the greyscale ultrasound to the definitive diagnosis intraoperative we find that, greyscale ultrasound successfully diagnosed 23 out of the 30 cases of placenta accreta and failed to diagnose the remaining 7 cases with sensitivity of 77.8 %. Also, greyscale ultrasound successfully diagnosed non-adherent placenta in 13 out of the 20 patients and showed criteria of adherence in the 7 remaining patients with specificity of 66.7 %. Positive predictive value 77.8 % and negative predictive value of 66.7 % with high significance (p value 0.02).

Also, on comparing 3D power Doppler results to intraoperative diagnosis, 3D power Doppler successfully diagnosed 20 patients and failed to diagnose 10 patients with sensitivity of 66.7 %. In addition 3D ultrasound ruled out the diagnosis of placenta accreta in 10 patients and had false positives in 3 patients with specificity of 83.3 % and positive predictive value of 85.7 % and negative predictive value of 62.5 % with high significance (p value 0.01).

According to our study, greyscale ultrasound had a higher sensitivity of 77.8 % and negative predictive value of 66.7 %, while 3D ultrasound showed higher specificity of 83.3 % and higher positive predictive value of 85.7 %. Also the addition of 2D ultrasound to 3D power Doppler will have higher sensitivity of 83.3 % and lower specificity of 66.7 %.

Compared to our study, Fukushima et al.<sup>16</sup> The presence of myometrial thickness less than 1 mm or huge placental lakes has been reported as a symptom of accretion of the placenta. When both findings are present, they have a substantial positive predictive value (72 percent). According to Mittal et al.<sup>17</sup>, the most relevant prognostic indicators were disruption of the placental-uterine wall interface and the presence of arteries traversing this site. Using a composite grading approach that included six sonographic observations, these researchers found 89 percent sensitivity and 98 percent specificity. The presence of "many coherent vessels in the basal view" has a 97 percent sensitivity, 92 percent specificity, and 76 percent positive predictive value on 3-dimensional power Doppler, according to a recent study. However, the number of people with placenta accreta who participated in these trials was limited, and there is no consensus on which characteristics are most useful in diagnosing placenta accreta. Also sonographic detection of these criteria

remain user dependent which require experience in the field remain the main drawback of ultrasound diagnosis. Finally, when the three groups were compared, MS-AFP was shown to be the most sensitive, with a sensitivity of 88.9%, followed by greyscale ultrasonography with a sensitivity of 77.8% and 3D power Doppler with a sensitivity of 66.7 percent. However, with a specificity of 33.3 percent, MS-AFP was the least specific, followed by greyscale ultrasonography with a specificity of 66.7 percent, and 3D power Doppler with a specificity of 83.3 percent.

## CONCLUSION

MS-AFP could be an excellent placenta accreta screening test, which, when combined with greyscale ultrasound and 3D power Doppler, could be a good predictor of this important source of maternal morbidity and mortality. In our study, we looked at greyscale ultrasound, 3D power Doppler, and MS-AFP, and discovered that MS-AFP was the most sensitive, with a sensitivity of 88.9%, followed by greyscale ultrasound with 77.8% sensitivity and 3D power Doppler with 66.7 percent sensitivity. MS-AFP, on the other hand, was the least specific, with a specificity of 33.3 percent, followed by greyscale ultrasonography (66.7 percent) and 3D power Doppler (83.3 percent).

Conflict of interest : none

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