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Original Research Article

Maternal Serum Alpha Fetoprotien as a marker of Placental Adherence in Placenta Previa and Low Lying Placenta

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Abstract

Background- To find out Maternal Serum Alpha Fetoprotien as a marker of Placental adherence in Placenta Previa and low lying placenta.

Methods- The present study was a prospective observational hospital based study conducted in the Department of Obstetrics and Gynaecology, SMS Medical College and Attached Group of Hospitals, Jaipur from April 2021 to June 2022.

Result- The level of Maternal Serum Alpha Fetoprotien was significantly elevated i.e more than 2.3 MoM in 18 out of 24 cases of adherent placenta with a Sensitivity of 66.7% , Specificity of 90.5% , Positive predictive value of 88.9% and Negative predictive value of 70.4%. The patients with significantly raised MSAFP levels underwent major surgical intervention.

Conclusion- Maternal serum AFP was significantly and positively related with placenta adherence. Such finding suggests the potential role of maternal serum AFP in identifying pregnancies that are at high risk for placenta accreta.

Keywords: Maternal Serum Alpha Fetoprotien, Magnetic Resonance Imaging

INTRODUCTION

Antepartum Hemorrhage is defined traditionally as bleeding from or in to the genital tract after the period of fetal viability until delivery.[1] APH forms one of most dangerous and devastating group of disorders in obstetrics.[2] Hemorrhage emerges as the major cause of severe maternal morbidity in almost all 'near miss' audits in both developed and developing country. The most important causes of APH are Placenta Previa and Placental abruption.[2] Placenta Previa is when internal OS is partially or completely covered by placenta whereas in Low lying placenta implantation is in lower uterine segment such that placental edge does not cover internal OS but lies within 2 cm wide perimeter around os.[3] Incidence of placenta previa is approximately 1 in 300 deliveries[3]. At least 5% of such pregnancies have associated placental invasion (placenta accreta), which can necessitate hysterectomy[3].

A study conducted in pregnant females screened at 14-22 weeks of gestation the risk for accrete syndromes was 8 fold higher with Maternal Serum Alpha Fetoprotein >2.5 MoM.[4] Berkeley[5] described that in pregnancy associated with morbidly adherent placenta where there is disruption of Nitabuch's membranes i.e. feto-maternal interface disruption causes leakage or seepage of AFP into maternal circulation thus causing elevation of MSAFP. Strategy can be implemented for early recognition or suspicion of placenta accreta spectrum in all placenta previa cases by screening them with MSAFP. Maternal Serum Alpha fetoprotein is composed of single polypeptide chain with carbohydrate moiety having molecular weight of 70000 and this tumor maker is encoded by AFP gene on Chr4q25. AFP is synthesized by yolk sac, liver, GIT, Kidney, Placenta.[6-7] It has been hypothesized that a disruption in the maternal fetal interface allows increased transfer of AFP into maternal circulation.[8] MSAFP is increased in Spontaneous abortion, Pre-eclampsia, gestational hypertension and PROM.

Material & Methods

An Observational study was conducted in the department of obstetrics and gynaecology ,SMS Medical College ,Jaipur from April 2021 to June 2022 .The study population was comprised of all the women attending antenatal clinic in the second trimester (from 14-22 weeks) with previous history of caesarean section and ultrasonography evidence of placenta previa or low lying placenta and women willing to give consent to participate in the study were included after applying the inclusion and exclusion criteria.Venous blood sample was taken and level of MSAFP was determined by ELISA method .Patient was followed up and those with placenta migrated to upper segment at 28-32 weeks period of gestation were excluded from study , the level of MSAFP was compared with USG/MRI and intraoperative findings.

Any women with Fetal Defects: Neural Tube defects such as spina bifida, anencephaly and hydrocephlous, Intestinal Obstruction. Abdominal wall defects like omphalocele and gastrochisis, Sacrococcygeal Teratoma, Maternal conditions: Preeclampsia, Gestational Hypertension and PROM, Ovarian tumors and malignancies were excluded from study population. Descriptive statistical methods were used for to calculate the variables for continuous and categorical data. The Chi-square test for proportion was used for the test of significance to find association between categorical variables. The critical levels of significance of the result were considered at 0.05, i.e. $p<0.05$ was significant.

Results

The mean (SD) of Age (Years) was 28.44 (3.11). The median (IQR) of Age (Years) was 28.00 (26-30). The Age (Years) ranged from 24 - 38.

Table-1

Association between 'Adherent Placenta (MRI)' and 'AFP (MOM)'

AFP (MOM)	Adherent Placenta (MRI)		Wilcoxon-Mann-Whitney U Test	
	Yes	No	W	p-value
Mean (SD)	2.61 (1.18)	1.66 (0.88)	213.500	0.007
Median (IQR)	2.45 (2.04-2.96)	1.5 (0.91-2.21)		
Min – Max	0.94 - 5.11	0.6 - 3.76		

There was a significant difference between the 2 groups in terms of AFP (MOM) (W = 213.500, p = 0.007), with the median AFP (MOM) being highest in the Adherent Placenta (MRI).

The bar graph below depicts the means of AFP (MOM) in the 2 different groups.

Figure: Association between Adherent Placenta (MRI) and AFP (MOM)

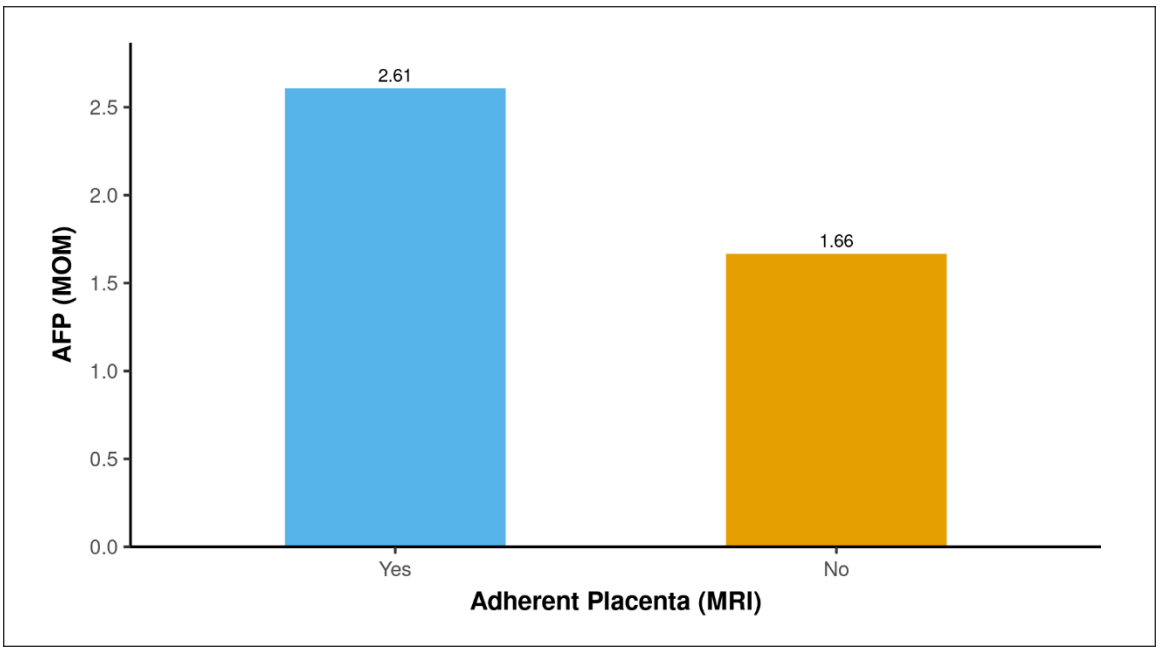


Table-2
Association between 'Adherent Placenta (Intraoperative)' and 'AFP (MOM)'

AFP (MOM)	Adherent Placenta (Intraoperative)		t-test	
	Yes	No	t	p value
Mean (SD)	2.59 (1.12)	1.62 (0.85)	3.304	0.002
Median (IQR)	2.44 (2.01-2.99)	1.5 (0.91-2.21)		
Min – Max	0.94 - 5.11	0.6 - 3.76		

There was a significant difference between the 2 groups in terms of AFP (MOM) (t = 3.304, p = 0.002), with the mean AFP (MOM) being highest in the Adherent Placenta (Intraoperative).

The bar graph below depicts the means of AFP (MOM) in the 2 different groups.

Figure: Association between Adherent Placenta (Intraoperative) and AFP (MOM)

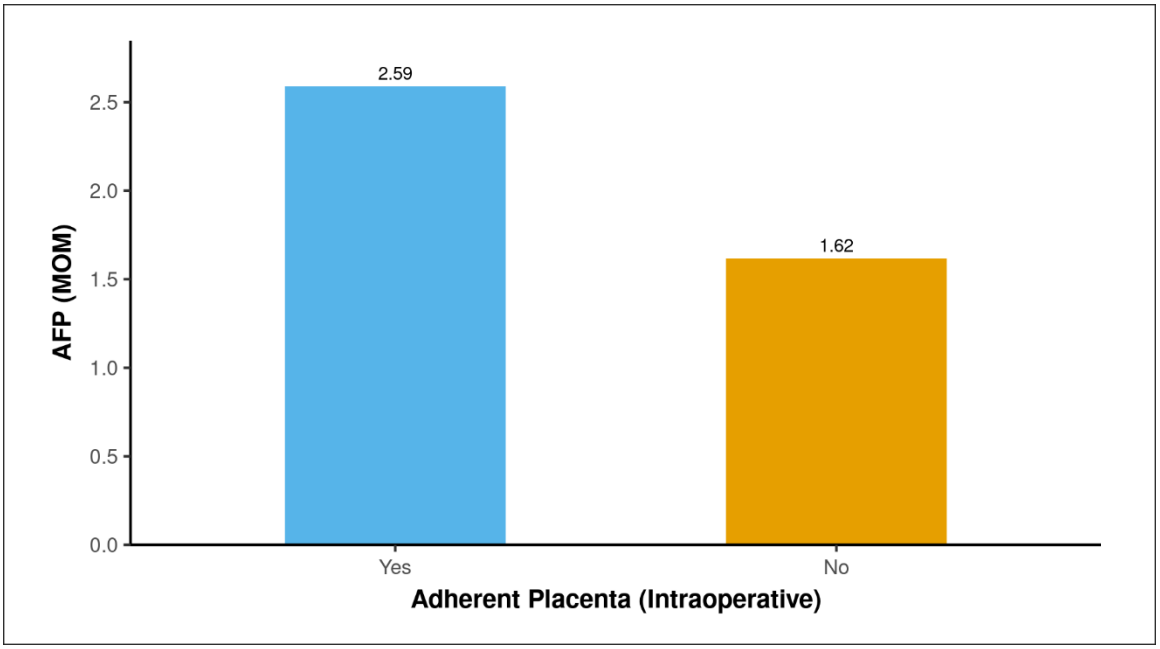


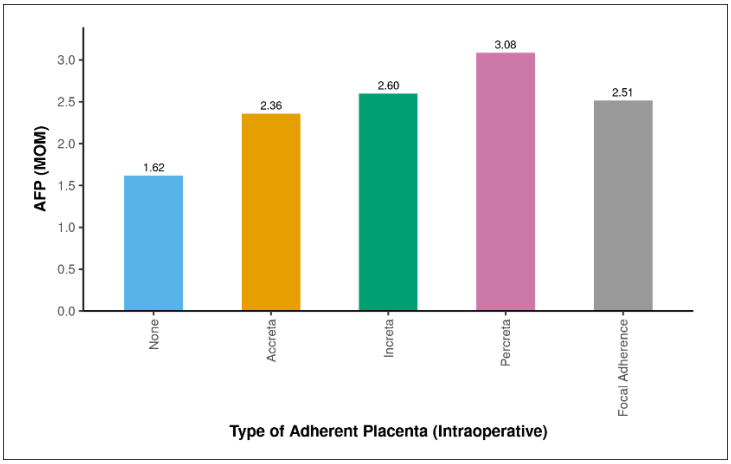
Figure: Association between Adherent Placenta (Intraoperative) and AFP (MOM)

Table-3
Association between 'Type of Adherent Placenta (Intraoperative)' and 'AFP (MOM)'

AFP (MOM)	Type of Adherent Placenta (Intraoperative)					Kruskal Wallis Test	
	None	Accreta	Increta	Percreta	Focal Adherence	χ^2	p-value
Mean (SD)	1.62 (0.85)	2.36 (0.90)	2.60 (1.05)	3.08 (1.86)	2.51 (0.45)	11.413	0.022
Median (IQR)	1.5 (0.91-2.21)	2.45 (1.94-3.04)	2.43 (2.39-2.43)	2.77 (1.67-4.89)	2.51 (2.29-2.73)		
Min – Max	0.6 - 3.76	0.94 - 3.49	1.36 - 4.55	0.98 - 5.11	2.07 - 2.96		

There was a significant difference between the 5 groups in terms of AFP (MOM) (χ^2 = 11.413, p = 0.022), with the median AFP (MOM) being highest in the PERCRETA Type of Adherent Placenta (Intraoperative).

Figure: Association between Type of Adherent Placenta (Intraoperative) and AFP (MOM)



Performance of Study Parameters for Predicting Adherent Placenta (Intraoperative): Yes Vs No

Description of Variables

Variable	Category(s) Suggesting Outcome Present	Category(s) Suggesting Outcome Absent	Total Positives	True Positives	True Negatives	False Positives	False Negatives
Adherent Placenta (Intraoperative)	Yes	No	24 (53.3%)	-	-	-	-
AFP (MOM) (Cutoff: 2.38 by ROC)	>=2.38	<2.38	18 (40.0%)	16 (36%)	19 (42%)	2 (4%)	8 (18%)

Primary Diagnostic Parameters

Variable	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
AFP (MOM) (Cutoff: 2.38 by ROC)	66.7% (45-84)	90.5% (70-99)	88.9% (65-99)	70.4% (50-86)	77.8% (63-89)

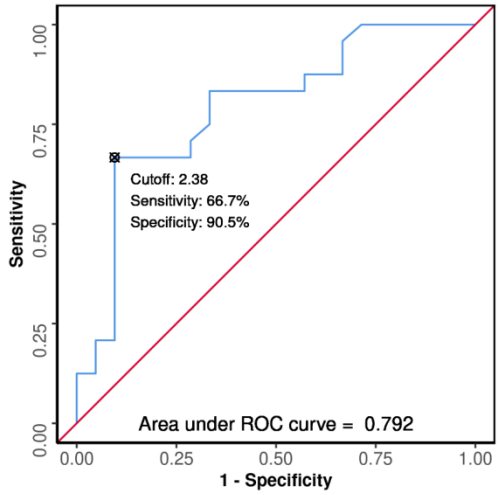
Other Diagnostic Parameters

Variable	LR+	LR-	Yuden Index	Odds Ratio	Kappa	p-value
AFP (MOM) (Cutoff: 2.38 by ROC)	7 (1.82-26.96)	0.37 (0.21-0.66)	57.1	19 (3.52-102.58)	0.56	<0.001

Ranking of Primary Diagnostic Parameters

Variable	Sensitivity	Specificity	PPV	NPV	Diag. Accuracy
AFP (MOM) (Cutoff: 2.38 by ROC)	1	1	1	1	1

ROC Curve Analysis Showing Diagnostic Performance of AFP (MOM) in Predicting Adherent Placenta (Intraoperative): Yes vs NON Adherent Placenta (Intraoperative) (n = 45)



Parameter	Value (95% CI)
Cutoff (p value)	≥2.38 (0.001)
AUROC	0.792 (0.655 - 0.929)
Sensitivity	66.7% (45-84)
Specificity	90.5% (70-99)
Positive Predictive Value	88.9% (65-99)
Negative Predictive Value	70.4% (50-86)
Diagnostic Accuracy	77.8% (63-89)
Positive Likelihood Ratio	7 (1.82-26.96)
Negative Likelihood Ratio	0.37 (0.21-0.66)
Diagnostic Odds Ratio	19 (3.52-102.58)

The area under the ROC curve (AUROC) for AFP (MOM) predicting Adherent Placenta (Intraoperative): vs NON Adherent Placenta (Intraoperative) was 0.792 (95% CI: 0.655 - 0.929), thus demonstrating fair diagnostic performance. It was statistically significant (p = 0.001).

At a cutoff of AFP (MOM) ≥2.38, it predicts Adherent Placenta (Intraoperative) with a sensitivity of 67%, and a specificity of 90%.

Table-4
Association between 'Previous LSCS' and 'AFP (MOM)'

AFP (MOM)	Previous LSCS			Kruskal Wallis Test	
	Previous 1	Previous 2	Previous 3	χ^2	p-value
Mean (SD)	1.77 (0.86)	2.39 (1.22)	2.42 (1.27)	3.016	0.221
Median (IQR)	1.67 (0.92-2.38)	2.36 (1.43-2.99)	2.43 (1.55-2.7)		
Min - Max	0.6 - 3.49	0.78 - 5.11	1.11 - 4.89		

There was no significant difference between the groups in terms of AFP (MOM) (χ^2 = 3.016, p = 0.221).

Figure: Association between Previous LSCS and AFP (MOM)

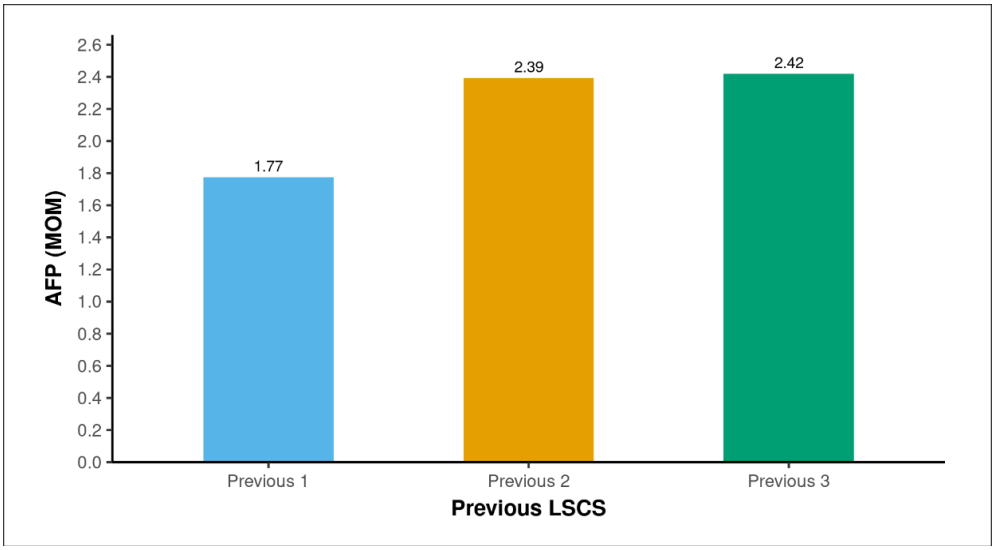


Table-5
Association between 'History of D/E (Abortions)' and 'AFP (MOM)'

AFP (MOM)	History Of D/E (Abortions)			Kruskal Wallis Test	
	None	1	2	χ^2	p-value
Mean (SD)	2.04 (1.07)	2.10 (1.18)	2.91 (0.75)	4.151	0.126
Median (IQR)	2.04 (0.99-2.45)	2.05 (1.23-2.38)	2.96 (2.45-3.49)		
Min - Max	0.6 - 4.89	0.65 - 5.11	1.91 - 3.76		

There was no significant difference between the groups in terms of AFP (MOM) (χ^2 = 4.151, p = 0.126).

Figure: Association between History Of D/E (Abortions) and AFP (MOM)

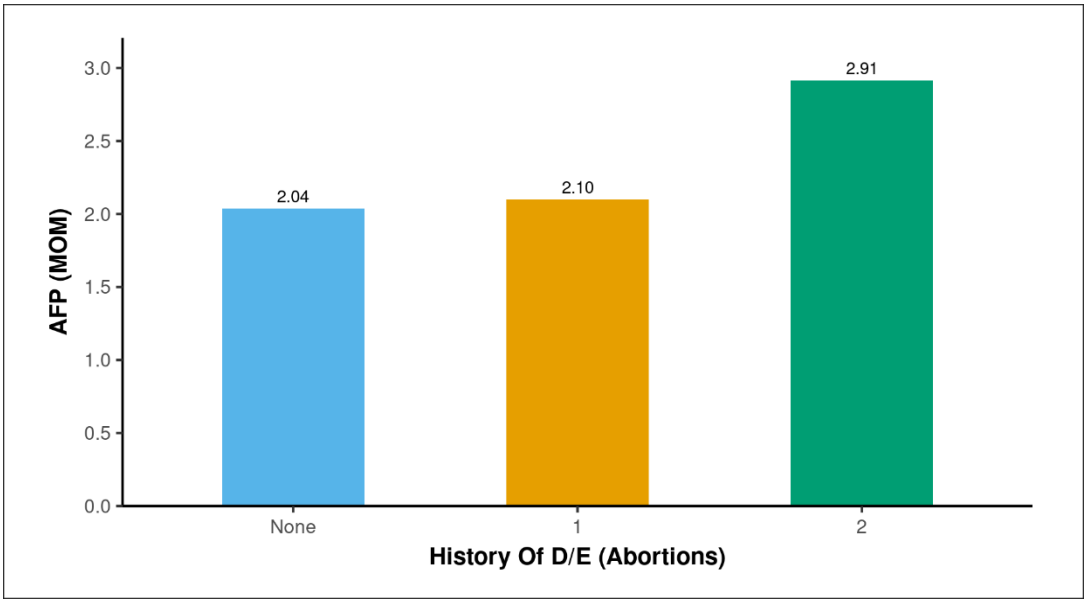


Table-6
Association between 'Outcome' and 'AFP (MOM)'

AFP (MOM)	Outcome				Kruskal Wallis Test	
	Obstetric Hysterectomy	Conservative Management	B/L Uterine Artery Ligation	Placenta Left In Situ	χ^2	p-value
Mean (SD)	2.59 (1.19)	1.95 (0.89)	1.43 (0.78)	2.45 (NA)	10.134	0.017
Median (IQR)	2.59 (1.91-3.1)	1.83 (1.4-2.41)	1.19 (0.86-1.85)	2.45 (2.45-2.45)		
Min – Max	0.94 - 5.11	0.65 - 3.76	0.6 - 3.16	2.45 - 2.45		

There was a significant difference between the 4 groups in terms of AFP (MOM) (χ^2 = 10.134, p = 0.017), with the median AFP (MOM) being highest in the obstetric hysterectomy group.

DISCUSSION

Placenta previa and placenta accreta is major life threatening obstetrical burden associated with high morbidity and high mortality.

The risk of placenta previa increases with increasing age. In the present study as shown above, maximum number of placenta previa was found in the age group of 26-30 years i.e. 60% of cases followed by 22.2% of cases in age group of >30 years. 17.8% of cases in the age group of 20-25 yrs. The mean age group in our study is 28.44 ± 3.11. A study done by Tuzovic L et al (2003)[6] also had showed similar results i.e. 3l year of mean age.

In our study, there was a significant difference between the 2 groups in terms of AFP (MOM) (W = 383.500, p = 0.002), with the median AFP (MOM) being highest in the Adherent Placenta. A cut off for Maternal Serum Alpha Feto Protein (MSAFP) was determined by ROC curve for adherent placenta group seen intraoperatively i.e. value of MSAFP >2.3 MoM was associated with placental adherence.

Similar study was conducted by Verma P (2016)[2] MSAFP >2.5 MoM in 11 out of 12 cases (91.6%) of placenta accreta, in both cases of placenta increta (100%) and the only case of placenta percreta (100%) (p= 0.00). The association was statistically significant. MSAFP was found normal in 68 out of 75 (90.6%) cases where the placenta was non-adherent. Another study done by Sarma P et al (2021)[9] had similar result with serum AFP >2.5 MoM was associated with placental adherence in patients with placenta previa. Study done by Goetzinger KR et al (2014)[10] also placed high levels of MSAFP in pregnancy as a surrogate marker for abnormal placentation as well as placental adherence and adverse maternal outcome. Hung T et al (1999)[11] performed a study which included 10672 antenatal patients, and they finally concluded that placenta previa with raised MSAFP levels and age >35 yrs are risk factors for placenta accreta. Kupferminc MJ et al (1992)[12] in a retrospective review of all patients who underwent emergency caesarean hysterectomy

reported that women with MOM >2.5 are at the higher risk of placenta accreta. Zelop C et al (1992)[13] in their study concluded that there is a significant association between elevated MSAFP and placenta accreta/percreta/increta (p=0.017).Gagnon A et al (2008)[14] suggested that the combination of raised MSAFP and placenta previa should strength the clinical suspicion of invasive placental disorder.

Another study conducted by Wang F et al (2021)[15] also concluded Raised MSAFP and previous cesarean sections are most significant and positive factor related to underlying mechanism of placenta accreta.

Mosbeh MH et al (2020)[16] revealed that maternal serum alpha-fetoprotein was significantly elevated in placenta accreta group (1.33 ± 0.38 MoM) compared to control group (0.66 ± 0.22 MoM). Also, serum alpha-fetoprotein has a high predictive value for placenta accreta in women with complete placenta previa with cutoff >0.84 MoM, area under curve of 0.958, with a sensitivity of 92%, specificity = 82% PPV = 83%, NPV = 87.2% and accuracy of 85% (p<0.01).

Dreux S et al (2012)[17] studied maternal serum markers and placenta accreta, they found that AFP concentration was 1.23 MoM in placenta accreta group (n=69) versus 0.99 MoM in control group (n=552), (p<0.01). Lyell DJ et al (2015)[18] conducted a study to examine associations with morbidly adherent placenta (MAP) among women with placenta previa. They concluded that elevated PAPP-A, elevated MS- AFP and prior LSCS are associated with morbidly adherent placenta among women with previa.In our study there was significant difference between four groups in terms of AFP with the median AFP being highest in placenta percreta group which was comparable to other studies. A study done by Shaukat A et al (2009)[19] showed MSAFP level increases with increased in placental invasion i.e. placenta accreta, placenta increta and placenta percreta with increase in Mean ± SD 153.2 ± 38.1, 178.3 ± 25.2 and 263.36 respectively. In our study out of 45 cases, 21 patients had obstetric hysterectomy; and all of them had elevated MSAFP levels, mean MSAFP was 2.3 MoM where as those managed conservatively had low levels of MSAFP and the result was statistically significant. Similar results were also found in the study of Verma P (2016)[2].

Significant association was seen between raised MSAFP and Urinary bladder injury, obstetric Hysterectomy, ICU admissions, multiple blood transfusions, preterm deliveries and prolonged hospitalization. Butler EC et al (2001)[20] performed the study on 107 antenatal patients with placenta previa, out of which 14 had elevated levels of MSAFP and these were the patients who required prolonged hospitalization, ICU monitoring, multiple blood transfusions. Thus concluded that raised MSAFP is associated with increased maternal and fetal morbidity. In study of Verma P et al (2016)[2] significant associations was seen with Raised MSAFP and maternal morbidity. 80% cases of placental adherence were associated with maternal morbidity.

In our study there was no significant association seen in patients with history of dilatation and evacuation with placental adherence. Similarly in the study conducted by Verma P et al (2016)[2] no association was found in patients with history of Dilatation and Evacuation. There was no statistical significance in the patients with Previous 1/2/3 LSCS with Serum AFP levels.

CONCLUSION

Maternal serum AFP was significantly and positively related with placenta adherence. Such finding suggests the potential role of maternal serum AFP in identifying pregnancies that are at high risk for placenta accreta. In our study there was good statistical significance of MSAFP i.e p-value < 0.05 with adherent placenta seen in USG, MRI and Intraoperatively, Also there was also good statistical significance of MSAFP i.e. p-value <0.05 with Maternal ICU Admissions, number of days of hospital stay, poor maternal outcome and NICU admissions of newborn.

With MSAFP value > 2.3 MoM, was associated with adherent placenta on USG and with **MSAFP value of <2.3 MoM** there is decreased likelihood of adherent placenta.

Strategy should be implemented for early recognition or suspicion of placenta accreta spectrum in all placenta previa cases by screening them with MSAFP (in second trimester). Furthermore, larger amounts of cases of prospective evaluation, including first- trimester and/or second-trimester maternal markers, are required to confirm these preliminary findings.

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