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Creatine kinase and alpha-fetoprotein as biochemical markers in diagnosis of placenta increta and percreta

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Abstract---Background: placenta accreta is a life-threatening pregnancy complication which usually accompanied with placenta previa. It is important to make the diagnosis before delivery therefore a preoperative planning will decrease complications. The aim of this study: was to compare between creatine kinase and α -fetoprotein as biological markers with ultrasound & Doppler findings for the sake of prenatal detection of morbid placentation in anterior placenta on scar of previous cesarean section. Patients and Methods: The present study was Prospective cohort observational study carried out at Beni Suef University Maternity Hospital and MUST Teaching Hospital. Women were recruited from the outpatient obstetrics clinic or emergency room and admitted to antepartum inpatient high risk service. Results: This study showed a significant increase in both CK (p value =0.014) and msAFP (P value=0.028) levels in cases compared to the control group. multiple of median (MOM) had been statistically used to assess the clinical diagnostic accuracy of MS-AFP as a predictor of morbid placental adherence (MAP) in the studied Population; the results of MS-AFP by MOM (ROC) curve analysis showed p-value = 0.001 so; the

MS-AFP by MOM diagnosed the MAP at a statistically significant level with a 80% Sensitivity (true positive cases) and 95% Specificity (true negative cases) at a cutoff point ≥ 1.42 MOM. Conclusion: This study showed significant increase in both serum CK and msAFP in cases with placenta accrete spectrum compared to the control group with no placenta accrete spectrum. Maternal serum creatine kinase and α -fetoprotein concentrations may serve in addition to ultrasonography in the diagnosis of placenta accreta spectrum.

Keywords---creatine kinase, alpha feto protein, placenta increta, placenta percreta.

Introduction

The incidence of placenta accreta has increased and seems to parallel the increasing cesarean delivery rate. Women at greatest risk of placenta accreta are those who have myometrial damage caused by a previous cesarean delivery with either an anterior or posterior placenta previa overlying the uterine scar (ACOG, 2012). In general, the recommended management of suspected placenta accreta is planned preterm cesarean hysterectomy with the placenta left in situ because attempts at removal of the placenta are associated with significant hemorrhagic morbidity (ACOG, 2012).

Prenatal diagnoses of placenta accreta through the use of gray-scale ultrasonography, color Doppler imaging, and magnetic resonance imaging have been reported previously (Chou *et al.*, 1997). Placenta increta and percreta have rarely been diagnosed antepartum, and ultrasonographic findings may provide the only objective evidence of placenta accreta. A biochemical marker for this condition would therefore be useful (Ophir *et al.*, 1999). It is critical to make the diagnosis before delivery because preoperative planning can significantly decrease blood loss and avoid substantial morbidity associated with placenta accreta (Shih *et al.*, 2009).

Despite the modern advances in imaging techniques, no single diagnostic technique affords complete assurance for the presence or absence of placenta accreta (ACOG, 2006). The diagnosis is most often made during the third stage of labor or on Cesarean delivery.

Patients and Methods

The present study was Prospective cohort observational study carried out at Beni Suef University Maternity Hospital and MUST Teaching Hospital. Women were recruited from the outpatient obstetrics clinic or emergency room and admitted to antepartum inpatient high risk service. After proper counseling, all women who were chosen for enrollment agreed to participate.

Inclusion criteria

Pregnant lady with history of previous cesarean section, hysterotomy, placenta previa, gestational age after 28 wks.

Exclusion criteria

Women with one or more of the following conditions: Pregnancies with aneuploidies and neural tube or abdominal wall defects, embolism, thrombosis, D.V.T., myocardial or brain infarction, drug overdose: Antipsychotics, antidepressants, hypnotics, narcotics, alcohol, halothane, salicylates, excessive muscle activity as epileptic fit, chronic hypertension & PIH and endocrine disorders: hyper-/hypothyroidism, and diabetes mellitus, history of liver disease or renal disease.

Sample size justification

The required sample size has been calculated using the Power Analysis and Sample Size (PASS©) software version 11.0.10 (NCSS©, LLC, Kaysville, Utah). The primary outcome measure is the accuracy of serum creatine kinase and alpha-fetoprotein for diagnosis of placenta accreta.

All women were subjected to the following: Obstetric history taking and examination. Investigations: Complete blood picture (CBC), Rhesus factor (RH), Blood group and blood sugar. Serum Creatine kinase assesment (reference range is (10-80 U/I). Serum alfa-fetoprotein (reference range is (0-40 U/I), Urine for: glucose, protein and bacteruria, Kidney function tests, Liver functions tests and thyroid function test. Ultrasound: The study was carried out in Beni Suef University Maternity hospital & MUST Teaching hospital ultrasound unit.

Maternal outcome

CS hysterectomy, blood transfusion, postoperative admission at ICU and other morbidities (massive blood transfusion leading to DIC, intestinal injury, bladder injury)

Ethics

The study was approved by the Ethical Committee of the Department of Obstetrics and Gynecology, Faculty of Medicine, Beni Suef University.

Statistical methods

Data were coded and entered using the statistical package SPSS version 22. Non parametric data was summarized as mean and sd. Comparisons between the two groups were done using Chi² test when comparing for the incidence of studied parameters and Mann-Whitney test and unpaired t test was used when comparing variables between the two groups. ROC analysis was done to detect the prediction value of CK, AFP. P value less than 0.05 is considered significant (Chan, 2003).

Results

Table (1): Basic Characteristics of the studied population; (N= 72)

Item	Minimum	Maximum	Mean $\pm$ SD
Age	20	39	33 $\pm$ 4.2
BMI (kg/m ²)	19	28	
GA (Weeks)	33	38	
Gravidity	1	8	3.28 $\pm$ 1.6
Parity	1	7	2.54 $\pm$ 1.3
Number of Previous (C.S.)	1	5	2.23 $\pm$ 1.0

Table (1) demonstrates the basic characteristics of the studied population, patients' age ranged from 17 to 42 years old with a mean value of 29.86 $\pm$ 5.2 (SD). The gravidity ranged from 1 to 8 with a mean value of 3.28 $\pm$ 1.6 (SD); while the parity ranged from 0 to 7 times with a mean value of 2.54 $\pm$ 1.3 (SD). The number of CS was ranged from 1 to 5 times with a mean value of 2.23 $\pm$ 1.0 (SD).

Table (2): Maternal serum total creatine kinase and AFP among the studied groups

	Control N=36	Cases N=36	P value
CK total			
Minimum	11	18	0.014
Maximum	93	182	
mean $\pm$ sd	47.4 $\pm$ 23.9	68.6 $\pm$ 35.6	
AFP			
Minimum	10	11	0.028
Maximum	29	96	
mean $\pm$ sd	19.11 $\pm$ 5.6	28.5 $\pm$ 20.16	

Table (2) and figure (16) show significant increase in both CK (p value =0.014) and msAFP (P value=0.028) in cases compared to the control group. The control's CK ranged from 11 to 93 with a mean value of 47.4 $\pm$ 23.9 (SD) while the patient's CK ranged from 18 to 181 with a mean value of 68.6 $\pm$ 35.6 (SD). The control's msAFP ranged from 10 to 29 with a mean value of 19.11 $\pm$ 5.6 (SD) while the patient's msAFP ranged from 11 to 96 with a mean value of 28.5 $\pm$ 20.16 (SD).

Table (3): The results of ROC curve analysis of CK as a predictor of PAS

	AUC	SE	95% CI	Sensitivity	Specificity	Cutoff value	p-value
CK	0.669	0.063	0.545 – 0.792	80%	40%	44.5	0.014

AUC= Area under the curve, SE= Standard Error, CI= Confidence interval of AUC.

As demonstrated in table (3) and figure (17); receiver operating characteristic (ROC) curve analysis was used to assess the clinical diagnostic accuracy of CK

Evaluation Total Score as a predictor of PAS in the studied Population; the results of CK (ROC) curve analysis showed p-value =0.014 so; the CK total Score diagnosed as statistically significant predictor with a 80% Sensitivity (true positive cases) and 40% Specificity (true negative cases) at a cutoff point level ≥ 44.5 total score.

Table (4): The results of ROC curve analysis of msAFP as a predictor of PAS

	AUC	SE	95% CI	Sensitivity	Specificity	Cutoff value	p-value
AFP	0.65	0.065	0.523 - 0.778	72%	50%	17.5	0.028

AUC= Area under the curve, SE= Standard Error, CI= Confidence interval of AUC

As demonstrated in table (4) and figure (18); receiver operating characteristic (ROC) curve analysis was used to assess the clinical diagnostic accuracy of msAFP Evaluation Total Score as a predictor of PAS in the studied Population; the results of msAFP (ROC) curve analysis showed p-value =0.028 so; the msAFP score diagnosed as statistically significant predictor with a 72% Sensitivity (true positive cases) and 50% Specificity (true negative cases) at a cutoff point level ≥ 17.5 total score.

Table (5): The results of ROC curve analysis of msAFP by MOM as a predictor of cases (PAS)

	AUC	SE	95% CI	Sensitivity	Specificity	Cutoff value	p-value
MOM	0.994	0.002	0.981-0.999	80%	95%	1.42	0.028

AUC= Area under the curve, SE= Standard Error, CI= Confidence interval of AUC.

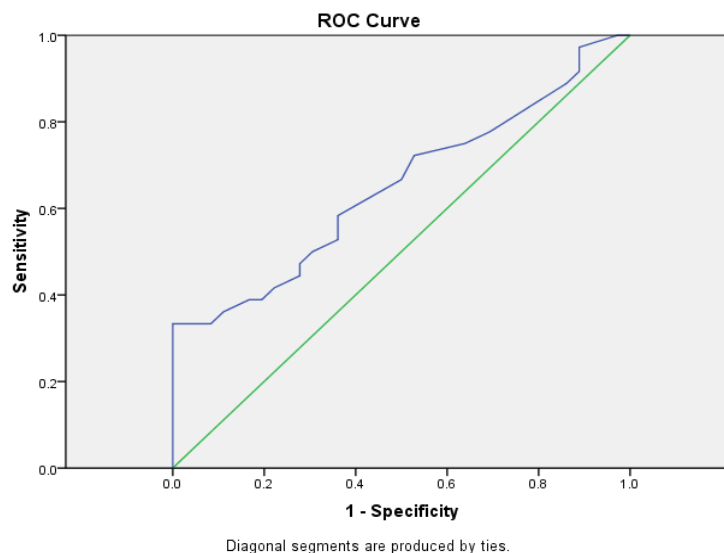


Figure (2): The results of ROC curve analysis of msAFP multiple of median as a predictor of PAS

As demonstrated in table (5) and figure (19); receiver operating characteristic (ROC) curve analysis was used to assess the clinical diagnostic accuracy of msAFP by multiple of median (MOM) Evaluation Total Score as a predictor of PAS in the studied Population; the results of msAFP multiple of median (ROC) curve analysis showed p-value =0.028 so; the msAFP multiple of median score diagnosed as statistically significant predictor with a 80% Sensitivity (true positive cases) and 95 % Specificity (true negative cases) at a cutoff point level ≥ 1.42 total score.

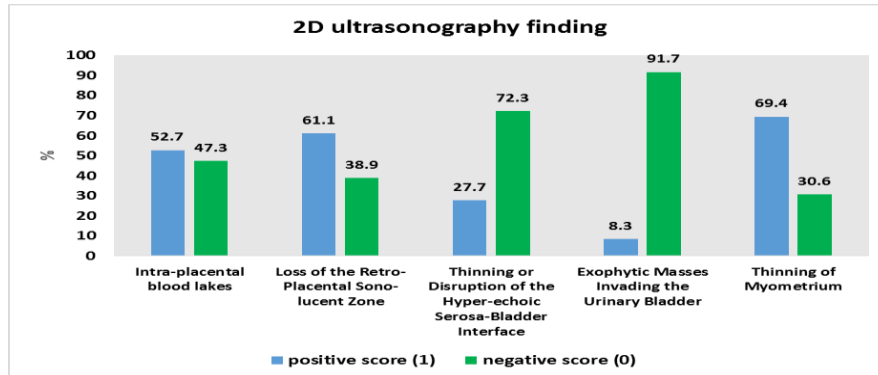


Figure (3): 2D Ultrasonography Evaluation of the cases (PAS)

the 2D ultrasonography findings of the studied population were; Intra-placental blood lake was detected in 19 cases out of 36(52.7%), loss of the retro-placental sono-lucent zone (Interruption of interface between the posterior bladder wall and the uterus) was detected in 22 cases out of 36 (61.1%), thinning or disruption of the hyper-echoic serosa-bladder interface was detected only in 10 cases out of 36 (27.7%) with 26 patients (72.3%) significantly have no thinning (p value=0.008). Figure (3)

Table (6): Intra-Operative Assessment of the cases (PAS); (N= 36)

Item	Negative	Positive	
PPH	31 (86.1%)	5 (13.9%)	
Blood Transfusion	7 (19.4%)	29 (80.6%)	
Pelvic de-vascularization	32 (88.9%)	4 (11.1%)	
CS HST	2 (5.6%)	34 (94.4%)	
Bladder injury	33 (81.7%)	3 (8.3%)	
Ureteric Injury	36 (100.0%)	0 (0.00%)	
Major vessel injury	36 (100.0%)	0 (0.00%)	
Bowel injury	36 (100.0%)	0 (0.00%)	
	Maximum	Minimum	Mean±SD
Amount of Transfused PRBCs	6	0	1.8±1.36
Amount of transfused FFP	3	0	0.83±0.9

Intra-Operative assessment of the studied cases revealed that; of the studied cases; 29 cases (80.6%) needed blood transfusion. The average amount of the transfused PRBCs was 1.8 ± 1.36 (SD) while the average amount of transfused FFP was 0.83

± 0.9 (SD). CS HST was positive in 34 (94.4%) of cases. Regarding intra-operative visceral injuries; bladder injury was reported in only 3 (8.3%), however no other visceral injuries were reported. Table (6)

Table (7): Comparison between cases and controls regarding Post-Operative ICU Admission; and post-operative maternal mortality (N= 36)

	Control N=36	Cases N=36	P value
ICU Admission			
Yes	1(2.8%)	28(77.8%)	<0.001
No	35(97.2%)	8(22.2%)	
Maternal mortality			
Survived	36 (100.0%)	34 (94.4%)	0.17
Died	0(0%)	2 (5.6%)	

Table (7) showed that post-operative ICU admission was significantly required for 28(77.8%) PAS cases compared only one case out of 36 studied controls (2.8%) (p value <0.001). No significant difference in the survival rate between cases and controls (p value =0.17).

Discussion

Age of the studied patients ranged between 20 and 39 years (mean of 33 ± 4.2). Gravidity of all patients ranged between 1 to 8 (mean of 3.28 ± 1.6). Parity ranged between 1 to 7 (mean of 3.1 ± 1.25 times ± 1.3). Number of previous CSs ranged between 1 to 5 (mean of 2.23 ± 1.0). This study showed a significant increase in both CK (p value =0.014) and msAFP (P value=0.028) levels in cases compared to the control group. MOM had been statistically used to assess the clinical diagnostic accuracy of MS-AFP as a predictor of morbid placental adherence (MAP) in the studied Population; the results of MS-AFP by MOM (ROC) curve analysis showed p-value = 0.001 so; the MS-AFP by MOM diagnosed the MAP at a statistically significant level with a 80% Sensitivity (true positive cases) and 95% Specificity (true negative cases) at a cutoff point ≥ 1.42 MOM.

Regarding 2D ultrasonography findings of cases (PAS), it was observed that, intra-placental blood lake was detected in 19 cases out of 36(52.7%), loss of the retro-placental sono-lucent zone (Interruption of interface between the posterior bladder wall and the uterus) was detected in 22 cases out of 36 (61.1%), thinning or disruption of the hyper-echoic serosa-bladder interface was detected only in 10 cases out of 36 (27.7%) with 26 patients (72.3%) significantly had no thinning , exophytic masses invading the urinary bladder was detected only in 3 cases out of 36 (8.3%) with 33 patients (91.7%) significantly had no exophytic masses. significant thinning of myometrium in 25 cases out of 36 (69.4%) (p value =0.02). Comparative studies of creatine kinase and α -fetoprotein as biological markers for prenatal diagnosing placenta increta and percreta have reported conflicting results.

El Didy et al. (2013) concluded that MS-AFP may be useful as a complimentary technique with ultrasound (2D and 3D) for the antenatal diagnosis of placenta

accreta. In their study, a total of 60 patients with prior CDs were chosen from those admitted for elective cesarean sections. Patients were divided into 2 groups; case group with placenta previa and control group with upper segment implanted placenta. Each group was subjected to ultrasound examination by greyscale ultrasound and 3D power Doppler. Maternal serum level of alpha-fetoprotein was estimated and the condition of placenta was determined by the surgeon intra-operatively. The results showed that Placenta accreta and its variants (including increta and percreta) were confirmed in 18 patients at the time of Cesarean delivery. They found that MS-AFP was the most sensitive with 88.9% sensitivity, followed by greyscale ultrasound with 77.8% sensitivity followed by 3D power Doppler with 66.7% sensitivity. However MS-AFP was the least specific with specificity of 33.3% followed by greyscale ultrasound with 66.7% specificity and the most specific was 3D power Doppler with 83.3% specificity. In agreement with their study, the current study found that the msAFP score diagnosed as statistically significant predictor with a 72% Sensitivity and 50% Specificity but, in the current study MS-AFP MOM had been statistically which add clinical accuracy of MS-AFP as a predictor of morbid placental adherence (MAP) at cutoff point was ≥ 1.42 MOM with a 80% Sensitivity and 95 % Specificity

Albehouty et al. (2014), concluded that an unexplained elevated MSAFP level $>2\text{MoM}$ can be used in predicting intra-operative morbid placental adherence and intra-operative complications in cases of suspected morbidly adherent placenta. In this study 60 pregnant women with suspected morbidly adherent placenta by trans-abdominal ultrasound had their maternal serum alpha-fetoprotein (MSAFP) levels measured. Women with other causes for MSAFP elevation were excluded. Their results showed that a sonographic score >3 was associated with morbid adherence at a sensitivity of 82.6% and specificity of 92.1% while in our results the cutoff point was ≥ 2 total score. Also in their study MSAFP $>2\text{MOM}$ was associated with morbid adherence of placenta at a sensitivity of 93.3%, specificity of 71.4% , while in our results cutoff point was ≥ 1.42 MOM with a 80% Sensitivity and 95% Specificity

Lyell et al. (2015), concluded that Elevated PAPP-A, elevated MS-AFP and prior cesarean deliveries are associated with MAP among women with previa. In this study Women with MAP (cases) and previa alone (controls) and prior cesarean deliveries were identified from a cohort of 236,714 singleton pregnancies with both first and second trimester prenatal screening, and live birth and hospital discharge records; pregnancies with aneuploidies and neural tube or abdominal wall defects were excluded. The results showed that in all 37 cases with MAP and 699 controls with previa alone were included. Risk for MAP was increased among multiparous women with pregnancy-associated plasma protein-A (PAPP-A) $\geq 95\text{th}$ percentile (≥ 2.63 multiple of the median (MoM); adjusted OR (aOR) 8.7, 95% confidence interval (CI) 2.8 to 27.4), maternal-serum alpha fetoprotein (MS-AFP) $\geq 95\text{th}$ percentile (≥ 1.79 MoM; 95% CI 1.0 to 8.0). The current study was in agreement of *lyell et al.* study, as regard significant elevation of MS-AFP in cases of PAS with previa and prior CDs , but there was retrospective while the present one was prospective which make it more superior to their study. They measured MS-AFP in different gestational age, second trimesteric versus third trimesteric in the current study. We measured MS-AFP and creatine kinase levels in third trimester after diagnosis of placenta previa and PAS by 2D ultrasonography

msAFP MOM diagnosed as statistically significant predictor of PAS at a cutoff point level ≥ 1.42 MOM with a 80% Sensitivity (true positive cases) and 95 % Specificity (true negative cases).

On the contrary ACOG (2018), found that, although an elevated MSAFP level supports an ultrasound-based diagnosis of abnormal placental implantation, it is an inconsistent finding and is not useful by itself for diagnosis. Moreover, a normal MSAFP does not exclude the diagnosis.

On the other hand, Ersoy *et al.* (2016), found no significans of measurement of maternal serum CK as biological markers in predicting PAS. In this case-control study, fifty-four pregnant women who attended our tertiary care center for perinatology with the diagnosis of PP totalis, and of them, 14 patients with placenta accreta were recruited as the study groups. Forty-six uncomplicated control patients who were matched for age, BMI were also included. Maternal venous ProBNP, CK, CK-MB and Troponin I levels, which are circulatory biomarkers related to cardiac functions, were compared between the three groups. The results showed that CK and CK-MB levels were similar among three groups. Troponin I levels in the previa and accreta groups were significantly higher than the controls. ProBNP levels in the accreta group were significantly higher than other two groups. In our study we measured MS-AFP and creatine kinase levels in third trimester in 2 groupes, 36 women with PAS & previa and prior CDs (cases) and 36 women uncomplicated with only prior cesarean deliveries (control), and the results showed a significant increase in both CK (p value =0.014) and msAFP (P value=0.028) levels in cases compared to the control group.

In the current study four cases (PAS) needed pelvic devascularization by intraoperative bilateral internal Iliac artery ligation) to control intraoperative haemorrhage. Other modalities of pelvic devascularization and their efficacy should be studied in management of PAS. Clausen *et al.* (2013), concluded that Prophylactic balloon occlusion of the internal iliac arteries as part of a multidisciplinary algorithm allowed for a safe management of all cases in our consecutive series of 17 women with placenta percreta. However, intraoperative blood loss and transfusion requirements were significant. They have therefore decided to modify multidisciplinary algorithm to include balloon occlusion of the common iliacarteries rather than the internal iliac arteries. Manzano-Nunez *et al.* (2018) found that the use of resuscitative endovascular balloon occlusion of the aorta (REBOA) is a feasible, safe, and effective means of prophylactic and remedial hemorrhage control in pregnant women with abnormal placentation undergoing cesarean delivery.

Conclusion

This study showed significant increase in both serum CK and msAFP in cases with placent accrete spectrum compared to the control group with no placent accrete spectrum. Maternal serum creatine kinase and α -fetoprotein concentrations may serve in addition to ultrasonography in the diagnosis of placenta acreta spectrum.

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