Creatine Kinase as a diagnostic biochemical Marker in Placenta Accreta, Mansoura experience

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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 evaluate the possibility of using creatine kinase as a diagnostic and prognostic marker in placenta accreta.

Methods: two groups were recruited; forty-five patients diagnosed by ultrasound with placenta accreta as patient group (group A) and another forty-five as controls (group B). Maternal Creatine kinase level was measured using CK-NAC FS* IFCC Technical bulletin and compared between patients group and controls group.

Results: Our results indicated the presence of significant difference between the patient group and the control group regarding age (P-value= 0.01), gravidity (P-value= 0.01) and parity (P-value= 0.006). While non-significant difference regarding medical history (P-value= 0.59), surgical history (P-value= 0.51), and D & C (P-value= 0.82). Our results indicated no significant difference between both groups regarding serum creatine kinase level (P-value= 0.29). We have identified surgical complications and intraoperative findings which occurred significantly higher in the patient group in compare with the control group (P value <0.001). Our finding also revealed the presence of significant difference between the patient and control group regarding secondary outcomes including the required blood units transfusion (P-value <0.001).

Conclusion: We conclude that maternal serum creatine kinase is not a reliable tool in predicting or diagnosing placenta accreta.

Keywords: Creatine kinase, placenta accreta, previa, ultrasonography, surgical outcome.

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Introduction

Abnormal invasive placentation is a potential life-threatening pregnancy complication that may cause serious adverse maternal and fetal outcomes [1].

There are three variants of invasive placentation which include placenta accreta where the placental villi occupy the surface of myometrium with a partial or complete absence of decidua basalis layer [2] and placenta increta which is characterized by the penetration of the placental villi into the myometrium and placenta percreta where the villi penetrate through the myometrium reaching the uterine serosa and could invade adjacent organs, such as the urinary bladder [3].

high cesarean section (CS) rates in the latest decades have increased placenta accreta cases and as a result, pregnancy and delivery complications are occurring increasingly [4].

It is critical to make the diagnosis before delivery because preoperative planning can significantly decrease intra-operative bleeding and avoid morbidity associated with placenta accreta [5].

Creatine kinase (CPK) (Adenosine-5–triphosphate) is an enzyme found in the heart, brain, and skeletal muscle, it is also found in non-muscle cells such as pancreas, myometrium, endometrium and placenta [6].

In literature, there are controversial results regarding the efficacy of using creatine kinase as a biochemical marker in predicting and diagnosing placenta accreta. One of those studies indicated elevated levels of creatine kinase in pregnant women diagnosed with placenta increta and percreta [7]. On the other hand, a second study failed to detect any elevations of creatine kinase levels in pregnant women diagnosed with placenta accreta [8].

Ultrasonography is the main tool in diagnosing placenta accreta, however, many cases with placenta accreta undiagnosed or misdiagnosed by ultrasound leading to poor maternal outcome and complications.

Therefore, the aim of our study was to indicate the possibility of using serum creatine kinase as a diagnostic and prognostic marker in placenta accreta.

Patients and methods

This was a prospective cohort study, patient group (Group A) which included 45 cases in their 2nd or 3rd semester who were diagnosed by ultrasound with placenta accreta and control group (Group B) which included 45 cases with normal placenta. Patients were examined and evaluated at the antenatal clinic and Inpatient department at Mansoura University hospitals from April 2019 till April 2020. Written informed patient consent was obtained from each case before the study.

Inclusion criteria included maternal age between 19-40 years old. Pregnant women with placenta accreta diagnosed with documented ultrasound and Doppler or MRI. Being at second or third trimester pregnancy and patient with previous hysterotomy or any uterine scar. Exclusion criteria included patient diagnosed with myocardial infarction (heart attack), autoimmune myositis, rhabdomyolysis or acute kidney injury.

Full History taking and examination including general examination, screening for risk factors of placenta increta and percreta, and past history of previous operations myomectomy or previous caesarian section.

Ultrasound examination was performed to ensure the presence of placenta accreta in the patient group. The ultrasound diagnostic criteria of placental accreta include disappearance of the hypoechoic retro-placental zone, disruption of the hyperechoic uterine serosa-bladder interface, increase intra-placental lacunae, and hyper-vascularity at the interface between the uterine serosa and the urinary bladder wall by color Doppler (irregularity of the bladder wall with positive flow on Doppler evaluation). Sagittal imaging was used to assess the depth of placental tissue, its vascularity and its relationship to the bladder wall, while coronal imaging was used to assess the extent of invasion. The presence of vascular structures on the bladder wall on Doppler ultrasound was classified as bladder invasion and the presence of other

sonographic findings on grayscale imaging with negative Doppler was classified as probable bladder invasion.

Measuring creatine kinase level, Blood samples were obtained after an overnight fasting by venipuncture and processed within 1 h after withdrawal by centrifugation at 5000 revolutions/min for 10 min, and analyzed at that time. Serum total creatine kinase was assayed by photometric systems using CK-NAC FS* IFCC Technical bulletin supplied along with the kit was followed.

Ethical consideration

Study protocol was submitted for approval by Institutional Research Board (IRB) faculty of medicine, Mansoura University. Approval of the mangers of the health care facilities in which the study was conducted. Informed verbal consent was obtained from each participant sharing in the study. Confidentiality and personal privacy were respected in all levels of the study.

Statistical Analysis of Data

Data were analyzed with SPSS version 21. The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test. Continuous variables were presented as mean ± SD (standard deviation) for parametric data and Median for non-parametric data. The two groups were compared with Student t test (parametric data) and Mann–Whitney test (non-parametric data).

Results

Table (1) represents the demographic characteristics of the studied cases.

Table 1: Demographic characteristics of the patient and control groups:

Parameters		Patient group(A)	Control group(B)	X^2	P value
Age (years)		30.36±5.16	27.7±5.21	2.41	0.01*
Gravidity		3.95±1.49	3.21±1.29	2.52	0.01*
Parity		2.45±0.99	1.79±1.19	2.81	0.006*
Gestational age (weeks)		35.7±2.41	35.7±2.41	1.63	0.11
No. of fetuses	Single	43 (95.6%)	41 (91.1%)	1.05	0.59
	Twins	1 (2.2%)	3 (6.7%)		
	Triplet	1 (2.2%)	1 (2.2%)		

P-value< 0.001: highly significant, P-value <0.05: significant, P-value >0.05: non-significant.

Table 1 showed the demographic characteristics of the patient and control cases. There was significant difference between the patient group and control group regarding age (30.36±5.16 years old vs 27.7±5.21 years old respectively), gravidity (3.95±1.49 vs 3.21±1.29 respectively), and parity (2.45±0.99 vs 1.79±1.19 respectively). However, there was no significant difference between the patient group and control group regarding gestational age at the time of the study (35.7±2.41 weeks vs 35.7±2.41 respectively).

Table 2: Comparison between studied cases regarding medical history:

Parameters	Patient group(A)	Control group(B)	X^2	P value
Negative	36 (80.0%)	36 (80.0%)	2.7	0.59
Type I DM	2 (4.5%)	0 (0.0%)		
GDM	1 (2.2%)	1 (2.2%)		
HTN	3 (6.7%)	1 (2.2%)		
GHTN	1 (2.2%)	3 (6.7%)		
PE	1 (2.2%)	3 (6.7%)		
PE+DM	1 (2.2%)	1 (2.2%)		

DM: diabetes mellitus. GDM: Gestational diabetes mellitus. HTN: Hypertension. GHTN: Gestational hypertension. PET: pre-eclampsia toxemia. P-value <0.05: significant, P-value >0.05: non-significant.

Table 2 showed that regarding the medical history, including gestational diabetes mellitus (GDM), gestational hypertension (GHTN), pre-eclampsia (PE), pre-eclampsia plus diabetes mellitus (PE+DM), hypertension (HTN) and type 1 DM, there were non-statistic significant difference between the patient group and control (P-value=0.59).

Table 3: Comparison between studied cases regarding surgical history:

Parameters	Patient group(A)	Control group(B)	X^2	P value
Negative	28 (62.2%)	21 (46.7%)	3.28	0.51
Appendectomy	7 (15.6%)	11 (24.4%)		
Cholecystectomy	3 (6.7%)	2 (4.5%)		
Ovarian Cystectomy	1 (2.2%)	1 (2.2%)		
Exploration	3 (6.7%)	0 (0.0%)		
Incisional hernia	2 (4.5%)	0 (0.0%)		
Placenta previa	1 (2.2%)	0 (0.0%)		

P-value< 0.001: highly significant, P-value <0.05: significant, P-value >0.05: non-significant.

Regarding surgical history. Table 3 indicated non-significant difference between the patient group and control (P-value=0.51).

Table 4: Comparison between studied cases regarding CPK at the time of the study:

Parameters	Patient group(A)	Control group(B)	T test	P value
CPK (IU/L)	70.38±62.81	58.73±37.67	1.05	0.29

CPK: creatinine phospho-kinase. P-value< 0.001: highly significant, P-value <0.05: significant, P-value >0.05: non-significant.

Table 4 indicated the measured creatinine phospho-kinase was not significantly different between patient group and control group (P-value = 0.29).

Table 5: Comparison between studied cases regarding placental site:

Parameters	Patient group(A)	Control group(B)
FA	0 (0.0%)	19 (42.2%)
FP	0 (0.0%)	24 (53.3%)
Fundal	0 (0.0%)	2 (4.5%)
Anterior type 1	4 (8.9%)	0 (0.0%)
Anterior type 2	11 (24.4%)	0 (0.0%)
PPCC	22 (48.9%)	0 (0.0%)
Posterior type 2	8 (17.7%)	0 (0.0%)

FA: fundal anterior. FP: fundal posterior. PPCC: placenta praevia complete centralis.
Table 5 indicated the site of placenta in the patient group was anterior type 1, anterior type 2, PPCC and posterior type 2 (8.9%, 11%, 22% and 8% respectively) which indicating placenta previa in most of the studied cases of the patient group. On the other hand, the placental locations in control group were fundal anterior, fundal posterior and fundal (42.2%, 73.3% and 4.5% respectively).

Table 6: Comparison between studied cases regarding surgical outcome intraoperative findings:

Parameters	Patient group(A)	Control group(B)	P-value
Negative	5 (11.1)	45 (100.0%)	<0.001*
Focal accretion	20 (44.4%)	0 (0.0%)	
CS Hysterectomy	9 (20.0%)	0 (0.0%)	
Diffuse accretion	4 (8.9%)	0 (0.0%)	
CS Hysterectomy+ bladder injury	2 (4.5%)	0 (0.0%)	
Diffuse accretion+ PPH	1 (2.2%)	0 (0.0%)	
Diffuse accretion+ bladder injury	1 (2.2%)	0 (0.0%)	
Bladder injury	2 (4.5%)	0 (0.0%)	
Focal accretion+ bladder injury	1 (2.2%)	0 (0.0%)	

CS: cesarean section. PPH: post-partum hemorrhage. P-value< 0.001: highly significant, P-value <0.05: significant, P-value >0.05: non-significant.

Regarding the primary outcomes, table 6 indicated there was significant difference between patient group and control group (P <0.001).

Table 7: Comparison between studied cases regarding secondary outcome:

Parameters		Patient group(A)	Control group(B)	X^2	P value
Negative		12 (26.7%)	39 (86.7%)	5.13	<0.001*
Blood transfusion units	2	8 (17.8%)	4 (8.8%)		
	3	3 (6.7%)	2 (4.4%)		
	4	8 (17.8%)	0 (0.0%)		
	5	2 (4.5%)	0 (0.0%)		
	6	6 (13.3%)	0 (0.0%)		
	7	6 (13.3%)	0 (0.0%)		

P-value< 0.001: highly significant, P value <0.05: significant, P-value >0.05: non-significant.

Regarding secondary outcome, Table 7 indicated highly significant difference between patient group and control group (P <0.001).

Discussion

Placenta accrete is a potential life-threatening pregnancy complication. There are three variants of abnormal invasive placentation including placenta accrete, placenta increta and placenta percreta [3].

Early diagnosis of placenta accreta may reduce the possible adverse outcomes. Despite the improvements in the imaging techniques and attempts to find a reliable marker to predict the abnormal invasion of the placenta, there is still debate for the accurate diagnosis [9,10].

In our study, there were significant difference between the patient group and control group regarding age (P value <0.05), gravidity (P value <0.05), and parity (P value <0.001). However, there was no significant difference between the patient group and control group regarding gestational age at the time of the study (P value= 0.11).

Such results were in agreement with Iacovelli et al [11] study which reported that maternal age older than 32 years old is one of the risk factors of placenta accreta. The same findings were confirmed by Saito et al [12] and Singh and Kumari [13] studies that revealed that both multiparty and advanced maternal age to be predisposing factors to the occurrence of placenta accrete without prior history of cesarean section delivery.

In our study, the measured creatinine phospho-kinase was not significantly different between patient group and control group (P-value = 0.29) indicating that creatine kinase does not represent an accurate tool as a diagnostic and prognostic marker of placenta accrete.

Such finding was in agreement with Ersoy et al (8) study that measured total creatine kinase and CK-MB levels in fifty-four pregnant women with diagnosed placenta previa and failed to predict the risk of placental accreta.

However, our results were in disagreement with Ophir et al [7] study that indicated an elevation in maternal serum creatine kinase in patients with adherent placenta (increta or percreta).

In our study, the patient group placental location was anterior type 1, anterior type 2, PPCC and posterior type 2 (8.9%, 11%, 22% and 8% respectively) which indicating placenta previa in most of the studied cases of the patient group. On the other hand, the placental locations in control group were fundal anterior, fundal posterior and fundal (42.2%, 73.3% and 4.5% respectively).

Previous studies indicated that anterior location of the placenta in placenta previa increases the risk of postpartum hemorrhage, massive transfusions, and hysterectomy especially if complicated with placenta accreta [14,15].

In the present study, we have identified eight surgical outcomes and intraoperative findings which occurred significantly in the patient group in compare with the control group (P value <0.001) including the presence of focal accretion, diffuse accretion, the incidences of bladder injury, CS hysterectomy alone, CS hysterectomy+ bladder injury, diffuse accretion+ PPH, diffuse accretion+ bladder injury and focal accretion+ bladder injury (P value<0.001).

Our results were in accordance with Clausen et al 16 study which revealed that 17% of placenta accreta patients are under the risk of cystotomy either unintentionally due to impaired visualization and poor dissection planes, or intentional injury to facilitate visualization.

Moreover, Hoffman et al 17 indicated that 10-15% of patients are under the risk of urethral injury during the surgical management of placenta accreta.

Regarding secondary outcome including number of units of blood transfused, our results revealed a significant difference between patient group and control group (P <0.001).

Our results were in agreement with AbdElfatah et al (18) study which indicated that 79.6% of placenta accreta patients required blood transfusion. Additionally, a study performed by Wright et al [19] revealed that the most common complication of placenta accreta is hemorrhage. Moreover, blood transfusion was required in more than 80% of cases; at least one half required 4 or more units of packed red blood cells.

In conclusion, maternal creatine kinase is not a reliable tool in predicting or diagnosing placenta accreta.

References

1. Garmi, G., and Salim, R., Epidemiology, etiology, diagnosis, and management of placenta accreta. Obstetrics and Gynecology International 2012, (8):873929.
2. Zhou, J., Li, J., Yan, P., Ye, Y.H., Peng, W., et al. Maternal plasma levels of cell-free β-HCG mRNA as a prenatal diagnostic indicator of placenta accrete. Placenta, 2014, 35(9), pp.691-695.
3. Kilcoyne, A., Shenoy-Bhangle, A.S., Roberts, D.J. MRI of placenta accreta, placenta increta, and placenta percreta: pearls and pitfalls. American Journal of Roentgenology, 2017, 208(1), pp.214-221.
4. Asıcıoglu, O., Şahbaz, A., Güngördük, K. Maternal and perinatal outcomes in women with placenta praevia and accreta in teaching hospitals in Western Turkey. Journal of Obstetrics and Gynaecology, 2014,34(6), pp.462-466.
5. Shih, J.C., Jaraquemada, J.P., Su, Y.N. Role of three-dimensional power Doppler in the antenatal diagnosis of placenta accreta: comparison with gray-scale and color Doppler techniques. Ultrasound in obstetrics and gynecology, 2009, 33(2), pp.193-203.
6. Teixeira, A.M. and Borges, G.F., Creatine kinase: structure and function. Brazilian Journal of Biomotricity, 2012, 6(2), pp.53-65.
7. Ophir, E., Tendler, R., Odeh, M. Creatine kinase as a biochemical marker in diagnosis of placenta increta and percreta. American journal of obstetrics and gynecology, 1999,180(4), pp.1039-1040.
8. Ersoy, A.O., Oztas, E., Ozler, S. Can venous ProBNP levels predict placenta accreta? The Journal of Maternal-Fetal & Neonatal Medicine, 2016,29(24), pp.4020-4024.
9. Pagani, G., Cali, G., Acharya, G. Diagnostic accuracy of ultrasound in detecting the severity of abnormally invasive placentation: a systematic review and meta-analysis. Acta obstetricia et gynecologica Scandinavica, 2018, 97(1), pp.25-37.
10. Warshak, C.R., Eskander, R., Hull, A.D. Accuracy of ultrasonography and magnetic resonance imaging in the diagnosis of placenta accreta. Obstetrics & Gynecology, 2006, 108(3), pp.573-581.
11. Iacovelli, A., Liberati, M., Khalil, A. Risk factors for abnormally invasive placenta: a systematic review and meta-analysis. The Journal of Maternal-Fetal & Neonatal Medicine, 2020, 33(3), pp.471-481.
12. Saito, K., Kuwahara, A., Ishikawa, T. Endometrial preparation methods for frozen-thawed embryo transfer are associated with altered risks of hypertensive disorders of pregnancy, placenta accreta, and gestational diabetes mellitus. Human Reproduction, 2019, 34(8), pp.1567-1575.
13. Singh, N. and Kumari, P. Placenta accreta: A mini review. J Preg Child Health, 2014, 1, p.e104.
14. Morgan, E.A., Sidebottom, A., Vacquier, M. The effect of placental location in cases of placenta accreta spectrum. American

journal of obstetrics and gynecology, 2019, 221(4), pp.357-e1.

15. Matsubara, S., Baba, Y. and Takahashi, H. Placenta previa and hemorrhage: the placental location may be an important determinant of the bleeding amount. The Journal of Maternal-Fetal & Neonatal Medicine, 2018, 31(10), pp.1390-1391.
16. Clausen, C., Lönn, L. and Langhoff-Roos, J. Management of placenta percreta: a review of published cases. Acta obstetricia et gynecologica Scandinavica, 2014, 93(2), pp.138-143.
17. Hoffman, M.S., Karlnoski, R.A., Mangar, D. Morbidity associated with nonemergent hysterectomy for placenta accreta. American journal of obstetrics and gynecology, 2010, 202(6), pp.628-e1.
18. AbdElfatah, E.A., Awad, E.E.M., Abd-Eldaym, T.M. and Ali, Z.H. Outcome of patients with placenta accreta at El Shatby Maternity University Hospital. Open Journal of Obstetrics and Gynecology, 2017, 7(07), p.725.
19. Wright, J.D., Pri-Paz, S., Herzog, T.J. Predictors of massive blood loss in women with placenta accreta. American journal of obstetrics and gynecology, 2011,205(1), pp.38-e1.