

Evaluation of Cesarean Section Scar Using Maternal Serum Level of Creatine Kinase Isoenzyme (Ck-Mb) Prior to Delivery

Original
Article

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ABSTRACT

Aim: This study aimed to evaluate cesarean scar by using maternal serum creatine kinase isoenzyme (CK-MB) prior to delivery as a soft marker to detect CS complications (uterine rupture, dehiscence).

Material and Methods: It was a prospective study carried out at Alzahraa University Hospital where 90 pregnant women divided into two groups : group A included 60 women with previous cesarean section. They were subdivided into 2 subgroups : group (A1) 19 patients who included cases with emergency cesarean delivery and group (A2) 41 patients which included cases with elective cesarean delivery. Group B included the control group which included 30 patients with planned normal vaginal deliveries. Before delivery blood sample were collected from both groups before cesarean delivery and during normal vaginal delivery. The plasma (heparinized/EDTA) was collected from our 90 subject. Total CK, CK-MB level analyses were done by immuno-inhibition method using auto- analyzer. The normal values of CK total (24-170 U/L) and CKMB (0-25U/L).

Results: Twenty patients had scar abnormality (defect=4,thin=16) and remaining forty cases had intact scar these patients had elevated levels of CKMB with sensitivity, specificity, PPV and NPV for thin scar 100%, 84.09%, 69.6% and 100%, respectively, and sensitivity, specificity, PPV and NPV for rupture scar 100%,78%,38.9% and 100%, respectively.

Conclusion: CKMB can be used as a soft marker beside other methods for detection of cesarean scar abnormality (uterine rupture , dehiscence) prior to delivery with high sensitivity and specificity.

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Key Words: Cesarean delivery, cesarean section, CKMB, uterine dehiscence, uterine rupture

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INTRODUCTION

Cesarean section is the commonest obstetric operation performed and one of the commonest surgical procedures in general. It is performed as both elective and urgent. However, as a surgical procedure, there are risks of complications and overuse can be harmful to both mothers and neonates^[1], one of these complications, Cesarean scar defect. Because of the stretching of the muscle during pregnancy or the strong contractions of labor, the old cesarean scar might not stand the strain of labor and it becomes thin or begins to separate. When it does, it is called scar dehiscence. Rarely, the scar opens and extends into other parts of uterus. This is called uterine rupture^[2] Uterine rupture can lead to many complications such as postpartum hemorrhage, hysterectomy, even maternal death and intrapartum/infant deaths, and post-hypoxic encephalopathy and admissions to NICU^[3].

However, The inability to precisely confirm the integrity of scarred lower uterine segment (LUS) becomes the indication of a repeat cesarean section^[2]. But there

is range of error during the sonographic measurement because many factors can affect the Lower uterine segment measurement (eg: contractile state of uterus, displacement of amniotic fluid, fetal movement and position, operator's pressure through the transducer during the examination and fullness of bladder^[4].

Creatine kinase (CK) is a key enzyme of energy metabolism, especially in muscle tissue. CK has two polypeptide chains of M and B, and three isomers, CK-BB, CK-MB and CK-MM. Creatine Kinase can also be elevated in absence of neuromuscular diseases or cardiac injury, CK and its isoenzyme activity show a great variation during pregnancy. Similar trends were observed for the CK isoenzymes CK-MB^[5].

Several reports indicate elevated activity of serum CK in the maternal blood during child birth, The uterus and placenta, two organs which were reported to embody substantial amounts of these enzymes, and which participate actively in the process of labor, are thought to release these enzymes to the circulation during labor^[6].

PATIENTS AND METHODS

A prospective study performed at Al-Zahraa University Hospital, where 90 pregnant women between 18 and 40 years old attending Al-Zahraa Outpatient Clinic and emergency ward, were included. These 90 subjects were divided into two groups; group A which included 60 women with previous cesarean section. They were subdivided into 2 subgroups; group A1 included 19 patients which included cases with emergency cesarean delivery and they were enrolled from emergency ward and group A2 included 41 patients which included cases with elective cesarean delivery and they were enrolled from outpatient clinic. Group B; the control group which included 30 patients with planned normal vaginal deliveries. Both primigravida and multigravida control cases, they were enrolled from both emergency ward and from outpatient clinic.

Image acquisition: Before delivery, routine fetal US was done for every case included fetal measures and biophysical profiles. Sonographic examination was done by Voluson 730 Pro V machine equipped with a 3.5-5- MHz transabdominal and 5.5-9- MHz transvaginal probe. Ultrasound examinations were performed by designated obstetrician sonologists who were not involved in management of the cases, the lower uterine segment was assessed by transabdominal route by 2D US. Transabdominal evaluation was performed with the women in a supine position with a comfortably full bladder (we avoided over distended bladder to avoid stretching of the lower uterine segment), to measure the whole thickness of the anterior wall of the lower uterine segment where it covers the fetal head, as follow, (one cursor positioned at urine-bladder interface and the other at decidua-amniotic fluid interface).

CKMB: Then blood sample were collected from both groups before cesarean delivery and during normal vaginal delivery. The serum or plasma (heparinized/EDTA) was collected from our 90 subject. The serum was separated from blood and were put in epindoorf tubes and sent immediately for analysis. Total CK, CK-MB level analyses were done by Immuno-inhibition method using auto-analyzer. The normal values of CK total (24-170 U/L) and CKMB (0-25U/L).

Intraoperative : In women who had elective and urgent cesarean section the actual measurement of LUS thickness was recorded using a Vernier caliper according to, technique. Thickness of the lower flap of LUS at center was measured after delivery of fetal head as follows: after uterine incision, open the movable jaw of a sterile vernier caliper away from the fixed jaw through the screw. The lower flap of the LUS is fixed in between the tips of the outer jaws of the caliper, without tissue compression, then, remove the jaw and take the reading. Measurements were

used for correlation with sonographically measured LUS thickness and CKMB values.

STATISTICAL ANALYSIS

Analysis of data was performed using SPSS v. 25 (Statistical Package for Scientific Studies) for Windows and Med Calc v. 18. Quantitative data were expressed as mean \pm standard deviation (SD). Qualitative data were expressed as frequency and percentage. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. Pearson correlation analysis was performed to determine changes in CKMB and its relation to scar integrity. Results were expressed in the form of correlation coefficient (R) and *P-values*. *P value* less than 0.05 was considered statistically significant.

RESULTS

Ninety pregnant women were included, sixty with previous cesarean delivery and forty with vaginal delivery. Our age groups were ranged from 18-40 years old with mean age for 30.53 for CS and 27.87 for NVD with SD 5.20, 5.83, respectively.

In our study, G0 numbers were three (10%), G2 numbers in CS were 21 (35%) and in NVD were 10 (33.3%), G3 numbers in CS were 22 (36.7%) and in NVD were 6 (20%), G4 numbers in CS were 10 (16.7%) and in NVD were 5 (16.7%), G5 numbers in CS were 3 (5%) and in NVD were 4 (13.3%), G6 numbers in CS were 3 (5%) and in NVD were 1 (3.3%), G7 numbers in CS were 1 (1.7%) and in NVD were 1 (3.3%) (Table 1).

The scar intraoperative was classified into four categories; number of defector ruptured scar 4 (6.7%), intact scar 39 (65%), thick scar 1 (1.7%) and thin scar 16 (26.7%) (Table 2).

CKMB was higher in CS group with mean 27.17 and SD 17.34 and was normal i.e. not affected in NVD group with mean 19.42 and SD 6.79 (Figure 1).

Intraoperative CKMB level was found to be high level in scar defect with mean value 39.60, SD value 9.02 and in thin scar with mean value 44.39 and SD 13.82, it was found to be normal in cases with intact and thick scar with mean value 19.04 and 18.70, respectively. There is statistically significant difference of mean CKMB in CS group according to scar integrity distribution by ANOVA test ($p < 0.05$). By doing Student-Newman-Keuls test; Post-hoc test that is used for pairwise comparison of subgroups, the significant difference appears between cases with defect and intact scar and between cases with intact and thin scar as shown in (Table 3, Figure 2)

Intraoperative CKMB was found to be high in both ruptured and thin scar by using vernier caliper with mean value 41.013 and 43.63, respectively. It was found to be normal in thick scar by using the same caliper measuring 43.63. (Table 4, Figure 3).

There is statistically significant difference of mean CK MB in CS group according to Vernier caliper distribution by ANOVA test ($p < 0.05$). By doing Student-Newman-Keuls test; Post-hoc test that is used for pairwise comparison of subgroups, the significant difference appears between cases with rupture and thick Vernier caliper and between cases with thick and thin Vernier caliper as shown in Table 4 and Figure 3.

There is statistically positive significant correlation between CK MB and CK in CS group ($p < 0.05$) (Figure 4). At a cut off level of CK MB > 24.3 U/L, there is statistically significant predictive value for prediction of thin scar ($p < 0.05$) with sensitivity 100% and specificity 84.09%. At a cut off level of CK MB > 27.3 U/L, there is statistically significant predictive value for prediction of rupture uterus ($p < 0.05$) with sensitivity 100% and specificity 78% (Figures 5 and 6).

Table 1: Gravidity distribution between both groups

Gravidity	CS group		NVD group	
	N	%	N	%
G0	0		3	10
G2	21	35	10	33.3
G3	22	36.7	6	20
G4	10	16.7	5	16.7
G5	3	5	4	13.3
G6	3	5	1	3.3
G7	1	1.7	1	3.3

Table 2: Scar integrity in CS group

Scar integrity	CS group	
	N	%
Defect	4	6.7
Intact	39	65
Thick	1	1.7
Thin	16	26.7

Fig. 1: Level of CKMB in vaginal delivery and cesarean delivery

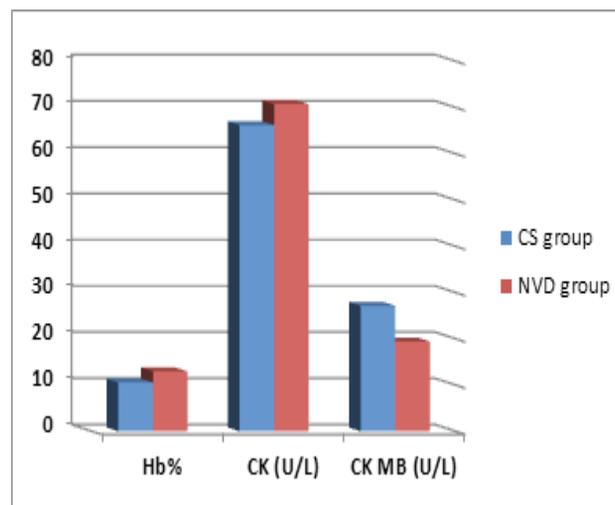


Table 3: Relation between CKMB and scar integrity

Scar integrity (CS group)	CK MB		P-value
	Mean	SD	
(1) Defect	39.60	9.02	
(2) Intact	19.04	13.19	< 0.001 (1) and (2) (2) and (4)
(3) Thick	18.70		
(4) Thin	44.39	13.82	

Fig.2: Relation between CKMB and scar integrity in CS group by ANOVA test

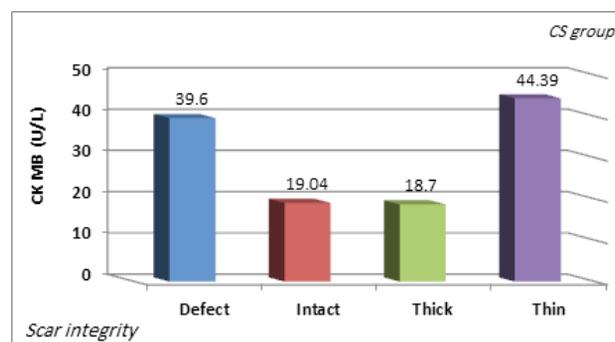


Table 4: Relation between CKMB and scar integrity in CS group by ANOVA test

Vernier caliper (CS group)	CK MB		P-value
	Mean	SD	
(1) Rupture	41.13	8.27	< 0.001
(2) Thick	19.96	14.18	(1) and (2) (2) and (3)
(3) Thin	43.63	15.21	

Fig. 3: Relation between CKMB and scar integrity in CS group by ANOVA test

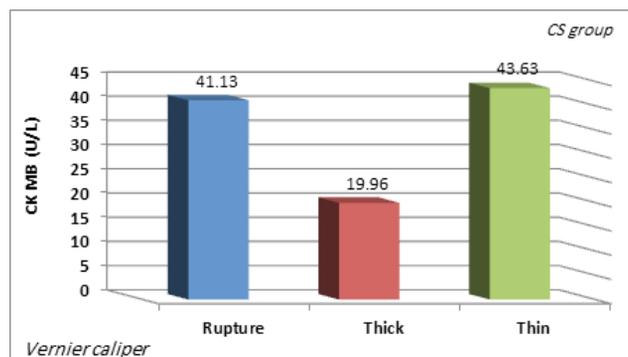


Fig. 4: Relation between CK and and CKMB in CS group

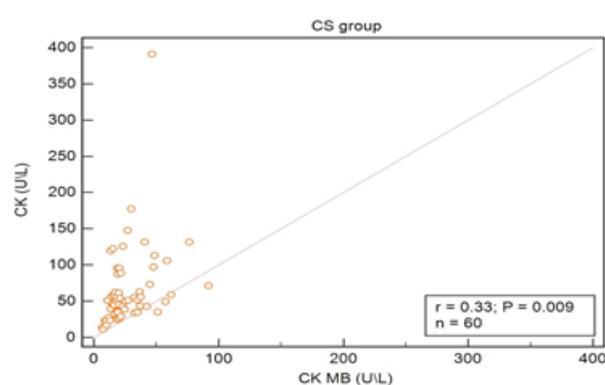


Fig. 5: CKMB as a marker of thin scar

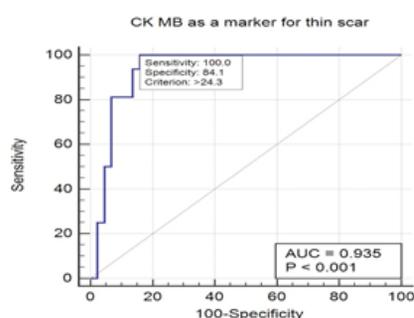
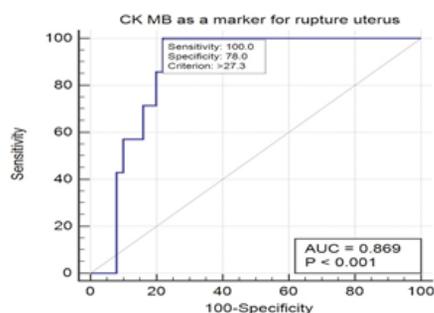


Fig. 6: CKMB as a marker of rupture uterus



DISCUSSION

The rapid increase in caesarean birth rates from 1996 to 2011 without clear evidence of concomitant decreases in maternal or neonatal morbidity or mortality raises significant concern that caesarean delivery is overused^[7]. With this significant increase in the number of cesarean deliveries there were increases of the number of complications, one of these complications cesarean scar defect (CSD) is the most common but also the most neglected. In pregnant patients with a history of prior cesarean delivery, a severe CSD is a risk factor for both early (i.e., uterine rupture) and for late complications (i.e., ectopic pregnancy at the scar level and other scar-related abnormalities), also uterine dehiscence or rupture in future pregnancy^[8].

Diagnosis of complete uterine rupture was underreported in the electronic patient record system (EPRS) by 35% and diagnosis of uterine dehiscence was missing in 100% of cases^[9], Frequency of lower uterine segment (LUS) scar dehiscence is reported to be similar to the uterine rupture during labor in women with unscarred uterus. Unsecure prediction of the integrity of the scarred LUS during labor appears to be one of the reasons for high repeat cesarean rates, But there are variation between two observations by sonographic measurement of LUS is believed to be due to contractile state of the uterus, displacement of amniotic fluid, fetal movement, compression of LUS by fetus, and degree of bladder filling. Inter-operator variability is taken care of by only one sonologist performing the measurements. The operator pressure through transducer can add to some difference in the measurements^[10].

The creatine kinase is considered as to be as key enzymes of muscular metabolism. Accordingly, most of its activity is concentrated within muscular organs. Indeed the enzyme can constitute up to 20% of the soluble sarcoplasmic protein in some types of muscle. In view of these facts we can use it as laboratory parameters for muscular damage. Interest has centered on the CKMB hybrid of myocardial origin^[11,12]. The uterus and placenta, two organs which were reported to embody substantial amounts of these enzymes, and which participate actively in the process of labor, are thought to release these enzymes to the circulation during labor^[13], Therefore, prediction of uterine dehiscence prior to onset of labour by using CKMB as a soft marker may have clinical significance; A prospective study performed at Al-Zahraa University Hospital where ninety women were included in our study, sixty women with previous cesarean section with forty two with elective CS and eighteen with emergency CS, thirty with NVD in active labour ranged from 18-40 years, the gravidity ranged from 0-7. Estimated gestational age ranged from 36-40 wks, The interdelivery interval ranged

from 12-48 months, The whole LUS thickness by 2D TAS ranged from (2.5-5.7 mm).

In our study, we found that there is significant increase of mean CKMB in CS group with thin and ruptured scar in comparisons with NVD group in active labour which was normal ($p < 0.05$). Soundravally *et al.*, reported that the elevated CK-MB during pregnancy should not be due myocardial infarction for CK-MB is found not only in myocardium but also in uterus and placenta^[14]. Our theory that CKMB may release from scarred uterus before delivery or from myometrial tissue or from area of dehiscence as this area subjected to ischemia .even though none of our patient had cardiac symptoms or complications and this may give idea about scar dehiscence or rupture. As CKMB mostly of muscle origin and reflecting labour stress or injury^[14].

This may support our theory as some research shows that rising level of CK occurs as a result of muscle tissue damage. Additionally, cesarean section known to increase CK levels. Also the destruction of the myometrial tissue causes serum CK increase. Turan and his coworkers measured CK levels to investigate if the locked method gave injury to the uterine muscle. The increase in the levels of CK in locked method was remarkable^[15]. Researchers believe that serum CK can be a diagnostic marker of tubal ectopic pregnancy (tEP) , as the theory on which it is claimed that CK can be marker of tEP is that the tubal musculature lacks a submucosal layer and hence the penetrating trophoblastic tissue is expected to injure the tubal smooth muscle and release a sufficient amount of this enzyme into circulation^[13]. Also serum CPK activity were reported significantly higher in women with tubal pregnancy that may or may not have ruptured and are reliable in the diagnosis of a tubal pregnancy. They observed significant elevation in CPK and CKMB serum activity in ectopic pregnancy^[13]. Shao and Yang used creatine kinase (CK) in the diagnosis of scar uterus and placenta previa implantation, CK expression in the implantation group were, significantly higher than non-implantation group^[16]. This is may be explained by Banu *et al.*, who suggested that an increasing amount of serum creatine kinase (CK) isoenzymes would give an idea about the destruction of the myometrial tissue^[17].

Our results did not match McNeely and his coworkers who measured serum CK activity of 28 women with normal pregnancy at six time interval; during the third trimester, between 30 and 36 weeks gestation, on admission to hospital in labor, within 30 mm after delivery, between 7 and 9 h after delivery, on the fifth day postpartum and at the time of the routine six-week check-up. Mean CK activity were 29, 45, 109, 132, 49 and 35 U/L at 1,2,3,4,5 and 6 time interval. Thus, showing that there is transit rise in CK activity as soon as time of delivery approaches and peak activity are obtained between 7 to 9 hrs after

the delivery. The CK activity tends to reach at normal levels within six-weeks after delivery. Similar trends were observed for the CK isoenzymes CKMB activity, there is significant association between serum CKMB activity and route of delivery^[12,5]. Also, did not match Leiserowitz and his coworkers who conducted his study on forty-nine normal pregnant women recruited late in the third trimester for serial determinations of creatine kinase (CK) and its MB isoenzyme fraction (CK-MB) at four different times; on recruitment between 36 and 40 weeks gestation, on admission in active labor, immediately after delivery and on the first postpartum day. In the patients with vaginal delivery total CK was significantly elevated at time 4 compared with times 1, 2 and 3 ($P \text{ value} < 0.0001$). CK-MB fraction was also significantly elevated at time 4 compared with times 1, 2 and 3 ($P \text{ value} < 0.0001$). In 35.7% of the patients at time 4, CK-MB was sufficiently elevated to give the laboratory interpretation of “borderline” or “consistent with a myocardial infarction,” even though none of the patients had cardiac symptoms or complications^[5]. But this not matches Torabi and coworkers: who found lower CK-MB in cesarean section than NVD. CK-MB isoenzymes levels in newborns delivered vaginally were higher than elective cesarean section. This may be CKMB were taken from neonates serum not from the mothers so it did not match our theory^[18].

Also, this may support our theory that area of dehiscence undergo ischemia that release markers of ischemia (CPK, K^+ , Ca^{2+}) this may explained by I/R (ischemia reperfusion theory while putting tourniquet at time of removal of myoma. These data assume that surgeries requiring any temporary arrest of the arterial circulatory system, such as tourniquet use, lead to ischemia reperfusion and apoptosis. This IR would itself be responsible for an increase marker of ischemia (CPK, K^+ , and Ca^{2+}). Oksuzoglu *et al.*, comparing plasma levels of CPK and interleukin-6 (IL6) in different types of uterine surgery, found higher levels of these markers during uterine abdominal versus laparoscopic surger^[19]. Khan and Rathore (2017) also concluded that the rise of total CK and CK-MB in maternal serum was directly correlated with the type of delivery also lower segment cesarean section LSCS mode of delivery is associated with increased CKMB activity^[5].

In our study, we found there was relation between CKMB and intraoperative scar grading was determined. And showed a significant relation of mean CK MB in CS group according to scar integrity distribution by ANOVA test ($p < 0.05$). By doing Student-Newman-Keuls test; Post-hoc test that is used for pairwise comparison of subgroups, the significant difference appears between cases with defect and intact scar and between cases with intact and thin scar (i.e. the patients with thin and defect scar have elevated levels of CKMB, while patients with intact scar have normal level of CKMB). Also this confirmed

by using Vernier caliper intraoperative which showed significant relation of mean CK MB in CS group according to Vernier caliper distribution by ANOVA test ($p < 0.05$), the significant difference appears between cases with rupture and thick Vernier caliper and between cases with thick and thin Vernier caliper (i.e. the patients which proved to be thin and defect scar by Vernier caliper have elevated level of CKMB and patients which were thick or intact scar have normal levels of CKMB).

And most of the significance of CKMB and prediction of scar integrity in cases with G3 and G2. There is statistically significant difference of mean CK MB in CS group according to gravidity distribution by ANOVA test ($p < 0.05$). By doing Student-Newman-Keuls test; Post-hoc test that is used for pairwise comparison of subgroups, the significant difference appears between cases with G2 and cases with G3 (i.e. most patients with G2 (P1CS), G3 (P2CS) were with elevated level of CKMB in comparisons with other gravidity) this may be attributed to most cases were G2 (P1CS 23 cases), G3 (P2CS 27 cases) and this may be related more to scar dehiscence itself not gravidity or parity. Also we did not find any significance between interdelivery interval and scar dehiscence as CKMB not affected if interdelivery interval was less or more than 24 months as it was affected by dehiscence this may be related to our small sample size. As Bujold *et al.* reported that 10.5% of dehiscence occurred in patients with interdelivery interval of less than 24 months compared to 3% after 24 months. This finding may be related to the time needed for proper scar healing. Using magnetic resonance imaging, Dicle *et al.* showed that uterine scars needed at least 6 months to reach a normal appearance^[20].

There is statistically no significant difference of mean CK MB in CS group according to pulse or scar tenderness distribution by ANOVA test ($p > 0.05$) (i.e. pulse or scar tenderness not indicative of scar dehiscence and CKMB was normal in these cases). This in agreement with Ramadan *et al.*, who could not find an association between having pain at the cesarean scar and the risk for developing dehiscence. Similar observations were reported by Suzuki *et al.*, who concluded that there was no increased rate of dehiscence in patients who felt pain and tenderness in the lower uterine segment^[20]. We did not find any correlation between CKMB and uterine contraction as CKMB not elevated with the patients have uterine contraction or in labour and these patients during CD had not dehiscence in their cesarean scar (no significant difference of mean CK MB in CS group according to presence of contraction by ANOVA test ($p > 0.05$)). This in agreement with Ramadan *et al.*, who found the presence of labor at the time of CD was noted to have no significant effect on the rate of dehiscence^[20]. May be there association between myocardium and myometrium isoenzymes as in non-controlled preliminary rabbit experiments indicate

that patches of uterine myometrium reinforced by greater omentum can be used as autologous transplant therapy for infarcted myocardium^[21].

Therefore, we can use CKMB as a soft marker beside other methods as LUS thickness by U/S to predict dehiscence scar before CS also before taking decision of TOLAC. At a cut off level of CK MB > 24.3 U/L, there is statistically significant predictive value for prediction of thin scar ($p < 0.05$) with sensitivity 100% and specificity 84.09%. And at a cut off level of CK MB > 27.3 U/L, there is statistically significant predictive value for prediction of rupture uterus ($p < 0.05$) with sensitivity 100% and specificity 78%.

Our limitation small sample size and most of our sample size were G2, G3, but this the first paper talking about CKMB and its relation to CS scar complication prior to delivery.

CONCLUSION

We can use CKMB as a soft marker beside other method for detection of cesarean section complication before delivery as it is cheap, available with high sensitivity and specificity.

CONFLICT OF INTERESTS

There are no conflicts of interests.

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