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RETROSPECTIVE CROSS-SECTIONAL STUDY

Effectiveness and Outcome of Uterine Embolization with Methotrexate in Treatment of Scar Ectopic Pregnancy in Comparison with Methotrexate and KCL Treatment

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Abstract

Background: Scar ectopic pregnancy has become one of the common medical conditions around the world. CSP could lead to severe complications including excessive hemorrhage, shock and uterine rupture with the potential necessity for hysterectomy as well as maternal mortality in a very severe case with CSP. However, there are no general guidelines for CSP management. The objective of this study is to compare the therapeutic effects and follow-up results among 3 different treatments and to identify the most effective treatment strategy for CSP.

Methodology: This is retrospective study that was conducted among patients with scar ectopic pregnancy. The data was collected for CSP patients who admitted for receiving treatment in the first month in 2022. Three treatment strategies were compared in this study including Uterine embolization intervention with Methotrexate, Methotrexate alone, and KCL with Methotrexate. The serum levels of β-human chorionic gonadotropin (β-HCG) were measured, and pelvic ultrasound scan was performed for all patients. After data were extracted, it was revised, coded, and fed to statistical software IBM SPSS version 22 (SPSS, Inc. Chicago, IL).

Results: A total of 29 females with scar ectopic pregnancy undergone methotrexate alone, uterine embolization with methotrexate or KCL with methotrexate were included. There is significant reduction in hormone level after intervention especially at the 4th post-intervention assessment (after 3 weeks) reaching near zero level at the period of 1 month and later.

Conclusion: The study showed no significant difference between different treatment strategies for CSP with none to low complications associated with each treatment. Combination of Ultrasound-guided local MTX injection and surgery seems to be an optimal option for CSP because of its safety, convenience, economy, and validity.

Introduction

Scar ectopic pregnancy has become one of the common medical conditions around the world [1]. Cesarean scar Pregnancy (CSP) refers to implantation of a placenta on a previous cesarean section delivery (CD) scar [2]. Cesarean scar pregnancy (CSP) is an uncommon but life-threatening complication of previous caesarean section, when the gestational sac is implanted in the site of a previous caesarean scar and is surrounded by uterine muscle fibers and soft scar tissues and myometrium which is adjacent to the bladder [3,4]. CSP

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could lead to severe complications including excessive hemorrhage, shock and uterine rupture with the potential necessity for hysterectomy as well as maternal mortality in a very severe cases with CSP [5,6].

Therefore, it is important that CSP to be diagnosed and effectively treated as quickly as possible. The increase in caesarean deliveries has increased the risk of CSP in the recent decades [2]. The incidence of CSP is estimated to be 1:1800 to 1:2000 pregnancies after CD [2]. Caesarean scar pregnancy (CSP), which was first reported by Larson and Solomon in 1978 [7], is one of the most common types of ectopic pregnancy.

In addition, due to the high speed of the advancement of technology, early CSP cases can be easily detected using ultrasound technology and other imaging techniques. This allows clinics to provide patients with appropriate and timely pregnancy options and to prevent life-threatening complications [8].

There are several treatment options for CSP. However, there are no general guidelines for CSP management. CSP therapies include MTX systemic or local administration, dilatation and curettage (D&C), laparoscopic, uterine artery embolization (UAE), transvaginal or transabdominal resection or hysterectomy, and adjuvant treatments such as local injection of lauromacrol, conservative surgery such as local resection of the ectopic gestational mass or suction curettage by operative hysteroscopy, high-intensity focused ultrasound, and finally hysterectomy [9-12].

The objective of this study is to compare the therapeutic effects and follow-up results among 3 different treatments and to identify the most effective treatment strategy for CSP.

Methodology

This is retrospective study that was conducted among patients with scar ectopic pregnancy.

Because of the design of the study, there is no need for informed consent. This study was carried out at the Obstetrics, Gynecology and intervention radiology department in Prince Sultan Military Medical City. The data was collected for CSP patients who admitted for receiving treatment in the first month in 2022. All patients were included in this study after applying the selection criteria. The inclusion criteria included all patients who had a history of cesarean sections and diagnosed as CSP based on clinical symptoms and transvaginal ultrasound [13]. The main symptoms used in diagnosis of CSP were amenorrhea, vaginal bleeding and lower abdominal pain [2]. The diagnosis of CSP must meet the CSP criteria including no gestational sac appears in the uterus and cervical canal, gestational sac embedded within the myometrium, gestational sac or mass located in the anterior wall of the isthmic portion, and absence or defect in the myometrium between bladder and the sac [14,15].

Treatment

Three treatment strategies were compared in this study including Uterine embolization intervention with methotrexate, Methotrexate alone and KCL with methotrexate. The serum levels of β-human chorionic gonadotropin (β-HCG) were measured, and pelvic ultrasound scan was performed for all patients. The UAE procedure was performed by a qualified intervention radiologist. After local anesthesia, a 5F-angiographic catheter was inserted into the right femoral artery and extended bilaterally into the uterine arteries. All patients' serum β-HCG levels were measured weekly until they declined a normal value.

Variables

In this study, we used data reports of the hospital as a source of information. We collected data considering the demographic factors of the patients including age (< 40 years, > 40 years), gravidity (< 5, 5-6 <, 7+), parity (1-2, 3-4, 5+), abortions (none, 1 time, 2-4 times), and number of CS (1-2, 3-6). Moreover, we collected data considering ectopic pregnancy among the study females including PV bleeding (Yes, No), pain (Yes, No), Weeks of pregnancy at diagnosis (6-7, 8-10, 11-14), 1st free BHCG, and 2nd free BHCG. Furthermore, we included data considering Interventions used for uterine embolization among females with ectopic pregnancy including Uterine embolization intervention (Material used, Complications), Methotrexate (Complications) and KCL (Complications). To assess the effectiveness of each intervention, BHCG was reported for each week and for 9 weeks.

Statistical methods

After data were extracted, it was revised, coded, and fed to statistical software IBM SPSS version 22 (SPSS, Inc. Chicago, IL). All statistical analysis was done using two tailed tests. P value less than 0.05 was statistically significant. Descriptive analysis based on frequency and percent distribution was done for all variables including study females' socio-demographic data, obstetric & gynecological data, and scar ectopic pregnancy related clinical data. Also, modalities of interventions for uterine embolization with associated complications were tabulated.

Crosstabulation was used to related the used interventions with the female's bio-demographic data. Relations were tested using Pearson chi-square test and exact probability test for small frequency distributions.

Results

A total of 29 females with scar ectopic pregnancy undergone methotrexate alone, methotrexate with uterine embolization or methotrexate with KCL were included. Female's age ranged from 21 to 46 years with

Table 1: Bio-demographic data of females with scar ectopic pregnancy undergone uterine embolization.

Bio-demographic data	No	%
Age in years		
< 40 years	18	62.1%
> 40 years	11	37.9%
Gravidity		
< 5	8	27.6%
5-6	11	37.9%
7+	10	34.5%
Mean ± SD	5.8 ± 2.4	
Parity		
1-2	7	24.1%
3-4	14	48.3%
5+	8	27.6%
Mean ± SD	3.9 ± 2.0	
Abortions		
None	14	48.3%
1 time	8	27.6%
2-4 times	7	24.1%
Mean ± SD	1.0 ± 1.0	
Number of C. S		
1-2	14	48.3%
3-6	15	51.7%
Mean ± SD	2.8 ± 1.2	

Table 2: Clinical data regarding ectopic pregnancy among the study females.

Clinical data	No	%
PV bleeding		
Yes	22	75.9%
No	7	24.1%
Pain		
Yes	21	72.4%
No	8	27.6%
Weeks of pregnancy at diagnosis		
6-7	13	44.8%
8-10	9	31.0%
11-14	7	24.1%
1st free BHCG		
Range	1162-144798	
Median	13141	
2nd free BHCG		
Range	795-134550	
Median	7602	

mean age of 37.8 ± 5.9 years-old. Regarding gravidity, 37.9% had 5-6 pregnancies and 34.5% had more than 6 pregnancies (5.8 ± 2.4). A total of 48.3% had 3-4 deliveries and 27.6% had 5 deliveries or more (3.9 ± 2.0). Also, 14 (48.3%) females had no history of abortions while 8 (27.6%) aborted for 1 time only (1.0 ± 1.0). Exact of 14 (48.3%) undergone 1-2 C. Ss while 15 (51.7%) had 3-6 previous sections (2.8 ± 1.2) (Table 1).

Clinical data regarding ectopic pregnancy among the study females. PV bleeding was reported among 22 (75.9%), and 21 (72.4%) complained of pain. Ectopic pregnancy diagnosis was done at 6th to 7th week of pregnancy among 13 (44.8%), 8th to 10th week of pregnancy among 9 (31%) and later among 7 (24.1%) females. BHCG was insignificantly reduced from 13141 to 7602 before intervention (Table 2).

Interventions used for uterine embolization among females with scar ectopic pregnancy. Exact of 13 (44.85) females undergone uterine embolization where 7 cases (53.8%) were injected with PVA, 2 cases (15.4%) injected

Table 3: Interventions used for uterine embolization among females with ectopic pregnancy.

Intervention	No	%
Uterine embolization intervention		
Yes	13	44.8%
No	16	55.2%
Material used (n = 13)		
Gel foam	2	15.4%
PVA	7	53.8%
Both	4	30.8%
Uterine embolization intervention complications (n = 13)		
Yes	1	7.7%
No	12	92.3%
Mention (n = 13)		
Right inguinal hematoma with 2 bleeding	1	7.7%
None	12	92.3%
Methotrexate		
Yes	17	58.6%
No	12	41.4%
Complications with methotrexate use (n = 17)		
No	17	100.0%
Misoprostol		
Yes	2	6.9%
No	27	93.1%
Complication misoprostol (n = 2)		
Yes	1	50.0%
No	1	50.0%
KCL		
Yes	6	20.7%
No	23	79.3%
Complication		
No	6	100.0%

with gel foam, and both materials were used for 4 (30.8%) cases. Only 1 case (7.7%) developed Right inguinal hematoma with bleeding. Methotrexate was given to 17 (58.6%) females with no reported complications. A total of 2 females were given Misoprostol while only 1 case experienced complication. KCL was used among 6 females (20.7%) with no reported complications (Table 3).

Distribution of uterine embolization intervention among study females' personal data. A total of 7.7% of females with diagnosed SEP at the first month of gestation undergone uterine embolization intervention compared to 88.9% of those diagnosed at 8th to 10th week with recorded statistical significance (P = 001). Also, uterine embolization intervention was done for 55.6% of young aged females with SEP versus 27.3% of old aged females (P = 0.049) (Table 4).

Distribution of KCL intervention among study females' personal data. Exact of 38.5% of females with diagnosed SEP at the first month of gestation undergone uterine embolization intervention compared to 11.1% of those diagnosed at 8th to 10th week with recorded statistical significance (P = 0.048). Also, uterine embolization intervention was done for 33.3% of young aged females with SEP versus none of old aged females (P = 0.032) (Table 5).

BHCG changes before and after uterine embolization intervention / KCL among female patients with scar ectopic pregnancy. All figures showed a significant reduction in hormone level after intervention especially at the 4th post-intervention assessment (after 3 weeks) reaching near zero level at the period of 1 month and later (Figure 1, Figure 2 and Figure 3).

Table 4: Distribution of uterine embolization intervention among study females' personal data.

Personal data	IR				p-value
	Yes		No		
	No	%	No	%	
Age in years					
< 40 years	10	55.6%	8	44.4%	0.049*$
> 40 years	3	27.3%	8	72.7%	
Gravidity					
< 5	4	50.0%	4	50.0%	0.498
5-6	6	54.5%	5	45.5%	
7+	3	30.0%	7	70.0%	
Parity					
1-2	4	57.1%	3	42.9%	0.732$
3-4	6	42.9%	8	57.1%	
5+	3	37.5%	5	62.5%	
Abortions					
None	6	42.9%	8	57.1%	0.411
1 time	5	62.5%	3	37.5%	
2-4 times	2	28.6%	5	71.4%	
Number of C.S					
1-2	6	42.9%	8	57.1%	0.837
3-6	7	46.7%	8	53.3%	
PV bleeding					
Yes	9	40.9%	13	59.1%	0.452
No	4	57.1%	3	42.9%	
Pain					
Yes	9	42.9%	12	57.1%	0.730
No	4	50.0%	4	50.0%	
Weeks of pregnancy at diagnosis					
6-7	1	7.7%	12	92.3%	0.001*$
8-10	8	88.9%	1	11.1%	
11-14	4	57.1%	3	42.9%	

P: Pearsons X^2 test; $: Exact probability test; *P < 0.05 (significant)

Table 5: Distribution of KCL intervention among study females' personal data.

Personal data	KCL				p-value
	Yes		No		
	No	%	No	%	
Age in years					
< 40 years	6	33.3%	12	66.7%	0.032*
> 40 years	0	0.0%	11	100.0%	
Gravidity					
< 5	2	25.0%	6	75.0%	
5-6	3	27.3%	8	72.7%	0.583
7+	1	10.0%	9	90.0%	
Parity					
1-2	2	28.6%	5	71.4%	
3-4	4	28.6%	10	71.4%	0.237
5+	0	0.0%	8	100.0%	
Abortions					
None	3	21.4%	11	78.6%	
1 time	2	25.0%	6	75.0%	0.874
2-4 times	1	14.3%	6	85.7%	
Number of C.S					
1-2	3	21.4%	11	78.6%	0.924
3-6	3	20.0%	12	80.0%	
PV bleeding					
Yes	5	22.7%	17	77.3%	0.631
No	1	14.3%	6	85.7%	
Pain					
Yes	4	19.0%	17	81.0%	0.724
No	2	25.0%	6	75.0%	
Weeks of pregnancy at diagnosis					
6-7	5	38.5%	8	61.5%	
8-10	1	11.1%	8	88.9%	0.048*
11-14	0	0.0%	7	100.0%	

P: Exact probability test; *P < 0.05 (significant)

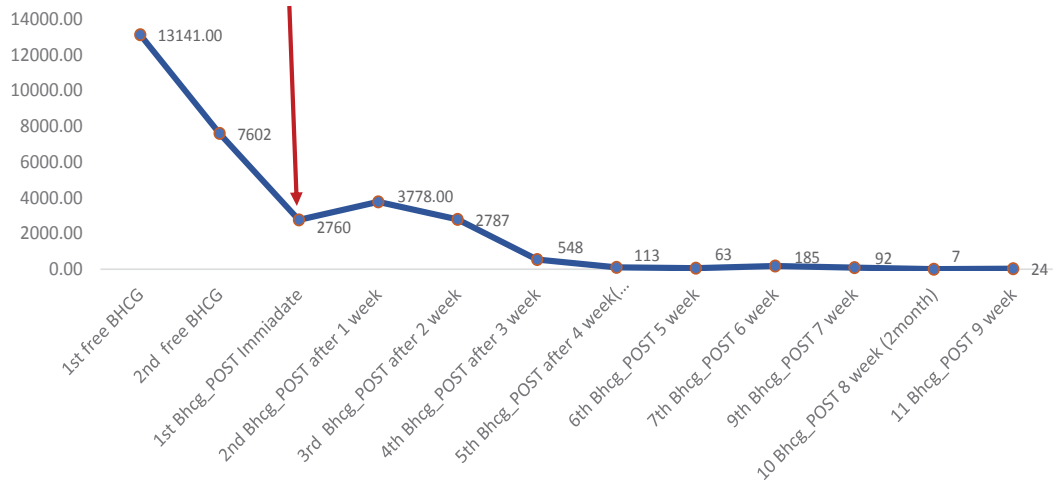

Figure 1: BHCG changes before and after IR among female patients with ectopic pregnancy uterine embolization intervention.

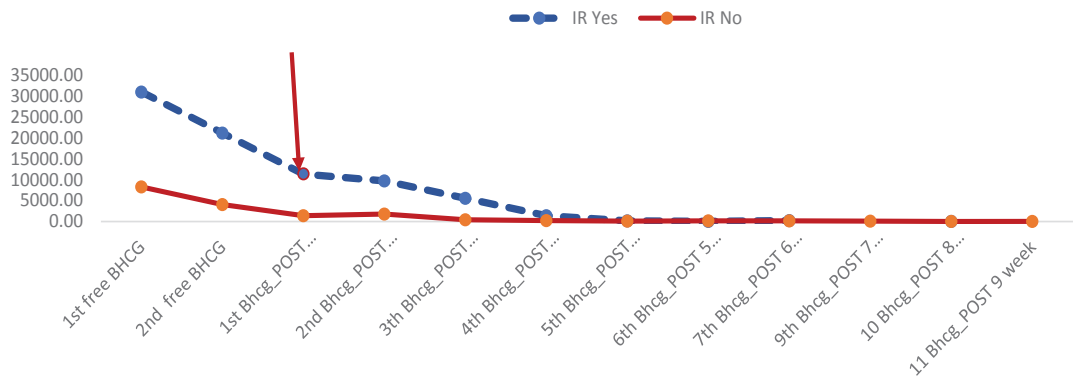

Figure 2: BHCG changes before and after IR among female patients with ectopic pregnancy among patients received IR and others.

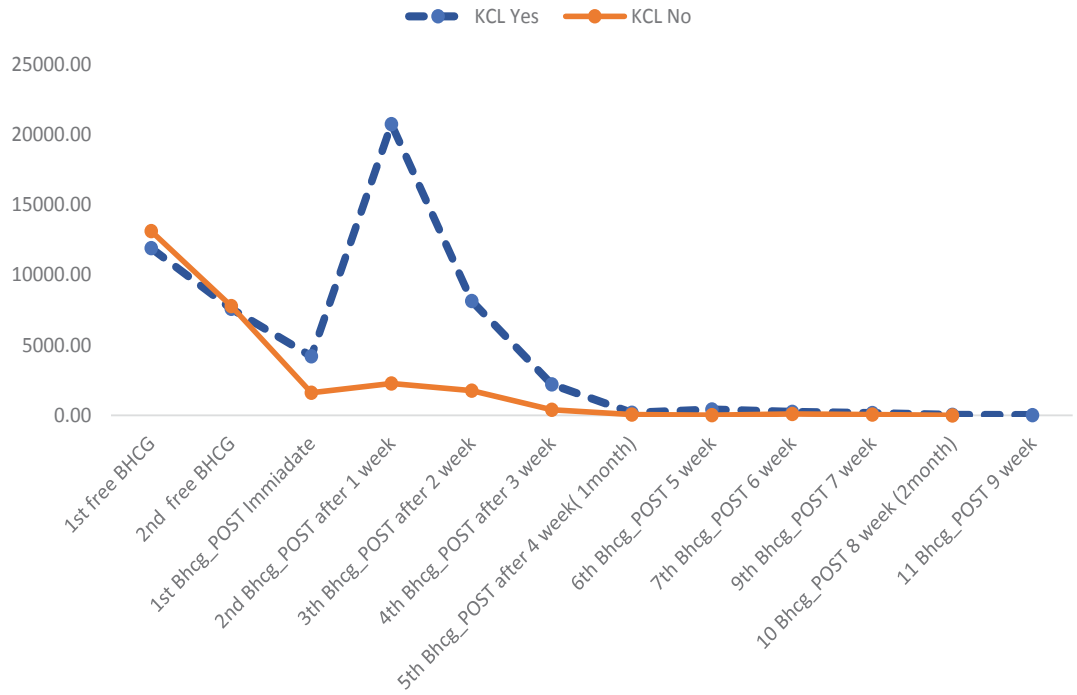

Figure 3: BHCG changes before and after KCL among female patients with ectopic pregnancy among patients received KCL and others.

Discussion

However, CSP was reported for the first time in 1978 as a special type of ectopic pregnancy [7], no universal management guideline is available for treatment of CSP. MTX was the most commonly used in the management of CSP and in different studies showed that both systemic and local injections of MTX as the priority treatment of CSP [16,17]. In our study, MTX was used in 58.6% of the patients as alone or in combination therapy which was the most common management strategy used in this study. However, this common use of MTX, there are many side-effects of the use of methotrexate injection which include oral ulceration, bode marrow depression and severe bleeding which severely limited the application of MTX [18]. In our study, no complications were reported in any of the patients which are similar to the results of Zhuoni X, et al., who found that the incidence of side-effects mentioned above is extremely low especially among those with local injection [19].

Moreover, in our study, Uterine embolization intervention was applied in 44.8% of the patients. UAE treatment was first reported in 1999 in treatment of CSP that has been widely used in controlling hemorrhage and preserves the uterus. The using Gel foam appears to promote the clotting throughout its physical effects by supporting thrombus development however the vascular occlusion with gel foam could lead to acute necrotizing arteritis [20] which explain the reason that gel foam used only in 15.4% of total cases treated with UAE. In our study, only one case of using of UAE showed side effect of right inguinal hematoma with 2 bleeding. A previous study reported that there are no severe complications associated with UAE as endometrial atrophy or permanent amenorrhea [21]. However, some studies reported few cases of side effects including ischemia-related complications as UAE temporarily

blocked the uterine arterial blood flow [22,23].

Moreover, we found in this study that UAE was used in younger participants significantly higher than older patients with a significant avoidance among those at early diagnosed patients. No other demographic factors of patients affect the choice of using UAE. However, previous study showed that UAE should be performed among patients with high blood flow near the sac or the enclosed mass, blood β-hCG > 10,000 mIU/ml and those with myometrial thickness of < 2 mm between the sac and the bladder [24].

Moreover, our results showed that all strategies showed a significant reduction in hormone level especially at the fourth post-intervention assessment (after 3 weeks) reaching near zero level at the period of 1 month and later. This is similar to results of previous case study which showed that hormone level reached near zero at the period of one month and later with using of methotrexate in treatment of CSP [25]. Moreover, in our study, we could not find a significant difference between the different strategies in reduction of hormonal levels. These results are similar to the results of previous studies which showed no significant differences in outcomes between different treatments [26-28].

This study had some limitations including low rates of CSP pregnancy which lead to small sample size which cause that our study could not be enough to draw a definite conclusion. Moreover, the depending on retrospective design may lead to some selection bias. Thus, the results cannot be compared with the controlled studies. Finally, we only followed the patients for 9 weeks and patients with complications were more likely to have a follow-up record which may underestimate the difference between the groups. Thus, longer follow-up periods are required in order to determine the long-term side effects among patients with different treatments. There is a need for multicentered prospective, and controlled studies using large sample sized in the future to verify these results found in our study and to establish a more reliable universal treatment guideline for CSP patients.

In conclusion, the study showed no significant difference between different treatment strategies for CSP with none to low complications associated with each treatment. Combination of Ultrasound-guided local MTX injection and surgery seems to be an optimal option for CSP because of its safety, convenience, economy, and validity.

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