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Recurrent Cesarean scar pregnancy: case series and literature review

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Running Head: *Recurrent CSP*

KEYWORDS: Cesarean scar pregnancy; CSP; scar pregnancy; ultrasound

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CONTRIBUTION

What are the novel findings of this work?

Recurrent CSP is apparently more common than was previously assumed. Following retrieval of data from our hospital databases for the period 2010–2109, we calculated a recurrence rate of Cesarean scar pregnancy (CSP) of 34.3% and report a rate of 20.5% from analysis of the published literature over a similar period. We could not find any association between type of treatment of the previous CSP and recurrence.

What are the implications of this work?

Knowledge of the risk of recurrence following a CSP is important in counseling patients undergoing treatment, particularly for those wishing to preserve fertility. Patients pregnant after treatment for a previous CSP should be encouraged to have an early (5–7-week) first-trimester transvaginal scan to determine the location of the gestation.

Abstract

Objectives To determine the rate of recurrent Cesarean scar pregnancy (CSP) in our clinical practices and to evaluate whether the mode of treatment of a CSP is associated with the risk of recurrent CSP, as well as to review the published literature on recurrent CSP.

Methods We performed a retrospective search of our six obstetrical and gynecologic departmental ultrasound databases for all CSPs and recurrent CSPs between 2010 and 2019. We extracted various data, including numbers of CSPs with follow-up, numbers attempting and numbers achieving pregnancy following treatment of the CSP and numbers of recurrent CSPs, as well as details of the treatment of the original CSP. After analyzing the clinical data, we evaluated whether the mode of treatment terminating the previous CSP was associated with the risk of recurrent CSP. We also performed a PubMed search for: 'recurrent Cesarean scar pregnancy' and 'recurrent Cesarean scar ectopic pregnancy'. Articles were reviewed for year of publication and extraction and analysis of the same data as those obtained from our departmental databases.

Results Our database search identified 252 cases of CSP. The overall rate of clinical follow-up ranged between 71.4% and 100%, according to treatment site (mean, 90.9%). Among these, 105 were followed by another pregnancy after treatment of the previous CSP. Of these, 36 (34.3%) pregnancies were recurrent CSP, with 27 women having a single recurrence and three women having multiple recurrences, one with two, one with three and one with four. We did not find any particular single or combination treatment mode terminating the previous CSP to be associated with recurrent CSP. The literature search identified 17 articles that yielded sufficient information for us to evaluate their reported prevalence of recurrent CSP. They reported 1743 primary diagnoses of CSP, and 944 had reliable follow-up. There were data for 489 cases in which a woman attempted to conceive again, and on 327 pregnancies achieved, after treatment of a previous CSP. Of these, 67 (20.5%) were recurrent CSP.

Conclusion On the basis of our pooled clinical data and review of the literature, recurrent CSP is apparently more common than was previously assumed based upon

mostly single case reports or series with few cases. This should be borne in mind when counseling patients undergoing treatment for CSP regarding their risk of recurrence. We found no obvious causal relationship or association between the type of treatment for the previous CSP and recurrence of CSP. Patients pregnant after treatment for a CSP should be encouraged to have an early (5–7-week) first-trimester transvaginal scan to determine the location of the gestation.

INTRODUCTION

There has been a gradual increase in numbers of Cesarean deliveries (CDs), both indicated elective and emergency. They are performed for multifetal pregnancy and prematurity, in most cases with history of previous CD and in many cases with breech presentation, with the rate of CD now reaching unprecedented numbers worldwide.

In 2000, the Swiss group of Yvan Vial *et al*.[1] published the first observation of a 'new', iatrogenic, obstetric and gynecologic pathology: Cesarean scar pregnancy (CSP)[1]. Since then, mirroring the increase in numbers of CDs, the number of articles published on CSP has increased exponentially. For example, a PubMed search for 'Cesarean scar pregnancy' and 'Cesarean scar ectopic pregnancy', between the years 2000 and 2005, yielded fewer than 50 citations[2], while a similar search of these two terms, performed recently, returned 2287 and 623 citations, respectively.

As early as 2004–2006, several authors had already warned that, even after successful treatment of CSP, there is a risk of recurrence[3–5]. However, this risk has not yet been fully elucidated. With CSP itself being relatively rare, it is logical that recurrence should be considered even more so. Yet, patients undergoing treatment for a CSP are keen to know about their risk of recurrence. While an approximation might be given, there is no clear, evidence-based answer to this, and no reliable epidemiologic data are at hand for patient counseling. Furthermore, while appropriate diagnostic methods are known, the optimal treatment for CSP and possible associated risk factors for recurrent CSP are not well understood and treatment has not been standardized.

Despite there being more than 30 publications on recurrent CSP, there has been no agreement on any single or cluster of risk factors to predict a subsequent scar implantation. The aim of this study was to report on our experience with CSP and determine its rate of recurrence and to evaluate whether the mode of treatment of a previous CSP is associated with the risk of recurrent CSP, alongside evaluation of current knowledge in the published literature, in the hope of

providing information to caregivers and their patients in and around our communities.

SUBJECTS AND METHODS

A search was performed of the database of each authors' obstetrical and gynecologic department (referred to herein as sites A–F) for all CSPs treated between 2010 and 2019. For each center, we sought to retrieve various clinical data including: number of CSP cases; number of cases with follow-up after treatment; number of these patients attempting another pregnancy; number of pregnancies achieved following treatment for CSP; number of these which were successful; number of miscarriages; type of treatment of the CSP; and number of recurrent CSPs. The inclusion and diagnostic criteria were the same for all six centers. Only first-trimester cases were included and in only two patients did a previous CSP and a recurrent CSP have a normal pregnancy occurring between them. No other case was excluded. In addition to reviewing patient charts, in more than half of the cases, we contacted the patient directly by telephone call to ascertain outcome and follow-up in the post-CSP period. After analyzing the clinical data according to site, we evaluated whether there was any association between the treatment mode terminating the previous CSP and recurrence.

We also searched for case series in the published literature between 2007 and 2019, by searched PubMed for the entries: 'recurrent Cesarean scar pregnancy' and 'recurrent Cesarean scar ectopic pregnancy'. The articles were reviewed for their year of publication, as well for the same data as those extracted from our departmental databases.

RESULTS

Data retrieved from our centers' databases are summarized in Table 1. Overall, between 2010 and 2019 across the six participating centers, there were 252 cases of CSP. The rate of clinical follow-up at different centers ranged between 71.4% and 100.0% (mean, 90.9%). Among 229 patients with follow-up, 169 (73.8%) attempted another pregnancy after treatment of their previous CSP, among whom 105 conceived. Of these, the pregnancy was a recurrent CSP in 36 (34.3% (95% CI, 25.5–44.3%)) cases, with the rate at different centers ranging from 19.4% to 66.7%. Twenty-seven women had a single recurrence and three had multiple recurrent CSPs: one patient had two, one had three and one had four subsequent CSPs.

We could not find any association between type of treatment used to terminate the previous CSP and recurrence of CSP (Table 2). There were slightly more local, intragestational injections than there were double cervical-ripening balloon treatments of the previous CSP (15 *vs* 11); however, the small numbers did not allow us to perform any meaningful analysis.

Our literature search identified 26 articles, of which 17 contained sufficient information for us to evaluate reliably their reported prevalence of recurrent CSP[6–22] (Table 3). Based on these 17 studies, there were 1743 diagnoses of CSP. Sixteen of these studies (including 1643 diagnoses of CSP) reported a total of 944 (57.5%) cases with reliable follow-up. Fourteen of the studies reported on numbers of women who attempted to conceive again after treatment of their previous CSP: these totalled 489/912 (53.6%) cases and 306 (62.6%) of these attempts were successful. Only 11 studies reported miscarriages, of which there were 15, and only 11 studies reported deliveries, of which there were 136. All 17 studies reported numbers of pregnancies achieved following a previous CSP: there were 327, of which 67 (20.5%) were diagnosed as recurrent CSP.

We found a further four articles reporting single, recurrent CSP cases[5,23–25], but these were not included in Table 3 due to a lack of pertinent data which made it impossible to include them in the statistical analysis.

DISCUSSION

In the present retrospective study, analyzing data from six obstetrical and gynecologic departmental ultrasound databases from the period 2010–2019, we calculated a rate of recurrence of CSP of 34.3%, somewhat higher than the overall recurrence rate of 20.5% from previous publications.

It seems logical that, in order to obtain a reliable rate of recurrence of CSP, it is necessary to achieve a high follow-up rate of patients treated for CSP, and to identify among them the patients who attempted an additional pregnancy as well as those who successfully conceived, documenting their outcome. We achieved high rates for all three of these parameters (90.9%, 73.8% and 62.1%, respectively), rendering our results reliable and trustworthy. Applying a similar thought process to the published studies reviewed herein, of which 12 had a high (> 85%) rate of patient follow-up after CSP, yields a mean rate of recurrent CSP of 26.9%, a rate much closer to our findings in the present study.

It is becoming clearer to all involved in the clinical management of CSP that there may be single, or even multiple, recurrence following treatment. It seems logical that knowledge of the underlying pathogenesis may help in understanding both its occurrence and its reoccurrence. A number of theories have been proposed. The most credible, supported by research, are those favoring the theory of deep invasion of the trophoblast at the site of the myometrial incision[26,27], and those proposing a role of low oxygen tension in attracting the proliferating trophoblast, leading to deep invasion of the placenta[28]. The increased endovascular trophoblasts and their proteases degrade extracellular matrix and promote trophoblast migration[29]. Tseng suggested that placenta accreta develops as a result of abnormal expression of growth-, angiogenesis - and invasion-related factors in trophoblast populations[30].

Qian *et al*.[31] researched possible high-risk factors for recurrent CSP. They compared 21 women with recurrent CSP with 42 women selected randomly from a pool of 619 with their first CSP. Their results revealed that one of the risk factors was CD in a rural community hospital rather than a university hospital in China (odds ratio (OR), 4.75) and they attributed this to the possibly lower quality of care. Other risk factors mentioned were: thinner lower-uterine segment (≤ 5 mm; OR, 7.10), gestational sac bulging into the uterovesical fold (OR, 6.25), history of irregular vaginal bleeding or lower abdominal pain in the first CSP (OR, 3.52) and early termination (≤ 56 days) of the first CSP (OR, 5.85). Their findings led the authors to try to reduce patient morbidity by identifying risk factors for, and thereby increasing awareness for early recognition of, recurrence of CSP. However, their relatively small numbers and the fact that the prevalence of recurrent CSP was not calculated, prevented us from including this study in Table 3.

Another factor that may affect the pathogenesis of CSP in general, and certainly the risk of recurrence, is the operative technique and the incision closure technique used at CD. There is a residual 'niche' or 'drop-out' of the myometrium at the incision site of the Cesarean scar, detectable by transvaginal ultrasound[32], in the uterus of most patients following CD. It is not unreasonable to assume that the size of a niche could be a factor not only in the pathogenesis of an initial CSP, but also, perhaps even more so, in that of a recurrent CSP. While the literature that we reviewed does not support this, a retrospective cohort study found that a new surgical technique, involving exclusion of the endometrium during endometrium-free uterine closure, was associated with fewer placental abnormalities in subsequent pregnancies and reduced life-threatening maternal morbidity for future pregnancies[33]. Unfortunately, this study did not report if there were any CSPs following this closure method of the CD incision.

Lu *et al*.[24] studied the recurrence rate of 492 CSPs treated by uterine artery embolization (UAE) alone, or in combination with chemotherapy or laparoscopy with dilatation and curettage, comparing differences in intraoperative bleeding, length of hospital stay, time taken for blood beta-human chorionic gonadotropin (β-hCG)

levels to return to normal, menstruation recovery time and the hospitalization expenses. Multivariate regression analysis was used to predict the recurrence risk of CSP, and the results showed that the treatment method was an independent predictor of CSP recurrence risk (OR, 2.407 (95% CI, 1.176–5.092), $P < 0.05$), and that using the comprehensive treatment, including UAE, could reduce the risk of recurrent CSP. They concluded that, as the efficacy of this interventional therapy for CSP was rapid and reliable, with fewer complications, faster recovery rates and lower risk of recurrence, the comprehensive treatment, including UAE, should be the first choice, particularly for those patients with CSP who want to preserve fertility.

An unusually large niche following a CD was proposed by Ben Nagi *et al*.[6] as a cause for CSP. However, they suggested that: ' …..a recurrence is more likely to be a chance event rather than being caused by a particular affinity of the pregnancy to implant into the deficient scar.' Hasegawa *et al*.[4] suggested repairing uterine scars to decrease the risk of recurrent CSP. Opposing this, Ben Nagi *et al*.[6] suggested that surgical correction of a CD niche may be fraught with too many complications and could be more harmful than helpful to women wishing to preserve fertility. Qian *et al*.[31] agreed, adding that only large uterine defects should be repaired in recurrent cases or in women wishing to preserve fertility.

In this follow-up of CSP patients, our analysis did not reveal any obvious causal relationship or association between the type of treatment for the previous CSP and recurrence. This observation is more or less in line with those of Qian *et al.*[31] and Lu *et al.*[24]. In our study, there were slightly more double cervical-ripening balloon treatments compared with local, intragestational injections (15 *vs* 11), but the numbers small were too small to allow any conclusions to be drawn.

In a review by Morlando *et al*.[34], forty-four studies assessed the subsequent reproductive performance of 3598 women after CSP. Recurrence was observed in 17.6% of these women. The rate of a subsequent pregnancy was 74.4% in women who had been treated surgically and 68.7% in those who underwent non-

surgical treatment, while the rate of recurrent CSP was 21% in women undergoing surgical management and 15.2% in those undergoing non-surgical management. The authors concluded that there was insufficient evidence to determine whether the type of management adopted (surgical *vs* non-surgical) affects reproductive outcome after CSP[34].

Until more data are generated, the issue of whether there is a causative or associative link between treatment for a CSP and recurrence remains unresolved. The data currently are insufficient in terms of numbers of patients eligible for statistical analysis, with too many different primary treatments resulting in relatively low numbers in each management category, preventing any firm conclusions from being drawn regarding the optimal clinical management of patients presenting with a CSP. It is important that cases of CSP are entered into the International CSP Registry (www.CSP-registry.com), to enable us eventually to arrive at a consensus regarding the diagnosis and treatment of this pathology[35].

Another little-explored feature of CSP is multiple recurrence. We have reported previously on a patient who experienced five first-trimester CSPs with heart activity, four being recurrent[13]. The first four were treated with local intragestational MTX injection; the patient continued the fifth pregnancy and gave birth to a liveborn by CD at 34 weeks. In the current series, our database searches revealed three patients with repeated recurrent CSP: one patient with two, one with three and the one with four subsequent CSPs.

In conclusion, our data show that, among women with a prior CSP, the recurrence rate is far higher than previously suspected based upon mostly single case reports or series with few cases[5,23–25]. This is also supported by reliably documented articles published in the literature. This information needs to be incorporated into the initial counseling of women presenting with CSP, regardless of their future obstetrical plans, in order that they understand realistically the outcome of any future pregnancy. Our analysis did not reveal any obvious causal relationship or

association between the type of treatment for CSP and recurrence, likely due the small numbers of patients managed in each treatment category.

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Table 1 Recurrent Cesarean scar pregnancy (CSP) rates according to treatment site between 2010 and 2019

Site	CSPs	Cases with f/u after treatment of CSP	Pregnancies attempted after treatment of CSP	Pregnancies achieved after treatment of CSP	Recurrent CSP
A	76	71 (93.4)	54/71 (76.1)	44/54 (81.5)	13/44 (29.5)
B	43	42 (97.7)	26/42 (61.9)	16/26 (61.5)	9/16 (56.3)
C	11	11 (100.0)	9/11 (81.8)	6/9 (66.7)	3/6 (50.0)
D	7	5 (71.4)	5/5 (100.0)	3/5 (60.0)	2/3 (66.7)
E	102	90 (88.2)	65/90 (72.2)	31/65 (47.7)	6/31 (19.4)
F	13	10 (76.9)	10/10 (100.0)	5/10 (50.0)	3/5 (60.0)
Total	252	229 (90.9) [83.7–93.8]	169/229 (73.8) [74.7–85.0]	105/169 (62.1) [39.5–52.3]	36/105 (34.3) [25.5–44.3]

Data are given as *n*, *n* (%), *n*/*N* (%) or *n*/*N* (%) [95% CI]. f/u, follow-up.

Table 2 Treatment/outcome of previous Cesarean scar pregnancy (CSP) among 36 patients with recurrent CSP

Treatment/outcome	*n*
Systemic MTX only	1
D&C	7
Local intragestational injection with KCl or MTX	15*†‡
Cook double cervical-ripening balloon and systemic MTX	11§
Simple/single Foley balloon catheter and systemic MTX	3¶^~
Pregnancy continued and neonate delivered	4
Spontaneous miscarriage	3

Information for treatment of initial CSP as well as some recurrent CSPs of selected patients was available as follows. *One patient also had D&C for initial CSP, got pregnant again and continued the recurrent CSP, had uterine rupture at 12 weeks followed by hysterectomy. †One patient also had D&C and Foley catheter. ‡One patient had local MTX injection, D&C and Foley catheter but required uterine artery embolization for severe enhanced myometrial vascularity. §One patient had an intrauterine pregnancy with normal delivery between initial CSP and recurrent CSP. ¶One patient continued recurrent CSP and delivered by Cesarean hysterectomy at 34 weeks for placenta percreta. ^One patient continued recurrent CSP of twin gestation and delivered at 36 weeks with minor postpartum vaginal bleeding. ~One patient continued recurrent CSP and delivered vaginally at 38 weeks. D&C, dilatation and curettage; KCl, postassium chloride; MTX, methotrexate.

Table 3 Recurrent cesarean scar pregnancies (CSP) reported in the literature

				Pregnancies attempted after treatment of CSP (*n*)					32/154	
Study	Year	CSPs	Cases with f/u after treatment of CSP	Yes	No	Pregnancies achieved (*n*)	Miscarried (*n*)	Delivered (*n*)	Recurrent CSP (*n* (%))	Main treatment(s) for initial CSP
B[illegible]	2007	40	29 (72.5)	24	5	20	7	18	1/20 (5.0)	28 D&C; 12 local MTX
Maymon[7]	2011	18	18 (100.0)	10	8	8	0	N/A	2/8 (25.0)	16 Local MTX; 2 laparotomy
Yu[10]	2011	100	N/A	N/A	N/A	8	0	N/A	1/8 (12.5)	56 D&C after UAE; 30 D&C; 14 other methods
Nguyen- Xuan[8]	2014	6	6 (100.0)	N/A	N/A	3	0	N/A	1/3 (33.3)	4 Local MTX; 2 systemic MTX
Yamaguchi[9]	2014	8	8 (100.0)	5	3	4	0	0	1/4 (25.0)	8 Local MTX
Wa[illegible]	2015	214	189 (88.3)	58	131	32	0	N/A	5/32 (15.6)	D&C
Gu[illegible][12]	2016	28	20 (71.4)	8	N/A	7	2	5	1/7 (14.3)	Systemic MTX and D&C
Uludag[15]	2016	44	44 (100.0)	27	N/A	11	0	10	1/11 (9.1)	17 Local MTX; 27 systemic MTX
Yurkovic[14]	2016	232	96 (41.4)	79	N/A	60	N/A	N/A	7/60 (11.7)	83% D&C; 13% other
Washburn[16]	2017	23	23 (100.0)	23	N/A	11	1	9	1/11 (9.1)	12 D&C; 11 no surgery
[illegible]	2017	5	5 (100.0)	5	0	5	0	1	5/5 (100.0)	All local MTX
Grechukhina[17]	2018	30	26 (86.7)	N/A	N/A	10	N/A	6	4/10 (40.0)	Local and systemic MTX, UAE and/or double balloon
Wei[22]	2018	138	138 (100.0)	50	N/A	42	N/A	19	6/42 (14.3)	54 UAE and D&C; 41 D&C; 43 laparoscopy
Chen[13]	2019	650	135 (20.8)	131	N/A	78	N/A	53	25/78 (32.1)	HIFU and UAE
Stepniak[19]	2019	22	22 (100.0)	10	N/A	4	N/A	3	1/4 (25.0)	All elective chemoembolization with MTX
Orhan[21]	2019	31	31 (100.0)	31	0	6	N/A	N/A	3/6 (50.0)	'Many different treatments'
Zhang[20]	2019	154	154 (100.0)	28	N/A	18	5	12	2/18 (11.1)	HIFU
Sub[illegible]		1743	944/1643 (57.5)	489/912 (53.6)	147	327 total; 306/489 (62.6)	15	136	67/327 (20.5)	
Present series	2010–2019	252	229/252 (90.9)	169/229 (73.8)	N/A	105/169 (62.1)	3	N/A	36/105 (34.3)	See Table 1
Total		1995	1173/1895 (61.9)	658/1141 (57.7)	147	411/658 (62.5)	18	136	103/432 (23.8) [20.4–28.5]	

Only first author of each study is given. Data are given as *n*, *n* (%), *n*/*N* (%) or *n*/*N* (%) [95% CI]. Calculations of percents in subtotal and total rows include only studies for which relevant data were available. EP, ectopic pregnancy; f/u, follow-up; N/A, not available; D&C, dilatation and curettage; MTX, methotrexate; HIFU, high intensity focused ultrasound; UAE, uterine artery embolization.