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Management of caesarean scar pregnancy with high dose intravenous methotrexate infusion therapy: 10-year experience at a single tertiary centre

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ABSTRACT

Objective: Incidence of caesarean scar pregnancy (CSP) is increasing due to rising caesarean section rate and advanced imaging modalities. At present, there is no consensus to recommend any specific intervention. In our centre, we have adopted the high dose intravenous methotrexate therapy followed by folinic acid for the management of CSP. In this retrospective study, we report the success rate and safety of this regimen.

Study design: This was a 10-year retrospective study of women with CSP who received high dose methotrexate therapy with folinic acid at a tertiary centre from 1 st January 2008 to 31 st December 2017. Treatment regimen consisted of a bolus dose of intravenous methotrexate followed by methotrexate infusion over 12 h. Oral folinic acid rescues were given post treatment. Successful treatment was confirmed with either resolution of serum beta-human chorionic gonadotropin or subsequent intrauterine pregnancy.

Results: Of 28 women with CSP who were treated with the regimen, 24 women (85.7%) were treated successfully with methotrexate alone. 3 women (10.7%) required suction evacuation following initial treatment with methotrexate and folinic acid. There was no serious side effect from methotrexate. Advanced gestational age, higher serum β-hCG, larger gestational sac diameter and crown-rump length, and the presence of embryonic cardiac activity were associated with methotrexate failure or need for additional therapy.

Conclusions: Our high dose intravenous methotrexate infusion therapy with folinic acid is effective and well tolerated. Caution is needed with factors associated with failure. Ensuring follow up ultrasound for live CSP and follow up β-hCG for all women with CSP is essential.

Introduction

Caesarean scar pregnancy (CSP) is defined as implantation into the myometrial defect occurring at the site of the previous uterine incision [1]. It is fundamentally different from the other types of ectopic pregnancy because it can result in a live neonate if managed expectantly [2,3]. However expectant management can also lead to severe maternal morbidity including placenta accreta, uterine rupture, and massive haemorrhage, usually resulting in hysterectomy [3–5]. The incidence of CSP was estimated to be 1 per 531 among women with at least one caesarean delivery [6]. The frequency of reported cases has increased significantly over the recent years [7], owing both to the increased use of caesarean section and more accurate diagnosis with advanced imaging modalities such as ultrasound and Magnetic Resonance Imaging (MRI) [8,9].

There is no consensus to recommend any specific intervention for CSP due to insufficient evidence [1,10]. More than 30 primary approaches to treat CSP have been reported [2]. They can be categorised into surgical, medical, combination or expectant management. Surgical treatment includes 1) evacuation of pregnancy using dilatation and curettage or hysteroscopic procedure, 2) excision of the pregnancy as an open, laparoscopic or

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transvaginal procedure, or 3) uterine artery embolisation. Medical management includes 1) local intragestational injection of methotrexate, potassium chloride (KCL) or vasopressin or 2) systemic methotrexate.

High dose intravenous methotrexate infusion therapy with folinic acid rescue has been used to treat CSP and interstitial ectopic pregnancies in our institution for more than 10 years. Its use in interstitial ectopic pregnancy has been shown to be highly effective and safe, despite no exclusion criteria for serum beta-human chorionic gonadotropin (β-hCG) level, gestational sac diameter or presence of embryonic cardiac activity [11,12]. In this retrospective single site study, we investigated the efficacy and safety of intravenous methotrexate with folinic acid in the treatment of CSP over a 10-year period between January 2008 and December 2017, and also possible prognostic factors for successful treatment.

Materials and methods

This was a retrospective study conducted at a university affiliated, tertiary referral centre. A list of women with ectopic pregnancy treated between 1 st January 2008 and 31 st December 2017 was provided by health information services. A chart review was carried out to identify women with CSP.

Diagnosis of CSP was made by ultrasound with criteria which included 1) empty uterus, [13] 2) empty endocervical canal [13], 3) thin or absent layer of myometrium between the gestational sac and the bladder [13,14], 4) gestational sac or solid mass of trophoblast located anteriorly at the level of the internal os embedded at the site of the previous lower uterine segment caesaren section scar [15], and 5) evidence of prominent trophoblastic/placental circulation on Doppler examination [16].

All clinically stable women with no evidence of rupture on ultrasound, normal liver and renal function, and patient reliability for follow-up, were offered medical management with high dose methotrexate and folinic acid as a first line therapy. There were no exclusion criteria on β-hCG level, gestational sac diameter or presence of embryonic cardiac activity. These women were treated with methotrexate intravenous bolus followed by intravenous infusion as per our protocol (Table 1). The following data were collected: maternal age, number of previous caesarean section, gestational age, mean gestational sac diameter, crown-rump length, presence of embryonic cardiac activity, initial and subsequent β-hCG levels, side effects of methotrexate, treatment outcome, length of hospital stay, and subsequent pregnancy. Successful methotrexate therapy was confirmed by either resolution of serum β-hCG level (< 5 IU/L) or subsequent intrauterine gestation.

Data were analysed using SPSS version 23 (IBM Corp, Armonk, NY). Categorical variables were examined using the Fisher's Exact test and continuous variables were examined using Mann-Whitney U test. P value less than 0.05 was considered significant.

The study was judged to meet the requirements of the National Health and Medical Research Council's National Statement on Ethical Conduct in Human Research, and ethics approval was obtained from the Institutional Human Research Ethics Committee (Reference number HREC/18/QRBW/363).

Results

Thirty-one women were diagnosed of CSP between 1 st January 2008 and 31 st December 2017. Two women had received initial treatment at a different facility before being transferred. One woman refused any treatment and continued with the pregnancy which resulted in emergency hysterectomy at 20 weeks gestation. All the remaining 28 women received high dose intravenous methotrexate therapy.

Their age ranged from 21 to 45 years (mean 31.4 years), and number of previous caesarean sections ranged from 1 to 6 (median 2) (Table 2). Gestational age ranged from 5 to 13 weeks based on either their last menstrual period or ultrasound scan. Mean sac diameter ranged from 5.1 mm to 38 mm (median 15.5 mm), and crown-rump length was identified in 18 women and ranged from 2 mm to 34 mm (median 7.5 mm). Embryonic cardiac activity was seen in 11 (39.3%) women. Baseline β-hCG level ranged from 69 to 249,230 IU/L (median 19,037 IU/L). There were no adverse effects of methotrexate such as marrow suppression, pulmonary fibrosis, nonspecific pneumonitis, liver cirrhosis, renal failure and gastric ulceration. Eleven women complained of nausea which resolved with or without additional antiemetic medication, and none experienced vomiting. Length of hospital stay ranged from 1 to 14 days (median 3 days).

Twenty-four women (85.7%) were successfully treated with methotrexate alone, three women (10.7%) were successfully managed with additional therapy after methotrexate therapy and there was one case (3.6%) of live birth.

Out of 24 women who were successfully treated with intravenous methotrexate alone, 19 patients completed regular β-hCG follow-up until resolution. The number of days from methotrexate to the date β-hCG resolution was achieved ranged from 14 to 176 days (median 89 days). Five women were lost to follow up and therefore there was no evidence of complete resolution from serial β-hCG testing. However successful management was confirmed in 3 women due to findings of a subsequent intrauterine pregnancy, and the remaining two women were found to have a negative β-hCG level at a subsequent hospital presentation unrelated to CSP.

The number of previous CS was not found to be associated with treatment success (Table 3). Women with higher baseline β-hCG were more likely to fail treatment ($p = 0.002$). Further advanced gestations were more likely to fail treatment ($p = 0.003$). Treatment failure was also shown to be more likely with larger mean sac diameter ($p = 0.003$) and crown-rump length ($p = 0.005$). The presence of embryonic cardiac activity was associated with treatment failure however it was still successful in 7 of 11 (63.6%) of women. It should be noted that these findings provide evidence but are not robust with only 4 treatment failures.

All four women with treatment failure with methotrexate alone demonstrated presence of embryonic cardiac activity. Three women (cases 1, 12 and 13) underwent additional therapy with

Table 1
IV methotrexate and folinic acid protocol at Royal Brisbane and Women's Hospital.

- Ural PO to achieve urinary pH >7.0 (Urinary alkalinisation to avoid potential risk of crystallisation of methotrexate in the kidneys)
- 3mg granisetron IV
- 100mg methotrexate IV push over 5–10 min
- 200mg methotrexate in 500mL normal saline IV infusion over 12 h
- 15mg folinic acid (leucovorin) PO given at 30, 42, 54 and 66 h post commencement of methotrexate
- 4mg ondansetron PO PRN

PO: oral; IV: intravenous; PRN: pro re nata (when necessary).

Table 2
Clinical features of potential variables in treatment success.

Case	Number of previous CS	Gestational age (week)	Baseline β-hCG (IU/L)	MSD (mm)	CRL (mm)	Embryonic cardiac activity	Success with Methotrexate alone	Success with additional therapy	Days to β-hCG resolution
1	2	8^{+2}	91,000	29.5	14.3	✓		✓	N/A
2	4	7^{+2}	23,000	20.0	–		✓		139
3	1	7	20,000	13.0	–		✓		–
4	1	9^{+6}	2,800	12.0	6.2	✓	✓		52
5	2	6	31,000	24.7	2.1		✓		95
6	1	13	210	32.3	8.0		✓		52
7	1	6	68,000	21.7	8.1	✓	✓		95
8	1	7	18,000	9.7	5.1	✓	✓		–
9	1	5^{+5}	930	31.2	3.4		✓		14
10	2	6	12,000	10.3	–		✓		–
11	1	6	1,500	9.3	–		✓		27
12	2	9^{+3}	60,000	36.9	26.6	✓		✓	N/A
13	6	11	150,000	38.0	18.0	✓		✓	N/A
14	1	5^{+4}	18,000	11.0	2.0	✓	✓		68
15	2	5^{+4}	12,000	11.0	3.3	✓	✓		100
16	3	7	29,000	15.5	–		✓		176
17	2	5	3,700	8.7	–		✓		109
18	1	7^{+6}	6,200	18.0	14.8		✓		26
19	1	6^{+5}	43,000	19.5	10.2		✓		120
20	3	6	8,600	12.5	–		✓		–
21	3	7^{+6}	51,000	28.6	19.9	✓	✓		–
22	1	5^{+5}	22,079	14.7	–		✓		93
23	2	7	69	7.0	–		✓		20
24	1	6^{+5}	249,230	21.0	2.7		✓		121
25	2	5	4,360	5.1	–		✓		41
26	3	9^{+6}	122,070	–	34.0	✓			N/A
27	2	5^{+5}	28,056	14.7	2.5	✓	✓		89
28	2	6	18,073	18.0	7.0		✓		79

CS: Caesarean section, MSD: Mean sac diameter, CRL: Crown-rump length, β-hCG: beta-human chorionic gonadotropin, N/A: Not applicable.

Table 3
Summary statistics of clinical features overall and by treatment success.

Clinical Feature	n	Statistic	Overall (n = 28)	Success (n = 24)	Failure (n = 4)	p-value
Number of previous CS	28	Median (IQR)	2 (1–2)	2 (1–2)	3 (2–5)	0.050
Gestational age (week)	28	Median (IQR)	6.9 (6.0–7.9)	6.4 (5.8–7.0)	9.6 (8.6–10.7)	0.003
Baseline β-hCG (IU/L)	28	Median (IQR)	19,037 (4,820–49,000)	18,000 (3,865–28,764)	106,535 (67,750–143,018)	0.002
MSD (mm)	27	Median (IQR)	15.5 (11.0–24.7)	14.7 (10.5–20.8)	36.9^	0.003
CRL (mm)	18	Median (IQR)	7.5 (3.2–15.6)	5.7 (2.7–8.6)	22.3 (15.2–31.2)	0.005
Embryonic cardiac activity	28	n (%)	11 (39.3 %)	7 (29.2 %)	4 (100.0 %)	0.016

CS: Caesarean section, MSD: Mean sac diameter, CRL: Crown-rump length, β-hCG: beta-human chorionic gonadotropin, ^n = 3.

successful outcomes. Case 1 received intragestational potassium chloride (KCl) injection 7 days post methotrexate therapy for persisting embryonic cardiac activity (Table 4). She then underwent suction curettage 21 days post methotrexate therapy for vaginal bleeding. Cases 12 and 13 underwent suction curettage 6 and 23 days post methotrexate therapy respectively. Indications were haemorrhage and persistence of embryonic cardiac activity. Foley catheter was inserted for haemostasis in both women and removed on day 1 post surgery, one woman required blood transfusion. In our series, none of the 28 women required laparoscopy, laparotomy or hysterectomy.

There was a case (case 27) of live birth after intravenous methotrexate therapy. She presented to the tertiary centre with a live CSP at 10 weeks gestation with β-hCG level of 122,070 IU/L, and underwent intravenous methotrexate infusion therapy. She was followed up at her local hospital with serial β-hCG levels but did not have follow up ultrasound scan initially. Serial β-hCG levels showed a decline until 45 days post methotrexate therapy and it

Table 4
Clinical features of the cases required additional intervention.

Case	Indication for curettage	Intervention	Number of days since methotrexate therapy	Additional measures	Intra operative EBL	Complications
1	Persistence of embryonic cardiac activity	Intragestational KCl injection	7	–	–	–
	Vaginal bleeding	Suction curettage	21	–	Minimum	–
12	Haemorrhage (1000 mls)	Suction curettage	6	Foley catheter	1100 mls	Blood transfusion
13	Persistence of embryonic cardiac activity	Suction curettage	23	Foley catheter	200 mls	–

EBL: estimated blood loss, KCL: potassium chloride.

increased from 15,098 to 16,603 IU/L. Ultrasound scan showed a live intrauterine pregnancy and was referred back to the tertiary centre. Following extensive counselling, the couple chose to continue with the pregnancy and had a live birth to a healthy baby.

6 women (21.4%) had a subsequent live birth by caesarean section and further 3 women had an intrauterine pregnancy which resulted in miscarriage (10.7%).

Comment

In the last 20 years, our institution has adopted high dose intravenous methotrexate infusion with folinic acid as the first line treatment of CSP, and this is the first study to report its efficacy and safety. In 2015, a systematic review on the efficacy of systemic methotrexate treatment of CSP identified a total of 40 cases from 27 articles, reporting a 55% (22 out of 40 cases) success rate with systemic methotrexate alone, and 85% (34 out of 40 cases) success rate with additional minor interventions such as local methotrexate, concomitant systemic and local methotrexate, dilatation and curettage or uterine artery embolization with dilatation and curettage [17]. In 2017, another systematic review reported 56% success rate for systemic methotrexate therapy alone [18]. In the literature, methotrexate is usually given as a single [19–21] or multiple dose regimen [22,23], either intramuscularly or intravenously using low dose. Single dose regimen involved a dosage of 50 mg/m^2 (body surface area) [19–21]. Dosage would be 80 mg for an average female body surface area of 1.6m^2. In multiple dose regimen, either 50 mg/m^2 (body surface area) [23] or 1.0 mg/kg (weight) [22] of methotrexate was given every other day for approximately 5 doses, therefore the total amount of methotrexate would be similar or slightly higher but given over a longer period of time compared to our regimen.

In the current study, 24 out of 28 women (85.7%) were treated successfully with high dose intravenous methotrexate therapy alone, and further 3 women (10.7%) required additional therapy following methotrexate. Our study suggests that high dose intravenous infusion therapy may be associated with a higher success rate than other systemic methotrexate therapies. This may be due to differences in dosage and timing of methotrexate administration. We have previously reported the efficacy of high dose intravenous methotrexate therapy in the management of interstitial ectopic pregnancy [12]. Our current study shows that efficacy of high dose intravenous methotrexate therapy for CSP (85.7%, 24 out of 28 women) is similar to its efficacy for interstitial ectopic pregnancy (93.9%, 31 out of 33 women). Some argue that systemic methotrexate may not be effective in the treatment of CSP because of the surrounding fibrous scar tissue rather than normally vascularised myometrium [24].

This study has shown that our methotrexate therapy is well tolerated, finding that is consistent with our previous publication on management of interstitial ectopic pregnancy with intravenous methotrexate therapy [12]. There was no severe adverse effect of methotrexate. Furthermore, it has shown that methotrexate infusion is safe, as only one woman (3.6%) suffered haemorrhage requiring blood transfusion and no one required laparoscopy, laparotomy or hysterectomy. A systematic review reported 13% of women who underwent systemic methotrexate therapy suffered severe complication including hysterectomy, bleeding > 1000 mL or blood transfusion, and laparotomy [25].

We have shown that factors including further advanced gestations, higher baseline β-hCG, larger sac diameter and crown-rump length, and the presence of embryonic cardiac activity were associated with treatment failure with statistical significance. These findings are consistent with studies on management of CSP with intramuscular methotrexate. A negative embryonic cardiac activity had five times increased odds of having a successful treatment than the women with a positive embryonic cardiac activity (OR 4.80, 95% CI, 1.14–20.08), [17] and methotrexate therapy was found to be more feasible in women with lower β-hCG level (<20,000mIU/mL) and smaller lesion (<3.0 cm in diameter) [21].

Systematic reviews have recommended surgical approaches such as 1) resection through a transvaginal approach, 2) laparoscopy, 3) uterine artery embolisation in combination with dilatation and curettage and hysteroscopy, 4) uterine artery embolisation in combination with dilatation and curettage, or 5) hysteroscopy, over medical approaches based on reported efficacy and safety [18,25]. However these approaches require surgical expertise, operating theatre with anaesthetic service, preparation for possible laparotomy, hysterectomy and massive transfusion protocol or interventional radiology service, which are not always accessible at many facilities. Our methotrexate regime may be particularly useful when women are not suited for general anaesthesia or surgery due to factors such as high BMI, previous surgical history, medical co-morbidities or patient preference. Furthermore medical treatments for CSP are fertility sparing. During our retrospective data collection at our facility, it was noted that at least 6 women (21.4%) had a subsequent live birth and further 3 women had an intrauterine pregnancy which resulted in miscarriage (10.7%). It is possible that there were more cases of subsequent pregnancy that were treated at other facilities. One of the difficulties with medical management noted in our study is that ensuring serial β-hCG tests until resolution is a challenge. Out of 24 women who were successfully managed with intravenous methotrexate therapy alone, 19 women completed regular β-hCG testing until resolution, and the remaining 5 women had limited β-hCG follow up. Experience with the recent case of methotrexate failure with a live birth has illustrated the importance of careful counselling and robust follow up of these women.

Another point raised by the case of a live birth after methotrexate is the difficulty in making diagnosis of CSP and distinguishing it from placenta accreta. Early placenta accreta and placental implantation in CSP are histopathologically indistinguishable and said to represent different stages in the disease continuum leading to morbidly adherent placenta in the third trimester [26]. At our facility, we practice multidisciplinary approach in making diagnosis of CSP collaborating with maternal fetal medicine specialists who perform tertiary ultrasound scans and radiologists who may consider MRI as an adjuvant to ultrasound.

Strength of our study is a modest sized cohort who underwent the same standardised treatment regimen over a 10 year period in the one institution. This cohort has led to statistically significant findings in characteristics between women with successful and failed methotrexate therapy. We did not differentiate two types of CSP reported by Vial et al. [27]. They stated that the first is due to the implantation of the amniotic sac on a scar with progression of the pregnancy in the cervico-isthmic space and in the uterine cavity with the possibility of a live birth, and the second is a deep implantation in a caesarean scar defect with progression towards rupture and bleeding. It was reported that the superficial form of CSP was more likely to be treated successfully with systemic methotrexate than deep CSP [20].

In conclusion, the high dose intravenous methotrexate regime is effective, well tolerated and safe in the management of CSP. However, caution is needed where gestational age is advanced, serum β-hCG level is high, and ultrasound scan shows a larger sac diameter, crown-rump length or embryonic cardiac activity where additional therapy may be required. Importance of follow up ultrasound scans for live CSP and regular β-hCG tests for all women with CSP should be emphasised.

Conflict of interest statement

We declare that we have no conflict of interest.

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