Original paper

Caesarean scar pregnancy. Analysis of medical intragestational therapy in a cohort of 35 patients

Ciąża w bliźnie po cięciu cesarskim. Analiza terapii dopęcherzykowej w retrospektywnej kohorcie 35 pacjentek

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Medical Studies/Studia Medyczne 2023; 39 (4): 359–363
DOI: https://doi.org/10.5114/ms.2023.134087

Key words: caesarean scar pregnancy, methotrexate, intragestational therapy, ultrasound-guided procedure.

Słowa kluczowe: ciąża w bliźnie po cięciu cesarskim, metotreksat, terapia dopęcherzykowa, procedury pod kontrolą USG.

Abstract

Introduction: Pregnancy in a scar after caesarean section (CSP) is a rare complication associated with the risk of morbidly adherent placenta (MAP) and adverse outcomes. The management of CSP is evolving, with various surgical and medical approaches employed.
Aim of the research: To analyse the outcomes of 35 cases of CSP and their treatment modalities.
Material and methods: Medical records of patients hospitalized at a single institution were reviewed. Data on patient characteristics, gestational age, treatment methods, hospitalization length, complications, and rehospitalization rates were collected. Statistical analysis was conducted using nonparametric Spearman correlation.
Results: The study included 35 CSP patients with a mean age of 33 years. The median gestational age at diagnosis was 6 weeks. Methotrexate (MTX) administration to the gestational sac, alone or with intragestational MTX injection, was the primary treatment method. The median length of hospitalization was 6 days. No significant correlation was found between hospital stay and patient age, number of previous caesarean sections, or pre-procedure β-human chorionic gonadotropin (β-HCG) levels. Spontaneous evacuation occurred in most cases, with only a minority requiring subsequent uterine evacuation. No significant complications occurred, but 1 patient experienced heavy bleeding requiring a blood transfusion.
Conclusions: Intra-amniotic MTX administration, combined with potassium chloride in certain cases, was found to be an effective and safe approach for managing CSP in the first trimester. This study contributes to the understanding of CSP management and supports the use of intra-amniotic MTX as a minimally invasive treatment option. Further research is needed to refine management guidelines and improve outcomes for this rare complication.

Streszczenie

Wprowadzenie: Ciąża w bliźnie po cięciu cesarskim (CSP) to rzadkie powikłanie związane z ryzykiem wystąpienia łożyska przyrośniętego i niekorzystnych wyników położniczych. Protokoły postępowania w przypadku CSP dynamicznie się rozwijają, wykorzystując podejście chirurgiczne i medyczne, jednak obecnie postępowanie nie jest jednoznacznie ustalone.
Cel pracy: Analiza wyników 35 pacjentek z rozpoznaniem CSP oraz zastosowanych metod leczenia. Dokonano przeglądu dokumentacji medycznej pacjentów hospitalizowanych w naszej placówce. Zebrano dane dotyczące charakterystyki pacjentek, wieku ciążowego, metod leczenia, długości hospitalizacji, powikłań i wskaźnika rehospitalizacji.
Materiał i metody: Badaniem objęto 35 pacjentek z CSP. Mediana wieku ciążowego w momencie rozpoznania wynosiła 6 tygodni. Podstawową metodą leczenia było podanie metotreksatu (MTX) do pęcherzyka ciążowego, samodzielnie lub z dożylnym wstrzyknięciem MTX.
Wyniki: Mediana czasu hospitalizacji wyniosła 6 dni. Nie wykazano istotnej korelacji między długością pobytu w szpitalu a wiekiem pacjentki, liczbą przebytych cięć cesarskich i stężeniem β-HCG przed zabiegiem. W większości przypadków dochodziło do spontanicznego poronienia po zabiegu. Nie stwierdzono zagrażających zdrowiu ciężarnej powikłań, u jednej chorej wystąpiło obfite krwawienie wymagające przetoczenia masy erytrocytarnej.
Wnioski: Dopęcherzykowe podawanie MTX (w niektórych przypadkach w połączeniu z chlorkiem potasu) jest skutecznym i bezpiecznym podejściem do leczenia CSP w pierwszym trymestrze ciąży. Badanie to przyczynia się do pogłębienia wiedzy o optymalnym postępowaniu w przypadkach CSP oraz przedstawia terapię dopęcherzykową jako mało inwazyjną i bezpieczną w przypadkach wcześnie rozpoznanej CSP.

Introduction

Pregnancy in a scar after caesarean section (CSP) is a rare complication of pregnancy. It is estimated that this form accounts for approximately 6% of all ectopic pregnancies [1]. The main concern with CSP is its association with the development of morbidly adherent placenta (MAP) in most cases, which carries a high risk of maternal peripartum mortality and morbidity, as well as neonatal prematurity [2]. Ultrasonographic imaging of CSP reveals a gestational sac (GS) on the anterior uterine wall, absence or thinning of the myometrium at the bladder junction, absence of GS in the cervical canal and uterine cavity, and visualization of blood flow around the GS using colour Doppler ultrasound [3].

The management of CSP is not yet clearly established, although with the emergence of studies involving larger patient cohorts, it is slowly becoming more clarified. Currently, surgical procedures such as operative resection (wedge resection) can be utilized for patients who want to preserve fertility, while gravid hysterectomy is an option for patients who do not express such a desire. In cases of medical therapy, intragestational injection of potassium chloride (KCl) and methotrexate (MTX) or transcervical Foley catheter placement can be employed. Additionally, supportive methods such as systemic administration of MTX, uterine artery embolization (UAE), and high-intensity focused ultrasound (HIFU) have been described in the literature [4, 5].

Aim of the research

The diagnosis of CSP contraindicates uterine curettage due to the high risk of haemorrhage and perforation at the scar site. Vaginal use of misoprostol, as in the case of missed miscarriage, is also not recommended. Given the lack of well-established management guidelines, the relatively small number of reported cases, and the increasing prevalence, we decided to present our study focusing on 35 cases of CSP hospitalized at our institution.

Material and methods

We reviewed the medical records of all patients hospitalized in the Department of Obstetrics and Gynaecology at the Provincial Integrated Hospital in Kielce from 2013 to 2023. We collected data on patient age, number of previous caesarean sections, gestational age, initial β-human chorionic gonadotropin (β-HCG) levels, size of the gestational sac, presence of an embryo with a heartbeat, treatment method used, length of hospitalization, rate of perioperative complications, and rehospitalization rate. The criteria for hospital discharge were as follows: a decrease in β-HCG of at least 15% during measurements taken after 4 days from MTX administration, the absence of clinically significant pain symptoms, and the absence of significant uterine cavity bleeding. Intramuscular doses were administered in cases where this reduction in the study was less than the aforementioned value. Another intramuscular dose was administered when the biochemical criterion for patient discharge from the ward was not met again after 4 days. The study was conducted retrospectively and relied on medical documentation.

Statistical analysis

For qualitative data, results were presented as percentages, while for quantitative data, the median or arithmetic mean was used, with the interquartile range or standard deviation used as measures of dispersion, respectively. Nonparametric Spearman correlation was used to assess correlations. Correlation was considered statistically significant at $p < 0.05$.

Results

A total of 35 patients with a diagnosis of pregnancy in a scar after CSP were included in the study. The mean age was 33 years, with patients ranging in age from 27 to 43 years. The demographic characteristics of the group are presented in Table 1. The median gestational age was 6 weeks. The gestational age range of patients included in the study was from 5 to 10 weeks of pregnancy. The maximum number of previous caesarean sections in a patient was 5 (1 patient). In all pregnancies beyond 6 weeks, an embryo with heartbeat was visualized (10 cases, 28.5%). In cases where no heartbeat was detected, transcervical administration of MTX to the GSunder ultrasound guidance was performed. In cases where an embryo with a heartbeat was visualized, in addition to transcervical administration of MTX, intragestational injection of 5 mEq into the GS was also used. The mean β-HCG concentration for gestational age expressed in weeks is presented in Table 2. Intragestational MTX doses ranged from 25 to 100 mg (intragestational administration involved a solution with a concentration of 50 mg/ml, so the volume of the solution adminis-

Table 1. Distribution of demographic characteristics in the group

Patient's age [years]	Mean = 33.7	SD = 4.1	Range: 27–43		
Number of previous caesarean sections	1 (58%, *n* = 20)	2 (29%, *n* = 10)	3 (85.7%, *n* = 3)	4 (3%, *n* = 1)	5 (3%, *n* = 1)
Time of pregnancy [weeks]	5 (29%, *n* = 10)	6 (35.29%, *n* = 12)	7 (14.7%, *n* = 5)	8 (11.76%, *n* = 4)	9 and above (8.57%, *n* = 3)

SD – standard deviation, n – number of patients.

tered to the GS ranged from 0.25 to 1 ml) and additionally, 11 (32%) patients received intramuscular MTX due to insufficient decrease in β-HCG levels (defined similarly to ectopic tubal pregnancy as a decrease of ≥ 15%). The intramuscular MTX dose ranged from 75 to 100 mg (intramuscularly, a solution of 20 mg/ml was administered). Additionally, 3 patients received a third dose of MTX, each with a gestational age of 7 weeks or more. The median length of hospitalization for patients was 6 days, with a range of 2 to 19 days. We did not observe a significant correlation between the length of hospitalization and pre-procedure β-HCG levels, number of previous caesarean sections, or patient age (Table 3). However, this may be attributed to the small sample size, which carries a high risk of type II error. In 7 (20%) patients, the uterine cavity was evacuated after the procedure, while the remaining cases experienced spontaneous evacuation. This procedure was performed earliest at 4 days after MTX administration into the gestational sac. One patient in our cohort experienced clinically significant vaginal bleeding. None of the patients required additional procedures such as operative resection, gravid hysterectomy, or UAE. One patient required blood transfusion (2 units of packed red blood cells and 2 units of fresh frozen plasma). This patient, who had 4 previous caesarean sections and was in the eighth week of pregnancy, experienced heavy bleeding after treatment based on transvaginal KCl and MTX administration, leading to miscarriage before evacuation of the uterine contents. The lowest haemoglobin concentration in the aforementioned patient was 6.8 g/dl.

Table 2. Mean β-HCG concentration in each week of pregnancy

Time of pregnancy [weeks]	β-HCG concentration on the first day of admission [IU/ml]
5	18274.30
6	23928.30
7	28 851.25
8	40183.50
9	50357.50

Discussion

Despite the relatively small sample size in our study, the findings suggest that the approach based on transcervical puncture of the GS with intragestational injection of MTX, along with additional KCl administration in the presence of foetal heart rate (FHR), is a safe procedure with a low incidence of perioperative complications and high treatment efficacy.

Untreated CSP left to its natural course can lead to various complications that pose a threat to the health and life of the mother, such as uterine rupture. In cases where this complication does not occur, there is a high incidence of postpartum hysterectomy due to the presence of placenta accreta spectrum (PAS). It is now recognized that the diagnosis of pregnancy in a caesarean scar in the first trimester is a natural precursor to PAS, and histologically, these 2 conditions represent a continuum and cannot be distinguished [6]. From the perspective of further pregnancy management, the position of the GS relative to the scar niche in the caesarean scar is crucial. Among women who chose to continue the pregnancy, 17% of those with the GS located "on the niche" in the first trimester developed PAS, requiring postpartum hysterectomy. On the other hand, in the group of patients with the GS located inside the niche, over 90% required postpartum hysterectomy, and histopathological examination confirmed the presence of MAP in the specimen. However, the study was limited by a relatively small sample size [7].

PAS is a pregnancy complication associated with a significant risk of perioperative haemorrhage in the patient. According to data from a systematic review published in 2013, the average number of units of packed red blood cells transfused per patient during the perioperative period is 5, with some women receiving more than 100 units of packed red blood cells. Additionally, intraoperative urinary tract injuries occur in up to one-third of patients, with a median operation time of 5 h [8, 9]. In cases of unexpected intraoperative finding of PAS in an unprepared centre, the mortality rate reached 22%, and the rate of intensive care unit hospitalization was 85% [10]. Studies indicate that the establishment of specialized centres for the treatment of this complication is the best solution because a significant proportion of deaths can be prevented by improving the qualifications of the personnel and surgical techniques [11, 12].

In the era of the contemporary epidemic of caesarean sections and increased availability of drugs used in postpartum atony, PAS may become the dominant indication for postpartum hysterectomy and replace uterine atony in countries with high CSP rates [13].

Table 3. Correlation matrix between length of hospitalization and quantitative variables

Pair of variables	Rho	*P*-value
Hospitalization time and number of previous caesarean sections	–0.192879	0.274436
Hospitalization time and gestational age	0.244872	0.162779
Hospitalization time and age of the patient	–0.209200	0.235069
Hospitalization time and baseline β-HCG concentration	0.347054	0.070386

Studies conducted on cohorts of patients in some countries have shown an increasing trend in the occurrence of this form of ectopic pregnancy. A study conducted in the Canton province of China, which included 3915 hospitalized patients with ectopic pregnancy between 2012 and 2019, demonstrated that the percentage of caesarean scar pregnancies among ectopic pregnancies increased from 5.42% to 12.48%, and this trend was statistically significant ($p < 0.05$) [14]. During this time, there was also an increase in the rate of caesarean sections in the country [15].

Early diagnosis of this complication is crucial in terms of management, and it is possible from the moment of GS appearance (i.e. from approximately 5 weeks of gestation) [16]. Our results show that early diagnosis allows for effective treatment with a low incidence of perioperative complications, which can be a solution for patients who do not wish to continue the pregnancy in the face of life-threatening complications and mortality associated with PAS.

Ultrasound is the basis for diagnosis. Currently, according to recommendations regarding ultrasound examinations in pregnancy, an ultrasound scan performed before the 10th week of pregnancy is indicated for medical reasons (not mandatory) [17]. However, it seems that the group of patients with a history of CSP should be stratified as a high-risk group and undergo early ultrasound examinations in the era of widespread access to ultrasound devices. This should especially apply to patients who had a documented caesarean scar niche before becoming pregnant, as this complication after CSP is associated with an increased risk of caesarean scar pregnancy [18].

Transvaginal ultrasound diagnosis demonstrates a sensitivity of 84.6% (95% CI: 0.763–0.905) in detecting caesarean scar pregnancy. Cases that were undiagnosed in the cited study were mistakenly interpreted as cervical pregnancy or ongoing miscarriage [19]. Awareness of this complication should also be present among individuals involved in first-trimester pregnancy diagnosis. However, studies indicate that this awareness is not comprehensive among physicians and sonographers [20].

After the diagnosis of this complication, the unresolved issue remains the choice of treatment method. Surgical treatment can be an alternative to the approach presented in our study. In the case of a procedure based on resection of pregnancy in a caesarean scar, a crucial factor is understanding the risk factors for increased perioperative blood loss. In a cohort of 273 patients treated with resection using a multivariable model, the major risk factors for a blood loss of 300 ml or more during the procedure were the size of the GS (adjusted odds ratio (aOR) = 0.51, 95% confidence interval (CI): 1.07–1.14) and the thickness of the myometrium at the border with the urinary bladder (adjusted odds ratio = 0.51, 95% CI: 0.36–0.73) (3). Myometrial thickness (MT) is also the strongest factor in the development of MAP. In one study, using a cut-off point of 3.3 mm for MT as a risk classifier for severe complications in pregnancy, such as intraoperative blood loss ≥ 1000 ml or severe forms of MAP, such as placenta increta or placenta percreta, an area under the curve (AUC) of 0.818 was obtained, with a sensitivity of 80.0% and specificity of 81.8% [21].

The treatment used in our centre is described in the literature as being applied both in cases of foetal demise and viable pregnancies. Such management is reported to be less effective than surgical treatment in terms of recurrence. In a group of 18 patients treated at King's College Hospital in London, operative treatment involving lesion excision was successful in 100% of cases, while intragestational MTX treatment was effective in 5 out of 7 cases, and conservative management was successful in only 1/3 of cases [22]. It is worth noting that, unlike surgical therapy, the effects of medical therapy require time. The reduction in β-HCG levels is not immediate. The literature also lacks clear data on the initial decline in β-HCG levels that is considered effective, as seen, for example, in the treatment of ectopic tubal pregnancy using MTX (a 15% decrease on the fourth day). In a cohort of 97 patients hospitalized at the General Hospital in Beijing, with a mean initial β-HCG level of 20.321 ±965 IU/l and a mean gestational age of 6.1 ±0.8 weeks, the average time to β-HCG normalization was 40 days (range: 21 to 140 days). The time for the disappearance of the scar lesion was shorter, with a mean of 39 days (± 29 days). The failure rate in this study was low, at 3.9%. The average β-HCG concentration in this group was higher, with a mean of 91.359 IU/l [23]. In our opinion, conservative management is a worthwhile consideration in every case of CSP in the first trimester. We have successfully used this method even in the case of a viable cervical pregnancy at 12 weeks of gestation, in a patient who retained her uterus, along with supportive measures such as the placement of a Foley catheter in the uterine cavity and UAE. In cases of treatment failure with local KCl injection and MTX, more invasive methods such as UAE in cases of bleeding or classical uterine artery ligation can always be applied.

The results presented in our study, in comparison to existing literature, demonstrate the relatively large sample size on which we conducted our analysis. The treatment was also highly effective. However, a limitation of this study was its retrospective nature and the lack of complete standardization of procedures. The doses of MTX varied among patients, both in cases of intragestational and intramuscular administration, and were subjectively determined by the operator based on the size of the GS and the stage of pregnancy. Additionally, we did not conduct follow-up after the completion of treatment. However, we did not observe any re-admissions to the hospital due to bleeding or other complications following the procedure.

Despite these limitations, we believe that our study provides valuable information regarding the ef-

fectiveness of treatment in cases of caesarean scar pregnancies diagnosed before 10 weeks of gestation.

Conclusions

Intra-amniotic administration of MTX (combined with KCl in cases of visible cardiac activity) is an effective and safe approach for managing CSP diagnosed in the first trimester. It is also the least invasive method among the described treatment options.

Acknowledgments

Paper were financed under Jan Kochanowski University project no SUB. RN 21.071.

Conflict of interest

The authors declare no conflict of interest.

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