Cesarean scar pregnancy — various methods of treatment

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Abstract: Ectopic pregnancy constitutes 2% of all pregnancies. In the last decades, due to the rising amount of caesarean sections, new localization of ectopic pregnancy has been observed — caesarean scar pregnancy (CSP). Cesarean scar pregnancy is an iatrogenic disease and a life-threatening condition which frequency will systematically rise. Because of possible serious complications, CSP should be swiftly diagnosed and treated. The purpose of this retrospective study was to demonstrate different methods of CSP treatment performed between 2015–2018 in the Clinic of Endocrinological Gynaecology and Gynaecology Jagiellonian University Medical College in Cracow. The clinical characteristics, diagnosis, various methods of treatment and clinical outcomes were analysed. Definitive algorithm of CSP treatment is still not established. Pharmacological and operative methods are approved while expectant observation is considered unsafe due to possible risk of complications for the patient, including death.

Key words: extrauterine ectopic pregnancy, methotrexate, cesarean scar.

Introduction

An ectopic pregnancy refers to the implantation of an embryo outside of the uterus and it is one of the most serious complications in early pregnancy [1]. First reports concerning extrauterine pregnancy stem from 10th century. However, it is several hundred years later, in 1604, Jean Riolan of Paris was the first to report an authentic extrauterine, tubal pregnancy. The patient in the fourth month of her eighth pregnancy died the day after the onset of symptoms. Until the 19th century, ectopic pregnancy was

known only as a universally fatal accident [2]. In 21st century extrauterine pregnancy is still a significant cause of morbidity and mortality among women. Ectopic pregnancy constitutes 2% of all pregnancies, however the number is still rising. The rate of ectopic pregnancies has increased from 0.5% in 1970 to 2% today [3].

Abnormal pregnancy localises most frequently in oviduct, precisely in the ampulla. Non-tubal ectopic pregnancies are implanted at sites other than the fallopian tube. These pregnancies amount for less than 10% of all extrauterine pregnancies [4]. Recently, due to the rising amount of caesarean sections, new location of ectopic pregnancy has been observed — caesarean scar pregnancy (CSP). In CSP, the gestation is implanted in a previous caesarean scar [5].

Despite of the fact that CSP is the least frequent type of ectopic pregnancy, its number is rapidly rising. The first time, CSP was described in 1978 [6]. Until 2001 only 19 cases of the pregnancy located in the scar after caesarean section were reported [7]. Frequency of CSP occurrence is hard to determine. Based on 6-year observation period, Seow *et al.* determined the frequency of CSP at the level of 1: 2000 among patients after caesarean section, that equals 0.15% patients after caesarean section and 6.1% of all ectopic pregnancy localisations. No correlation between CSP and age was revealed. There was also no link between time after caesarean section and CSP, as it was observed after 6 months after caesarean section as well as after 12 years [5]. Risk for caesarean scar implantation is not clearly correlated to the number of prior caesarean sections and has not been correlated to single versus double layer closure of the hysterotomy at the time of caesarean section [8].

Two types of CSP are recognized. Type I (endogenic) — CSP with progression to the cervico-isthmic space or uterine cavity. Type II (exogenic) — CSP with deep invasion of caesarean scar defect with progression toward the bladder and abdominal cavity. The endogenic type of CSP could result in a viable pregnancy, yet with a high risk of bleeding at the placental site [9]. The accurate cause and mechanism is not well understood. We know that implantation of a pregnancy within the scar of a previous caesarean section is different from an intrauterine pregnancy with placenta accreta [8]. The pregnancy with placenta accreta is within the uterine cavity. In CSP, the gestation sac is wholly surrounded by myometrium and the fibrous tissue of the scar, quite separate from the endometrial cavity [10].

The most practical and effective technique to diagnosis CSP is transvaginal ultrasonography. The ultrasonographic criteria of CSP are: a) absence of intrauterine gestation and empty cervical canal with clearly visible endometrium, b) A gestational sac located in the anterior isthmus, surrounded by the caesarean scar tissue, separated from the uterine cavity, c) gestational sac with or without fetal pole in presence or absence of cardiac activity [11].

Clinical manifestation of the pregnancy implanted in the scar after caesarean section may vary from symptomless to sharp abdominal pain with vaginal bleeding

even to hypovolemic shock [12]. In analysis of 57 cases of CSP, 36.8% patients did not have any symptoms, while in 24.6% cases sharp abdominal pain was the main complaint [13, 14].

Materials and Methods

This is a retrospective review with data collection on 23 women with diagnosed CSP who were hospitalized in the Clinic of Endocrinological Gynaecology and Gynaecology Jagiellonian University Medical College in Cracow between 2015 and 2018. The article presents treatments of patients with caesarean scar pregnancies, in which the first-trimester diagnosis was documented by transvaginal sonography, and their prospectively documented clinical courses and outcomes. Standard anthropometric data and medical history were obtained from each subject.

Results

A total of 23 women were included in the analysis. Subjects' mean age was 33.87 ± 3.31 years. 10 patients underwent one caesarean section (43%), 11 patients-two caesarean sections (48%) and two patient — four caesarean sections (8.6%). In all the patients' diagnosis were made based on ultrasound examination. In 18 patients, embryo with present heart rate was found. In one patient embryo without heart rate was revealed. In the rest of the patients gestational sack without echo of the embryo was found. In 43% cases, diagnosis was made in 6th week of pregnancy. The mean bHCG level on admission was 36444 mIU/ml. The mean gestational age was 7 weeks. Patients admitted to the Department were hemodynamically stable, in good general condition. In 9 patients (39%) vaginal bleeding of poor intensity was observed, 4 patients (17%) reported abdominal pain. The rest of the patients (43%) did not report any complaints.

One of the hospitalised patient conceived after in vitro fertilisation procedure (IVF). The bHCG level on admission was 86497 mIU/ml. Ultrasound examination revealed triplet heterotopic pregnancy: diamniotic twin pregnancy in caesarean scar and intrauterine, alive singleton pregnancy. Three gestational sacks were described, among them one of normal intrauterine location: GS = 22 mm, CRL = 7.7 mm, FHR = 130/min. Two sacks were localised in the caesarean scar area. One gestational sack GS = 12 mm was empty with normal decidual sign. The second gestational sack GS = 27 mm contained an embryo with CRL = 5.7 mm that equals gestational age of 6 weeks 2 days with present FHR = 126/min. The patient was classified for selective embryo reduction. In general anaesthesia, under control of transabdominal ultrasound, 2.5 ml of potassium chloride (KCl) was administered to each gestational sack localised in caesarean scar. In consecutive ultrasound examinations stable activity of trophoblast in caesarean scar was found and correctly developing intrauterine

pregnancy was confirmed. Around the date of delivery, the patient had a caesarean section. The operation underwent without complications and the patient delivered a healthy new-born.

Among hospitalised patients, the highest gestational age of abnormally implanted pregnancy was 14 weeks. The patient was admitted to the hospital with abdominal pain in the area of caesarean scar without bleeding. Ultrasound examination revealed living pregnancy with FHR = 145/min, BPD = 30.4 mm that was equal 15 weeks 4 days. Trophoblast was localised in more than 50% in protruding caesarean scar dehiscence. The patient was classified for operative treatment. After opening of the abdomen and urine bladder preparation, the foetus in the amniotic sack with trophoblast partly present in the abdominal cavity, partly in caesarean scar was taken out. Uterine curettage was performed. Uterine muscle was sutured with double-layer stitches.

36-year old patient with diagnosed caesarean scar pregnancy, was admitted to the department with vaginal bleeding. Ultrasound examination revealed gestational sack with an echo of an embryo with CRL = 2.2 mm that equals 5 weeks 5 days with present FHR. During hospitalisation death of the embryo was diagnosed. The patient was administered 200 mg methotrexate systemically. Despite of the treatment, rise in bHCG levels was observed — from 19343 mIU/ml to 25568 mIU/ml. Under general anaesthesia and control of the ultrasound, the content of the uterine cavity was evacuated by suction. After the treatment satisfying drop in bHCG level was observed.

37-year old patient, who had undergone four caesarean sections, was diagnosed with obsolete caesarean scar pregnancy. On admission she was reporting fatigue and vaginal spotting. b-HCG level was 42000 mIU/ml. Due to the rise of bHCG level during hospitalisation, decision about hysteroscopic evacuation of the pregnancy and electrocoagulation of the niche was made. The procedure was performed under general anaesthesia, without any complications.

In two cases, collapsing gestational sack without an embryo was observed. Both patients presented with vaginal bleeding. In the first patient, decrease of bHCG level from 480 mIU/ml to 72 mIU/ml was observed. Control ultrasound revealed no gestational sack in caesarean scar, therefore the patient did not require any intervention. In the second case, bHCG level on admission was equal 12 881 mIU/ml, after two days — 16 903 mIU/ml despite no observed differences in ultrasound examination. Due to the rise of bHCG, the patient was classified for hysteroscopic evacuation of caesarean pregnancy. After the procedure the bHCG level was 7522 mIU/ml.

In a 30-year-old-patient, after four caesarean sections, a gestation sack with an embryo (CRL = 7.2 mm) without FHR was observed. A conservative treatment was implied. 100 mg of methotrexate was administered systemically. After this procedure, Foley's catheter was put into uterine isthmus for 24 hours.

The other patients hospitalised due to caesarean pregnancy with present FHR were between 6th and 8th week of pregnancy. The highest bHCG level was 117 210 mIU/ml, the lowest 993 mIU/ml. In ultrasound examination highest CRL was equal 15.5 mm, smallest — 5.5 mm. Conservative treatment was implied. Under general anaesthesia, transvaginal ultrasound transducer was inserted and after that a special puncture needle was placed in gestational sack. Fluid was partially removed by suction. Subsequently 5 ml of 10% KCl or 2 ml of 15% KCl and 50 mg methotrexate were administered into the sack. After that, 100mg of methotrexate was administered systemically as a continuation of the treatment. Two patients required additional 200 mg of methotrexate administered systemically due to abnormal bHCG level after the procedure. In two cases, patients had to be rehospitalized because of vaginal bleeding with occurred about 4 and 6 weeks after hospitalizations ending. In both cases, hysteroscopy with electrocoagulation od caesarean scar was performed without complications.

Discussion

Definitive algorithm of CSP treatment is still not established. Pharmacological and operative methods are approved while expectant observation is considered unsafe due to possible risk of complications for the patient, including death [8, 13]. It was reported that in half of the patients with no implemented treatment uterine rupture was the consequence, with consequent hysterectomy [15]. It is suggested to choose pharmacological or operative treatment in hemodynamically stable patients with CSP as a fertility preserving method [13].

Pharmacological treatment options include systemic or local administration of methotrexate (MTX), chloride potassium, hyperosmolar glucose solution, prostaglandin or combination of the medications in laparoscopic assist or its direct injection to the gestational sack under transabdominal or transvaginal ultrasound control.

Numerous reviews report local or systemic methotrexate administration as a most effective way of treatment. Single dose of 50 mg/m^2 administered i.m. may be safe in CSP treatment up to 8th week of pregnancy with no FHR [12]. It is considered that MTX treatment is effective when serum bHCG levels are lower than 5000 mIU/ml [13, 14]. However, some authors criticize systemic MTX administration as an effective treatment method due to the fact, that fibrous tissue is poorly vascularised therefore drug penetration is insufficient. They suggest local administration of MTX directly to gestational sack [16]. MTX treatment alone as first line treatment showed low success rate [17].

As per our experience, the most effective and safe method of CSP treatment is locally administered 5 ml 10% KCl and 50 mg MTX into the gestational sack and

100 mg MTX systemically in CSP between 6th–8th weeks pregnancy (in our cases CRL <21 mm). After this treatment, we observed satisfying decrease in bHCG level.

Operative methods include laparotomy, uterine artery embolization, hysteroscopy and curettage with gestational sack suction. They may be undertaken in patients hemodynamically unstable or when pharmacological treatment proves ineffective. Combination of pharmacological and operative treatment is also implemented to increase success of treatment and limit risk of complications [16].

In our case, we only once were forced to make a surgery because of acute abdominal pain in patient in 14th weeks pregnancy in caesarean scar.

One of the first methods used in CSP is uterine curettage with secondary intrauterine insertion of a Foley catheter [18]. Vo and colleagues carried out a study to demonstrate the efficacy of management for CSP up to 8 weeks' gestation using ultrasound-guided Foley balloon catheter placement combined with dilation and curettage. In their research, the Foley balloon catheter was placed inside the uterus under ultrasound guidance and was left in place for 24 h. Afterward, the patient underwent ultrasound-guided dilation and curettage. Follow-up to confirm success included serial blood draws to measure beta-human chorionic gonadotropin (bHCG) levels until a value of 0, and routine ultrasounds to confirm absence of a gestational sac and no evidence of vascularity at the site of the caesarean section scar. More than 90% their patients were successfully treated with this methods. They claimed that these treatment is more effective compared to standard treatment with methotrexate injection [19]. We proceed in a similar way in case of embryo without FHR but in all incidents we administrata MTX systemically as intensification of treatment.

Similar research was performed by Timor-Tritsch *et al.* The aim of them study was to describe the placement of a cervical ripening double-balloon catheter as a novel treatment in patients with caesarean scar to terminate the pregnancy and at the same time prevent bleeding by compressing the blood supply of the gestational sac. The authors claimed that the double balloon is a successful, minimally invasive and well-tolerated single treatment for caesarean scar pregnancy and does not require any additional invasive therapies. However, the study has to be validated on a larger patient population [20].

Liu *et al.* analysed which method is safer and more effective in CSP treatment. Between 2005–2013, 38 patients with diagnosed CSP were treated with uterine artery embolization and curettage, while 26 patients were given methotrexate systemically with consequent curettage. Based on statistical analysis of blood loss during the procedure, time required to normalisation of bHCG level and time of hospitalisation, uterine artery embolization with curettage proved as a better method of CSP treatment [21].

Jurcovic *et al.* made similar observations based on 232 cases of CSP diagnosed in the first trimester, treated between 1997–2004. 82% of the patients were treated

by vacuum aspiration with ECCU under ultrasound control. 4.7% patients required blood transfusion due to massive bleeding, while in one case hysterectomy was performed due to haemorrhage. In part of the patients modified Shirodkar suture was performed [22]. Zheng *et al.* in their retrospective analysis based on 43 cases of CSP patients report; that in 91% patients the suction curettage under ultrasound control was the successful treatment method. According to the authors, neither uterine scar thickness nor time from caesarean section had an influence on the outcome. Only CRL was statistically significant. The method proved effective and safe in CRL under 6 mm [23]. On the contrary, Feng *et al.* in their study based on 30 cases of CSP report that in 25 patients who underwent prophylactic uterine artery embolization with methotrexate administration and subsequent ECCU under ultrasound control, no complications were observed, suggesting that this method is most efficient and safe [24].

Different approach was presented in another research. It reports results of CSP treatment with the use of hysteroscopy in patients with myometrium thickness greater than 3 mm. According to the authors, this method is safe, efficient, requires short hospitalisation period and preserves fertility. Hysteroscopy may deal as a diagnostic method to confirm the preliminary diagnosis Due to authors operative hysteroscopy might be recommended as a first-line treatment modality for patients with a CSP, especially when myometrium thickness between bladder and gestational sac is more than 3 mm [25]. Similar opinion have Kim and colleagues. The authors claimed that wedge resection (100%) and hysteroscopy (66.7%) were relatively safe and they were the most successful treatment modalities in their retrospective study [16].

Xiao *et al.* carried out a retrospective case-control study to compare diffrent methods of treatment for CSP. The aim of their study was to explore the optimal intervension for CSP. 103 patients diagnosed with CSP received 1 of the 3 treatments: I. local or systemic methotrexate injection and surgery (MTX+Surg), II. uterine arterial embolization and surgery (UAE+Surg), III. only surgery (Surg-only). They compared their therapeutic effects and their follow-up results. Only, the initial bHCG levels was highest in the MTX+Surg group. Exept for bHCG levels, clinical characteristic of the groups were similar. It was found that the intraoperative hemorrhage was highest in the Surg-only group (16.67%), compared to the MTX+Surg group (15.38%) and the UAE+Surg group (0%). The incidence of intrauterine adhesions was highest in the UAE+Surg group (20%), compared to the MTX+Surg group (0%) and the Surg only group (0%). The incidence of embryo residue was highest in Surg-only group (21.43%). They came to conclusion that MTX injection with surgery might be the best treatment for CSP patients [26].

There are few datas about CSP without intervention. However, there are still reports about delayed diagnosis of CSP. Jo and colleagues described a case of confirmed a CSP with a live fetus with a CRL of 4.83 cm, corresponding to 11 weeks

pregnancy. They had to inject 50 mg of methotrexate in the amniotic sac under transabdominal ultrasonographic guidance but FHR was still observed 2 days later so they decided to perform open laparotomy because of the possibility of massive bleeding [27]. In the other hand, in systematic review and meta-analysis, it was explored the outcomes in patients managed expectantly following the diagnosis of CSP. 17 studies were analyzed. It was found that CSP with FHR managed expectantly is associated with a high burden of maternal morbidity including severe hemorrhage, early uterine rupture, hysterectomy. Despite this, a significant proportion of pregnancies complicated by CSP may progress to, or close to, term, thus questioning whether termination of pregnancy should be the only therapeutic option offered to these patients. Expectant management of CSP with no FHR might be a reasonable option in view of the low likelihood of maternal complications requiring intervention, although close surveillance is advisable to avoid adverse maternal outcome [28].

Conclusion

Cesarean scar pregnancy is an iatrogenic disease. Despite the fact the frequency of cesarean scar pregnancy increases, CSP still represents a rare but serious pregnancy pathology [29]. CSP is a life-threatening condition with high risk of serious complications, therefore should be early diagnosed and treated and it should be managed with respect to preserve fertility [29]. Treatment of CSP is challenging. Because of definitive consensus of CSP treatment is still not established — the type of treatment method depends on many factors such as size of pregnancy, presence or absence of uterine continuity, bHCG level, the possibility of further fertility and patient's hemodynamic state and should be based on the experience of the treatment centre.

Disclosures

The authors declare that they have no competing interests.

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Conflict of interest

None declared.

List of abbreviations

bHCG — beta-human chorionic gonadotropin
BPD   — Biparietal Diameter
CRL   — Crown-Rump Length
FHR   — Fetal Heart Rate
KCl   — potassium chloride
MTX   — Methotrexate
SCP   — caesarean scar pregnancy
UAE   — uterine arterial embolization

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