Int J Clin Exp Med 2017;10(3):4780-4786
www.ijcem.com /ISSN:1940-5901/IJCEM0044666

Original Article

Contrast-enhanced ultrasound-assisted lauromacrogol sclerosing therapy as a novel method for treatment of cesarean scar pregnancy

Mingkui Li[1,2], Yiqing Zhang[1], Rongrong Ru[1], Qinjuan Wang[1], Jiaying Xu[1], Dong Xu[3]

[1]Department of Ultrasound, Zhejiang Xiaoshan Hospital, Hangzhou, China; [2]Trying Medicine Doctors Group, Hangzhou, China; [3]Department of Ultrasound, Zhejiang Cancer Hospital, Hangzhou, China

Received November 20, 2016; Accepted January 6, 2017; Epub March 15, 2017; Published March 30, 2017

Abstract: Cesarean scar pregnancy (CSP) is a rare form of ectopic pregnancy taking place at the site of a previous uterine scar, with the increased rate. Contrast-enhanced ultrasound (CEUS) has been shown to improve the sensitivity of plain ultrasonography, and further developments of CEUS technique have significantly increased its clinical utility. Lauromacrogol is widely recognized as the international ideal sclerosing agent. This study investigated the clinical efficacy and safety of CEUS-assisted lauromacrogol sclerosing therapy for the treatment of CSP. 37 patients with CSP were enrolled. Under the CEUS, the lauromacrogol sclerosing therapy was performed, followed by embryo forceps curettage under the guidance of ultrasound. The overall treatment outcome, complications, CEUS findings before and after lauromacrogol sclerosing therapy, changes of β-HCG level and follow-up results were observed. Results showed that, all patients successfully received the CEUS-assisted lauromacrogol sclerosing therapy and embryo forceps curettage. The success rate of treatment was 100%. There was no severe complication such as massive hemorrhage during and after treatment. CEUS findings showed that, after lauromacrogol sclerosing, 94.6% (33/37) scar defects were present as patchy inhomogeneous enhancement, and 5.4% (2/37) as ring enhancement at CEUS, with significant difference compared with before ($P < 0.01$). The β-HCG level was obviously decreased after lauromacrogol sclerosing therapy and after embryo forceps curettage. β-HCG became normal 7-28 days (mean 14.2 ± 2.1 days) after embryo forceps curettage. CEUS-assisted lauromacrogol sclerosing therapy is a safe and effective technique for the treatment of CSP.

Keywords: Cesarean scar pregnancy, contrast enhanced ultrasound, lauromacrogol, sclerosing, forceps curettage

Introduction

Ectopic pregnancy (EP) is a life-threatening condition that remains the leading cause of death in the first trimester of pregnancy. It is most commonly located in the ampullary portion of the fallopian tube and rarely in unusual sites such as the cervix, cesarean scar, anomalous rudimentary, horn of the uterus and peritoneal abdominal cavity [1]. Although the occurrence of EP has decreased markedly in recent years because of the great improvement in treatment, it still needs great attention because of the high death rate. Cesarean scar pregnancy (CSP) is a rare form of EP taking place at the site of a previous uterine scar. With the increased rate of cesarean section in China in recent years, the incidence of CSP is also on the rise, reaching 1/1800 to 1/2216 [2]. CSP has serious complications and a high death rate when the embryo directly implants in the uterine cesarean scar that lacks the normal muscle layer and tunica intima [3]. With the progression of pregnancy, villi erode local blood vessels, or even penetrate into the uterus in some cases, leading to hysterorrhexis and threatening the life. So, it is necessary to find and solve the problem promptly. Conventional treatment includes medical therapy, uterus portion resection and hysterectomy. Currently, uterine artery embolization combined with curettage or methotrexate treatment is used, but the disadvantages of this treatment are obvious such as high cost, difficult technology, and the possibility of hemorrhage.

Ultrasound is the most user-dependent imaging modality that is convenient, real-time and popu-

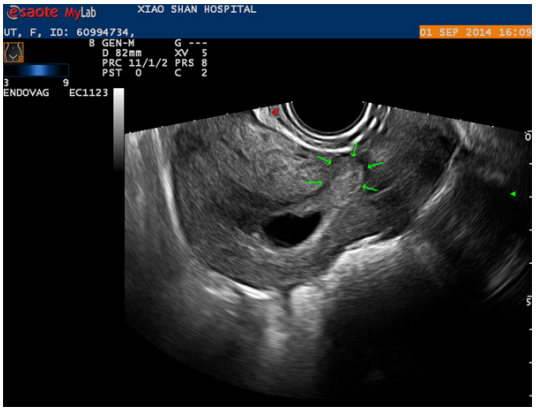

Figure 1. B-mode ultrasound was performed to confirm the location and internal echo of the lesion, showing that the range of villi implant was larger than 50% of the cesarean scar.

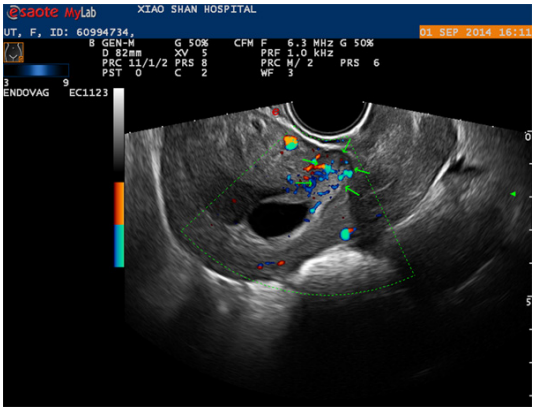

Figure 2. Color Doppler mode ultrasound was performed to observe the blood flow information of the lesion, showing abundant color flow around the cesarean scar.

lar for preoperative assessment and biopsy guidance. Contrast-enhanced ultrasound (CEUS) has shown to improve the sensitivity of plain ultrasonography. Recently, further developments of CEUS technique have significantly increased its clinical utility. Continuous mode, low mechanical index scans performed with harmonic imaging and contrast specific software appears as a very useful technique for the visualization of both macro- and microcirculation with depiction of lesion vascularisation [4]. Lauromacrogol is widely recognized as the international ideal sclerosing agent, which has been used to varicose veins, venous malformation, sclerotherapy hemorrhoids and other diseases [5, 6]. This study investigated the clinical efficacy and safety of CEUS-assisted lauromacrogol sclerosing therapy for the treatment of CSP. The objective was to provide a reference for its further clinical application.

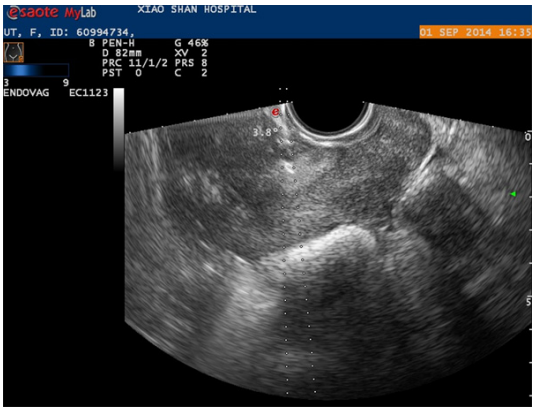

Figure 3. The lauromacrogol sclerosing therapy was applied under transvaginal ultrasound.

Patients and methods

Patients

37 patients (mean age 33, range 27-42 years) who were diagnosed with CSP by transvaginal ultrasound in our hospital between April 2012 and May 2013 were enrolled in this study. All patients had the symptom of irregular vaginal bleeding and a 3-14-year history of cesarean section using a transverse incision of the lower uterine segment. The mean menopause time of these patients was 44 days (30-67 days), and the range of serum human chorionic gonadotropin (β-HCG) was 2476-122444 U/L (mean 6589 ± 567.5 U/L). All patients received gynecological examination, serum β-HCG, blood and urine routine examination, blood coagulation function test, liver/kidney function test, and electrocardiography (ECG). CEUS was performed before sclerosing therapy and 12-24 hours after sclerosing therapy in all patients. The study protocol was approved by the Ethics Committee of Zhejiang Xiaoshan Hospital. Informed consent was obtained from all participants after explanation of the procedure and purpose of the study to all of them.

Ultrasound

ESAOTE medical diagnostic ultrasound system type My Lab90 was used with a transvaginal probe fitted with a 3-9 MHz transducer, and

Table 1. CEUS findings before and after lauromacrogol sclerosing therapy

CEUS findings		Cases	Rate	P
Ring enhancement	Before therapy	33	89.2%	< 0.01
	After therapy	2	5.4%	
Patchy inhomogeneous enhancement	Before therapy	4	10.8%	< 0.01
	After therapy	35	94.6%	

contrast Tuned Imaging (CnTI) function was active in the system. The transducer was covered with a condom filled with ultrasonic conducting gel. The procedure was performed with the patient lying in the lithotomy position. All patients received routine transvaginal ultrasound scan of the uterus, ovary and pelvis. The location, size, shape, internal echo and relation of the lesion with the surrounding tissues were observed and recorded. At the same time, color and power Doppler ultrasonography was used to observe flow information of the lesion (**Figures 1**, **2**).

During the performance of conventional ultrasound, the contrast medium SonoVue (Bracco, Italy) consisting of inert gas (SF6) with lecithin was prepared. Before use, it needs to be suspended in physiological saline for injection. Most SonoVue microbubbles are smaller than 8 μm. They are stabilized by the inclusion of a trace amount of lecithin, which forms a molecular film around the microbubbles that lowers their surface tension. SonoVue dried powder in the pack with 5 ml physiological saline was used for microbubble suspension. The procedure was performed by firstly activating CnTI in the ultrasound system, observing the cesarean section scar and scar defect, and then using 1.2 ml suspension for quick injection via the elbow vein and 5 ml physiological saline for quick continued injection. It was noteworthy that the SonoVue suspension was prepared for use by shaking for 20 seconds before injection. Continuous dynamic images for contrast-enhanced ultrasound were acquired, and stored on a hard disk for offline analysis.

The criteria proposed by Godin et al [7] were used for the diagnosis of CSP in this study, including i) no cystic echo in the palace cavity; ii) no cystic echo in the cervical canal; iii) the presence of the gestational sac in the anterior uterine isthmus; and 4) the presence of thin muscle between the capsule and the bladder.

Lauromacrogol sclerosing therapy and embryo forceps curettage

The patient receiving the transvaginal ultrasound-guided interventional therapy was advised to lie in the lithotomy position (**Figure 3**) for the convenience of determining the location, size and shape of CSP by CEUS. After routine surgical skin preparation and draping, an 18G needle was inserted under the guidance of transvaginal ultrasound to inject 10 ml lauromacrogol at multipoints around the gestational sac and at the same time extract the cystic fluid in it. After 12-24 h from lauromacrogol sclerosing therapy, the embryo forceps curettage was performed under the guidance of ultrasound.

Observation indexes

The overall treatment outcome and complications were evaluated. The CEUS findings before and after lauromacrogol sclerosing therapy were observed. In addition, the β-HCG data before lauromacrogol sclerosing therapy, 12 h after lauromacrogol sclerosing therapy and 24 h after embryo forceps curettage were recorded.

Follow-up

All patients were followed up for a mean period of 2.7 months (range 1.5-4) after the procedure for menstrual cycles, incontinence, bleeding and healing on the clinical basis.

Statistical analysis

All dynamic images were diagnosed by two experienced ultrasound doctors who had more than five-year clinical experience. The CEUS characters of the scar defects were observed to determine the location, size, shape and relation with the surrounding tissues. The chi-squared test was used to determine the diagnostic value of CEUS on CSP before and after lauromacrogol sclerosing therapy. Statistical values of $P < 0.05$ were considered statistically significant. Statistical analysis was performed using the SPSS 13.0 statistical package (SPSS. Inc. Chicago, IL, USA).

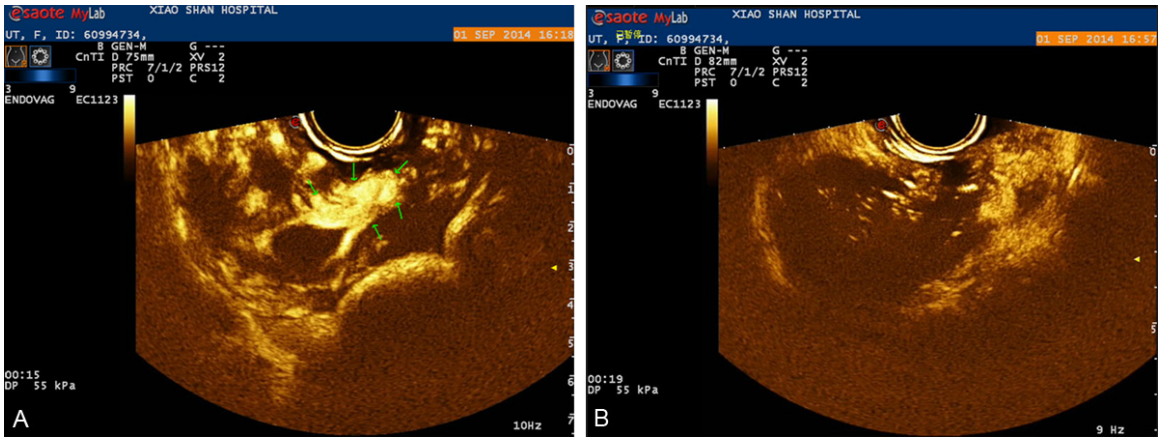

Figure 4. CEUS performance was observed before (A) and after (B) the lauromacrogol sclerosing therapy.

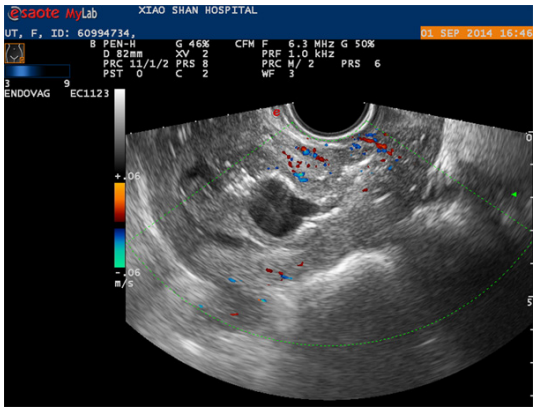

Figure 5. No obvious color flow was observed around cesarean scar after the lauromacrogol sclerosing therapy.

Results

Overall treatment outcome

All 37 patients successfully received the CEUS-assisted lauromacrogol sclerosing therapy, and the embryo forceps curettage was successfully performed within 12-24 h after lauromacrogol sclerosing therapy. The success rate of treatment was 100%. The postoperative pathology examination showed that, the curettage materials were the degenerated villi and decidua. The mean intra-operative blood loss was 10 ml.

Complications

Lauromacrogol sclerosing therapy-related complications were dizziness, nausea and acid reflux. In this study, 7 of the 37 patients (18.9%) complained of dizziness and nausea. After symptomatic treatment, these were relieved. There was no severe complication such as massive hemorrhage during and after treatment.

CEUS findings before and after lauromacrogol sclerosing therapy

CEUS findings before and after lauromacrogol sclerosing therapy were summarized in **Table 1**. The presence or absence of ring enhancement was the main character of contrast-enhanced ultrasound that best discriminated between defects classified by the ultrasound examiner. Before lauromacrogol sclerosing therapy, 89.2% (33/37) scar defects were present as quick ring enhancement, and the other 10.8% (4/37) were present as patchy inhomogeneous enhancement, where the remaining myometrium over the defect showed early, rapid and inhomogeneous enhancement, linked to the gestational sac wall. After the therapy, 94.6% (33/37) scar defects were present as patchy inhomogeneous enhancement, and 5.4% (2/37) as ring enhancement at CEUS. The difference between them was statistically significant ($P < 0.01$) (**Figures 4**, **5**).

Changes of β-HCG level after lauromacrogol sclerosing therapy and after embryo forceps curettage

β-HCG data before lauromacrogol sclerosing therapy, 12 h after lauromacrogol sclerosing therapy and 24 h after embryo forceps curettage were observed. Based on β-HCG data before lauromacrogol sclerosing therapy, the decline after lauromacrogol sclerosing therapy and after embryo forceps curettage were ana-

Table 2. β-HCG decline 12 h after lauromacrogol sclerosing therapy and 24 h after embryo forceps curettage

β-HCG	β-HCG decline (n, %)		
	≤ 30%	30%-90%	≥ 90%
12 h after lauromacrogol sclerosing therapy	2 (5.4)	30 (81.1)	5 (13.5%)
24 h after embryo forceps curettage	0 (0%)	2 (5.4%)	35 (94.6%)

lyzed. After 12 h from lauromacrogol sclerosing therapy, there were 2 (5.4%), 30 (81.1%) and 5 (13.5%) cases with β-HCG decline by ≤ 30%, 30%-90% and ≥ 90%, respectively. After 24 h from embryo forceps curettage, there were 0, 2 (5.4%) and 35 (94.6%) cases with β-HCG decline by ≤ 30%, 30%-90% and ≥ 90%, respectively (**Table 2**).

Outcomes of follow-up

The follow-up was successfully performed in all patients. There was no reported incontinence during follow-up. In all patients, β-HCG became normal 7-28 days (mean 14.2 ± 2.1 days) after embryo forceps curettage. All patients had recovered normal menstruation during the follow-up period.

Discussion

The increased rate of cesarean section and associated complications has awakened an interest in cesarean section scars [8-10]. Because of the gestational sac, the remaining myometrium over the defect is thin, which may result in bleeding, hemorrhagic shock and the risk of death. As there are no generally accepted guidelines for the treatment of CSP, it is significant to find a safe and effective therapy method. Cesarean section scar defects can be detected by transvaginal ultrasound [11, 12]. Transvaginal ultrasound also plays a definite role in early diagnosis, early therapy and relief of CSP-associated complications [13]. However, it is usually difficult for unenhanced ultrasound to determine the number and size of scar defects or the thickness of the remaining myometrium over the defect [11, 12, 14], and therefore a more sensitive diagnostic technique has to be developed. Contrast-enhanced ultrasound provides a new method, because it can clearly show the microcirculation information of the defect. CEUS is considered essential for evaluating cesarean section scar defects, and is also useful for assessing the location, number, size and relation with the surrounding tissues, in particular for detecting and distinguishing the gestational sac implants or necrotic tissues, and checking the thickness of the remaining myometrium as well to get evidence for treatment.

This study has determined the agreement of CEUS performed via the transvaginal approach before and after lauromacrogol sclerosing therapy with regard to the number, size and shape of cesarean section scar defects. Before lauromacrogol sclerosing therapy, scar defects were present as quick ring enhancement caused by blood flow around the gestational sac implant. After the therapy, the defects were present as patchy inhomogeneous enhancement, because lauromacrogol injection closed the vessel and reduced the blood flow around the gestational sac. The characters of CEUS could give us the clue for the diagnosis of CSP and help find an appropriate treatment. To the best of our knowledge, there is no previous report about the use of CEUS to examine Cesarean section scar defects before and after lauromacrogol sclerosing therapy. Lauromacrogol is mainly used for clinical sclerosis, atrophy and hemostasis of varicose veins safely, efficiently and conveniently with no obvious toxic and adverse effects. In addition, it has a mild anesthetic effect and therefore can be used to relieve postoperative pain.

In the present study, we used lauromacrogol sclerosis as a new method to treat CSP by multi-point injection around the gestational sac, especially in tissues with rich blood perfusion as detected by color Doppler and CEUS. The defects showed “cap” hardening after sclerosing therapy, because the vessels around the gestational sac were closed and hardened. In this study, all patients received embryo forceps curettage 12-24 h after lauromacrogol sclerosing therapy, though more clinical trials are needed to confirm whether it is the optimal time for lauromacrogol sclerosing therapy. In addition, as sufficient time is needed to achieve the hardening effect of lauromacrogol, we can close the vessel to reduce bleeding. On the other hand, the possibility of vessel recanalization around the gestational sac and softening of the myometrium over the defect may increase the risk of embryo forceps curettage.

There is no generally accepted guideline for the treatment of CSP at present, although medical

treatment, uterine artery embolization and surgical treatment are usually suggested. Methotrexate (MTX) is commonly used for medical treatment of CSP, but it only applies to patients with β-HCG < 5000 U/L, gestational age < 8 weeks, and the myometrium between the defect and the bladder > 2 mm. It does not seem to be a good method for the treatment of CSP because of the high dosage, long cycle and slow effect. In addition, MTX is one chemotherapy drug with obvious toxicity on the whole body. Uterine artery embolization combined with drug therapy or curettage is a newly emerging treatment by reducing bleeding during drug therapy and curettage through blockage of the uterine blood flow supply. But it is not commonly used in clinical practice due to the high risk, difficult technology and high cost. In addition, it may cause some complications such as ectopic embolism and ovarian vein thrombosis, and affect the ovarian function, leading to postoperative bleeding.

Surgical treatment of CSP includes curettage, hysteroscopy or laparoscopic resection and hysterectomy. Curettage is usually performed in combination with medical therapy or uterine artery embolization to reduce bleeding. Hysteroscopy is usually applied to early pregnancy incision to minimize bleeding or lower β-HCG [15]. Laparoscopy is also an ideal method for the treatment of CSP [16, 17], especially under the guidance of ultrasound, because it can get an accurate position [18] and cause less damage, but there is still the possibility of bleeding during the procedure. Patients with a history of abdominal and pelvic adhesion, easily could receive laparoscopic puncture, this was related to the result of the operation [19]. Laparoscopic resection or hysterectomy is applicable to patients with uncontrolled vaginal bleeding, or those who fail conservative treatment or have no fertility requirement. It is usually used in an emergency situation to save life. The disadvantages of this method are relatively large surgical damage, slow postoperative recovery and associated complications.

There is no optima clinical treatment for CSP at present in terms of safety, quickness and effectiveness. In the present study, we used a new method of combining lauromacrogol sclerosing therapy with embryo forceps curettage to treat CSP by closing the vessels around the gestational sac with lauromacrogol injection guided by transvaginal ultrasound. The new technique is real-time and safe. In addition, the thickness of the remaining myometrium over scar defects and height of scar defect [20] could be detected more clearly by CEUS. All patients in our series received the procedure of sucking the gestational sac after the sclerosing therapy. In cases where the scar defect was hard, we applied embryo forceps curettage so that the gestational sac was eliminated more easily and bleeding was reduced. With ultrasound guidance, embryo forceps curettage on time is still the primary procedure that we need to consider. Curettage could be performed 12-24 h after sclerosing therapy, but for uterine artery embolization, the intervention time was 24-72 h until the condition was stabilized for the sake of achieving a better outcome. All 37 patients in our series who received lauromacrogol sclerosing therapy underwent embryo forceps curettage successfully without severe complications. Therefore, we believe that lauromacrogol sclerosing therapy combined with embryo forceps curettage is a safe and effective new therapy for CSP.

Serum β-HCG is a biochemistry index to assess the status of CSP. It can be measured during the therapy. To reduce the risk of bleeding, serum β-HCG should be detected in all patients who are scheduled to receive medical therapy, uterine artery embolization, hysteroscopy or laparoscopy. According to our experience, serum β-HCG should be monitored meticulously throughout the procedure even in cases where it is maintained at a relatively low level. In our series, serum β-HCG data decreased by less than 10% in 90% of our patients 24 h after embryo forceps curettage, as compared with the baseline level. This could be used as an index for therapy assessment.

In conclusion, CEUS-assisted lauromacrogol sclerosing therapy is safe and effective for the treatment of CSP, and has some advantages over the conventional treatment. Firstly, it is real-time and safe under ultrasound guidance. Secondly, the dose of lauromacrogol is relatively low with no significant toxic effect. In addition, the vessels around the gestational sac are closed by lauromacrogol injection, thus facilitating curettage, devoid of massive bleeding. Finally, the procedure is easy to follow with a low risk, a low cost and a high curative effect. As the sample size of the present study is rela-

tively small, more larger-sample clinical trials are needed to verify our conclusion.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Dong Xu, Department of Ultrasound, Zhejiang Cancer Hospital, 38 Guangji Road, Gongshu, Hangzhou 310022, China. E-mail: xdzjzlyy@126.com

References

[1] Younger JB. Diagnosis and management of ectopic pregnancy. Ala J Med Sci 1986; 23: 444-446.

[2] Rotas MA, Haberman S, Levgur M. Cesarean scar ectopic pregnancies: etiology, diagnosis, and management. Obstet Gynecol 2006; 107: 1373-1381.

[3] Ben Nagi J, Ofili-Yebovi D, Sawyer E, Aplin J, Jurkovic D. Successful treatment of a recurrent cesarean scar ectopic pregnancy by surgical repair of the uterine defect. Ultrasound Obstet Gynecol 2006; 28: 855-856.

[4] Claudon M, Cosgrove D, Albrecht T, Bolondi L, Bosio M, Calliada F, Correas JM, Darge K, Dietrich C, D'Onofrio M, Evans DH, Filice C, Greiner L, Jäger K, Jong Nd, Leen E, Lencioni R, Lindsell D, Martegani A, Meairs S, Nolsøe C, Piscaglia F, Ricci P, Seidel G, Skjoldbye B, Solbiati L, Thorelius L, Tranquart F, Weskott HP, Whittingham T. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS)-update 2008. Ultraschall Med 2008; 29: 28-44.

[5] Wang Z, Yang X, Wu L, Shi H, Lu Y, Yuan B, Wang Y, Wang F. Blue rubber bleb nevus syndrome: treatment of lesions in the small intestine with repeated injection of lauromacrogol. Gastrointest Endosc 2015; 81: 1274-1275.

[6] Xue J, Geng X. Curative effect of lauromacrogol and absolute ethyl alcohol injection guided by ultrasound on simplex hepatic cyst. Pak J Pharm Sci 2015; 28 Suppl 2: 697-700.

[7] Godin PA, Bassil S, Donnez J. An ectopic pregnancy developing in a previous caesarian section scar. Fertil Steril 1997; 67: 398-400.

[8] Betrán AP, Merialdi M, Lauer JA, Bing-Shun W, Thomas J, Van Look P, Wagner M. Rates of cesarean section: analysis of global, regional and national estimates. Paediatr Perinat Epidemiol 2007; 21: 98-113.

[9] Ash A, Smith A, Maxwell D. Caesarean scar pregnancy. BJOG 2007; 114: 253-263.

[10] Getahun D, Oyelese Y, Salihu HM, Ananth CV. Previous cesarean delivery and risks of placenta previa and placental abruption. Obstet Gynecol 2006; 107: 771-778.

[11] Ofili-Yebovi D, Ben-Nagi J, Savyer E, Yazbek J, Lee C, Gon-zalez J, Jurkovic D. Deficient lower-segment cesarean section scars: prevalence and risk factors. Ultrasound Obstet Gynecol 2008; 31: 72-77.

[12] Vikhareva Osser O, Jokubkiene L, Valentin L. High prevalence of defects in Cesarean section scars at transvaginal ultrasound examination. Ultrasound Obstet Gynecol 2009; 34: 90-97.

[13] Armstrong V, Hansen WF, Van Voorhis BJ, Syrop CH. Detection of cesarean scars by transvaginal ultrasound. Obstet Gynecol 2003; 101: 61-65.

[14] Li N, Zhu F, Fu S, Shi X. Transvaginal ultrasound-guided embryo aspiration plus local administration of low-dose methotrexate for caesarean scar pregnancy. Ultrasound Med Biol 2012; 38: 209-213.

[15] El-Mazny A, Abou-Salem N, El-Sherbiny W, El-Mazny A. Insulin resistance, dyslipidemia, and metabolic syndrome in women with polycystic ovary syndrome. Int J Gynecol Obstet 2010; 109: 239-241.

[16] Roa Barrios M, Arata-Bellabarba G, Valeri L, Velázquez-Maldonado E. Relationship between the triglyceride/high-density lipoprotein-cholesterol ratio,insulinresistance index and cardiometabolic risk factors in women with polycystic ovary syndrome. Endocrinol Nutr 2009; 56: 59-65.

[17] Morans LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2010; 16: 347-363.

[18] Lankarani M, Valizadeh N, Heshmat R, Peimani M, Sohrabvand F. Evaluation of insulin resistance and metabolic syndrome in patients with polycystic ovary syndrome. Gynecol Endocrinol 2009; 25: 504-507.

[19] Menada Valenzano M, Lijoi D, Mistrangelo E, Costantini S, Ragni N. Vaginal ultrasonographic and hysterosonographic evaluation of the low transverse incisin after caesarean section: correlation with gynaecological symptoms. Gynecol Obstet Invest 2006; 61: 216-222.

[20] Wang CB, Chiu WW, Lee CY, Sun YL, Lin YH, Tseng CJ. Cesarean scar defect: correlation between cesarean section number, defect size, clinical symptoms and uterine position. Ultrasound Obstet Gynecol 2009; 34: 85-89.