

Management of Ectopic Pregnancy in Unusual Locations: Five-Year Experience in A Single Center

Ismet Hortu, Levent Akman, Ali Akdemir, Mete Ergenoğlu, Ozgur Yeniel, Fatih Sendag

Ege University School of Medicine
Department of Obstetrics and
Gynecology, Izmir, Turkey

*Corresponding Author: Ismet Hortu,
Ege University School of Medicine
Department of Obstetrics and
Gynecology, Izmir, Turkey
E mail: ismethortu@yahoo.com

ABSTRACT

Objectives: The aim of this study is to evaluate the diagnostic and therapeutic strategies in patients with unusual ectopic pregnancy and present a brief review of the literature.

Patients and methods: Twenty- seven cases with ectopic pregnancy in unusual locations were classified in five groups; two cesarean scars, six cervical, six cornual, two ovarian, and eleven heterotopic pregnancies. All of data were retrospectively analyzed according to the patient's gestational week, gestational sac location, obstetric history, treatment modality and treatment success.

Results: Eleven patients with heterotopic pregnancy treated by surgery. Five of remaining sixteen patients were treated medically and two of them required major surgical procedure (hysterectomy and bilateral internal iliac artery ligation). Minimal invasive procedures and follow-up were done each remaining patient.

Conclusion: The suspicion of the ectopic pregnancy and evaluation the whole pelvic cavity through ultrasonography are crucial for diagnosis of ectopic pregnancy. Three-dimensional ultrasonography can be helpful tool for accurate diagnosis. Early diagnosis of ectopic pregnancy provides patients to utilize fertility preservation as well as choice several treatment modalities.

Key words: Ectopic pregnancy, unusual location, 3D Ultrasonography, Laparoscopy

INTRODUCTION

Ectopic pregnancy (EP), is a pathological condition caused by the implantation of a fertilized ovum outside the endometrial cavity. It accounts for approximately 2% of all pregnancies and is the most common cause of pregnancy related mortality in the first trimester [1]. The fallopian tube is the most common location for EP. Half of all women diagnosed with ectopic pregnancy do not show any known risk factors. Previous cesarean section, pelvic inflammatory disease, previous tubal surgery, history of EP and presence of an intrauterine device are mainly associated with a higher risk of EP [1,2]. Women who are subfertile are also at increased risk for an EP because of altered tubal integrity. Unusual located ectopic pregnancies involve implantation in the cervix, interstitial portion of tube, ovary,

abdomen or cesarean scar account for less than 10% of all ectopic pregnancies and are associated with higher morbidity and mortality [3,4].

However, by the advanced use of assisted reproductive techniques, incidence of ectopic pregnancies increased and also higher rates of cesarean section led to an increase in the occurrence of abnormal pregnancies implanted in the cesarean scar [5,6].

The aim of this study is to evaluate the diagnostic and therapeutic strategies in patients with unusual located ectopic pregnancy and present a brief review of the literature including novel treatment modalities.

PATIENTS AND METHODS

Retrospective analyses were performed on twenty seven cases who diagnosed with ectopic

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pregnancy with unusual implantation site following assisted reproductive technique or conceived spontaneously presented in our clinic between 2008-2013. The clinical and demographic features were summarized in Table 1.

Table 1. Clinical characteristics of the cases

Location of Ectopic Pregnancy	Cases	Gestational Weeks	Contraceptive Methods	Previous Delivery/ Uterine Surgery	Treatment
Cesarean scar	1	6-7 weeks	None	Cesarean section – 4 years ago	Single dose MTX
Cesarean scar	2	6-7 weeks	None	Cesarean section – two times (5 years and 3.5 years ago)	Single dose MTX
Cervical	1-4	7-8 weeks	Condom and withdrawing	Case 1; two vaginal delivery, case 2,3,4; two times cesarean section	Vacuum Aspiration
Cervical	5-6	7-8 weeks	Condom and withdrawing	Case 5,6; one cesarean section	Vacuum aspiration prior to Total Abdominal Hysterectomy as well as, bilateral hypogastric artery ligation
Cornual	1,2,3	8-9 weeks	None	None	Single dose MTX
Cornual	4	10-11 weeks	None	None	Removal of cornual segment via laparotomy
Cornual	5	12-13 weeks	None	None	Removal of cornual segment via laparoscopy
Cornual	6	8-9 weeks	None	None	Proceeded successfully
Ovarian	1	6-7 weeks	None	None	Laparoscopic excision of ovarian ectopic mass (Wedge resection)
Ovarian	2	7-8 weeks	Intra-uterine device	One cesarean section	Salpingo-ophorectomy via laparotomy
Heterotopic	1-2	7-8 weeks	None	Clomiphene citrate usage	Laparoscopic unilateral salpingectomy
Heterotopic	3	6-7 weeks	None	One Vaginal delivery- Intrauterine Device usage	Laparoscopic unilateral salpingectomy
Heterotopic	4	6-7 weeks	None	None-In vitro fertilization- Male actor	Laparoscopic unilateral salpingectomy
Heterotopic	5-11	8-9 weeks	None	Case 5-9 have one vaginal delivery, 10-11 have one cesarean section history	Unilateral salpingectomy via laparotomy

RESULTS

Cesarean scar pregnancy

Two cesarean scar pregnancies were diagnosed and treated. Their history included cesarean delivery, besides initial β -HCG levels were 13156 mIU/mL and 18240 mIU/mL respectively. Both patients have 6-7 weeks cesarean scar pregnancy and treated medically with single dose Methotrexate (MTX). Then, intrauterine sonographic signs and β -HCG levels regressed successfully in 10 days. β -HCG levels were found 4200 mIU/mL and 5156 mIU/mL respectively after treatment. Both patients were diagnosed by transvaginal ultrasonography A Voluson E8 expert scanner, 3-9 MHz [GE Healthcare, Milwaukee, WI, USA] [Fig. 1]. Both of them were not using contraceptive method. One patient gave

birth a caesarean section [4 years ago] and the other one had a twice [5 years and 3.5 years ago] lower segment cesarean section operation.

Cervical Pregnancy

Six cervical pregnancies were diagnosed and treated. Four patients who have 7-8 weeks cervical pregnancy were treated with cervical dilatation and vacuum aspiration [VA] successfully. Their contraception method was condom and withdrawing. One patient's obstetric history revealed two vaginal delivery [G2P2 and no cesarean section] and three of them include two cesarean section.

Also, VA was performed to remaining two patients [6-7 weeks and 7-8 weeks G2P1] Their obstetric history include one cesarean section operation. However, abdominal total hysterectomy was

performed in one patient and the other patient was managed with bilateral ligation of the internal iliac artery due to uncontrollable bleeding after VA (Fig. 2).

Cornual Pregnancy

Six cornual pregnancies were diagnosed and treated. Cornual pregnancy was diagnosed by two dimensional and three-dimensional trans-vaginal ultrasonography in all patients (Fig. 3). Three patients who have 8-9 weeks cornual pregnancies were treated medically with single dose MTX successfully. All three patient's pregnancies were first pregnancy and no including previous uterine surgery.

One patient referred to our clinic at her 10th gestation week for cornual pregnancy. Her vital signs and hemodynamic parameters were instable due to hemorrhagic shock. We performed laparotomy and removed the ruptured of cornual segment of uterus. This pregnancy was the first pregnancy of her obstetric history.

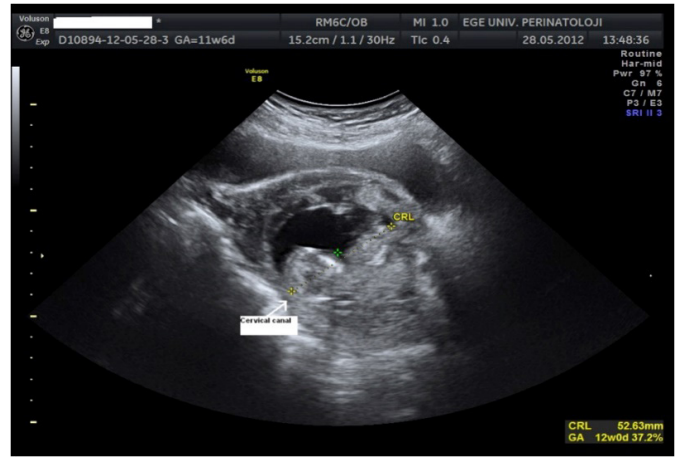


Figure 3. Three dimensional sonographic view of cornual pregnancy, black arrow indicates gestational sac

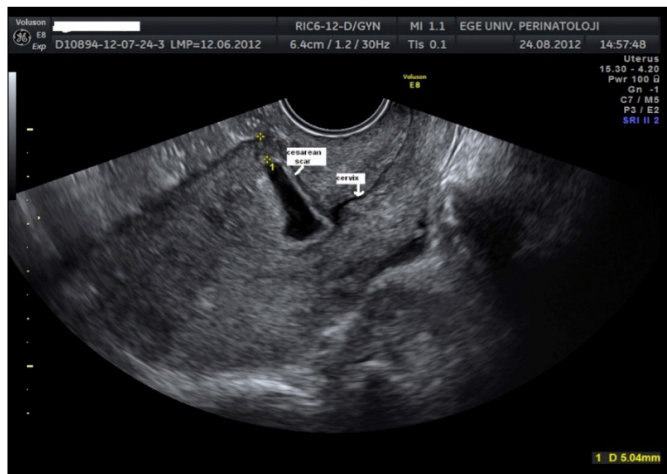


Figure 1. Transvaginal ultrasound image of the cesarean scar pregnancy. Gestational sac in the lower anterior wall of the uterus. Between two yellow pointer indicates scar defect Wall

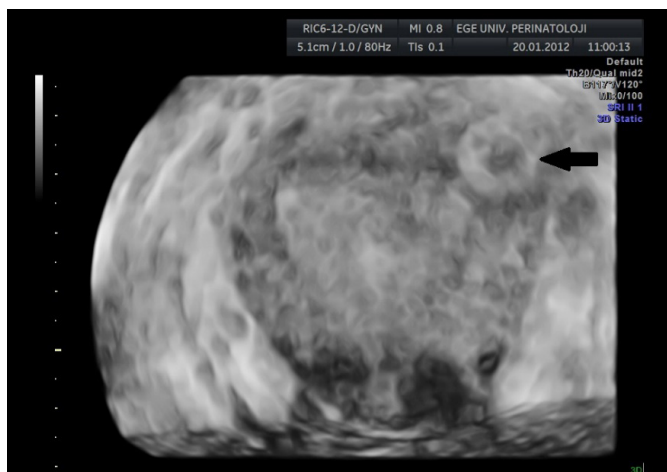


Figure 2. Transvaginal ultrasound image of the cervical pregnancy crown-rump length 52.6 mm with fetal cardiac activity

Other patient who have 12-13 gestational weeks gravida 2 para 1 was referred to hospital by sonographic findings (located on right uterine corn) for cornual pregnancy. Cornual part of uterus resected through laparoscopy. Her first delivery was vaginal route.

The last patient was admitted to our clinic because of pregnancy doubt. No abnormal clinical findings were determined on physical examination and laboratory parameters. We determined 8 weeks 1 day with heart beat embryo, implanted on the right uterine corn by using trans-vaginal ultrasonography. This was her own first pregnancy. The patient was informed about cornual pregnancy risks as well as possible complications. Then, she decided to continue her pregnancy. She was closely followed-up throughout the pregnancy at our clinic. Few weeks later, fetus developed towards the uterine cavity and the placenta was located at cornual region. There was not recorded any pathological condition during follow-up her pregnancy [Her pregnancy proceeded unremarkably]. At 37 weeks gestation, cesarean section was applied and 3140 gr healthy baby was delivered. At the time of operation placenta, which was located on the right uterine cornual region, removed easily from the uterine wall without heavy bleeding.

Ovarian Pregnancy

Two ovarian pregnancies were diagnosed and treated. First patient was presented at 6th gestational week with lower abdominal pain and vaginal bleeding. Her pregnancy was spontaneous. Serum β -HCG level was 1104 mIU/mL. Her pregnancy was first pregnancy and no contraceptive method usage noticed from her history. 6 weeks embryo on the left ovarian cortex was diagnosed by trans-vaginal ultrasonography. Laparoscopic excision [wedge resection] of the ovarian pregnancy was performed.

Other patient was presented with amenorrhea of six weeks duration and slight vaginal bleeding. She was using intra-uterine device. Ultrasonography showed a normal uterus and heterogenous

echogenic right adnexal mass besides intra-abdominal fluid collection. Serum β -HCG level was 3054 mIU/mL. Because of the gestational sac containing the entire ovary, salpingo-oophorectomy was performed via laparotomy. Both patient's specimens were confirmed with ovarian pregnancy by pathologist.

Heterotopic Pregnancy

We examined eleven patient who were heterotopic tubal pregnancy. Seven of them were spontaneous pregnant. All of seven patients were diagnosed at 8-9 gestational weeks. Remaining other four patients' pregnancy were could be ordered as follows; two of whom clomiphene citrate usage due to normogonadotropic anovulatory dysfunction. They were detected in 7-8. gestational weeks. Third was, spontaneous pregnant with 6-7 weeks coexisting intrauterine device usage. Last patient was 6-7 weeks in vitro-fertilization pregnant due to male factor. We recorded retrospectively her history that, two embryos were transferred to uterine cavity. Four patients underwent laparoscopic unilateral salpingectomy and seven patients were underwent unilateral salpingectomy via laparotomy. We applied salpingectomy to six patients who were spontaneous conception group, because of active intra-abdominal bleeding due to the tubal rupture. All patient's intrauterine pregnancy were proceeded and long-term follow-up was performed. Two of eleven patients to whom laparotomy was performed, aborted their fetuses in second-trimester (at 14. and 16. gestational weeks). Eight of eleven cases pregnancy resulted in live births with healthy babies at term and as well as the last pregnancy resulted in live birth with healthy baby at 32. gestational weeks.

DISCUSSION

The fallopian tube is the most common location for an ectopic pregnancy [1,4,5]. Half of all women with diagnosis ectopic pregnancy do not show any known risk factors. Diagnosis of ectopic pregnancies with trans-vaginal ultrasonography should be the standard practice in all units specializing about early pregnancy care. Despite the advanced visualization techniques and laboratory tests, the early diagnosis of unusual located ectopic pregnancy is still difficult and it is one of the most important and common causes of maternal mortality and morbidity [7,8].

Cesarean scar pregnancy accounts for 6.1 % of all ectopic pregnancies with a history of at least one cesarean section [9]. Some authors have shown association between the number of previous cesarean section and cesarean scar pregnancy while other authors have shown no association about this condition [9,10]. Early diagnosis of cesarean scar pregnancy is crucial. Delayed diagnosis can lead to uterine rupture and/or massive hemorrhage. Early diagnosis allowed the fertility preservation [11]. Almost all cases are detected by ultrasonography. Especially, transvaginal route and three-dimensional power doppler ultrasonography have been used to increase the diagnostic accuracy. All our patients were accurately diagnosed by transvaginal three-dimensional power doppler ultrasonography. In the literature, most authors suggest the termination of cesarean scar pregnancy

[12]. However, cesarean scar pregnancy may grow towards to the uterine cavity rarely and fetus may grow to term and may be delivered without complications [11]. In this condition, our cases were informed about cesarean scar pregnancy risks. Methotrexate [MTX] treatment is the most commonly chosen method for termination of cesarean scar pregnancy. Systemic or ultrasound-guided transvaginal injection into gestational sac or combined technique can also be used [13]. Medical treatment is appropriate in patients with unruptured cesarean scar whose gestational week less than 8 and myometrial thickness < 2 mm between the gestational sac and the bladder [14]. Systemic MTX treatment is more effective in patient with β -HCG level less than 5000 mIU/mL. MTX is successful in 71-80% of cases, with 6% of women requiring hysterectomy [10]. Our both patient treated with systemic single dose MTX [50 mg/m²] successfully. Both patients pregnancy were less than 8 gestational weeks and β -HCG levels were less than 5000 mIU/mL. Dilatation-curettage is performed as a surgical management [15]. Also, hysterectomy may be performed via laparoscopy or laparotomy. Hysterectomy may be necessary in the case of other treatment modalities are failed [9].

Cervical pregnancy accounts for less than 1% of all ectopic pregnancies [16]. Painless vaginal bleeding is the most common symptom and enlarged cervix is usually found. Cervical pregnancy is a potentially life-threatening condition. It may present with massive hemorrhage leading to hysterectomy. Ultrasonography and MRI are used for the diagnosis of cervical pregnancy. Also, three-dimensional power doppler ultrasonography have been used to increase diagnostic accuracy. All of our patients were diagnosed by three-dimensional power doppler ultrasonography easily. Dilatation and curettage was done for termination of pregnancy, cesarean section and assisted reproductive techniques increase the incidence of the cervical pregnancy. In presented cases, most of them [5/6] had a prior cesarean section history. Early diagnosis of the cervical pregnancy is crucial because of treating by non-surgical management and preserving fertility. Systemic MTX can be used for cervical pregnancy. If gestational week is greater, the success rate of the systemic MTX treatment will reduce [17]. During dilatation/curettage, hemorrhagia that is life threatening situation is critical step. Tamponade of the cervix with balloon or uterine artery embolization followed by curettage, bilateral ligation of the descending branch of uterine artery or ultrasound-guided transvaginal injection of Potassium Chloride [KCL] into gestational sac prior to the curettage, can be control the bleeding [18-20]. If the hemorrhage is not controlled, bilateral internal iliac artery ligation or hysterectomy may be necessary [21]. In both presented cases, uncontrollable bleeding after vacuum - aspiration [VA] occurred and hysterectomy was performed in one case, while bilateral ligation of the internal iliac artery was performed in other patients.

Cornual pregnancy is one of the most hazardous type of ectopic pregnancy. Cornual pregnancy accounts for 2-4% of all ectopic pregnancies and has a mortality rate of 2.0-2.5% [22]. Cornual pregnancy may remain asymptomatic until late weeks because this region has capacity of myometrial distensibility. If

the rupture of cornual pregnancy occurs in late gestational weeks [average 7-16 weeks], it can result in life-threatening hemorrhage [23]. Therefore, early detection of cornual pregnancy is important to reduce the morbidity and mortality. Salpingectomy, previous ectopic pregnancy, Assisted Reproductive Techniques [ART], history of sexual transmitted disease are main risk factors of the cornual pregnancy [24]. Angular pregnancy which the embryo is implanted in the lateral angle of the uterine cavity medial to the uterotubal junction and round ligament are misdiagnosed as a cornual pregnancy. In diagnosis, three-dimensional TV-US gives more detailed view of the endometrial cavity than two-dimensional TV-US. Cornual pregnancy, that gestational sac surrounded by myometrium below the corn lying outside easily could be demonstrated by three-dimensional TV-US [25]. Systemic MTX can be used for cornual pregnancy. This treatment is safe and effective. However, if MTX will be used for treatment, early detection of cornual pregnancy is critical. Jermy et al. reported that successfully treating rate is 94% of 17 cases about cornual pregnancy with systemic MTX. All cases about cornual pregnancy whose have initial hCG level less than 5000 mIU/mL were treated successfully with single-dose methotrexate while other cases whose have hCG more than 5000 mIU/mL required additional dose [26]. Our patients with unruptured cornual pregnancy; were treated successfully [100%] with a single dose MTX. A large ectopic pregnancy and presence of a heart beat are relatively contraindications of medical treatment [22]. Cornual pregnancy could be treating with local injection of MTX or KCl in patient with unruptured alive ectopic pregnancy. Local injection can be administer through laparoscopically, hysteroscopically or ultrasonography guidance [27,28]. Surgical techniques without hysterectomy such as cornual resection or cornuostomy can apply laparoscopy or laparotomy [29]. Also, in the literature it is reported that laparoscopic salpingotomy or hysteroscopic removal of ectopic tissue procedure can be implement for the treatment of cornual pregnancy [29,30]. Early detection of cornual pregnancy, especially before rupture, allows to minimal invasive surgical treatment to patients. Radical or invasive surgery such as hysterectomy can be necessary in patients with life-threatening hemorrhage due to cornual rupture.

Ovarian pregnancy accounts for 1-3% of all ectopic pregnancies [31]. Endometriosis, pelvic inflammatory disease, ART, ovulation induction drugs and intrauterine device increases the incidence of ovarian pregnancy [32]. Secondary amenorrhea and abdominal pain are the most common symptoms of ovarian pregnancy. These symptoms are similar to tubal pregnancy. Intraabdominal bleeding may occur and sometimes it could be severe. Both preoperatively and intraoperatively, diagnosis of ovarian pregnancy may be difficult; so it can be misdiagnosed such as corpus luteum or hemorrhagic cyst. Early diagnosis is necessary to avoid maternal morbidity and mortality. Preservation of ovarian tissue should be the therapeutic goal to maintain ovarian reserve and preserving fertility in young women with ovarian pregnancy. Ovarian pregnancy could be cure by surgically either with laparoscopy or laparotomy. Generally, ovarian wedge resection is preferred

in these patients. However, gestational sac containing the entire ovary salpingo-oophorectomy is performed instead of wedge resection. Previously presented in our first case, there was no risk factor regarding ovarian pregnancy. Ectopic pregnancy sac on the ovary diagnosed by TV-US and laparoscopic wedge resection was performed. The second case was inserted intrauterine device previously history. Laparotomy was performed because of the intra-abdominal massive bleeding. Intraoperatively, it was seen that ruptured gestational sac was containing the entire ovary, then unilaterally salpingo-oophorectomy was applied.

The incidence of heterotopic pregnancy varies widely, from 1/100 to 1/30000 pregnancies [33]. The incidence of heterotopic pregnancy increases with ovulation induction. The diagnosis of heterotopic pregnancy sometimes may be difficult. During scanning by ultrasonography, the presence of intrauterine pregnancy delays the detection of extra-uterine gestational sac. Therefore, it is potentially a life-threatening condition. Soriano et al. reported that there is increased risk of pregnancy loss after treatment of heterotopic pregnancy [34]. They indicated that the surgical intervention may have some role in the process of pregnancy loss. In our presented cases, pregnancy loss rate after surgery of heterotopic pregnancy was 18% [2 of 11 patients]. Both patients managed by laparotomy procedure due to massive abdominal bleeding besides hemodynamic instability. Clayton et al. reported that the rate of preterm labor for singleton pregnancies was 19% and not statistically significant between the heterotopic pregnancy and normal intrauterine pregnancy after ART [35]. Also, they indicated that there was no difference in perinatal outcomes between heterotopic and intrauterine-only pregnancies progressing to live birth. One of our case was delivered before 37 weeks [9%].

Treatment of patient with ectopic pregnancy is not standardized regarding initial level of β -HCG, gestational age and size of gestational mass [2]. There are several treatment modalities to unusual located ectopic pregnancy: expectant management, systemic or local medical treatment, surgical treatments including laparotomy, laparoscopy, hysteroscopy or vacuum - aspiration. The management of each case depended on size of the lesion, patient status, and also desiring for fertility preserving [35]. The early diagnosis of ectopic pregnancy significantly decreases not only the mortality, but also the morbidity associated with later diagnosis. Earlier diagnosis also enables the use of non-surgical conservative treatment options. Cervical, cornual, or ovarian pregnancies may be associated with excessive bleeding, especially in the later weeks. If the patient with ectopic pregnancy was treated by surgically or medically, we must keep in mind the risk of hemorrhage due to rupture in following days. If medical treatment is ineffective, surgical approaches should be performed. The management of heterotopic pregnancy, ovarian pregnancy, and advanced week cervical and cornual pregnancy firstly can be depends on surgical procedures, preferably minimal invasive surgery. But laparotomy may be performed in patients to whom severe instable hemodynamic vital signs are present, or contraindication for laparoscopic procedure.

In conclusion, every clinician who cares women of reproductive age should keep this diagnosis in mind. TV-US is the most important diagnostic tool for ectopic pregnancy, also three-dimensional US may be helpful in diagnosis. The whole pelvis must be evaluated with TV-US, even in the intrauterine pregnancy to exclude a heterotopic pregnancy. The surgical approach mainly depends on the surgeon's experience at minimal invasive surgery, especially in laparoscopy. Minimal invasive procedures should be preferred to *hemodynamically stable* patients.

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