

## CLINICAL ANALYSIS OF SPONTANEOUS HETEROTOPIC PREGNANCY: REPORT OF 13 CASES

SHUJUAN SHU, CHANGCHENG LV, JUANQING LI  
Gynecology Department, Women's Hospital of Zhejiang University, 1st xueshi road, Hangzhou, 310006, China

### ABSTRACT

**Objective:** Spontaneous heterotopic pregnancy is rare but it is a dangerous condition in pregnant women. This paper discusses its incidence, diagnosis and management. **Methods:** We retrospectively analyzed 13 spontaneous heterotopic pregnancies diagnosed at the Women's Hospital of Zhejiang University. The chief complaints, diagnostic characteristics, intraoperative findings, treatment of each patient were reviewed.

**Results:** 13 cases were identified between January 2000 and December 2014, involving tubal, ovarian, intramural, and cesarean scar heterotopic pregnancies conceived spontaneously. The common chief complaints and symptoms were abdominal pain (7 of 13), vaginal bleeding (7 of 13), and adnexal mass or thickening (9 of 13). Transvaginal ultrasound was an important aid in diagnosis. Surgery was performed in 10 patients, and the medical or expectant managements were also successful.

**Conclusion:** Heterotopic pregnancies are rare but it has an increasing incidence. Transvaginal ultrasound is usually useful, and timely treatment can improve the prognosis.

**Keywords:** Cesarean Scar Pregnancy, Extrauterine Pregnancy, Spontaneous Heterotopic Pregnancy, Transvaginal Ultrasound.

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### Introduction

Heterotopic Pregnancy is an uncommon pregnancy complex with multiple gestations in two or more implantation sites<sup>(1)</sup>. The most common cases are simultaneous occurrence of viable intrauterine pregnancy and single or multiple non-viable ectopic pregnancies<sup>(2)</sup>. It occurs very rarely in normal conception with a reported occurrence of 1 in 30,000 pregnancies<sup>(3)</sup>. But, heterotopic pregnancy is very common in Assisted Reproductive Techniques (ART), where the occurrence remains higher as 1%<sup>(4)</sup>.

In some studies, it has been shown that heterotopic pregnancy prevailed in about 2% of gestations followed by IVF, in women who have gnarled tubal anatomy<sup>(5)</sup>. Transferring either 4 or many embryos is also an added risk factor for heterotopic pregnan-

cy<sup>(5)</sup>. This is because the affected tubes are unable to expel them by peristaltic movement.

Spontaneous heterotopic pregnancies are most commonly tubal (almost 90%), and Ovarian<sup>(4,6)</sup>. Interstitial tubal segments, abdomen, cornual as well as early cesarean scar implantation have also been found extensively in literature. Only two cases of spontaneous heterotopic cervical pregnancy are recorded<sup>(7)</sup> in medical literature (although more common in ART). The common high-risk factors for the prevalence of spontaneous heterotopic pregnancy are tubal surgery, pelvic inflammation syndrome and previous cesarean section.

Diagnosing heterotopic pregnancy early stage is generally extremely complicated and preoperative determination of heterotopic pregnancy forms a challenge because of absence of defining clinical

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symptoms. Although transvaginal ultrasound as well as assessing entire pelvis, even in stage of intrauterine pregnancy during the early weeks could remain as significant tool to diagnose heterotopic pregnancy. Detecting the heterotopic gestation during the early weeks is merely 41 to 84%<sup>(8)</sup>. Pains in abdomen, adnexal mass, peritoneal irritation as well as an enlarged uterus are the most general sign and symptom for early diagnosis of heterotopic pregnancy.

Literature review between 1994 to 2004 show that out of 80 cases, just 21 are said to be identified using Ultrasonography also 59 cases were diagnosed only at laparoscopy or laparotomy<sup>(9,4)</sup>. Based on viewing the functioning of heart for the two intra as well as extra uterine could confirm identification of heterotopic pregnancy which is very rare possibility. Therefore, a very higher index of suspicion is needed even at lesser risk suspected patient where using ultrasound, confirms the intra uterine gestation sac but free fluid is also observed in pelvis in presence or absence of adnexal mass<sup>(4)</sup>.

The common differential diagnosis of spontaneous heterotopic pregnancy are Intra uterine gestation that has hemorrhagic corpus luteum; other complication that needs surgery due to acute abdomen pain and Bicornuate uterus with gestation in both cavities which can kindle a heterotopic gestation and lead to delayed diagnosis. Due to the delayed diagnosis, many patients having spontaneous heterotopic pregnancy end up in emergency care treatment having symptoms like ruptured ectopic gestation, which remains one of the main reasons of maternal death during early pregnancy. Women having heterotopic pregnancy suffer much risk for hypovolemic shock that needs blood transfusion compared to ones having ectopic pregnancy<sup>(10)</sup> due to ovarian hyperstimulation and increased vascularity.

Treatment of heterotopic pregnancy should be prompt to avoid maternal mortality and improve the outcome of viable intra uterine gestation. A standardized treatment for ectopic pregnancy is by using surgery with laparoscopy or laparostomy that depends on patient stability. Main aim of surgery is to preserve intra uterine pregnancy manipulating uterus to minimum. Salpingocentesis is a newer technique used successfully for ectopic pregnancy.

However, for rupturing cornual heterotopic pregnancy as well as tubal ectopic conditions, laparotomy remains the therapy chosen. If there is no cornual rupturing, managing it medically as well

as Transvaginal Ultrasound guided aspiration/injection of Potassium Chloride (KCl) forms a choice that could eliminate risks in performing operation as well as anesthesia<sup>(1)</sup>.

Treatment using surgery else combined systemic as well as intra gestational methotrexate are also used successfully to manage cesarean delivery scars pregnancy<sup>(1)</sup>. The final decision however must depend on factors like clinical presentation, experience of surgeon, side effects, total cost, as well as need of patient for future pregnancies. Diagnosing it earlier as well as to treat promptly, about 70% of the intra uterine pregnancy could be viable<sup>(2)</sup> and result in successful term delivery. The study becomes relevant since higher index of suspicion is required in non ART patients to promptly diagnose and identify heterotopic pregnancy at the earliest so that non-surgical or minimally invasive procedures can be implemented and can permit earlier laparoscopy intervening prior to life-threatening intra abdomen bleeding occurs<sup>(10)</sup>.

We report 13 cases of spontaneous heterotopic pregnancies which are the results of natural occurrence without applications of ovulation induction agents or ART. The report underlines the prevalence, diagnosis and management of the spontaneous heterotopic pregnancies.

## Materials and methods

We analyzed patients who, without application of ovulation inducing agents or ART, were diagnosed with heterotopic pregnancy from January 2000 to December 2014 at the Women's Hospital of Zhejiang University. We reviewed the profiles, chief complaints, diagnostic characteristics, intraoperative findings and treatment of each individual patient, and the occurrence of spontaneous incidence of spontaneous heterotopic pregnancy from our center is computed to roughly evaluate the current prevalence.

## Results

We reviewed the profiles, chief complaints, diagnostic characteristics, intraoperative findings and treatments of these patients.

Between January 2000 and December 2014, there were 240256 pregnancies (included deliveries, ectopic pregnancies, abortions and gestational trophoblastic diseases) at the Women's Hospital of Zhejiang University. A total of 13 patients were

identified with spontaneous heterotopic pregnancy, ten of them were confirmed by surgery and pathology and another three were given medical or expectant management. The incidence was 1 in 18481 pregnancies. Age of patients varied between 22 and 40, (mean ± SD, 30.5 ± 4.6 years); within reproductive ages (Table 1). All patients had a history of induced abortion, ranging from 1 to 6 times. Among 13 patients, two patients had a history of ectopic pregnancy with consequent salpingectomy, and three patients previously had a cesarean delivery. One patient used the intrauterine device for conception, one patient who showed history of pelvic inflammation, and one had a history of tubal surgery.

The chief complaints were amenorrhea with lower abdominal pain (7 of 13) or vaginal bleeding (7 of 13 patients). Lower abdominal pain and vaginal bleeding simultaneously occurred in 2 of 13 patients and others presented with either lower abdominal pain (5 of 13 patients) or vaginal bleeding (5 patients). The highest levels of preoperative β-hCG ranged from 795.5 to 167774.0 IU/L (median, 37138 IU/L) (Table 1).

On gynecological examination, tender adnexal masses were palpable in 4 of 13 patients, and thickened adnexa in 5 patients with concomitant masses occurring in 4 patients. The others were found with non-specific symptoms with enlarged uterus and vaginal bloody discharge (data not shown).

Among the 13 patients, a total of 4 patients initially missed the diagnosis with an extrauterine gestation and underwent induced abortion to terminate the intrauterine pregnancy (Table 1). The diagnosis was corrected 13-24 days later, after presentation of abdominal pain or vaginal bleeding, or finding intrauterine residue (Table 1). In the other 9 patients, the last menstrual period ranged from 40 to 90 days (median, 47 days) prior to diagnosis. One patient (case 9) was diagnosed with ectopic pregnancy first and the intrauterine pregnancy was found 7 days later owing to monitoring β-hCG level. A total of 8 out of 13 ectopic pregnancies are spotted in fallopian tubes, two in the ovary, two (case 11 and 12) on the caesarean scar, and one (case 10) was intramural pregnancy (Table 2).

In the tubal and ovarian pregnancy, almost all (except case 6) presented with tender adnexal mass or thickened adnexa on gynecological

examination.

Every patient underwent the transvaginal ultrasound scan. Among the 10 patients who were tubal or ovarian heterotopic pregnancy, an adnexal mass was visible on the ultrasound images of 8 patients, with or without internal anechoic area and/or peripheral blood flow (detailed data not shown), and only one (case 6) presenting both intrauterine and extrauterine gestational sacs which were more specific for heterotopic pregnancy, while one patient (case 1) presenting with pelvic fluid. The ultrasound image of case 13 which was diagnosed with intramural pregnancy presented an anechoic area within a heterogeneous echoes area at the right cornu, with peripheral abundant blood flow and a resistant index of 0.39.

Case	Age	Parity	Chief complaints	Ultrasound characteristics	Preopera- β-hCG (IU/L)
1	26	G1P0	Amenorrhea, LAP, vaginal bleeding	A gestational sac in uterus, a medium amount of pelvic fluid	No data
2	27	G2P0	LAP after induced abortion	Slightly enlarged uterus; a heterogeneous mass of 3.6 cm in MD close to the left ovary	2085.0
3	22	G1P0	LAP after induced abortion	Right tubal mass of 4.7 cm in MD	3006.0
4	40	G4P1	LAP and vaginal bleeding after induced abortion	Slightly enlarged uterus; a heterogeneous mass of 7.4 cm in MD with peripheral blood flow close to the left ovary	3698.0
5	29	G1P0	Amenorrhea, LAP	Intrauterine pregnancy; a heterogeneous mass of 5.3 cm close to the left ovary	66669.0
6	30	G1P0	Amenorrhea, vaginal bleeding	A 3-cm intrauterine gestational sac with yolk sac and heartbeat; a 2-cm gestational sac with a CRL of 0.27 cm and heartbeat in right interstitial tube	142233.0
7	28	G3P0	Amenorrhea, vaginal bleeding	An anechoic area of 0.5 cm in uterine cavity; an anechoic area of 0.9 cm within the heterogeneous echoes area close to the right ovary	4941.0
8	34	G4P0	Amenorrhea, vaginal bleeding	An intrauterine gestational sac with heartbeat; a 2.4-cm hypoechoic mass with internal anechoic area and surrounded by blood flow close to the left ovary	51474.0
9	34	G3P1	Amenorrhea, LAP	Uterus of normal size; a heterogeneous mass of 8.4 cm posterior to the uterus with undefined boundary and the left ovary was embedded	795.5
10	32	G3P2	Amenorrhea, LAP	An intrauterine gestational sac with heartbeat; a 2.1-cm heterogeneous mass in the left ovary	55316.0
11	32	G4P1	Amenorrhea, vaginal bleeding	An intrauterine gestational sac with heartbeat; a second gestational sac within the anterior wall of the lower uterus, with a CRL of 0.6 cm but no heartbeat	167774.0
12	35	G6P1	Amenorrhea, vaginal bleeding	A 2.1-cm intrauterine gestational sac; a 1.9-cm gestational sac in the isthmus uteri	66807.0
13	28	G6P0	Finding intrauterine residue after curettage	Uterus of normal size; a heterogeneous echoes area of 2.4 cm in MD at the right cornu, with peripheral strengthened echoes and abundant blood flow, as well as an internal anechoic area	22802.0

**Table 1:** Characteristics of 13 patients with heterotopic pregnancies.

G: gravidity; P: parity; LAP: lower abdominal pain; MD: maximum diameter; CRL: crown-rump length.

In the 2 cesarean scar pregnancies, the extrauterine gestational sacs were visualized at the lower part of the uterus (Table 2). A total of 10 of the 13 patients were treated with a surgical approach, two with medical treatment and one (case 5) with expectant management (Table 2).

them delivered healthy babies. The hospitalized days ranged from 5 to 22 days (median, 9 days) (Table 2).

Case	Type	The first visit(week)	Diagnosis (week)	Intraoperative findings	Treatment	Hospital stay (day)
1	Tubal	13+1	13+1	Laparotomy: uterus of 30-day gestational size; enlarged left tubal ampulla of 8 cm in MD Curetage: chorionic villi tissue	Curetage and Salpingectomy	7
2	Tubal	6	9+4	Curetage: chorionic villi tissue	Curetage, MTX and misoprostone	22
3	Tubal	7+2	10+3	Curetage: chorionic villi tissue Laparotomy: ampulla of right tube enlarged forming a 4-cm, purple-blue mass containing villi	Curetage, Salpingotomy and MTX	9
4	Tubal	6	8	Curetage: chorionic villi tissue Laparotomy: thickened left tubal isthmus of 6 cm in MD	Curetage and Salpingectomy	6
5	Tubal	6+5	6+5	No surgery.	Expectant management	13
6	Tubal	6+3	6+3	No surgery.	Injection of MTX into the ectopic embryo	20
7	Tubal	7+4	7+4	Laparoscopy: thickened right tubal interstitial of 1.5 cm in MD Curetage: chorionic villi	Salpingectomy and Curettag	9
8	Tubal	6+4	6+4	Laparotomy: thickened ampulla of left tube which contained villi-like tissues	Salpingectomy and progesterone injection to prevent miscarriage	7
9	Ovarian	10+6	11+6	Laparotomy: enlarged cystic left ovary of 4.0 cm in MD with chorionic villi. Curetage: degenerated placenta tissue	Partial oophorectomy, then MTX and diagnostic curettag	11
10	Ovarian	5+5	6+2	Laparoscopy: embryo-like tissue of 3 cm in the left ovary. Curetage: chorionic villi	Ovarian wedge resection and pregnancy tissues resection	10
11	Cesarean Scar	6+5	6+5	Curetage: about 5 × 4 × 4 cm tissues were cusetaged with fresh and stale chorionic villi	MTX and misoprostone followed by uterine arterial embolization and curettag	16
12	Cesarean Scar	7+1	7+1	Curetage: fresh chorionic villi	Uterine arterial embolization and arterial infusion with MTX then curettag	5
13	Intra-mural	7+4	9+3	Curetage: chorionic villi Laparoscopy and hysteroscopy: a purple-blue 1.5-cm cyst containing villi-like tissues in the myometrium of swollen right cornu and no abnormality in uterine cavity	Curettag and Intra-mural pregnancy removal by incision of myometrium	7

**Table 2:** the treatment of the 13 heterotopic pregnancies. MTX: methotrexate; MD: maximum diameter. G: gravidity; P: parity; LAP: lower abdominal pain; MD: maximum diameter; CRL: crown-rump length.

Among the 8 patients who were tubal heterotopic pregnancy, 5 patients underwent laparotomic or laparoscopic salpingectomy, or salpingotomy. Case 2 was given MTX systemically and case 6 with interstitial heterotopic pregnancy chose aspiration and injecting MTX locally to the ectopic embryo with ultrasound guidance to preserve the intrauterine pregnancy, and case 5 underwent expectant management. In the two ovarian pregnancies, in case 13 ovarian wedge resection was performed to remove the ectopic pregnancy, while in case 9 the ectopic pregnancy spontaneously aborted so partial oophorectomy were performed. The intra-mural pregnancy in case 13 was removed through a linear incision of the cornual myometrium.

The two cases having cesarean scar pregnancy were all cured using MTX combined with bilateral uterine artery embolization and curettag.

A total of three patients decided to preserve the intrauterine pregnancy, of whom, case 5 underwent expectant management, case 6 underwent local MTX injection to the ectopic pregnancy, and case 8 underwent laparotomic salpingectomy. All of

## Discussion

It is reported that occurrence of heterotopic pregnancy is gradually increasing<sup>(1)</sup>, while spontaneous heterotopic pregnancy without use of ART or ovulation induction remains rare<sup>(2)</sup>.

However, no observational assessment was reported about recent incidence of spontaneous heterotopic pregnancy. Here we found that occurrence of heterotopic pregnancy was 1 in 18481 pregnancies (or 0.0054%). It implies that the incidence is rising even in those who conceive without using any reproduction technologies. Risks in spontaneous heterotopic pregnancy include damage to tubes from previous Pelvic Inflammatory Disease (PID) or surgery in tubes, previous ectopic pregnancy and endometriosis, as well as a previous cesarean scar for cesarean scar pregnancy<sup>(11)</sup>. Of the reported 13 cases of spontaneous heterotopic pregnancy, a total of 7 patients had at least one of the above risk factors. And other risk factors of ectopic pregnancy could contribute to the morbidity of heterotopic pregnancy, such as the use of IUD<sup>(12)</sup> and

increased ages<sup>(13)</sup>, which also can be seen in our case series, with one using IUD and one aged 40. Noticeably, all of our patients had a history of induced abortion before heterotopic pregnancy occurred.

It can be explained by the increased chance of ectopic pregnancy in women who have undergone induced abortion previously<sup>(14,15)</sup>. Still, neglecting or even excluding identification of heterotopic pregnancy which depends on risk factors is inappropriate, as it could occur in patients without any risk factors also<sup>(2)</sup>.

In the literature, four symptoms are common in heterotopic pregnancy: pain of abdomen, adnexal mass, peritoneal irritation, as well as an enlarged uterus<sup>(16)</sup>. In our 13 cases, abdominal pain occurred in 7 of 13 (53.8%) patients, and vaginal bleeding occurred in 7 patients (53.8%), suggesting that vaginal bleeding is another prominent symptom in heterotopic pregnancy. Adnexal masses or sensible thickened adnexa, with or without masses, were palpable in 9 patients (69.2%). These signs and symptoms are nonspecific, however, when one woman with a positive pregnancy test presented with some of them, physicians should consider heterotopic pregnancy for differential diagnosis.

Transvaginal ultrasound scan can make diagnosing the heterotopic pregnancies in case of intrauterine pregnancy as well as simultaneous extrauterine pregnancy are visible, especially with cardiac activity. However, it is not common and accounts for only 3/13 in our series. Almost all ectopic pregnancy in our report had adnexal mass on ultrasound images, except the case 1 whose pelvic fluid might have influenced the detection. The intramural pregnancy was difficult to distinguish from a cornual pregnancy by ultrasound<sup>(17)</sup>, as in our series, case 13 was diagnosed at the time of surgery. When transvaginal ultrasound is inconclusive and there is no indication for surgery, magnetic resonance imaging can be an alternative method to help make an early and accurate diagnosis.  $\beta$ -hCG measurements may be of little benefit for the diagnosis, but is valuable for evaluating efficacy and prognosis.

In this report, case 9 highlights the importance of the  $\beta$ -hCG measuring both preoperatively and postoperatively in ectopic pregnancy for ruling out heterotopic pregnancy or persistent ectopic pregnancy.

Considering individual circumstances, surgical, medical and expectant management can be cho-

sen for optimal personalized treatment. The surgery is the main approach<sup>(18)</sup>, especially for patients with complications such as hemorrhage, adhesions and endometriosis. Laparoscopy is the gold standard of surgical treatment for extrauterine pregnancy. Medical treatment with MTX or potassium chloride is another option, but it may fail or result in persistent ectopic pregnancy which needs secondary treatment or surgery<sup>(19)</sup>.

In tubal heterotopic pregnancy, salpingectomy, salpingotomy and MTX injections are common management modalities. Intrauterine pregnancy was supposed to preserve in three patients, with one undergoing laparotomic salpingectomy, one (case 6) undergoing ultrasound-guided local injection of MTX and the other undergoing expectant management. All the three patients delivered healthy babies. With a potential risk of embryo toxicity, MTX was not recommended in these cases. However, the ectopic pregnancy of case 6 implanting in the interstitial segment of the fallopian tube, and interstitial heterotopic pregnancy with surgical management is associated with risk of intrauterine pregnancy failure and the maternal risk of hemorrhage or hysterectomy, so local injection of potassium chloride and MTX were reported<sup>(20,21)</sup>.

Deciding to preserve the intrauterine pregnancy, case 6 at our center underwent local MTX injection to the ectopic embryo, and the intrauterine one developed normally resulting in delivery of a healthy baby without any abnormality who is now 6 years old. In the case of cesarean scar pregnancy, systemic and local use of medicine like MTX or potassium chloride, suction curettage or dilation and curettage, and surgery for uncontrolled bleeding are common treatment options. In our two cases, we performed uterine artery embolization and used MTX to reduce blood flow and attenuate vitality of ectopic embryo, and then curettage was performed, without postoperative events. When uncontrolled bleeding occurs during curettage because of the cesarean scar pregnancy, hypogastric artery ligation can be an alternative treatment<sup>(11)</sup>.

In conclusion, spontaneous heterotopic pregnancy remains rare but has an increasing incidence. Early diagnosis and early management could result in a better prognosis. When a woman with a positive pregnancy examination presents common symptoms like pain in abdomen, vaginal bleeding as well as adnexal mass, heterotopic pregnancy must be taken into account for differential diagnosis. Transvaginal ultrasound play an important role

in diagnosis, repeating scan may be necessary in some cases. The treatment methods, surgical, medical, and expectant as well as combined treatment depend on individual situation.

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Corresponding author

JUANQING LI  
Gynecology Department, Women's Hospital of Zhejiang University, 1st xueshi road  
Hangzhou 310006  
(China)