

Laparoscopic Strategy for Heterotopic Interstitial Pregnancy Following Assisted Reproductive Techniques

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ABSTRACT

Background and Objectives: Heterotopic interstitial pregnancy (HIP) is a rare but potentially life-threatening condition that occurs more commonly in the setting of assisted reproductive technology (ART). It is significant to introduce a safe and effective laparoscopic strategy to manage HIP following the use of ART.

Methods: This study included 9 cases of patients with HIP who underwent laparoscopic management in our department. Our approach involves placement of a purse-string suture around the cornua of the uterus followed by removal of the interstitial pregnancy using a flushing technique. This is followed by repair of the uterine cornua, leaving the intrauterine pregnancy (IUP) undisturbed. The outcomes were reported regarding surgical complications during the procedure as well as outcomes for the remaining IUP including gestational age at delivery and any neonatal adverse events.

Results: Five of the 9 cases were asymptomatic at presentation. All cases underwent laparoscopic management with successful removal of the interstitial gestational product and preservation of the IUP. With the exception of one case that was lost to followup, all cases resulted in full-term delivery. The average intraoperative blood loss was 24.44 ± 14.23 mL and the average operation time was 70.44 ± 22.48 minutes. There were no postoperative complications, including persistent ectopic pregnancy, rupture of the uterus, spontaneous abortion, or preterm delivery. All newborns for whom data was available were healthy.

Conclusion: This laparoscopic strategy is a safe, relatively simple, effective, and minimally invasive approach to address the challenging case of HIP after ART in the first trimester.

Key Words: Heterotopic pregnancy; Interstitial pregnancy; Surgical management; Laparoscopy; Pregnancy outcomes; Case series.

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Author Contributions: DX gave the concept and designed the study. BG, CC, QP and GJ drafted the manuscript. DX, XQ, and CC revised the manuscript. BG, CC and GJ carried out the acquisition of data and participated in literature search. DX and CC supervised this manuscript. All authors read and approved the manuscript.

Financial Support: This study is supported by the Natural Science Foundation of China (Grant No. 81671492).

Ethics: Informed consent was obtained after the procedure was fully explained and approval given to the study by The Institutional Review Board of the third Xiangya Hospital, Central South University.

Conflicts of Interest: The authors declare that they have no conflict of interest.

Informed consent: Dr. Xu declares that written informed consent was obtained from the patient/s for publication of this study/report and any accompanying images.

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DOI: 10.4293/JSLS.2018.00109

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INTRODUCTION

A heterotopic pregnancy (HP) is a twin pregnancy in which one pregnancy is intrauterine and the other is ectopic.¹ The incidence of HP is extremely rare among women who conceive naturally, about 1/30,000. However, in recent years, the incidence of HP has increased dramatically with the rise of assisted reproductive technology (ART), with some estimates of incidence as high as 1:100.^{2,3} Risk factors for HP include a history of ectopic pregnancy, abortion, ovarian hyperstimulation syndrome, and smoking in women of reproductive age.^{4,5} The most common extrauterine site of HP is the fallopian tube,⁶ accounting for 98% of all ectopic gestations. Other possible sites include cervical, interstitial, cesarean scar, intramural, ovarian, or abdominal.⁷ The clinical presentation of HP is variable^{8,9} and diagnosis is typically made by transvaginal ultrasonography or diagnostic laparoscopy.^{10,11} When the ectopic gestation occurs within the interstitial portion of the uterus it is referred to as a heterotopic interstitial pregnancy (HIP). This is a particularly rare occurrence with unique risks for the pregnant woman as

well as the coexisting intrauterine gestation. The primary risk to the mother is rupture of the cornual pregnancy leading to significant bleeding or even hemorrhagic shock as the cornua is extremely well vascularized, and the risk to the intrauterine gestation including primarily abortion, preterm labor, infection, etc., All of them would lead to adverse pregnancy outcomes.

Various methods have been proposed for management of HIP: 1) expectant, 2) medical, or 3) surgical. Expectant management involves serial ultrasound observation of the ectopic gestation to determine whether it will spontaneously resolve. Medical management involves direct administration of feticidal drugs, such as potassium chloride, methotrexate, prostaglandin or hyperosmolar glucose into the extrauterine gestational sac under ultrasonographic or laparoscopic guidance.¹² Systemic administration of an agent like methotrexate typically used in the treatment of ectopic pregnancy is not feasible as this would also affect the ongoing intrauterine pregnancy (IUP).^{13–15} Surgical management involves removal of the extrauterine sac either through laparotomy or laparoscopy. Of the two, laparoscopy is preferred due to its shorter operative times, more rapid recovery, and decreased postoperative pain.^{16,17}

Although it is the preferred method, laparoscopic management of HIP is challenging for three main reasons: 1) difficulty controlling intraoperative blood loss, 2) close proximity of the interstitial gestation to the intrauterine gestation, and 3) maintenance of uterine structural integrity to support the ongoing IUP.

Various methods for controlling intraoperative blood loss have been proposed. The most promising of these was initially proposed by Aust et al¹⁸ and involves placing a purse string suture around the uterine cornua prior to incision of the myometrium to prophylactically reduce bleeding. Monopolar electrocautery is then used to coagulate and incise the cornua overlying the interstitial pregnancy. Unfortunately, the report did not quantify intraoperative blood loss¹⁸ and the case resulted in a missed abortion several weeks after the procedure. While there is no ability to determine whether the miscarriage was caused by the procedure, there is concern that use of monopolar electrocautery may cause uterine muscle contraction and increase miscarriage rates. On the other hand, Kwon et al¹⁹ described a case in which cornual incision was similarly made with monopolar electrocautery but resulted in delivery of a healthy infant at term of the intrauterine gestation. More data are needed regarding safety of monopolar electrocautery.

Maintaining structural integrity of the uterus while providing complete treatment of the interstitial gestation also proves challenging. Lialios et al¹² present a case of a ruptured HIP in which they performed a laparoscopic cornual resection. Although this case had a good outcome for the ongoing IUP, the uterine musculature can be weakened by cornual resection, thus increasing the risk of uterine rupture for current and future pregnancies. Effective methods for treating HIP must focus on ways to maintain structural integrity.

To the best of our knowledge, no standard of care exists for laparoscopic management of HIPs, nor do we have sufficient data regarding long-term pregnancy outcomes after various forms of laparoscopic management of HIP.

We present a case series of 9 patients with HIP who underwent treatment in our department between November 2014 and March 2017. Each of these patients underwent laparoscopic management with the technique described in the following report. Similar to the approach proposed by Aust et al,¹⁸ our technique makes use of a purse-string suture secured around the cornua prior to incision of the myometrium to control intraoperative blood loss. However, instead of monopolar electrocautery we use a Harmonic scalpel to incise the myometrium, thereby minimizing uterine muscle contraction. We remove the interstitial gestation by irrigation using a “flushing” technique leaving the interstitial portion of the uterus intact and the IUP undisturbed. The serosal layer is then closed via laparoscopically placed sutures. To the best of our knowledge, this is the first clinical article demonstrating the efficacy and safety of this technique.

MATERIALS AND METHODS

Nine patients with HIP following ART who underwent laparoscopic management in our center between November 2014 and March 2017 were retrospectively analyzed. Information was gathered from medical records of the Gynecology Department of the third Xiangya Hospital, Central South University. Main characteristics are summarized in **Table 1**.

Four of the patients presented to our emergency department with lower abdominal pain and vomiting. The other 5 patients were diagnosed through ultrasonography in routine prenatal examination. These patients had no abdominal tenderness or peritoneal signs. Bimanual examination was similarly benign in all patients, even those who presented with abdominal pain. 3-D transvaginal ultra-

Table 1
Summary of 9 Cases of Heterotopic Interstitial Pregnancy Following Assisted Reproductive Technology

Case No.	Age (y)	Days After ET	Symptom	Mass Under Ultrasound	Gestational Sac of IUP (mm)	Fetal Viability	Past History	Side of Interstitial Pregnancy	Pregnancy Outcome
1	25	28	None	Right adnexal mass	29 × 9	Yes	G1P0A1, TCRS, bilateral salpingostomy	Left	Term, CS
2	31	28	None	Left adnexal mass	31 × 11	Yes	G1P0A1, bilateral benign ovarian cystectomy, bilateral tubal ligation	Left	Term, CS
3	28	28	Lower abdominal pain for 3 days	Right adnexal mass	35 × 20	Yes	G1P0A1, Right salpingectomy, laparoscopic left salpingostomy	Right	Term, CS
4	31	22	Abdominal pain for 10+ hours	Left adnexal mass	13 × 6	N/A	G1P0A1, Right ovariectomy, bilateral tubal ligation	Left	Term, CS
5	28	41	Abdominal pain for 3 days	Left adnexal mass	35 × 25	Yes	G1P1A0, None	Left	Term, CS
6	31	26	None	Left adnexal mass	23 × 15	Yes	G0P0, hysteroscopic myomectomy	Left	N/A
7	36	30	None	Right adnexal mass	25 × 13	Yes	G0P0, bilateral tubal ligation	Right	Term, CS
8	33	44	Abdominal pain for 3 days	Left adnexal mass	49 × 41	Yes	G0P0, PCOS	Left	Term, Vaginal delivery
9	28	27	None	Right adnexal mass	25 × 11	Yes	G0P0, bilateral tubal ligation	Right	Term, CS

CS, cesarean section; ET, embryo transfer; IUP, intrauterine pregnancy; N/A, no answer; TCRS, transcervical resection of septum.

sonography played an important role in the early diagnosis of all cases (**Figure 1**).

Culdocentesis was carried out in case No. 4 (Table 1). One milliliter of dark, nonclotting blood was collected, suggesting intraperitoneal hemorrhage due to ruptured HIP. This was later confirmed laparoscopically. Culdocentesis was not performed in the remaining 8 cases as there was no free fluid seen in the pelvis by ultrasound. In these cases, it was thought that performing culdocentesis may lead to uterine contractions and interfere with the ongoing IUP with limited additional diagnostic information. In each case, the existence of HIP was confirmed under direct laparoscopic visualization.

Our laparoscopic technique is as follows (**Figure 2**): Following induction of anesthesia, the patient is prepped and draped in the usual fashion. Abdominal entry is performed using the Veress needle in the upper portion of the umbilicus. Intra-abdominal pressure is maintained at 12 mm Hg with carbon dioxide. Once pneumoperitoneum is achieved, a 10-mm Trocar is placed and a general survey of the pelvis and abdominal cavity is performed using video laparoscopy (Karl-Storz Company, Tuttlingen, Germany) (**Figure 2A**). An additional 10-mm and 5-mm Trocar are placed in the right and left lateral lower quadrants of the abdomen, respectively. First, intracorporeal sutures are placed using a 1-0 absorbable suture (Johnson

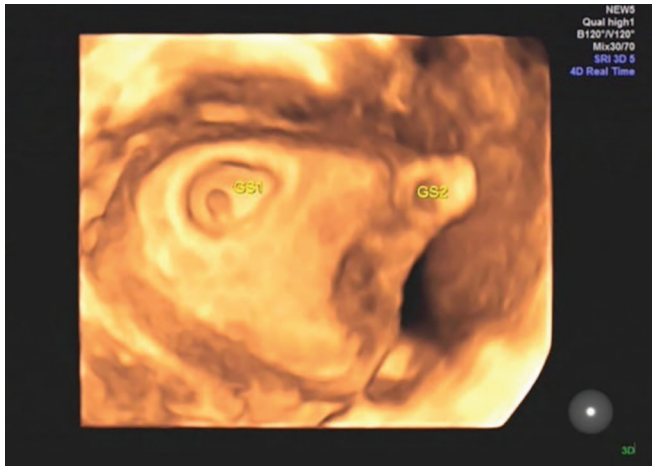


Figure 1. Transvaginal 3-D ultrasound with intrauterine pregnancy and interstitial pregnancy. GS1, gestational sac 1 (intrauterine pregnancy); GS2, gestational sac 2 (left interstitial pregnancy).

& Johnson, New Brunswick, New Jersey, USA) around the cornua of the uterus using a purse-sting technique (**Figure 2B**). The suture is knotted to prevent significant bleeding following incision of the cornua (**Figure 2C**). The Harmonic ultrasonic scalpel (Johnson & Johnson) is then used to expose the ectopic/interstitial gestation (**Figure 2D**). A metal irrigator is employed to flush the chorionic villi and gestational sac out of the lumen of the interstitial portion of the uterus (**Figure 2, E and F**). After the gestational product is completely removed, the defect in the uterine wall is repaired by both interrupted and continuous sutures placed laparoscopically (**Figure 2, G and H**).

Intramuscular progesterone was given to patients pre- and postoperatively to prevent intra- and postoperative uterine contractions (40 mg IM twice daily, gradually tapering dose beginning 3 days postoperatively). Serum beta human chorionic gonadotropin (β -HCG) and progesterone levels were followed postoperatively. Transvaginal ultrasound was performed postoperatively to exclude persistent ectopic pregnancy and to confirm a viable IUP.

RESULTS

All cases underwent laparoscopic management as described above. In each case, the interstitial gestational product was removed and the IUP was successfully preserved. All cases for whom data was available resulted in term deliveries without uterine rupture (7 cesarean section, 1 vaginal delivery). Case No.6 (**Table 1**) was lost to followup. The intraoperative blood loss ranged from 10 to 50 mL (24.44 ± 14.23 mL) and the operation time ranged

from 51 minutes to 120 minutes (70.44 ± 22.48 minutes). There were no postoperative complications including loss of the IUP, persistent ectopic pregnancy, rupture of the pregnant uterus, or preterm delivery. All newborns for whom outcome data was available were healthy.

DISCUSSION

HP refers to the presence of coexisting gestations at two or more implantation sites. With the increased use of ART, the incidence of HP has also increased.²⁰ It has been reported that 70% of HP are diagnosed between 5 and 8 weeks of gestation.²¹ Early diagnosis, particularly of interstitial heterotopic pregnancies, is crucial as patients presenting with ruptured interstitial pregnancies may have massive bleeding leading to hemorrhagic shock and even death in a short period of time. As an interstitial pregnancy is adjacent to the uterine cavity, it is easily misdiagnosed as a second IUP by those not experienced with ultrasound and therefore presents a diagnostic challenge, particularly if the patient is asymptomatic.²² Ultrasound is the primary method of diagnosis; however, magnetic resonance imaging could also be used and diagnosis may be confirmed by laparoscopy.²³

The primary goals when treating HIP are removal of the interstitial pregnancy and, at the same time, preservation of the IUP.²⁴ Many approaches have been taken to treat HIP, including expectant, medical, and surgical management; however, no clear consensus exists on the correct method.

Expectant management relies on the principle that some ectopic pregnancies resolve spontaneously through either regression or tubal abortion without causing harm to the patient. However, this method requires very close observation with repetitive assessment of the ectopic gestational sac to determine whether or not it is resolving spontaneously.⁵ The importance of compliance with followup and ease of access to the hospital are crucial requirements to carry out this type of management. This approach should be pursued cautiously and would not be optimal when there is risk of such catastrophic complications as rupture with hemorrhage resulting in maternal morbidity or mortality.²³

Medical treatment for HIP involves local injection of Methotrexate, potassium chloride, prostaglandin or hyperosmolar glucose under transabdominal ultrasound guidance or by direct laparoscopic injection. This approach has been used for patients with unruptured tubal ectopic pregnancies who were hemodynamically stable, mini-

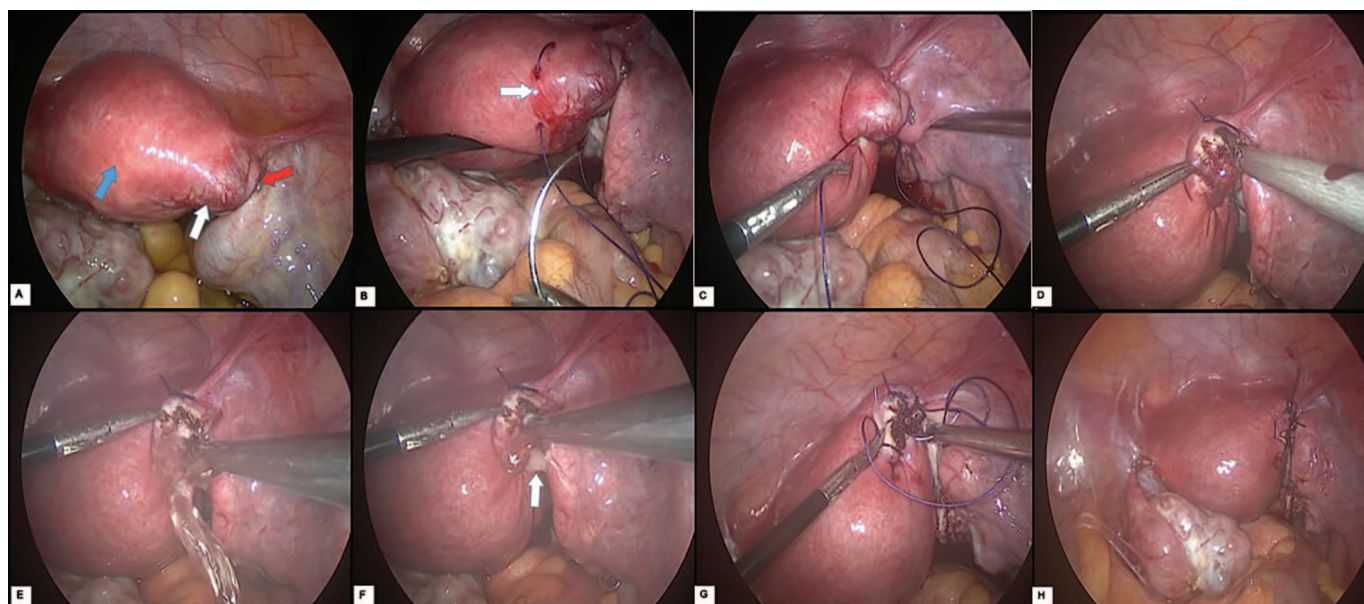


Figure 2. Laparoscopic strategy for heterotopic interstitial pregnancy. (A) Pelvic overview under diagnostic laparoscopy. Blue arrow, intrauterine pregnancy; white arrow, interstitial pregnancy; red arrow, titanium clip. (B) Suture around the interstitial gestation using purse-sting technique. White arrow, purse-sting technique using No. 1 absorbable suture. (C) Knot the suture. (D) Expose the ectopic gestation by Harmonic ultrasonic scalpel. (E) Flush the chorionic villi or gestational sac away using a metal flushing pipe head. (F) Flush the chorionic villi or gestational sac away from the myometrium of interstitial portion. White arrow, chorionic villi. (G) Suture the wound using interruptedly and continuously skills. (H) Pelvic overview after laparoscopy.

mally symptomatic, and with a low volume of free intraperitoneal fluid on ultrasound scan.²⁵ Qin et al²⁶ have presented retrospective data that transabdominal ultrasound-guided aspiration of the ectopic gestational sac has the best maternal outcome with the lowest abortion rate. We, however, have concerns about this method as the intrauterine and the interstitial pregnancy are in such close proximity that the potential for complications for the IUP is high. As nearly all of the patients in our series had a strong desire to preserve the IUP great care was taken to select a treatment method with the lowest risk for the ongoing gestation. An additional consideration is that bleeding may occur in the course of medical treatment, which would require emergent surgical invention. Therefore, medical treatment is not optimal.

Both laparotomy and laparoscopy have been used for surgical management of HIP. Although there are theoretical risks of CO₂ pneumoperitoneum during surgery,²⁷ laparoscopy is considered the preferred method as it not only allows the provider to confirm the diagnosis of HIP but also provides a minimally invasive approach with less uterine manipulation, more rapid healing times, and lower risk of postoperative infection than laparotomy.²⁸ Only in cases where laparoscopic expertise is not available or

when expeditious laparoscopy cannot be achieved for a hemodynamically unstable patient would laparotomy remain the preferred treatment approach.²³

Control of intraoperative bleeding is the main challenge encountered during laparoscopic management of HIP. During laparoscopic surgery it is impossible for the surgeon to apply direct pressure as one could with a hand during open surgery. Additionally, controlling a laparoscopic needle holder and performing the intracorporeal suturing required to repair the interstitium is significantly more challenging than performing the same repair through a laparotomy incision.

Kwon et al¹⁹ have described a case of laparoscopic management of HIP with subsequent term delivery. In their approach, the bulging cornua was transversely incised with monopolar electrocautery. After removing the ectopic gestational sac, simple interrupted sutures were cautiously placed laparoscopically to control bleeding from the surgical bed of the cornua.¹⁹ In the approach described no prophylactic measures were taken to control intraoperative bleeding, and there was no mention of the intraoperative occurrence or amount of bleeding or need for intraoperative blood transfusion. The authors of this

study have reservations regarding the use of monopolar electrocautery and its potential to cause uterine contractions thus increasing the likelihood of miscarriage of the IUP following the procedure. However, this case report establishes the feasibility of laparoscopic treatment of HIP.

In efforts to reduce blood loss through prophylactic measures not involving vasopressin or other chemical agents that may lead to uterine contraction, Aust et al¹⁸ propose a purse-string suture technique for the management of HIP. In their approach, hemostasis is achieved by the placement of a circumferential suture around the cornua prior to excision of the ectopic gestation to control intraoperative blood loss prophylactically. The myometrium overlying the cornual gestational sac is then coagulated and the cornual area incised by monopolar electrocautery and the interstitial gestational sac removed. The uterine wall was then strengthened with serosal closure. Unfortunately, there was no quantification of intraoperative blood loss.¹⁸ The case described resulted in a missed abortion sometime after the procedure, and, although it is impossible to attribute the miscarriage to this procedure itself, further study of whether the use of monopolar electrocautery stimulates uterine contraction is warranted.

To address the challenge of surgically managing HIP while maintaining excellent hemostatic control, we report a series of 9 cases of women who underwent treatment in our center between November 2014 and March 2017 with the surgical approach described above. The key elements and advantages of our strategy are as follows: 1) a purse-string suture is placed circumferentially around the cornua and tied snugly to prevent significant bleeding following cornual incision; 2) A Harmonic ultrasonic scalpel, rather than monopolar electrocautery, is used to incise the cornua and expose the interstitial gestational sac. The Harmonic is suggested to work intermittently and flushed with cold saline to minimize its uterine stimulation and reduce potential heat damage to adjacent tissue; 3) The gestational sac and chorionic villi are gently flushed out of the interstitium using irrigation. This technique allows for less uterine manipulation and therefore less impact on the IUP. This technique also provides more thorough clearance of the interstitial pregnancy than with other techniques previously published which decreases the risk for persistent ectopic pregnancy. 4) Rather than resect the cornua, we performed excision of the interstitial gestational sac followed by reinforcement of the uterine serosa with laparoscopic sutures theoretically decreasing the risk of uterine rupture for the ongoing pregnancy. Each of our 9 cases were successfully managed (including 2 ruptured cases and 7 nonruptured cases). The average intraopera-

tive blood loss was 24.44 ± 14.23 mL and the average operation time was 70.44 ± 22.48 minutes.

Some authors in related references have placed a laparoscopic loop ligature around the cornua prior to excising the HIP. In these procedures, the loop was tightened inferior to the tube and distal to the cornua prior to removing the ectopic gestation.²⁶ However, with this technique there is risk of the loop ligature slipping at an inopportune moment, which could lead to uncontrolled bleeding. The report describing this technique reported a single case. Further reports would be needed to validate its safety.

Other authors have performed cornual resection to ensure more thorough clearance of the interstitial pregnancy. Dumesic et al²⁹ report a case of cornual resection with removal of a ruptured interstitial pregnancy. The patient was transfused two units of packed red blood cells postoperatively. The patient had an uneventful postoperative course though was later found to have a missed abortion. Lialios et al¹² describe laparoscopic management of a ruptured interstitial pregnancy by cornual resection. Their operation had minimal blood loss and resulted in a successful ongoing IUP. Bipolar electrocautery was used and a minimal portion (about 0.5 cm around the cornua) of the uterus was excised. The defect was closed using 2-0 Ethibond suture tied intracorporeally to strengthen the wall defect. The patient delivered by elective cesarean section at term resulting in a live birth without complications.¹²

Cornual resection has the benefit of providing complete and thorough clearance of the interstitial gestational product; however, there is theoretically increased risk of uterine rupture at the site of excision. We propose instead a “flushing” technique using a metal irrigator to gently and thoroughly remove the interstitial gestational sac and chorionic villi. This technique has minimal effect on the IUP while allowing complete clearance of the interstitial gestational sac. Using this technique there were no postoperative complications such as persistent ectopic pregnancy, abortion of the IUP, or uterine rupture.

All patients for whom data was available (one of the 9 cases was lost to followup) delivered healthy infants at term. Of these 8, 7 had elective cesarean sections and one patient had a vaginal delivery. The thickness of uterus cornu was monitored with ultrasound during the gestation. Cesarean section will be recommended when symptoms of the uterus rupture occurs, especially in the cornu of uterus. However, cesarean section is not the strict indication for those cases without symptoms of uterus rupture due to the cornu not playing the essential contracting function when compared with the fundus during

delivery. Despite of this, the majority of the pregnant and its family request to have cesarean strongly due to personal will and social concern. Therefore, the way of delivery need to be well weighted by the obstetrics.

All of our documented cases were fresh interstitial pregnancies, thus the flushing technique could be successfully used to separate the chorionic villi and the uterine wall. This technique might not be sufficient for the clearance of an organized interstitial pregnancy due to its relatively low power.

CONCLUSIONS

In conclusion, our laparoscopic strategy for HIP has many benefits over existing therapies. Intraoperative blood loss is kept to a minimum by use of the purse string suture placed prior to any myometrial incision. A harmonic scalpel is used to access the ectopic gestational sac, thereby reducing the risk of uterine contractions commonly seen with monopolar electrocautery. The interstitial gestational sac is thoroughly removed by use of a gentle flushing technique rather than cornual excision, greatly diminishing the risk of persistent ectopic pregnancy while maintaining the structural integrity of the uterus. As the outcomes from our 9 cases show, this is a reasonable strategy for management of HIP.

Although there were some limitations to this study, e.g., the number of patients was relatively small (n = 9), we believe that the data will provide valuable information for the surgical process of HIP for clinical treatment in the future, and further large sample studies will be needed to validate its feasibility, safety, and efficacy.

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