

Opinion

Interstitial and Cornual Ectopic Pregnancy: A Review of the Management Options

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Abstract

Interstitial or cornual ectopic pregnancies are a rare form of ectopic pregnancy which account for 2% to 4% of all ectopic pregnancies. While it is a rare type of ectopic pregnancy, the mortality rate is 6–7 times higher than other ectopic pregnancies. Therefore, early recognition and accurate diagnosis of an interstitial or cornual ectopic pregnancy is critical for the safety and wellbeing of the patient especially due to the increased risk of massive hemorrhage. Treatment options include conservative medical management with methotrexate or surgical intervention with laparoscopy or laparotomy.

Keywords: interstitial pregnancy; cornual pregnancy; ectopic pregnancy; methotrexate

1. Introduction

Ectopic pregnancies are one of the most common gynecological emergencies comprising 2% of all pregnancies in the United States [1,2]. As more and more women delay child-bearing until their later years, the use of assisted reproductive technology has increased which has also led to higher rates of ectopic pregnancies, especially heterotopic pregnancies and interstitial or cornual pregnancies. Interstitial or cornual ectopic pregnancies are a rare form of ectopic pregnancy accounting for only 2% to 4% of all ectopic pregnancies [3]. While they are a rare form of ectopic pregnancy, their mortality rate is high with a mortality rate of 2% to 2.5% [3,4]. Furthermore, the anatomic location of an interstitial or cornual pregnancy often leads to a delay in diagnosis which may increase the incidence of rupture rates of the ectopic pregnancy. The cornus of the uterus is dense with vascular tissue due to the anastomosis of the ovarian artery and the uterine artery. When the ectopic gestational tissue implants in this area, the chorionic villi may invade the blood vessels in this area which will cause massive hemorrhage if ruptured. Therefore, early diagnosis and treatment of an interstitial or cornual ectopic pregnancy is very important for the patients wellbeing.

2. Discussion

An ectopic pregnancy is when the fertilized egg implants itself outside of the uterine cavity. It is one of the most common gynecological emergencies and comprises about 1% to 2% of all pregnancies in the United States [2]. The most common site of ectopic pregnancies is the fallopian tubes. Only 2% to 4% of all ectopic pregnancies occur in the interstitial or cornual part of the uterus

[3]. Other rare conditions, such as recurrent ectopic pregnancy in the ipsilateral oviduct after previous laparoscopic partial salpingectomy have also been reported [5]. Oftentimes, the terms interstitial ectopic pregnancy and cornual ectopic pregnancy are used interchangeably. However, strictly speaking, an interstitial ectopic pregnancy refers to a gestational sac implantation within the proximal intramyometrial segment of the fallopian tube whereas a cornual ectopic pregnancy refers to a gestational sac implantation in the upper lateral cornus of the uterine cavity of a bicornuate uterus [4,6]. While it may be an uncommon type of ectopic pregnancy, an interstitial pregnancy has a mortality rate that is 6–7 times higher than other ectopic pregnancies due to its implantation zone and proximity to the major uterine blood vessels and its susceptibility to rupture at a later gestational age which may cause severe hemorrhage [7]. Furthermore, the unique anatomic location of the ectopic pregnancy allows for the myometrial layer of the uterus surrounding the interstitial part of the fallopian tube to protect the gestational sac and allow it to expand which may delay the rupture of the sac until 7–16 weeks of gestation and allow for the formation of a large amount of blood vessels [3,4]. This often results in catastrophic hemorrhage at the time of rupture due to the rich supply of blood in the area. Therefore, early diagnosis and timely treatment is critical to avoid further complications and possible mortality.

Risk factors for interstitial or cornual ectopic pregnancy are generally similar to those of all ectopic pregnancies. Past studies have found that pelvic inflammatory disease, previous pelvic or abdominal cavity surgery, uterine anomalies or malformations, uterine tumors, and assisted reproductive technologies all increase the rate of ectopic pregnancies [2,8–11].



Table 1. Management Options for Interstitial or Cornual Ectopic Pregnancy

Medical Management	Surgical Management
Ideal indications:	Indications:
<ul style="list-style-type: none"> - Hemodynamically stable patient - Patient is reliable to adhere to follow-up appointments - Sonography: no fetal cardiac activity; gestational sac <3.5 cm in diameter; unruptured mass - Beta-hCG levels <5000 mIU/mL - No significant comorbidities or contraindications to methotrexate (e.g., active pulmonary disease, active peptic ulcer disease, breastfeeding, intrauterine gestational sac, thrombocytopenia, immunodeficiency, hepatic disease, renal disease, leukopenia) 	<ul style="list-style-type: none"> - Hemodynamic instability - Physical exam: peritoneal signs present - Sonography: fetal cardiac activity; substantial ascites; ruptured mass - Patient preference or suspected poor patient compliance - Significantly elevated beta-hCG levels - Failure of conservative treatment - Significant comorbidities or contraindications to medical management with methotrexate

As with all ectopic pregnancies, the management plan of action is split into medical management and surgical management. Management plans for an interstitial or cornual ectopic pregnancy are presented in Table 1. Generally, treatment plans should be specific to the patient considering the obstetric history of the patient, the gestational age of the ectopic pregnancy at time of diagnosis and the need for preservation of fertility. Traditionally, medical management consists of single-dose or multi-dose courses of methotrexate whereas surgical management generally consists of a salpingectomy or salpingostomy. However, due to the position of the interstitial or cornual pregnancy, a cornual resection is generally necessary if surgical intervention is warranted.

If an early diagnosis of interstitial or cornual ectopic pregnancy can be made while the patient is hemodynamically stable, with a lower beta-human chorionic gonadotropin (beta-hCG) level, and at an earlier gestational age, there is a chance of success with medical management via methotrexate [3,12]. However, patients should be well counseled that this conservative medical management has a relatively high failure rate with past reports showing a failure rate ranging from 9% to 65% and an operation may still be necessary if there is rupture of the ectopic pregnancy [13,14]. Methotrexate is an antifolate antimetabolite which can halt the division of cells in the ectopic pregnancy [15]. Before the administration of methotrexate, blood laboratories with complete blood count, complete metabolic panel, and beta-hCG should be obtained due to the contraindications to methotrexate which include breastfeeding, intrauterine pregnancy, active peptic ulcer disease, liver disease, anemia, leukopenia, thrombocytopenia and renal insufficiency [16]. Systemic administration of methotrexate for an interstitial or cornual ectopic pregnancy generally follows the same guidelines as all ectopic pregnancies with either a single-dose or multi-dose treatment course. Beta-hCG levels must be closely monitored to ensure the effectiveness of the treatment regimen. Past studies have shown that unruptured ectopic masses in size greater than 3.5 cm in diameter, with fetal heart beats, and/or with beta-hCG levels greater than 5000 mIU/mL have a higher propen-

sity for failure of conservative treatment [17]. Studies have found that the success rates of single-dose methotrexate for treatment of ectopic pregnancies have decreased as beta-hCG levels increase. At a beta-hCG level less than 1000 mIU/mL, the success rate has been found to be 98% but this success rate decreases to 81% if the beta-hCG level is higher than 10,000 mIU/mL [14,17–20]. Therefore, past studies have found that medical management with methotrexate should be used in caution with patients who present with an ectopic pregnancy and a beta-hCG level higher than 5000 mIU/mL [20]. Traditionally, a beta-hCG threshold of 5000 mIU/mL was utilized as a predictor of the potential success of conservative treatment. However, many recent studies have noted the possibility of utilizing a combination of methotrexate and mifepristone to treat interstitial ectopic pregnancies with a high level of serum beta-hCG [21–24]. Past studies have found that the combination of mifepristone and methotrexate have a synergistic effect and could induce the trophoblast lysis more rapidly than methotrexate alone [24]. While results are promising, more studies are needed to assess the efficacy of this protocol. A viable alternative to systemic methotrexate administration is direct methotrexate injection to the interstitial ectopic pregnancy either via transvaginal ultrasound guided or laparoscopically which has been shown to be a safe and effective treatment option [25]. Some studies have found that with the right patient selection, local methotrexate treatment had a success rate of 91% [3]. Another strategy for conservative treatment involves uterine artery embolization under fluoroscopic guidance with or without the use of methotrexate. However, this treatment protocol remains experimental until more studies can be conducted regarding its safety and efficacy in the treatment of interstitial ectopic pregnancies [26]. Furthermore, there have been some cases where women treated with uterine artery embolization experienced endometrial atrophy and infertility [27].

Immediate surgical intervention should be conducted if the patient exhibits serious signs and symptoms of a ruptured ectopic pregnancy or impending shock signs due to the high mortality rate of interstitial ectopic pregnancies. Generally, due to its placement, surgical management of an

interstitial or cornual ectopic pregnancy requires a hysterectomy, wedge resection or partial cornual resection either via laparoscopy or laparotomy [28–30]. As with any surgical operation involving the fallopian tube or uterus, adequate patient education and counseling should be conducted to educate the patient regarding future fertility and possible risk of uterine rupture in subsequent pregnancies. Traditionally, treatment of an interstitial or cornual ectopic pregnancy was via hysterectomy or cornual resection. Intraoperatively, to minimize blood loss, there have been a wide variety of different techniques reported including laparoscopic injection of vasoconstrictors, vaginal misoprostol insertion, ligation of the ascending branches of the uterine vessel, uterine devascularization, the use of fibrin glue, or the use of tourniquets [31–34]. With recent advances in minimally invasive surgeries, in women who still require fertility and with an interstitial ectopic pregnancy at an earlier gestational age, a laparoscopic cornuostomy may be considered but gestational tissue should be removed as completely as possible to avoid further complications [3,35,36]. The laparoscopic cornuostomy is a more conservative surgical approach which can better preserve the integrity of the uterus to aid in future fertility. To prevent the risk of uterine rupture in future pregnancies, all efforts should be made in the preservation of normal uterine tissue, avoid excessive electrocauterization, minimal excision of the cornual tissue, and suture closure of the defect [33,37,38]. The type of suture used intraoperatively can decrease the intraoperative blood loss and ensure optimal myometrial status. Past studies have presented a wide variety of sutures that may be utilized during the interstitial or corneal pregnancy operation including a square suture to achieve hemostasis by compression, an encircling suture which may act like a tourniquet around the ectopic gestational sac, automatic staplers, and the use of endoloop or stapler devices [39]. During subsequent pregnancies, close antenatal surveillance is necessary to monitor the risk of uterine rupture and decrease the incidence of recurrent cornual or interstitial ectopic pregnancies. Usually, future pregnancies will require cesarean deliveries to reduce the risk of uterine rupture in labor [26,37].

3. Conclusions

Interstitial ectopic pregnancy is a rare type of ectopic pregnancy but it has a high mortality rate. Early recognition and accurate diagnosis of an interstitial or cornual ectopic pregnancy is critical for the safety and wellbeing of the patient especially due to the increased risk of massive hemorrhage. With advances in both diagnostic techniques and advances in minimally invasive surgery, interstitial pregnancies can be treated with success either medically or surgically. The hemodynamic status of the patient as well as any future fertility desires can assist both the patient and physician in making a decision regarding treatment modality.

Author Contributions

Authors YLL and EY contributed equally to the conception of this review. EY conducted the review of literature and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Creanga AA, Shapiro-Mendoza CK, Bish CL, Zane S, Berg CJ, Callaghan WM. Trends in Ectopic Pregnancy Mortality in the United States. *Obstetrics & Gynecology*. 2011; 117: 837–843.
- [2] Marion LL, Meeks GR. Ectopic pregnancy: History, incidence, epidemiology, and risk factors. *Clinical Obstetrics and Gynecology*. 2012; 55: 376–386.
- [3] Lau S, Tulandi T. Conservative medical and surgical management of interstitial ectopic pregnancy. *Fertility and Sterility*. 1999; 72: 207–215.
- [4] Sharma N, Rohini, Upasana. An ectopic pregnancy in the tubal interstitium: beware! *Journal of Clinical and Diagnostic Research*. 2013; 7: 160–162.
- [5] Liu YL, Hwang KS, Chu PW, Ding DC. Recurrent ectopic pregnancy in the ipsilateral oviduct after prior laparoscopic partial salpingectomy. *Taiwanese Journal of Obstetrics & Gynecology*. 2009; 48: 417–419.
- [6] Malinowski A, Bates SK. Semantics and pitfalls in the diagnosis of cornual/interstitial pregnancy. *Fertility and Sterility*. 2006; 86: 1764.e11–1764.e14.
- [7] Loukopoulos T, Zikopoulos A, Mastora E, Galani A, Stavros S, Kolibianakis E. Multidose methotrexate treatment of cornual pregnancy after *in vitro* fertilization: Two case reports. *Case Reports in Women's Health*. 2021; 33: e00376.
- [8] Bu Z, Xiong Y, Wang K, Sun Y. Risk factors for ectopic pregnancy in assisted reproductive technology: a 6-year, single-center study. *Fertility and Sterility*. 2016; 106: 90–94.
- [9] Kashanian M, Baradaran HR, Mousavi SS, Sheikhsari N, BararPour F. Risk factors in ectopic pregnancy and differences between adults and adolescents, is consanguinity important? *Journal of Obstetrics and Gynaecology*. 2016; 36: 935–939.
- [10] Ranji GG, Usha Rani G, Varshini S. Ectopic Pregnancy: Risk Factors, Clinical Presentation and Management. *The Journal of Obstetrics and Gynecology of India*. 2018; 68: 487–492.
- [11] Weiss A, Beck-Fruchter R, Golan J, Lavee M, Geslevich Y, Shalev E. Ectopic pregnancy risk factors for ART patients undergoing the GnRH antagonist protocol: a retrospective study. *Reproductive Biology and Endocrinology*. 2016; 14: 12.
- [12] Po L, Thomas J, Mills K, Zakhari A, Tulandi T, Shuman M, *et al*. Guideline no. 414: Management of Pregnancy of Unknown Location and Tubal and Nontubal Ectopic Pregnancies. *Journal of Obstetrics and Gynaecology Canada*. 2021; 43: 614–630.e1.

- [13] Tulandi T, Al-Jaroudi D. Interstitial Pregnancy: Results Generated from the Society of Reproductive Surgeons Registry. *Obstetrics & Gynecology*. 2004; 103: 47–50.
- [14] Tang A, Baartz D, Khoo SK. A medical management of interstitial ectopic pregnancy: a 5-year clinical study. *The Australian and New Zealand Journal of Obstetrics and Gynaecology*. 2006; 46: 107–111.
- [15] Stika CS. Methotrexate: the pharmacology behind medical treatment for ectopic pregnancy. *Clinical Obstetrics & Gynecology*. 2012; 55: 433–439.
- [16] Shetty A, Cho W, Alazawi W, Syn W. Methotrexate Hepatotoxicity and the Impact of Nonalcoholic Fatty Liver Disease. *The American Journal of the Medical Sciences*. 2017; 354: 172–181.
- [17] Bachman EA, Barnhart K. Medical management of ectopic pregnancy: a comparison of regimens. *Clinical Obstetrics & Gynecology*. 2012; 55: 440–447.
- [18] Dardalas I, Rigopoulos P, Pourzitaki C. Treatment of ectopic pregnancy with methotrexate. *Archives of Gynecology and Obstetrics*. 2019; 300: 1093–1094.
- [19] Levin G, Dior UP, Shushan A, Gilad R, Benschushan A, Rottenstreich A. Success rate of methotrexate treatment for recurrent vs. primary ectopic pregnancy: a case-control study. *Journal of Obstetrics and Gynaecology*. 2020; 40: 507–511.
- [20] Menon S, Colins J, Barnhart KT. Establishing a human chorionic gonadotropin cutoff to guide methotrexate treatment of ectopic pregnancy: a systematic review. *Fertility and Sterility*. 2007; 87: 481–484.
- [21] Gómez García MT, Aguarón Benítez G, Barberá Belda B, Callejón Rodríguez C, González Merlo G. Medical therapy (methotrexate and mifepristone) alone or in combination with another type of therapy for the management of cervical or interstitial ectopic pregnancy. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*. 2012; 165: 77–81.
- [22] Sorrentino F, Vaschiaveo L, De Feo V, Zanzarelli E, Grandone E, Stabile G, *et al.* Interstitial Pregnancy Treated with Mifepristone and Methotrexate with High Serum β -hCG Level in a Patient Wishing to Preserve Fertility: Time to Define Standardized Criteria for Medical/Surgical Therapy? *International Journal of Environmental Research and Public Health*. 2022; 19: 11464.
- [23] Stabile G, Romano F, Buonomo F, Zinicola G, Ricci G. Conservative Treatment of Interstitial Ectopic Pregnancy with the Combination of Mifepristone and Methotrexate: our Experience and Review of the Literature. *BioMed Research International*. 2020; 2020: 1–7.
- [24] Stabile G, Romano F, Zinicola G, Topouzova GA, Di Lorenzo G, Mangino FP, *et al.* Interstitial Ectopic Pregnancy: The Role of Mifepristone in the Medical Treatment. *International Journal of Environmental Research and Public Health*. 2021; 18: 9781.
- [25] Monteagudo A, Minior VK, Stephenson C, Monda S, Timor-Tritsch IE. Non-surgical management of live ectopic pregnancy with ultrasound-guided local injection: a case series. *Ultrasound in Obstetrics and Gynecology*. 2005; 25: 282–288.
- [26] Moawad NS, Mahajan ST, Moniz MH, Taylor SE, Hurd WW. Current diagnosis and treatment of interstitial pregnancy. *American Journal of Obstetrics and Gynecology*. 2010; 202: 15–29.
- [27] Torre A, Fauconnier A, Kahn V, Limot O, Bussierrres L, Pelage JP. Fertility after uterine artery embolization for symptomatic multiple fibroids with no other infertility factors. *European Radiology*. 2017; 27: 2850–2859.
- [28] Hwang JH, Lee JK, Lee NW, Lee KW. Molar Ectopic Pregnancy in the Uterine Cornus. *Journal of Minimally Invasive Gynecology*. 2010; 17: 239–241.
- [29] Khawaja N, Walsh T, Gill B. Uterine artery ligation for the management of ruptured cornual ectopic pregnancy. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2005; 118: 269.
- [30] Dagar M, Srivastava M, Ganguli I, Bhardwaj P, Sharma N, Chawla D. Interstitial and Cornual Ectopic Pregnancy: Conservative Surgical and Medical Management. *The Journal of Obstetrics and Gynecology of India*. 2018; 68: 471–476.
- [31] Pluchino N, Ninni F, Angioni S, Carmignani A, Genazzani AR, Cela V. Spontaneous Cornual Pregnancy after Homolateral Salpingectomy for an Earlier Tubal Pregnancy: a Case Report and Literature Review. *Journal of Minimally Invasive Gynecology*. 2009; 16: 208–211.
- [32] Nirgianakis K, Papadia A, Grandi G, McKinnon B, Bolla D, Mueller MD. Laparoscopic management of ectopic pregnancies: a comparison between interstitial and “more distal” tubal pregnancies. *Archives of Gynecology and Obstetrics*. 2017; 295: 95–101.
- [33] Hwang JH, Lee JK, Lee NW, Lee KW. Open cornual resection versus laparoscopic cornual resection in patients with interstitial ectopic pregnancies. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2011; 156: 78–82.
- [34] Choi Y, Eun D, Choi J, Shin K, Choi J, Park H. Laparoscopic cornuotomy using a temporary tourniquet suture and diluted vasopressin injection in interstitial pregnancy. *Fertility and Sterility*. 2009; 91: 1933–1937.
- [35] Chan LY, Yuen PM. Successful treatment of ruptured interstitial pregnancy with laparoscopic surgery. A report of 2 cases. *The Journal of Reproductive Medicine*. 2003; 48: 569–571.
- [36] Moon HS, Choi YJ, Park YH, Kim SG. New simple endoscopic operations for interstitial pregnancies. *American Journal of Obstetrics and Gynecology*. 2000; 182: 114–121.
- [37] Ng S, Hamontri S, Chua I, Chern B, Siow A. Laparoscopic management of 53 cases of cornual ectopic pregnancy. *Fertility and Sterility*. 2009; 92: 448–452.
- [38] Moon HS, Kim SG, Park GS, Choi JK, Koo JS, Joo BS. Efficacy of bleeding control using a large amount of highly diluted vasopressin in laparoscopic treatment for interstitial pregnancy. *American Journal of Obstetrics and Gynecology*. 2010; 203: 30.e1–30.e6.
- [39] Biffi A, Damiani GR, Pellegrini AM, Quartucci A, Di Gennaro D, Boca GD. Cornual Pregnancy. *Journal of Minimally Invasive Gynecology*. 2022; 29: 327–328.