



The Medical Management of Interstitial Pregnancy: A Case Series and Literature Review

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Abstract

Introduction: Interstitial pregnancies are a rare form of ectopic pregnancy, and their diagnosis and treatment can be challenging.

Results: This case series presents three cases of interstitial pregnancies successfully treated with intramuscular methotrexate.

Conclusion: Methotrexate is an effective treatment for interstitial pregnancies, even in cases with high β -hCG levels or fetal cardiac activity. For patients who can be closely monitored, medical treatment provides a good alternative to surgery.

Introduction

An interstitial pregnancy is a rare form of ectopic pregnancy. It occurs when the blastocyst implants in the interstitial portion of the fallopian tube [1,2]. This interstitial segment is the most proximal part of the fallopian tube located within the myometrium, measuring approximately 0.7 mm in width and 1 to 2 cm in length [3]. The incidence of ectopic pregnancies is 11 per 1,000 pregnancies [4]. Interstitial pregnancies account for 2–6.8% of all ectopic pregnancies [5].

Most ectopic pregnancies occur in the fallopian tubes. However, in recent years, there has been a significant increase in the number of ectopic pregnancies that occur outside the uterine cavity but within the boundaries of the uterus, such as cesarean scar pregnancies, cervical, intramural, and interstitial pregnancies. Risk factors for these types of ectopic pregnancies include scar formation or incomplete uterine healing after surgical trauma, for example, from a cesarean section, myomectomy, or operative hysteroscopy [1]. The increase in interstitial pregnancies can be attributed to advancements in ultrasound diagnostics and the use of assisted reproductive techniques. Risk factors for interstitial pregnancies include previous ectopic pregnancies, tubal surgery, in-vitro fertilization (IVF), and a history of sexually transmitted infections [6].

These uterine ectopic pregnancies often initially present with mild clinical symptoms and frequently involve a living embryo [1]. The surrounding uterine wall around the interstitial pregnancy prevents early rupture,

therefore women present with a higher gestational age compared to tubal ectopic pregnancies. The diagnosis of an interstitial pregnancy can be complex due to the difficulty of distinguishing it from eccentric intrauterine or isthmic tubal pregnancies on ultrasound [7,8]. The high sensitivity of ultrasound, provided adequate expertise is available, makes it the best first-line diagnostic method for detecting interstitial pregnancies. According to the guidelines of the ‘Royal College of Obstetricians and Gynaecologists’ (RCOG) [9], the following ultrasound criteria can be used for diagnosis: 1) an empty uterine cavity, 2) a gestational sac or pregnancy products located laterally in the interstitial part of the fallopian tube, surrounded by less than 5 mm of myometrium in all planes, and 3) the presence of the interstitial line sign. The interstitial line sign is an echogenic line extending from the endometrium to the interstitial mass or gestational sac, with a sensitivity of 80% and a specificity of 98% for the diagnosis of an interstitial pregnancy [10]. There is no evidence that 3D ultrasound is more accurate than 2D ultrasound for diagnosing interstitial pregnancies. However, it is easy to demonstrate the interstitial nature of the pregnancy with 3D ultrasound by assessing the coronal plane.

Interstitial pregnancies are a subtype of tubal ectopic pregnancies and can be classified as partial or complete. In a partial interstitial pregnancy, the gestational sac is partially implanted in the interstitial segment of the fallopian tube but also partially protrudes through the ostium of the fallopian tube into the uterine cavity. In a complete interstitial pregnancy, the gestational sac is entirely

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located in the intramural portion of the fallopian tube [1]. Most interstitial pregnancies grow laterally in the proximal segment of the fallopian tube, and ectopic pregnancies that stay confined to the interstitial segment of the fallopian tube are relatively rare [8].

Interstitial pregnancies are considered one of the most dangerous forms of ectopic pregnancy due to the risk of life-threatening hemorrhage. These hemorrhages occur due to rupture of the intramural part of the fallopian tube, which is surrounded by the myometrium and proliferating blood vessels. This can lead to hypovolemic shock or maternal death. Interstitial pregnancies have an estimated mortality rate of 2–5%, which is seven times higher than the average for all ectopic pregnancies [11]. Another explanation for the significant blood loss during the rupture of an interstitial pregnancy is that these ectopic pregnancies are larger at the time of rupture compared to tubal ectopic pregnancies, as the overlying myometrium can accommodate larger pregnancies before rupture occurs compared to the fallopian tube. Early diagnosis is essential to reduce complications and allow timely intervention.

Case series

Case 1

The first case concerns a 43-year-old patient with an undesired pregnancy and amenorrhea of 5 weeks and 4 days. The patient was G4P2A1. Her obstetric history included two cesarean sections and a spontaneous early miscarriage. Her

medical history noted paraplegia caused by post-measles encephalomyelitis. She was asymptomatic and presented with stable parameters and no tenderness in the abdomen. Serum β -hCG was 11,389 IU/L, and progesterone was 31 ng/ml. Ultrasound revealed a thin endometrium, an empty uterine cavity, a normal right ovary, a left ovary with a corpus luteum, and no fluid in the pouch of Douglas. A complete interstitial pregnancy was observed on the left side, measuring 22x26x24 mm, without a yolk sac or embryo. It was surrounded by a thin myometrium (< 5 mm), and the interstitial line sign was observed (Figure 1).

The patient was treated with 95 mg intramuscular (IM) methotrexate (a dose of 1 mg/kg body weight). Between day 4 and day 7, there was only a 4% decrease in β -hCG (Figure 2), necessitating a second methotrexate injection on day 7. The patient remained asymptomatic during the treatment. On day 14, the interstitial pregnancy appeared unchanged in size on ultrasound, but had a slightly collapsed aspect. Weekly clinical and biological follow-ups were planned. β -hCG became negative after 149 days. After β -hCG negativity, she started progestogen-only oral contraception. The follow-up ultrasound, performed two months after achieving β -hCG negativity, confirmed the complete resolution of the interstitial mass.

Case 2

The second case describes a 42-year-old patient with an unplanned but desired pregnancy and 10 weeks and 3 days of amenorrhea. She presented to the emergency department due

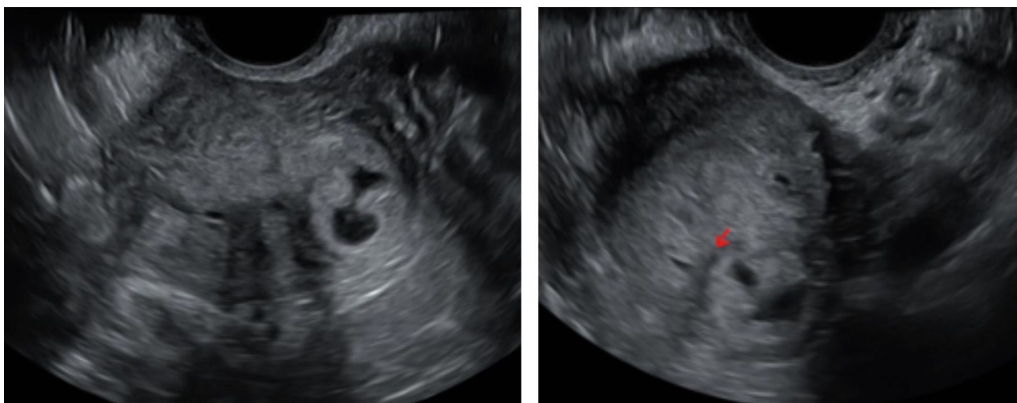


Figure 1. Case 1: A) 2D ultrasound B) 2D ultrasound, the arrow indicates the 'interstitial line sign'

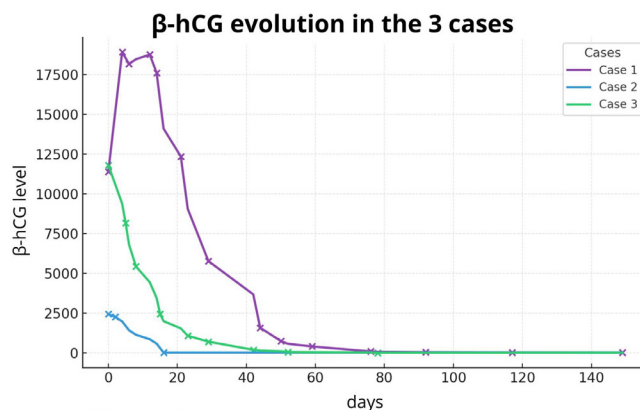


Figure 2. The evolution of β -hCG levels in the 3 cases

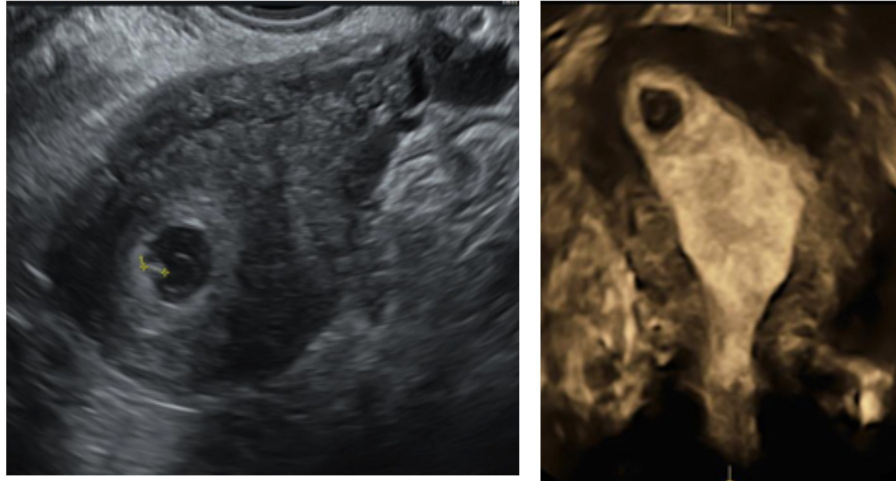


Figure 3. Case 2: A) 2D ultrasound with CRL measurement B) 3D ultrasound

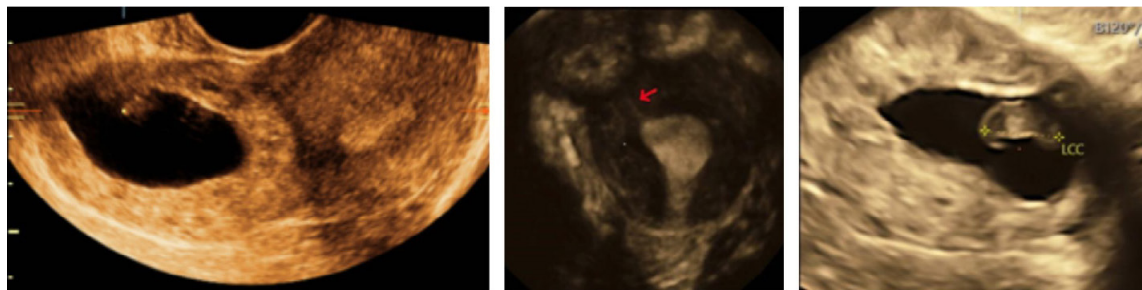


Figure 4. Case 3: A) 2D ultrasound B) 3D ultrasound, the arrow indicates the 'interstitial line sign' C) 2D ultrasound with CRL measurement

to vaginal bleeding. The patient was G4P2A1, with a history of two vaginal deliveries and a spontaneous early miscarriage. She reported no pain, was clinically stable, and had a non-tender abdomen. Only a small quantity of brown spotting was observed. Her β -hCG level was 2,425 IU/L, and progesterone was 5.3 ng/ml. Ultrasound showed a thick endometrium but an empty uterine cavity, a right ovary with a corpus luteum, a normal left ovary, and no fluid in the pouch of Douglas. A partial interstitial pregnancy was observed on the right side, measuring 15x13x10 mm. It contained a gestational sac with a yolk sac and an embryo with a crown-rump length (CRL) of 3.4 mm without cardiac activity (Figure 3). The surrounding myometrium was thinner than 5 mm, and no interstitial line sign was observed.

Due to the low progesterone level and the patient's age, a spontaneous abortion of the pregnancy was suspected, and initial clinical and biological follow-up was scheduled 48 hours later. At the follow-up 2 days later, β -hCG had slightly decreased to 2,246 IU/L, and progesterone remained at 5.3 ng/ml. However, ultrasound showed an increase in CRL to 4.4 mm and presence of cardiac activity. She received medical treatment, a single dose of 75 mg methotrexate IM. By day 16 after the methotrexate injection, β -hCG was negative (Figure 2). However, the patient did not attend further follow-up appointments, and follow-up imaging was not available.

Case 3

The third case involves a 30-year-old patient with a desired

spontaneous pregnancy and amenorrhea of 5 weeks and 5 days. She was G3P0A2, with a history of two medical abortions. She was asymptomatic and clinically stable with a soft abdomen. Her β -hCG was 11,798 IU/L, and progesterone was 3.1 ng/ml. Ultrasound showed a thick endometrium but an empty uterine cavity, two normal-appearing ovaries, and no fluid in the pouch of Douglas. A complete interstitial pregnancy was observed on the right side, measuring 30x32x42 mm, with a gestational sac, no yolk sac and an embryo with a CRL of 10 mm without cardiac activity (Figure 4). The surrounding myometrium measured less than 5 mm, and the interstitial line sign was identified.

Given her nulliparity and desire for future pregnancy, medical treatment with systemic methotrexate (85 mg IM) was chosen. β -hCG decreased by 33% between day 4 and day 7 and became negative after 78 days (Figure 2). Follow-up ultrasound 2 months after β -hCG negativity showed the persistence of the interstitial mass, however a reduction in size and decomposition of the gestational sac was noted. Complementary imaging was performed using magnetic resonance imaging (MRI), which revealed an interstitial mass on the right side with a necrotic center, measuring 44x38x36 mm (Figure 5). The patient expressed a desire to conceive within a year. She was advised to undergo ultrasound evaluations every three months to monitor resolution.

The evolution of β -hCG in the three cases is depicted in Figure 2.



Figure 5. Case 3: T2 weighted MRI image in the axial plane.

Literature Review and Discussion

Medical treatment and route of administration

Methotrexate is a folic acid antagonist that inhibits the enzyme dihydrofolate reductase, thereby disrupting DNA synthesis in rapidly dividing cells, such as trophoblasts [12]. Over the past decades, systemic methotrexate has been widely accepted as the first-line treatment for non-ruptured tubal ectopic pregnancies [13]. This has led to research on the use of methotrexate for the treatment of interstitial pregnancies. Medical treatment is now considered a promising alternative to surgery, particularly in cases where fertility preservation is a priority. Conservative treatments, including expectant management or medical treatment, can only be offered to patients who are hemodynamically stable and have no clear risks of immediate rupture, such as rapidly rising β -hCG levels. Strict follow-up is essential to ensure the success of this approach. However, the optimal medical treatment regimen for interstitial pregnancies remains unknown.

Methotrexate can be administered systemically, intramuscular and intravenous, or locally—via injection into or near the gestational sac under laparoscopic, ultrasound, or hysteroscopic guidance. Potassium chloride can also be injected directly into the gestational sac. These local methods are more invasive, require specialized facilities and trained personnel, and are therefore less accessible and more expensive than systemic methotrexate injections. A review found no evidence that local injections are advantageous in the treatment of interstitial pregnancies [5].

Success rates for methotrexate treatment range from 79.9% for systemic methotrexate to 97.8% for local methotrexate injection; however, study sizes were too small to demonstrate a statistically significant difference [5]. Factors such as initial β -hCG levels, gestational sac size, gestational age, maternal age, or fetal cardiac activity do not appear to significantly affect the effectiveness of methotrexate treatment [5]. A retrospective Australian study of 31 interstitial pregnancies found a single high-dose intravenous methotrexate regimen, combined with folinic acid, to be successful with a 93.9% success rate. This study showed that 22 of 24 women (91.7%) with β -hCG levels

above 5,000 IU/L, as well as six of seven cases (85.7%) with fetal cardiac activity, were successfully treated. In this study, one patient even had a very high initial β -hCG level of 106,000 IU/L [14]. Factors that appear to correlate with the failure of medical treatment include persistent embryonic cardiac activity or a rise in β -hCG levels after an initial decline [14], as well as a history of two previous ectopic pregnancies [15]. Additionally, it was shown that a declining β -hCG level after methotrexate treatment does not exclude the possibility of rupture.

The time to β -hCG negativity reported in the literature varies between 10 and 97 days. No difference in β -hCG resolution time was observed between expectant management, systemic methotrexate, or local methotrexate [16]. The combination of methotrexate with a single dose of oral mifepristone (600 μ g) has also been proven successful in studies [17,18].

Although methotrexate remains an effective conservative treatment, there is insufficient evidence to favor a systemic or local approach [9]. Future studies are needed to determine the optimal treatment regimen and further investigate specific risk factors for treatment failure.

Surgical treatment

For patients who are hemodynamically unstable or in whom medical therapy fails, surgery remains the primary option. More conservative techniques, such as cornuostomy instead of cornual resection, and laparoscopy instead of laparotomy, are increasingly being used [5,9]. Cornuostomy removes the interstitial pregnancy while preserving the uterine anatomy. Cornuostomy causes less damage to the fallopian tubes than cornual resection and results in better future pregnancy outcomes [19]. In contrast, cornual resection carries an increased risk of uterine rupture in future pregnancies due to the removal of myometrium and the creation of an extensive uterine scar. Liao et al. reported an incidence of 30% for uterine rupture and dehiscence following cornual resection. This is significantly higher than the rates of uterine rupture after a myomectomy, which typically range from 0.49% to 0.70% in subsequent pregnancies [20]. Therefore, this procedure is recommended only in cases of rupture or when there is no desire for future pregnancies. A systematic review by Cucinella et al. compared 156 cases of cornuostomy with 198 cases of cornual resection. Pregnancy rates were 72% and 62%, respectively, with live birth rates of 48% versus 62% [19]. The differences were not statistically significant.

Conservative surgical techniques can be combined with uterine artery embolization to reduce the risk of bleeding. Uterine arterial embolization has also been combined with systemic methotrexate injections [21]. Alternative surgical techniques include hysteroscopic resection under laparoscopic or ultrasound guidance [22,23] and transcervical aspiration under laparoscopic or hysteroscopic guidance [24]. However, there is insufficient evidence regarding the safety and complications in future pregnancies to recommend these alternative surgical methods [9].

Currently, there is no standardized treatment, emphasizing the need for further studies [5]. For tubal ectopic pregnancies, a randomized controlled trial (RCT) demonstrated that future pregnancy rates do not differ between women treated with medical therapy (methotrexate), conservative surgery (salpingostomy), or radical surgery (salpingectomy) [25].

Follow-up after medical treatment

β -hCG Resolution interval

In cases 1 and 3 respectively, a double and single dose of methotrexate were administered, resulting in β -hCG levels becoming negative after 149 and 78 days. This is significantly longer than what is reported in the literature. A review demonstrated that the initial β -hCG level is not indicative of treatment success [5]. However, it may impact the time to negativity. An observational study of 17 women with interstitial pregnancies treated with systemic methotrexate reported a success rate of 94%, with a median time to β -hCG negativity of 48 days [26]. In this study however, a multidose regimen was used when the initial β -hCG exceeded 5,000 IU/L. A meta-analysis comparing multidose and single-dose methotrexate protocols for the treatment of tubal ectopic pregnancy found similar success rates, but the multidose methotrexate regimen was associated with more side effects [27]. However, the study by Poon et al. on interstitial pregnancies showed that the biochemical resolution of β -hCG after methotrexate treatment does not occur faster than the resolution after expectant management [28]. It remains unclear whether a multidose methotrexate regimen for interstitial pregnancies would result in faster β -hCG resolution and be more advantageous for patients with a desire for future pregnancies compared to a single-dose treatment protocol.

Residual ectopic pregnancy

In case 3, the patient had a desire for pregnancy, and the interstitial mass remained visible on ultrasound and MRI imaging despite β -hCG negativity. To our knowledge, no studies have been published that track ultrasound findings after methotrexate-treated interstitial pregnancies. The impact on future pregnancy chances and the safe interpregnancy interval is unknown. Successful pregnancies following medical treatment of interstitial pregnancies have been documented [14].

For conservatively treated tubal ectopic pregnancies, 95% were no longer detectable on ultrasound three months after serum β -hCG normalized (29). The term 'residual ectopic pregnancy' is used when an ectopic pregnancy remains visible on ultrasound for more than three months after serum β -hCG has dropped to <20 IU/L [1].

Conclusion and Recommendation

This case series demonstrates the successful medical management of three interstitial pregnancies, two of which were associated with high β -hCG levels ($> 10,000$ IU/L) and one with fetal cardiac activity. The conservative treatment of interstitial pregnancy avoids surgical interventions and can improve obstetric outcomes for future pregnancies. The applicability of this conservative medical treatment must be tailored to the patient, taking into account her obstetric history and any desire for future pregnancies. We present a case where the interstitial mass remains visible on both ultrasound and MRI imaging despite β -hCG negativity and the impact on a future pregnancy remains uncertain.

Medical treatment with systemic methotrexate can be considered as a first-line treatment for interstitial pregnancy in a hemodynamically stable patient, even in cases presenting with fetal cardiac activity or high β -hCG levels.

Declarations

Conflict of Interest Statement

The authors have no competing interests to declare that are relevant to the content of this article.

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