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MEDICAL MANAGEMENT OF INTERSTITIAL ECTOPIC PREGNANCY WITH METHOTREXATE–MIFEPRISTONE COMBINATION: A CASE REPORT.

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ABSTRACT:
Interstitial ectopic pregnancy (IEP) is a rare condition with a high risk of rupture and hemorrhage. While surgical intervention is the gold standard, this case highlights successful medical management using methotrexate combined with mifepristone, offering an alternative to surgery and its related complications. A 30-year-old primigravida presented with abdominal pain and per vaginal spotting. Transvaginal ultrasound with doppler confirmed an 8+1weeks interstitial pregnancy. Despite counselling on surgical options, the patient preferred medical management. A multi-dose methotrexate protocol with leucovorin rescue, supplemented by mifepristone, led to a complete resolution. This case demonstrates the potential of a combined methotrexate-mifepristone regimen in managing IEP non-surgically. The main aim of our medical management approach was to reduce the morbidity and complication associated with surgical management thus emphasising the need for further investigation into its efficacy.
KEYWORDS: Interstitial ectopic pregnancy, Methotrexate, Mifepristone, Medical management, Non-surgical treatment, Beta-hCG monitoring, Transvaginal ultrasonography (TVUS), MRI pelvis, Fertility preservation, Ectopic pregnancy treatment.

INTRODUCTION:

Interstitial ectopic pregnancy (IEP) is a condition in which the blastocyst implants in the interstitial portion of the fallopian tube. Although it is a rare condition and accounts for only 2-6.8% of all ectopic pregnancies it is still potentially life-threatening with a 2-2.5% mortality rate due to complications like massive haemorrhage and uterine rupture because of its close proximity to intramyometrial arcuate vasculature [1][2][3].

Clinical presentation of IEP varies, ranging from symptomatic cases with abdominal pain and vaginal bleeding to asymptomatic cases detected incidentally on early obstetric ultrasound. If missed or left undiagnosed can lead to uterine rupture presenting with haemodynamic instability requiring emergency surgery. Advancements in high resolution transvaginal ultrasonography (TVUS) combined with quantitative beta-human chorionic gonadotropin (beta-hCG) are crucial for diagnosis. In stable patients' magnetic resonance imaging (MRI) can help confirm diagnosis [1][4][5,6].
This case report presents a novel approach to the conservative management of interstitial pregnancy by combining systemic methotrexate with oral mifepristone. This combination has shown promise in other ectopic pregnancies however its application in interstitial pregnancy remains underreported. The feasibility of this non-invasive approach was demonstrated in our case, offering an alternative for patients seeking non-surgical treatment options in IEP.

CASE REPORT:
A 30-year-old primigravida came to our hospital with chief complaints of severe pain in lower abdomen, lower back-pain, giddiness since 2 days and complaint of per vaginal spotting since 1 day. The patient gave history of two months of amenorrhea and her urine pregnancy test was positive. Her gestational age was 8+1 weeks based on her last menstrual period. Her menstrual cycles were regular. The patient was married since 2 years and the current pregnancy was spontaneously conceived. She had no history of co-morbidities, prior ectopic pregnancy, or abdominal surgeries. On examination, the patient was vitally stable. Per abdominal examination revealed a soft, non-tender abdomen. On per speculum examination, minimal bleeding was noted at the cervical OS. Per vaginal examination showed a uterus corresponding to 8 weeks' gestation, with bilateral fornices that were free and non-tender, and no cervical motion tenderness. The patient and her spouse had been trying to conceive for the past two years, but financial constraints hindered her access to professional fertility evaluation and treatment. Now at 30 years of age, she and her spouse voiced concerns regarding their reproductive future.
The patient was admitted, and routine biochemical, serological and haematological investigations, including β-hCG, were conducted. Results were within normal limits, with a β-hCG level of 2940 mIU/ml. The first ultrasonography with doppler revealed a tiny cystic structure beneath the serosal surface in relation to the left uterine cornua, measuring 5.2 mm (corresponding to 5 weeks 2 days), with a thick echogenic rim and peripheral vascularity, uterine cavity was empty. A thin rim of myometrial tissue (2 mm) surrounding the cystic structure was noted, raising suspicion for an interstitial ectopic pregnancy which is a a rare but high-risk condition requiring immediate evaluation and management.
To further confirm the diagnosis, an MRI pelvis with contrast was performed. The scan revealed a well-defined T2 hyper-intense cystic lesion measuring approximately 5 × 5 mm in relation to the left cornua of the uterus, located 1.1 cm from the uterine cavity/endometrium. It was surrounded by a slightly T2 hypo-intense rim measuring 2–3 mm in thickness. Multiple foci of blooming were observed on GRE (Gradient Echo Imaging), indicative of haemorrhage. The contrast-enhanced study showed peripheral rim enhancement on sequential T1FS (T1-Weighted Fat-Suppressed) sequences, which became isointense with the rest of the myometrium in delayed sections, further supporting the diagnosis of interstitial ectopic pregnancy (Fig. 1)

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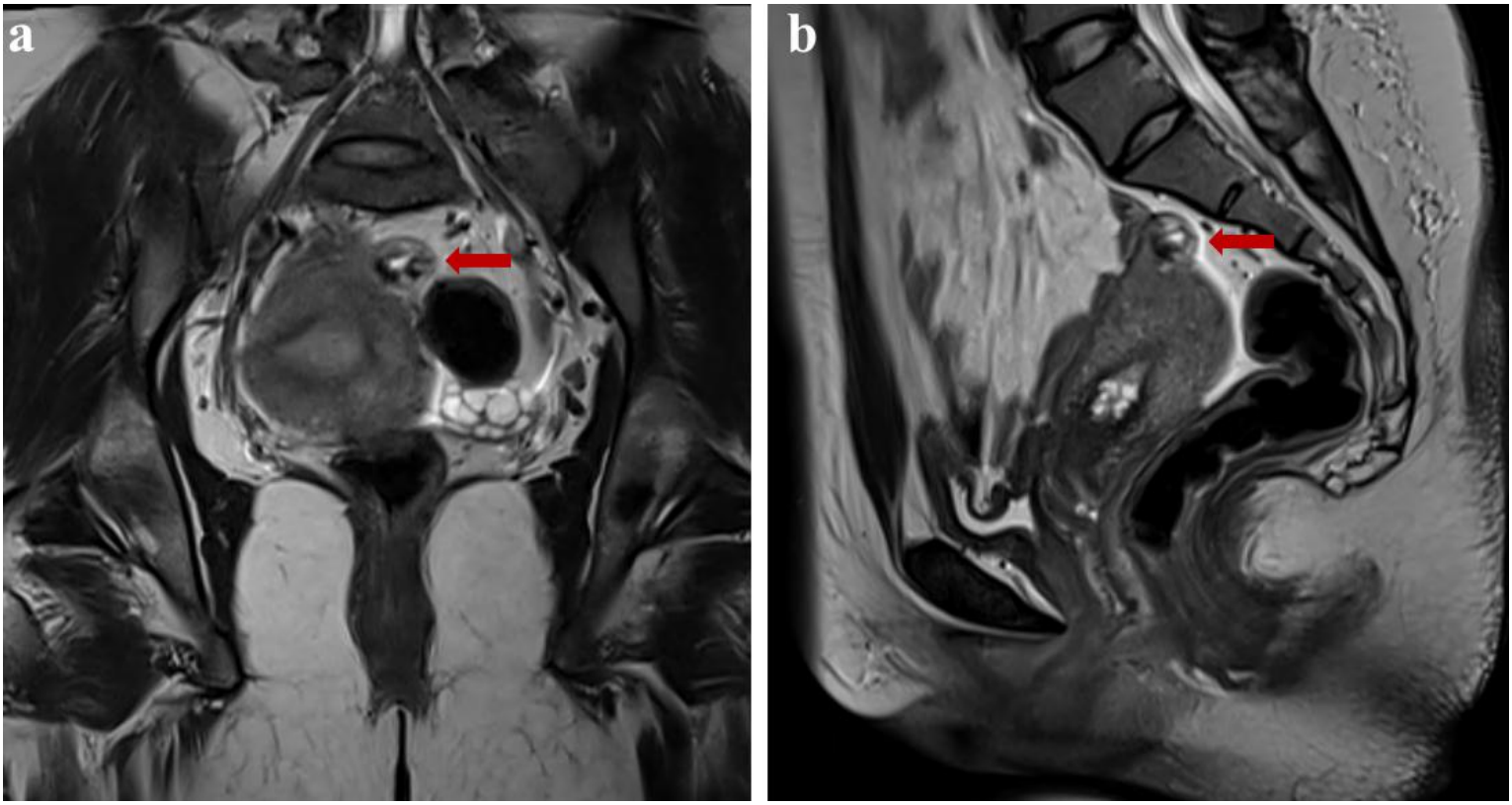

*Fig. 1: MRI with contrast images showing left interstitial ectopic pregnancy (a) Arrow indicating a gestational sac of 5*5 mm in T2-weighted axial magnetic resonance imaging (b) Arrow indicating a gestational sac in relation to the left cornua of the uterus surrounded by slightly T2 hypo-intense rim of 2-3 mm thickness in T2-weighted sagittal magnetic resonance imaging.*

The patient was counselled regarding the high-risk nature of her condition, including the possibility of massive haemorrhage and the need for hysterectomy in case of complications. She was provided with detailed information about various management options, including medical management with systemic methotrexate, surgical interventions such as intragestational injection of methotrexate, laparoscopic cornual wedge resection and cornuostomy, and minimally invasive techniques such as ultrasound-guided transcervical suction under laparoscopic and hysteroscopic guidance. Despite counselling, the patient refused surgical management and opted for medical treatment with systemic methotrexate, expressing willingness to remain hospitalised for close monitoring and agreeing to surgical intervention if an emergency arose. Written informed consent was obtained and high-risk was explained, blood and blood products were reserved, and the anesthesia and operating room teams were alerted regarding the potential need for emergency surgery.

As the patient remained hemodynamically stable, with all laboratory investigations within normal limits. The patient received a total of four intramuscular (IM) doses of methotrexate (50 mg), administered on alternate days, each followed by four IM doses of leucovorin (5 mg) as a rescue therapy to mitigate potential methotrexate toxicity.

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Parameters	Day 1	Day 3	Day 5	Day 7	Day 9	Day 13	Day 27
Hemoglobin (g/dl)	9.2	9.1	8.8	9.3	8.7	8.7	9.5
Total leukocyte count (/µL)	9180	5900	6400	6800	5200	5980	7800
Platelet count (/µL)	376000	339000	305000	312000	257000	305000	308000
Neutrophils (%)	72	76	68	81	68	76	64
Absolute neutrophil count (/µL)	6610	4130	4352	5508	3536	4545	4992

On Day 1 of treatment, in addition to systemic methotrexate therapy, an oral dose of mifepristone (200 mg) was administered to enhance β-hCG decline. The patient's hemogram and serial β-hCG levels were monitored throughout the treatment period (Table 1, Table 2).

She remained hospitalised for 16 days. Initially, β-hCG levels rose from 2940 mIU/ml (Day 1) to 3202 mIU/ml (Day 7), a rise of 10%, raising concerns about inadequate response to methotrexate. However, a subsequent decline to 2402 mIU/ml (Day 9), reflecting a 24.99% reduction from Day 8, indicated treatment efficacy. The β-hCG levels continued to decrease steadily, reaching 638 mIU/ml on Day 16 which is >78% decline from baseline, confirming treatment success. A second ultrasound with doppler also revealed reduction in the size of the gestational sac and reduced peripheral vascularity around gestational sac (Fig. 2) Illustrates the graphical trend of β-hCG decline.

Table 1: Representation of hemogram values from day of admission till day of discharge during Injection Methotrexate therapy

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Days of admission/treatment	Beta-human chorionic gonadotropin (mIU/ml)	Remarks
Day 1	2940	Methotrexate 50mg/dl 1st dose + Mifepristone 200mg per oral
Day 3	3000	Methotrexate 50mg/dl 2nd dose
Day 5	3042	Methotrexate 50mg/dl 3rd dose
Day 7	3202	Methotrexate 50mg/dl 4th dose
Day 8	2766	-
Day 9	2402	-
Day 11	1680	-
Day 14	935	-
Day16	638	Discharged from hospital
Day 29	317	-
Day 43	56	-
Day 60	<1.2	Follow up with beta hCG at non pregnant levels

Table 2: Representation of Serum beta human chorionic gonadotropin on various days of treatment

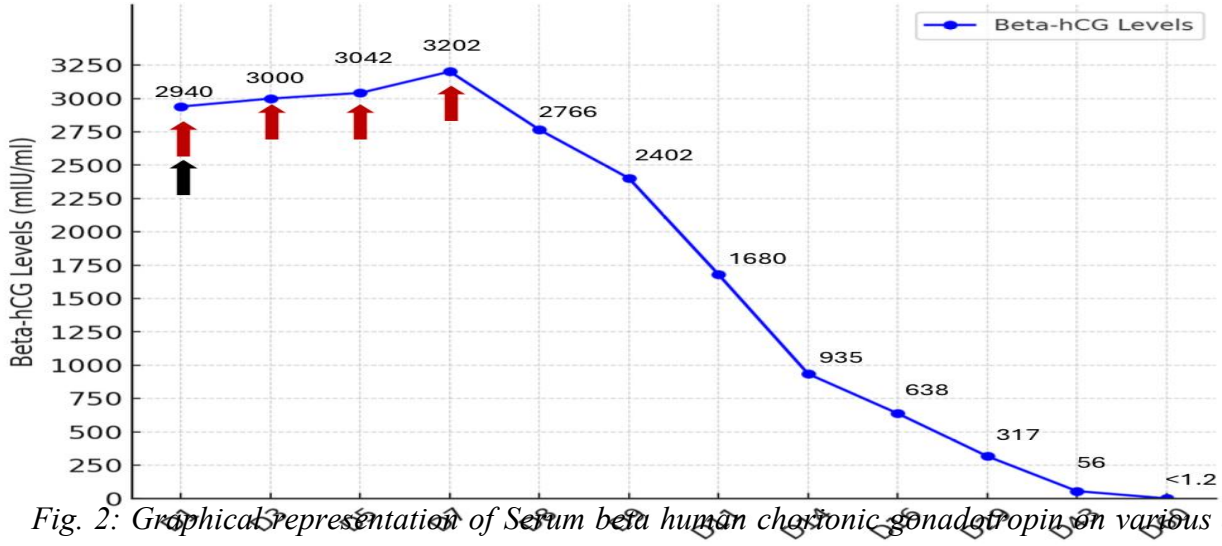

Fig. 2: Graphical representation of Serum beta human chorionic gonadotropin on various days of treatment with red arrow indicating methotrexate 50mg intramuscular dose and black arrow indicating tablet Mifepristone 200mg given per oral.

The patient was discharged and followed up for two months till beta-hCG levels were <1.2mIU/ml which are non-pregnant levels, and a third Ultrasonography report revealed absence of gestational sac at previous left interstitial location.

DISCUSSION:

Interstitial pregnancy is a rare type of ectopic pregnancy in which the blastocyst implants in the interstitial portion of the fallopian tube, the proximal segment that is approximately 0.7 mm wide and 1–2 cm long, embedded within the myometrium [1]. Interstitial ectopic pregnancy constitutes 2–6.8% of all ectopic pregnancies [1]. With a 2–2.5% mortality rate, early detection of interstitial ectopic pregnancy is crucial [2]. Previous history of ectopic pregnancy, previous pelvic surgeries are factors that impair tubal patency and assisted reproductive technologies and ovulation induction therapy impair implantation dynamics making them risk factors for interstitial pregnancy. these factors were ruled out in our case. Additionally, pelvic inflammatory disease (PID) and sexually transmitted infections (STIs) are important considerations [1][2]. Mortality in these cases is due to ectopic rupture causing haemorrhage as the gestational sac lies in close proximity with the intramyometrial arcuate vasculature [3]

The clinical presentation of interstitial pregnancy varies widely, ranging from abdominal pain and/or vaginal bleeding, as seen in our case, to asymptomatic detection on routine early obstetric scan. In severe cases, rupture can lead to hemodynamic instability, requiring emergency surgery. The advent of high-resolution transvaginal ultrasonography (TVUS) in combination with quantitative beta-human chorionic gonadotropin (beta-hCG) assays has facilitated earlier and more precise diagnosis, reducing the risk of complications [1]. Magnetic Resonance Imaging (MRI) can be utilised to confirm the diagnosis of interstitial pregnancy in clinically stable patients [1]. In the present case, all three criteria for diagnosis of interstitial pregnancy were met which are an empty uterine cavity, a gestational sac separate and at least 1 cm from the lateral edge of the uterine cavity and a thin (<5mm) myometrial layer surrounding the chorionic sac [4][5] confirming the diagnosis of interstitial ectopic pregnancy.The patient was thoroughly counselled regarding various management options, including medical therapy with systemic methotrexate and surgical interventions such as intragestational methotrexate injection, laparoscopic cornual wedge resection, and cornuostomy. Minimally invasive approaches like ultrasound-guided transcervical forceps extraction and transcervical suction under laparoscopic and hysteroscopic guidance were also discussed [1].Despite detailed counselling, the patient declined surgical management due to concerns about reduced fertility following unilateral salpingectomy, potential uterine rupture due to myometrial loss, uterine scarring [6]. She opted for medical management with systemic methotrexate, agreed to prolonged hospitalisation for close monitoring, and consented to surgical intervention when needed.In our study, we evaluated the therapeutic efficacy and safety of combination therapy using Mifepristone 200 mg orally and Methotrexate 50 mg/m^2 intramuscularly for the treatment of interstitial ectopic pregnancies. This approach aims to leverage the antiprogesterone effect of mifepristone—which facilitates decidual breakdown and trophoblastic regression—along with methotrexate's cytotoxic action on rapidly dividing trophoblastic cells.Our findings align with existing literature supporting combination regimens. Grynberg et al. (2011) reported successful medical management of interstitial pregnancies using MTX in selected cases, emphasizing the importance of early diagnosis via high-resolution transvaginal sonography.[7] However, methotrexate monotherapy has shown variable success rates, particularly in cases with higher β-hCG levels or persistent gestational cardiac activity. This has led to interest in combining agents to improve outcomes.Cohen et al. (2003) demonstrated that the adjunctive use of mifepristone with MTX improved treatment efficacy in non-tubal ectopic pregnancies, including cervical and interstitial types. [8] Similarly, Rozenberg et al. (2003) in a randomized controlled trial found that the mifepristone-methotrexate combination achieved a shorter resolution time and reduced need for surgical intervention compared to methotrexate alone.[9]In our case, the combination therapy was well-tolerated, with no reported cases of rupture or need for surgical conversion. The mean time to resolution of β-hCG levels was shorter than that historically reported for methotrexate monotherapy. Stovall et al. (1991) had previously outlined methotrexate success rates around 80% in tubal ectopics; however, interstitial

pregnancies are more challenging, and combination therapy may offer a more robust medical approach.[10]Another consideration is the safety profile. No significant adverse effects such as hepatic dysfunction, gastrointestinal toxicity, or hematologic abnormalities were observed, aligning with prior pharmacovigilance studies on mifepristone and methotrexate when used at single-dose protocols (Tang et al., 2001) [11]. Importantly, uterine integrity was preserved in all patients, supporting the role of this regimen in fertility-preserving management. Due to its selective action on rapidly dividing cells, methotrexate may cause neutropenia, generalized myelosuppression, gastrointestinal toxicity (nausea, vomiting, diarrhea, mucositis), and dermatologic reactions (rash, erythema, photosensitivity, alopecia). Hence, regular monitoring of hemogram and beta-hCG levels is essential before administering subsequent doses as done in this case [12].Mifepristone, a steroidal progesterone antagonist, treats ectopic pregnancy (EP) by blocking progesterone secretion, leading to corpus luteum regression, trophoblastic degeneration, and decidual shedding [13]. Studies indicate that mifepristone combined with methotrexate enhances treatment efficacy by synergistically inhibiting embryonic development and promoting trophoblast apoptosis, thereby accelerating symptom resolution (vaginal bleeding, abdominal pain) and mass absorption [13]. Methotrexate-mifepristone, alone or with minimally invasive techniques, may be considered for interstitial ectopic pregnancy management [13].The patient was discharged after a significant decline in beta-hCG levels and a follow-up transvaginal ultrasound (TVUS) with Doppler confirmed a reduction in gestational sac size. She was monitored for two months post-discharge, with beta-hCG levels reaching non-pregnant levels, and a third TVUS confirming complete resolution of the gestational sac, indicating successful medical management. Medical management of interstitial ectopic pregnancy requires vigilant monitoring and patient counselling on associated risks, benefits and potential need for surgical intervention.

Conclusion:

Interstitial pregnancy is a rare type of ectopic pregnancy with an interesting management dilemma as highlighted by this case. The incidence of interstitial pregnancies is rising due to growing use of assisted reproductive technologies and advancements in imaging modalities. Undiagnosed or inadequately managed interstitial pregnancies can lead to catastrophic life-threatening complications like uterine rupture and massive hemorrhage. This case highlights a non-invasive treatment approach with systemic intramuscular methotrexate and oral mifepristone combination therapy for successful management of interstitial ectopic pregnancy for couples desirous of future pregnancy.Due to the non-invasive nature of this approach the advantages were avoidance of surgical morbidity and associated complications, cost-effectiveness, and fertility preservation. However, the strict selection criteria, extended hospitalisation for monitoring, potential methotrexate-related adverse effects and delayed resolution compared to surgical approach were the limitations we encountered.In cases of ruptured interstitial pregnancy or failure of medical management, surgical management remains gold standard, but this case highlights that carefully selected patients can benefit from medical treatment. Further research is needed in this direction to optimise non-surgical protocols.

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AUTHORS CONTRIBUTION

Dr. Pankaj S conceptualised, designed the study and drafted the manuscript. Dr. Rushikesh P collected the data, including relevant photographs, and contributed to manuscript writing. Dr. Vidya G was involved in the final editing and proofreading of the manuscript. All authors collectively revised and approved the final version of the manuscript.

CONFLICT OF INTEREST

Nil.

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