

Successful Treatment of Interstitial Ectopic Pregnancy Using Courses of Methotrexate and Folinic Acid Rescue: A Case Report

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ABSTRACT: The diagnosis of interstitial pregnancy (IP) is a challenge to the healthcare provider and has been documented to be the most difficult ectopic pregnancy (EP) to be diagnosed or managed. Unlike the diagnosis of other forms of EP that has now become precise and reliable, the diagnosis of IP has remained a challenge. Here, we report a case of IP that was suspected intraoperatively during evacuation of retained product of conception. It was successfully managed medically using methotrexate and folinic acid rescue.

KEYWORDS: interstitial pregnancy, medical, methotrexate, folinic acid

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Introduction

The morbidity and mortality rate of interstitial pregnancy (IP) is still high because IP remains the most difficult type of ectopic pregnancy (EP) to be diagnosed preoperatively and is also the most difficult to manage.¹ An overall increase in the incidence of EP has been documented since the introduction of assisted reproductive technology (ART). When the fertilized ovum is implanted well within the cornual/interstitial portion, rupture usually does not occur until 14–16 weeks, but often occurs with severe hemorrhage. Interstitial pregnancies have a mortality rate of 2–2.5%, and these deaths account for 20% of all deaths as a result of ectopic pregnancies.² The development of new technologies and increased awareness and experience of the gynecologist have led to an improved understanding of the best ways to manage non-tubal ectopic pregnancies. Ultrasound scan is the main stay of its diagnosis in modern gynecology. Ultrasound scan, however, can miss the diagnosis of IP or IP can be misinterpreted during ultrasound scan as an eccentrically located intrauterine pregnancy.³ Misdiagnosis of IP as an eccentrically located intrauterine pregnancy led to the failed evacuation of the product of conception. Transvaginal ultrasonography should reveal a gestational sac located in uterine cornual/interstitial aspect of the tube, surrounded by thin myometrial rim with increased vascularity. We present a case of IP that was suspected intraoperatively because of failed evacuation of product of conception. It was managed medically using methotrexate and folinic acid rescue.

Case Report

A woman in her 30s, para 0+3, presented to the Gynaecology Clinic of Abuja Clinics Limited on July 1, 2014 with a year history of inability to conceive. She was married for four years and had three recurrent first trimester miscarriages. Her last miscarriage was about 15 months before her presentation. The other aspects of the history were not contributory. Physical examination was essentially normal. Her hysterosalpingography and her husband's seminal analysis were normal. Her folliculometry suggested anovulation because of polycystic ovarian syndrome. She had ovulation induction using clomifene citrate and timed intercourse. She received the tablet clomifene citrate 100 mg daily for five days starting from the second day of her menses. She had three cycles of treatment before she achieved this index pregnancy.

She presented to the clinic immediately she missed her period. Beta-human chorionic gonadotropin (β hCG) test was positive. The pregnancy was later confirmed using ultrasonography, which revealed single gestational sac with a fetal pole and heartbeat at six weeks. There were fibroid seedlings of varying sizes. She was on preconception folic acid tablet 5 mg daily, which was sustained post-conception. Three weeks later, she presented at the accident and emergency unit with vaginal spotting of five hours duration. Urgent ultrasound scan done revealed a bulky uterus harboring an eccentrically located singleton with no fetal cardiac activity at nine weeks gestation.

She was counseled on the findings and was booked for evacuation of retained product of conception using manual vacuum aspiration. Intraoperatively, the endometrial cavity was empty. A screening ultrasound scan done with uterine sound in situ suggested an interstitial EP. The procedure was discontinued, and the patient was counseled again and referred to the radiology department for further evaluation. A detailed transvaginal ultrasound scan (TVS) done in our radiology department showed a bulky uterus with empty endometrial cavity with its plate well outlined in its course. There was a well-defined 4.5 cm gestational sac located inferior to the endometrial cavity (but not within it) and more to the right cornual end (intramural portion). This sac contained a non-viable fetus with crown rump length of 1.4 cm corresponding to a gestational age of eight weeks and five days. Both adnexae were within normal limits. There was no fluid in the pouch of Douglas. The conclusion was that features were suggestive of a corneal intramural gestation at eight weeks and five days, with coexisting intramural fibroid seedlings.

The couple was counseled extensively on the findings, management options, possible complications, and prognosis. They gave their consent for medical management. The baseline full blood count consisting of packed cell volume, hemoglobin concentration, platelet count, red blood cell count, white blood cell total and differential count – liver function test (LFT), and serum electrolyte, urea, and creatinine (SEUC) done were within normal limits. β hCG quantification was 70,000 mIU/mL.

She was then commenced on the first course of methotrexate and folinic acid. She received intramuscular methotrexate 70 mg (MTX – 1 mg/kg) daily on days 1, 3, 5, and 7, followed by leucovorin calcium (folinic acid 0.1 mg/kg) 7 mg daily on days 2, 4, 6, and 8. She was monitored with ultrasound scan (USS) and β hCG. USS did not show any appreciable change in the status of the pregnancy until three weeks, while the β hCG started dropping after one week of treatment. In the fourth week of follow-up, USS findings remained static and

the β hCG had plateaued at 42,000 mIU/mL. As a result, she received another course of methotrexate and folinic acid, with a resultant steady decline of β hCG until it became negative. FBC, LFT, and SEUC were reassessed, and they remained within normal limits before the commencement of the second course of treatment. On the 21/5/15 (12 weeks after commencement of treatment), the repeat USS revealed that the IP was no longer visualized and the β hCG test was negative. Two weeks later, her menstrual flow returned.

Discussion

EP is still one of the leading causes of maternal morbidity and mortality in sub-Saharan Africa and the world over. The incidence of EP generally is quoted as 2% of all pregnancies with over 95% of the cases being tubal pregnancies. IP is a very rare event in gynecology with an incidence of 1 in 2,500–5,000 live births and accounts for 2–6% of all ectopic pregnancies.^{1,4}

The risk factors of IP are similar to that of other ectopic pregnancies in general, and they include advanced maternal age, ART, previous EP, tubal surgeries, pelvic inflammatory diseases, sexually transmitted diseases, and previous ipsilateral salpingectomy. Other risk factors include tubal sterilization, various tubal pathologies, intrauterine instrumentation, cigarette smoking, infertility and intrauterine exposure to diethylstilbestrol. The risk factors noted in this case were recurrent miscarriages, intrauterine instrumentation, and ovulation induction. Recurrent miscarriages and repeated intrauterine instrumentations can lead to subclinical infections and subsequent subtle damage to the microscopic structures of the tubes.

The morbidity and mortality rates of IP are still high because IP remains the most difficult type of EP to be diagnosed preoperatively and is also the most difficult to manage.¹ IP has a mortality rate of 2–2.5%, and this accounts for 20% of all deaths because of ectopic pregnancies.^{2,4,5} Its rupture usually does not occur until 14–16 weeks of gestation, and it is often associated with severe hemorrhage.

Unlike the diagnosis of other forms of EP that has now become precise and reliable, the diagnosis of IP has remained a challenge. The combination of ultrasound, qualitative and quantitative β hCG testing, and laparoscopy has led to a rising incidence of diagnosed EP prior to rupture. TVS is the imaging modality of choice in the evaluation of early pregnancy complications, including IP.

As noted in this case, the misinterpretation of IP as eccentrically located, intrauterine gestation on ultrasound scan evaluation has been corroborated in other studies.^{3,6,7} To distinguish between these two, the following sonographic criteria can be utilized – empty uterine cavity, separately seen gestational sac, sac <1 cm from the most lateral edge of the uterine cavity, and a thin myometrial layer surrounding the sac.⁸ These criteria were used to diagnose IP in this patient. The diagnosis of IP, however, was first suspected intraoperatively when evacuation of retained products of conception



Figure 1. Shows the ultrasound picture of the IP.



failed, leading to the intraoperative transabdominal ultrasound scan. The use of intrauterine marker in this case during the intraoperative transabdominal ultrasound scan was helpful in the suspicion and diagnosis and improved the sensitivity. The experience and knowledge of the sonographer is very important in prompt diagnosis of interstitial EP.

Three-dimensional sonography could be an important diagnostic tool as it may impart better anatomical orientation and precise location of the gestational sac as compared to other imaging modalities.³ Other diagnostic modalities include laparotomy, laparoscopy, and magnetic resonance imaging.^{9,10}

The treatment options for ectopic pregnancies are the same as IP. The options are surgery, medical treatment, and conservative treatment. Where the IP is diagnosed in unruptured state, it can be medically treated using a methotrexate injection. Surgical management is still indicated for ruptured and unruptured IP. Surgical management could be by laparoscopy, laparotomy, or laparoscopy followed by laparotomy¹¹ and hysteroscopy.¹²

The traditional treatment of IP with laparotomy, hysterectomy, or cornual wedge resection is associated with high morbidity and detrimental effects on future fertility. Conservative surgery using laparoscopy, hysteroscopy, or medical management is appropriately indicated if the patient desires conservation of future fertility and the conditions for such management are appropriate as in this case. A diverse array of alternative treatments has been introduced over the last three decades, with the common goal of achieving a minimally invasive, standardized management strategy.¹³ Some conservative surgical treatment options such as laparoscopically assisted transcervical suction evacuation, laparoscopically assisted hysteroscopic removal of an IP,¹⁴ and intraarterial chemoembolization of the uterine artery¹⁵ have been reported.

Our patient was skeptical about surgery and did not want any treatment, which may have an appreciable risk of compromising her future fertility. Consequently, she gave her consent for medical or conservative treatment, and she was managed according to her preference.

Recent reports have described successful treatment of interstitial ectopic pregnancies using different regimens of methotrexate; however, no consensus seems to exist regarding the best management option for this complication of pregnancy. Medical management could be by single-dose regimen, two-dose regimen, or fixed multi-dose regimen protocols. The efficiency and high tolerability of methotrexate therapy with folinic acid rescue has been corroborated.¹⁶ The successful use of combined systemic and direct intrasac injection of methotrexate for the treatment of IP has been reported.^{16,17}

Medical management is cost effective and avoids the risk of morbidities associated with surgery and anesthesia. The inclusion criteria for medical treatment are hemodynamic stability, unruptured EP, β hCG $<5,000$ U/L, size of ectopic mass <3.5 cm, and normal LFT, SEUC, and FBC.

Patient's compliance to both treatment and follow-up is extremely important.^{18,19}

Complications of medical management include treatment failure,²⁰ rupture, rescue surgery, and death. Common predictors of treatment failure with methotrexate include gestational sac larger than 3.5 cm, presence of embryonic cardiac activity, presence of free blood in peritoneum, a high progesterone level, and a high initial β hCG level. There is no absolute β hCG level at which medical treatment is contraindicated.²¹ A systemic review by Menon et al confirmed that there is a substantial increase in failure in medical management of EP with single-dose MTX when the initial β hCG is above 5,000 IU/L.²²

She received two courses of methotrexate injections with alternate-day folinic acid at three weeks interval. The patient was admitted throughout the first course of treatment. After first course of methotrexate, a fall in β hCG level was recorded. The patient was followed up by β hCG test and TVS weekly till the results were negative and the first normal menstrual cycle returned. Complete resolution of the IP was achieved within two months of commencement of treatment. The success of this treatment was confirmed by a negative blood and urine β hCG, disappearance of the gestational sac, and return of her menstrual flow. The use of multiple-dose therapy in this patient was intended to reduce the time lag of treatment, response, follow-up, risk of treatment failure, risk of rupture, and other associated morbidities and mortalities. Rupture is an urgent medical situation associated with higher morbidity and mortality. β hCG level and the size of the ectopic mass can be predictive of failure and rupture.^{23,24}

No adverse reaction or complication was noted throughout the course of treatment. Adverse effects of methotrexate include diarrhea, dizziness, gastric pain, nausea, vomiting, stomatitis, pneumonitis, and reversible alopecia.

Methotrexate is contraindicated in patients with immune system compromise, blood dyscrasia, anemia, thrombocytopenia, intrauterine pregnancy, evidence of rupture, kidney disease, liver disease, peptic ulcer, asthma, acute pulmonary disease, alcoholism, breastfeeding, and sensitivity to methotrexate.²⁵ Other drugs such as potassium chloride and etoposide¹⁴ have also been used successfully.

As noted in this case, early diagnosis has made the use of medical, conservative, or minimal access technique options possible for the management of EP.

Increased awareness and experience have led to an improved understanding of the best way(s) to manage non-tubal ectopic pregnancies and the development of new techniques.

A high index of suspicion combined with meticulous review of clinical findings and imaging modalities to make an accurate diagnosis is essential. Treatment with the least invasive method, by medical treatments, minimal access techniques, or non-invasive radiological procedures, should be encouraged.



Early and prompt diagnosis and treatment of IP is important to prevent catastrophic hemorrhagic complications. Multiple-dose methotrexate with folinic acid rescue could be successful in patients who did not meet the strict criteria for medical management of IP.

Author Contributions

Conceived and designed the experiments: SUM. Analyzed the data: SUM, ICM. Wrote the first draft of the manuscript: SUM. Contributed to the writing of the manuscript: SUM, ICM. Agree with the manuscript results and conclusion: SUM, ICM. Jointly developed the structure and arguments for the paper: SUM, ICM. Made critical revisions and approved final version: SUM, ICM. Both authors reviewed and approved of the final manuscript.

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