

Case Report

Successful multiple-dose methotrexate therapy for unruptured repeat ectopic pregnancy with high β -human chorionic gonadotropin value: a case report

Azuka C. Ezeike*, Idris M. Liman, Rukayya M. Babandi,
Elizabeth O. Austin-Amadi, Mfon Nehemiah

Department of Obstetrics and Gynaecology, National Hospital, Abuja, Nigeria

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***Correspondence:**

Dr. Azuka C. Ezeike,

E-mail: h.hephzibah@yahoo.co.uk

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ABSTRACT

Successfully managing an unruptured ectopic pregnancy necessitates prioritizing the preservation of fertility as the primary objective. Medical management is traditionally considered to be more successful at lower β -human chorionic gonadotropin (HCG) values. However, there is emerging evidence that successful treatment can be achieved with modification of dosage regimen in the presence of high β -HCG value. We reported the successful management of a case of unruptured repeat ectopic pregnancy in a patient with high β -HCG. Mrs PA is a 25-year-old G4P0+3 with previous right salpingectomy due to ruptured ectopic gestation who presented with an ultrasound diagnosis of unruptured left tubal ectopic gestation at a gestational age of 6 weeks. The pre-treatment quantitative β -HCG level was 7066 IU/l. She had multiple dose methotrexate therapy which was well tolerated with normalization of β -HCG levels within 44 days. Hysterosalpingography done six (6) months post-treatment demonstrated patent left fallopian tube. She subsequently had spontaneous conception of an intrauterine pregnancy 16-months post-treatment. The pregnancy was carried to term and culminated in successful delivery at term. Multiple-dose chemotherapy was successful in this patient with high β -HCG level with no reported adverse effect.

Keywords: Unruptured, Repeat, Ectopic gestation, Multiple dose, β -HCG, Methotrexate

INTRODUCTION

Ectopic pregnancy is the implantation and maturation of the fertilized ovum outside the endometrial lining of the uterus. Without timely diagnosis and treatment, ectopic pregnancy can become a life threatening condition.¹ Because of increasing incidences of sexually transmitted infections, assisted reproductive technology, and enhanced sensitivity of diagnostic tests, the incidence of ectopic pregnancy has relatively increased.

The classic triad of ectopic pregnancy is amenorrhea, vaginal bleeding and abdominal pain.¹ A high index of suspicion is needed to make diagnosis as the triad may only be recognizable in only a percentage of cases.

Diagnosis is basically made by transvaginal ultrasound with clinical findings and serum β -HCG level as adjuncts.²⁻⁴ Early diagnosis gives room for conservative management and fertility preservation.

Ectopic pregnancy can be managed expectantly, medically or surgically.^{2,3} Conservative management is the preferred option in patients with unruptured ectopic pregnancy especially if fertility preservation is a priority.² Expectant management is considered when the β -human chorionic gonadotropin (HCG) is 1500 IU/L and declining.^{2,3} Medical management is favoured in unruptured ectopic pregnancies with quantitative β -HCG less than 5000 IU/l, absence of cardiac activity and gestational sac diameter less than 3.5 cm.^{2,3} The failure rate has been reported to be

higher in the presence of high β -HCG values and a rise in β -HCG level after the commencement of therapy.³⁻⁵

Intramuscular methotrexate therapy is the predominant form of medical therapy. Successful management with single dose, two doses and multiple doses has been reported in the literature.^{6,7} Though multiple-dose treatment is less popular, reports of its safety and effectiveness in patients with high serum β -HCG levels have been published.^{8,9}

This is a case report of successful treatment of unruptured repeat ectopic pregnancy with multiple dose methotrexate therapy in a patient with high β -HCG value. Permission was sought for and obtained from the patient before writing up this case report.

CASE REPORT

Mrs. PA is a married 25-year-old G4, P0⁺³ who presented at the gynecological emergency unit on 11 July 2020, at a gestational age of six (6) weeks, one (1) day with a day history of abdominal pain. The pregnancy was earlier confirmed with a urine pregnancy test. There was no history of vaginal bleeding or dizziness. She earlier presented at a peripheral hospital where she had a Transvaginal Ultrasound scan which revealed a left unruptured tubal ectopic pregnancy and she was scheduled for surgery. She however declined and presented at our facility for a second opinion and with a request for medical management. The patient had a ruptured right tubal ectopic pregnancy in 2016 for which she had a right salpingectomy. She also had two voluntary termination of pregnancies prior to that. She has no relevant medical history. She was married in a monogamous setting. The vital signs were stable on presentation with the presence of left lower abdominal tenderness and cervical motion tenderness.

A transvaginal ultrasound revealed an empty uterus with an oval-shaped left adnexal mass measuring 2.6 cm by 1.64 cm containing a gestational sac and yolk sac gestational sac equivalent to a gestational age of 4 weeks, 6 days (Figure 1). There was no fluid in the Pouch of Douglas. The packed cell volume was 33% with haemoglobin of 11.7 g/dl and the white blood cell and

platelet counts were normal. The liver and renal function tests were also normal. The initial serum quantitative β -HCG was 6240 IU/l with a repeat 48-hour value of 7066 IU/l. Based on the above findings, the diagnosis of unruptured left ectopic gestation was made.

Given the history of previous salpingectomy, her stable hemodynamic state and her desire for fertility conservation, the option of medical management was adopted. The pros and cons were discussed with the couple. On account of the high β -HCG value, we opted for multiple dose therapy with intramuscular Methotrexate at 1 mg/kg (on days 1, 3, 5 and 7) to alternate with oral folic acid (leucovorin rescue) at 0.01 mg/kg (Table 1).

Table 1: The schedule of methotrexate administration.

Date	Day	Time (am)	Medication
14/07/20	1	8:40	IM MTX 91.5 mg (3.6 mls)
15/07/20	2	9:00	Tabs folic acid 9.15 mg
16/07/20	3	8:40	IM MTX 91.5 mg (3.6 mls)
17/07/20	4	8:40	Tabs folic acid 9.15 mg
18/07/20	5	8:40	IM MTX 91.5 mg (3.6 mls)
19/07/20	6	8:50	Tabs folic acid 9.15 mg
20/07/20	7	8:40	IM MTX 91.5 mg (3.6 mls)

Patient's weight – 91.5 kg

She was admitted for the duration of the treatment and monitoring was continued on an outpatient basis thereafter (Table 2). There was complete resolution of the ectopic gestation with the return of β -HCG to normal values within 44 days of commencement of therapy. She had hysterosalpingography (HSG) six months post management which revealed patent left fallopian tube (Figure 2).

In November 2021, she presented with a history of amenorrhea. A transvaginal ultrasound done on 15/11/21 revealed a singleton intrauterine gestation at 6 weeks, 1 day. She had an uneventful antenatal period and subsequently delivered at term.

Table 2: The timeline of radiological and laboratory investigations.

Date	Packed cell volume (%)	Serum B-HCG (IU/l)	Transvaginal ultrasound/hysterosalpingography
11/07/20	33	6240	Empty uterus with an oval shaped left adnexal mass measuring 2.6 cm by 1.64 cm containing a gestational sac and yolk sac gestational sac equivalent to a gestational age of 4 weeks, 6 days
13/07/20		7066	
17/07/20	33	9767	Left sided adnexal mass with oval shaped, well defined irregularly outlined cystic lesion, measuring 1.10 cm in its widest diameter with no fetal poles or cardiac activity seen

Continued.

Date	Packed cell volume (%)	Serum B-HCG (IU/l)	Transvaginal ultrasound/hysterosalpingography
20/07/20		9167	
23/07/20	28	5955	
27/07/20		2202	Irregular gestational sac in the left adnexium consistent with a gestational age of 5 weeks, 2 days with no fetal pole or cardiac activity
03/08/20		164.32	
10/08/20		17.54	
27/08/20 (44 days post treatment)		2.23	
5/10/20 (76 days post treatment)			Essentially normal study, no adnexal mass and no pelvic collection seen
27/5/21			HSG-normal uterine cavity with patent left fallopian tube



Figure 1: Transvaginal ultrasound scan showing empty uterus and left adnexal mass.



Figure 2: Hysterosalpingogram showing patent left fallopian tube with spillage into the peritoneal cavity.

DISCUSSION

The diagnosis of ectopic pregnancy is usually received with concern given the immediate risk of mortality if not promptly managed and the negative impact it may have on future fertility. Various options of management exist and are usually tailored to the patient’s clinical state,

reproductive wishes, available expertise and facilities.³ The mode of management of ectopic pregnancy has an impact on the subsequent reproductive performance of a patient. Though radical surgical treatment is invariably inevitable in ruptured ectopic pregnancy, efforts have been made over the years to adopt fertility-conserving forms of treatment in patients with unruptured ectopic pregnancy particularly when future fertility is of concern.^{2,8,9}

Methotrexate is a dihydrofolate reductase inhibitor that disrupts DNA and RNA synthesis. It has been found its place in the medical management of unruptured tubal ectopic pregnancy and is the most widely used medical method of management.² The utility has also been extended to the management of non-tubal ectopic pregnancies where there is a high risk of haemorrhage with surgical management.^{3,10} Methotrexate therapy is administered intramuscularly at a dose of 1 mg/kg or 50 mg/m².

Single-dose therapy is the most common regimen, however successful two (2) dose regimens and multiple-dose regimens have been reported particularly in the presence of higher β-HCG levels.^{6,7,9} Over time, the single-dose regimen has been the more popular regimen because of its ease of administration and follow-up, it may however be associated with a higher failure rate when compared to multiple doses.³ The success rate of any particular regimen however is determined by the inclusion criteria used.² β-HCG levels less than 5000 IU/l, the lack of fetal cardiac activity, a slower increase in pre-treatment β-HCG, and a drop in HCG level from day 1 to day 4 of treatment are all favourable factors for methotrexate therapy.^{2,3,5,9}

The choice of medical management for this patient was determined by her history of salpingectomy and desire for fertility conservation. The multiple-dose regimen was utilized because of the high β HCG level of 7066 IU/l. Contrary to popular belief, this patient's treatment was successful despite an initial increase in HCG value, even

though an increase in β -HCG is a poor predictor of success.^{2,11} Furthermore, no adverse drug effect was reported.¹¹

A 10-year review of single dose methotrexate therapy in a tertiary hospital in Jordan by Sindiani et al showed a success rate of 74.45%.¹² Ozynuncu et al in a retrospective hospital study in Turkey reported a higher success rate with single-dose therapy (86.9%) when compared to two-dose (28.6%) and multiple-dose therapy (40%).⁴ However the majority of the patients who received the multiple-dose therapy in that study, had cervical or caesarean ectopic pregnancies. Mergenthal et al showed a faster reduction of β -HCG in the single dosage group than the two-dose group in a prospective three-center cohort study done in the United States, implying a better prognosis; nevertheless, the researchers recognized site, race, and initial reported pain level as important confounders.⁷ Avcioglu et al's study at Adnan Menderes University School of Medicine reported a success rate of 70.14% and 70% for the single-dose and multiple-dose groups respectively, higher HCG value and greater diameter of the gestational sac were associated with higher failure rate, also Sedny et al in a retrospective study done in Saudi Arabia reported success rate of 72% with the use of single dose treatment.^{13,14}

HCG levels have been proven to be an important prognostic factor for methotrexate therapy effectiveness. However, there have been reports of cases where this challenge was overcome by using two-dose and multiple-dose therapy. Maleki et al reported successful management of unruptured ectopic pregnancy with an initial B-HCG level of 26, 900 IU/l with the two-dose regimen.⁸ Six patients with high HCG levels over 12000iu/l were successfully treated with a multiple-dose regimen, according to Safdarian et al.⁹

Likewise Tug et al reported an 88.5% success rate with minor side effects in 28 patients with HCG >5000 IU/l who had multiple-dose methotrexate regimen.¹⁵ Medical management of ectopic pregnancy remains a viable method of management in patients who meet the criteria. The ideal regimen to use depends on the individual patient's clinical, laboratory and radiological parameters.

CONCLUSION

Multiple-dose chemotherapy was successful in this patient with high β -HCG level with no reported adverse effect. When a patient's β -HCG levels are unsuitable for a single-dose chemotherapy dose, multiple-dose therapy may be considered, provided that early surgical intervention and adequate monitoring facilities are available.

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