

Medical management of Ectopic Pregnancy and Fertility Outcome

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Abstract

Ectopic pregnancy management has generated enormous debates relating to treatment outcomes, especially with regards to future fertility. It can be managed expectantly, medically and surgically, depending on various parameters. This paper is a retrospective study and analysis of 79 medically managed ectopic pregnancies from 2005 to 2020. Age, parity, previous obstetric performance, mode of conception for the index pregnancy, presenting symptoms, ultrasound diagnosis, serum β -hCG levels, treatment given and outcomes. The highest incidence of ectopic pregnancy was seen in women 26 – 30 years of age, the majority being primigravida or second gravidae. 69 of 79 were spontaneous pregnancies, while the remaining were ovulation induced / IUI / IVF. Trans vaginal ultrasound and serum β -hCG levels were used for diagnosis and follow-up. Medical management involved administration of Inj. Methotrexate as per the protocol explained. Outcomes: 18 out of 79 patients had rupture of the ectopic sac during medical management, requiring emergency surgical management. 37 patients included in this study conceived subsequently; 4 had repeat ectopic pregnancy, 2 had spontaneous miscarriage while 31 women had a live birth. Among the 4 patients who had recurrent ectopic, 2 were medically managed and 2 were surgically managed. The remaining 42 patients were lost for follow-up.

Keywords: Ectopic pregnancy, Medical management, Fertility outcome.

Introduction

Ectopic pregnancy is any pregnancy that occurs outside the uterine cavity. According to the Center for Disease Control and Prevention, ectopic pregnancy accounts for approximately 2% of all reported pregnancies¹. Pregnancies in the fallopian tube account for 97 percent of ectopic pregnancies: of these, 55 percent occurred in the ampulla, 25 percent in the isthmus, and 17 percent in the fimbria. The remaining 3 percent of ectopic pregnancies occurred in the abdominal cavity, ovary, and cervix². However, the true current incidence of ectopic pregnancy is difficult to estimate because many patients are treated in an outpatient setting, where events are not tracked, and national surveillance data on ectopic pregnancy have not been updated since 1992.

The diagnosis and management of ectopic pregnancy have undergone a paradigm shift over the past two decades. In 1995 CDC reported ectopic pregnancy as a leading cause of first-trimester morbidity and mortality^{1, 2}. This can be attributed to late diagnosis and heavy blood loss caused by rupture. However, now we are able to diagnose and manage most cases well before rupture occurs.

Here we now attempted to study and evaluate the immediate and long - term outcomes of medical management of unruptured ectopic pregnancy.

Aim of study

To analyze the short term and long-term outcome of medical management of ectopic pregnancy

Objective

To develop a plan of medical management of ectopic pregnancy that would give good outcomes with minimum maternal morbidity. A well-planned protocol will also reduce failures and subsequent emergency surgical procedures. Preventing damage to the tube and avoiding salpingectomy or scarring will also be beneficial from the patient's future fertility point of view.

Methodology

This is a retrospective study done at Ramakrishna Medical Centre LLP, a 40 bedded hospital in Tiruchirapalli, Tamil Nadu, South India. Case details of patients were retrieved from the Medical Records Department of the hospital. These cases span over a period of 15 years from 2005 to 2020. Out of a total of 224 cases of ectopic pregnancies, 79 cases of unruptured ectopic pregnancies were fulfilling the criteria for this study and hence included. The following

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parameters were analyzed:

Age, parity, previous obstetric performance, mode of conception for the index pregnancy, presenting symptoms, ultrasound diagnosis, serum β -hCG levels, treatment given and outcomes.

SPSS (IBM SPSS Statistics for Windows, Version 20.0 was used to analyze the data.

Inclusion criteria

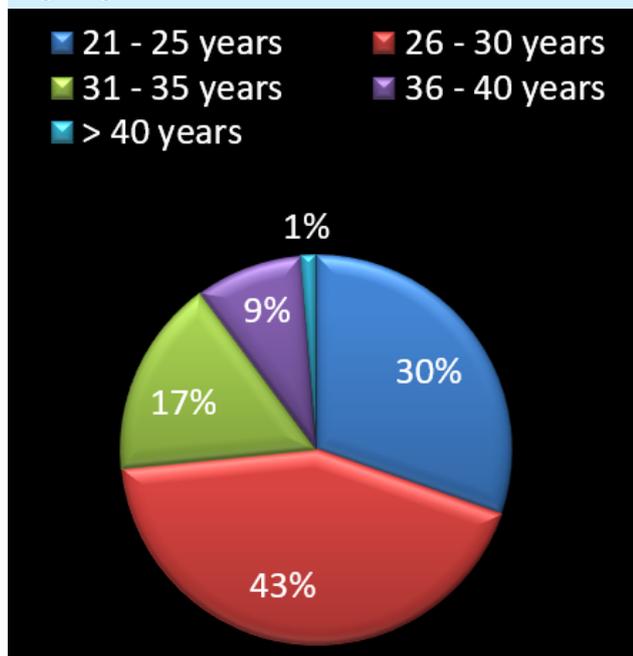
- Hemodynamically stable patients
- Unruptured ectopic pregnancy
- Size of the ectopic sac < 4 cms
- Absence of embryonic heart pulsations
- Base line β -hCG level
- Willingness for follow up
- Informed consent for medical management
- Exclusion criteria
- Hemodynamically unstable patients
- Ruptured ectopic pregnancy
- Sac size > 4 cms
- Presence of embryonic heart pulsations
- Refusal of medical management / follow up
- Contraindication for methotrexate - renal disorders, liver disease, active infection and known alcoholics

Results of the study

Age

In our study the highest incidence of ectopic pregnancy was seen in women between 26 – 30 years followed by women between 21 to 25 years of age.

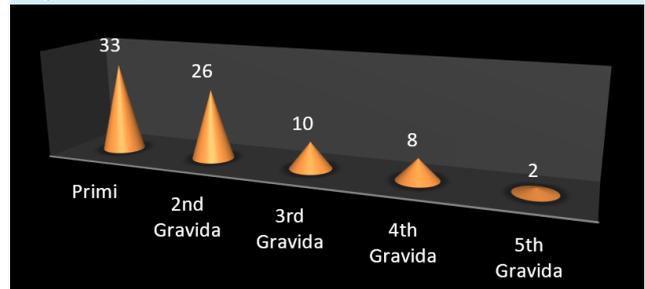
Fig 1: Age



Parity

Parity ranged from primi gravida to 5th gravida. The majority of the patients, 59 out of 79, were either primi-gravida or second gravida.

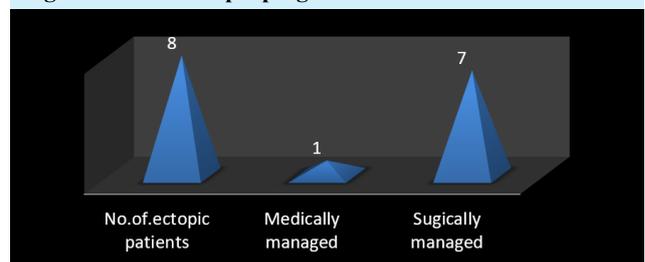
Fig 2: Parity



Obstetric profile

6 / 79 patients had previous ectopic pregnancy. Out of these patients, 2 of them had two prior ectopic pregnancies.

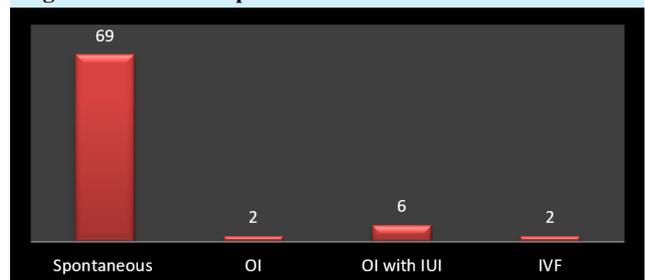
Fig 3: Previous ectopic pregnancies



Mode of conception

69 of the pregnancies were spontaneous conceptions. Two of the pregnancies were following ovulation induction, six following ovulation induction with intra-uterine insemination, and two were following IVF procedure.

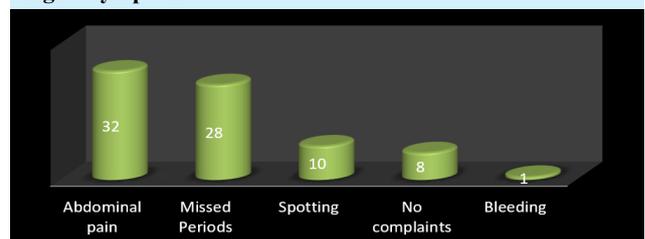
Fig 4: Mode of conception



Presenting symptoms

8 patients (10.1%) were totally asymptomatic, while 28 patients (35.4%) gave a history of missed period. Rest of the patients had abdominal pain, spotting, or profuse bleeding.

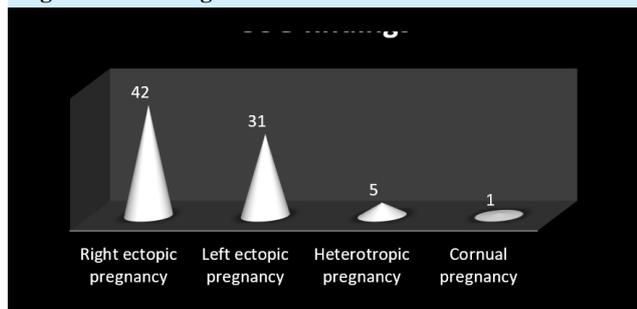
Fig 5: Symptoms



TV USG examination

Ultrasound scan examination revealed right sided ectopic pregnancy in 42 patients (53.2%) as against left sided ectopic pregnancy in 31 patients (39.2%); 5 patients (6.3%) had heterotopic pregnancy, and 1 patient (1.3%) had a cornual pregnancy. In our study, patients with heterotopic pregnancy were given in depth counselling before enrolling into medical management. They opted for medical management. They were willing to forego the intrauterine pregnancy.

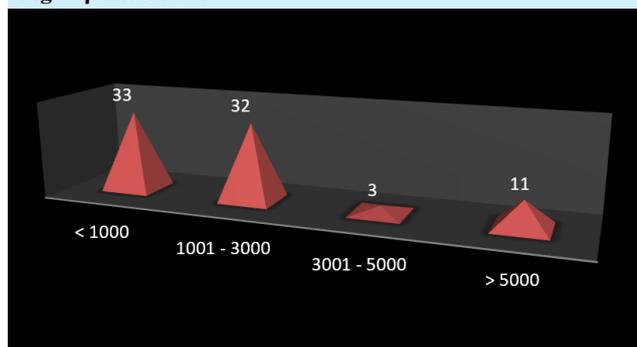
Fig 6: USG findings



Serum β -hCG Levels

On a general note, β -hCG levels are low in ectopic gestations. One patient in the study had a β -hCG level of 17,572 mIU/ml. This was the highest β -hCG level recorded in this study. This particular patient was having a heterotopic pregnancy. She was included in the study because of her desire to terminate the intra uterine pregnancy also. Majority of the patients 65/79 had β -hCG levels <3000 mIU/ml.

Fig 7: β -hCG level

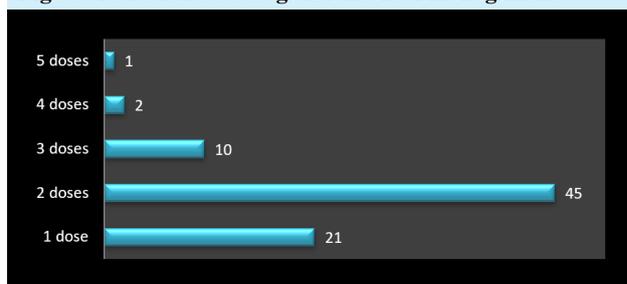


Medical management

Dosage of methotrexate

All patients included in this study received one dose of Inj. Methotrexate 50mg/m² intramuscularly. Additional doses were administered based on serum β -hCG levels. Patients were advised to refrain from strenuous physical activity, sexual intercourse, avoid alcohol and sun exposure. 21 patients had single dose of methotrexate, 45 patients had two doses of methotrexate and 13 patients required more than two doses. Patients with more than 3 doses were supplemented with folic acid.

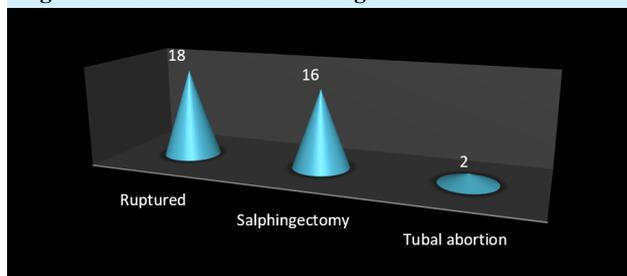
Fig 8: Methotrexate dosage for medical management



Outcome of medical management

Out of 79 patients 18 patients had rupture of the ectopic sac during the course of medical management. 16 underwent emergency laparoscopic salpingectomy while, 2 showed tubal abortion and hence, only laparoscopic suction lavage was done.

Fig 9: Outcome of medical management



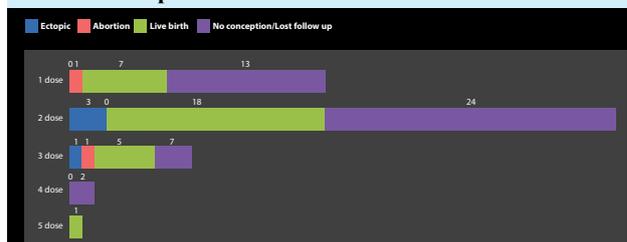
Subsequent reproductive outcomes

37 patients included in this study had subsequent pregnancy. 4 of them were ectopic implantations again, and 2 women had spontaneous miscarriage of singleton intrauterine pregnancies. 31 women had a live birth. The remaining 42 were lost to follow-up in our centre, and therefore it is not known if there were conceptions in this group.

Fig 10: Outcome after medical management of ectopic pregnancy



Fig 11: Outcome after medical management depending upon the dose



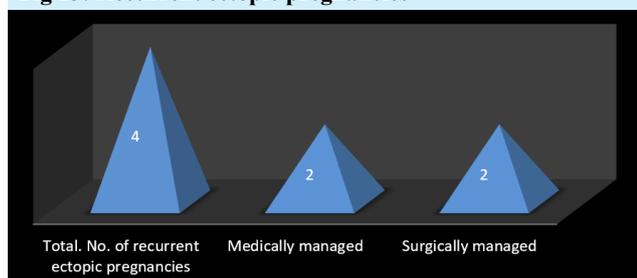
The graph shows the incidence of ectopic, abortions and live births outcome following the number of doses of Methotrexate.

Fig 12: Outcome after surgical management



There was no significant difference in the outcome following salpingectomy / suction lavage. Among the 4 patients who had recurrent ectopic, 2 were medically managed and 2 were surgically managed.

Fig 13: Recurrent ectopic pregnancies



Discussion

Epidemiology

In our study the highest incidence of ectopic pregnancy was seen in women between 26 – 30 years followed by women between 21 to 25 years of age, whereas in a study conducted by Marion LL *et al* the highest incidence of ectopic pregnancy was between the ages of 35 and 45 years of age, perhaps because of the cumulative effect of multiple risk factors over time³.

The number of ectopic pregnancies has increased dramatically in the past few decades. The rise can be attributed partly to increase in certain risk factors but mostly to improved diagnostics. Some ectopic pregnancies detected today, for instance, would have spontaneously resolved without detection or intervention in the past. This theory has paved the way for expectant management in those women with very low β -hCG levels.⁴ Early diagnosis and more conservative management strategies have brought down the morbidity and mortality due to ectopic pregnancy, and have contributed to effective conservation of fertility.

Risk factors for ectopic pregnancy

Ectopic pregnancy is of multifactorial origin. Up to half of all women with an ectopic pregnancy have no recognized risk factors for it. Prior tubal surgery or a prior tubal pregnancy are the most important risk factors for tubal pregnancy, which is obvious in our study also.^{5,6} In our study previous history of ectopic was present in

7.7% of the population studied. Patients with risk factors should be monitored closely to diagnose recurrent ectopic much earlier. If a woman becomes pregnant despite having undergone a putatively sterilizing procedure, ectopic pregnancy must be considered as a possibility, as about 15% - 33% of pregnancies after sterilization are extra uterine.⁷ The risk of tubal pregnancy is higher after electrocoagulation of the fallopian tubes, because of tubal recanalization and/or the formation of a utero/tubo-peritoneal fistula.⁷

There is always a higher risk of ectopic pregnancy in women who have conceived following infertility treatment. In our study, 22.7% of ectopic were in women who underwent fertility treatment among which 2 women had ectopic pregnancy following ovulation induction, 6 of them following OI with IUI, and 2 had following ART.⁸

Assisted reproductive technology (ART) has also been reported to elevate the risk of an extra uterine pregnancy from 0.025% (the value in the general population) to 1% among women who have undergone in vitro fertilization⁸. The incidence of extra uterine pregnancy after ART seems to have fallen somewhat in recent years⁹ possibly due to tubal clipping, improved techniques and single embryo transfers.

Ectopic pregnancy should be strongly suspected in women with risk factors such as history of a previous ectopic, previous tubal surgery, genital tuberculosis, etc. The odds ratios for individual risk factors are given in the table below: The following table gives an account of the odds ratio for the occurrence of ectopic, based on risk factors:^{3,5}

Table 1: Risk factors for ectopic pregnancy

Risk factor	Number of studies	Odds ratio*
Previous tubal surgery	3	21
Previous ectopic pregnancy	10	8.3
Infertility	9	2 to 2.5
Current smoking	6	2.3
Diethylstilbestrol exposure in utero	5	5.6
Previous intrauterine device use	16	16
Previous genital infections	24	2.4 to 3.7

Odds ratio* - A higher odds ratio indicates a stronger risk factor.^{3,5}

In the general population, pelvic inflammatory disease is the most common risk factor for ectopic pregnancy. Organisms that preferentially attack the fallopian tubes include *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and mixed aerobes and anaerobes. Unlike mixed aerobes and anaerobes, *N. gonorrhoeae* and *C. trachomatis* can produce silent infections. In women with these infections, even early treatment does not necessarily prevent tubal damage. In these cases, the tubes may remain structurally normal and patent, but have compromised function due to abnormal cilia, contributing to ectopic pregnancies.

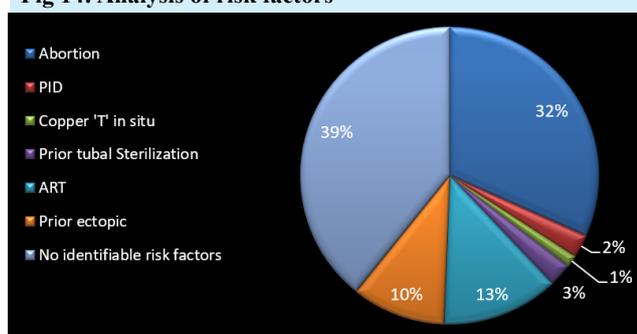
Age > 35 years, history of infertility, ART, endometriosis, previous surgery for tubal pregnancy, previous pelvic surgery, are all strong risk factors for ectopic pregnancy. Presence of pregnancy in women with IUCD, should alert one to the possibility of ectopic pregnancy. Intrauterine devices (IUDs) used for contraception do not increase the risk of ectopic pregnancy, and no evidence suggests that

currently available IUDs cause pelvic inflammatory disease. One explanation for the mistaken association of IUDs with ectopic pregnancy may be that when an IUD is present, ectopic pregnancy occurs more often than intrauterine pregnancy, simply because IUDs are more effective in preventing intrauterine pregnancy than ectopic pregnancy, implantation is more likely to occur in an ectopic location.⁵ In utero exposure to diethylstilbestrol (DES) is associated with utero-tubal anomalies ranging from gross structural abnormalities such as a double uterus to more subtle microscopic abnormalities resulting in tubal dysfunction.^{1,9, 10} Any utero-tubal anomalies, with or without DES exposure, increases the risk of ectopic pregnancy.

Cigarette smoking has an independent and dose-related effect on the risk of ectopic pregnancy. It is known to affect ciliary action in the nasopharynx and respiratory tract. A similar effect may occur within the fallopian tubes.¹¹ Multiple sexual partners, early age at first sexual intercourse and vaginal douching are also associated with an increased incidence of ectopic pregnancy.

Risk factor analysis in our study

Fig 14: Analysis of risk factors



A closer look at the women with no obvious risk factors may reveal multiple sex partners, early age at sexual intercourse, smoking either active or passive, DES exposure etc.

Diagnosis of ectopic pregnancy

A high degree of suspicion, history, and risk assessment are important. The minimum diagnostic evaluation of a suspected ectopic pregnancy is a transvaginal ultrasound evaluation and confirmation of pregnancy. Serial evaluation with transvaginal ultrasonography, or serum β -hCG levels, or both, often is required to confirm the diagnosis.

Women with clinical signs and symptoms of a ruptured ectopic pregnancy, such as hemodynamic instability or an acute abdomen, should be evaluated and treated urgently. Early diagnosis is aided by a high index of suspicion^{12, 13}. Every sexually active, reproductive-age woman who presents with abdominal pain and vaginal bleeding should be screened for pregnancy, regardless of whether she is currently using contraception or not. Women who become pregnant and have known significant risk factors should be evaluated for possible ectopic pregnancy even in the absence of symptoms.

Once the diagnosis of ectopic is made, the management depends upon the clinical condition of the patient, ultrasound findings and β -hCG levels. Management could be: conservative, medical or surgical. It is imperative that one must remain mindful of both the advantages and

limitations of each method and when it is appropriate to use a specific treatment¹⁴.

All patients with ruptured ectopic pregnancy should be managed surgically. Unruptured ectopic pregnancies can be managed by any modality depending upon parity, size of the ectopic sac, and β -hCG levels. Nulliparity, low β -hCG levels, small sac, absent embryonic cardiac pulsations will qualify for either expectant or medical management. Counselling on the available modalities of treatment is important; patient autonomy should be respected within the frame of safety.

Diagnostic tools

Transvaginal ultrasound

Transvaginal ultrasonography should be the initial investigation for pregnant patients presenting to the emergency department with first-trimester bleeding or pain. An intrauterine pregnancy can be seen on TVS by 5 to 6 weeks, when the β -hCG levels are around 1000miu/ml. Diagnosis of ectopic pregnancy should be based upon the positive identification of an adnexal mass using TVS rather than the absence of an intra-uterine gestational sac. Due to the increased availability of high resolution TVS in early first trimester, more than 80% of ectopic pregnancies are now detected before rupture and more than 50% are diagnosed in asymptomatic women by transvaginal ultrasonography alone. The finding of an IUP almost always excludes the diagnosis of ectopic pregnancy. However, it is important to maintain a high index of suspicion in the symptomatic woman or where the woman has conceived using ARTs. The presence or absence of embryonic cardiac pulsations in the ectopic pregnancy sac will guide management. Presence of free fluid in the cul-de-sac strengthens diagnosis.

β -hCG

Urine pregnancy tests can detect β -hCG if the levels exceed 25 miu/ml. Serum levels are measurable from less than 5 (non-pregnant) units upwards. In ectopic pregnancies, the levels are generally low, and therefore, even if the urine pregnancy test is negative, it is worthwhile getting a serum β -hCG done, if ectopic pregnancy or pregnancy of unknown location is strongly suspected. The risk of tubal rupture appears to be similar across a wide range of β -hCG values. While in normal pregnancy the first trimester β -hCG levels rapidly increase, with doubling in about every two days, ectopic pregnancy may present with rising, falling or plateau levels.

Clinical features

Symptoms may present as early as five weeks in tubal ectopic pregnancies. The spectrum of presentations ranges from the asymptomatic woman picked up on transvaginal ultrasound (TVS) to massive intra-abdominal haemorrhage and collapse presenting to the emergency department. The classic clinical presentation for ectopic pregnancy is described as a triad of amenorrhoea, followed by vaginal bleeding and pelvic pain. Shoulder tip pain (not always volunteered by the patient) should clinically raise the suspicion for intrabdominal bleeding. Abdominal and cervical motion tenderness in a woman with a positive

pregnancy test should alert the clinician to the possibility of an ectopic pregnancy. However, the classical clinical findings are present in only 30% of patients.

Management

The management of ectopic pregnancy has undergone a shift from life-saving to fertility-preserving strategies.

Expectant management

Ectopic pregnancy can resolve spontaneously through regression or tubal abortion. Expectant management should be offered only when transvaginal ultrasonography fails to show the location of the gestational sac and the serum levels of β -hCG levels are <1500 mIU/ml and declining on follow up⁴. Because of the possibility of tubal rupture, these patients must be carefully monitored until the serum β -hCG concentration falls below 20 mIU/ml; at this point almost, all ectopic pregnancies resolve spontaneously, without rupture¹⁵.

Medical management

Methotrexate (MTX), a folic acid antagonist, inhibits DNA synthesis in actively dividing cells, including trophoblasts. Administered to properly selected patients, it has a success rate of up to 94%. The success in ectopic pregnancy depends mainly on β -hCG concentration. A meta-analysis of data of 1327 women with ectopic pregnancy treated with MTX showed, that resolution was inversely associated with β -hCG levels, and that increasing levels were significantly correlated with treatment failure. Fetal cardiac activity was also associated with MTX treatment failure. However, tubal diameter, a measure of embryonic size, is unrelated to outcome.¹⁶

The criteria for MTX treatment of ectopic pregnancy are as follows:

- Hemodynamic stability.
- Ability and willingness of the patient to comply with post-treatment monitoring.
- Pretreatment serum β -hCG concentration less than 5000 mIU/ml.
- Absence of ultrasound evidence of fetal cardiac activity.
- Heterotopic pregnancy, where the patient wants termination of the intrauterine pregnancy also.

Pre-treatment investigations should include CBC and blood grouping and Rh typing, serum β -hCG and TVS scan. Liver and renal function tests may be performed if functional impairment is suspected.

Methotrexate protocol

Day 0: Informed consent is taken, and Folic acid preparation is withdrawn. A dose of Methotrexate 50mg/m² or 1mg per kg body weight is given intramuscularly. Inj. Anti D 300mcg intramuscular, is also given in indicated cases. Patient is advised to refrain from strenuous physical activity, sexual intercourse, avoid alcohol and sun exposure.

Day 4: Serum β -hCG level is measured. If the decrease is $> 15\%$, serum β -hCG levels are monitored weekly until reaching non-pregnant level. If the decrease is $<15\%$, a repeat dose of MTX, 50 mg/m² IM is given and repeat β -hCG level checked on 4th day of 2nd dose.

The multiple dose regimen consists of intramuscular injection of 1 mg/kg of methotrexate with 0.1 mg/kg leucovorin factor rescue 24 hours later. Leucovorin is folinic acid, which is the active form of folic acid. It is used to protect cells from effects of methotrexate and decrease its side effects. Weekly follow-ups are done with TVS scan and β -hCG, till it touches <15 mIU/ml.

An increased level is not uncommon 3 to 4 days after MTX administration. Patients may experience abdominal pain from tubal abortion or tubal distention due to hematoma.

At any time, an emergency laparoscopy / laparotomy needs to be performed if the patient has severe abdominal pain or TVS shows > 100 ml free fluid in the pelvis.

The overall success rate is greater with multiple-dose MTX therapy than with single-dose therapy (93% v. 88%); however, single-dose therapy is less expensive, has a lower rate of side effects (29% v. 48%), requires less intensive monitoring, does not require rescue with folinic acid and is effective for most women¹⁶.

A study by Mol *et al*¹⁷ recommends single dose methotrexate for initial β -hCG values $<1,500$ and multi-dose methotrexate for initial β -hCG values >1500 . There is no established true cut-off, only a suggestion regarding a value below which methotrexate therapy may be more successful. The decision to proceed with medical or surgical management depends on the clinician's experience and discussion with the patient.

Serum β -hCG greater than 5000 mIU/ml and ultrasound evidence of fetal cardiac activity are indications for surgical management. Even at this level of β -hCG and a live fetus, if there is only one available tube carrying the ectopic, medical management may be offered under strict vigilance. Women who are hemodynamically unstable or unlikely to be compliant with post-treatment monitoring and those who do not have immediate access to medical care, also are candidates for surgical management.

In our patients, the performance with Methotrexate was as follows: 86.4% of our patients had low levels of serum β -hCG; only 13.6% had more than 5000 units. Medical management was given to those with β -hCG levels of <5000 mIU/ml and were hemodynamically stable. Most of our patients required only 2 doses of methotrexate. Very few required 3 doses and one patient was successfully treated with 5 doses of methotrexate. Patients treated with MTX should be subsequently followed up closely. The time for the serum β -hCG concentration to decline to less than 15 IU/L is 33.6 days on an average but may be up to 109 days.¹⁶

In a study by Stovall *et al* (11) 96 of 100 patients were successfully treated and none required more than four doses. The overall success rate of multi-dose treatment in a meta-analysis by Barnhart *et al* is reported as 92.7% (241 of 260 patients) with a 95% CI 89–96%⁵.

The advantages to the single dose protocol over multi-dose protocol are that patients require fewer visits and fewer injections. As more clinicians are using the single dose protocol, it was clear that convenience was chosen over efficacy. In an attempt to increase efficacy and maintain convenience, a novel protocol was introduced in 2007²⁰. The two-dose protocol maximized the dose of methotrexate, without the need for leucovorin rescue. The goal of this treatment is to improve the success rate of single dose therapy, by administering two doses of methotrexate (on day 0 and day 4) while continuing the same surveillance of β -hCG values on days 4 and 7. Thus, no extra visits were added, maintaining convenience for patients.

The success rate of methotrexate treatment is variably

reported in the literature, with rates ranging from 63% to 97%; this is presumably due to the heterogeneity of patient groups and inclusion criteria, differences in methotrexate treatment protocols, and varying definitions of treatment response¹⁸.

The two most common protocols are the single-dose and the multi-dose protocol⁵. A meta-analysis of nonrandomized studies revealed an 89% overall success rate of pharmacotherapy (1181 of 1327 patients treated); the multi-dose protocol was successful significantly more often than the single-dose protocol (93% versus 88%) but caused more side effects⁵.

Surgical management

Out of 79 cases studied, 18 (22.8%) ended up in surgery. 15 of them (19%) were treated with salpingectomy where 3 patients underwent laparoscopic lavage for tubal abortion.

Follow up

Only 50/79 (63%) patients could be followed up. It was found that 31/50 of the patients had a live birth, 2/50 had abortion and 4/50 had recurrent ectopic for which 2 were treated medically and 2, surgically.

To sum up, early diagnosis and clear and conservative management protocols will give good treatment outcomes, and facilitate future fertility in women with unruptured ectopic pregnancies.

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