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Conservative Management of Unruptured Ectopic Pregnancy—A Retrospective Study

Yazhini Selvaraj

Department of Obstetrics and Gynecology, Ponni Hospital and Fertility Research Centre, Madurai, India
Email: yazhiniselvaraj1956@gmail.com

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Abstract

An ectopic pregnancy (EP) is defined as any pregnancy that occurs outside the uterine cavity. The most common site of ectopic pregnancy is the fallopian tube. The goal of this retrospective study is to address medical and conservative surgical management of unruptured fallopian tube EP as an effective manner to preserve tubes to prevent secondary infertility. This study was conducted between January 1, 2010, and April 30, 2024, in Ponni Hospital, Madurai. It included 319 women, out of 6248 pregnant women diagnosed with ectopic pregnancy by using an Inexecreen kit, trans-abdominal scan, transvaginal scan, and doubling of beta-human chorionic gonadotropin (β-HCG) in 48 hours and Magnetic Resonance Imaging (MRI). Medical and conservative surgical management were given to those patients effectively. Out of 319 patients, 62 patients (19.4%) had a ruptured ectopic pregnancy and underwent surgical treatment; 257 patients (80.6%) had an unruptured ectopic pregnancy. The conservative medical management was provided to 257 patients. Out of 257 patients, 235 patients were treated by injecting methotrexate and folic acid rescue when the criteria were met. 14 patients had salpingostomy and injection methotrexate (Inj. Methotrexate) and inj. Prostaglandin F2 alpha was administered into the tubal wall to preserve tubes. 8 patients had a live ectopic pregnancy; for those patients, Inj. Methotrexate was injected into the gestational sac through ultrasound guidance. 225 out of 257 patients reached out to us to seek fertility treatment; the remaining 32 patients were not seeking fertility. All fertility-seeking patients had successful pregnancies. We lost follow-up of 12 patients in this study. Out of 213 patients who came for fertility treatment, a 76.1% success rate was achieved with live birth, the recurrent ectopic pregnancy rate was 13.6%, the miscarriage and stillbirth rates were 10.3%. 32 patients, who were not seeking fertility, had quality life without surgical scars for ectopic pregnancy and cost-effective treatment. 25 patients out of 32 had laparoscopic sterilization later, and 7 patients followed temporary contraception as per our advice. This clinical data was retrieved

from medical records.

Keywords

Ectopic Pregnancy (EP), Beta-Human Chorionic Gonadotrophin (β-HCG), Medical Management, Methotrexate (MTX), Salpingostomy

1. Introduction

An ectopic pregnancy (EP) is defined as any pregnancy that occurs outside the uterine cavity. Usually, ectopic pregnancies are not only non-viable but are also very dangerous for the mother, as they are used to be followed by massive internal bleeding [1]. Indian studies have found an incidence of ectopic pregnancies as 2% of all pregnancies. The most common location (97%) is the fallopian tubes (ampullary, isthmo-ampullary, isthmial, and fimbrial) cornual [2], cervical, ovary, and scar ectopic, heterotopic pregnancy [3]. Congenital causes of ectopic pregnancy are tubal hypoplasia, tortuosity, congenital diverticula, accessory ostia, partial stenosis, and tubal elongation [4]. Acquired causes of ectopic pregnancy are increasing age, pelvic tuberculosis, PID (Pelvic Inflammatory Disease), tubal ligation, contraception failure, previous ectopic pregnancy, tubal reconstructive surgery, infertility, previous abortions, tubal endometriosis, cigarette smoking, DES (Diethylstilbestrol) exposure, fibroids, transperitoneal migration of the ovum, and invitro fertilization [5].

In India, there is a high prevalence of pelvic tuberculosis. Pelvic tuberculosis has been identified as an important etiological factor of ectopic pregnancy. In one study, genital tuberculosis was found in 13.2% of all cases of ectopic pregnancy [6]. Clinical triads of ectopic pregnancy are (3As) abdominal pain, amenorrhea, and abnormal vaginal bleeding [7]. Current diagnostic methods for ectopic pregnancy rely on serum β-HCG levels in correlation with a transvaginal ultrasound scan and trans-abdominal ultrasound scan findings [8]. If β-HCG is below optimal, it may indicate ectopic pregnancy. A fall in β-HCG levels may also indicate either ectopic pregnancy or impending miscarriage [9]. An early scan at 40 days of amenorrhea can be used to identify the site of implantation, *i.e.*, whether implantation occurred inside the uterine cavity or not. This early scan will prevent complications of ectopic pregnancy [10]. Its complications are massive bleeding, anemia, pelvic abscess, peritonitis, sepsis, DIC (disseminated intravascular coagulation) [11], and pulmonary embolism. It is the leading cause of maternal mortality in the first trimester, *i.e.*, 10% - 15% of all maternal deaths [12]. A special investigation can be done with laparoscopy, laparotomy, dilation and curettage, MRI, and culdocentesis (where ultrasound facilities are not available) [13]. Ectopic pregnancy with tubal factor infertility is very distressing to a couple. They have gone through both physical and emotional trauma during the treatment process. They are counseled to undergo assisted reproductive technology (ART)

treatment in the future to conceive; this treatment process is costly [14].

Medical treatment of ectopic pregnancy is quite less expensive than surgical management. In the 1980s, a safe alternative to surgery, Inj. Methotrexate (MTX) treatment, was established. A folic acid antagonist, MTX interferes with Deoxyribonucleic acid (DNA) synthesis and cell proliferation, and tissues with rapid cellular turnover, e.g., trophoblasts, are most susceptible [15]. MTX results in successful resolution of ectopic pregnancy [16]. Many different agents have been used to treat ectopic pregnancies, including Local Inj. potassium chloride (0.5 - 1 mL 2 meq/mL solution) injected into the fetal thorax, producing immediate cessation of cardiac activity [17], hyperosmolar glucose (local injection of 50% glucose after aspiration of the tubal gestational sac fluid under transvaginal ultrasonographic guidance) [18], inj. prostaglandins (500 micrograms) injected into the gestational sac [19], inj. danazol (400 mg, injected directly into the tubal ectopic site) [20] and Inj. etoposide (two doses of 50 mg each, three days apart) [21].

This study aims to address medical and conservative management of ectopic pregnancy to avoid tubal factor infertility with Inj. Methotrexate and prostaglandins.

2. Materials and Methods

2.1. Inclusion Criteria

This retrospective study was conducted between January 1, 2010 and April 30, 2024, at Ponni Hospital, Madurai, Tamil Nadu, India. Patients who arrived at the hospital with clinical, biochemical, and ultrasound signs of an unruptured tubal ectopic pregnancy were included in the study population. It fulfilled the following inclusion criteria: the patient should be hemodynamically stable. Serum β-HCG level should be under 5000 mIU/ml. The patient had no fetal cardiac activity seen on the ultrasound scan, unruptured ectopic pregnancy with a mass smaller than 35 mm, minimal (under 100 ml) or no free fluid in Pouch of Douglas (POD) on the scan and no liver, renal impairment, or bone marrow impairment evidenced by leukopenia, thrombocytopenia, or anemia.

2.2. Exclusion Criteria

Patient who came for ruptured ectopic pregnancy, serum β-HCG level >5000 mIU/ml, gestational sac (>3.5 cm), embryonic cardiac activity present, hemodynamically unstable, sensitivity to MTX, active pulmonary disease, renal disease, chronic liver disease, preexisting blood dyscrasia, immunodeficiency, peptic ulcer disease, free fluid more than 100 ml in the POD.

2.3. Study Design

This study included 319 out of 6248 pregnant women, diagnosed with ectopic pregnancy by using an Inexecreen kit, trans-abdominal scan, trans-vaginal scan, doubling of β-HCG in 48 hours, and MRI. Out of 319 patients, 62 patients (19.4%) had a ruptured ectopic pregnancy and underwent surgical treatment, 257 patients

(80.6%) had an unruptured ectopic pregnancy. 225 out of 257 patients reached us for fertility, the remaining 32 patients were not seeking fertility (Figure 1). Conservative management was given to those patients effectively.

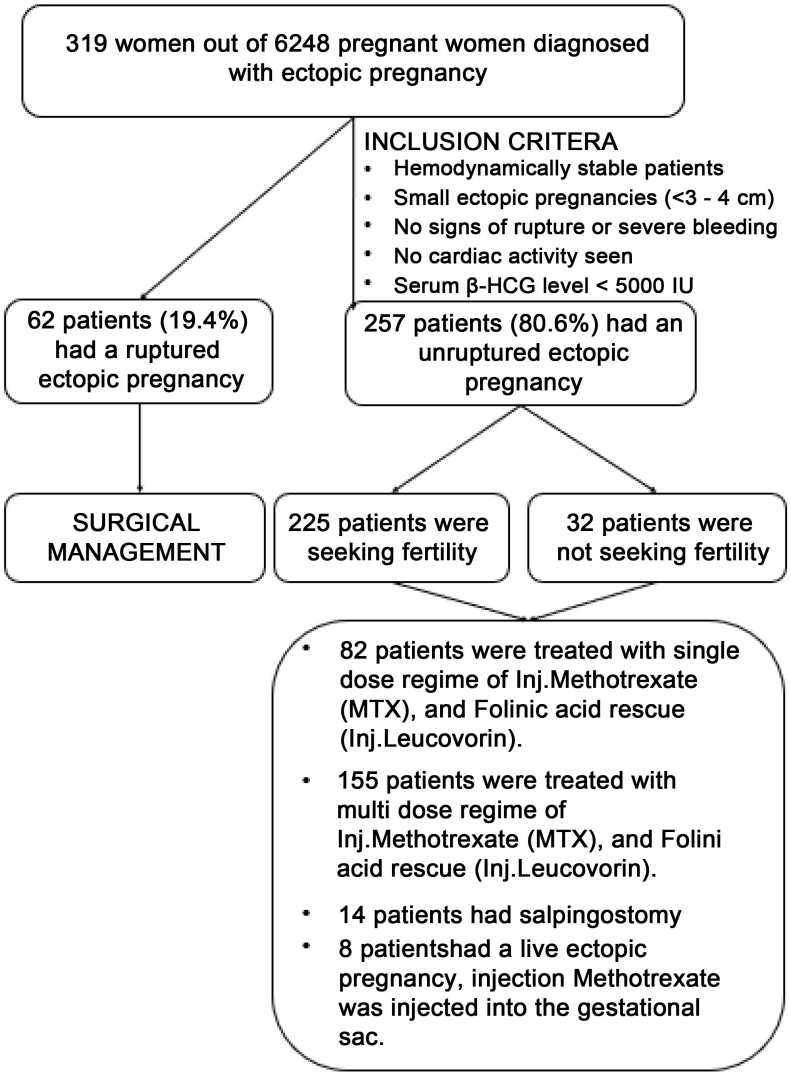


Figure 1. Study design—Flowchart.

Their age lies between 25 to 40 years (Table 1). Patients in the age group between 31 to 35 years had a high prevalence of ectopic pregnancy.

Table 1. Prevalence of ectopic pregnancy based on age group.

Age	N = 257	Percentage
25 - 30 years	97	38%
31 - 35 years	112	44%
35 - 40 years	39	15%
>40	9	4%

Clinical triads of ectopic pregnancy are (3As) abdominal pain, amenorrhea, and abnormal vaginal bleeding (7). In our study, 59.1% of patients came with all 3 symptoms together. About 27.6% of patients had amenorrhea, and 12.5% of patients had vaginal bleeding. Table 2 shows the data on the patient's past medical history. Patients with a history of previous Lower Segment Cesarean Section (LSCS) and Pelvic Inflammatory Disease (PID) had a high prevalence of ectopic pregnancy in our study (Table 2).

Table 2. Prevalence of Ectopic pregnancy based on history.

History	N = 257	Percentage
Previous LSCS	67	26%
PID	49	19%
Un-Identified	35	14%
Previous Sterilization	32	12%
Previous Ectopic Pregnancy	26	10%
Previous Abortion	24	9%
Other Pelvic Surgery	11	4%
Invitro Fertilization (IVF)	8	3%
Intrauterine Contraceptive Device (IUCD) instilled	5	2%

3. Treatment Protocol

235 patients were treated with Inj. Methotrexate (MTX) and Folinic Acid Rescue (Inj. Leucovorin) when the criteria were met. During pregnancy, the active form of folic acid, *i.e.*, L. methyl folate, is an important compound for embryonic development and fetal growth [22]. The administration of methotrexate intramuscularly is a suitable treatment for ectopic pregnancy in certain circumstances. Methotrexate is an anti-metabolite that inhibits folate reductase, inhibits deoxyribonucleic acid replication, and affects rapidly proliferating tissues such as trophoblastic cells developing embryos [23]. Even when administered at low doses, methotrexate is not devoid of side effects. Leucovorin is a crucial coenzyme in nucleic acid synthesis and an active metabolite of folic acid; it is utilized to selectively rescue cells from the detrimental effects of methotrexate. Additionally, it facilitates the continuation of nucleic acid synthesis even in the presence of methotrexate, thereby preventing toxicity [24]. There are single-dose regimens, double-dose regimes, and multi-dose regimens of Inj. Methotrexate. In a single-dose regimen, Inj. Methotrexate 50 mg/m^2 was administered intramuscularly. Serum β-HCG levels are evaluated on days 4th and 7th after treatment, and a 15% reduction in β-HCG levels from the 4th day to the 7th day is considered an indication of successful treatment, and an increase of 20% in β-HCG change between day 0 and 4th day after treatment, 2nd dose MTX needs to be administered [25]. For individuals who are more likely to experience treatment failure, such as those with elevated β-HCG levels, a multi-dose regimen is recommended.

However, it entails increased side effects, e.g., abdominal pain, vomiting, hepatic failure, neutropenia, thrombocytopenia, and alopecia, and necessitates a greater number of follow-up visits and folinic acid rescue treatments [25]. Before planning multiple-dose regimens of methotrexate, blood investigations such as a complete blood count (CBC) and liver function test (LFT) are done to avoid methotrexate toxicity [26]. 82 patients were treated with single-dose regimes, and 135 patients were treated with multiple-dose regimes. 14 patients had salpingostomies, and Inj. Methotrexate or Inj. Prostaglandin F2 alpha [27] was administered into the tubal wall to preserve tubes. 8 patients had a live ectopic pregnancy; for those patients' injection, methotrexate was injected into the gestational sac. Clinical data were retrieved by medical records. All fertility-seeking patients had results in successful pregnancies. We lost follow-up of 12 patients in this study. For the two cases we had discussed, these criteria were broken and out of the way conservative management had been done for them.

3.1. Ethical Considerations

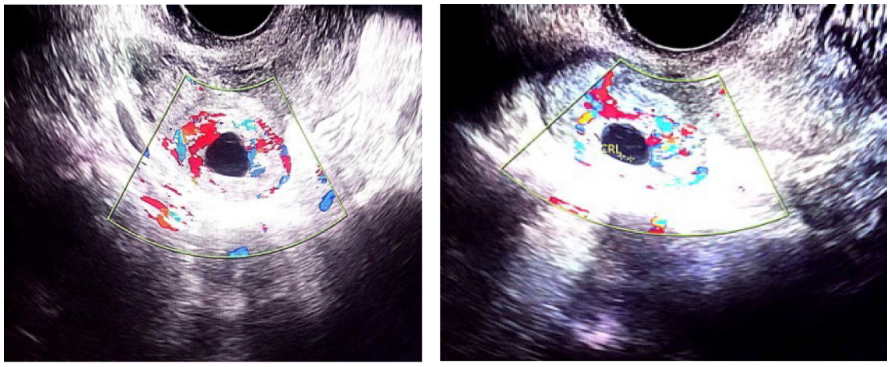
Ethical approval and authorization for the research from the ethics committee of the Ponni fertility hospital and research center were obtained, and patient records were selected from hospital registers. We obtained the patient's verbal consent and followed up for the pregnancy outcome after medical management was given.

3.2. Case 1

A 28-year-old patient came with a complaint of 51 days of amenorrhea with a Urine Pregnancy Test (UPT) card positive. No other complaints except severe abdomen pain. On examination, the patient was hemodynamically stable. Her pulse rate (PR) was 108/min, and her blood pressure (BP) was 110/70 mmHg. She had been married for 5 years. She had a history of left ectopic pregnancy and laparoscopic salpingectomy done in 2018, and she had a miscarriage at 6 weeks of gestational age (GA), with no living child at present. The scan was done and diagnosed as right ectopic pregnancy with fetal cardiac activity ++, crown-rump length (CRL) −0.24 cm, corresponding to 6 weeks and 4 days. Her β-HCG was 9987 mIU/mL. 2 doses of Inj. methotrexate were given intramuscularly. T. RU486-600 mg (anti-progesterone) was given orally. Irrespective of these medications, a "Ring of Fire" pattern (**Figure 2(a)** and **Figure 2(b)**) was seen, there was no drop in β-HCG level, and fetal cardiac activity was seen. Hence, under ultrasound guidance, Inj. Methotrexate was directly injected into the gestational sac, fetal cardiac activity stopped, and the β-HCG level was gradually coming down and reaching 948 mIU/mL after a week. The ectopic sac was reducing, and vascularity was regressing. The patient was discharged on the 7th day. Patient conceived naturally after 6 months and delivered a healthy male baby the very next year.

3.3. Case 2

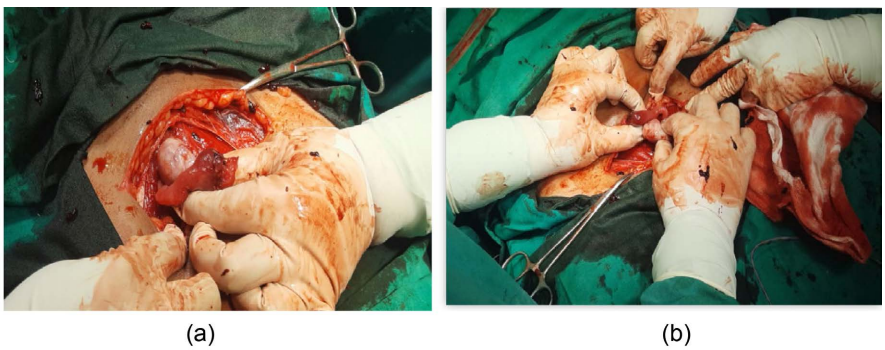
A 23-year-old patient came with a complaint of severe pain in the lower abdomen



(a) (b)

Figure 2. (a) and (b) Ring of Fire pattern seen around the gestational sac of ectopic right ectopic pregnancy.

and spotting Per Vagina (PV) after 43 days of pregnancy. She had regular periods and was married for 3 months. On examination, the patient was pale but conscious; her PR was 124/min, BP was 90/60 mmHg, intravenous venous (IV) fluid started, injection of Tramadol 1 g intramuscular (IM) was given, and the patient was admitted to the Intensive Care Unit (ICU) and under continuous monitoring. We suspected ectopic pregnancy after doing ultrasound sonography guidance (USG), and MRI revealed ruptured left tubal ectopic pregnancy with pelvic clots and a hemoperitoneum of more than 1.5 liters. Immediately, an emergency laparotomy was scheduled. Her hemoglobin (Hb) was 7.8 gm. Blood transfusion and laparotomy were carried out parallelly. Under general anesthesia, the abdomen opened in. 1.5 liters of blood were found inside the intraperitoneal cavity. The left ampullary end was the site of ectopic pregnancy, and there was no rupture. The products of conception were milked out, local methotrexate was injected, actively bleeding vessels were cauterized, and after securing perfect hemostasis, tubal patency was checked using normal saline and found to be patent. The patient was stable, and the tube was secured (Figure 3(a) and Figure 3(b)). The postoperative period was uneventful; the patient was discharged on the 5th postoperative day.



(a) (b)

Figure 3. (a) and (b) Secured left fallopian tube.

4. Results and Discussion

This study was mainly presented to preserve the fallopian tubes of unruptured

tubal ectopic pregnancy in fertility-seeking patients with conservative medical and surgical management. The fallopian tube may burst due to the erosion caused by chorionic villi, which resulted in intra-abdominal hemorrhage. The likelihood of conservative treatment options improved with early diagnosis and treatment. Maternal morbidity and death rates have been linked to delays in obtaining medical attention [28]. When unruptured ectopic pregnancy is diagnosed early, more conservative treatment approaches can be used that protect the fallopian tubes. Folic acid antagonists like methotrexate are well-researched medicinal molecules. Dihydrofolate reductase is deactivated by methotrexate, which lowers the amounts of tetrahydrofolate, an essential component for ribonucleic acid and deoxyribonucleic acid synthesis. Lozeau *et al.* explained that the percentage of success rate in methotrexate therapy varied based on β-HCG level. High levels of β-HCG have a low success rate of methotrexate treatment and vice versa [29]. In our study, 235 patients were treated with Inj. Methotrexate (MTX) and Folinic Acid Rescue (Inj. Leucovorin) when the criteria were met. 82 patients were treated with single-dose regimes, and 155 patients were treated with multiple-dose regimes. All cases were turned into successful methotrexate therapy.

Halperin *et al.* performed systemic and local injection of 1 ml of 25 mg/mL methotrexate solution into the intra-gestational sac of 12 patients who were diagnosed with viable tubal ectopic pregnancy. They achieved a 91.6% success rate. 75% of patients conceived within 6 months following the combined treatment, and all the pregnancies were intrauterine [30]. In our study, 8 patients had a live ectopic pregnancy; for those patients' injection, methotrexate was injected into the gestational sac through ultrasound guidance. Ectopic fetus cardiac activity was stopped. β-HCG level was gradually reduced averagely from 12,042 mIU/mL to 668 mIU/mL. Systemic treatment with MTX was found to be safe and effective for treating tubal pregnancy; it did not result in a cost reduction compared to salpingostomy. For individuals who are not suitable candidates for MTX treatment, salpingostomy is the preferred treatment option, as it may improve the chances of future pregnancies. Awadi *et al.* preferred laparoscopic tubal salpingostomy could be offered for surgical management of tubal ectopic as regards future fertility, desire for pregnancy, and surgical situation [31]. In our study, 14 patients who were seeking infertility had salpingostomies, and Inj. Methotrexate or Inj. Prostaglandin F2 alpha was administered into the tubal wall to preserve tubes. As Vejtorp *et al.* studied the effect of inj. prostaglandin F2 alpha on management of ectopic pregnancy, inj. Prostaglandin F2 alpha was administered into the tubal wall to preserve tubes. They treated eleven women with small unruptured tubal pregnancies with laparoscopically guided injection of prostaglandin F2 alpha in the oviduct and in the ovary, which contained the corpus luteum. They had no side effects of the treatment and were discharged from the hospital 1 - 3 days later [32].

This helped our patient to maintain their tube's integrity, increasing the chances of natural conception. After the salpingostomy, tubal patency was checked through the hysterosalpingogram (HSG) method and found to be normal in all patients.

These conservative medical management services were provided to 257 patients. Out of 213 patients who came for fertility treatment, a 76.1% success rate was achieved with live birth, the recurrent ectopic pregnancy rate was 13.6%, and the miscarriage and stillbirth rate were 10.3% (Table 3). 12 patients were failed to follow up.

Table 3. Pregnancy outcome of fertility seeking patients.

Fertility treatment seeking patient's outcome	N = 213	Percentage
Recurrent ectopic pregnancy	29	13.6%
live birth rate	162	76.1%
Miscarriage and still birth	22	10.3%
12 Patients were failed to follow up		

32 patients, who were not seeking fertility, had quality life without surgical scars for ectopic pregnancy and cost-effective treatment. 25 patients out of 32 had laparoscopic sterilization later, and 7 patients followed temporary contraception as per our advice. There were no severe adverse effects of Inj. Methotrexate and Inj. prostaglandin F2 alpha reported in our studies.

5. Conclusion

Effective conservative management is only possible with early detection of ectopic pregnancy by doing an ultrasound scan at 40 days of amenorrhea with positive UPT, which is reported on site of implantation, and looking for doubling of β-HCG in 48 hours and criteria met with β-HCG below 5,000 mIU/ml. Conservative management of ectopic pregnancy using MTX, salpingostomy, and intra-gestational sac administration offers an alternative to surgical management. This approach preserves fertility, reduces complications, and improves the patient's outcome. A multidisciplinary approach, patient education, and close monitoring are essential for successful conservative management. This conservative management is cost-effective.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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