

SUCCESSFUL TREATMENT OF ADVANCED INTERSTITIAL PREGNANCY WITH METHOTREXATE AND HYSTEROSCOPY

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Abstract

A review of studies showing successful treatment of interstitial pregnancy when used methotrexate with hysteroscopy INTRODUCTION

Ectopic pregnancy was first discovered in the 11th century, and until the middle of the 18th century, it was usually fatal. John Bard a surgeon in New York reported the first successful surgical intervention to treat an ectopic pregnancy in 1759[1]. it was usually fatal. John Bard a surgeon in New York reported the first successful surgical intervention to treat an ectopic pregnancy in 1759(1).According to Sepilian, the survival rate in the 19th century was dismal, however, in the beginning of the 20th century, improvement in blood transfusion, anesthesia, and antibiotics contributed to the decrease in the maternal mortality. Ectopic pregnancy currently is the leading cause of pregnancy-related deaths in the first trimester. Sepilian stated that ectopic pregnancy is derived from the Greek word “ektopos” meaning out of place, and it refers to the implantation of the fertilized ovum in a location outside of the uterine cavity including the fallopian tubes, cornual or interstitial region of the uterus and fallopian tubes, cervix, ovary, and the abdominal cavity. This abnormally implanted pregnancy grows and draws its blood supply from the site of abnormal implantation, as the gestation enlarges it creates the potential for organ rupture because only the uterine cavity is designed to expand and accommodate fetal development. (1)The arterial blood supply to the mesosalpinx provided by branches of the ovarian artery that derive directly from the aorta as well as the branches from the uterine artery that derive from the internal iliac artery, provides the fallopian tubes with a rich arterial supply that can bleed in the event of a perforated tube, to massive catastrophic hemorrhage and maternal death.

Seeber et al reported in 2006 from a study at the University of Pennsylvania in Seeber et al reported in 2006 from a study at the University of Pennsylvania in Obstetrics and Gynecology that the incidence of ectopic pregnancy has increased 6-fold since 1970, and is responsible for approximately 9 percent of all pregnancy related deaths in the United States. The author further reported that a rise in the quantitative Beta sub unit of human chorionic gonadotropin of a maximum of 53% over two days would be required for a viable pregnancy, and a decline of 21 to 35 % in 48 hours would be mandatory for a diagnosis of spontaneous abortion (2).

Seeber stated that the absence of an intrauterine pregnancy above an established cut point of hCG is consistent with an abnormal pregnancy, but does not distinguish a miscarriage from an ectopic pregnancy.

Seeber stated that the symptoms of abdominal pain or pelvic pain and vaginal bleeding are the most common complaints suggestive of ectopic pregnancy, The multiple

potential sites of ectopic pregnancies add to the complexity of the diagnosis. Seeber also stated that these symptoms may be erratic and variable, and in some cases, absent. Likewise, such symptoms are non specific, and also have been associated with spontaneous abortion, cervical irritation, or trauma, and infection (2).

Sepelian wrote that the classic triad of amenorrhea, pain, and vaginal bleeding has been strongly associated with the clinical presentation of ectopic pregnancy, however, 50% of patients with ectopic pregnancy present without this triad. They may have symptoms associated with early pregnancy, including nausea, fatigue, lower abdominal pain, painful uterine cramping, recent dyspareunia, and shoulder pain (1).

Due to increased technology, most ectopics are diagnosed prior to rupture. Sepilian reported that approximately 20% of ectopic patients are hemodynamically unstable at initial presentation suggesting There is a 10-25% chance of a recurrent ectopic pregnancy (1).

Risk factor included progesterone intrauterine device. Increasing maternal age plays important roles in ectopic pregnancy and women age 35 -44 have a 3 to 4-fold.

Increase of ectopic pregnancy compared to women aged 15-24 (1).

Smoking may alter tubal and uterine motility, and is associated with a risk of 1.6-3.5 times more than non smokers. Other factors associated with an increased risk of ectopic pregnancies include prior abdominal surgery, a ruptured appendix, exposure to diethylstilbesterol and uterine developmental abnormalities. (1). Most authors list prior tubal infection. Chlamydia may be asymptomatic and untreated as well as other infectious agents associated with an increased risk of salpingitis and potential tubal damage. (1)

Pathophysiology

Most ectopic pregnancies are located in the fallopian tube. The most common site is the ampullary portion of the tube, where over 80% occur. The next most common sites are the isthmic segment of the tube (12%), the fimbria (5%), and the cornual and interstitial region of the tube (2%). Nontubal sites of ectopic pregnancy are a rare occurrence, with abdominal pregnancies accounting for 1.4% of ectopic pregnancies and ovarian and cervical sites accounting for 0.2% each(3).

Clinical

The classic clinical triad of ectopic pregnancy is pain, amenorrhea, and vaginal bleeding. Unfortunately, only 50% of patients present typically. Patients may present with other symptoms common to early pregnancy, including nausea, breast fullness, fatigue, low abdominal pain, heavy cramping, shoulder pain, and recent dyspareunia. Astute clinicians should have a high index of suspicion for ectopic pregnancy in any woman who presents with these symptoms and who presents with physical findings of pelvic tenderness, enlarged uterus, adnexal mass, or tenderness.

Remember, however, that only 40-50% of patients with an ectopic pregnancy present with vaginal bleeding, 50% have a palpable adnexal mass, and 75% may have abdominal tenderness. Approximately 20% of patients with ectopic pregnancies are hemodynamically compromised at initial presentation, which is highly suggestive of

rupture. Fortunately, using modern diagnostic techniques, most ectopic pregnancies may be diagnosed prior to rupturing.

Numerous conditions may have a presentation similar to an extrauterine pregnancy. The most common of these are appendicitis, salpingitis, ruptured corpus luteum cyst or ovarian follicle, spontaneous abortion or threatened abortion, ovarian torsion, and urinary tract disease. Intrauterine pregnancies with other abdominal or pelvic problems such as degenerating fibroids must also be included in the differential diagnosis.(4,5)

Interstitial ectopic pregnancy (sometimes called cornual) occurs in the interstitial portion of the fallopian tube. It accounts for 2% - 4% of all ectopics. The morbidity and mortality are higher due to later presentation, and the tendency to massive haemorrhage. The diagnosis is suggested by visualisation of an intrauterine gestational sac or decidual reaction located high in the fundus, that is not surrounded by more than 5mm of myometrium in all planes.(5)

An interstitial line sign - an echogenic line from the mass to the endometrial echo complex - reportedly has high sensitivity (80%) and specificity (98%).

Cornual ectopic pregnancies have traditionally been treated with systemic methotrexate, cornual resection, or hysterectomy(6) and recently by hysteroscopy. Endoscopy began in 1805 with Bozzini (7), but it was Pantaleoni(8) who, in 1869, performed the first hysteroscopy, not only diagnosing an endometrial polyp with the aid of an endoscope, but cauterizing it with silver nitrate. A second generation of endoscopes was developed by Nitze (9) in 1879 who constructed a cystoscope with a lens system and a light source inside the endoscopic tube. With this innovation, vision was clearer, lighting more intense and the field of vision wider.

In spite of these early attempts, hysteroscopy was more a curiosity than a truly useful technique until the 1970s when technical improvements in lenses and distension media resolved some of the difficulties that had prevented its widespread use before that time. It was Hamou (10) who revolutionized the field of hysteroscopy with new, improved visual optics and instruments of fine diameter (4 mm). Improved optics, simpler techniques and the ability to perform the examination in the outpatient clinic without anaesthesia or cervical dilatation have further popularised hysteroscopy in the 1980s and 90s (11,12)

Hysteroscopy is the process of viewing and operating in the endometrial cavity from a transcervical approach. The basic hysteroscope is a long, narrow telescope connected to a light source to illuminate the area to be visualized. With a patient in the lithotomy position, the cervix is visualized by placing a speculum in the vagina. The distal end of the telescope is passed into a dilated cervical canal, and, under direct visualization, the instrument is advanced into the uterine cavity. A camera is commonly attached to the proximal end of the hysteroscope to broadcast the image onto a large video screen. Other common modifications are inflow and outflow tracts included in the shaft of the telescope for fluids. Media, such as sodium chloride solution, can be pumped through a hysteroscope to distend the endometrial cavity, enabling visualization and operation in an enlarged area.

Hysteroscopy is a minimally invasive intervention that can be used to diagnose

and treat many intrauterine and endocervical problems. Hysteroscopic polypectomy, myomectomy, and endometrial ablation are just a few of the commonly performed procedures. Given their safety and efficacy, diagnostic and operative hysteroscopy have become standards in gynecologic practice.(13)

Medical treatment

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% (4)The success in ectopic **pregnancy** depends mainly on β -hCG concentration: a meta-analysis of data for 1327 women with ectopic **pregnancy** treated with MTX showed that resolution was inversely associated with β -hCG level, 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 fetal size, is unrelated to outcome(14).

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 IU/L.
- Absence of ultrasound evidence of fetal cardiac activity.

Common side effects of methotrexate treatment for ectopic pregnancy include:

- Abdominal pain. Cramping abdominal pain is the most common side effect, and it usually occurs during the first 2 to 3 days of treatment. Because abdominal pain is also a sign of a ruptured ectopic pregnancy, **report any abdominal pain to your health professional.**
- Vaginal bleeding or spotting.
- Nausea, vomiting, and indigestion.
- Fatigue, lightheadedness, or dizziness.

Rare side effects from methotrexate treatment for ectopic pregnancy include:

- Skin sensitivity to sunlight.
- Inflammation of the membrane covering the eye.
- Sore mouth and throat.
- Temporary hair loss.
- Severe low blood counts (bone marrow suppression).
- Inflammation of the lung (pneumonitis).

Because of the risk of side effects, methotrexate treatment requires close medical supervision by a health professional who is experienced with this medicine. During methotrexate treatment, keep your health professional informed of **any** symptoms that you have.

Methotrexate is sometimes used just after surgical treatment to stop the growth of any remaining fetal cells.

Methotrexate versus surgery

If your ectopic pregnancy is not too far advanced and has not ruptured, methotrexate may be a treatment option for you. Methotrexate treatment avoids the risks of surgery, may be less likely to damage the fallopian tube than surgery, and may offer a better chance of maintaining your fertility after treatment.

If you are not concerned with preserving fertility, surgery for an ectopic pregnancy is faster than methotrexate treatment and causes less bleeding.

Some women who receive a methotrexate series for ectopic pregnancy report more side effects and less overall comfort than women who have laparoscopy. On the other hand, women who have laparoscopy may experience side effects related to general anesthesia and surgery, such as fatigue, abdominal bloating, and shoulder pain.

Successful methotrexate treatment is less expensive than laparoscopic surgery for ectopic pregnancy

Methotrexate instead of surgery

Methotrexate can be used instead of surgery in the following cases:

- Pregnancy hormone (hCG) levels are low. Methotrexate treatment is not likely to be successful when hCG levels are high.
- No fetal heart movement is noted on ultrasound (methotrexate treatment is not as likely to be successful when the embryo is more developed and growing and has heart activity).
- The ectopic pregnancy is smaller than 4 cm.
- There is no bleeding into the abdomen.
- The fallopian tube has not ruptured.
- The use of anesthesia during surgery would pose a significant risk (for example, if you have a respiratory infection).
- You want to maximize your chances of becoming pregnant in the future.(15)

When methotrexate cannot be used

Methotrexate cannot be used if you:

- Are breast-feeding.
- Have liver or kidney disease.
- Have a low red blood cell count (anemia).
- Have an impaired immune system.
- Have a ruptured fallopian tube.

Benifla JL study which was done in Hôpital Bichat, Paris, France.

To evaluate medical treatment of interstitial pregnancy.: This series was a retrospective study of medical treatment of interstitial pregnancies which was managed in two French Departments of Obstetrics and Gynecology (Bichat public Hospital. Paris and A. Bécère public Hospital, Clamart, France). Fifteen patients with clear evidence of an unruptured interstitial pregnancy were treated by injection of methotrexate (MTX) or

potassium chloride (KCL) without surgery since January 1988. The diagnosis was established either by sonography and laparoscopic confirmation in eight cases or by only transvaginal ultrasound in seven cases. Three out of 15 cases in this series, had a heterotopic pregnancy who were treated by transvaginal ultrasound-guided injection of KCL. Others received systemic MTX injection in four cases, and local MTX injection in eight cases under either laparoscopy or transvaginal ultrasound guidance. Four different protocols of MTX (Ledertrexate) administration was performed in this series with time: at the beginning of our experience, MTX1 protocol, 15 mg i.m. daily for 5 days was used; and after MTX2 protocol, 1 mg/kg body weight i.m. daily for 4 days; MTX3 protocol, 1 mg/kg body weight intratubal associated with 1 mg/kg body weight i.m. daily for 3 days; and now MTX4 protocol, only intratubal 1 mg/kg body weight is especially used. The success was defined as declining serum human chorionic gonadotropin (hCG) to undetectable levels, and no further surgical management was required. Outcome of subsequent fertility was also evaluated. RESULTS: Complete resolution was obtained in 13 (86.6%) out of 15 interstitial pregnancies. Two out of 15 patients, with medical treatment's failure required secondary surgery. No severe side effects of medical treatment were observed. Follow-up hysterosalpingography was performed in 12. Outcome of intra-uterine pregnancy of the three patients who had heterotopic gestation, was two miscarriages and one delivery at term. Out of the other 12 patients in this series, nine became pregnant within 1 year: eight pregnancies at term, and one induced abortion. At present, among the last three patients, two have no desire to(16).

Groutz 1998 Aug, reported a case of advanced interstitial pregnancy treated successfully conceive by combining methotrexate (MTX) and hysteroscopy. CASE: A routine ultrasonic evaluation of a 10-week pregnancy revealed a right interstitial gestational sac 58 mm in diameter and containing an embryo with a crownrump length of 29 mm and embryonic heartbeats. Serum beta-human chorionic gonadatropin (hCG) level was 97,950 mIU/mL. The patient was treated with a systemic MTX/leucovorin regimen. At the end of the one-week course, no embryonic cardiac activity was detected, and a decrease in beta-hCG levels commenced(17).

SanzLE in Georgetown university, A 36-year-old newly gravida presented with an 8-week history of amenorrhea and a positive home pregnancy test. A transabdominal sonogram revealed a left cornual ectopic pregnancy. The patient was treated with multiple methotrexate doses, but the gestational sac persisted. Through the hysteroscope, the sac was ruptured, and the placental tissue was removed from the left cornu under sonographic guidance. Two weeks postoperatively, the patient's beta-human chorionic gonadotropin level was negative, and she had a normal pelvic examination and sonogram(18).

Darai E in franc university

Between November 1988 and December 1993, 100 patients with a common, unruptured ectopic pregnancy were treated with 1 mg/kg injection of intratubal methotrexate under transvaginal sonographic control. Patients were not excluded from this series on the basis of the size of the adnexal mass, the term of ectopic pregnancy or initial beta-human chorionic gonadotrophin (HCG) concentrations. Patients were

excluded following uncertain diagnosis, signs of a ruptured ectopic pregnancy, or a significant haemoperitoneum on ultrasound scans. The mean age of the patients was 29.5 years (range 20-41). The mean gestational age and initial HCG concentration were 7.5 weeks (5-11) and 11,614 mIU/ml (192-105,000 respectively). Of the 100 patients, 22 (22%) had an ectopic pregnancy with active cardiac activity. Complete resolution was obtained in 78 out of these 100 ectopic pregnancies. Of these, 66 patients (85%) needed only one intratubal methotrexate injection, and 12 patients (15%) required a second i.m. methotrexate injection of 1 mg/kg. In this study, local treatment with one single intratubal methotrexate injection was successful in only 66% of patients. The mean resolution time for reduction of beta-HCG concentrations was 23.5 days (range 7-40). There was no statistically significant correlation between initial beta-HCG concentrations and outcomes after methotrexate treatment of ectopic pregnancy in our study. Where embryonal heart beats were observed, the success rate of the procedure was 40.9% (nine out of 22 cases). In the absence of cardiac activity, or when ultrasound examination showed no embryo, the success rate achieved was 84.6% (66 out of 78 cases) ($P < 0.01$). In all, 34 patients were considered to be incompletely cured after only one intratubal methotrexate injection: 12 patients required a second i.m. injection, a stagnation of beta-HCG concentrations was observed in 15 patients, abdominal pain occurred in six patients, and one patient suffered tubal rupture with haemoperitoneum. A total of 22 patients required secondary surgical management (salpingectomy). No biochemical or clinical side-effects of methotrexate (19).

Result

Result of study	Number of patient	Medical treatment	hysteroscopy
Benifla	15	13	2
Groulze	1	1	1
SANZLE	1	1	1
Darai	100	78	22

The total number of the patients in these studies is 117. 93 of them was treated medically by methotrexate complete cure not occur so hysteroscopy was performed.

Discussion

In Benifla et al study in France included 15 patients with unruptured interstitial obtained in 13 while 2 of them need hysteroscopy. **H**esuggest that unruptured interstitial pregnancies now can be managed with local MTX administration of 1 mg/kg body weight under transvaginal ultrasound or under hysteroscopy procedure. This approach is particularly attractive in these patients, where the only alternative to therapy is laparoscopy with cornual resection (16).

GROUTZ who reported a case of advanced interstitial pregnancy treated successfully by

combining methotrexat and hysteroscopy Persistent trophoblastic tissue, manifested by a low (26 mIU/mL) beta-hCG level in plateau, was successfully removed by way of hysteroscopy (17).

Sanzle in Georgetown university who reported a case of advanced interstitial pregnancy treated with multiple doses of methotrexate still having high HCG. The author suggests that using hysteroscopy increase chance of complete resolution (18).

Darai included 100 patients in his study, 78 of them received medical Treatment and complete cure occurred the other 22 was treated by Hysteroscopy (19)

Conclusion

Early detection of interstitial pregnancy may facilitate combined medical and hysteroscopy management.

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