Virtue of methotrexate in ectopic pregnancy

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Article History: In recent times there is a shortfall of care about ectopic pregnancy among everyone, inciting conceded finding and potentially non-violent results. Ectopic pregnancy is a very dangerous medical disorder. This occurs when a fertilised egg implants outside of the uterus, generally in the fallopian tube. Making up 5%–10% of all pregnancy-related deaths, ectopic pregnancies are the leading cause of maternal death in the first trimester. Methotrexate is a folic acid inhibitor. It interferes with DNA synthesis and cell multiplication by inhibiting the spontaneous synthesis of purines and pyrimidines. Methotrexate will be used in the middle of six and eight weeks of pregnancy. The likelihood of a future pregnancy succeeding after using methotrexate is generally positive, according to studies. However, a few things could have an impact on these odds. As per to research, ectopic pregnancies are more common among women of reproductive age, usually between the ages of 20 and 35. Given that they are more likely to be sexually active and trying to get pregnant, women in this age range are at their most fertile. Additionally, the prevalence of sexually transmitted diseases (STIs) is higher in this age group, which can mark up the chance of an ectopic pregnancy. Factors affecting ectopic pregnancy risk include previous pelvic surgeries, infections, in vitro fertilization [IVF], endometriosis, smoking, assisted reproductive technologies, and tubal sterilization or previous pregnancies. This review of the literature attempts to shed insight on how methotrexate is currently used to treat ectopic pregnancies

Keywords: Ectopic pregnancy, Methotrexate, Fallopian tube, Purines and pyrimidines, Pregnant women

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INTRODUCTION

METHOTREXATE is a folate antagonist, analogues of which were initially used to treat acute leukaemia by Farber in 1948 [1]. Medical therapy with methotrexate (MTX) was developed for EP in the 1980s. Previously, Pregnancy-related trophoblastic neoplasia was often treated with MTX, a folic acid antagonist. MTX was shown to be effective for the majority of early-stage EPs in the...
early 1990s because of its capacity to target and impede the proliferation of prenatal trophoblastic neoplasia cells that proliferate fast [2]. When the patient is hemodynamically stable as well as the hCG level is 5000 mIU/mL, medical therapy has a higher chance of being successful.

When the ectopic is 3.5 cm in size, there are no symptoms of ruptured EP, and there is no fetal heart activity, the patient is considered stable. Patients must be continuously watched to ensure that their hCG levels falls and eventually returns to zero.

It should be noted that serial ultrasounds are not the standard of therapy unless the patient develops significant quality abdominal discomfort; at this point, peritoneal fluid is critical. The effectiveness of mifepristone in preventing IUP has been established. Its achievement in this area has prompted the thought of mifepristone as an additional treatment together with MTX. Early results indicated that this combination minimized persistent EP. Though the combination appears secure, more recent studies have not supported this advantage. As a result, very few medical professionals combine mifepristone with MTX [3].

Methotrexate is a folate antagonist that works by directly inhibiting dihydrofolate reductase (DHR). DHR transforms dihydrofolates to tetrahydrofolates, which are chemically active and totally reduced. Tetrahydrofolates help to synthesise thymidylate, an essential precursor for DNA synthesis. Methotrexate inhibits DHR, which results in the depletion of intracellular tetrahydrofolates, reduced thymidylate production, as well as subsequent suppression of DNA synthesis. Methotrexate metabolism to polyglutamate derivatives also contributes to DNA synthesis suppression by directly inhibiting other folate-dependent enzymes involved in purine along with thymidylate synthesis. Methotrexate inhibits DNA synthesis in a variety of ways, including depletion of DNA precursors through substrate depletion and direct inhibition of folate-dependent [4]. Despite major breakthroughs in laparoscopy and MTX, expectant care is recommended for select individuals with pregnancy of unknown location (PUL). When transvaginal ultrasound shows no IUP or extrauterine pregnancy and the serum hCG titer is <1000 mIU/mL, 88% of women with suspected EP resolve spontaneously with expectant care. Expectant management appears to be suitable in this situation, although more severe criteria are necessary. Many doctors consider 200 mIU/mL to be the crucial threshold for expectant treatment. Serum progesterone, Doppler blood flow in fallopian tube arteries, culdocentesis computer tomography scanning (CT), and magnetic resonance imaging (MRI) are other EP diagnostic procedures. None of these can replace serum hCG and transvaginal sonography as the primary options for sonography remains the preferred imaging technique, however it may be complemented with CT or MRI. A consensus statement issued in 2011 offered new criteria and ultimate outcome metrics for this often perplexing diagnosis. PUL has been proposed for women who are known to be pregnant but lack an apparent IUP. Sonographic findings are characterised as one of the five categories: There are five types of EP: definite, likely, PUL, probable, and definite IUP. Women with a PUL have four possible outcomes: visualised EP, visualised IUP, spontaneously resolved PUL, and continuing PUL. Persistent PUL is further classified as nonvisualized EP, treated persistent PUL, resolved persistent PUL, and histologic IUP. Although these definitions appear complicated, they describe the location (intrauterine vs. extrauterine) and natural history of early gestations in which the starting site is uncertain. The hope for the new terminology along with outcome [5].

A commercially marketed methotrexate sodium tablet has the same amount of medication as 2.5 mg of oral methotrexate. The 25 mg/mL solution of parenteral methotrexate sodium is available in vials containing 50 and 250 mg. Given that benzyl alcohol is present in this conserved formulation, intrathecal or high-dose therapy cannot be performed with it. Parenteral solutions without preservatives are offered in vials containing 50, 100, 200, and 250 mg. A freeze-dried powder with a low-sodium, preservative-free parenteral formulation is also available in vials containing 20 mg, 50 mg, and 1 g. It is recommended to reconstitute these formulations using a suitable sterile, preservative-free medium, such as sodium chloride injection or 5% dextrose solution (per the USP). Reconstituted vials for intrathecal usage should have a concentration of 1 to 2 mg/mL [6]. It is possible to give methotrexate intravenously,
intramuscularly, intrathecally, intraventricularly, or intra-arterial. In pediatric oncology, typical oral dosages range from 7.5 to 40 mg/m². When treating acute lymphocytic leukemia, it is often given as a weekly oral or intramuscular dose. A wide variety of dosages, ranging from a 10-mg bolus to 33 g over 24 hours, have been employed for intravenous infusion. To avoid severe toxicity, doses above 100 to 300 mg/M² must be followed with leucovorin "rescue." For the treatment of osteogenic sarcoma, a typical high-dose methotrexate regimen includes 12 [g/ml] given over 4 hours, and 15 mg given orally or intravenously every 6 hours for 10 doses of leucovorin commencing 24 hours following the commencement of the first dosage [7]. The main side effects of methotrexate are gastrointestinal mucositis and myelosuppression, which appear 5 to 14 days after the drug is administered. Treatment. The length and intensity of the drug exposure determine how severe these effects will be 5 by administering leucovorin as described above, severe toxicities are typically prevented.

Methotrexate precipitation in the renal tubules can lead to acute nephrotoxicity. Because renal impairment may further decrease drug excretion and increase subsequent toxicity, it must be identified and treated right away.

This problem is typically avoided by vigorous hydration and urine alkalinization. A temporary increase in serum transaminases is a typical side effect of high-dose methotrexate, and persistent low-dose therapy has been linked to cirrhosis and portal fibrosis. High-dose or intrathecal methotrexate has been linked to three different neurotoxic disorders [8].

Ectopic pregnancy is characterized by implantation that takes place anywhere other than the uterine cavity. This syndrome is distinguished from ectopic intrauterine growth. Pregnancies. The latter include cervical pregnancies, in which the fetus is born in the uterine cervix, and cornual pregnancies, in which the fetus is born in the proximal section of the fallopian tube. The gestational product is completely enveloped by the myometrium and has no contact with the uterine cavity in intramural pregnancies, which are rather uncommon. Intramural cervical pregnancy is another uncommon type of ectopic pregnancy.

These different types of intrauterine pregnancy are set apart from extrauterine varieties. In the fallopian tube, 99 percent of extrauterine pregnancies take place. The location of the pregnancy is most usually in [8] only 1% to 2% of pregnancies take place in the fimbria, or interstitial space. Extrauterine ovarian or non-tubal [9].

Abdominal pregnancies are quite uncommon. In an abdominal pregnancy, implantation can take place in the Douglas pouch, the omentum, or (rarely) on the peritoneal surface of the ovary. Primary or secondary implantation may result in the development of an abdominal pregnancy. When trophoblastic tissue protrudes from the fallopian tube, the latter is the situation. Only one in 30,000 cases of simultaneous extra- and intrauterine pregnancy is heterotopic. However, this problem is becoming increasingly widespread due to the increased usage of in vitro fertilization. Over the past 30 years, extrauterine pregnancy has become more common. Methotrexate is a folic acid antagonist whose activity is mostly shown in trophoblasts, which are rapidly growing cells at the site of implantation [10].

Compared to the English-speaking world, Germany uses systemically given methotrexate for pharmacotherapy far less frequently. Due to the accessibility of gynaecological treatment in all nations. The literature varies in its reporting of the methotrexate treatment's success rates, which range from 63% to 97%; this is likely because different There are several patient groups and inclusion standards, distinct methotrexate treatment regimens, as well as distinct definitions of treatment response exist [11].

EPIDEMIOLOGY

According to reports, extrauterine pregnancies make up 1.3-2.4% of all pregnancies. Statistics often only include cases that were treated with surgery and in a hospital, thus it is impossible to determine the true frequency more precisely than this [12]. According to recent data, the extrauterine pregnancy rate in the United States is now higher than 1.4%, compared to an estimate of 0.4% in the middle of the twentieth century. For every 1000 live births in Germany today, there are thought to be 20 extrauterine pregnancies. The increasing exploitation of technology for assisted reproduction, the rising number of fallopian tube
operations, the aging of the mother, and more accurate diagnosis are just a few of the factors contributing to the rising frequency of (diagnosed) extrauterine pregnancies [13].

**INCIDENCE**

It is challenging to estimate the incidence of EP because it is no longer exclusively addressed in an inpatient hospital environment and many interactions have evolved into the norm for a single EP. But the incidence of EP seems to have increased steadily from the middle of the 20th century until plateauing in the 1990s. 17,800 occurrences in total in 1970 decreased to 108,800 cases in 1992 (19.7/1000 confirmed pregnancies according to the Centres for Disease Control), ectopic gestation was more frequently recorded [14]. The increased reported incidence most likely reflects a real rise in the disease's prevalence. Improved diagnostic methods enable earlier diagnosis than was previously possible, which is another factor. In actuality, both elements probably come into play. Improved diagnostic methods enable earlier diagnosis than was previously possible, which is another factor. In actuality, both elements probably come into play. This rising incidence is closely linked to a rise in pelvic inflammatory disease (PID) incidence [15].

Today, just 2% of all known pregnancies are caused by EP. In women between the ages of 15 and 44, the mean annual rate of EPs was estimated by a 2010 study to be 0.64%. The 35 to 44 age group had the greatest yearly rate of EP at 0.99%.

There are regional variations in the annual rate of EP. The region with the largest percentage of EPs is the south (0.77%), Northeast (0.56%) and North Central (0.59%) came next. The west saw a sharp decline in trend at 0.48%. June and December have the highest number of EP diagnoses.

There are no known explanations for these variations. Up to 16% of women who present to a hospital emergency room with pain, bleeding, or both during the first trimester have an EP, which is an intriguing clinical finding[16].

**MORTALITY**

Maternal mortality from EP has significantly decreased in recent years, most likely because to earlier diagnosis and greater access to care. It was 3.5 per 10,000 pregnancies in 1970, 3.8 per 10,000 in 1987, and 2.6 per 10,000 in 2014. Deaths decreased from 1.15 to 0.50 per 100,000 live births when stated using conventional definitions of maternal mortality births. The risk of maternal death during extrauterine gestation is 50 times higher than the risk of miscarriage in the first trimester and 10 times higher than the risk of birth in the third trimester. Mortality continues to be a major factor, accounting for about 12% of all maternal fatalities in 1987 and 9% today. Sadly, mortality is 3.5 times higher for women over 35 and 6.8 times higher for African American women than for white women. Hemorrhage, infection, and anesthesia complications are the three main reasons of death for women with EP in the US. These are also the most common factors in all pregnancies that result in mortality. Between 1998 and 2007, 76 of the women who were finally determined to have EP, who may have had access to cutting-edge diagnostic equipment, and who were hospitalized for assessment or observation perished. Approximately 8% of all maternal deaths were caused by this. Any number of other illnesses can pass for EP. In fact, the illness that claimed the lives of In half of the cases, PID, gastrointestinal ailments, psychiatric disorders, spontaneous abortion, induced abortion sequelae, and intrauterine pregnancy were misdiagnosed as other pathologies. Not all of the women who died from haemorrhages had surgery; 70% did not.

Even though a proper diagnosis had been reached in 5% of these cases, prompt care was not provided. These findings highlight the potentially fatal nature of this illness if an early diagnosis and subsequent treatment action are postponed. The fallopian tubes, as opposed to other locations, were the site of the ectopic pregnancy in the majority of fatalities. However, ectopic tubal pregnancies only made up 5% to 10% of the fatalities, while interstitial pregnancies were responsible for 20% of all fatalities [17].

**RISK FACTORS**

Risk-raising factors [odds ratio (OR) > 4.0]

The two most significant risk factors for tubal pregnancy are previous tubal surgery or a tubal pregnancy. Although sterilization is a fairly successful means of contraception, extrauterine pregnancy should be taken into account as a
possibility if a woman falls pregnant after having the surgery that is supposed to sterilize her. About 30% of post-sterilization pregnancies are extrauterine. The probability of tubal pregnancy over the course of 15 years is 2.9 per 1000 sterilizations. Following fallopian tube electrocoagulation, the likelihood of tubal pregnancy is elevated due to fallopian tubes or the formation of a utero-/tuboperitoneal fistula [18]. When compared to women who don’t use any kind of contraception, intrauterine device users have a lower chance of ectopic pregnancy. Extrauterine pregnancy should be ruled out if a woman utilizing an intrauterine device is yet discovered to be pregnant because 50% of these pregnancies are extrauterine.

Factors with a moderately elevated risk (OR > 2.0) Extrauterine pregnancy rates have been found to be higher in women taking the hormone clomifene to treat infertility, despite the population’s higher prevalence of tubal pathology and history of surgical procedures being obvious confounding factors. Compared to women who don’t take any form of contraception, intrauterine device users had a lower chance of ectopic pregnancy. Because 50% of pregnancies utilising intrauterine devices are extrauterine, extrauterine pregnancy should be investigated if a woman is still confirmed to be pregnant.

Despite the population’s higher prevalence of tubal pathology and history of surgical procedures being obvious confounding factors [19], extrauterine pregnancy rates have been found to be higher in women taking the hormone clomifene to treat infertility.

DIAGNOSIS

Extrauterine pregnancies are often identified between weeks six and nine of pregnancy, with the majority of patients presenting with vague problems. pregnancy in an unspecified region

It's critical to differentiate "pregnancy of unknown location" (PUL) from ectopic pregnancy.

The lack of an intrauterine pregnancy visible on an ultrasound scan separates the two.

An intrauterine pregnancy is often not readily visible on the first ultrasound performed during pregnancy, depending on the date and the examiner’s experience; in 7–20% of such situations, an extrauterine pregnancy turns out to be present. Both an early miscarriage and an intact early intrauterine pregnancy that cannot yet be spotted by ultrasonography are included in the differential diagnosis. The trajectory of the human chorionic gonadotrophin (hCG) level, individual clinical characteristics, and imaging investigations all point to the proper diagnosis [20]. In between 30 and 50 percent of cases with murky results, an intact early intrauterine pregnancy is present. It should be kept in mind that if the hCG level is below 1000 IU/L, ultrasonography may not always be able to detect even an intrauterine pregnancy. When the hCG level is higher than this, an intrauterine pregnancy appears as a hyperechogenic ring structure positioned eccentrically.

There is unquestionably an intrauterine pregnancy present if an embryo or yolk sac is visible. If just a circular, empty if a structure is present, it can be an ectopic pregnancy's pseudogestational sac. Pseudogestational sacs never contain a yolk sac or other embryonic features, and they always show as a little collection of fluid in the uterine cavity. As a result, they are not situated eccentrically.

Unknown pregnancy locations are linked to almost half of all early losses. The diagnosis of an early complete abortion does not correspond with endometrial thickness as determined by ultrasonography [21].

A tubal pregnancy is more likely if there is a heterogeneous mass in the tubal area. A gestational sac that often includes a yolk sac or embryonic characteristics must be visualised in order to support the working hypothesis of an unidentified pregnancy. A consensus statement [22] suggests the categories listed below:

- pregnancy in an unidentified location: no indications of an intrauterine or extrauterine pregnancy; definite ectopic pregnancy: extrauterine gestational sac containing the embryo and/or yolk sac; probable ectopic pregnancy: heterogeneous mass in the adnexal region; probable intrauterine pregnancy: presence of an intrauterine ring structure, a gestational sac inside the uterus that contains an embryo, yolk sac, or both.
TREATMENT

The development of MTX medical treatment regimens in the late 1980s led to its acceptance as the main therapy for ectopic pregnancy. MTX inhibits the absorption of folic acid. Dihydrofolate reductase (DHFR), an enzyme involved in the production of DNA and RNA precursors, generally converts folic acid to tetrahydrofolate.

Cofactors needed for the synthesis of DNA and RNA are depleted when MTX suppresses DHFR. In particular when greater dosages of MTX are taken, folinic acid (leucovorin), an antagonist to MTX, can help decrease otherwise severe side effects. A potential patient for medical care with MTX should ideally fulfill the requirements listed below: The following criteria must be met: hemodynamic stability [23]; no severe or chronic abdominal discomfort; a commitment to follow-up care until the ectopic pregnancy has ended; and baseline liver and renal function tests that are within normal ranges.

Women should undergo screening before starting MTX treatment, patients should be evaluated with a full blood count, tests for liver function, serum creatinine, blood type, as well as Rh. Women who have had pulmonary disease in the past should also get a chest x-ray since individuals with underlying lung disease are more susceptible to interstitial pneumonitis. Two typical MTX treatment plans exist: "single dose" and "multiple dose." A summary of the treatment and monitoring plans for both regimens. The multiple-dose approach was the first treatment for ectopic pregnancy and was adopted from early experience with MTX treatment for trophoblastic illness. The multiple-dose strategy alternates leucovorin therapy with MTX treatment. MTX is kept up until the hCG level drops 15% from its high [24].

The whole 8-day regimen will not be necessary in about 50% of individuals who get this treatment. Actually, the phrase "single dose" is a misnomer. The regimen contains provisions for extra MTX doses when the response is insufficient, even though it specifies the number of MTX injections anticipated. In general, MTX is a secure and successful method of treating an unruptured ectopic pregnancy [25].

CONCLUSION

As per to research, ectopic pregnancies are more common among women of reproductive age, usually between the ages of 20 and 35. Given that they are more likely to be sexually active and trying to get pregnant, women in this age range are at their most fertile. Additionally, the prevalence of sexually transmitted diseases (STIs) is higher in this age group, which can mark up the chance of an ectopic pregnancy. Factors affecting ectopic pregnancy risk include previous pelvic surgeries, infections, in vitro fertilization [IVF], endometriosis, smoking, assisted reproductive technologies, and tubal sterilization or previous pregnancies. This review of the literature attempts to shed insight on how methotrexate is currently used to treat ectopic pregnancies.

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