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Review Article

Methotrexate in the Management of Ectopic Pregnancy: A Comparative Review of Single-Dose Versus Multi-Dose Protocols

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Abstract:

Ectopic pregnancy ruptures account for five percent to ten percent of all pregnancy-related deaths and are the primary reason for maternal mortality throughout the first trimester of pregnancy, with a rate of nine percent to fourteen percent. An ectopic pregnancy is a gestational sac that implants somewhere other than the uterus. The implantation of an embryo outside the uterus, usually in the fallopian tube, is the essence of ectopic pregnancy. To aid in the passage of an egg and embryo by the fallopian tubes, smooth muscle contraction, and ciliary beat have been used. Damage to the fallopian tubes, typically caused by inflammation, can lead to tubal dysfunction and the retention of an embryo or ovum. The anti-metabolite methotrexate is most frequently used as an immunosuppressant in autoimmune illnesses and as a chemotherapy drug. This activity explains methotrexate's actions, side effects, and recommended dosage for treating a range of neoplastic conditions. The single-dose, 2-dose, and multi-dose methotrexate protocols are the most popular ones. Studied cases who are more likely to require additional doses due to medical treatment failure may benefit from the multi-dose strategy. To reduce side effects, the multidose protocol calls for the adding of folinic acid rescue in addition to methotrexate doses, which are alternated. This is because of how frequently the regimen is administered. Although the single dose was intended to cut down on visits, it frequently necessitates more care and follow-up

Key words: ectopic pregnancy; methotrexate; folinic acid; pregnancy-related mortality; immunosuppressive therapy; tubal dysfunction; embryo implantation

Introduction

Ectopic pregnancy ruptures account for five percent to ten percent of all pregnancy-related deaths and are the primary reason for maternal mortality throughout the 1st trimester of pregnancy, with a rate of nine percent to fourteen percent. An EP is a gestational sac that implants somewhere other than the uterus. Women who have an EP may experience vague symptoms including vaginal bleeding and lower abdominal pain, which frequently manifest clinically as appendicitis, urinary calculi, early pregnancy loss, or trauma [1]. Methotrexate (MTX), a folate antagonist, has gained prominence in managing early, stable ectopic pregnancies, reducing the need for invasive surgical interventions. This review discusses the etiology, epidemiology, diagnostic criteria, and the role of methotrexate therapy in ectopic pregnancies, comparing single-dose and multi-dose treatment protocols.

Etiology

The implantation of an embryo outside the uterus, usually in the fallopian tube, is the essence of ectopic pregnancy. To aid in the passage of an egg and embryo by the fallopian tubes, smooth muscle contraction and ciliary beat have been used. Damage to the fallopian tubes, typically caused by inflammation, can lead to tubal dysfunction and the retention of an embryo or ovum. Numerous local variables, involving those that are poisonous, viral, immunological, or hormonal, may cause inflammation [2].

After tubal injury, pro-inflammatory cytokines have been upregulated, which facilitates angiogenesis, invasion, and embryo implantation in the fallopian tube. When tubal epithelial cells are infected with Chlamydia trachomatis, they produce interleukin-1, which is an essential marker for the implantation of embryos in the endometrium. Additionally, interleukin-1 plays a part in the recruitment of neutrophils downstream, which exacerbates the damage to the fallopian tubes. Smoking and infections have a deleterious impact on cilia beat frequency. Additionally,

changes in hormone levels throughout the menstrual cycle have been shown to impact the frequency of cilia beats [3]. Ectopic pregnancy is influenced by a range of contributing factors, including prior pelvic infections, tubal abnormalities, and previous tubal surgeries or procedures. (Figure 1), [4].

Figure 1: Causes of ectopic pregnancy. This figure summarizes major causes such as fallopian tube abnormalities, prior pelvic infections, and previous tubal surgeries or procedures [4].

Epidemiology

Ectopic pregnancy is thought to occur at a rate of one to two percent in the general population and two to five percent in individuals who have used assisted reproductive technologies. Less than ten percent of ectopic

pregnancies involve implantation that takes place outside of the fallopian tube. four percent of all ectopic pregnancies and one in five hundred pregnancies in women who have had at least 1 prior caesarean section are caesarean scars ectopic pregnancies. Up to four percent of ectopic implantation sites are reported to have interstitial ectopic pregnancies, which have morbidity and mortality rates up to seven times higher than those of other ectopic implantation sites [5].

The high rate of bleeding in interstitial ectopic pregnancies is the cause of this higher morbidity and death. One percent of ectopic pregnancies were documented to have an intramural implant, meaning the pregnancy was implanted in the myometrium. 1.3 percent of ectopic implantation sites are in the abdominal cavity; these sites are most frequently seen on the serosa of the uterus and adnexa, as well as in the pouches anterior and posterior to the uterus. Ectopic pregnancies that implant in this manner account for these implantation sites. Additionally, reports of implantation sites in the spleen, liver, omental, and retroperitoneum exist [6].

Diagnostic Evaluation

When making a suspected ectopic pregnancy diagnosis, transvaginal ultrasound imaging is essential. To confirm the diagnosis, repeat tests using serum beta hCG level assays, transvaginal imaging, or both are required. The earliest ultrasound indicator of an intrauterine pregnancy is a little sac situated eccentrically inside the decidua. The sac will develop 2 tissue rings around it; this is known as the "double decidual" indication. On abdominal ultrasonography, the double decidual sign often appears throughout the fifth week of pregnancy [7].

At this point, the yolk sac will become visible, although transvaginal ultrasound imaging will be necessary to identify it. Transvaginal imaging will reveal an embryonic pole at about 6 weeks of pregnancy. The ability of ultrasound imaging to detect an early intrauterine pregnancy may be hampered by uterine fibroids or a very higher body mass index. In severe cases, like massive blocking uterine fibroids, MRI imaging can be beneficial; however, further research is needed to determine its sensitivity and specificity, and it is important to consider the possible dangers associated with gadolinium contrast exposure [8].

Methotrexate is an anti-metabolite that is most frequently used as an immunosuppressant in autoimmune disorders and in chemotherapy. This activity explains methotrexate's actions, side effects, and recommended dosages for treating a range of neoplastic conditions [9].

Indications

Due to its great potency and efficacy in treating rheumatoid arthritis, methotrexate has been an FDA-approved folic acid antagonist that may be helpful in treating juvenile idiopathic arthritis. Gubner conducted a double-blinded, placebo-controlled clinical trial of methotrexate in individuals with rheumatoid arthritis before recommending its usage in this condition. Aminopterin was initially utilized to treat paediatric leukaemia and was thought to as the parent chemical of methotrexate [10].

Methotrexate is one of the main chemotherapeutic options available nowadays for treating different kinds of cancer. studied cases with psoriasis, vasculitis, inflammatory bowel disease, systemic lupus erythematosus, and numerous other connective tissue illnesses can safely and effectively use the medicine. Pregnant women are not advised to take the medication, since its safety and effectiveness in treating blood dyscrasia studied cases have not been shown. Due to the drug's anti-inflammatory and immunomodulatory properties, organ transplant

recipients can benefit from it [11].

Additionally, methotrexate has demonstrated efficacy when paired with anti-TNF medicines in the treatment of individuals with ulcerative colitis, non-Hodgkin's type lymphoma, breast carcinoma, lung small-cell carcinoma, head and neck epidermal tumors, and ovarian carcinoma. For individuals with graft-versus-host disease, the drug works in the same way as cyclosporin. In off-label cases of non-Hodgkin lymphoma (advanced stage), non-metastatic osteosarcoma, pityriasis rubra pilaris, dermatomyositis, eczema, and sarcoidosis, methotrexate is utilized [12].

Mechanism of Action

When it comes to immunosuppression in autoimmune illnesses and chemotherapy, methotrexate has a unique method of action. Methotrexate functions as an antifolate antimetabolite in cancer. Methotrexate-polyglutamate is formed when the medication has been absorbed into the cell via carriers known as human decreased folate carriers (SLC19A1). The enzyme dihydrofolate reductase, which catalyzes the transformation of dihydrofolate into tetrahydrofolate, the active form of folic acid, has been inhibited by both methotrexate and methotrexate-polyglutamate. The synthesis of the nucleotides in both DNA and RNA requires tetrahydrofolate **(Figure 2).** DNA synthesis is further inhibited by methotrexate-polyglutamate, which prevents thymidylate synthase and purine from synthesizing de novo. Due to this mechanism's cytotoxic action, cancer is treated with it [13].

There are various mechanisms at play when selecting methotrexate as the preferred medication for autoimmune disorders. Because of adenosine's anti-inflammatory properties, it also inhibits the enzyme AICAR transformylase, which hinders the metabolism of adenosine and guanine and accumulates adenosine. Additionally, adenosine represses T-cell activation, down-regulates B-cells, and increases the sensitivity of activated CD-95 T cells. Finally, it represses methyltransferase activity, which prevents beta-1 interleukin from attaching itself to its cell surface receptor [14].

Mechanism of action of methotrexate as a medical treatment for ectopic pregnancy

Methotrexate is a medication used in the treatment of ectopic pregnancy, which is a condition where a fertilized egg implants and grows outside the uterine cavity, usually in a fallopian tube. The mechanism of action of methotrexate in this context includes several key aspects:

Anti-folate Action: Methotrexate is a folic acid antagonist. It inhibits the enzyme dihydrofolate reductase, which is crucial for the synthesis of nucleotides, the building blocks of DNA and RNA. By blocking this enzyme, methotrexate impairs the production of DNA and RNA, leading to reduced cellular proliferation.

Inhibition of Cell Division: Ectopic pregnancy involves the growth and division of trophoblastic cells (the cells that form the outer layer of the placenta). Methotrexate disrupts the proliferation of these cells by interfering with their ability to synthesize DNA and RNA, which ultimately leads to the termination of the ectopic pregnancy.

Induction of Apoptosis: Methotrexate may also induce apoptosis (programmed cell death) in rapidly dividing cells. This contributes to the resolution of the ectopic pregnancy by causing the death of the trophoblastic cells that are growing abnormally [14].

Indications for methotrexate in ectopic pregnancy

Methotrexate is used for the treatment of ectopic pregnancy under specific conditions. Its use is generally indicated when:

Early Diagnosis: The ectopic pregnancy is diagnosed early, usually within the first few weeks. This is because methotrexate is most effective in treating small, early-stage ectopic pregnancies.

Unruptured Ectopic Pregnancy: The ectopic pregnancy has not ruptured. Methotrexate is typically used when the ectopic pregnancy is still intact and has not caused internal bleeding.

Stable Patient Condition: The patient is hemodynamically stable with no signs of significant internal bleeding or shock. Methotrexate is not suitable for patients who are experiencing severe pain or have signs of hemorrhage**.**

Low Serum Beta hCG Levels: The serum levels of human chorionic gonadotropin are relatively low, usually less than 5,000-6,000 IU/L. Higher Beta hCG levels are often associated with more advanced or larger ectopic pregnancies, which may not respond as well to methotrexate.

No Contraindications: There are no contraindications to methotrexate therapy. These contraindications involve liver disease, renal impairment, peptic ulcer disease, immunodeficiency, and active pulmonary disease, among others.

Patient Consent and Understanding: The patient is informed about the treatment plan and consents to methotrexate therapy. They should be aware of potential side effects and the need for follow-up monitoring.

Absence of Fetal Cardiac Activity: In some cases, the absence of fetal cardiac activity is also considered, as the presence of a fetal heartbeat might suggest a more advanced ectopic pregnancy that might be less responsive to methotrexate [14].

Drug interactions: Due to its strong plasma protein binding, methotrexate's blood levels can rise with any medication that removes it from proteins. Additionally, the concentration of any medication may increase if it influences methotrexate's renal clearance. The risk of MTX toxicity in the blood is increased by NSAIDs, salicylates, TMP, penicillin, warfarin, valproate, proton pump inhibitors, cyclosporin, and cisplatin; the absorption of MTX is decreased by aminoglycosides, neomycin, and probenecid. Due to their widespread use as treatment options, NSAIDs and PPIs have the most notable and dangerous interactions [15].

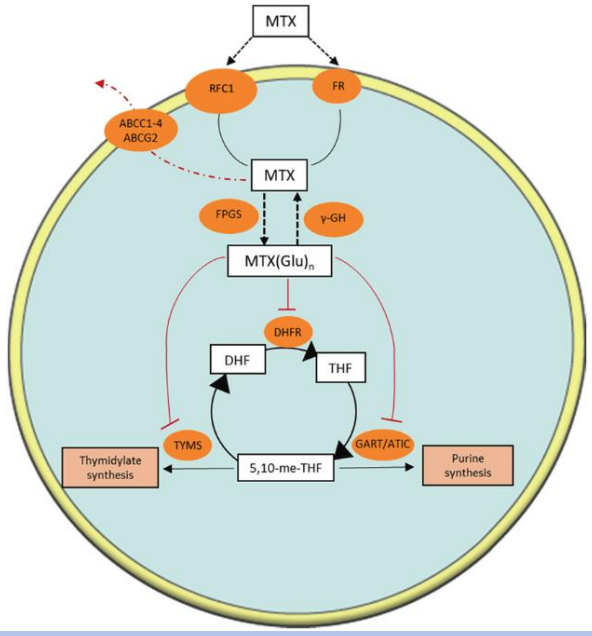

Figure 2: Mechanism of action of methotrexate. Methotrexate (MTX) enters the cell mainly through the reduced folate carrier (RFC1) and to a lesser extend through receptor-mediated endocytosis via a folate receptor (FR). Upon entry, MTX gets polyglutamated (MTX(Glu) n) by folylpolyglutamate synthase (FPGS). Polyglutamates of MTX are a superior antifolate agent compared to MTX, capable of highly potent irreversible inhibition of DHFR. Furthermore, MTX induces inhibition of other enzymes like TYMS and GART/ATIC, ultimately blocking de novo thymidylate and purine syntheses. γ-glutamyl hydrolase (γ-GH) (compartmentalized in lysosomes) removes glutamate residues from MTX, while ATP-binding cassette (ABC) transporters assist in the excretion of MTX from the cell [16].

Monitoring

It is advised that patients receiving methotrexate have their CBC, serum creatinine, and transaminases checked weekly for the 1st 4weeks, and then at least every two months after that. Before administering methotrexate, a comprehensive inventory of all current medications must be reviewed to rule out any potential drug interactions. In instances of hepatotoxicity, liver function tests (which measure serum AST, ALT, and albumin levels) and liver biopsies may be performed. Before prescribing methotrexate, creatinine clearance must be monitored (50ml/min is required) to prevent potential nephrotoxicity [17].

Due to the possibility of fever, dyspnoea, or dry cough, studied cases must be monitored for pulmonary toxicity. To identify pleural effusions, pulmonary fibrosis, hilar adenopathy, and interstitial and alveolar infiltrates, baseline chest radiographs are advised. Testing to rule out tuberculosis is necessary because methotrexate can reactivate the disease in endemic locations. Additionally, keep an eye out for bone marrow toxicity because a folate shortage can cause myelosuppression. A sharp decline in blood counts should raise suspicions about that [18].

Multidose versus single dose methotrexate in ectopic pregnancies management

Although ectopic pregnancies only occur in about two percent of pregnancies, they are the primary reason for pregnancy-related deaths in the 1st trimester and account for nine percent of maternal mortality. Early identification of ectopic pregnancies has been made possible by advancements in imaging technology and screening techniques for women who pose a risk. The spectrum of treatment choices for women with ectopic pregnancies has broadened from surgical therapy to medicinal management as more of them present clinically stable without risk of rupture. Methotrexate, a folate antagonist that binds to dihydrofolate reductase and inhibits DNA synthesis, repair, and cell replication downstream, has been the cornerstone of medical care [19].

Numerous studies have shown that when treating stable ectopic pregnancies, medicinal management is just as effective as surgical management. The single-dose, 2-dose, and multi-dose methotrexate protocols are the most popular ones. studied cases who are more likely to require additional doses due to medical treatment failure may benefit from the multi-dose strategy. But to reduce side effects, the multidose strategy necessitates the addition of folinic acid rescue in addition to methotrexate doses in alternation. Although the single dose was intended to cut down on visits, it frequently necessitates more care and follow-up. The 2 dosage protocol was developed to use the same simple visit schedule as the single dose protocol, but to balance the advantages of enhanced treatment success from additional doses of methotrexate [20].

When treating ectopic pregnancies medically, the success rates have ranged from seventy to ninety percent for single doses, between eighty and ninety percent for 2 doses, and eighty-nine to ninety-six percent for multidose protocols. The population under study, the standards for medicine administration, and the definition of therapeutic success can all have an impact on variation in rates. Treatment failure rates, or the likelihood that a given protocol will fail, are crucial factors to consider because they can be clinically helpful in-patient counselling and influence the recommendation of a particular protocol [21].

In general, ectopic pregnancy has become more common in recent decades, accounting for around two percent of pregnancies. From 4.5/1,000 reported pregnancies in 1970 to 20/1,000 pregnancies in1992, there was an upsurge in the United States. On the other hand, from 96.4/100,000 women aged fifteen to forty-four in 1992 to 95.3/100,000 in 2002, the overall EP rate in France fell by two percent. Nonetheless, there

was a seventeen percent rise in the "reproductive failure" rate. It is believed that the growing prevalence of pelvic inflammatory illness and the use of assisted reproductive technologies are responsible for the rising trend in the USA. Between six and sixteen percent of women treated in hospitals because of discomfort, bleeding, or both during the first trimester had EP. The early identification of endometriosis is now possible because of the use of high-resolution transvaginal ultrasonography and sensitive quantitative hCG assays for measuring hCG. For surgical, medicinal, or expectant care to be effective, an accurate diagnosis is necessary. The likelihood of using conservative treatment choices that preserve tubal function increases with early

diagnosis [22].

Methotrexate-based medical treatment for EP is a crucial step in the management of this dangerous illness. According to reports, the success rate ranges from seventy-five percent to ninety-six percent for studied cases who are carefully chosen. Methotrexate inhibits dihydrofolic acid's competitive binding to the enzyme dihydrofolate reductase, which disrupts the de novo production of purines and pyrimidines. As a result, there is an inhibition of decrease to folinic acid, a crucial cofactor in cell development ways [23].

The method of therapeutic administration that is most frequently employed is systemic methotrexate therapy. It can be given as a single dose regimen or as several doses, though opinions on the optimal technique are divided. The "two dose" protocol is a novel dosing schedule that has recently been proposed to reduce the number of injections and surveillance visits. The most common dosage is a single dose because it has fewer adverse effects and needs fewer hospital stays; however, a recent meta-analysis found no statistically significant differences in the success rates of single and multiple doses. A single dose had been related to increased treatment failure rates in their systematic analysis. The varying success rates could be ascribed to the physicians' inclination to select multiple-dose treatments for elevated levels of Beta hCG [24].

Discussion

Methotrexate has been well-established as a safe, effective, and non-invasive treatment for ectopic pregnancies when used under proper conditions. Compared to surgical intervention, MTX therapy preserves tubal function and future fertility. The single-dose protocol offers a more patient-friendly approach with lower costs and fewer hospital visits. However, multi-dose protocols can be advantageous in cases where higher initial hCG levels or other risk factors suggest a greater likelihood of treatment failure.

MTX has been the most widely used medication for the medical treatment of ectopic pregnancy since it is safe and has almost no documented negative effects on reproductive results. When using MTX for treatment, there are 3 commonly accepted protocols: single, double, and multiple dose regimens. MTX therapy has been generally effective and has a decent success rate. It is also considerably less expensive and does not come with the hazards associated with surgery or anaesthesia. On the other hand, a single dosage schedule lowers total expenses and increases patient compliance. Pregnancy rates ranging from 79.6 percent to 100 percent have been recorded in studies employing MTX therapy, indicating that all three regimens are safe and effective overall [25].

When evaluating ectopic pregnancy and pregnancy of unknown location, which has been described as a positive pregnancy test but no indication of an intrauterine or extrauterine pregnancy via transvaginal ultrasound (TVS), the serum level of beta-human chorionic gonadotropin is a crucial factor to consider in conjunction with TVS results. By observing tiny masses in the adnexa (approximately 10mm in diameter) and carefully assessing its characteristics, the contents of the endometrial cavity, and the existence of free peritoneal fluid, TVS may be able to identify ectopic pregnancy. Additionally, the aforementioned many factors have extremely high diagnostic sensitivity and specificity [26].

An empty uterus on TVS with a β-HCG concentration of ≥1500IU/L helps detect ectopic pregnancy with an accuracy of one hundred percent. Thus, the early detection of ectopic pregnancy has been made possible by the combination of transvaginal ultrasonographic observations and the β-HCG level. Serum progesterone levels may also be useful in the assessment of ectopic pregnancy [27].

Conclusion

Methotrexate (MTX) remains a safe and effective treatment for ectopic pregnancy, offering a non-invasive alternative to surgery. Both single-dose and multi-dose regimens have proven successful, with single-dose MTX being preferred in uncomplicated cases due to its convenience. Multi-dose protocols may be more effective in larger or more advanced pregnancies, potentially leading to higher success rates. Early diagnosis using ultrasound and serial hCG monitoring is essential for determining the appropriate treatment approach and achieving optimal outcomes, with success rates ranging from 70% to 96%.

MTX is generally well-tolerated, with minimal adverse effects on fertility, making it a preferred choice for patients wishing to preserve their reproductive potential. However, there is a need for further research to refine treatment protocols and evaluate the long-term impact of MTX on fertility and reproductive health. These studies will help guide clinicians in selecting the best treatment strategies for individual patients and enhance the understanding of MTX's role in managing ectopic pregnancy.

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