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REVIEW ARTICLE

Transformations in fertility management: evaluation of the effect of methotrexate in the treatment of ectopic pregnancies

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ABSTRACT

Introduction: ectopic pregnancy constitutes a significant complication in reproductive health, characterized by the extrauterine implantation of the embryo and associated with serious risks to maternal life.
Objective: to evaluate the efficacy of methotrexate as a pharmacological alternative in the management of ectopic pregnancy.
Methods: a systematic review of the scientific literature was conducted across multiple databases. The search was performed using an algorithm with keywords and Boolean operators, allowing the identification of relevant sources. Selected studies, after applying inclusion and exclusion criteria, were critically analyzed considering timeliness, methodological quality, and thematic relevance, and subsequently integrated into the final synthesis of the review.
Development: the reviewed literature confirms that methotrexate, a folic acid antagonist, interrupts cellular proliferation of trophoblastic tissue, promoting its reabsorption and preventing tubal rupture. Administration protocols in single, double, and multiple doses were identified, with success rates close to 90 %. Benefits include reduced pain, faster recovery, and lower hospital costs compared to laparoscopic surgery. Nevertheless, emphasis is placed on selecting hemodynamically stable patients without fetal activity, given the risk of hepatic, renal, and hematological toxicity.
Conclusions: Methotrexate is consolidated as a safe and effective therapeutic option for selected ectopic pregnancies, offering advantages over surgery. Its implementation requires strict monitoring and precise clinical criteria, representing a significant contribution to the optimization of contemporary gynecological management.

Keywords: Ectopic Pregnancy, Methotrexate, Pharmacological Treatment, Gynecological Management, Noninvasive Alternatives.

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INTRODUCTION

Pregnancy is a biological process that marks the beginning of a new life in the uterus, which involves significant physical, emotional, and psychological changes in the body that will house this new life. However, throughout its development, different complications can arise, such as ectopic pregnancy, which is a condition in which the fertilized egg implants outside the uterus, usually in the fallopian tube. This condition represents a major medical challenge and has significant physical and emotional implications for affected women.[1]

An ectopic pregnancy represents a significant complication in the field of reproductive health; proper diagnosis and treatment are fundamental in preserving a woman's fertility in the future, since the importance of knowing an appropriate approach to the issue lies in preventing life-threatening risks for the mother, such as internal bleeding, and avoiding surgical interventions that could affect the patient's fertility and natural life course.[2]

Over time, it has become clear that ectopic pregnancy is a multifactorial pathology. The mechanism related to implantation outside the uterus is not fully understood; however, it can be mentioned that anatomical obstruction, abnormal uterine motility, abnormal conception, and chemotactic factors play a role. Underlying tubal pathology is a high-risk factor, as it is more closely associated with future infertility. Other causes include congenital anomalies or endometriosis. A moderate risk factor is infection with Chlamydia trachomatis or Neisseria gonorrhoeae, which increases the risk of ectopic pregnancy up to four times.[3]

Based on this, the need to avoid invasive surgical procedures in the management of ectopic pregnancy is raised, since many times when they are diagnosed late, the life of the mother is put at risk or many times they leave irreversible sequelae such as infertility.[4] Taking into account the above, the present review is carried out, which had the objective of This article aims to evaluate the efficacy of methotrexate as a pharmacological alternative in the management of ectopic pregnancy.

METHODS

A systematic review of the scientific literature was conducted, following the PRISMA guidelines to ensure transparency and reproducibility. The search period spanned from January 2010 to December 2024, with the aim of encompassing the most recent and relevant evidence on the use of methotrexate in the management of ectopic pregnancy.

Information sources and search strategy

The search was conducted in internationally recognized biomedical databases, including PubMed, SciELO, ScienceDirect, Google Scholar, LILACS, and BVSALUD. Additionally, secondary references from peer-reviewed articles and grey literature available in institutional repositories and technical documents from health organizations were consulted. This strategy broadened the scope of information and reduced publication bias.

A search algorithm was designed using DeCS/MeSH keywords and descriptors related to "ectopic pregnancy," "methotrexate," "fertility," and "pharmacological treatment." Boolean operators (AND, OR, NOT) were used to combine terms and refine the search. Articles in Spanish, English, and Portuguese were considered to include both regional and global literature. The strategy was adapted to the specific characteristics of each database, ensuring the retrieval of relevant studies.

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Selection process

The selection process was carried out in three stages: title screening, abstract review, and full-text analysis. Initially, 356 records were identified; after removing duplicates and filtering based on relevance criteria, 214 articles remained. Finally, 14 studies met the inclusion criteria and were incorporated into the analysis. Articles published within the defined time frame, with full text access, and directly addressing the topic of interest were included. Original studies, systematic reviews, and meta-analyses evaluating the efficacy of methotrexate in ectopic pregnancies were accepted. Duplicates, publications without full-text access, irrelevant studies, studies outside the search period, and anecdotal reports lacking methodological rigor were excluded.

Data extraction and analysis

Key variables were collected from each study: author, year of publication, methodological design, sample characteristics, and main results. The information was organized into comparative matrices and subjected to qualitative synthesis, identifying trends and common findings. A meta-analysis was not performed due to the heterogeneity of the designs and results, but a narrative analysis was conducted to integrate the evidence and highlight the clinical implications of methotrexate use in ectopic pregnancy.

DEVELOPMENT

Methotrexate is a structural antagonist of folic acid which inhibits the enzyme dihydrofolate reductase, acting as an antimetabolite in cell proliferation.[5] The objective of this drug is to slow the growth of the fertilized ovum before rupture occurs.[6]

The mechanism of action centers on the inhibition of the enzyme dihydrofolate reductase, which reduces the synthesis of tetrahydrophobic acid, important for the generation of pyrimidines and purines, i.e., cell division. Consequently, by halting this division, methotrexate essentially interrupts the development of ectopic pregnancy cells and reabsorbs the trophoblastic tissue at the implantation site. It is also important to mention that it induces programmed cell death to reduce complications.[7]

The use of this drug may be an option for women with a confirmed ectopic pregnancy who are hemodynamically stable and do not have free fluid around the mass as determined by ultrasound. However, those receiving this treatment must be carefully monitored, as methotrexate affects cell proliferation in the bone marrow, gastrointestinal tract, and respiratory epithelium. Furthermore, the drug has potential toxic effects on the liver and is excreted via the kidneys.[8]

Risk factors for ectopic pregnancy

Ectopic pregnancies account for 2 % of all pregnancies. Currently, an increase in the incidence of ectopic pregnancies is attributed to the increased frequency of the following risk factors, which are important to mention because of the condition that compromises the health of the woman:[7,9,10,11]

- History of pelvic inflammatory disease (PID)This condition can cause scarring of the fallopian tubes, increasing the risk of ectopic pregnancy.
- History of abdominal or pelvic surgery: Surgery in the abdominal or pelvic region can cause adhesions in the fallopian tubes, which can lead to an ectopic pregnancy.

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- Use of intrauterine devices (IUDs)Although the risk is low, IUD use may slightly increase the likelihood of an ectopic pregnancy.
- Advanced maternal ageWomen over 35 have a higher risk of ectopic pregnancy.
- History of previous ectopic pregnancyWomen who have had an ectopic pregnancy previously are more likely to experience another one in the future.
- Tobacco useSmoking increases the likelihood of ectopic pregnancy.
- In vitro fertilization (IVF)Women undergoing IVF treatments have a high risk of ectopic pregnancy.

Methotrexate is recommended for hemodynamically stable patients without active bleeding or signs of hemoperitoneum. It should be considered for patients who wish to have children in the future and for patients who cannot tolerate general anesthesia, which would be life-threatening. Finally, it is essential to ensure that the mass is unruptured, measures less than 3,5 cm, that the hCG level does not exceed the established threshold, and, most importantly, that there is no fetal activity.[9]

Its use is contraindicated in breastfeeding, impaired renal function (creatinine greater than 1,3) and hepatic function twice the normal value. It is also suggested to avoid its use in cases of thrombocytopenia, anemia or leukopenia, immunodeficiency, including diseases such as bone marrow hypoplasia, peptic ulcer, pre-existing blood dyscrasias, and finally, certain gynecological characteristics such as a gestational sac greater than 3,5 cm and fetal cardiac activity should be taken into account.[8,9]

Administration protocol[7,8,9]

- Single doseMethotrexate 50 mg/m²/day IM: hCG hormone levels should be measured on the 4th and 7th days to verify a 15 % decrease. If levels do not decrease, another dose should be administered and hCG tests repeated.
- Double dose:50 mg/m² IM is administered on day 0 and repeated at 50 mg/m² on day 1. A decrease in hCG should occur between days 4 and 7. If this does not happen, methotrexate is administered again on days 7 and 11, and if it still does not decrease, surgical treatment is considered.
- MultidoseAdminister methotrexate 1 mg/kg IM (on days 1, 3, 5, 7), alternating with folic acid 0.1 mg/kg IM(2,4,6,8) ,HCG should be measured until it decreases, and measured weekly until non-pregnancy levels are obtained.

It is worth mentioning that, since the use of methotrexate as a pharmacological treatment for ectopic pregnancy, a success rate of 90 % has been reported for single and multiple doses. This management has resulted in significant cost savings compared to laparoscopic surgery, representing approximately 2 to 6 times more effective and less costly than surgical interventions, in addition to reducing complications and hospital stay.[9]

Methotrexate is an effective treatment option for women with a confirmed ectopic pregnancy who are hemodynamically stable and have no free fluid around the ectopic tissue visible on ultrasound. Its administration is preferred in these cases, as it offers a less invasive alternative to surgery. However, methotrexate use must be accompanied by close monitoring due to its potential adverse effects, including toxicity to the bone marrow, gastrointestinal tract, and respiratory epithelium.[12]

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Several risk factors are associated with an increased risk of ectopic pregnancy, such as a history of pelvic inflammatory disease (PID), which can cause scarring of the fallopian tubes. In addition, previous abdominal or pelvic surgeries can result in adhesions that increase the risk of ectopic pregnancy. IUD use, advanced maternal age, and a history of ectopic pregnancy are also identified as factors that increase the likelihood of recurrence. Other factors, such as smoking and IVF treatments, have also been shown to be associated with an increased risk.[13]

Contraindications for methotrexate use include its administration during breastfeeding and in patients with impaired renal or hepatic function. It should also be avoided in individuals with thrombocytopenia, anemia, or leukopenia, as well as in those with bone marrow hypoplasia or peptic ulcer. Furthermore, treatment may not be appropriate if the gestational sac is larger than 3,5 cm or exhibits movement, which could complicate the management of the ectopic pregnancy.[14]

Regarding administration protocols, the single dose of methotrexate is administered at 50 mg/m² intramuscularly, with an assessment of hCG hormone levels at four and seven days to ensure a 15 % reduction. If an adequate decrease is not observed, another dose should be considered and the tests repeated. For the double dose, 50 mg/m² is administered on day 0 and again the following day, with a similar hCG assessment to determine the need for additional doses or surgical treatment. The multidose regimen includes the administration of methotrexate every other day with folic acid, and continuous monitoring of hCG levels.[7]

CONCLUSIONS

Methotrexate is a relevant therapeutic alternative in the management of ectopic pregnancy, since by inhibiting the enzyme dihydrofolate reductase it limits the synthesis of purines and pyrimidines necessary for cell proliferation, favoring the reabsorption of trophoblastic tissue and preventing tubal rupture without the need for surgery; however, its use requires strict patient selection and continuous monitoring due to possible adverse effects on bone marrow, gastrointestinal system, liver and kidneys, so only under careful control can its efficacy and safety in resolving the clinical picture be guaranteed.

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