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DIAGNOSIS AND TREATMENT OF ECTOPIC PREGNANCY: A SYSTEMATIC REVIEW OF CONSERVATIVE AND SURGICAL APPROACHES

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ABSTRACT

Objective: To report the main aspects of ectopic pregnancy (EG), including diagnostic and therapeutic methods. Methodology: Review of 231 articles in PubMed Central (PMC) using the descriptors "Ectopic Pregnancy," "Infertility," and "Pregnancy Complications." The inclusion criteria were: articles in English, Portuguese and Spanish; published between 2019 and 2024; addressing the proposed themes. Review, observational and experimental studies, available in full, were also included. The exclusion criteria were: duplicate articles, abstracts, which did not directly address the proposal studied and did not meet the inclusion criteria. After applying the selection criteria, 13 studies were used to compose the collection. Results: EG is a potentially fatal gynecological condition, being one of the main causes of maternal mortality in the first trimester. Early and accurate diagnosis is essential, using serum b-hCG levels and ultrasound. Management of EG involves pharmacological approaches with methotrexate, surgical approaches with salpingostomy or salpingectomy, and expectant management, depending on the clinical presentation and patient preferences. Conclusion: EG represents a condition of high relevance in obstetrics, requiring adequate diagnosis and treatment to prevent serious complications. Research and development of new diagnostic markers and personalized therapies are essential to improve clinical outcomes and reduce the morbidity and mortality associated with ectopic pregnancy.

Keywords: Ectopic pregnancy, Infertility, Pregnancy Complications, Diagnosis, Treatment.

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INTRODUCTION

Ectopic pregnancy (EG) remains one of the most frequent gynecological emergencies and is one of the main causes of maternal death in early pregnancy, affecting between 1% and 2% of all pregnant women. Ectopic pregnancy occurs when a fertilized egg implants outside the uterine cavity, occurring predominantly in the fallopian tube (96%). The prevalence of ectopic pregnancies in the United States is estimated to be between 1% and 2%, but this number may be underestimated, as this condition is often managed in doctors' offices, where it is not monitored. The mortality rate from ruptured ectopic pregnancies has fallen steadily over the past three decades and, between 2011 and 2013, accounted for 2.7% of pregnancy-related deaths. (HENDRIKS; ROSENBERG; PRINE, 2020) (HAO et al., 2023)

A history of ectopic pregnancy increases the risk by 10% in subsequent pregnancies, and a history of two or more ectopic pregnancies raises this risk to more than 25%. Other risk factors for ectopic pregnancy include age over 35 years, smoking, infertility, pelvic inflammatory disease, and previous fallopian tube surgeries (HENDRIKS; ROSENBERG; PRINE, 2020). In recent years, its incidence has increased due to the growth in cases of pelvic inflammatory diseases, use of fertility drugs and pelvic surgical interventions. Although maternal mortality from ectopic pregnancy has recently decreased, it is still one of the leading causes of death in the first trimester of pregnancy; Therefore, the early management of ectopic pregnancy is extremely relevant. (GHORBANI; KERAMAT; LEDARI, 2020)

The definitive diagnosis of ectopic pregnancy can be established with ultrasound visualization of a yolk sac and/or embryo in the adnexa. However, most ectopic pregnancies do not reach this stage. Most often, the patient's clinical signs combined with serial ultrasound and trends in human chorionic gonadotropin beta levels are used for diagnosis. An undefined pregnancy refers to a transient state in which the pregnancy test is positive, but ultrasound does not reveal an intrauterine or ectopic pregnancy. Serial levels of human chorionic gonadotropin beta, serial ultrasound, and sometimes uterine aspiration can be used to make a conclusive diagnosis. (HENDRIKS; ROSENBERG; PRINE, 2020)

Treatment of diagnosed ectopic pregnancy includes clinical management with intramuscular methotrexate, surgical treatment by means of salpingostomy or salpingectomy, and, in exceptional cases, expectant management. A patient diagnosed with an ectopic pregnancy should be referred immediately for surgery if she has peritoneal signs or hemodynamic instability, if the initial level of human chorionic gonadotropin beta is

elevated, if fetal cardiac activity outside the uterus is detected on ultrasound, or if there is a contraindication to medical treatment. (HENDRIKS; ROSENBERG; PRINE, 2020)

This systematic review article aims to compile and analyze the scientific evidence on the management of Ectopic Pregnancy. The objective is to provide a comprehensive and up-to-date view, which synthesizes existing knowledge and identifies gaps in research, guiding future investigations and clinical practices. In-depth analysis of the evidence is intended to be a useful resource for healthcare professionals, researchers, and academics, contributing to the improvement of diagnostic and therapeutic approaches.

METHODOLOGY

This is a systematic review that seeks to understand the main aspects related to the development of ectopic pregnancy, as well as to demonstrate the main methods used in the diagnosis and treatment of the condition, aiming to ensure a greater clinical elucidation of this pathology. For the development of this research, a guiding question was elaborated through the PVO (population, variable and objective) strategy: "What are the main aspects that permeate the development of ectopic pregnancy, as well as what are the diagnostic and therapeutic resources used in clinical practice?"

The searches were carried out through searches in the PubMed Central (PMC) databases. Three descriptors were used in combination with the Boolean term "AND": Ectopic Pregnancy, Infertility and Pregnancy Complications. The search strategy used in the PMC database was: Ectopic Pregnancy AND Infertility and Ectopic Pregnancy AND Pregnancy Complications. From this search, 231 articles were found, which were later submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 231 articles were found. After applying the inclusion and exclusion criteria, X articles were selected from the PubMed database, and a total of 13 studies were used to compose the collection.

RESULTS

Author's Name	Year	Key Information Reviewed
HENDRIKS, M.; ROSENBERG, M. ; PRINE, L.	2020	Comprehensive discussion on diagnostic and therapeutic methods for ectopic pregnancy (EG). It stresses the importance of using ultrasound and b-hCG levels for early diagnosis.
HAO, H.; et al.	2023	It presents data on the prevalence and mortality of EG in the USA. It discusses risk factors such as advanced age, smoking, and pelvic inflammatory diseases.
GHORBANI, R.; KERAMAT, A.; LEDARI, F.	2020	It explores the usefulness of bhCG and serial ultrasound in the diagnosis of EG. It highlights the importance of identifying and treating GE early to avoid complications.
ZHAI, J.; CHEN, Y.; ZHANG, H.	2024	It analyzes the increased incidence of EG and associates it with known risk factors, including history of assisted reproductive technologies.
ANTEQUERA, J.; et al.	2021	It classifies EG into tubal, non-tubal, and heterotopic types. Discusses common sites of implantation and associations with risk factors.
XU, J.; et al.	2024	It emphasizes the impact of assisted reproductive technologies on the incidence of EG. It evaluates the correlation between in vitro fertilization (IVF) and heterotopic ectopic pregnancy.
MULLANY, S.; et al.	2023	It focuses on heterotopic ectopic pregnancy, highlighting the complexity and associated clinical challenges, especially in patients undergoing IVF.
GEORGE, M.; POWERS, R.; GUN BY, D.	2021	It analyzes abdominal ectopic pregnancy, addressing the prevalence, risk factors, and possible implantation sites outside the uterine cavity.
WANG, P.; ZHANG, L.	2024	It studies variations in the clinical presentation of extrauterine pregnancy, including symptoms such as abdominal pain and vaginal bleeding. Importance of early diagnosis to avoid serious complications.
XIAO, W.; et al.	2021	It examines methotrexate treatment protocols for EG, comparing efficacy between single-dose, two-dose, and multiple-dose regimens.
LEZIAK, A.; et al.	2022	Discusses the adverse effects of methotrexate and success rates in the treatment of GE. It emphasizes the need for close monitoring of b-hCG levels.
SOLANGON, T.; et al.	2023	It evaluates the efficacy of expectant management of EG, presenting success rates and associated risks, such as tubal rupture and hemorrhage.
ZAŁĘCKA, A.; et al.	2022	It explores the relationship between endometriosis and GE, discussing possible pathogenic mechanisms and the need for additional research for effective prevention.

Source: author

DISCUSSION

Ectopic pregnancy (EG) is a gynecological condition that is potentially fatal to maternal life. As one of the prevalent types of acute abdomen in obstetrics and gynecology,

the incidence of PE is increasing significantly, accounting for 2–3% of other diseases of pregnancy have become a leading cause of maternal death in the first trimester. The ectopic pregnancy rate is 11 per 1000 pregnancies, with a maternal mortality of 0.2 per 1000 estimated ectopic pregnancies (HAO et al., 2023) (ZHAI; CHEN; ZHANG, 2024) (ANTEQUERA et al., 2021) The term "GE" is used to describe the implantation of a developing blastocyst outside the uterine endometrium. Broadly speaking, EG is divided into tubal, non-tubal and heterotopic types of pregnancy, which refers to the simultaneous presence of intrauterine and extrauterine pregnancy. In most cases, the implantation site is the fallopian tube. However, it can occur in the cervix, ovary, abdomen, previous cesarean section, scar, the rudimentary horn of a unicorn uterus, and the interstitial part of the tube. Estimates around the world suggest that 1-2% of all pregnancies may be GEs. Several factors are known to be associated with the occurrence of EG, including fallopian tube damage, pelvic inflammatory disease, previous tubal surgery, previous EG, and history of assisted reproductive technologies (XU et al., 2024)

Heterotopic EFs are particularly complex, and their incidence is increasing due to a correlation with assisted reproductive technologies (ART), with an incidence of 1/100 pregnancies with in vitro fertilization (IVF) and 1/7,000 pregnancies with OVULATION-induction ART.1 Increased IVF rates are correlated with increased reports of EFs among these individuals. The rate of GE among IVF pregnancies is 2.1% to 8.6% after embryo transfer, compared to 2% in natural conceptions. In addition, the World Health Organization (WHO) notes an increasing rate of cesarean sections, currently reported as 21% of births globally, which may, in turn, increase the rate of cesarean scar GEs (CSPs) over time. (MULLANY et al., 2023)

Abdominal ectopic pregnancy (AEP) is a subtype of ectopic pregnancy, which is scarce and does not go beyond the clinical. Reported incidents are 1:10,000 pregnancies, and the increase is 1.3% of ectopic pregnancies. AEP can be included in both primary and secondary form. The primary form of primary implantation in the abdomen, but secondly, is the result of a reimplantation of pregnancy after a tubal abortion, and ectopic pregnancy or perforation of the uterus by in vitro fertilization (IVF) procedure. PEA can be located in the serosa of the entire peritoneal body or in organs and abdominal parts. Risk factors are the same for PRCA as for other types of ectopic pregnancy. (GEORGE; POWERS; GUNBY, 2021)

Abdominal pregnancy is the rarest type of ectopic pregnancy, with maternal mortality and morbidity rates eight times higher than non-abdominal cases. According to the criteria established by Studdiford in 1942, only a very small fraction of the reported cases could be

exclusively diagnosed as primary abdominal pregnancy. Common reported sites of primary abdominal pregnancy are Douglas' pouch, posterior uterine wall, uterine fundus, anterior abdominal wall, omentum, liver, spleen, and diaphragm. However, abdominal pregnancy in the retroperitoneal space is an extremely rare occurrence. Due to its rarity, it is impossible to accurately calculate the incidence of REP. Retroperitoneal ectopic pregnancy (REP), in which the gestational sac is implanted into the retroperitoneal cavity of the pelvis and abdomen, refers to an extremely rare type of abdominal ectopic pregnancy. Once a retroperitoneal gestational sac ruptures, it can cause catastrophic hemorrhage, especially for those located near large blood vessels. The mortality of EPR was 7 times higher than that of ordinary ectopic pregnancy (XU et al., 2022) (HUANG et al., 2023)

The presentation of extrauterine pregnancy varies, from an asymptomatic state to postmenopausal uterine bleeding, lower abdominal pain that is worse on one side, or tubal rupture with hemorrhagic shock**.** (WANG; ZHANG, 2024**)** Vaginal bleeding in women with ectopic pregnancies is due to desquamation of the deciduous endometrium and can range from spotting to levels equivalent to menstruation. This endometrial deciduous reaction occurs even with ectopic implantation, and the passage of a deciduous cast can mimic the passage of gestational tissue. Thus, a history of bleeding and tissue passage cannot be trusted to differentiate ectopic pregnancy from early intrauterine pregnancy failure. (HENDRIKS; ROSENBERG; PRINE, 2020)

GE requires an accurate and timely diagnosis. A delay in diagnosis can cause life-threatening bleeding due to rupture of the fallopian tube. Beta human chorionic gonadotropin (b-hCG) can be detected in pregnancy eight days after ovulation. The rate of increase in b-hCG levels, typically measured every 48 hours, can aid in distinguishing between normal and abnormal early pregnancy. In a viable intrauterine pregnancy with an initial b-hCG level of less than 1,500 mIU per mL (1,500 IU per L), there is a 99% chance that the b-hCG level will increase by at least 49% over 48 hours. As the initial b-hCG level increases, the rate of increase over 48 hours decreases, with an increase of at least 40% expected for an initial ÿ-hCG level of 1,500 to 3,000 mIU per mL (1,500 to 3,000 IU per L) and 33% for an initial b-hCG level greater than 3,000 mIU per mL. (HENDRIKS; ROSENBERG; PRINE, 2020) (HAO et al., 2023)

A slower-than-expected rate of increase or decrease in b-hCG levels suggests early pregnancy loss or ectopic pregnancy. The rate of increase decreases as pregnancy progresses and typically plateaus at around 100,000 mIU per mL (100,000 IU per L) by 10 weeks gestation. A decrease in b-hCG of at least 21% over 48 hours suggests a likely unsuccessful intrauterine pregnancy, while a smaller decrease should raise concern for

ectopic pregnancy. The discriminatory level is the level of b-hCG above which an intrauterine pregnancy is expected to be seen on transvaginal ultrasound; It varies with the type of ultrasound machine used, the ultrasound and the number of pregnancies. A combination of b-hCG level greater than the discriminatory level and ultrasound that does not show an intrauterine pregnancy should raise concern for early pregnancy loss or ectopic pregnancy. The discriminatory zone was previously defined as a b-hCG level of 1,000 to 2,000 mIU per mL (1,000 to 2,000 IU per L). (HENDRIKS; ROSENBERG; PRINE, 2020)

Intrauterine pregnancy visualized on transvaginal ultrasound essentially rules out ectopic pregnancy, except in the extremely rare case of heterotopic pregnancy. Definitive diagnosis of ectopic pregnancy can be made with ultrasound when a yolk sac and/or embryo is seen in the appendages; however, ultrasound alone is rarely used to diagnose ectopic pregnancy because most do not progress to this stage.5 More often, the patient's history is combined with serial quantitative ÿ-hCG levels, sequential ultrasound, and sometimes uterine aspiration to reach a final diagnosis of ectopic pregnancy. (HENDRIKS; ROSENBERG; PRINE, 2020)

CPK is an intracellular enzyme present in muscle cells and their plasma and that increases in level during cell lysis. Lysis of trophoblastic cells leads to an increase in plasma CPK levels. Therefore, the level of this enzyme can be used for evaluation of tubal ectopic pregnancy because increased CPK may be associated with trophoblastic invasion and trophoblastic mass. Increasing the total CPK level may increase its diagnostic value in diagnosing tubal ectopic pregnancy; however, there is a need for larger-scale studies to determine the cutoff point for this marker. (GHORBANI; KERAMAT; LEDARI, 2020)

Endometriosis is a common inflammatory disease characterized by the presence of endometrial and stromal glandular cells outside their physiological location. It is estimated that symptomatic endometriosis affects 10% of women. It seems that the most likely mechanism for the appearance of endometrial cells outside the uterine cavity is retrograde menstruation, proposed by Sampson. However, retrograde menstrual flow is a common event, and there are other concomitant factors necessary for the development of the disease. One of the most serious complications of endometriosis is an ectopic pregnancy. Currently, the exact mechanism that explains this phenomenon is unknown; therefore, there are no effective methods of prevention. The pathogenesis of EG is hypothesized to be influenced by abnormalities in fallopian tube muscle contraction, cilia motility, and the fallopian microenvironment. Endometriosis can disrupt function at all three levels and

therefore contribute to embryo implantation beyond the physiological site. (ZAŁĘCKA et al., 2022)

Once the diagnosis of EG is confirmed, treatment may take a conservative or aggressive approach, depending on the location of the EG, the gestation schedule, and the size of the SG. There are three different approaches to the treatment of pharmacological, surgical, and expectant management GEs that are based on the type of GE. The decision to treat ectopic pregnancy clinically or surgically should be informed by individual patient factors and preferences, clinical findings, sonographic findings, and b-hCG levels. (HENDRIKS; ROSENBERG; PRINE, 2020) (MULLANY et al., 2023) Patients with suspected or confirmed ectopic pregnancies who present with signs and symptoms of ruptured ectopic pregnancies should be transferred on an emergency basis for surgical intervention. If ectopic pregnancy has been diagnosed, the patient is considered clinically stable, and the affected fallopian tube has not ruptured, treatment options include medical treatment with intramuscular methotrexate or surgical treatment with salpingostomy (removal of the ectopic pregnancy, leaving the fallopian tube in place) or salpingectomy (removal of part or all of the affected fallopian tube). (HENDRIKS; ROSENBERG; PRINE, 2020)

Intramuscular (IM) injection of MTX is the current standard for the medical treatment of GEs. MTX, a folate antagonist, inhibits DNA synthesis at various stages of the cell cycle and consequently generating the death of fast-dividing cells, including trophoblastic cells. (MULLANY et al., 2023) (LEZIAK et al., 2022) The most common regimens are single-dose (i.e., intramuscular injection of MTX 50mg/m2), two doses (i.e., 50mg/m2 injected on days 1 and 4), and multiple doses (i.e., intramuscular injection of 1mg/kg on days 1, 3, 5, 7). (XIAO et al., 2021) The single-dose protocol has the lowest risk of adverse effects, while the two-dose protocol is more effective than the single-dose protocol in patients with higher baseline b-hCG levels. (HENDRIKS; ROSENBERG; PRINE, 2020)

Prior to administering methotrexate, b-hCG levels should be measured on days 1, 4, and 7 of treatment. The first measurement helps the clinician decide between one- and two-dose protocols. Levels usually increase between days 1 and 4, but should decrease by at least 15% between days 4 and 7. If this decrease does not occur, the clinician should discuss with the patient whether she prefers to repeat the methotrexate course or seek surgical treatment. If the b-hCG level decreases by at least 15% between days 4 and 7, the patient should return for weekly b-hCG measurements until the levels become undetectable, which can take up to eight weeks. Close follow-up is essential for the safe use of methotrexate in women with ectopic pregnancies. Patients should be informed that

the risk of rupture persists until b-hCG levels are undetectable and that they should seek emergency care if signs of ectopic pregnancy occur. (HENDRIKS; ROSENBERG; PRINE, 2020)

The use of methotrexate requires specific conditions, both in relation to the general condition of the patient and the characteristics of the ectopic pregnancy. Contraindications to medical treatment include hemodynamic instability, presence of fetal cardiac activity, serum ÿ-hCG levels> 5000 mIU/mL or GE> 4 cm in diameter, anemia, leukopenia, thrombocytopenia, pelvic pain, or hemoperitoneum. indicative of GE rupture, renal or hepatic failure, pulmonary disease, active peptic ulcer disease, coincident UTI, breastfeeding. The current literature estimates that the percentage of resolution of GEs through MTX treatment without the need for surgical intervention is 70% to 95%, with lower success rates in patients with higher initial b-hCG levels. (MULLANY et al., 2023) Although methotrexate is a relatively safe substance, its administration may be associated with various adverse effects, such as nausea, stomach pain, diarrhea, stomatitis, fever, headache, fatigue, hepatotoxicity, and myelosuppression. Side effects usually affect approximately 37% of women treated. (LEZIAK et al., 2022)

Salpingostomy and salpingectomy are the two common approaches to the surgical treatment of GEs. Salpingostomy consists of removing only the GE through an incision in the fallopian tube, whereas salpingectomy includes the removal of part or all of the fallopian tube along with the EG. Salpingectomy is recommended for patients with GEs larger than 5 cm in diameter, significant tubal damage, tubal rupture, bleeding, or anterior tubal ligation. However, patients who undergo salpingectomy and have absent/obstructed contralateral fallopian tubes will not be able to procreate without ART, making salpingostomy preferred by patients who wish to maintain fertility. In patients with normal contralateral fallopian tubes, salpingostomy and salpingectomy have been shown to have equivalent outcomes in future pregnancy. In cases where methotrexate is contraindicated or is not preferred by the patient, surgical treatment can usually be performed laparoscopically if the patient is hemodynamically stable. (HENDRIKS; ROSENBERG; PRINE, 2020) (MULLANY et al., 2023)

After salpingectomy, pathologic confirmation of EG in the removed fallopian tube is sufficient to confirm the success of the procedure. In contrast, salpingostomy requires subsequent b-hCG measurements to ensure the absence of residual trophoblastic tissue (~20% of patients), which often requires additional treatment with MTX. A retrospective clinical trial found that baseline b-hCG values post-linear salpingostomy are predictive of persistent GE prior to Day 5, with a positive predictive value of 88% and negative predictive

value of 99%. Overall, surgical treatment has been shown to have a higher success rate in stopping GEs than pharmacologic treatment and is indicated in patients who have signs of EG rupture (e.g., hemodynamic instability), have contraindications to medical treatment, or express personal preference for surgical treatment. (MULLANY et al., 2023)

Expectant management is the most conservative approach to the treatment of GEs. This method may be considered for patients with decreasing or stagnant b-hCG levels. Observational studies have shown that expectant management of ectopic pregnancy (EG) has a high success rate in women with tubal GE and serum hCG levels <1500 IU/L. (MULLANY et al., 2023) (SOLANGON et al., 2023) Patients who choose to follow expectant treatment should have b-hCG testing every 48 h and should consider other options if levels do not decrease. Risks of expectant management include tubal rupture, hemorrhage, and emergency surgery. The relative efficacy and safety of expectant management is an ongoing area of research, with medical and surgical management remaining the main approaches to the treatment of GE. (MULLANY et al., 2023)

CONCLUSION

Ectopic pregnancy (EG) remains a condition of great relevance in the field of obstetrics, representing one of the main causes of maternal mortality in the first trimester. With the increase in the use of assisted reproductive technologies (ART) and cesarean sections, there is an increase in the incidence of rarer subtypes, such as heterotopic and abdominal ectopic pregnancy, which present additional clinical challenges.

Early and accurate diagnosis, with the use of serum b-hCG levels and ultrasound, is essential to prevent serious complications, such as tubal rupture and catastrophic hemorrhages. In terms of treatment, the management of EG involves pharmacological, surgical, and expectant approaches, which must be individualized according to the patient's clinical condition and preferences. Despite advances in diagnosis and treatment, the prevention of GE, especially in at-risk populations, remains a significant challenge. The study and development of new diagnostic markers and personalized therapies are essential to reduce the morbidity and mortality rates associated with ectopic pregnancy.

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