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ECTOPIC PREGNANCY: DIAGNOSTIC AND THERAPEUTIC APPROACHES FOR A GYNECOLOGICAL EMERGENCY - A CURRENT SYSTEMATIC REVIEW

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Ana Clara Souza Freitas[1], Cintia Sousa Lucas de Andrade[2], Maria Heloísa Raiz Plácido[3], Guilherme Teófilo Magrin[4], Yuri Vacari Florêncio[5] and Nathalia Barbosa Furlan[6]

ABSTRACT

Objective: The general objective of this study is to analyze the scientific literature on ectopic pregnancy, identifying the main risk factors, diagnoses, and treatments for this condition. Methodology: This is a systematic review focused on understanding the essential aspects of ectopic pregnancy. The research was guided by the question: "What are the main risk factors, diagnoses, and treatments for ectopic pregnancy?". To find answers, searches were performed in the PubMed database using four descriptors combined with the Boolean term "AND": (Ectopic pregnancy) AND (Early diagnosis), (Ectopic pregnancy) AND (Pathophysiology), (Ectopic pregnancy) AND (Prognosis), and (Ectopic pregnancy) AND (Prevention). This resulted in a total of 139 articles, of which 10 were selected for detailed analysis after applying the inclusion and exclusion criteria. Results: The main complications identified include a high risk of rupture and internal hemorrhage, acute abdominal pain, and potential infertility. Hormonal treatments, such as methotrexate, are frequently used, as are surgical interventions, including salpingostomy and salpingectomy, depending on the extent of damage and the patient's reproductive needs. New therapies, such as chemoembolization, are also being investigated. The review highlights the importance of early diagnosis and appropriate management to improve clinical and reproductive outcomes. Conclusion: It is concluded that ectopic pregnancy is an emerging medical

[1] A doctor from the University of Franca (UNIFRAN) and resident in Gynecology and Obstetrics at Santa Casa da Misericórdia de Franca. E-mail: anasoitas@hotmail.com
LATTES: http://lattes.cnpq.br/6529445907332632
[2] A physician from the Uni-FACEF University Center and a postgraduate in Gynecology and Obstetrics from Santa Casa de Franca
E-mail: dracintiaandradego@gmail.com
LATTES: http://lattes.cnpq.br/4283645586909270
[3] Undergraduate in Medicine at the University of Franca - (UNIFRAN)
E-mail: mariaheloisaraiz123@gmail.com
[4] Undergraduate in Medicine at the University of Franca - (UNIFRAN)
E-mail: tmbrguilherme@gmail.com
[5] Undergraduate in Medicine at the University of Franca - (UNIFRAN)
E-mail: yurivacari12@hotmail.com
[6] Advisor
Medical student at the Unilago School of Medicine - São José do Rio Preto
Gynecologist and Obstetrician at the Santa Casa de Misericórdia de Franca – SP
E-mail: nathalia.furlan@hotmail.com

condition that requires a multidisciplinary approach for its effective management. Characterization of risk factors and development of evidence-based treatment strategies are essential to reduce maternal mortality and improve the quality of life of patients. The combination of advanced diagnostics, medical and surgical treatments, and new therapies in development offers hope for more effective control of the condition.

Keywords: Ectopic Pregnancy. Risk Factors. Diagnosis. Treatment.

INTRODUCTION

Ectopic pregnancy (EP) is defined as the implantation of the blastocyst outside the endometrial cavity of the uterus, with the fallopian tubes being the most common site of ectopic implantation (LEZIAK et al., 2022). This emerging gynecological condition is one of the leading causes of acute abdominal pain in pregnant women and represents a significant medical emergency due to the risk of rupture and internal hemorrhage (XIAO et al., 2021). EP can also occur in other locations, such as the abdomen, ovaries, and cervix, although these locations are less frequent (WANG & ZHANG, 2024).

Epidemiologically, ectopic pregnancy affects approximately 1% to 2% of all pregnancies, with a reported incidence of 20 per 1,000 confirmed pregnancies (LEZIAK et al., 2022; HAO et al., 2023). In the United Kingdom, the EP rate is 11 per 1,000 pregnancies, with an estimated maternal mortality of 0.2 per 1,000 ectopic pregnancies (BOLAJI et al., 2024). The recurrence of ectopic pregnancy (REP) is also a significant concern, with an incidence rate ranging from 10% to 27%, representing a 5- to 15-fold increase compared to the general population (BOLAJI et al., 2024).

Historically, the identification and management of ectopic pregnancy have evolved significantly over the past decades. In the past, EP frequently resulted in fatal outcomes due to the lack of early diagnostic methods and effective treatments. However, with advancements in imaging technology, such as high-resolution transvaginal ultrasound, and the development of sensitive human chorionic gonadotropin (hCG) tests, the early detection of EP has increased considerably (XIAO et al., 2021; HAO et al., 2023). These advances have allowed many ectopic pregnancies to be diagnosed and treated before severe complications occur, significantly reducing the need for emergency surgical interventions and associated mortality (XIAO et al., 2021; HAO et al., 2023).

Ectopic pregnancy remains one of the most common gynecological emergencies and a leading cause of maternal mortality in early pregnancy (HAO et al., 2023). Additionally, EP is associated with significant risks of infertility and recurrence, making it a major concern for women of reproductive age (LEZIAK et al., 2022). Early detection and appropriate management are crucial to improving clinical and reproductive outcomes.

Although various therapeutic options exist for EP, the choice of optimal treatment depends on several factors, including the location of the pregnancy, the patient's hemodynamic conditions, and future reproductive needs (XIAO et al., 2021). This systematic review is justified by the need to consolidate current knowledge, identify gaps in the literature, and promote the use of evidence-based treatments.

The objective of this systematic review is to compile and critically analyze existing data on ectopic pregnancy (EP), focusing on definitions, epidemiology, risk factors, diagnosis, treatment options, and reproductive outcomes. The goal is to provide a comprehensive and updated overview that can assist healthcare professionals in clinical decision-making and contribute to the formulation of more effective health policies.

METHODS

This study is a systematic literature review aimed at understanding the clinical aspects of ectopic pregnancy to ensure early diagnosis of this condition and demonstrate the available diagnostic and therapeutic methods and their relationship with prognosis.

For the development of this research, a guiding question was formulated using the PVO (population, variable, and objective) strategy: "What is the importance of understanding the clinical aspects of ectopic pregnancy in ensuring early diagnosis of this condition, and what are the benefits for prognosis?"

Searches were conducted in the PubMed database. Four descriptors were used in combination with the Boolean term “AND”: Ectopic pregnancy, Early diagnosis, Pathophysiology, Prognosis, and Prevention. The search strategy used in the PubMed database was:

- (Ectopic pregnancy) AND (Early diagnosis), resulting in 37 articles;
- (Ectopic pregnancy) AND (Pathophysiology), yielding 13 articles;
- (Ectopic pregnancy) AND (Prognosis), with 42 articles;
- (Ectopic pregnancy) AND (Prevention), resulting in 47 articles.

From this initial search, a total of 139 articles were found. After removing 55 duplicate articles and applying inclusion and exclusion criteria, an additional 28 articles were excluded.

The inclusion criteria covered articles in English, Portuguese, and Spanish, published between 2019 and 2024, addressing the topics proposed for this research. Review studies, observational studies, and experimental studies were included, provided they were available in full.

The exclusion criteria considered duplicate articles, articles available only in abstract form, those that did not directly address the studied topic or those that did not meet other inclusion criteria.

After this rigorous screening, 10 articles were selected to compose the final collection of this study. These articles provided the basis for an in-depth analysis of the

clinical, diagnostic, and therapeutic aspects of ectopic pregnancy, enabling a comprehensive understanding of the condition and its implications for patient prognosis.

RESULTS

Authors	Main Contributions
Leziak et al. (2022)	Defined ectopic pregnancy, highlighting the importance of β-hCG levels in early diagnosis and treatment, while also providing detailed epidemiological data.
Xiao et al. (2021)	Emphasized the evolution of diagnostic and therapeutic techniques for ectopic pregnancy, particularly the role of transvaginal ultrasound and β-hCG tests in early detection.
Wang & Zhang (2024)	Described the occurrence of ectopic pregnancy in less common locations, such as the abdomen, ovaries, and cervix, offering a broad perspective on location diversity.
Hao et al. (2023)	Analyzed the importance of β-hCG levels and advances in diagnostic and therapeutic methods for ectopic pregnancy, including high-resolution imaging techniques.
Bolaji et al. (2024)	Discussed maternal mortality and ectopic pregnancy recurrence, providing epidemiological data and analyses of risk factors and associated complications.
Hendriks, Rosenberg & Prine (2020)	Thoroughly evaluated the medical and surgical management of ectopic pregnancy, including methotrexate dosage protocols and efficacy comparisons between medical and surgical treatments.
Almahloul et al. (2023)	Focused on the diagnosis and treatment of ovarian pregnancy, highlighting the importance of laparoscopy and minimally invasive techniques, as well as discussing specific risk factors.
Tremmel et al. (2024)	Discussed maternal mortality in non-tubal ectopic pregnancies, analyzed risk factors, and severe complications, and compared different therapeutic approaches, including hysterectomy.
Salari et al. (2020)	Analyzed complications associated with methotrexate treatment, highlighting adverse effects and the importance of continuous monitoring.
Kłobuszewski et al. (2024)	Examined advanced diagnostic methods, such as chemoembolization and methotrexate use, addressing innovative techniques to improve the diagnosis and treatment of ectopic pregnancy.

Source: table 1 - created by the author.

DISCUSSION

Ectopic pregnancy occurs when a fertilized egg implants outside the uterine cavity. The prevalence in the United States is estimated to be between 1% and 2%, but this may be an underestimate due to frequent office-based treatment, where it is not adequately screened for (HENDRIKS; ROSENBERG; PRINE, 2020). Risk factors include the use of intrauterine devices (IUDs). Although the overall prevalence of pregnancy with an IUD is less than 1%, the prevalence of ectopic pregnancy can reach 53% in the rare cases in which a woman becomes pregnant with an IUD (HENDRIKS; ROSENBERG; PRINE, 2020).

Typical signs and symptoms of ectopic pregnancy include vaginal bleeding, due to shedding of the decidual endometrium, and lower abdominal pain, which can vary in intensity and location. The pain usually begins as abdominal or pelvic cramping and may become generalized if there is a rupture of the fallopian tube and the development of hemoperitoneum (HENDRIKS; ROSENBERG; PRINE, 2020).

β-hCG is an important marker in the diagnosis of ectopic pregnancy. The rate at which β-hCG levels rise or fall can help distinguish between a normal and abnormal pregnancy. A slower-than-expected rate of increase may suggest early pregnancy loss or ectopic pregnancy. The discriminatory level, the level of β-hCG above which an intrauterine pregnancy would be expected to be seen on transvaginal ultrasound, is essential for diagnosis (HENDRIKS; ROSENBERG; PRINE, 2020). In a desired pregnancy, a higher discriminatory level can be used to avoid misdiagnosis and termination of a viable pregnancy.

OVARIAN ECTOPIC PREGNANCY

Among ectopic locations, ovarian pregnancy is one of the rarest and most complex forms. This type of ectopic pregnancy presents specific challenges in diagnosis and treatment, standing out for its association with risk factors similar to those of extrauterine pregnancies, such as a history of pelvic inflammatory disease (PID) or tubal surgery (ALMAHLOUL et al., 2023).

Ovarian pregnancies share causal factors with other extrauterine pregnancies, including a history of PID and tubal surgery. However, some occurrences are unexpected, such as ovarian pregnancy in the ovary contralateral to the corpus luteum and in women with blocked oviducts. These observations raise hypotheses about alternative mechanisms of sperm transport, such as micro fistulas between the uterine stump and the peritoneal cavity, although this idea is considered speculative (ALMAHLOUL et al., 2023).

The diagnosis of ovarian pregnancy is particularly challenging. It should be considered in all women with suspected extrauterine pregnancy, regardless of the presence of vaginal bleeding. The diagnostic accuracy of imaging tests, such as ultrasound and magnetic resonance imaging, is insufficient to completely exclude this condition, and ovarian pregnancy is often identified unexpectedly during surgery (ALMAHLOUL et al., 2023). This highlights the need for high clinical suspicion and the use of appropriate imaging techniques for an accurate diagnosis.

Most ovarian pregnancies are diagnosed in the first 8 weeks of pregnancy. However, some may occur even before the menstrual delay or be identified as late as 44 weeks of gestation. In addition, the association of ovarian pregnancies with intrauterine pregnancies is an unexpected and clinically relevant aspect. This condition can lead to serious complications, such as the development of choriocarcinoma in rare cases (ALMAHLOUL et al., 2023).

Laparoscopy and laparoscopic surgery are the preferred techniques for the diagnosis and treatment of ovarian pregnancies. These minimally invasive techniques allow for one-day surgery with minimal risk of ovarian damage and postoperative adhesions. However, laparoscopy can be challenging in cases of occult bleeding from severe adnexal adhesions. Recognizing a bleeding ovarian lesion as an ovarian pregnancy during laparoscopy can be difficult, especially when differentiating it from a bleeding corpus luteum (Almahlou et al., 2023). Diagnosis of ovarian pregnancy remains a significant challenge, with most cases being discovered unexpectedly during surgical procedures (Almahlou et al., 2023).

The diagnosis of ovarian pregnancy remains nonspecific, and surgery remains the treatment of choice. Clinicians should be aware that ovarian pregnancies should be suspected in all women with abdominal bleeding, even in the absence of a missed period or blocked fallopian tubes. It is crucial to take care not to interrupt a possible intrauterine pregnancy with a uterine cannula and to avoid damaging the corpus luteum during surgery. Laparoscopy offers an effective and minimally invasive approach but requires expertise to limit ovarian damage and improve outcomes. Of the treatment (ALMAHLOUL et al., 2023).

RETROPERITONEAL ECTOPIC PREGNANCY (REP)

On the other hand, retroperitoneal ectopic pregnancy (REP) is an extremely rare and complex condition, characterized by the implantation of the blastocyst in the retroperitoneal space, outside the uterus. This form of ectopic pregnancy has high rates of maternal mortality and morbidity due to the significant risk of hemorrhage, especially considering the proximity of the great vessels. The pathogenesis of REP is not yet fully elucidated, but hypotheses include iatrogenic uterine perforation during assisted reproduction techniques, trophoblastic invasion from the posterior peritoneal surface, and lymphatic dissemination. In the case of iatrogenic uterine perforation, embryos may be placed in the retroperitoneal space due to damage caused during medical procedures. Trophoblastic invasion suggests that the embryo initially implants on the posterior peritoneal surface and then invades the retroperitoneal space. The lymphatic dissemination hypothesis proposes that fertilized eggs reach the retroperitoneal space via the lymphatic system, similar to gynecologic cancer metastasis, with lymphatic tissue often found around ectopic masses (XU et al., 2022).

Clinical features of REP include amenorrhea, abdominal pain, and vaginal bleeding. REP tends to be located along the great vessels, increasing the risk of significant hemorrhage. Due to the large and complex space of the retroperitoneum, the ectopic gestational sac can grow substantially before being diagnosed, which can lead to serious complications (XU et al., 2022).

Early diagnosis of REP is challenging due to nonspecific clinical manifestations and complex implantation sites, requiring advanced imaging modalities such as abdominal ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) for accurate identification. The main treatment for REP is surgery, which may involve laparoscopy or laparotomy, often in conjunction with a multidisciplinary approach to optimize management and reduce risks (XU et al., 2022).

CORNUAL PREGNANCY

Cornual pregnancy, also known as interstitial pregnancy, is a rare and particularly dangerous form of ectopic pregnancy. It occurs when the fertilized egg implants in the horn or lateral region of the uterus, outside the normal uterine cavity. This location is associated with a high risk of serious complications due to the rich vascularization of the area, which can lead to significant hemorrhage (TREMMEL et al., 2024).

1. Increased Risk of Severe Hemorrhage: Due to the vascular anastomosis between the uterine and ovarian arteries, cornual pregnancy has a five-fold increased risk of severe hemorrhage compared to other forms of ectopic pregnancy. This high risk of bleeding can result in emergencies that require immediate surgical intervention (TREMMEL et al., 2024).

2. Challenging Diagnosis: The diagnosis of corneal pregnancy can be complicated. Transvaginal ultrasound is the standard method for detecting this condition, but in cases where the location is unclear or there is suspicion of infiltration of neighboring organs, magnetic resonance imaging may be useful (TREMMEL et al., 2024).

3. Conservative Treatment: In many cases, conservative treatment with methotrexate (MTX) is effective for corneal pregnancy. Studies indicate that systemic and local administration of MTX can avoid the need for additional surgical interventions and is associated with a high success rate (TREMMEL et al., 2024).

4. Surgical Approaches: When medical treatment is not sufficient, surgical procedures such as cornectomy or cornostomy may be considered. These surgeries remove the corneal pregnancy and reconstruct the affected area, reducing the risk of hemorrhage and improving future reproductive outcomes (TREMMEL et al., 2024).

5. Post-Treatment Complications: Even after successful treatment, patients with corneal pregnancy may face long-term complications, such as adhesion formation and fertility problems. Continuous monitoring and appropriate follow-up are essential to ensure the reproductive health of patients (TREMMEL et al., 2024).

RELATIONSHIP BETWEEN COVID-19 PANDEMIC AND ECTOPIC PREGNANCY

The COVID-19 pandemic has had a significant impact on the management of ectopic pregnancies, affecting both the diagnosis and treatment of these cases. Here are some important points to consider. During the pandemic, there has been an increase in the rates of ruptured ectopic pregnancies. This was mainly due to delayed seeking medical care, as many women avoided visiting hospitals for fear of COVID-19 infection. Werner et al. reported an increased rate of undiagnosed PE during the peak of COVID-19, resulting in a higher number of hemodynamically unstable patients requiring surgical treatment (MORIN et al., 2022). Similarly, a case series in India revealed that 28 of 32 diagnoses of ectopic pregnancies during 8 months at the peak of the pandemic resulted in rupture (MORIN et al., 2022).

In hospitals with Early Pregnancy Unit (EPU) structures, there was a clear trend towards non-surgical management of ectopic pregnancies. Conservative or medical treatment was recommended for appropriately selected patients, following advice from national bodies aimed at limiting unnecessary exposure to the virus and reducing hospital overcrowding. Multicenter studies by Platts and Kyriacou confirmed this trend, showing that conservative management was preferred during the pandemic (MORIN et al., 2022).

COMPARISON OF PRE-COVID AND DURING COVID-19 COHORTS

The systematic review compared data from 12 studies, analyzing the management of ectopic pregnancies during the peak of COVID-19 and comparing them with a similar period pre-pandemic. Despite the initial perceived risks of viral transmission associated with surgery, there was no significant difference in the rate of surgical treatment between the COVID-19 and pre-COVID cohorts overall. However, in hospitals without EPU facilities, there was an increase in surgical treatment rates due to the higher incidence of ruptures (MORIN et al., 2022).

EPU facilities are effective in reducing the rates of complications associated with ectopic pregnancies during the pandemic. In comparison, the lack of these facilities in some health systems led to a significant increase in complications. Structured EPU systems in the UK have enabled women to self-refer for care, avoiding delays in seeking medical help and reducing the risk of rupture (MORIN et al., 2022).

The pandemic has highlighted the need to develop and implement EPU systems worldwide to mitigate the negative impacts of future pandemics. Safe use of conservative and medical methods is recommended whenever possible, and minimal access surgery is recommended when necessary, to reduce the risk of hospital-acquired viral infection.

Creating a self-referral system where women are triaged according to their symptoms and risk factors and offered a screening appointment within 24 hours, may be an effective strategy to improve the management of ectopic pregnancies during pandemic crises (MORIN et al., 2022).

MATERNAL MORTALITY IN THE CONTEXT OF ECTOPIC PREGNANCY

Maternal mortality associated with ectopic pregnancy is a significant concern, especially in non-tubal pregnancies. Studies indicate that maternal mortality is approximately eight times higher in non-tubal ectopic pregnancies compared to tubal ones (TREMMEL et al., 2024). This high mortality rate is mainly associated with the increased risk of serious complications, such as severe hemorrhage and uterine rupture, which can result in hemorrhagic shock or sepsis (TREMMEL et al., 2024).

The presence of ectopic pregnancy, especially in atypical locations, such as corneal (interstitial) pregnancy and cesarean scar pregnancy (CSP), is associated with an increased risk of severe hemorrhage due to the rich vascularization of these areas (TREMMEL et al., 2024). The risk of fatal complications requires emergency interventions, such as a hysterectomy, which is often the last option to control bleeding and save the patient's life (TREMMEL et al., 2024).

RISK FACTORS FOR ECTOPIC PREGNANCY

Several risk factors contribute to the incidence of ectopic pregnancy. These factors can be divided into two main categories: anatomical factors and factors associated with the patient's lifestyle and medical history.

ANATOMICAL FACTORS

1. Uterine and Tubal Anomalies: Anomalies in the structure of the uterus and fallopian tubes, such as adhesions, scars, or congenital malformations, can impair the transport of the fertilized egg, resulting in its implantation outside the uterine cavity (TREMMEL et al., 2024). 2. History of Cesarean Section (CS): The presence of previous cesarean section scars is a significant risk factor for CSP. Inadequate healing can create a site conducive to the implantation of the fertilized egg in the scar tissue (TREMMEL et al., 2024).

3. Pelvic Inflammatory Disease (PID): PID causes inflammation and scarring of the fallopian tubes, increasing the risk of ectopic pregnancy. Women who have had previous episodes of PID are more likely to develop this condition (TREMMEL et al., 2024).

FACTORS ASSOCIATED WITH LIFESTYLE AND MEDICAL HISTORY

1. Use of Intrauterine Devices (IUDs): Although IUDs are highly effective in preventing intrauterine pregnancies, their use is associated with an increased risk of ectopic pregnancy if contraception fails (TREMMEL et al., 2024). al., 2024).

2. Reproductive Medicine Interventions: Assisted reproductive techniques, such as in vitro fertilization (IVF), can increase the risk of ectopic pregnancy, especially when multiple embryos are transferred (TREMMEL et al., 2024).

3. Smoking: Nicotine use is associated with an increased risk of ectopic pregnancy. Nicotine can affect ciliary motility in the fallopian tubes, impairing the transport of the fertilized egg (TREMMEL et al., 2024).

4. History of Previous Ectopic Pregnancy: Women who have had an ectopic pregnancy have an increased risk of recurrence. Recurrence can occur in up to 10% to 27% of cases, representing a 5 to 15-fold increase compared to the general population (BOLAJI et al., 2024). 5. Advanced Maternal Age: Women over 35 years of age have a higher risk of developing an ectopic pregnancy due to changes in reproductive function and a higher likelihood of having associated conditions, such as PID and use of assisted reproductive techniques (LEZIAK et al., 2022).

COMPLICATIONS ASSOCIATED WITH ECTOPIC PREGNANCY

Ectopic pregnancy is a high-risk condition that can lead to several serious complications. The main complications include:

1. Tubal Rupture: One of the most common and serious complications of ectopic pregnancy is the rupture of the fallopian tube. This can result in significant internal bleeding, leading to hemorrhagic shock and, in severe cases, death of the patient (SALARI et al., 2020). 2. Severe Hemorrhage: Ectopic pregnancies, especially in highly vascularized sites such as cesarean section scar (CSP) and corneal pregnancy, have a high risk of severe hemorrhage. Bleeding can be difficult to control and often requires emergency surgical interventions, such as hysterectomy (TREMMEL et al., 2024).

3. Septic Shock: In cases of septic abortion, the infection can spread rapidly, leading to septic shock. This is a potentially fatal condition that requires immediate medical treatment (TREMMEL et al., 2024).

4. Treatment-Related Complications: The use of medications such as methotrexate (MTX) can cause adverse effects, including nausea, vomiting, renal toxicity, hepatotoxicity, and pneumonitis (SALARI et al., 2020). Furthermore, surgical procedures present risks of

complications, such as uterine perforation and adhesion formation (KŁOBUSZEWSKI et al., 2024).

DIAGNOSIS OF ECTOPIC PREGNANCY

Early diagnosis of ectopic pregnancy is essential for effective management and prevention of serious complications. Several diagnostic tools and methods have been used to identify this condition, allowing appropriate therapeutic interventions.

TRANSVAGINAL ULTRASONOGRAPHY

Transvaginal ultrasound is one of the main tools used in the diagnosis of ectopic pregnancy. This method is highly effective in visualizing the location of the pregnancy, allowing the identification of ectopic pregnancies in the fallopian tubes, ovary, cesarean scar, and other atypical locations (HAO et al., 2023). High-resolution transvaginal ultrasound can detect more than 90% of ectopic pregnancies and is particularly effective when ÿ-hCG levels are elevated (XIAO et al., 2021).

For cesarean scar pregnancy (CSP), two-dimensional (2D) B-mode transvaginal ultrasound, in conjunction with three-dimensional (3D) ultrasound and color Doppler, is considered the gold standard for diagnosis. These methods allow visualization of the gestational sac within the cesarean scar, measurement of its size, and determination of its location and viability (KŁOBUSZEWSKI et al., 2024). Detailed ultrasound assessment is crucial for selecting the appropriate treatment and preventing associated complications (KŁOBUSZEWSKI et al., 2024).

HUMAN CHORIONIC GONADOTROPIN (HCG) LEVELS

Measurement of human chorionic gonadotropin (HCG) levels is another essential diagnostic tool. Abnormal HCG levels may indicate the presence of an ectopic pregnancy. In women with suspected ectopic pregnancy, ÿ-hCG levels greater than 1500-2000 mIU/mL, without visualization of an intrauterine gestational sac on transvaginal ultrasound, are highly suggestive of an ectopic pregnancy (XIAO et al., 2021; SALARI et al., 2020).

The rapid immunoassay of serum human chorionic gonadotropin (b-hCG) is widely used to clinically diagnose pregnancy. Studies show that if the b-hCG level is 3500 mIU/mL or higher, the sensitivity and specificity of transvaginal ultrasound in the diagnosis of ectopic pregnancy range from 87.0% to 99.0% and 94.0% to 99.9%, respectively (XIAO et al., 2021).

ADVANCED DIAGNOSTIC TOOLS

In addition to conventional methods, advanced diagnostic techniques have been developed to improve the accuracy of the diagnosis of ectopic pregnancy. The introduction of Standardized ultrasound assessment and reporting of CSP in early pregnancy, for example, allows for detailed classification of the location of the gestational sac and selection of the most appropriate treatment (KŁOBUSZEWSKI et al., 2024).

A new advanced standardized system for ultrasound assessment and reporting of CSP was created in 2022, categorizing pregnancies with cesarean scar based on the location of the gestational sac (KŁOBUSZEWSKI et al., 2024). Depending on the location of the gestational sac, the following types of CSP can be diagnosed: CSP type 1, where most of the gestational sac protrudes towards the uterine cavity; CSP type 2, where most of the sac is embedded in the myometrium without crossing the serosal contour; and CSP type 3, where the sac is partially located beyond the external contour of the cervix or cervix (KŁOBUSZEWSKI et al., 2024).

Magnetic resonance imaging (MRI) is a crucial advanced diagnostic tool in the management of ectopic pregnancies, especially in complex and non-tubal cases. Providing detailed images of the soft tissues, MRI allows an accurate assessment of the location and extent of the pregnancy, as well as the identification of possible infiltration into adjacent organs. Its advantages include superior anatomical detail, essential for accurately assessing the anatomy of the pelvic organs in cases of corneal (interstitial) and cesarean scar pregnancy (CSP), where the exact location may be difficult to determine using transvaginal ultrasound alone. In addition, MRI allows the assessment of the thickness of the uterine wall in cases of CSP, crucial for determining the risk of uterine rupture and planning the best therapeutic approach. MRI is also effective in identifying infiltrations in neighboring organs, such as the bladder or intestine, vital information for choosing the safest surgical intervention. Another important advantage is the absence of ionizing radiation, making MRI a safer option for pregnant patients compared to X-rays and computed tomography (CT) (TREMMEL et al., 2024).

In clinical practice, MRI is especially useful in the evaluation of CSP, allowing detailed visualization of the implantation of the fertilized egg in the scar tissue, and aiding in the choice of therapeutic interventions such as the administration of methotrexate (MTX) or surgical approaches. In cases of corneal pregnancies, MRI provides an accurate assessment of the extent of the gestation and the vascularization involved, essential to avoid serious hemorrhage during surgical procedures. For cervical pregnancies, MRI helps to visualize the implantation and adjacent structures, guiding minimally invasive

interventions. However, despite the advantages, there are technical considerations, such as longer examination time compared to ultrasound, high cost, and limited availability, which can delay diagnosis and treatment (TREMMEL et al., 2024).

Early diagnosis of ectopic pregnancy is crucial for effective management and minimization of serious complications, such as tubal rupture and internal bleeding, which can lead to high maternal mortality (SALARI et al., 2020). The ability to identify ectopic pregnancy early allows the use of less invasive treatments and increases the chances of preserving future fertility.

USE OF CREATINE PHOSPHOKINASE (CPK) AS A DIAGNOSTIC MARKER

Creatine phosphokinase (CPK) is an intracellular enzyme present in muscle cells and involved in the transfer of high-energy phosphate groups. Increased levels of CPK in plasma are indicative of cell lysis, which can occur during pathological processes such as ectopic pregnancy (EP). In PE, abnormal implantation of the blastocyst outside the uterine endometrium, predominantly in the fallopian tubes, leads to lysis of trophoblast cells, resulting in elevated plasma CPK levels (GHORBANI; KERAMAT; LEDARI, 2020). CPK levels increase significantly in response to trophoblast invasion and the presence of a trophoblast mass in ectopic pregnancies. This suggests that CPK can be used as a diagnostic marker for PE. Different studies have investigated the efficacy of CPK as a diagnostic marker, demonstrating that elevated plasma CPK levels are correlated with the presence of PE, especially in comparison with normal intrauterine pregnancies (GHORBANI; KERAMAT; LEDARI, 2020). Traditional diagnostic methods for PE include transvaginal ultrasonography and serial measurement of serum beta-hCG levels. Transvaginal ultrasound is used to identify the presence of gestational tissue in the adnexa without evidence of intrauterine pregnancy. However, approximately 40% to 50% of early cases of PE are not diagnosed due to the limitations of these methods. Measurement of serum beta-hCG levels is another common method, but it also has limitations in distinguishing between an intrauterine pregnancy and pregnancies. intrauterine inviability and PE (GHORBANI; KERAMAT; LEDARI, 2020).

The systematic review conducted by Ghorbani, Keramat, and Ledari (2020) indicates that increasing CPK levels may be a valuable complement to traditional diagnostic methods. Studies show that determining total CPK levels may increase their diagnostic value for PE. Despite the promising results, there are variations in the findings and the need for larger-scale studies to determine a reliable cutoff point for CPK as a diagnostic marker (GHORBANI; KERAMAT; LEDARI, 2020).

The use of CPK as a diagnostic marker for PE has some limitations. The reviewed studies indicated that although there are elevated CPK levels in patients with PE, there is a significant overlap in CPK levels compared to normal pregnancies and miscarriages. In addition, diagnostic accuracy may be influenced by gestational age, with variations in CPK levels at different stages of pregnancy. Therefore, it is necessary to consider these factors when using CPK as a diagnostic marker (GHORBANI; KERAMAT; LEDARI, 2020).

TREATMENT OF ECTOPIC PREGNANCY

Treatment of ectopic pregnancy can be performed through medical or surgical approaches, with the choice of method depending on specific clinical factors and patient preferences. Intramuscular methotrexate is widely used in medical treatment, functioning as a folate antagonist that interrupts rapid cell division. There are different protocols for administering methotrexate, including single dose, two doses, and multiple doses, with the single dose presenting the lowest risk of adverse effects, while the two-dose is more effective for patients with high initial levels of β-hCG (Hendriks, Rosenberg & Prine, 2020). Surgical treatment, which generally has a higher success rate than methotrexate treatment, includes procedures such as salpingostomy and salpingectomy, depending on the extent of fallopian tube damage and the patient's preferences regarding future fertility (Hendriks, Rosenberg & Prine, 2020). The decision between medical and surgical treatment should carefully consider clinical factors and the individual needs of the patient.

Expectant management may be considered for patients whose β-hCG levels are decreasing and very low. Patients who elect this treatment should be closely monitored due to the risks of spontaneous rupture and the need for emergency surgery. The rate of successful spontaneous resolution decreases with higher β-hCG levels, and patients should be informed of the risks involved (HENDRIKS; ROSENBERG; PRINE, 2020).

SURGICAL TREATMENT

Surgical treatment is often considered the gold standard in the management of ectopic pregnancy, especially in cases of hemodynamic instability or severe complications. Surgical options include salpingectomy, salpingostomy, and other more conservative approaches recently developed for specific cases, such as cesarean scar pregnancy (CSP).

1. Salpingectomy is the total removal of the affected fallopian tube. This procedure is often indicated in cases of tubal rupture or when there is significant hemorrhage, as it completely removes the ectopic pregnancy and damaged tissue, preventing future complications (WANG & ZHANG, 2024; LEZIAK et al., 2022).

2. Salpingostomy is a procedure that involves the removal of the ectopic pregnancy while keeping the fallopian tube intact. This approach is mainly used in cases where fertility preservation is an important consideration. Salpingostomy can be performed by laparoscopy or laparotomy, depending on the patient's condition and the location of the ectopic pregnancy (WANG & ZHANG, 2024; LEZIAK et al., 2022).

3. Surgical Treatment for Cesarean Scar Pregnancy (CSP): Historically, hysterectomy was often considered the only treatment option for CSP, especially in cases of severe complications. However, more conservative approaches have been developed and are increasingly being used as alternatives to hysterectomy, allowing fertility preservation and minimizing the impact on the patient's reproductive health (KŁOBUSZEWSKI et al., 2024).

Contemporary treatment methods for CSP include:

1. Laparoscopic Removal: This minimally invasive procedure involves the removal of gestational tissue through small incisions, using a laparoscope to guide the surgery. This method is often preferred due to the shorter recovery time and lower risk of complications (KŁOBUSZEWSKI et al., 2024).

2. Hysteroscopic evacuation: Uses a hysteroscope to visualize and remove the gestational tissue through the cervix. This procedure is less invasive than laparotomy and allows for a faster recovery (KŁOBUSZEWSKI et al., 2024).

3. Dilation and Curettage (D&C): Involves dilation of the cervix followed by removal of gestational tissue using surgical instruments. Although effective, this method may be associated with an increased risk of complications, such as uterine perforation and adhesion formation (KŁOBUSZEWSKI et al., 2024).

4. Suction Sac Aspiration: A minimally invasive method in which the contents of the gestational sac are removed by suction, guided by ultrasound. This procedure may be an option for selected cases of CSP (KŁOBUSZEWSKI et al., 2024).

ENDOVASCULAR CHEMOEMBOLIZATION

Chemoembolization, particularly uterine artery endovascular chemoembolization (UAC), is an innovative and minimally invasive method used to treat cesarean scar pregnancies (CSP). This procedure combines intra-arterial administration of methotrexate with embolization of the uterine arteries, using occlusive agents such as polyvinyl alcohol and Gelfoam particles. The technique allows a higher concentration of methotrexate directly into the arteries that irrigate the gestational foci, combining chemotherapy with tissue ischemia, thus promoting regression of the ectopic pregnancy (Kłobuszewski et al., 2024).

Studies have demonstrated the high efficacy of chemoembolization, with success rates ranging from 83% to 99%. Successful chemoembolization procedures have been reported even in the presence of fetal cardiac activity. The efficacy of this method is comparable to high-intensity focused ultrasound (HIFU), although HIFU has been associated with a lower incidence of minor complications but with a longer hospital stay compared to endovascular chemoembolization (Kłobuszewski et al., 2024). Additionally, chemoembolization may be especially effective when followed by suction curettage, enhancing the positive results of treatment (Kłobuszewski et al., 2024).

Comparative studies indicate that surgical treatments, such as salpingectomy and salpingostomy, have different impacts on reproductive outcomes. Salpingostomy generally preserves fertility better compared to salpingectomy, as the latter completely removes the affected fallopian tube (HAO et al., 2023).

METHOTREXATE (MTX) TREATMENT

Methotrexate (MTX) treatment is one of the main non-surgical approaches for ectopic pregnancy. Methotrexate is a folic acid antagonist that inhibits dihydrofolate reductase, an enzyme essential for DNA synthesis. By inhibiting this enzyme, methotrexate interferes with the synthesis of new purines and pyrimidines, resulting in the interruption of the proliferation of rapidly dividing cells, such as trophoblast cells present in ectopic pregnancy (SALARI et al., 2020; KŁOBUSZEWSKI et al., 2024).

Methotrexate therapeutic regimens for ectopic pregnancy can be classified into three main categories: single dose, double dose, and multiple doses.

• Single Dose: In this regimen, a dose of 50 mg/m² of methotrexate is administered intramuscularly. ÿ-hCG levels are measured on days 4 and 7 after administration. If ÿ-hCG levels decrease by 15% or more, treatment is considered successful and monitoring is done weekly. Otherwise, a second dose may be necessary (SALARI et al., 2020).

• Double Dose: In this regimen, methotrexate is administered in two doses on days 1 and 4. ÿ-hCG levels are monitored on days 4 and 7. If the reduction in ÿ-hCG levels is less than 15%, a third dose is administered on day 7 and, if necessary, a fourth dose may be prescribed. If there is no adequate response to treatment, surgery is recommended (SALARI et al., 2020).

• Multiple Doses: In this regimen, methotrexate is administered in up to four doses of 1 mg/kg on alternate days (days 1, 3, 5, and 7). The effectiveness of treatment is assessed based on the reduction in ÿ-hCG levels. If there is no adequate reduction, surgery is recommended (SALARI et al., 2020).

SUCCESS CRITERIA AND INFLUENCE FACTORS

The efficacy of methotrexate treatment is influenced by several factors, including the initial ÿ-hCG level, the presence of fetal cardiac activity, and the gestational age of the patient. Elevated ÿ-hCG levels before treatment are associated with a higher likelihood of treatment failure. Studies have shown that ÿ-hCG levels greater than 3000-4000 mIU/ml increase the likelihood of needing surgical intervention (SALARI et al., 2020; KŁOBUSZEWSKI et al., 2024).

In addition, the presence of fetal cardiac activity is a negative factor that may reduce the efficacy of methotrexate treatment. In patients with ÿ-hCG levels greater than 5000 mIU/ml or the presence of fetal cardiac activity, methotrexate treatment should be carried out with caution (SALARI et al., 2020).

LOCAL AND SYSTEMIC ADMINISTRATION

Methotrexate can be administered both systemically and locally. In systemic administration, methotrexate is administered intramuscularly or intravenously. In some cases, a single dose of 100 mg of methotrexate is administered intravenously followed by an infusion of 200 mg over 12 hours (KŁOBUSZEWSKI et al., 2024).

Local administration involves direct injection of methotrexate into the gestational sac under ultrasound guidance. This method allows a high concentration of the drug at the site of the ectopic pregnancy, minimizing systemic adverse effects. Studies have shown that local administration is particularly effective in cases of pregnancies with a cesarean scar (KŁOBUSZEWSKI et al., 2024).

Methotrexate treatment can be associated with several adverse effects. Gastrointestinal complications, such as nausea and vomiting, are common. Furthermore, renal toxicity may occur due to drug deposition in the renal tubules, especially in patients with reduced urine volume and acidic urine. Hematological complications, hepatotoxicity, and pneumonitis are other possible adverse effects (SALARI et al., 2020). In one study, it was observed that up to 70% of patients treated with systemic methotrexate experienced vaginal bleeding (KŁOBUSZEWSKI et al., 2024). Furthermore, repeated administration of methotrexate may be necessary to achieve an adequate therapeutic response, which exposes patients to higher doses of the drug and increases the risk of adverse effects (KŁOBUSZEWSKI et al., 2024). Fertility preservation is an important consideration in the treatment of ectopic pregnancy. Comparative studies indicate that methotrexate offers a high success rate under appropriate conditions and is associated with better reproductive outcomes compared to more invasive surgical treatments. For example, Hao et al. (2023)

reported that fertility was significantly higher after methotrexate treatment compared with surgical treatment. However, reliable data on the impact of methotrexate on subsequent female fertility and the incidence of pregnancy recurrence in cesarean scar are still scarce, and further research is needed (KŁOBUSZEWSKI et al., 2024; SALARI et al., 2020). In conclusion, methotrexate is an effective and noninvasive option for the treatment of ectopic pregnancy, offering significant advantages in preserving fertility and minimizing complications associated with surgical treatments. The choice of dosing regimen and administration approach should be individualized based on the patient's clinical characteristics and identified risk factors. Additional studies are needed to fully elucidate the impact of methotrexate on long-term reproductive outcomes and to optimize treatment protocols.

ALTERNATIVE THERAPIES

Several alternative treatments have been studied and used in the management of ectopic pregnancy, especially in cases where the conventional approach is not suitable or desired by the patient. Below, I discuss some of these alternatives based on the texts you shared.

Aromatase inhibitors, such as letrozole, are one of the therapeutic alternatives studied for the treatment of ectopic pregnancy. Letrozole acts by reducing estrogen levels, which is essential for pregnancy progression. Mitwally et al. showed that treatment with letrozole in tubal ectopic pregnancy had the same efficacy as methotrexate (MTX), with ÿ-hCG levels decreasing more quickly and fewer adverse effects in the letrozole group (LEZIAK et al., 2022). Other aromatase inhibitors could also be investigated for ectopic pregnancy due to the same mechanism of action.

Gefitinib, an epidermal growth factor receptor (EGFR) inhibitor, has been studied in combination with methotrexate. EGFR expression is higher in placental tissue than in other non-malignant tissues, making gefitinib an interesting option (LEZIAK et al., 2022). Clinical studies have shown that the combination of gefitinib with methotrexate inhibited placental cell growth more effectively than when used separately, with an efficacy of 85% to 86% in clinical trials (LEZIAK et al., 2022). Despite the high efficacy, combination therapy is not free of side effects, which may be acceptable to patients if it results in a reduction in the duration of therapy. Mifepristone is an anabolic steroid that competitively binds to progesterone receptors, inhibiting their activity and leading to villous tissue degeneration, atrophy, and necrosis of decidual tissue, resulting in embryo death (XIAO et al., 2021). Studies indicate

that mifepristone can be used in combination with methotrexate to treat ectopic pregnancy, especially in cases where surgery is not a viable option.

CONCLUSION

The present study aimed to analyze the scientific literature on ectopic pregnancy, addressing the main risk factors, diagnostic methods, and treatment options. The systematic review revealed that ectopic pregnancy is a significant medical emergency, representing one of the main causes of acute abdominal pain and early maternal mortality. The importance of β-hCG levels was emphasized as a crucial marker for early diagnosis, allowing the distinction between normal and abnormal pregnancies.

The review identified that the treatment of ectopic pregnancy can be performed through medical approaches, using methotrexate, or surgical approaches, such as salpingostomy and salpingectomy. The choice of method depends on specific clinical factors and the patient's reproductive preferences. Methotrexate, with its different dosing protocols, was highlighted as an effective and less invasive option, while surgical treatment showed a generally higher success rate, especially in cases of significant damage to the fallopian tubes. Furthermore, endovascular chemoembolization of the uterine artery has emerged as a promising and innovative technique for the treatment of complex cases, such as pregnancies with cesarean scars. This approach combines the administration of methotrexate with embolization of the uterine arteries, promoting regression of the ectopic pregnancy and presenting high success rates.

The characterization of risk factors, such as pelvic inflammatory disease, use of intrauterine devices, and history of cesarean section, is essential for the prevention and adequate management of ectopic pregnancy. Early detection, through transvaginal ultrasound and monitoring of β-hCG levels, is essential to improve clinical outcomes and reduce the need for emergency interventions.

It is concluded that ectopic pregnancy requires a multidisciplinary and personalized approach, considering the diagnostic and therapeutic advances available. The integration of advanced techniques, medical and surgical treatments, and new therapies under development is crucial to reduce maternal mortality, preserve fertility, and improve patients' quality of life. Continued research and application of evidence-based practices are essential to optimize the management of this complex condition.

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