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ECTOPIC PREGNANCY: CURRENT APPROACHES TO CLINICAL MANAGEMENT

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INTRODUCTION

Ectopic pregnancy (EP), defined as the implantation of the embryo outside the uterine endometrial cavity, represents an important obstetric emergency and corresponds to approximately 2% of all clinically recognized pregnancies. (Leziak et al., 2022), 2022)The most common locations include the fallopian tube, although atypical forms, such as cervical pregnancy (CG) and pregnancy over a caesarean scar, have also been described with significant associated morbidity. (Stabile et al., 2020) EG is the leading cause of maternal mortality in the first trimester, accounting for up to 10% of pregnancy-related deaths, mainly due to tubal rupture and intra-abdominal bleeding. (Mullany et al., 2023)

Early diagnosis is essential to avoid serious complications, including hemodynamic instability, loss of fertility and maternal death. However, diagnosis can be challenging, as the symptoms - abdominal pain, vaginal bleeding and menstrual delay - are non-specific and often mimic other acute abdominal conditions. The diagnosis of choice is based on clinical correlation with serial dosages of the hormone β-human chorionic gonadotrophin (β-hCG) and imaging tests, especially transvaginal ultrasound. In selected cases, an endometrial biopsy can be performed by means of a uterine curettage, which can help to exclude intrauterine pregnancy and increase the accuracy of the diagnosis. (Mullany et al., 2023) In cases classified as pregnancy of unknown location (PUL), which represent up to 31% of initial consultations with suspected ectopic pregnancy, diagnostic confirmation depends on the evolution of β-hCG levels and serial ultrasound examinations. In recent protocols, such as the one published by the Journal of Obstetrics and Gynaecology Canada, serial monitoring of β-hCG and transvaginal ultrasound has been recommended to adequately stratify risk, allowing expectant, medical (with the use

of methotrexate) or surgical management (in cases of clinical instability, rupture or failure of drug treatment) according to hormonal progress, clinical signs and response to treatment (Po et al., 2021; Wiesenfeld et al., 2020).

Therapeutic strategies for the management of GE include a clinical, surgical or expectant approach, with the choice guided by parameters such as serum β-hCG levels, hemodynamic stability and the presence of embryonic cardiac activity. (Mullany et al., 2023) Clinical treatment with methotrexate (MTX) has been shown to be effective in up to 90% of selected cases, 2023) Clinical treatment with methotrexate (MTX), in single or multiple dose regimens, has been shown to be effective in up to 90% of selected cases, and is preferred because of its potential to preserve fertility and because it avoids the risks inherent in surgery. (Abdelfattah-Arafa et al., 2024; Leziak et al., 2022) However, therapeutic failures have been reported, especially in patients with elevated β-hCG, the presence of severe pelvic pain or embryonic cardiac activity, leading to the need for subsequent surgical intervention. Factors such as advanced maternal age and high initial β-hCG levels have been associated with a higher risk of clinical treatment failure (Abdelfattah-Arafa et al., 2024). More specifically, Abdelfattah-Arafa et al. (2024) identified that initial β-hCG levels of more than 2500 IU/L, the presence of severe abdominal pain and an adnexal mass greater than 35 mm are independent predictors of MTX treatment failure in tubal ectopic pregnancies, highlighting the importance of careful selection to avoid adverse outcomes.

Therapeutic and diagnostic innovations have evolved significantly, including the development of new pharmacological agents and the improvement of minimally invasive techniques, with the aim of improving maternal safety and preserving fertility (Mullany et al., 2023).

The search for therapeutic alternatives to MTX includes the use of drugs such as letrozole and gefitinib, as well as locally administered agents such as potassium chloride (KCl) and absolute ethanol. These agents have shown promise, especially in ectopic pregnancies of unusual location, such as cervical pregnancy or over uterine scarring. Recently, Leziak et al. (2022) highlighted letrozole as an emerging option in the conservative management of EG, as it interferes with estrogen synthesis and promotes regression of trophoblastic tissue. Although still in the experimental phase, letrozole has shown promising results in reducing β-hCG levels and favoring non-surgical resolution, especially in selected cases of tubal and cervical GE. A significant advance has been the combination of the systemic use of methotrexate with the local administration of agents - such as potassium chloride (KCl) or methotrexate injected under ultrasound guidance - which has shown high clinical success. A study of 82 patients with viable tubal pregnancies achieved a success rate of 93.3%, considerably higher than systemic treatment alone (73%) (Del Martel & Stanwood, 2014). Hysteroscopy, alone or in combination with MTX, has also been explored as an effective conservative strategy in early GC, promoting a faster drop in serum β-hCG levels and shortening the time to resolution of the clinical picture (Stabile et al., 2020). GC, despite its rarity, represents a clinical challenge due to the high risk of severe bleeding. Stabile et al. (2020) point out that, in cases diagnosed early, conservative treatment with local or systemic MTX associated with hysteroscopy enables effective control, reducing hysterectomy rates and optimizing future reproductive outcomes.

In addition, it is worth highlighting the importance of individualized nutritional monitoring in the run-up to pregnancy, throughout pregnancy and also in the postpartum period.

Future prospects in the management of ectopic pregnancy include the development of personalized protocols based on biomarkers and new pharmacological therapies. According to Leziak et al. (2022), in addition to letrozole, agents such as gefitinib, an epidermal growth factor receptor (EGFR) inhibitor, are being studied for their ability to induce regression of ectopic gestational tissue with less toxicity. At the same time, the incorporation of artificial intelligence and predictive algorithms promises to improve diagnostic accuracy and optimize therapeutic decisions, contributing to greater maternal safety and fertility preservation (Mullany et al., 2023).

Given the diversity of clinical presentations and therapeutic approaches, it is essential to critically review the current evidence related to the diagnosis and clinical management of ectopic pregnancy. This article aims to summarize the main diagnostic, therapeutic and prognostic advances related to EG, with an emphasis on approaches aimed at preserving fertility and reducing maternal morbidity and mortality (Abdelfattah-Arafa et al., 2024; Leziak et al., 2022; Mullany et al., 2023; Stabile et al., 2020).

METHODOLOGY

This is a literature review aimed at gathering and critically analyzing the most recent clinical approaches related to the diagnosis and treatment of ectopic pregnancy. To this end, a targeted search was carried out in the PubMed database, considering publications from the last five years. The descriptors used to select the studies were: "Pregnancy, Ectopic", "Treatment" and "Diagnosis", combined to ensure a relevant and up-to-date sample of scientific literature on the subject.

Articles available in full that directly or indirectly addressed the diagnostic and therapeutic strategies applied to ectopic pregnancy were included. Publications in different languages were accepted, as long as they presented methodological clarity, thematic pertinence and scientific relevance. Original studies, narrative reviews and update articles were considered eligible. Duplicate publications, studies not related to the scope of the research and articles not accessible on the PubMed database were excluded from the analysis.

RESULTS AND DISCUSSION

The therapeutic approach to ectopic pregnancy (EG) requires rigorous stratification according to clinical, laboratory and ultrasound criteria. Conservative treatment with **methotrexate (MTX)** has been shown to be viable in hemodynamically stable patients with serum β-hCG < 1500 IU/L and a mass < 35 mm in diameter, with overall efficacy of 70-90% in single-dose regimens. However, absolute contraindications include hemodynamic instability, fetal cardiac activity, β-hCG > 5000 IU/L, hepatic/renal insufficiency and active bleeding, scenarios that require immediate surgical intervention. Therapeutic failure correlated directly with increasing levels of β-hCG, necessitating conversion to a surgical approach (Abdelfattah-Arafa et al., 2024; Leziak et al., 2022; Mullany et al., 2023).

As for **surgical treatment**, **salpingostomy** emerged as preferred for patients wishing to preserve fertility, especially in the presence of compromised contralateral fallopian tubes, while **salpingectomy** was indicated for EG ≥ 5 cm, tubal rupture or active bleeding. Persistent trophoblastic tissue after salpingectomy occurred in ≈20% of cases, requiring serial β-hCG monitoring or adjuvant therapy with MTX. On the other hand, **expectant management** proved safe only for EG with β-hCG < 200 IU/L, achieving spontaneous resolution in 88% of cases, but with an increased risk of complications above this threshold (Leziak et al., 2022; Mullany et al., 2023).

The selection of the therapeutic approach should integrate clinical and laboratory parameters and patient preferences, highlighting unresolved dilemmas. **MTX** remains the mainstay of conservative treatment, but its application is limited by controversial β-hCG thresholds: while guidelines contraindicate levels > 5000 IU/L, studies suggest efficacy even at values up to 4000 IU/L, highlighting inconsistencies in current protocols. This disparity reflects the need for standardization based on robust evidence, especially considering that β-hCG > 1500 IU/L already implies a significant reduction in the efficacy of MTX (Abdelfattah-Arafa et al., 2024; Leziak et al., 2022; Mullany et al., 2023).

The **safety of surgical treatment** also requires critical analysis. Although salpingectomy ensures immediate resolution, its association with future infertility in patients without functional contralateral fallopian tubes justifies the preference for salpingostomy when feasible. However, the rate of trophoblastic persistence (≈20%) post-salpingostomy requires rigorous laboratory monitoring, burdening the health system and generating anxiety in patients. Alternative biomarkers - such as progesterone, serum CPK and hematimetric indices - have emerged as promising tools for predicting therapeutic success, but lack validation in large cohorts (Leziak et al., 2022; Mullany et al., 2023).

Finally, **expectant management** remains underused despite its potential in selected EGs (β-hCG < 200 IU/L). Clinical reluctance stems from risks such as tubal rupture and bleeding, reinforcing that this strategy requires careful selection and adherence to follow--up. Recent trials suggest that MTX does not offer superior benefit to placebo in stable tubal GE with β-hCG < 1500 IU/L, questioning therapeutic paradigms and paving the way for re-evaluation of management algorithms (Leziak et al., 2022; Mullany et al., 2023).

In addition to the widely established approaches, recent innovative proposals have emerged in the literature to improve the management of ectopic pregnancy, both in terms of diagnosis and therapy. These advances seek to reduce dependence on invasive procedures, increase diagnostic accuracy and expand pharmacological options in selected cases (Leziak et al., 2022; Mullany et al., 2023).

In the diagnostic field, biomarkers such as activin-AB, ADAM-12, PAPP-A and certain microRNAs have been studied as promising tools for differentiating early ectopic from intrauterine pregnancies. Although not yet incorporated into routine clinical practice, these indicators show relevant potential for more precise and rapid decisions, especially in cases of undefined location on ultrasound (Mullany et al., 2023).

In therapeutic terms, hysteroscopy stands out as a particularly effective conservative alternative for cervical ectopic pregnancies. This technique allows for the selective removal of the gestational sac while preserving fertility, and is particularly useful in hemodynamically stable patients with high β-hCG levels. When associated with the systemic use of methotrexate, hysteroscopy has shown a faster reduction in hormone levels and a shorter hospital stay, as well as enhancing future reproductive recovery (Stabile et al., 2020).

In addition, recent studies point to the importance of identifying predictors of methotrexate treatment failure, such as high initial β-hCG levels, the presence of pelvic pain, detectable fetal heart activity and advanced maternal age. Careful assessment of these parameters can help choose the most appropriate and safest treatment, minimizing the risk of complications and the need for emergency interventions (Abdelfattah-Arafa et al., 2024; Leziak et al., 2022).

Other targeted and localized therapies are emerging as alternatives to conventional methods and have been studied due to their abi-

lity to provide less invasive interventions and thus preserve fertility. Uterine artery embolization (UAE), often combined with intracavitary infusion of MTX, has been effective and may offer a less invasive approach to the treatment of ectopic pregnancy than hysterectomy, especially in cases with cesarean scar pregnancies, where it may decrease the need for this type of surgery (Mullany et al., 2023). UAE combined with MTX and 5-fluorouracil (5-FU) has been studied, but the inclusion of 5-FU was associated with more adverse effects (Mullany et al., 2023). High-intensity focused ultrasound followed by curettage and dilation or UAE is a viable non-surgical approach aimed at fertility preservation, especially for patients with ectopic pregnancy with a cesarean scar (Mullany et al., 2023). In short, many of these techniques represent a move towards interventions with greater precision and less harm to fertility, further recognizing the impact of ectopic pregnancy on women's reproductive health and well-being (CHONG, et al., 2025).

Although ectopic pregnancy is a gynecological condition whose management is predominantly clinical and surgical, nutrition, as a complementary therapy, plays a key role in women's recovery and in promoting long-term reproductive health. Despite the scarcity of specific nutritional protocols for this condition, there is evidence to support the importance of a balanced diet and adequate nutrient intake for restoring nutritional status and preparing for future pregnancies (Silva et al., 2023; Lima et al., 2023). Folic acid supplementation is widely recommended in the pre-conception period and after adverse reproductive events. Doses of between 0.4 and 1 mg/day, for at least 2 to 3 months, have been shown to be effective in preventing megaloblastic anemia, reducing homocysteine levels and promoting healthy embryonic development in future pregnancies (Rodrigues et al., 2023). In addition, folate deficiency can compromise tissue regeneration, an essential process in the recovery period after an ectopic pregnancy. Nutrients such as zinc, magnesium, calcium and vitamin D are considered essential for maintaining fertility, preserving the endometrium and regulating hormones. Zinc, for example, is involved in DNA synthesis and oocyte maturation, while vitamin D has immunomodulatory potential and anti-inflammatory properties, which, when associated with the gestational context, are related to better reproductive outcomes (Almeida et al., 2023). Calcium and magnesium deficiency, in turn, can have a direct impact on uterine muscle contraction and cell metabolism.

In addition to the physical damage to patients, ectopic pregnancy is associated with a high emotional burden, with symptoms of anxiety, depression and post-traumatic stress persisting for up to nine months. A recent multicenter study showed that 38% of pregnant women had post-traumatic stress disorder (PTSD), 20% anxiety and 5% depression three months after diagnosis, with a major impact on their social and professional contexts. Low self-esteem was also identified as a predictor of greater psychological distress in these patients. Despite this, few guidelines include structured psychological support, highlighting a gap in multidisciplinary care (Farren et al., 2021; Rahimi et al., 2021).

CONCLUSION

Although medical management is a priority in ectopic pregnancy, nutritional management should be considered as an integral part of multidisciplinary care, with the aim of optimizing physiological recovery and preserving the woman's reproductive potential. Future research is needed to establish specific, evidence-based nutritional guidelines for the post-ectopic period.

The consolidation of evidence-based therapeutic approaches, combined with the ju-

dicious use of emerging diagnostic technologies, represents an essential step towards improving the management of ectopic pregnancy. The recognition of predictive factors of therapeutic failure and the expansion of the pharmacological arsenal, with alternatives such as letrozole and the selective use of hysteroscopy, allow for a safer, individualized approach aimed at preserving fertility. In this context, it is essential to develop clinical guidelines that integrate clinical, laboratory, psychological and nutritional aspects, favoring truly multidisciplinary care.

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