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DIAGNOSIS AND THERAPEUTICS OF GESTATIONAL TROPHOBLASTIC DISEASE: CURRENT PERSPECTIVES

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Abstract: Introduction: Gestational Trophoblastic Disease (GTD) represents a group of conditions characterized by abnormal proliferation of placental trophoblasts. The main type is the Hydatidiform Mole (MH). DTG can evolve into invasive neoplasia, where 25% of cases resist chemotherapy treatment. Diagnosing these conditions early is essential for a better prognosis and maintenance of the reproductive capacity of affected patients. This work presents a focus on the diagnostic approach and therapeutic strategies of DTG. Methodology: review article based preferably on works published in the last 5 years in the MEDLINE, LILACS and SciELO databases, in Portuguese and English, using the descriptor "gestational trophoblastic disease" and the combined descriptors: hydatidiform mole, pregnancy and management. Works that did not fit into the delimited time frame or topic addressed were excluded. Literature Review: Early diagnosis of GTD, established by specific ultrasound criteria and high hCG titers, allows complete resolution of the condition. Late diagnosis requires more aggressive therapy, with a worse prognosis. In addition to uterine emptying, post-molar follow-up with serum hCG measurement is recommended, and staging of post-molar GTD must be performed with pelvic-transvaginal Doppler ultrasound and chest radiography. In lung metastases larger than 1 cm, chest computed tomography and brain magnetic resonance imaging must be requested. Monochemotherapy, generally using methotrexate (MTX) or actinomycin-D (Act-D), cures around 70% of low-risk patients, with polychemotherapy being reserved, such as the Etoposide, MTX, Act-D, Cyclophosphamide and Oncovin, for high-risk cases, generally metastatic. Conclusion: Even though the recognition of this condition is low cost and can be carried out from the first half of pregnancy, delay in diagnosing GTD increases maternal morbidity and mortality,

reduces chances of cure and makes it difficult to maintain women's reproductive potential. affected.
Keywords: Pregnancy complications; Gestational Trophoblastic Disease; Hydatidiform spring; Maternal Health.

INTRODUCTION

Gestational Trophoblastic Disease (GTD) constitutes a complex set of conditions marked by the disordered proliferation of placental trophoblasts, manifesting itself in diverse and challenging ways for healthcare professionals (BRAGA et al., 2021). GTD takes many forms, among which Hydatidiform Mole (MH) stands out, a clinical entity whose consequences can range from spontaneous remission to transformation into a high-risk invasive neoplasm (LURAIN, 2011). The relevance of early identification and effective treatment of GTD is indisputable, since delays in diagnosis and intervention can significantly impact the prognosis and reproductive health of affected patients (LIMA et al., 2016). In this review article, we propose a deep dive into contemporary approaches to the diagnosis and therapy of GTD, highlighting the most recent advances and perspectives.

The interconnection between the different subtypes of GTD, such as complete and partial hydatidiform mole and invasive forms, is a challenging scenario that requires a refined understanding of the clinical and biological particularities of each variant (NGAN et al., 2021). Early detection not only provides patients with the opportunity for more effective intervention, but also offers vital information to guide therapeutic decisions. In this context, it is essential to explore in depth emerging diagnostic tools, such as the identification of specific biomarkers or the use of advanced imaging techniques, which have the potential to revolutionize the clinical management of this disease (PAGANI et al., 2018).

MH, as the prominent manifestation of DTG, deserves particular attention. Understanding the clinical and molecular variations within this subtype is a crucial step towards identifying predictive markers of disease progression. The evolution of MH to invasive forms, although rare, is a possibility that requires continuous surveillance. The use of diagnostic and imaging tools, such as high-resolution transvaginal ultrasound and magnetic resonance imaging, has shown promise in evaluating potential invasions and metastases (DHANDA; RAMANI; THAKUR, 2014; GARCIA et al., 2023).

In this context, the selection of the most appropriate treatment must consider the individualization of therapies, taking into consideration, clinical characteristics, risk of progression and preservation of fertility. Significant advances in therapeutic options include target-specific therapies, minimally invasive approaches and strategies to preserve reproductive capacity (PAGANI et al., 2018). The development of personalized therapeutic regimens, based on the molecular and clinical characteristics of each patient, has the potential to increase efficacy and minimize side effects (LURAIN, 2011; PAGANI et al., 2018).

METHODOLOGY

The preparation of this review article was conducted through the investigation of studies preferably published in the last 5 years, available in the MEDLINE, LILACS and SciELO databases. In order to cover a targeted range of pertinent information, the individual specific descriptor "gestational trophoblastic disease" and the combined descriptors "hydatidiform mole", "pregnancy" and "management" were used. The selection of descriptors was guided by their relevance and scope, seeking to encompass both clinical and therapeutic aspects related to GTD.

The systematic search was conducted carefully, including original studies, reviews, meta-analyses and clinical guidelines that made significant contributions to the understanding of the diagnosis and treatment of GTD. Additionally, those works that were related to the scope of the research or that were not relevant to the analysis were excluded.

The literature review carried out in this research went beyond just a compilation of information. Each selected article was evaluated for its methodological quality, relevance to the scope of the research and contribution to the advancement of knowledge in the field of DTG. The critical analysis of the studies allowed a coherent and informed synthesis of recent advances, as well as the gaps that still persist in the diagnosis and management of the disease.

The organization of the literature review sought to follow a clear logic, addressing different aspects of the diagnosis and treatment of GTD. The latest scientific evidence, clinical case reports and updated guidelines were considered in order to provide a complete and up-to-date overview of contemporary approaches. The careful analysis of the selected studies allowed us to identify emerging trends, persistent challenges and potential paths for future investigations and developments.

DEVELOPMENT

NEW ADVANCES IN THE DIAGNOSIS OF GESTATIONAL TROPHOBLASTIC DISEASE

The accurate and early diagnosis of GTD represents a clinical challenge due to its heterogeneous presentations and possible serious consequences. Over the years, significant advances have been made in the field of GTD diagnosis, aiming to improve timely detection and intervention to optimize clinical outcomes. In current clinical practice, the diagnosis of GTD involves a multidisciplinary approach that combines clinical criteria, laboratory tests and imaging techniques (LIMA et al., 2016).

The use of specific serum biomarkers has gained prominence as a promising strategy in the diagnosis of GTD. The hormone human chorionic gonadotropin (hCG) is a classic and sensitive marker that is often elevated in patients with GTD. Furthermore, other biomarkers, such as free human thyrotrophic hormone beta (hCGβ) and pregnancy-associated protein-1 (PP13), have demonstrated usefulness in complementing clinical assessment (EYSBOUTS et al., 2017).

High-resolution ultrasound is an essential tool in the early detection and monitoring of GTD, a rare gestational condition characterized by trophoblastic abnormalities in the placenta. When a detailed ultrasound examination is performed to evaluate GTD, several specific ultrasound patterns can be identified, each with distinct clinical implications. In cases of complete mole, ultrasound often reveals an abnormal uterine mass, which exhibits a "bunch of grapes" appearance (LURAIN et al., 2010; LIMA et al., 2016). In the case of partial mole, which is a variant of GTD, the ultrasound findings may be similar, but generally present a less homogeneous appearance, and there may be areas of normal fetal tissue interspersed with molar vesicles, making the diagnosis a challenge (LIMA et al., 2016). Furthermore, in advanced stages of GTD, local invasion of molar tissue into the myometrium or cervix may occur, and ultrasound is capable of detecting this local invasion, which manifests as areas of hyperechogenicity on ultrasound, often with irregular patterns. (DHANDA, S.; RAMANI, S.; THAKUR, M, 2014). The presence of complex adnexal cysts is also common in cases of GTD due to abnormal hormonal stimulation, and these complex

ovarian cysts exhibit distinct ultrasound characteristics, including thick walls, internal septations and variable contents (LIMA et al., 2016). Another frequent ultrasound finding is increased uterine volume, which can be easily identified on ultrasound examination, contributing to diagnostic suspicion. At the same time, in advanced stages, analysis of the uterine blood flow pattern is also relevant, as abnormal flow patterns can be observed, suggesting atypical vascularization associated with GTD. This approach not only helps in identifying the disease, but also in distinguishing between different GTD subtypes, guiding clinical decision-making. (DHANDA, S.; RAMANI, S.; THAKUR, M, 2014; LIMA et al., 2016).

Magnetic resonance imaging (MRI) has emerged as an additional component in the evaluation of GTD, especially in complex cases that require greater anatomical detail and extent assessment. MRI allows a more precise view of local invasion and metastatic spread, helping in risk stratification and therapeutic planning, as, for example, in lung metastases larger than 1 cm, chest computed tomography and brain magnetic resonance imaging are necessary for evaluation. targeted, and this applies to other forms of DTG metastasis (LURAIN et al., 2010).

Molecular and genetic diagnosis represents a cutting-edge approach in the diagnosis of GTD. The identification of disease-associated mutations, such as mutations in the NLRP7 gene, has provided additional insights into the underlying mechanisms and genetic heterogeneity of GTD. This information has the potential to contribute to a better understanding of the pathophysiology of the disease and to the identification of potential therapeutic targets (NGAN et al., 2018).

Furthermore, the evolution of genetic sequencing techniques has allowed a more comprehensive approach to analyzing the molecular profile of trophoblastic lesions, allowing a more precise identification of genetic and molecular alterations that may be associated with the development and progression of GTD (NGAN et al., 2018; NING et al., 2019).

However, the challenge remains in translating these molecular discoveries into effective and accessible clinical applications. Standardization of testing protocols and clinical validation of these genetic biomarkers are areas that require continued attention to ensure that genetic information is meaningfully integrated into the GTD diagnostic process and therapeutic decisions (NING et al., 2019).

RISK STRATIFICATION AND TREATMENT PERSONALIZATION

Risk stratification plays a fundamental role in the clinical management of GTD, allowing a more personalized and effective approach for each patient. Recent advances have allowed the identification of prognostic factors that help predict the risk of progression to persistent trophoblastic neoplasia, enabling the adoption of more assertive interventions (GARCIA et al., 2023).

Several clinical, laboratory and imaging factors have been investigated as risk predictors in GTD. The time elapsed between molar pregnancy and complete resolution after uterine evacuation, serum hCG levels at the time of diagnosis and ultrasound characteristics are examples of variables that have been associated with the risk of progression to persistent or malignant disease (NIEMANN, I; HANSEN, E. S.; SUNDE, 2007; GARCIA et al., 2023).

The application of risk scoring systems has shown to be a promising approach in stratifying patients with GTD. These scores combine clinical, laboratory and imaging information to calculate a numerical value

that reflects the individual risk of progressing to persistent trophoblastic neoplasia. These scoring systems assist clinicians in making decisions regarding the need for more intensive follow-up or additional treatment. An example is the DTG Risk Score from the International Federation of Gynecology and Obstetrics, which considers factors such as initial gestational age, beta-hCG levels, ultrasound findings, obstetric history and comorbidities, where, based on these factors, the score calculates a numerical value, categorizing it as low, intermediate or high risk, guiding decision-making about treatment and follow-up. (RAMÍREZ et al., 2022; GARCIA et al., 2023).

Risk stratification not only influences the decision on appropriate surveillance, but also directs the choice of the most appropriate treatment. In low-risk patients, based on stratification, conservative approach with clinical and hCG monitoring may be sufficient. On the other hand, high-risk patients may benefit from more aggressive therapeutic interventions, such as polychemotherapy, which involves the use of combined chemotherapy regimens, such as the EMA/CO regimen (Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide and Oncovin), which has shown good results for high-risk cases, which are often metastatic (ZHAO et al., 2017). It is important to remember that only the regimen with Methotrexate and Actinomycin-D is capable of curing around 70% of low-risk patients, reserving the aforementioned polychemotherapy (such as the Etoposide, MTX, Act-D, Cyclophosphamide and Oncovin regimen), for high-risk cases, according to the scores mentioned previously (ZHAO et al., 2017; RAMÍREZ et al., 2022).

Treatment personalization has been widely explored as a means of improving clinical outcomes and minimizing adverse effects. Risk stratification allows for a more individualized approach, avoiding excessive treatments in low-risk patients and ensuring more intensive interventions in high-risk patients. This results not only in better treatment results, but also in a significant reduction in the psychological and physical impact on patients (BRAGA et al., 2021).

TARGET-SPECIFIC THERAPY IN GESTATIONAL TROPHOBLASTIC DISEASE

The search for more effective treatments with less toxicity in GTD has led to the development of target-specific therapeutic approaches, focused on inhibiting the molecular processes involved in the abnormal proliferation of placental trophoblasts. This approach aims to improve clinical outcomes and reduce side effects associated with conventional therapies (FENG et. al, 2019).

Within this context, innovative pharmacological agents have been investigated as possible target-specific interventions in GTD. Among these agents, angiogenesis inhibitors stand out, which aim to interrupt the blood supply necessary for abnormal trophoblastic growth. Therapies that aim to specifically inhibit abnormal trophoblast activity may represent a promising therapy to prevent malignant evolution and increase cure rates (GHASEMALI et al., 2021).

Combination therapy, which involves the simultaneous or sequential administration of different therapeutic agents, has proven to be an interesting strategy to improve efficacy and reduce resistance to treatments in GTD. The combination of angiogenesis inhibitors with chemotherapeutic agents, for example, has the potential to reach multiple molecular targets involved in trophoblastic growth, resulting in a more consistent approach (PFISTERER et al., 2020).

Postmolar follow-up plays a crucial

role in early detection of recurrences or complications after GTD treatment. Serum hCG measurement is an essential marker in this process, allowing early identification of abnormal elevations that may indicate persistence of the disease. Furthermore, performing imaging tests, such as pelvic ultrasound, helps to evaluate the response to treatment and detect complications (AYATI et al., 2017).

In more challenging cases, where metastatic spread occurs, a more aggressive approach is necessary. Multimodal therapy, which involves the combination of different therapeutic modalities such as surgery, chemotherapy and radiotherapy, can be considered to treat metastatic lesions in specific organs. The choice of therapeutic regimens depends on the location, extent and characteristics of the metastases (LIMA et al., 2017).

MINIMALLY INVASIVE APPROACHES AND EMERGING TECHNOLOGIES

The continuous search for less invasive approaches has led to the development of surgical techniques that aim to minimize trauma and improve the recovery of patients with GTD. Videolaparoscopy, for example, has stood out as an alternative to open surgery, allowing precise surgical interventions with smaller incisions. The adoption of this minimally invasive technique results in shorter hospital stays, less postoperative pain and faster recovery (LIMA et al., 2017; GARCIA et al., 2023).

In addition to the advantages offered by videolaparoscopy, advances in surgical techniques have made it possible to preserve fertility in patients with GTD. In cases of invasive hydatidiform mole, for example, the conservative approach that involves removing the invasive trophoblastic tissue while preserving the uterus has become a viable option for women who wish to maintain reproductive capacity. These techniques have revolutionized the management of GTD, offering better future prospects for patients (YANG et al., 2021).

In parallel to surgical approaches, the exploration of emerging technologies has positively impacted the treatment of GTD. External beam radiotherapy is an example of an approach that has been investigated to treat selected cases of persistent or metastatic disease. This technique involves the precise administration of radiation to the affected areas to destroy the abnormal trophoblast cells. Although still in the study phase, external beam radiotherapy shows promising disease control rates (LAAN et al., 2023).

Technological developments have also enabled the use of more advanced imaging methods in the diagnosis and treatment of GTD. Positron emission tomography (PET-CT), for example, allows more precise visualization of metastatic lesions and assessment of response to treatment. This technology is particularly useful in cases of metastatic disease, helping to determine the extent of dissemination and therapeutic planning (JONEBORG et al., 2021).

THERAPY FOCUSED ON FERTILITY PRESERVATION

Preservation of reproductive capacity in patients with GTD has become a fundamental consideration in therapeutic planning. Strategies that aim to maintain the fertility of these women during treatment have evolved significantly in recent years, allowing personalized approaches that take into consideration, both therapeutic efficacy and the preservation of reproductive quality of life (MANGILI et al., 2016).

One of the approaches to preserving fertility during GTD treatment is the careful selection of chemotherapeutic agents that are least

toxic to reproductive organs. Agents such as Methotrexate and Actinomycin-D, which have been shown to be effective in treating GTD, can be chosen to minimize damage to the ovaries and germ cells. This careful selection of chemotherapy agents has the potential to preserve ovarian function and egg reserve (MANGILI et al., 2016; WINTER, 2021).

In addition to the appropriate choice of chemotherapy agents, assisted reproductive techniques also play a fundamental role in preserving fertility in patients with GTD. Cryopreservation of eggs or embryos before chemotherapy or surgical treatment offers the possibility of future pregnancies after treatment is complete. These techniques allow patients to postpone pregnancy until they are disease-free and in better health (HASANZADEH et al., 2016).

Strategies to restore fertility after GTD treatment have also evolved with the advancement of assisted reproduction techniques. In vitro fertilization (IVF) is a common option for patients whose ovarian reserve has been compromised by treatment. IVF allows the fertilization of eggs in the laboratory and the transfer of healthy embryos to the uterus, increasing the chances of a successful pregnancy (VUKOVIĆ et al., 2022).

PSYCHOSOCIAL ASPECTS AND QUALITY OF LIFE

The diagnosis and treatment of GTD go beyond purely clinical aspects, deeply impacting the psychosocial sphere of patients. The moment of diagnosis, often unexpected and full of uncertainty, can trigger a series of emotional reactions ranging from anxiety and fear to depression and stress. Facing these challenges requires a multidisciplinary approach that considers not only the medical dimension, but also the emotional one (SOPER et al., 2021).

Assessing the psychosocial impact of DTG on patients has become a growing concern in clinical practice. Understanding the emotional implications of diagnosis and treatment is essential to providing the necessary support. The implementation of psychological support services and the creation of specific support groups for women with GTD have proven to be effective in promoting patients' psychological well-being (SOPER et al., 2021; BLOK et al., 2022).

A multidisciplinary approach is essential to meet the emotional and psychological needs of patients with GTD. In addition to health professionals, such as oncologists, obstetricians and nurses, psychologists and social workers play a crucial role in comprehensive care for these patients. Collaboration between different specialties guarantees a holistic approach that aims not only at clinical cure, but also at improving patients' quality of life (BLOK et al., 2022; FRANÇA et al., 2022).

Quality of life has become an increasingly relevant parameter in evaluating the success of GTD treatment. In addition to clinical remission, patients' ability to resume their daily activities, relationships and personal projects must also be considered. Assessing patients' quality of life throughout treatment and after completion is essential to monitor the impact of medical interventions and identify opportunities for improvement (LEENHARATTANARAK; LERTKHACHONSUK, 2014).

FUTURE PERSPECTIVES AND ONGOING RESEARCH

The DTG research landscape is constantly evolving, with an increasing focus on experimental therapies and innovative approaches to optimize treatment. The search for more effective therapeutic alternatives with fewer side effects has led to the exploration of new pharmacological agents and targeted therapies. Agents under development, such as

angiogenesis inhibitors and signaling pathway modulators, show promising prospects for the treatment of GTD (GHASEMALI et al., 2021; CHEN et al., 2022).

Ongoing clinical studies and trials play a crucial role in investigating innovative treatment strategies and improving current approaches. Rigorous evaluation of the efficacy and safety of these interventions is critical to inform clinical practice. Randomized controlled trials and prospective studies have evaluated different therapeutic regimens, including the combination of multiple chemotherapeutic agents and targeted therapies, aiming to improve outcomes and minimize risks, with the most used currently continuing to be the EMA/CO regimen, for cases of high risk, generally metastatic (ZHAO et al., 2017; CLARK; SLATER; SECKL, 2021).

Precision medicine has emerged as a promising approach in the management of GTD. The integration of genomic and molecular information allows the identification of specific mutations associated with the disease, directing treatment in a more personalized way. The identification of specific therapeutic targets and the selection of therapies based on patients' genetic characteristics have the potential to increase treatment efficacy and reduce adverse effects (NING et al., 2019; BUZA; HUI, 2021).

In-depth understanding of the molecular basis of DTG has driven the development of more effective targeted therapies. Inhibitors of signaling pathways, such as the use of epidermal growth factor receptor (EGFR) inhibitors, have demonstrated promising results in preclinical models. These targeted approaches aim to interrupt the processes of abnormal trophoblast proliferation and invasion, paving the way for a new generation of more effective treatments with lower toxicity (CAO et al., 2022).

CONCLUSION

GTD represents a multifaceted clinical challenge that involves not only the medical dimension, but also the emotional, social and psychological aspects of patients. Through a detailed analysis of the various topics covered in this review article, the complexity of this condition and the importance of innovative approaches to diagnosis and therapy become evident.

The evolution of diagnostic methods, including the application of serum biomarkers, the use of high-resolution ultrasound and the incorporation of advanced imaging techniques, such as magnetic resonance imaging, has allowed earlier detection of GTD. These advances are crucial for the success of treatment, since early diagnosis is associated with more favorable prognoses and the choice of less invasive therapies.

Risk stratification has emerged as a fundamental element in the DTG approach. The careful assessment of clinical, laboratory and imaging factors allows us to identify subgroups of patients with different probabilities of progressing to persistent trophoblastic neoplasia. This personalized approach has the potential to target treatment more effectively, optimizing therapeutic strategies and improving overall outcomes.

In the therapeutic sphere, we have observed a movement towards more targeted and less invasive approaches. Research and development of targeted therapies, as well as the exploration of minimally invasive techniques and emerging technologies, are redefining available treatment options. Furthermore, fertility preservation and consideration of patients' psychosocial aspects and quality of life are becoming increasingly central to clinical decisions.

Integrating these advances into a multidisciplinary approach and continuing research are crucial to addressing the complex

challenges presented by DTG. As new therapies emerge and understanding of the molecular basis of the disease advances, there is renewed hope for better prognoses and a better quality of life for patients affected by this condition.

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