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Review Article

Clinical complications related to the benign form of gestational trophoblastic disease

Complicações clínicas relacionadas à forma benigna da doença trofoblástica gestacional

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ABSTRACT

Gestational Trophoblastic Disease (GTS) includes benign diseases such as hydatiform mole or malignant diseases such as coriocarcinoma, trophoblastic tumor of the placental site, epithelioid trophoblastic tumor and invasive mole. The hydatiform mole (HM) is classified according to morphology, genetics, and histopathology into complete hydatiform mole (CHM) and partial hydatidiform mole (MHP). The following study aims to know the main clinical complications associated with GTS and to report the main diagnostic methods, besides the therapeutic approach after molar pregnancy. It is an integrative literature review study in Portuguese and English, in the following databases: Medline, Pubmed, SciELO, Lilacs, Bireme and Clinicalkey. In particular, MHC has diploid character, resulting from the duplication of haploid genetic material from a single sperm, while MHP is triploid and occurs after fertilization of a normal egg by two sperm or by a diploid sperm. The HM is defined as a pregnancy outside the normal pattern due to the varying degrees of trophoblast proliferation and edema of the villi associated with absence or abnormalities in the embryo or fetus. There are a number of serious clinical complications which affect up to 25% of patients with advanced stage hydatidiform mole (HM), including hyperthyroidism, ovarian cysts, bleeding, invasive mole, cardiopulmonary complications and pre-eclampsia. It is essential to alert the importance of beta-hCG measurement to obtain an early diagnosis and so it should be performed on all pregnant women with vaginal bleeding in order to identify the normal development of pregnancy or intercurrences requiring intervention.

RESUMO

A Doença Trofoblástica Gestacional (DTG) inclui doenças benignas como mola hidatiforme ou malignas como coriocarcinoma, tumor trofoblástico do sítio placentário, tumor trofoblástico epitelióide e mola invasora. A mola hidatiforme (MH) é classificada, segundo a morfologia, genética e histopatologia, em mola hidatiforme completa (MHC) e mola hidatiforme parcial (MHP). O seguinte estudo tem como objetivos conhecer as principais complicações clínicas associadas à DTG e relatar os principais métodos diagnósticos, além da abordagem terapêutica após gravidez molar. Trata-se de um estudo de revisão integrativa de literatura nas línguas portuguesa e inglesa, nas seguintes bases de dados: Medline, Pubmed, SciELO, Lilacs, Bireme e Clinicalkey.Em particular, a MHC tem caráter diploide, resultante da

duplicação do material genético haploide de um único espermatozóide, enquanto, o MHP é triploide e ocorre após a fertilização de um óvulo normal por dois espermatozoides ou por um espermatozoide diploide. A MH é conceituada como uma gravidez fora do padrão de normalidade devido aos variados graus de proliferação do trofoblasto e edema das vilosidades associado à ausência ou anormalidades no embrião ou feto. Faz-se presente uma série de complicações clínicas graves que chegam a acometer 25% das pacientes com MH em fase avançada, fazendo parte desta: o hipertireoidismo, cistos ovarianos, hemorragia, mola invasora, complicações cardiopulmonares e pré-eclâmpsia. É fundamental alertar a importância da dosagem do beta-hCG para se obter um diagnóstico precoce e assim deve ser realizado em todas as gestantes com sangramento vaginal, a fim de identificar o desenvolvimento normal da gravidez ou intercorrências que necessitem de intervenção.

INTRODUCTION

Gestational Trophoblastic Disease encompasses diseases related to the proliferation of placental trophoblastic tissue, which can be benign, such as hydatidiform mole (HM), or malignant, represented by choriocarcinoma, trophoblastic tumor of the placental site, epithelioid trophoblastic tumor, and invasive mole. Benign molar pregnancy is subdivided according to morphological, genetic, and histopathological characteristics into complete hydatidiform mole and partial hydatidiform mole[1].

Complete hydatidiform mole (CHM) is characterized by the absence of fetal tissue, intense proliferation of trophoblastic tissue, and hydropic degeneration, as well as morphologically consisting of large vesicles with thin walls connected by villous trunks resulting from a fertilization error in which the egg without a nucleus is fertilized by a normal sperm. It has a higher incidence compared to partial hydatidiform mole. Additionally, CHM presents a higher risk of progression to malignant diseases, especially choriocarcinoma[2].

Partial hydatidiform mole (PHM) is characterized by the presence of fetal tissue and can present blood vessels with nucleated red blood cells. The proliferation of trophoblastic tissue may involve only the syncytiotrophoblast, and cellular atypias are discreet. Macroscopically, the vesicles are smaller and less hydropic. The karyotype is triploid and occurs due to errors such as dispermy, fertilization of a haploid egg by a diploid sperm, or fertilization of a diploid egg by a haploid sperm[3]. Patients with HM usually present with an enlarged uterus for the gestational age and have vaginal bleeding in the first trimester of pregnancy as the main clinical manifestation, which can also present early pre-eclampsia, hyperemesis, and the persistence of ovarian theca-lutein cysts[4].

Currently, the complications of this disease are infrequent since diagnosis through ultrasonography and quantitative measurement of human chorionic gonadotropin (hCG) is early, identifying asymptomatic patients[3]. hCG is a physiological hormonal marker of pregnancy. However, in Gestational Trophoblastic Disease, serum levels of this hormone are excessively elevated[4].

The treatment of HM consists of intrauterine molar evacuation, with vacuum aspiration being the recommended technique, but the most appropriate method for each patient should be chosen. The collected material should be sent for histopathological examination, considered the gold standard for diagnosis, as it can identify the morphological characteristics of the moles and thus define the trophoblastic neoplasia[4].

This work aims to identify the main clinical complications related to the benign form of Gestational Trophoblastic Disease, report the main diagnostic methods, and the therapeutic approach to molar pregnancy.

MATERIAL AND METHODS

This study is a literature review on the be-

nign form of Gestational Trophoblastic Disease, as well as treatments for associated comorbidities, diagnostic methods, management, and follow-up after molar pregnancy. Research was conducted using data from MEDLINE/PUBMED and SciELO. The keywords used were: HM, molar pregnancy, gestational trophoblastic disease, complications, bleeding, hyperthyroidism, pre-eclampsia, diagnosis, and treatment. For the review, studies were selected with preference given to the most recent on each subject addressed, including only the works cited in the mentioned research databases. Thus, inclusion criteria were: articles published in full in Portuguese or English present in these databases. Exclusion criteria were: articles that deviated from the study objective or were based on animal studies, theses, or opinion articles.

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RESULTS AND DISCUSSION

All forms of Gestational Trophoblastic Disease derive from the placenta, more specifically from the villous and extravillous trophoblast[5]. The trophoblast is subdivided into cytotrophoblast, syncytiotrophoblast, and intermediate trophoblast, and GTD can occur in any of the three due to cell proliferation[6].

The HM can be defined as an abnormal pregnancy due to varying degrees of trophoblast (syncytiotrophoblast and cytotrophoblast) proliferation and villous edema associated with the absence or abnormalities of the embryo or fetus[6].

Most CHM are diploid and result from the duplication of haploid genetic material from a single sperm, while PHM are mostly triploid and occur after the fertilization of a normal egg by two sperms or a diploid sperm. After a case of CHM, the chance of persistent trophoblastic disease (trophoblastic neoplasia – invasive mole or choriocarcinoma) is around 20%, while for PHM it is 5%, demonstrating the importance of differentiating these two entities[5,7].

Macroscopic findings of CHM include the absence of fetal tissue and ovular membranes, as well as translucent vesicles with clear fluid due to hydropic degeneration described as “grape-like clusters” intermixed with clots. PHM, on the other hand, presents the conceptus or ovular membranes and smaller vesicles mixed with areas of normal villi[4].

Histological findings of CHM include edematous and avascular villi, as well as conferential trophoblastic hyperplasia. However, in early molar pregnancies, these findings may not be present, and CHM is identified through the visualization of bulbous terminal villi, hypercellular myxoid stroma, villi with focal atypias, and extravillous trophoblast hyperplasia[7].

The presence of fetal tissue with nucleated red blood cells or fetal membranes indicates the diagnosis of PHM. However, this differentiation is not simple. PHM has fewer histological characteristics than CHM. Additionally, in some situations, complete moles can present fetal tissue[7].

Clinical data pointing to the diagnosis of HM are primarily vaginal bleeding of varying intensity and a uterine volume incompatible with gestational age[8]. Bleeding is often painless and occurs between the 4th and 16th week of amenorrhea. Between hemorrhagic episodes, a fetid, serous-clear secretion due to the liquefaction of intrauterine clots may be observed[9].

In more advanced molar pregnancies, when uterine content is voluminous and due to endocrine changes, persistent and difficult-to-control nausea and vomiting (hyperemesis gravidarum) are frequently reported, which can lead to weight loss and dehydration. Increased uterine volume is a risk factor for developing Gestational Trophoblastic Neoplasia (GTN) and also determines a higher risk of massive trophoblastic embolization to the lungs[9].

A small percentage of patients may present with hyperthyroidism, which may or may not require treatment until beta-hCG levels normalize. More severe conditions such as pre-eclampsia occur in up to a quarter of patients, while the elimination of hydropic vesicles and clots through the vagina may not be observed, as early diagnosis can be made through ultrasound, instituting appropriate treatment[9].

The hCG is a glycopeptide formed by two alpha and beta subunits. The alpha subunit of hCG is homologous to the alpha subunit of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH), which explains some clinical manifestations of GTD. Quantitative beta-hCG measurement is necessary when GTD is suspected, as levels of this hormone are higher than expected for gestational age in a normal pregnancy, making it an important biological marker[9].

All women with suspected GTD should undergo a pelvic ultrasound with Doppler to confirm the absence of pregnancy, determine uterine volume, disease spread, and its vascularization[5]. Approximately 90% of molar pregnancy diagnoses are made through ultrasonography. The CHM is more easily identified by US, allowing visualization of irregular hypoanechoic images centrally or marginating the myometrium in the absence of embryo-fetus, an enlarged uterus for gestational age, and ovarian cysts (simple cysts usually up to 8 cm in diameter and bilateral). Regarding PHM, a fetus with malformations due to triploidy can be observed, but most commonly the conceptus evolves to death, and placental degeneration and embryonic resorption occur, so PHM can be confused with hydropic abortion. Therefore, only 30% of PHM are diagnosed through US[9].

After diagnosis, laboratory tests should be performed before molar evacuation or intrauterine content, including complete blood count, blood typing and Rh factor, quantitative plasma beta-hCG detection, thyroid function evaluation (TSH and free T4) when uterine size is greater than 16 weeks gestational age and/or serum beta-hCG value above 100,000 mIU/mL, syphilis and anti-HIV serology, and chest X-ray. According to clinical complications, other tests may be requested[9].

Dilation and suction curettage guided by ultrasound is the method of choice for the treatment of HM in cases where fertility preservation is desired. Hysterectomy (HTA) should be considered in women with completed families and over 40 years of age, thus reducing the occurrence of post-molar trophoblastic neoplasia[8,9].

Due to the high rates of false-positive or false-negative ultrasound (USG), anatomopathological study is necessary[5]. Thus, early diagnosis and uterine curettage are the only ways to prevent complications related to gestational trophoblastic disease[9].

Moreover, all patients need to be followed up due to the risk of developing gestational trophoblastic neoplasia (GTN). Monitoring beta-hCG levels in cases of PHM should be performed with an additional measurement after normalization, while in cases of CHM, monthly measurements are recommended for six months after normalization[8].

Currently, Gestational Trophoblastic Disease (GTD) diagnosis is increasingly early, often before the onset of symptoms, mainly due to the use of ultrasonography and serum beta-hCG measurement[9]. However, it is not uncommon in developing countries, and delayed diagnosis contributes to the occurrence of complications that endanger the lives of patients.

Severe clinical complications affect approximately 25% of patients with advanced HM, being rare before 12 weeks of gestation[3]. Among them, we can highlight: hyperthyroidism, ovarian cysts, bleeding, invasive mole, cardiopulmonary complications, and pre-eclampsia.

Hyperthyroidism

Hyperthyroidism occurs when there is suppression of Thyroid Stimulating Hormone (TSH) and elevated levels of triiodothyronine and thyroxine (T3 and T4, respectively), being more frequent in GTD than in normal pregnancies[10].

The hCG is about four thousand times less potent than TSH, so for thyroid gland stimulation to occur, hCG levels must be very high. It is known that most patients who develop hyperthyroidism have serum hCG levels greater than 100,000 mIU/L[10].

Hyperthyroidism is present in 5% of molar pregnancies due to molecular mimicry between the alpha subunit of hCG and TSH[11]. Patients may present with subclinical hyperthyroidism to thyrotoxic crisis, a severe complication with a risk of life and mortality of 10-30%[12], characterized by tachycardia, hypertension, sweating, hyperre-

flexia, heat intolerance, muscle weakness, weight loss, irritability, myopathy, fine tremors, fever, and mental state alterations[11].

The approach in these cases is to reduce the synthesis, release, and peripheral effects of thyroid hormones. Additionally, propylthiouracil (PTU) and methimazole (MMI) can be used as they inhibit thyroid iodine organification, blocking hormone production associated with propranolol for peripheral symptom control and iodine. In more severe cases, plasmapheresis can be chosen. After clinical control, uterine cavity dilation and evacuation should be performed[11],[13].

Theca-Lutein Cysts

Ovarian cystosis can occur in 20% of molar pregnancies due to hyperstimulation by high levels of hCG, which acts on the ovarian theca as a LH analogue. The cysts are usually bilateral, multiloculated, and tend to regress after hCG negativation[9]. Theca-lutein cysts represent a benign condition, occurring in up to 25% of CHM cases and 10% of choriocarcinoma cases, with a much lower incidence in PHM cases[9],[11].

In most cases, as it is a benign situation, the approach is expectant. However, 3% of patients with exaggeratedly voluminous theca-lutein cysts may develop complications such as adnexal torsion or hemorrhagic rupture, both presenting with acute abdomen, requiring surgical intervention by laparotomy or laparoscopy[11].

Preeclampsia, Eclampsia, and HELLP Syndrome

Currently, cases of preeclampsia, eclampsia, and HELLP syndrome associated with HM are rare due to the detection of the mole in the first trimester through ultrasound when it is still asymptomatic[14].

The clinical picture is usually the same as in women with non-molar pregnancies: hypertension, proteinuria, pulmonary edema, and anasarca[11]. However, symptoms such as severe headache, generalized tonic-clonic seizure, vaginal bleeding, visual disturbances, confusion, and hyperreflexia have been described[14].

Preeclampsia associated with molar pregnancy occurs due to intense trophoblastic hyperplasia and excessive serum beta-hCG concentration. Therefore, the clinical presentation involves very voluminous uteri[11,14].

Induction of labor with prostaglandins in pregnancies with hypertensive conditions has shown good maternal outcome results[15]. Magnesium sulfate should always be started before the surgical procedure at a dose of 4g (loading dose) followed by 1–2 g per hour intravenously. The medication aims to improve maternal prognosis and prevent possible seizures[11]. Clinical and supportive treatment is done with antihypertensives such as hydralazine and nifedipine. In cases unresponsive to these medications, diazoxide and sodium nitroprusside can be used under intensive monitoring[11].

To perform uterine cavity evacuation, the technique of choice is vacuum aspiration due to the shorter surgery time and lower risk of complications, including uterine perforation[11].

Patients must be followed up after the procedure due to the risk of progressing to GTN in those who presented with molar pregnancy associated with preeclampsia. This follow-up is done through serial beta-hCG measurements. Additionally, contraception should be advised for one year[11],[14].

Cardiopulmonary Manifestations

Regarding uterine cavity evacuation, it is known that about 2-11% of women develop cardiopulmonary complications. The clinical picture is varied, ranging from tachycardia, tachypnea, hypoxemia, to even acute respiratory distress syndrome (ARDS) with pulmonary hypertension and hypoxemia unresponsive to standard treatment, with rapid progression to death[17].

Another pulmonary complication that may occur is pulmonary arteriovenous malformations (PAVMs). Most are congenital, but about 20% of cases have been related to chronic liver disease, schistosomiasis, mitral valve stenosis, previous cardiac surgery, actinomycosis, Fanconi syndrome, tuberculosis, or tumors[18].

When related to tumors, PAVMs may arise in individuals with neoplasms susceptible to treatment and cure with chemotherapy after a long period of drug administration. It is not precisely known what causes the development of PAVMs, but it is suspected that they form near metastatic trophoblastic tumors, as they are highly vascularized. While metastatic tumors are controlled and sometimes cured with chemotherapy, the same does not happen with PAVMs[18].

Cases of peripartum cardiomyopathy, a rare complication of HM cases, have also been reported. Little is known about this pathology, but it is a principle of heart failure that arises during pregnancy or the postpartum period in the absence of previous heart disease. The mechanism contributing to the development of cardiomyopathy is unknown, but there are hypotheses pointing to the release of toxins by the large, underperfused placenta that ends up damaging the heart muscle[19].

Treatment consists of administering anticoagulants and diuretics. Complete recovery occurs in about half of the patients who develop peripartum cardiomyopathy, but some may progress to progressive heart disease. In these cases, heart transplantation may be necessary[20].

Pulmonary symptoms related to uterine cavity evacuation usually occur immediately after the procedure but can occur hours or even days later. In cases where symptoms are mild, with the presence of cough, tachypnea, and hypoxemia, the use of a mask with O2 supplementation is performed. However, in more severe cases, with ARDS with severe and treatment-resistant hypoxemia due to significant intrapulmonary shunt, ventilatory support becomes necessary, as well as immediate uterine cavity evacuation. Additionally, some extrapulmonary symptoms may be present, such as disseminated intravascular coagulation[11,17].

Regarding PAVMs, most cases are asymptomatic, but they can also present with dyspnea and complications such as hemoptysis, hemothorax, bacterial endocarditis, brain abscesses, and embolism. Treatment for this pathology can be performed through surgery or embolization, and the choice of treatment is at the discretion of the responsible physician. A complication of embolization treatment is the recurrence of PAVMs[18].

Pulmonary tissue embolization is performed by trophoblastic tissue when chorionic villi enter the myometrium and, through uterine veins, reach the inferior vena cava, heart, and consequently the lungs. There are theories that pre-induction of uterine cavity evacuation would increase existing embolization. The more extensive and intense the embolization, the more exuberant the symptoms presented by the patient. However, this characteristic alone should not be the only one considered in suspected ARDS cases due to uterine cavity evacuation in molar pregnancies, but also preexisting hemodynamic alterations due to anemia, preeclampsia, hyperhydration, and hyperthyroidism associated with very voluminous uteri. Additionally, identifying patients with pulmonary complications in HMs is essential, as these women are at risk of developing persistent trophoblastic disease, and the introduction of chemotherapy should be early[11,17].

Immediate uterine cavity evacuation reduces the probability of patients developing pulmonary disorders. Thus, delaying molar uterine evacuation can lead to patient death. The physician responsible for the procedure should be aware of the amount of fluid to be given to the patient, as excess can overload the left ventricle and cause severe pulmonary complications[11].

Gestational Trophoblastic Disease is a term that includes different diseases that can be malignant, such as choriocarcinoma, trophoblastic tumor of the placental site, epithelioid trophoblastic tumor, and invasive mole, or benign, such as HM. This is an infrequent pregnancy complication, mainly represented by vaginal bleeding but has the potential to develop comorbidities requiring systemic treatment. Two types of HM are known: complete and partial, with the first more frequently associated with persistent forms of the disease. A minority present associated hyperthyroidism, and about 2-11% of pregnant women have cardiopulmonary manifestations associated with

GTD. Severe complications such as preeclampsia, eclampsia, and HELLP syndrome can occur in over 25% of patients with advanced molar pregnancy but are rare before 10-12 weeks of gestation. Ovarian cystosis may be present in 20% of molar pregnancies due to hCG hyperstimulation, which acts on the ovarian theca as a LH analogue. Theca-lutein cysts occur in up to 25% of CHM cases and 10% of choriocarcinoma cases and are rare in PHM cases. Ultrasonography is essential for early diagnosis and should be performed on all pregnant women with vaginal bleeding to identify normal pregnancy development or intercurrences requiring intervention. The main pillars of treatment for patients with HM are early diagnosis, immediate uterine cavity evacuation (preferably by vacuum aspiration), stabilization of clinical complications, and regular follow-up through weekly serum gonadotropin measurements and effective hormonal contraceptive method during follow-up. Currently, it is possible to make an early diagnosis of Gestational Trophoblastic Disease, as treatment delays and the appearance of complications endanger women's health with GTD.

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