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Updates in the Diagnosis of Gestational Trophoblast Disease

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Abstract

GTD (Gestational Trophoblastic Disease) is a pathology that encompasses benign and malignant clinical forms, affects women of childbearing age, has a variable incidence and is more frequent in developing or underdeveloped countries, colliding with the economic barrier. The frequent absence of clear protocols and guidelines for the correct diagnosis of the pathology results in inadequate classification, imprecise treatment and failed post-therapeutic observation, increasing the risk of relapses, morbidity and mortality. The present study aims to point out updated national and international practice protocols of diagnosis of GTD, through an integrative review. Seven articles were selected and it was observed that the main international reference centers are agreed with the management suggested by the IFGO (International Federation of Gynecology and Obstetrics), being the conduct in the Hydatidiform Mole (HM): evacuation by suction and curettage under ultrasound guidance, followed by hCG monitoring every 1 - 2 weeks until normalized (usually one month for Partial Hydatidiform Mole six months for Complete Hydatidiform Mole and one year for Gestational Trophoblastic Neoplasia). Unfortunately, regarding the diagnosis of MH, the guidelines of some countries show the absence or difficulty of access to the karyotype test and ploid p57 or pelvic ultrasound accompanying the uterine curettage, contrary to what is proposed by the IFGO guideline. Establishing and complying with

consistent guidelines can improve patient care, with early diagnosis of the pathology and its complications, reducing the rate of recurrence, morbidity and mortality, especially in less developed countries.

Keywords

Diagnosis, Gestational Trophoblastic Disease, Updates

1. Introduction

GTD is characterized as a group of heterogeneous diseases defined as pregnancy-related placental proliferative anomalies [1]. They are divided into benign forms of the disease represented by HM, which constitute two subtypes: CHM (Complete Hydatidiform Mole) and PMH (Partial Hydatidiform Mole) or MHI (Incomplete Hydatidiform Mole) and by the malignant forms, represented by the set of Gestational Trophoblastic Neoplasia (GTN) and subdivided into type histopathological, such as Invasive Mole (IM), CCA (Choriocarcinoma), ETT (Epithelial Trophoblastic Tumor) and PSTT (Placental Site Trophoblastic Tumor) [2] (**Figure 1**).

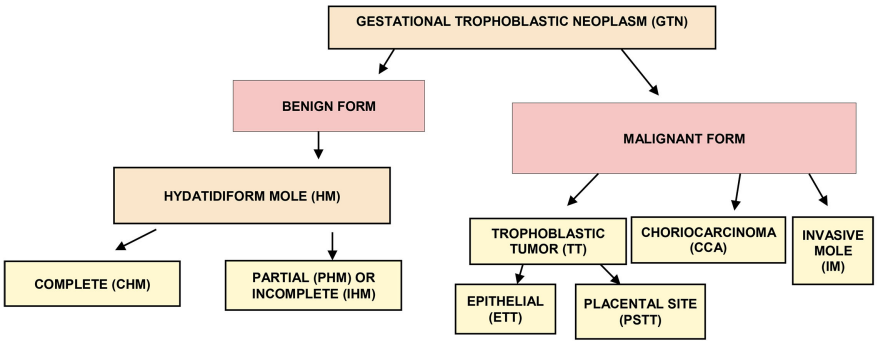

Figure 1. Flowchart of histopathological forms and subtypes of GTD. Source: Authors (2022).

The indication that worldwide incidence of GTD is 1:1000 pregnancies, with a threefold increase in countries Asians and those in Latin America, when compared to Europe and North America [1]. In Brazil, it is estimated that the disease occurs in about 1:200 - 400 pregnancies, that is, a number almost 10 times higher than in Europe and North America [3]. GTD has the following risk factors: reproductive extremes, previous history of GTD (repeat in 1% to 2% of cases) and poor nutritional status of the pregnant woman [1].

There are several signs and symptoms that have been, over time, related to molar pregnancy, among them: hyperemesis gravidarum, preeclampsia early onset, increased uterine size, theca lutein cyst, anemia, hyperthyroidism and respiratory distress. The recurrence of these last events is less and less frequent due to routine ultrasonography, first line, which leads to early diagnosis of molar pregnancy. The correlation of clinical history, physical examination, transabdo-

minal or transvaginal ultrasonography with Doppler flowmetry study, as well as serum levels of beta hCG, become essential for a correct diagnosis [4].

Pelvic Doppler ultrasound should be performed in all women with suspected GTD, it is necessary to confirm the absence of pregnancy, measurement of uterine size and volume, if the disease is disseminated and its vascularization [4]. The most found commonly found in the uterine cavity of CHM are multiple cystic images or vesicular, with heterogeneous and hyperechogenic content, also known as "snowflake storm", "bunch of grapes" or "granular" signs, which vary from 1 to 30 mm in size and are seen on first trimester transvaginal US [5] (**Figure 2**).

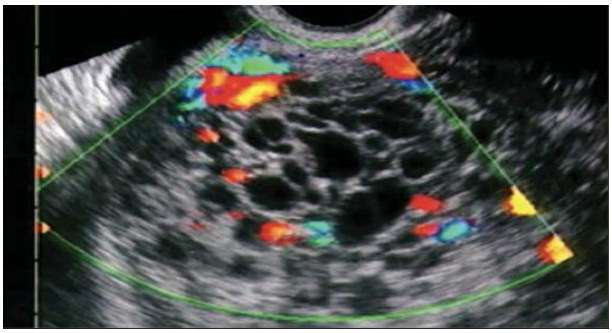

Figure 2. Transvaginal ultrasound in a patient at the 14th week of gestation, suggesting MHC. Source: Lima *et al.* (2016).

In partial hydatidiform mole, an embryo and decidual area are filled by anechoic images [5] [6]. Bellow, in **Figure 3**, an embryo and decidual area filled with anechoic images, which suggests MHP, being verified fetal death on the 14th week of gestation, indicating induction of molar abortion.

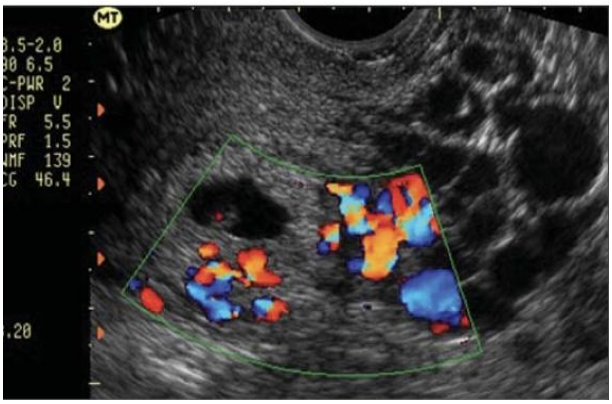

Figure 3. Transvaginal ultrasound in a patient with MH. Source: Lima *et al.* (2016).

It is important to highlight that the lung is the organ most affected by metastasis and CCA, the most common subtype. The initial exam of choice for evaluation of lung metastasis in GTN is a chest X-ray, computerized Tomography is an exam of fundamental importance for the investigation of metastatic in GTN, less in the vagina and brain [5].

The beta hCG fragment is present in all forms of presentation of GTD, making its dosage important in the diagnostic hypothesis, when it presents levels higher than expected for the age gestational period of a normal pregnancy [3]. After uterine evacuation, if there is any doubt about the persistence of GTD or its malignant transformation, the dosage of beta hCG will be able to detect if there is persistent trophoblastic tissue. So, the hCG dosage is a necessary test for monitoring the DTG patient [3] [7].

In post molar patients with spontaneous remission of HM, quantitative beta-hCG dosage is requested weekly or fortnightly, with normalization after three consecutive dosages and monthly evaluation for six months and proposed the use of oral hormonal contraceptive, soon after the procedure [8].

The post molar with evolution to GTN is diagnosed by the beta-hCG dosage, either by stationary levels (plateau curve), by four values or more than beta-hCG, for at least three consecutive weeks (1st, 7th, 14th and 21st day) or in elevation (ascending curve), for at least two consecutive weeks (1st, 7th and 14th day) (**Figure 4**).

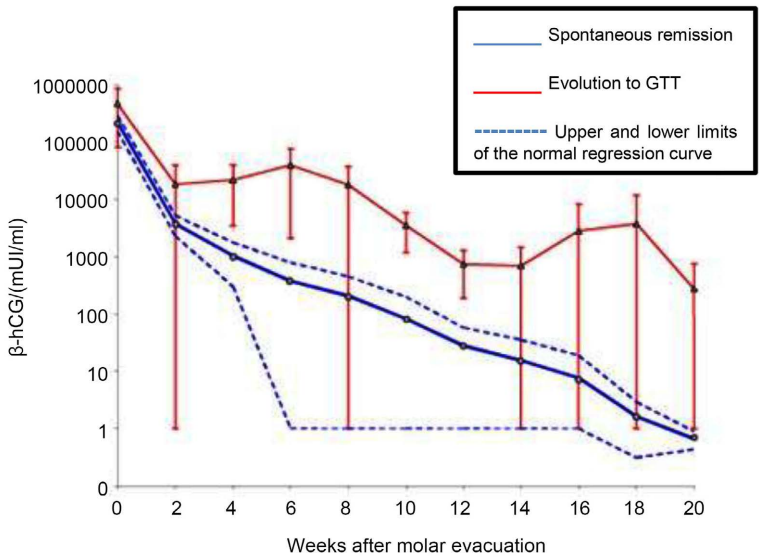

Figure 4. Beta hCG regression curve in patients with spontaneous remission and those who developed GTT. Source: Maestá *et al.* (2000).

After the diagnosis of GTN is performed the IFGO staging and the risk score, to develop the appropriate therapeutic approach for each stage [8]. After treatment of GTN, monthly monitoring of serum hCG levels is required for at least 12 months. In most patients, there is a progressive decrease in beta hCG values and no additional treatment is necessary [8].

The primary prevention of GTD is still not getting pregnant. Patients who have spontaneous remission of HM have a 98% to 99% chance of developing a subsequent normal pregnancy. There is a 1% to 2% risk of new HM, which, although small, is around 4 to 50 times higher compared to the general population [7] [9].

The karyotype and ploidy p 57 is used in several countries, as the main way to

refine the diagnosis of early molar pregnancies to differentiate between PHM and CHM: PMH is typically triploid and p57 is absent in CMH [10] [11].

After diagnostic confirmation and observation of hemodynamic stability of the patient, molar evacuation is performed. Evacuation by suction and curettage is the method of choice, for patients who wish to preserve their fertility, regardless of uterine size [12].

In histopathology the MHC presents with vesicles in the entire placenta and absence of fetal tissue and an ovular membrane. The vesicles, interspersed with clots blood cells, are classically described as "grape clusters" due to the appearance translucent and filled with clear fluid, have a diameter of 1 to 1.5 mm at the first trimester and from 1.5 to 3 cm in the second trimester [8]. Otherwise, MHP is characterized by the focal presence of vesicles in the placenta, associated with the presence of conceptus and/or ovular membranes, the vesicles being smaller (5 mm in the first trimester to 2 cm in the second trimester) and interspersed per area of normal villi. The fetus is usually small and presents multiple characteristic malformations of triploid, rarely exceeding the second trimester alive [8].

The initial exam of choice for the assessment of lung metastasis in GTN is the chest X-ray. There are three ways classic presentation of the image in the disease, they are: typical, alveolar and embolic. The typical image of the findings is of dense nodules with well-defined borders, multiple and bilateral [9].

CT is an examination of fundamental importance for the investigation of sites metastatic in NTG, less in the vagina and brain [9]. In high-risk patients with lung or vaginal metastases, it is recommended with abdominal CT and, if there is hepatic involvement, these lesions appear as multiple, heterogeneous, hypointense and with intense avidity to contrast in the arterial phase [4].

Currently, studies with PET-CT have been shown to be quite efficient in cases of NTG, from the identification of the extent of the tumor and metastases, as in the evaluation of therapeutic response in high-risk tumors. Although the indication is unusual for diagnosis, there is value in cancer resistant to chemotherapy and recurrence of the neoplasm [9].

A RM MRI is not part of the NTG evaluation routine, being chosen only in doubtful or complicated cases, such as suspected TTSP, in advanced disease and recurring. Having the ability to assess the location vasculature and extent of the tumor with greater accuracy; is an excellent choice to identify invasion parametrial and vaginal, compared to ultrasonography. In relation to imaging findings are nonspecific and there may be difficulty in differentiating among retained products of conception or an ectopic pregnancy with NTG [4].

The approach of this study aims to point out consistent national and international practice protocols, which result in an early and accurate diagnosis, consequently, a more effective management of GTD, generating a decrease in the rate of recurrence, morbidity, and mortality of affected patients.

2. Methods

An integrative review was carried out, from August 25th to October 29th, 2022,

through searches in the following database: PUBMED, MEDLINE and LILACS; using the descriptors: "Diagnosis", "Gestational Trophoblastic Disease", and "Updates". From this search, 52 articles were found that were submitted to the inclusion criteria: articles in Portuguese and English published in the last 5 years (2017 to 2022).

The exclusion criteria were articles with research not correlated to human beings, duplicate articles, unavailable in Portuguese or English, available only in abstract form, articles that did not directly address the studied proposal or did not meet the other inclusion criteria. After reading the titles and later the abstracts, 17 articles were considered by the selection criteria, of these 8 articles were not accessible for full reading and another 2 were excluded due to inadequacy to the theme, ending the total of 5 articles and 2 that contemplate national guidelines. The results were presented in a descriptive way, divided into thematic categories addressing the various national and international guidelines (Figure 5).

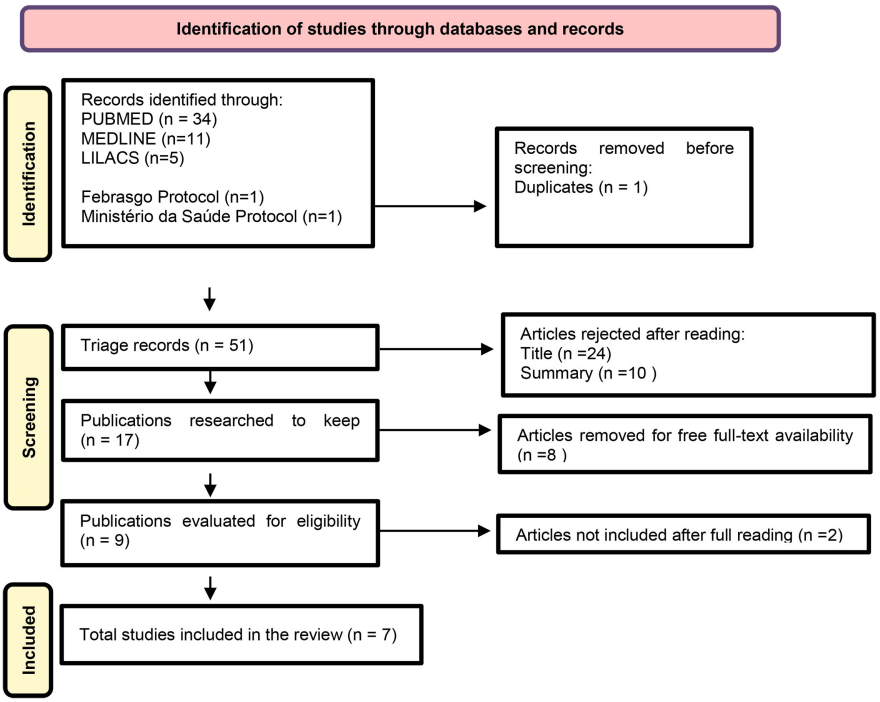

Figure 5. Flowchart representing the methodology used for the study. Source: Authors (2022).

3. Results

3.1. National (Brazil)

3.1.1. Ministry of Health

To fill a gap in the SUS (Sistema Único de Saúde), since there were no guidelines for GTD, the Brazilian Ministry of Health launched the Care Line with this theme, which was published recently, in 2022 [9].

According to the Ministry of Health molar emptying occurs by vacuum aspiration, ultrasound guidance is more indicated in cases of uterus >20 cm, retro-

verted uterus or Mullerian anomalies [9]. A week later, the patient should continue the post-molar follow-up, either in an outpatient basis or in a referral center, the risk of malignancy should be emphasized to the patient and, therefore, when recognized at an early stage, possibly, will have a better prognosis [9]. For the follow-up of molar pregnancy after dissection, the tumor marker hCG is used, measured in a week or fifteen days, after three normal weekly values, it is in spontaneous remission, in cases of PHM, the follow-up remains for 1 month and CHM for 6 months. Consecutively, however when presenting elevated hCG or in plateau, they represent evolution to NTG (**Figure 6**) [9].

1. When the hCG plateau lasts for four measurements, over a period of three weeks or more, on days 1,7,14,21;
2. When there is an increase in hCG for three consecutive weekly measurements, over a period of 2 weeks or more, on days 1,7,14;
3. If there is a previous diagnosis of choriocarcinoma;
4. When the hCG level remains elevated for 6 months or more.

Figure 6. Follow-up scheme after molar emptying. Source: IFGO (2002).

In cases of GTN after a non-molar pregnancy, vaginal bleeding abnormal and at least one pregnancy in a lifetime, is enough to star investigation, requesting hCG to confirm the diagnosis. The approach NTG therapy dependent on FIGO staging, in low-risk cases it is recommended single-agent chemotherapy and hysterectomy if hepatic patient age > 40 years, with complete offspring, or if there is non-adherence to follow up and proposed treatment, high-risk and ultra-high-risk should be treated with multidrug therapy [9].

MHP is a pregnancy that progresses with placental thickening and the conceptus malformed. Its sonographic presentation depends on the gestational age of the diagnosis and have the most suggestive ultrasonographic findings of this pathology: focal cystic changes in the placenta, increased ratio of diameter transverse and anteroposterior and changes in the shape of the gestational sac. In addition, other MHP-related findings would be fetal growth restriction and multiple malformations associated with focally hydropic placenta. In most cases, ultrasonography does not lead to diagnostic suspicion, and the diagnosis conclusive performed by the anatomopathological examination [9].

3.1.2. Febrasgo (Brazilian Federation of Gynecology and Obstetrics) Protocol

The Febrasgo protocol, described by Braga et al. (2019b) resembles everything the recent guideline from de Ministry of Health regarding the management of GTD [6].

3.2. International

3.2.1. Title: SEOM Clinical Guidelines in Gestational Trophoblastic Disease Authors: Santaballa, A. *et al.* Year of Publication: 2018. Referenced: Clinical & Translation Oncology

In the SEOM guidelines, the clinical presentation of HM consists of symptoms

and signs associated with molar pregnancy, along with the routine use of USG in early pregnancy, promotes early diagnosis of molar pregnancy, but false-positive and false-negative results are high with this imaging method, and histological examination is essential to close the diagnosis [4]. In addition, a quantitative hCG should be evaluated in all women diagnosed with a molar pregnancy and in any woman of childbearing age who has abnormal bleeding or unexplained metastatic disease; therefore, an elevated hCG is often considered the first possible evidence of GTN [3].

Pelvic Doppler ultrasonography should be performed in all women with suspected GTD. Therefore, it is necessary to confirm the absence of pregnancy, measurement of uterine size and volume, whether the disease is disseminated and its vascularization [3]. A blood test should also be performed to assess kidney and liver function, peripheral blood counts, and baseline serum hCG levels. All patients with suspected GTD should undergo an initial chest x-ray, if this suggests pulmonary metastasis, a CT scan should be request. Brain MRI should be obtained if a patient has metastatic lung disease [3].

3.2.2. Title: Diagnosis and Management of Gestational Trophoblastic Disease: A Comparative Review of National and International Guidelines. Authors: Tsakiridis, I. *et al.* Year of Publication: 2020. Referenced: Obstetrical & Gynecological Survey

Sonographic findings that are consistent with a complete mole include detection of a heterogeneous mass with a "blizzard" or cystic appearance, absence of fetal parts, bilateral ovarian cysts, and a deformed gestational sac. In addition, serum hCG dosage is recommended, if it is at high levels, it is suggestive of molar pregnancy [10]. The karyotype and ploidy p57, is used in several countries, as the main way to refine the diagnosis of early molar pregnancies, differentiating between MHP and MHC. MHP is typically triploid and p57 is absent in. After treatment of NTG, hCG monitoring during a period of at least 12 months is essential for surveillance of recurrence [10].

3.2.3. Title: Update on the Pathology of Gestational Trophoblastic Disease. Authors: Heller, D. S. Year of Publication: 2017. Referenced: Journal of Pathology, Microbiology, and Immunology (APMIS)

Hydatidiform mole is usually diagnosed in the second trimester of pregnancy, when it becomes apparent as clinical manifestations. With US being performed early, most complete moles are diagnosed in the third trimester, before the development of the histological characteristics observed in complete moles, such as edematous avascular villi with anterior circumferential trophoblastic [13]. Partial moles will present less pronounced histological characteristics and less edema and trophoblast proliferation. The presence of fetal tissue, including red blood cells and fetal membranes, favors the diagnosis of a partial mole. In addition, they may have irregular and jagged villi, with the presence of trophoblasts, in addition to other chromosomal abnormalities detected by auxiliary techniques, such as the distinction between diploidy and triploid during pregnancy

[13]. The p57 immunostaining is also very useful for the diagnosis, but care is needed in interpreting the results: P57 is a maternal gene imprint that stains tissue, allowing the decidua to serve as a positive or negative control [13].

3.2.4. Title: Treatment of Gestational Trophoblastic Disease in the 2020s. Authors: Clark, J. J. *et al*. Year of Publication: 2021. Referenced: Current Opinion in Obstetrics & Gynecology

The initial diagnosis is made through clinical examination. Patients usually experience bleeding in the first trimester of pregnancy. With this, an ultrasound is performed and an abnormal image suggestive of molar pregnancy induces the evacuation of the uterus contents for pathological examination. USG provides the diagnosis and results in further monitoring of pregnancy hCG. This ensures recognition of the early stage of malignant transformation through a plateau or rise in the hCG level, which occurs in approximately 16% and 1% of women with complete mole and a partial mole, respectively [7].

3.2.5. Title: Placental Site Trophoblastic Tumor: Successful Treatment of 13 Cases. Authors: Alexander, A. L. *et al*. Year of Publication: 2020. Referenced: Gynecologic Oncology Report

The present study suggested that the diagnosis was initially established by endometrial biopsy or curettage. Being the average time of the last pregnancy, until the diagnosis of approximately 13 months, with a range of 0 to 2400 months. The serum levels of hCG at the time of diagnosis ranged from 1 to 2606 mIU/mL. Hymunohistochemical (IHC) staining reveals the diffuse presence of cytokeratin and human placental lactogen (hPL), while human chorionic gonadotropin (hCG) is only focally positive [14].

4. Discussion

In agreement with previous studies, it was observed here that the correlation between clinical history, physical examination, ultrasound examinations (transabdominal or transvaginal) and serum levels of beta hCG, become essential for an early and correct diagnosis of trophoblastic disease gestational [6] [9] [10].

Maestá *et al* (2000) in a comparative study between serum hCG dosage and weeks after molar evacuation was carried out in Brazil and demonstrated a normal regression curve in patients with spontaneous remission between the 14th week after molar removal and those who developed GTT. If the patients clinical condition remains unchanged and serum levels continue to decline, no further treatment is required. Therefore, the normality of the beta hCG regression curve is fundamental for the early recognition of GTT [15].

In all studies pointed out in this research [3] [10] [13] [14], the evacuation of the uterus is followed by the monitoring of hCG every 1 to 2 weeks, until it normalizes, for CHM, for 6 months or 1 month for PHM. In Morocco the dosage of hCG, at CHM, is done every 10 days, instead of the recommended weekly, up to 3 successive "negative" values during the first 6 months, and for one year it is followed by a monthly test; this conduct is justified by the absence of

reference histopathology in Morocco [12].

It was noted that, for uterine emptying in HM, all international guidelines found in this study recommend evacuation by suction and curettage, which must be guided by ultrasound, regardless of uterine size; this recommendation differs from the Ministry of Health protocol in which ultrasound-guided evacuation of the uterus is only recommended in cases of uterus >20 cm, retroverted uterus or Mullerian anomalies [9].

Tsakiridis, I. *et al.* in a descriptive review that included guidelines from the Royal College of Obstetricians and Gynecologists (RCOG), IFGO, ESMO, and RANZCOG, studies agree that suction evacuation is the optimal management for HM pregnancy, not just to ensure uterine emptying, but also to prevent uterine perforation [10].

Finally, regarding the diagnosis of HM, the guidelines of Morocco, Brazil and some countries of Europe show the absence or difficulty of access to the karyotype test and p57 ploidy, unlike the guidelines of IFGO, Spain, Australia, United Kingdom and New Zealand that routinely resort to these exams [6] [9] [10] [13] [14].

5. Conclusion

In summary, the studies included in this survey have very similar guidelines for diagnosing GTD; the few discordant points, unfortunately, reflect socioeconomic disparities and end up reflecting not only in the higher incidence of GTD cases in less developed countries, but also in the higher rate of morbidity, recurrence, and complications of this pathology. A worldwide effort must be made to apply effective guidelines in line with local realities, especially for the neediest populations.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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