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# Management of Gestational Trophoblast Disease: An Integrative Review of National and International Guidelines

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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 and treatment of the aforementioned pathology results in inadequate risk classification, imprecise treatment and failed post-therapeutic observation, increasing the risk of relapses, morbidity and mortality. The present study aims to compare the different national and international guidelines in the management of GTD, through an integrative review. Nine 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; in low-risk GTN (Gestational Trophoblastic Neoplasm): chemotherapy with methotrexate or actinomycin D, in high-risk:

EMA/CO protocol, in ultra-high-risk EMA/PE, methotrexate with radiotherapy for brain metastases. All medical societies recommend the registration of these patients in GTD screening centers, endorse the use of the IFGO scoring system (2000) and recommend the surgical management of placental site trophoblastic or epithelioid tumors, as chemotherapy is less effective in these cases. The controversies are in the proper follow-up after the treatment of HM, use of ultrasound to evacuate the uterus, administration of anti-D immunoglobulin, time of oxytocin infusion and rescue regimens that can be used in cases of resistant or recurrent GTN. 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

Guidelines, Gestational Trophoblastic Disease, Treatment

## 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**).

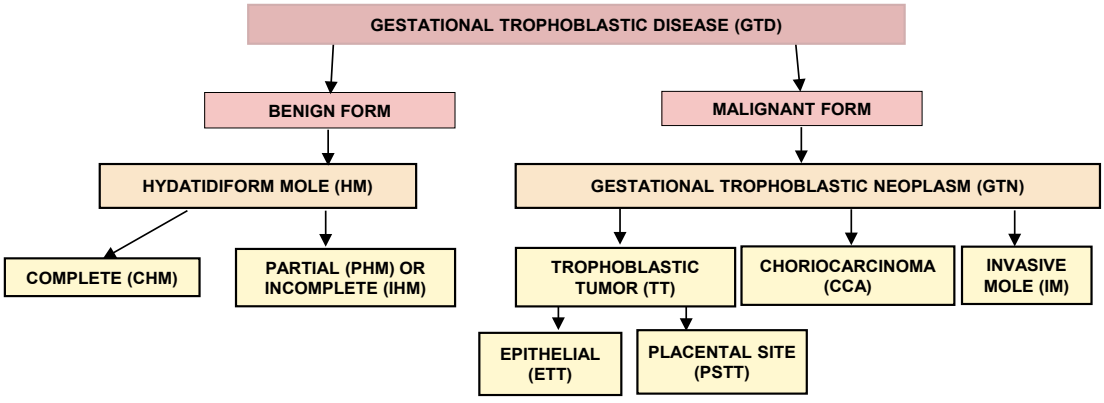



**Figure 1.** Flowchart of histopathological forms and subtypes of GTD. Source: Authors (2022).

The clinical presentation, in general, of GTD consists of abnormally high level of hCG for pregnancy; uterus enlarged for gestational age, greater than 4 cm than expected; absence of fetal beats; cystic enlargement of the ovaries (cysts

thecalutein); nausea and vomiting and elimination of hydropic vesicles through the vagina [3]. The indication that worldwide incidence of GTD is 1:1000 pregnancies, with a threefold increase in countries Asians and those of 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 [4]. 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]. 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 [5].

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 [6]. In partial hydatidiform mole, an embryo and decidual area filled by anechoic images [7].

It is important to highlight that the magnitude 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 [6].

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 [4]. 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 [4].

The karyotype and ploidy p57 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 [8]. 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 [9]. IFGO recommends that evacuation is always accompanied by ultrasound examination to have the make sure the uterus has been completely evacuated and decrease the risk of perforation [10].

IFGO recommends the use of intravenous oxytocin, from the beginning of the evacuation to hours after the end of the procedure, as the use of this drug helps to increase contractility uterine [10]. Rh immunoglobulin should also be administered to women with factor Rh negative, at the time of molar evacuation, be-

cause the RhD factor is expressed in the trophoblast [8].

Hysterectomy is also an alternative to suction curettage. In addition to evacuate the molar remains, hysterectomy provides permanent sterilization and decreases the need for subsequent prophylactic chemotherapy association, which eliminates the risk of local invasion of the myometrium, due to persistent disease [5].

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 [10].

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 and14th day). In these cases, a detailed clinical and gynecological examination is essential and complementary exams such as transvaginal ultrasound with dopplerflowmetry to exclude pregnancy and assess pelvic involvement and the presence of other findings such as thecalutein cyst, chest X-ray is essential due to the risk of by hematic dissemination [10].

After the diagnosis of GTN is performed the IFGO staging (**Table 1**) and the risk score (**Table 2**), to develop the appropriate therapeutic approach for each stage [10].

**Table 1.** Staging of GTN.

| Staging | Gestational Trophoblastic Neoplasm |
|---|---|
| | Features |
| Stage I | Restricted to the uterine body |
| Stage II | Neoplasm present in pelvis, vagina, adnexa, and broad ligament |
| Stage III | Neoplasm with extension to the lung, with or without extension to the genital region |
| Stage IV | All other metastasis sites |

Source: IFGO (2002).

**Table 2.** Risk Score of GTN.

| Parameters | Risk Score | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Age (years) | <40 | ≥40 | - | - |
| Previous pregnancy | Mola | Abortion | Term pregnancy | - |
| Interval (months) between the previous pregnancy and NTG | <4 | 4 - 6 | 7 - 12 | >12 |
| hCG (UI/L) NTG pretreatment | <10,000 | <10,000 - <100,000 | >100,000 - 1,000,000 | >1,000,000 |

**Continued**

| | | | | |
|---|---|---|---|---|
| Largest tumor (cm), considering uterus | - | 3 - 4 cm | ≥5 cm | - |
| Sites of metastases | Lung | Spleen, kidney | Gastrointestinal | Brain, liver |
| Number of metastases | - | 1 - 4 | 5 - 8 | >8 |
| Chemotherapy failure | - | - | Single agent | 2 or more agents |

Source: IFGO (2002).

In low-risk GTN (stages I, II or III: score less than 7), treated with QT initially with MTX (Methotrexate) or ACTD (Actinomycin D), is usually more indicated the use of MTX are preferred GTN's first-line choice of bass risk due to its effectiveness, lower toxicity and low cost, ACTD is indicated in cases of contraindication of MTX, it is considered consolidation of the treatment of low GTN risk with three additional cycles and reach the first normal beta hCG value (<5 mIU/mL) [10].

There are several chemotherapeutic regimens of agents for the treatment of high-risk GTN, among them, the most used is the EMA-CO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, Vincristine), observed in **Figure 2** [3]. Rescue therapy is used for patients who, through IFGO staging and classification, have ultra-high risk GTN with extensive brain metastases to the liver and are resistant to initial chemotherapy, chemotherapy drugs are listed in **Figure 2** [3].

1. EMA-EP(Etoposide, Cisplatin, Etoposide, Methotrexate and Actinomycin D)
2. TP/TE (Paclitaxel, Cisplatin/Paclitaxel, Etoposide)
3. MBE (Methotrexate, Bleomycin, Etoposide)
4. VIP or ICE (Etoposide, Ifosfamide and Cisplatin or Carboplatin)
5. BEP (Bleomycin, Etoposide, Cisplatin)
6. FAEV (Floxuridine, Actiomycin D, Etoposide, Vincristine)
7. High-dose chemotherapy with autologous bone marrow or stem cell transplantation
8. Immunotherapy with Pembrolizumab

**Figure 2.** Chemotherapy drugs for ultra-high risk GTN. Source: IFGO (2002).

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 [10]. 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 [4].

## 2. Methods

An integrative review was carried out, from March 25th to October 29th 2022, through searches in the following databases: LILACS, MEDLINE, BIGG and IBECS; using the descriptors: "Guidelines", "Gestational Trophoblastic Disease" and "Treatment". From this search, 88 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, 32 articles were considered by the selection criteria, of these 10 articles were not accessible for full reading and another 13 were excluded due to inadequacy to the theme, ending the total of 9 articles and including 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 3**).

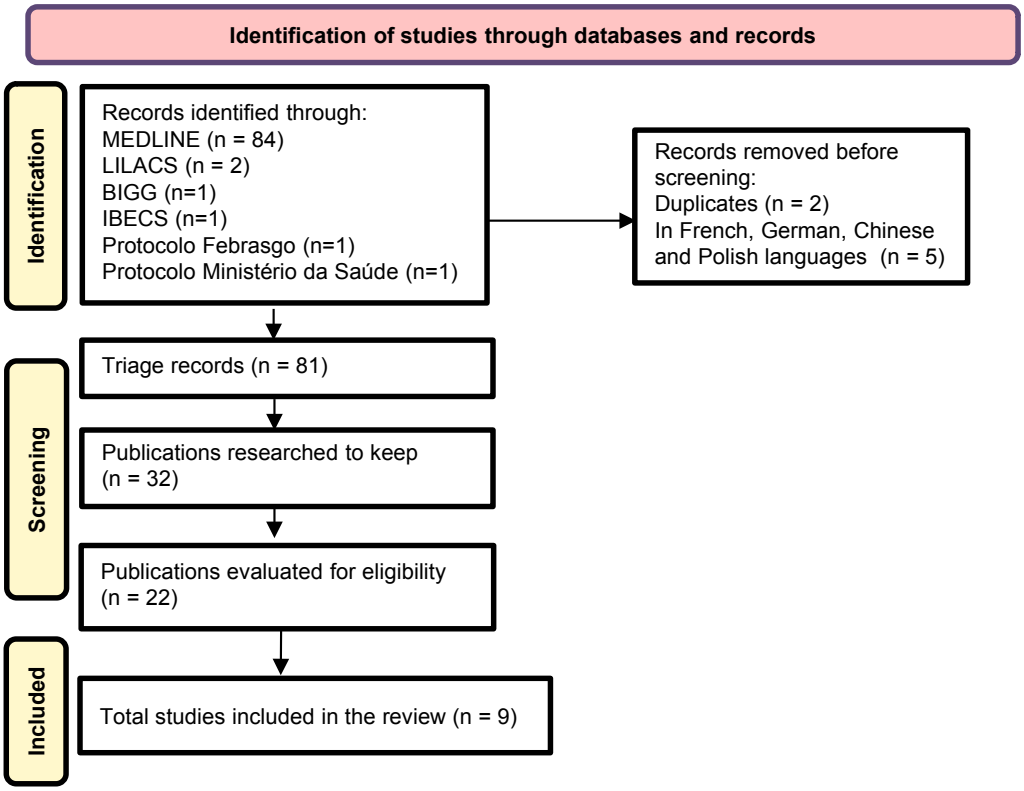



**Figure 3.** Flowchart representing the methodology used for the study. Source: Authors (2022).

## 3. Results

### 3.1. National Guidelines (Brazil)

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 [3]. The FEBRASGO protocol, described by is like the recent guideline of the Ministry of Health regarding the management of GTD [4]. Molar emptying occurs by vacuum aspiration, ultrasound guidance is more indicated in cases of uterus > 20 cm, retroverted uterus

or Mullerian anomalies [3].

In view of this, it was found that 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 [3]. 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. Consecutive, however when presenting elevated hCG or in plateau, they represent evolution to NTG (**Figure 4**) [3].

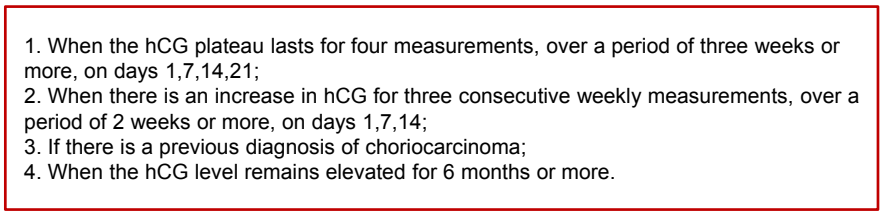



**Figure 4.** Follow-up scheme after molar emptying. Source: IFGO (2002).

In cases of GTN after a non-molar pregnancy, abnormal vaginal bleeding and at least one lifetime pregnancy is sufficient to begin the investigation, ordering hCG to confirm the diagnosis. The therapeutic approach of GTN depends on the staging of IFGO, in low-risk cases, single-agent chemotherapy and hysterectomy are recommended, if the patient is >40 years old, with complete offspring, or if there is non-adherence to the proposed follow-up and treatment, high risk and ultra-high risk should be treated with multidrug therapy [3].

## 3.2. International Guidelines

### 3.2.1. Marrocco

In Morocco, for many years, little research was carried out on GTD, and the few studies published at the same time did not raise major concerns regarding irregular surveillance, treatment abandonment and late diagnosis of avoidable complications of this pathology, however, a protocol for management [11]. In the first evaluation of the patient, both for those who are consulting for the first time and for those referred with clinical and/or imaging suspicion, a new ultrasound and quantitative hCG plasma assay are requested, with confirmation by histopathological examination [11].

The therapeutic measure addressed, in cases of HM, consists of ultrasound-guided vacuum aspiration to reduce second aspirations for intrauterine trophoblastic retentions as recommended by the IFGO, monitoring for surveillance is done every 10 days, instead of the recommended weekly, up to 3 values successive "negatives" during the first 6 months, and for one year is followed by a monthly test. In this way, due to the absence of a reference histopathology in Morocco, the surveillance scheme adopted for GTD guarantees greater safety for

patients and avoids an underestimated diagnosis and, in cases of GTN, IFGO staging and risk score are followed and chemotherapy is performed according to the patient's classification [11].

#### 3.2.2. Europe—European Society for Medical Oncology (ESMO)

The safest treatment for HM is ultrasound-guided aspiration to ensure uterine emptying and prevent uterine perforation. The diagnosis of GTN is based on the clinic together with the dosage of hCG and IFGO criteria [9]. Hysterectomy may be considered in patients of infertile age, but may not prevent the need for chemotherapy. In accordance with the IFGO, for almost all low-risk GTN patients, single-agent chemotherapy with MTX or ACTD is preferred, and for high-risk patients, EMA/CO protocol is more indicated, ultra-high-risk is a convenient therapy, low-dose initial therapy for massive disease followed by consolidation chemotherapy for 8 weeks [9].

#### 3.2.3. United Kingdom—Royal College of Obstetricians and Gynecologists (RCOG)

In addition to the clinical presentation, the diagnosis is made through histopathological examination, ploidy and immunohistochemical staining for p57, to help distinguish between partial and complete. The treatment of choice for HM is suction evacuation and ultrasound-guided curettage, the choice of hysterectomy is restricted to patients in the non-reproductive stage. After therapy it is necessary to monitor the hCG dosage every one to two weeks until the levels normalize and then for CHM follow up for 6 months or 1 month for MHP [12]. In cases of GTN, classify the stage and start treatment, according to the IFGO criteria.

#### 3.2.4. Spain—Sociedad Española de Oncología (SEOM)

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-positive rates negative results are high with this imaging method, and histological examination is essential to close the diagnosis [4].

The treatment of choice in HM is evacuation by suction and curettage under mandatory ultrasound control. Either medical induction of labor or hysterectomy is not recommended, due to the increased risk of developing postmolar GTN. After evacuation of the HM, weekly serum hCG assays should be obtained until 3 consecutive weekly assays are normal [4]. From this, in MHP, the patient can be discharged from follow-up.

In summary, if repeated suction curettage is required, patients should be monitored until 3 consecutive weekly serum hCGs are normal and thus monthly serum hCG levels for 6 months. In CM, patients should be monitored with monthly serum hCG levels for 6 months [4]. For GTN, staging is done according to the IFGO, identifying patients who are likely to be cured with single-agent chemotherapy or if more aggressive treatment should be the initial choice [4].

#### 3.2.5. Australia and New Zealand—Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)

The diagnosis of GTD is concluded with histopathological examination, but ultrasound and other tests such as p57 ploidy and karyotype are necessary to differentiate between CHM and PHM. In the presence of molar pregnancy, the therapy of choice is evacuation by suction and after treatment, quantitative monitoring of weekly serum beta HCG is started, after 3 consecutive normal results, if PHM ceases monitoring, if CHM should be tested monthly, for at least 6 months [13].

When diagnosing GTN, the IFGO classification becomes essential to assess the best therapeutic approach. It is recommended to inform the patient of the risks of a future pregnancy and of his predisposition to develop a new GTD and to avoid pregnancy until advised, since it is a disease with persistent risk [13].

#### 3.2.6. Japan

The guidelines of the Japanese Society of Gynecology and Obstetrics (2018) described in the studies present the treatment method only for GTN, with no reference to benign disease. Through GTN, staging is performed according to IFGO, radiotherapy is suggested only for cases in which brain metastases are found, and its indication is carefully considered [14].

Regarding the surgical indications for ACC, surgical resection is considered when there is a uterine or metastatic lesion associated with chemoresistance, uterine hemorrhage that is difficult to control, or brain metastases with symptoms of intracranial hypertension. The recommended treatment in cases of PSTT or ETT are total hysterectomy, when the tumor is limited to the uterus, or combined therapy with surgical treatment, which includes total hysterectomy and chemotherapy, in cases of patients with metastatic lesions [14] [15].

## 4. Discussion

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 [3].

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. In contrast, Figo recommends hysterectomy as an alternative to suction, alleging evidence from retrospective studies pointing to an increased risk of post-molar GTN and maternal morbidity after suction evacuation [8].

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 [12].

The IFGO recommends the prophylactic administration of MTX or ACT-D at the time of molar evacuation or immediately after the procedure, based on studies that associate this procedure with a decrease in the incidence of post molar GTN. However, in the guidelines of this study, countries such as Brazil and Spain only recommend prophylactic chemotherapy for patients considered at risk for developing GTN [3] [10].

In most of the studies pointed out in this research, 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, the only exception is Morocco in which 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 [11].

Finally, there are different approaches regarding the surveillance protocol and adequate follow-up after treatment of molar pregnancy, in this way, ESMO recommends the evaluation of serum and urinary hCG, every 2 weeks, until normalization, while RANZCOG recommends weekly assessment until 3 consecutive serum levels are normal and then for another 6 months [13].

The guideline from Japan, found in this research, shows only the treatment of GTN, using the same therapeutic approach as the others after classification using the IFGO criteria [14]. Therefore, it was a consensus, among the guidelines of this study, to follow the IFGO staging and risk score to classify the risk and guide the conduct of GTN. It is also observed that all recommend the registration of these patients in specific GTD screening centers and refer that the diagnosis of GTN should be based on the clinical presentation sites [5]-[11].

In low-risk GTN, chemotherapy with methotrexate or actinomycin D will be used, however, in high-risk patients, the EMA/CO protocol will be followed and in ultra-high-risk patients, EMA/EP, MTX and radiotherapy for brain metastases [5] [12] [13]. The UK, Spain, Australia and New Zealand guidelines do not address ultra-high-risk GTN, only high-risk GTN, whereas Europe approaches it differently, initiating low-dose chemotherapy for massive disease and consolidation chemotherapy for 8 weeks [5] [9] [12] [13].

In this study, there was a consensus among the various guidelines in which a future pregnancy should be avoided during the follow-up of the treatment, in this way, the use of an effective contraceptive method is recommended, as a barrier to a possible pregnancy, due to the risk of a new molar pregnancy [12].

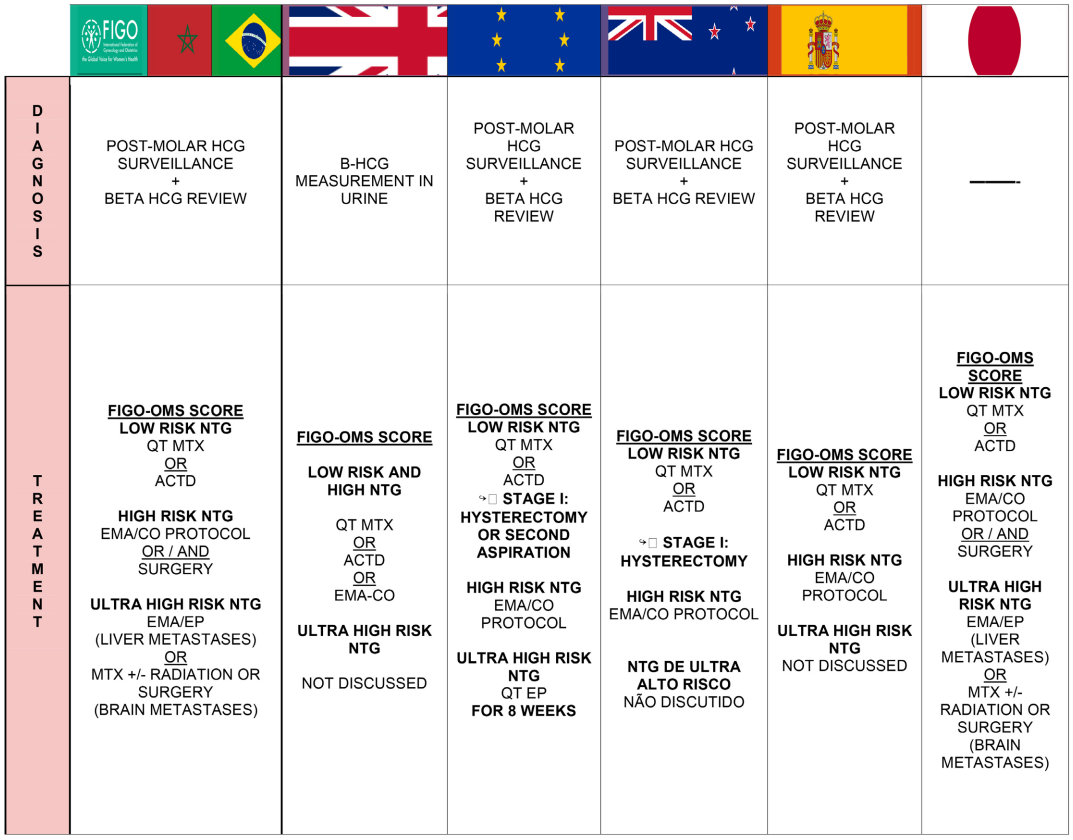
In addition, all guidelines studied here recommend the surgical management of placental site trophoblastic tumors or epithelioid trophoblastic tumors, as chemotherapy is less effective in these cases. However, there were controversies among these regarding the administration of anti-D immunoglobulin, the infusion of oxytocin and the rescue regimens that can be used in cases of resistant or

recurrent GTN [5] [9] [12]. All comparisons were organized in Figure 5 and Figure 6.

| | FIGO International Federation of Gynecology and Obstetrics the Global Voice for Women's Health | | | |
|---|---|---|---|---|
| DIAGNOSIS | HISTOPATHOLOGICAL EXAMINATION + PELVIC USG + HIGH B-HCG + PLOIDY, P57 | HISTOPATHOLOGICAL EXAMINATION + PELVIC USG + HIGH B-HCG + PLOIDY, P57 | HISTOPATHOLOGICAL EXAMINATION + PELVIC USG + HIGH B-HCG + PLOIDY, P57 | HISTOPATHOLOGICAL EXAMINATION + PELVIC USG |
| TREATMENT | VACUUM ASPIRATION, GUIDED BY USG **HYSTERECTOMY** | VACUUM ASPIRATION | VACUUM ASPIRATION, GUIDED BY USG | VACUUM ASPIRATION, GUIDED BY USG |
| FOLLOW UP | **HCG MONITORING:** EVERY 1 - 2 WEEKS UNTIL NORMALIZATION MHC - FOR 6 MONTHS MHP - FOR 1 MONTH | **HCG MONITORING:** EVERY 6 MONTHS OR HCG NORMALIZATION | **HCG MONITORING:** EVERY 10 DAYS 3 CONSECUTIVE TIMES OF NORMALIZED LEVELS FOR 6 MONTHS + MONTHLY TRIAL FOR 1 YEAR | **HCG MONITORING:** EVERY 2 WEEKS UNTIL NORMALIZE (SERUM AND URINARY HCG) + MONTHLY URINARY HCG TEST |

| | | | |
|---|---|---|---|
| DIAGNOSIS | HISTOPATHOLOGICAL EXAMINATION + PELVIC USG + HIGH B-HCG + PLOIDY, P57 + **KARYTYPE** | HISTOPATHOLOGICAL EXAMINATION + PELVIC USG + HIGH B-HCG | HISTOPATHOLOGICAL EXAMINATION + PELVIC USG + HIGH B-HCG + PLOIDY, P57 |
| TREATMENT | VACUUM ASPIRATION, GUIDED BY USG | VACUUM ASPIRATION, GUIDED | VACUUM ASPIRATION, GUIDED BY USG |
| FOLLOW UP | **HCG MONITORING:** WEEKLY UP TO 3 CONSECUTIVE TIMES OF NORMALIZED LEVELS MHC - FOR 6 MONTHS MHP - CEASE TRACKING | **HCG MONITORING:** EVERY 1 - 2 WEEKS UNTIL NORMALIZATION MHC - FOR 6 MONTHS MHP - FOR 1 MONTH | **HCG MONITORING:** WEEKLY UP TO 3 CONSECUTIVE TIMES OF NORMALIZED LEVELS MHC - FOR 6 MONTHS MHP - CEASE TRACKING |

Figure 5. Comparison of results from the management of Hydatidiform Mole. Source: Authors (2022).



| | FIGO / Morocco / Brazil | United Kingdom | European Union | New Zealand / Australia | Spain | Japan |
|---|---|---|---|---|---|---|
| DIAGNOSIS | POST-MOLAR HCG SURVEILLANCE + BETA HCG REVIEW | B-HCG MEASUREMENT IN URINE | POST-MOLAR HCG SURVEILLANCE + BETA HCG REVIEW | POST-MOLAR HCG SURVEILLANCE + BETA HCG REVIEW | POST-MOLAR HCG SURVEILLANCE + BETA HCG REVIEW | ——— |
| TREATMENT | **FIGO-OMS SCORE**<br>**LOW RISK NTG**<br>QT MTX<br>OR<br>ACTD<br><br>**HIGH RISK NTG**<br>EMA/CO PROTOCOL<br>OR / AND<br>SURGERY<br><br>**ULTRA HIGH RISK NTG**<br>EMA/EP<br>(LIVER METASTASES)<br>OR<br>MTX +/- RADIATION OR SURGERY<br>(BRAIN METASTASES) | **FIGO-OMS SCORE**<br><br>**LOW RISK AND HIGH NTG**<br><br>QT MTX<br>OR<br>ACTD<br>OR<br>EMA-CO<br><br>**ULTRA HIGH RISK NTG**<br><br>NOT DISCUSSED | **FIGO-OMS SCORE**<br>**LOW RISK NTG**<br>QT MTX<br>OR<br>ACTD<br>**STAGE I: HYSTERECTOMY OR SECOND ASPIRATION**<br><br>**HIGH RISK NTG**<br>EMA/CO PROTOCOL<br><br>**ULTRA HIGH RISK NTG**<br>QT EP<br>**FOR 8 WEEKS** | **FIGO-OMS SCORE**<br>**LOW RISK NTG**<br>QT MTX<br>OR<br>ACTD<br><br>**STAGE I: HYSTERECTOMY**<br><br>**HIGH RISK NTG**<br>EMA/CO PROTOCOL<br><br>**NTG DE ULTRA ALTO RISCO**<br>NÃO DISCUTIDO | **FIGO-OMS SCORE**<br>**LOW RISK NTG**<br>QT MTX<br>OR<br>ACTD<br><br>**HIGH RISK NTG**<br>EMA/CO PROTOCOL<br><br>**ULTRA HIGH RISK NTG**<br>NOT DISCUSSED | **FIGO-OMS SCORE**<br>**LOW RISK NTG**<br>QT MTX<br>OR<br>ACTD<br><br>**HIGH RISK NTG**<br>EMA/CO PROTOCOL<br>OR / AND<br>SURGERY<br><br>**ULTRA HIGH RISK NTG**<br>EMA/EP<br>(LIVER METASTASES)<br>OR<br>MTX +/- RADIATION OR SURGERY<br>(BRAIN METASTASES) |

**Figure 6.** Comparison of the results of Gestational Trophoblastic Neoplasia. Source: Authors (2022).

## 5. Conclusion

In summary, the countries included in this research have very similar guidelines for managing GTD; the few discordant points, unfortunately, translate the socio-economic disparities and end up reflecting not only the higher incidence of GTD cases in less developed countries, but also the higher rate of recurrence and complications of this pathology. A worldwide effort is being 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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