Update on the diagnosis and management of gestational trophoblastic disease

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Abstract
Gestational trophoblastic disease (GTD) arises from abnormal placenta and is composed of a spectrum of premalignant to malignant disorders. Changes in epidemiology of GTD have been noted in various countries. In addition to histology, molecular genetic studies can help in the diagnostic pathway. Earlier detection of molar pregnancy by ultrasound has resulted in changes in clinical presentation and decreased morbidity from uterine evacuation. Follow-up with human chorionic gonadotropin (hCG) is essential for early diagnosis of gestational trophoblastic neoplasia (GTN). The duration of hCG monitoring varies depending on histology type and regression rate. Low-risk GTN (FIGO Stages I–III: score <7) is treated with single-agent chemotherapy but may require additional agents; although scores 5–6 are associated with more drug resistance, overall survival approaches 100%. High-risk GTN (FIGO Stages II–III: score >7 and Stage IV) is treated with multiple agent chemotherapy, with or without adjuvant surgery for excision of resistant foci of disease or radiotherapy for brain metastases, achieving a survival rate of approximately 90%. Gentle induction chemotherapy helps reduce early deaths in patients with extensive tumor burden, but late mortality still occurs from recurrent resistant tumors.

Keywords
Choriocarcinoma; Epithelioid trophoblastic tumor; FIGO Cancer Report; Gestational trophoblastic neoplasia; Moles; Placental site trophoblastic tumor

1 | INTRODUCTION

Gestational trophoblastic disease (GTD) is a group of uncommon conditions associated with pregnancy. Histologically, it includes the premalignant partial (PHM) and complete hydatidiform mole (CHM), as well as the malignant invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). The malignant forms can arise after any type of pregnancy and...
are collectively known as gestational trophoblastic neoplasia (GTN). The GTD spectrum has recently been expanded to also include atypical placental site nodule (APSN) as 10%–15% may coexist with or develop into PSTT/ETT.1 While PSTT, ETT, and APSN have more varied production of the pregnancy hormone—human chorionic gonadotropin (hCG)—all other forms of GTD produce this hormone very well. Indeed, hCG is an excellent biomarker of disease progression, response, and subsequent post-treatment surveillance. Thus, a plateaued or rising hCG level enables the early detection of progression of CHM and PHM to GTN that occurs in 15%–20%, and 0.5%–5% of cases, respectively.2,3 The use of this biomarker together with the development of highly effective therapies has transformed survival outcomes so that today nearly all women affected by GTN can expect to be cured if managed properly.

2 | EPIDEMIOLOGY

Although epidemiological studies have reported a wide variation in the incidence of hydatidiform mole, in most parts of the world it is 1 per 1000 pregnancies.4 In high-income countries, the incidence of complete mole is approximately 1–3 per 1000 pregnancies and the incidence of partial mole is about 3 per 1000 pregnancies.3 Hydatidiform mole appears to be caused by abnormal gametogenesis and fertilization,5,6 more frequent at the extremes of reproductive age (<15 and >45 years) and pregnancies at these ages are a risk factor for hydatidiform mole. The risk increases after age 35 and there is a 5–10 times increased risk after 45 years. Teenagers have a two-fold risk of having a molar pregnancy. There is an increasing risk for complete moles with advancing maternal age.7 History of a previous molar pregnancy increases the risk to 10 times that for sporadic moles.

The reported incidence of choriocarcinoma ranges from 1 in 40 000 pregnancies in North America and Europe, to 9.2 and 3.3 per 40 000 pregnancies in Southeast Asia and Japan, respectively.2 Dietary deficiency of beta-carotene and animal fat is considered to be etiological factor for complete mole, but not for partial mole.8

3 | GENETICS AND PATHOLOGY

3.1 | Molar pregnancy

Grossly, CHM consists of hydropic villi to semi-transparent vesicles of variable sizes with absence of normal placenta. Early complete hydatidiform moles have minimal or no gross evidence of abnormal villi.

Differential diagnoses include partial hydatidiform mole, hydropic abortion, and early nonmolar gestation with some degree of trophoblastic hyperplasia. Histologically, complete mole has florid cistern formation, trophoblastic proliferation, and absence of fetal parts. Significant cytological atypia and mitotic figures are common. In the first trimester, CMH villi may not be enlarged but have a distinct polypoid appearance with abnormal villous stromal changes and mild to moderate trophoblastic hyperplasia. In contrast, such histologic features are less marked in partial mole and fetal parts or cells are present.3 Hydropic spontaneous abortion may mimic the appearance of partial mole.

A cyclin-dependent kinase inhibitor p57 is encoded by the paternal imprint and maternally expressed gene and hence is absent in CHM without the maternal genome. In contrast, PHM and nonmolar abnormal gestations with maternal genome have strong nuclear p57 staining, which can be used to exclude complete mole. However, p57 cannot differentiate PHM from nonmolar gestations. Cytogenetics can help to differentiate CHM from PHM and hydropic spontaneous abortion. Typically, CHM is diploid and has 46,XX chromosomes with both X’s from paternal origin, whereas PHM is triploid with maternal and paternal genetic origin. Hydropic spontaneous abortion normally has 46,XX or XY from both parents.3

Rarely, invasive and metastatic moles can be diagnosed by removal of the uterus or biopsy of a metastatic lesion.

3.2 | Choriocarcinoma

Grossly, the tumor is bulky with hemorrhagic and necrotic areas. Apart from the uterus, it can be found in tubes, ovaries, lung, liver, spleen, kidneys, bowel, or brain.3

Histologically, choriocarcinoma shows absence of chorionic villi and presence of abnormal intermediate trophoblast and cytotrophoblast, rimmed with syncytiotrophoblasts with areas of necrosis, and hemorrhage. Highly complex karyotypes have been reported and an XX sex chromosome composition is seen in the majority.

3.3 | Placental site trophoblastic tumor

Grossly, PSTT appears as white-tan to yellow nodular masses varying from 1–10 cm (average 5 cm) in the endometrium with half of the cases invading deep into the myometrium. Histologically, PSTT arises from the mononuclear intermediate trophoblast on the maternal side of the placental bed. Tumor cells have irregular nuclear membranes, hyperchromatic nuclei, and dense eosinophilic to amphophilic cytoplasm. Most tumors have a low mitotic count. Chorionic villi are absent. Tumor cells diffusely express human placental lactogen (hPL), MUC-4, HSD3B1, HLA-G, and Mel-CAM (CD146). Expression of hCG and inhibin is focal. The proliferation index is generally modestly increased, with Ki-67 expressed in 10% to 30% of cells—higher than that of benign exaggerated placental site reaction.7 PSTT shows rare genetic imbalances.

3.4 | Epithelioid trophoblastic tumor

Grossly, the tumor appears as white-tan to brown discrete nodules or cystic hemorrhagic masses invading deep into surrounding tissues. Nearly half arise in the cervix or lower segment of the uterus and some in the fundus and broad ligament.

Histologically, ETT arises from the chorionic-type intermediate trophoblast. Islands of relatively uniform intermediate trophoblastic cells with moderate amount of eosinophilic to clear cytoplasm and round nuclei are surrounded by extensive necrosis and associated with a hyaline-like matrix. The mitotic count ranges from 0–9 per 10 HPF.
Extensive or “geographic” necrosis is often present. ETT may coexist with other trophoblastic neoplasms.

4 | CLINICAL PRESENTATION, INVESTIGATIONS, AND DIAGNOSIS

4.1 | Molar pregnancy

Patients usually present with second trimester vaginal bleeding and a uterus greater than the gravid date. As diagnosis is often made in the first trimester with ultrasound examination, complications such as hyperemesis gravidarum, pre-eclampsia, and hyperthyroidism are less common. If there is vaginal passage of the gestational product, vesicles may be seen. The typical honeycomb appearance of a complete mole is rarely seen, especially in the first trimester. Typically, there is absence of fetal parts, cystic appearance of the placenta, and a deformed gestational sac that may appear like a spontaneous abortion. Hence, some molar pregnancies are only diagnosed on histologic examination after evacuation for a spontaneous abortion.

4.2 | Gestational trophoblastic neoplasia

Postmolar GTN is usually diagnosed by hCG surveillance without symptoms. At the FIGO Gynecology Oncology Committee meeting in 2000, the definition of postmolar GTN based on hCG-level changes, histology, and specific investigations was agreed (Boxes 1 and 2).9

4.3 | Human chorionic gonadotropin monitoring

For monitoring of GTN, an hCG assay that can detect all forms of hCG including beta-hCG, core hCG, C-terminal hCG, nicked-free beta, beta core, and preferably the hyperglycosylated forms, should be used. A persistently low hCG level needs continuous monitoring as some may progress to GTN with rising hCG levels.10,11 To exclude a false-positive result, retest with another assay kit or a test for urine hCG may be used.

4.4 | Gestational trophoblastic neoplasm after nonmolar pregnancy

As only about 50% of GTN follows molar pregnancy, the rest can occur after a spontaneous abortion, ectopic pregnancy, or a term pregnancy. Aside from abnormal vaginal bleeding, other clinical presentations can include bleeding from metastatic sites such as the liver, spleen, intestines, lung, or brain; pulmonary symptoms; and neurological signs from spine or brain metastasis.2 GTN should be considered in the differential diagnosis of patients with unusual presentations and serum hCG should be performed as part of the workup of such patients.

5 | TREATMENT

5.1 | Molar pregnancy

Suction evacuation and curettage, ideally performed under ultrasound guidance, is the preferred method of evacuation of a molar pregnancy independent of uterine size if maintenance of fertility is desired. It is recommended that a 12–14 mm suction cannula is used and that an intravenous oxytocin infusion is started at the onset of suction curettage and continued for several hours postoperatively to enhance uterine contractility. Because the risk of bleeding increases with uterine size, blood for transfusion should be available when the uterus is greater than 16 weeks in gestational size. Rh immune globulin should be given to Rh-negative women at the time of molar evacuation as RhD factor is expressed on the trophoblast. Judicious use of appropriate evacuation equipment and techniques, access to blood products, careful intraoperative monitoring, and early recognition and correction of complications results in improved outcomes.2,12 If there is no persistent bleeding, a second evacuation is usually not needed.

Hysterectomy is an alternative to suction curettage if childbearing is complete. In addition to evacuating the molar pregnancy, hysterectomy provides permanent sterilization and decreases the need for subsequent chemotherapy by eliminating the risk of local myometrial invasion as a cause of persistent disease. Medical induction of labor and hysterotomy are not recommended for molar evacuation, since these methods increase maternal morbidity and the development of postmolar GTN requiring chemotherapy.

Prophylactic administration of either methotrexate or actinomycin D chemotherapy at the time of or immediately following molar evacuation is associated with a reduction in the incidence of postmolar GTN to 3%–8%. However, it should be limited to special situations in which the risk of postmolar GTN is much greater than normal or where adequate hCG follow-up is not possible.13

**Box 1** FIGO criteria for diagnosis of postmolar gestational trophoblastic neoplasia.

- When the plateau of hCG lasts for four measurements over a period of 3 weeks or longer; that is, days 1, 7, 14, 21.
- When there is a rise in hCG for three consecutive weekly measurements over at least a period of 2 weeks or more; days 1, 7, 14.
- If there is a histologic diagnosis of choriocarcinoma.

Abbreviation: hCG, human chorionic gonadotropin.

**Box 2** Tools for investigation of gestational trophoblastic neoplasia.

- Chest X-ray is appropriate to diagnose lung metastases and can be used for counting the number of lung metastases to evaluate the risk score. Lung CT may be used.
- Liver metastases may be diagnosed by ultrasound or CT scanning.
- Brain metastases may be diagnosed by MRI or CT scanning.
Follow-up hCG monitoring every 1–2 weeks is essential for early diagnosis of and management of postmolar GTN. On the other hand, postmolar GTN rarely occurs after the spontaneous return of hCG levels to normal, allowing for a shortened follow-up period for most women. Hence, a single additional confirmatory normal hCG measurement 1 month after first hCG normalization is recommended for a PHM and monthly hCG measurements should be obtained for only 6 months after hCG normalization for a CHM.\textsuperscript{2,14} Termination of pregnancy is not indicated if accidental pregnancy occurs during surveillance after the hCG level has returned to normal. In addition, data now show that it is safe to recommend oral contraceptives.\textsuperscript{15}

The risk of recurrence is low (0.6%–2%) after one molar pregnancy, although much increased after consecutive molar pregnancies.\textsuperscript{16} Mutations in NLRP7 and KHDC3L have been reported in women with recurrent molar pregnancy.\textsuperscript{5,6}

5.2 | Coexisting normal pregnancy with mole

Molar pregnancy rarely coexists with a normal pregnancy. The diagnosis is usually made on ultrasound. Although there is a high risk of spontaneous abortion, about 40%–60% result in live births. The risk of GTN in coexisting molar and normal pregnancy compared with singleton molar pregnancy is increased from 15% to 20% to 27% to 46%.\textsuperscript{17,18} In the absence of complications and normal genetic and ultrasound findings, pregnancy can proceed.

TABLE 1 FIGO staging and classification for gestational trophoblastic neoplasia.

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Gestational trophoblastic tumors strictly confined to the uterine corpus</td>
</tr>
<tr>
<td>II</td>
<td>Gestational trophoblastic tumors extending to the adnexae or to the vagina, but limited to the genital structures</td>
</tr>
<tr>
<td>III</td>
<td>Gestational trophoblastic tumors extending to the lungs, with or without genital tract involvement</td>
</tr>
<tr>
<td>IV</td>
<td>All other metastatic sites</td>
</tr>
</tbody>
</table>

5.3 | Gestational trophoblastic neoplasia

Treatment of GTN is generally by chemotherapy. The best regimen depends on stage and classification. In the 2000 FIGO staging and classification (Tables 1 and 2), a risk score of 6 and below is classified as low risk and above 6 is considered high risk.

5.3.1 | Low-risk gestational trophoblastic neoplasia

Patients with low-risk GTN (WHO risk score 0–4) should be treated with one of the single agent methotrexate or actinomycin D protocols listed in Box 3. The Cochrane Review in 2012, including 513 patients in five randomized controlled trials, showed that actinomycin D (Act-D) appeared to be superior to methotrexate (MTX) (risk ratio [RR] 0.64; 95% confidence interval, [CI] 0.54–0.76).\textsuperscript{19} Methotrexate was associated with significantly more treatment failure than actinomycin D (RR 3.81; 95% CI 1.64–8.86).

Chemotherapy should be changed to the alternative single agent if there has been a good response to the first agent but the hCG level plateaus above normal during treatment, or if toxicity precludes an adequate dose or frequency of treatment. If there is an inadequate response

Box 3 First-line single agent chemotherapy regimens for low-risk gestational trophoblastic neoplasia.

- MTX-FA 8-day regimen (50 mg MTX intramuscularly on days 1, 3, 5, 7 with folic acid 15 mg orally 24 hours after MTX on days 2, 4, 6, 8); repeat every 2 weeks.
- MTX 0.4 mg/kg (max. 25 mg) intravenously or intramuscularly for 5 days every 2 weeks.
- Actinomycin D pulse 1.25 mg/m\textsuperscript{2} intravenously every 2 weeks.
- Actinomycin D 0.5 mg intravenously for 5 days every 2 weeks.
- Others: MTX 30–50 mg/m\textsuperscript{2} intramuscularly weekly, MTX 300 mg/m\textsuperscript{2} infusion every 2 weeks.

Abbreviations: MTX-FA, methotrexate–folinic acid.

TABLE 2 WHO scoring system based on prognostic factors.

<table>
<thead>
<tr>
<th>WHO risk factor scoring with FIGO staging</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;40</td>
<td>&gt;40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>Mole</td>
<td>Abortion</td>
<td>Term</td>
<td></td>
</tr>
<tr>
<td>Interval from index pregnancy, months</td>
<td>&lt;4</td>
<td>4–6</td>
<td>7–12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Pretreatment hCG mIU/mL</td>
<td>&lt;10\textsuperscript{2}</td>
<td>&gt;10\textsuperscript{3}–10\textsuperscript{4}</td>
<td>&gt;10\textsuperscript{4}–10\textsuperscript{5}</td>
<td>&gt;10\textsuperscript{5}</td>
</tr>
<tr>
<td>Largest tumor size including uterus, cm</td>
<td></td>
<td>3–4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of metastases including uterus</td>
<td>Lung</td>
<td>Spleen, kidney</td>
<td>Gastrointestinal tract</td>
<td>Brain, liver</td>
</tr>
<tr>
<td>Number of metastases identified</td>
<td></td>
<td>1–4</td>
<td>5–8</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Previous failed chemotherapy</td>
<td></td>
<td></td>
<td>Single drug</td>
<td>Two or more drugs</td>
</tr>
</tbody>
</table>

To stage and allot a risk factor score, a patient’s diagnosis is allocated to a Stage as represented by a Roman numeral I, II, III, or IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals e.g. Stage II:4, Stage IV:9. This Stage and score will be allotted for each patient.
to the initial single agent, multiple agent chemotherapy as for high-risk disease should be initiated if there is a significant elevation in hCG level, development of metastasis, or resistance to sequential single agent chemotherapy. Studies showed that change to single agent Act-D gives a good response rate of between 76% and 87% in patients with relatively low hCG levels, as there are continuous updates on the cutoff level based on evolving data, physicians should refer to local guidelines from time to time. Otherwise, multiple agents should be considered.

Higher WHO risk score (5–6) and clinicopathologic diagnosis of choriocarcinoma are both associated with an increased risk of resistance to single agent chemotherapy. Lowering the threshold for the use of multiple agent chemotherapy in these otherwise low-risk patients can be considered.

After the hCG level has returned to normal, consolidation with 2–3 more cycles of chemotherapy will decrease the chance of recurrence. The overall complete remission rate is close to 100%. About 20% of patients fail EMA-CO therapy but most can be salvaged with further therapy; the overall survival rates for patients with high-risk GTN are now running as high as 95%. A number of adverse features that predict poorer outcomes, including liver and/or brain metastasis and the management of such patients together with salvage therapies are discussed below.

### TABLE 3 EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) chemotherapy.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoposide</td>
<td>100 mg/m² intravenous infusion over 30 min</td>
<td>100 mg/m² intravenous infusion over 30 min</td>
</tr>
<tr>
<td>Actinomycin-D</td>
<td>0.5 mg intravenous bolus</td>
<td>0.5 mg intravenous bolus</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>100 mg/m² intravenous bolus</td>
<td>100 mg/m² intravenous bolus</td>
</tr>
<tr>
<td>Folinic acid rescue</td>
<td>15 mg intramuscularly or orally every 12 h for four doses (starting 24 h after beginning the methotrexate infusion)</td>
<td></td>
</tr>
</tbody>
</table>

5.3.3 | Ultra high-risk gestational trophoblastic neoplasia and salvage therapy

Among the high-risk group as defined by the FIGO staging and classification, a subgroup with score of 13 or greater, as well as patients with liver, brain, or extensive metastases, do poorly when treated with first-line multiple agent chemotherapy. Similar findings have been reported by others.

For those with massive disease, starting with standard chemotherapy may cause sudden tumor collapse with severe bleeding, metabolic acidosis, myelosuppression, septicemia, and multiple organ failure, any or all of which can result in early death. To avoid this, the use of initial gentle rather than full-dose chemotherapy seems logical. Indeed, induction etoposide 100 mg/m² and cisplatin 20 mg/m² on days 1 and 2, repeated weekly for 1–3 weeks, before starting normal chemotherapy appears to have eliminated early deaths in one series, with promising results now reported by others.

For those patients with liver metastases, with or without brain metastases, or a very high-risk score, EP (etoposide and platinum)/EMA or another more intensive chemotherapy regimen (Box 4), rather than EMA-CO, may yield a better response and outcome. For such high-risk patients, a longer consolidation with four cycles of chemotherapy should be considered.

In patients with brain metastases, an increase in the methotrexate infusion to 1 g/m² will help the drug cross the blood–brain barrier and intrathecal methotrexate 12.5 mg may be used in some centers. This can be given at the time of CO when EMA-CO is used, or with the EP in the EP/EMA regimen. Some centers may give whole brain radiotherapy 3000 cGy in 200 cGy daily fractions concurrent with chemotherapy or use stereotactic or gamma knife radiation to treat existing or residual brain metastases after chemotherapy. Patients failing EMA-CO are mostly salvaged with paclitaxel and etoposide alternating with paclitaxel and cisplatin (TE/TP) or with EP/EMA. In China, the 5FU-based FAEV regimen is also an effective salvage treatment. For women failing EP/EMA or TE/TP, options include a number of other standard or high-dose chemotherapy regimens with autologous stem cell transplant.

### Box 4 Salvage therapies.

- EP-EMA (etoposide, cisplatin, etoposide, methotrexate and actinomycin-D)
- TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide)
- MBE (methotrexate, bleomycin, etoposide)
- VIP or ICE (etoposide, ifosfamide, and cisplatin or carboplatin)
- BEP (bleomycin, etoposide, cisplatin)
- FA (5-fluorouracil, actinomycin-D)
- FAEV (5-fluorouracil, actinomycin-D, etoposide, vincristine)
- High-dose chemotherapy with autologous bone marrow or stem cell transplant
- Immunotherapy with pembrolizumab
Peripheral stem cell support (Box 4). Recent work suggests that checkpoint immunotherapies such as pembrolizumab may also save some women. Finally, surgical salvage should not be overlooked.

5.4 | Role of surgery

Surgery may have an important role in the management of GTN. Hysterectomy can be considered in uncontrolled uterine bleeding, although it can often be avoided with the use of uterine artery embolization. Laparotomy may be needed to stop bleeding in organs such as the liver, gastrointestinal tract, kidneys, and spleen. Neurosurgery is needed if there is bleeding into the brain or increased intracranial pressure. The resection of an isolated drug-resistant tumor may also be curative.4,11

5.5 | Role of radiotherapy

Radiotherapy has a limited role in GTN, except in treatment of brain metastasis, although its efficacy compared with intrathecal methotrexate is controversial.4,11

5.6 | PSTT/ETT

Both PSTT and ETT are less chemosensitive than choriocarcinoma. Hysterectomy is the primary mode of treatment in most cases and surgery also plays an important role in metastatic disease. If fertility preservation is desired, especially in a localized lesion, conservative management such as uterine curettage, hysteroscopic resection, and chemotherapy may be considered.29 Fertility preservation is not suitable in diffuse lesions. In advanced stage, EP-EMA or TE/TP can be considered. Interval from antecedent pregnancy of more than 48 months seems to be the most significant adverse prognostic factor.30

5.7 | Follow-up

After treatment of GTN, follow-up hCG monitoring every month for at least 12 months is essential for surveillance of relapse. Reliable contraception must be used throughout this period.

Future fertility, pregnancy, and offspring are not affected, although psychosocial and sexual counseling may be needed for some patients.

6 | ESTABLISHMENT OF A (NATIONAL) GTD CENTER

Centralized care is needed for optimal management of a rare disease like GTD. Without some type of centralization, treatment decisions will be inconsistent. Centralized management can vary from only hCG monitoring with treatment advice to patient referral. Creating a center is not easy. It starts with sharing the idea with colleagues and promoting it at national meetings. Make sure you have support from the national obstetrics and gynecology governing body. Create a multidisciplinary team of gynecology, gynecological oncology, medical oncology, pathology, and the hCG laboratory. Work with a clear model of care. Create a clinical guidelines committee, create a database, and develop a website. Some form of annual funding will be needed for the center to develop and maintain a database, website, patient information, reading material, and nursing staff, and to allow presentations at national meetings. Try to establish central pathology review for the whole region.

AUTHOR CONTRIBUTIONS

Each author contributed in writing different sections of the article as well as critical appraisal of the whole article.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES