MANAGEMENT OF HYDATIDIFORM MOLE

R. Pascal, M. Palacio, MD Gómez Roig

1. INTRODUCTION

Gestational trophoblastic disease (GTD) forms a group of heterogeneous diseases arising from abnormal trophoblastic proliferation of the placenta with the potential to locally invade the uterus and metastasise. Histologically, we can classify them into:

- Hydatidiform mole:
• Complete
• Partial

- Gestational Trophoblastic Neoplasia:
• Invasive mole
• Choriocarcinoma
• Placental site trophoblastic tumour
• Epithelioid trophoblastic tumour

In this protocol, the management of hydatidiform mole is discussed. For the management of gestational trophoblastic neoplasia (GTN), refer to the specific protocol. About 80% of gestational trophoblastic disease corresponds to hydatidiform mole, 15% to invasive mole and 5% to choriocarcinoma[1]. The incidence for complete and partial mole is 1-3:1000 pregnancies and 3:1000 pregnancies respectively[2].
The best-established risk factor for hydatidiform mole is advanced maternal age (>40 years-old) followed by a previous history of molar pregnancy, without being modified by the change of partner (1% if history of one previous molar pregnancy and 15-20% if two previous molar pregnancies). There is less evidence regarding repeated abortions and blood groups A and AB[1].

2. DIAGNOSTIC APPROACH

The confirmatory diagnosis of hydatidiform mole requires a pathological or genetic study. Currently, in our environment, the most frequent suspicion of hydatidiform molar disease prior to uterine evacuation is given by the ultrasound image.

2.1. Symptoms:
They usually manifest in the form of:
- First trimester metrorrhagia, being the most frequent symptom.
- First trimester abortions.
- Pelvic pain and pressure, probably secondary to increased uterine size and/or presence of theca lutein cysts.
- Expulsion of hydropic vesicles through the vagina, being rare but diagnostic.
Other classic symptoms are: anaemia, preeclampsia onset before 20 gestational weeks, hyperemesis, hyperthyroidism (if ß-HCG>100,000 mIU/ml persists for weeks, probably due to
homology between thyroid-stimulating hormone (TSH) and beta human chorionic gonadotropin (ß-HCG) and respiratory distress (in cases of lung involvement), all of

which are less frequent findings nowadays given the routine practice of early ultrasound.

2.2. Ultrasound:

In the transvaginal ultrasound of these patients we can find:
- Adnexal masses compatible with theca lutein cysts, more frequent in complete moles.
- Intrauterine image in "snowstorm" without fetal development, in complete moles (Figure A).
- Heterogeneous image corresponding to the trophoblastic mass with concomitant embryo image, in partial moles (Figure B).

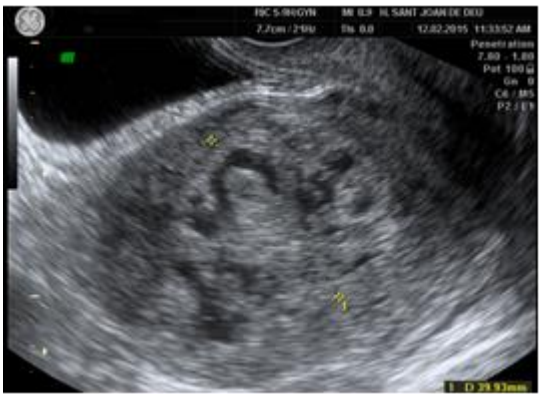

Figure A

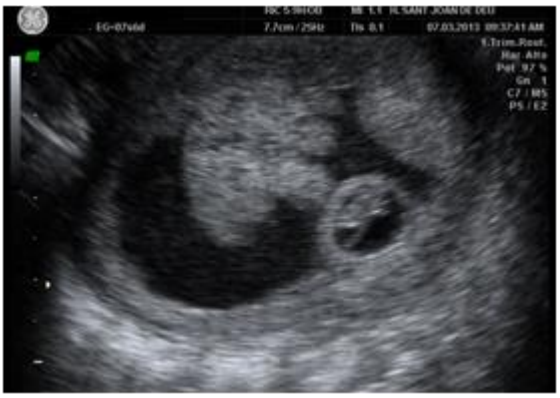

Figure B

2.3. Other complementary exams:

- Blood test: Complete blood count, blood group, coagulation, hepatorenal function and determination of ß-HCG.
- Baseline pre-evacuation chest X-ray.
- Thyroid function (TSH and T4) if there is clinical suspicion of its impairment (in the form of tachycardia, hypertension, hyperreflexia, tremors... which occur in <10% patients).
- Gasometry and pulmonary CT if there is clinical suspicion of trophoblastic embolism in the lungs.

The differential diagnosis of partial and complete mole can be found in the following table[3]:

Table 1

Features	PARTIAL MOLE	COMPLETE MOLE
Aetiology	1 ovum + 2 sperms	Empty ovum + 1 sperm which duplicates (90%) Empty ovum + 2 sperms (10%)
Karyotype	Triploid (69,XXX or 69,XXY)	Diploid (46,XX or 46,XY)
Histology		
• **Fetus and fetal erythrocytes**	Usually present	Not present
• **Villous oedema**	Variable, focal	Diffuse

• **Trophoblast proliferation**	Focal, Moderate	Diffuse, severe
Clinical presentation		
• **Diagnosis**	Miscarriage	Molar gestation
• **Uterine size**	Small for gestational age	50% large for gestational age
• **Theca lutein cysts**	Rare	15-25%
• **Medical complications**	Rare	<25% (more frequent if uterine size >14-16 GA)
• **Malignancy risk**	1-5%	15-20%

3. TREATMENT:

- Suction curettage prior to mechanical cervical dilatation and under ultrasound guidance is the method of choice. If necessary, you can use a curette after suction.
- Medical evacuation is formally contraindicated in cases of complete moles. In partial moles, medical evacuation may be considered when the size of the fetus contraindicates suction curettage, assessing the risk-benefit of a potential increase of the GTN risk.
- The administration of uterotonics is only recommended in the event of post-mortem bleeding evacuation.
- Anti-D immunoglobulin will be administered to all Rh-negative patients, after the evacuation procedure.
- Hysterotomy is contraindicated due to the risk of spreading the disease.
- Adnexal-preservation in hysterectomy may be a therapeutic option in patients who present a fulfilled reproductive desire, since it presents a lower risk of postmolar malignant sequelae compared with suction curettage.

4. PATHOLOGICAL STUDY

The study of the material obtained by suction curettage will be carried out (a sample will be sent to the pathology laboratory) or by chorionic biopsy (one sample will be sent to the pathology laboratory and another to the genetics laboratory) in any of the following cases:
- There is no previous evidence of a gestational sac, vesicle or embryo.
- Existence of clinical, analytical or ultrasound suspicion of hydatidiform mole (history of a previous mole, enlarged uterus, theca lutein cysts, hyperemesis, hyperthyroidism symptoms, vaginal expulsion of vesicular material, de novo hypertension, etc.)
- Finding of ß-HCG> 150,000 IU/L (it is not necessary to carry out routine determination of ß-HCG).

In the rest of the cases it is not necessary to send the sample to the pathology laboratory. In these cases and when no sample is available, a urine pregnancy test will be recommended at 3 weeks of the evacuation/expulsion, and reconsultation in the event of a positive result.

5. FOLLOW-UP

All patients with a diagnosis of hydatidiform mole will be referred to hospital follow-up, whether there has been suspicion prior to evacuation or if it has been an unexpected finding in the pathology study. In both cases we will carry out:

- Serial monitoring of ß-HCG:

• First determination 24-48 hours after evacuation (except if there has been no suspicion of hydatidiform mole prior to evacuation).
• Weekly determination until 3 negative consecutive determinations are achieved (ß-HCG <5 m IU/l).
• Subsequently, monthly determinations will be made.

If the negativisation of ß-HCG levels has been observed 8 weeks before or after evacuation, the monthly determination of ß-HCG will continue until the 6 months post evacuation.
If the negativisation is later than 8 weeks after evacuation, the monthly follow-up will be performed for 6 months from the last negative weekly determination of ß-HCG.

- Transvaginal ultrasound within the first 7-10 days of post-evacuation follow-up. Subsequently, the need for transvaginal ultrasound will be evaluated according to the evolution of ß-HCG.

- Chest X-ray if no previous X-ray is available (when the diagnosis of hydatidiform mole is a pathology finding after uterine evacuation). If there is a preevacuation chest X-ray available, it is NOT necessary to repeat it.

- Given the suspicion of persistence of intrauterine disease, rebiopsy or reevacuation is not indicated to confirm malignancy of gestational trophoblastic disease given the risk of triggering very serious uterine bleeding. These patients will be referred to oncological gynaecologists.

- In case of persistence of ß-HCG without an ultrasound image that justifies it, a gynaecological examination will be done to monitor involution of pelvic structures and rule out the presence of vaginal metastases.

- The ß-HCG follow-up will also be carried out in patients who have undergone hysterectomy, given the risk of malignant sequelae in 3-5% of cases.

6. REFERRAL TO ONCOLOGICAL GYNAECOLOGISTS

Given the suspicion of GTN, the referral of the patient to the oncological gynaecologists should be considered:
- Piled up intrauterine image, with abundant perfusion that can be observed by colour Doppler and that suggests a potential surgical risk.
- Suspected persistence of intrauterine disease after a first evacuation.
- Suspicion of GTN:
• Plateau ß-HCG levels during 4 determinations in a period of three weeks or more (days 1, 7, 14 and 21).
• Elevation >10% of ß-HCG levels in three consecutive weekly determinations for a period of two weeks or more (days 1, 7 and 14).
• ß-HCG levels remain elevated for 6 months or longer.
• Pathology laboratory reports the diagnosis of choriocarcinoma.
• Evidence of metastatic disease.

7. CONTRACEPTIVE ADVICE

It is necessary to inform the patient of the importance of avoiding a new pregnancy during ß-HCG monitoring. Oral contraceptives will be recommended during follow-up since in these patients there is sufficient evidence that they do not increase the risk of subsequent GTN, they may even decrease it, and have a lower pregnancy rate compared to the use of barrier methods.

The patient will be discharged from the unit and/or a new pregnancy may be considered once the ß-HCG follow-up has been concluded (according to point 5).

8. SPECIAL SITUATIONS: TWIN PREGNANCY WITH A COEXISTENT FETUS AND MOLE

Twin gestation with coexistence of a molar gestation and a viable fetus is relatively rare (1/22,000 to 100,000) gestations[4]. In these cases, the patient should be informed of: the perinatal morbidity, with less than a 25% probability of achieving a live child and with an increase in the risk of intrauterine fetal death (40%) and premature birth (36%); the increase in medical complications: such as hyperthyroidism, haemorrhage and hypertensive state of pregnancy, as well as metastatic molar disease requiring chemotherapy.

If the patient wishes to continue with the pregnancy, the following will be performed:

- Fetal karyotype.
- Fetal morphological ultrasound to rule out malformations.
- Chest X-ray to rule out metastatic disease.
- Serial monitoring of ß-HCG during pregnancy and postpartum follow-up as in patients with molar pregnancy (section 5).

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1 Guía clínica Sociedad Española Oncologia Médica (SEOM). 2017

2 Clinical guideline European Society for Medical Oncology (ESMO). 2013

3 Modified from ACOG Practice Bulletin No 53. Diagnosis and Treatment of Gestational Trophoblastic Disease

4 ACOG Practice Bulletin No 53. Diagnosis and Treatment of Gestational Trophoblastic Disease