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RESEARCH PERSPECTIVES AND CURRENT MANAGEMENT OF GESTATIONAL TROPHOBLASTIC DISEASES IN EUROPE.

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14.1 Introduction

Despite a growing literature in the field of gestational trophoblastic diseases (GTD) published this last decade by expert teams and international societies[1,2], randomized clinical trials comparing treatment or follow-up strategies are generally either not available or cannot provide evidence at a level of detail sufficient to apply to the wide range of patients seen in everyday clinical practice. Moreover, European national reference centres are still faced with unsuitable management cases with unfortunate consequences. As cure rates of gestational trophoblastic neoplasia (GTN) should now approach 100%, it is mandatory to favour fertility sparing treatments as well as a rationalized follow-up. In this chapter, we will describe the missions and approaches of the European Organisation for Treatment of Trophoblastic Diseases (EOTTD) and the consensus among European experts on the management of gestational trophoblastic diseases.

14.2 Missions of the EOTTD

The EOTTD was created in 2010 to optimize and rationalize treatment and follow-up protocols by bringing together knowledge of clinicians and researchers from 29 countries working in the field of GTD in Europe (Table 1).

Table 14.1. Member Countries of the European Organization for Treatment of Trophoblastic Diseases.

1) Country	2) National reference centre
Austria	
Belgium	*
Bosnia	
Bulgaria	
Croatia	
Czech Republic	
Denmark	
Finland	
France	3) *
Germany	
Greece	
Herzegovina	
Hungary	
Ireland	4) *
Italy	
Lithuania	
Netherlands	5) *
Norway	
Poland	
Romania	
Serbia	
Slovakia	
Slovenia	
Spain	
Sweden	

Switzerland

6) *

Turkey

Ukraine

United Kingdom

*

Through EOTTD, experienced European centres support the creation of new reference centres such as in Switzerland, Belgium and more recently Ireland. The annual congress of EOTTD, which is alternately held in member countries, is a privileged place to discuss about the management of difficult cases for clinicians, pathologists and geneticists. Since EOTTD was launched, four working parties involving multiple European countries have been created focusing on clinical management, pathology, genetics and human chorionic gonadotropin (hCG). Each group conducts projects involving the maximum number of EOTTD countries and is due to make a presentation on the first achievements of EOTTD at a specific session of each European Society of Gynaecological Oncology meeting. For instance, the agreement level among EOTTD experts on the management of GTD was assessed and the results will be detailed below. Delineating optimal management of GTD in the context of European countries is then the next goal of the clinical working group. The pathology group is developing early diagnosis criteria for hydatidiform moles and GTN, while the genetics group is evaluating the need for genetics tools in certain GTDs. The hCG group is educating members of EOTTD on the differential value of available hCG testing kits, with the aim of homogenizing practice between European countries. The biobank of gestational trophoblastic diseases samples created in France in 2014 illustrates the will to share knowledge and expertise on rare diseases to favour basic science research. Such single-centre initiatives set the stage for sustainable collaboration between centres.

Since the development of EOTTD, other networks will be developed on a Europe-wide scale. As it is particularly difficult to provide high quality and cost effective healthcare for patients who

have rare diseases requiring a concentration of resources and expertise, co-operation in healthcare between European Union member states has increased following the development of European Union health policy. Also, accessibility to healthcare for patients varies across the European Union. More efficient and coordinated sharing of resources and expertise was thus needed, and can be achieved through the creation of European Reference Networks (ERNs). The objectives of the ERNs are seen to be best achievable at European Union level. These encompass:

- better access of patients to highly specialised and high quality and safe care,
- European co-operation on highly specialised healthcare,
- pooling knowledge,
- improving diagnosis and care in medical domains where expertise is rare,
- helping Member States with insufficient number of patients to provide highly specialised care,
- maximising the speed and scale of diffusion of innovations in medical science and health technologies.
- being focal points for medical training and research, information dissemination and evaluation.

EOTTD will be linked and recognised as an existing network to further work as permanent platforms at European Union level.

14.3 Management consensus among EOTTD experts

In order to improve the level of healthcare in the field of gestational trophoblastic diseases, EOTTD experts rated the appropriateness of statements related to everyday clinical practice. A large agreement was found among experts, which reflects a common will to standardize the management of diagnosis, treatment and follow-up of GTD. This section will summarize the principles of management among EOTTD countries. Except when mentioned, almost all EOTTD experts approved the following statements.

14.3.1 Diagnosis of hydatidiform moles

The management of patients with GTD should preferentially be coordinated through national reference centres, which bring together the knowledge of specialized physicians. During the first trimester of pregnancy, it is desirable to strive for the diagnosis of hydatidiform moles, which are premalignant entities of GTD. Patients with suspected cases of hydatidiform mole should have a pelvic ultrasonography. A normal ultrasonography does not exclude the diagnosis of hydatidiform mole. In any ultrasound suspected case, a quantitative determination of serum hCG is recommended. Since histology is mandatory to achieve a correct diagnosis of hydatidiform mole, national reference centres should ensure the confirmation of each suspected case by a refering pathologist. Gold standard histological criteria for diagnosis of partial and complete hydatidiform mole were described by Sebire et al.[3] and Genest et al. [4] and should be applied in every suspected case. These criteria require the use of ancillary techniques in difficult cases of hydatidiform mole. After the diagnosis confirmation of hydatidiform mole, it is unclear among exerts whether it is justified to look for metastases. This is still a matter of debate within the International Society for Study of Trophoblast Diseases since Northern American societies recommended in 2002 and 2004 to perform baseline chest x-ray for patients with suspected or confirmed partial or complete hydatidiform mole[5,6], while the Royal College of Obstetricians and Gynaecologists and the French Reference Centre for Trophoblastic Diseases do not[7,8]. However, recent international recommendations on the management of trophoblastic diseases do not mention the need for baseline chest x-ray [1,2].

14.3.2 Treatment of suspected hydatidiform mole

The uterine evacuation should rather be performed under ultrasound control to ensure completeness in the standard treatment hydatidiform mole. A second uterine evacuation can be considered in case of persistent ultrasound abnormalities suspicious of residual molar tissue,

while a third uterine evacuation is not recommended because of the increased risk of synechia. There is no justification to operate on functional cysts associated with hydatidiform mole in the absence of complications (cyst rupture and haemorrhage, adnexal torsion). As pathological diagnosis confirmation may sometimes require several weeks, it is recommended to inject anti-D immunoglobulin to Rhesus negative women in both cases of partial and complete hydatidiform mole. Hysterectomy might only be considered to treat confirmed hydatidiform mole when childbearing considerations have been fulfilled.

14.3.3 Post-molar follow-up

A regular quantitative hCG follow-up is recommended after hydatidiform mole at least until the values are within the normal range. This quantitative determination of hCG will provide the basis for a potential further diagnosis of GTN. After normalization, hCG follow-up of hydatidiform mole should be done on a monthly basis. In case of complete mole, this post-normalization follow-up should last at least 6 months and no pregnancy should be initiated during this time. Contraception is therefore recommended after evacuation of an HM. A decreasing hCG does not require any routine imaging. In case of partial mole, not all EOTTD experts agreed on the delay after which a new pregnancy can be initiated. Among the rare published series, no post molar GTN diagnosis was made after hCG normalization[9-11]. It is therefore reasonable to recommend that a new pregnancy can be safely started once hCG returned to normal after a PHM.

14.3.4 Gestational trophoblastic neoplasia

Malignant stages are constituted of invasive hydatidiform mole, choriocarcinoma, placental site trophoblastic tumour and epithelioid trophoblastic tumour. Since symptoms vary widely and may be misleading, a quantitative determination of hCG is recommended in case of persistent

bleeding after a pregnancy, if retained pregnancy material has been excluded, whatever the pregnancy outcome. Similarly, in case of metastasis (lung, liver, brain, renal or vaginal) of unknown origin in a woman in reproductive age, a quantitative determination of hCG is recommended.

The following criteria were established by FIGO in 2002[12] to define the malignant transformation in GTN:

- A plateau of hCG (less than 10 % variation) lasting for at least four measurements over a period of 3 weeks or longer (days 0, 7 14 and 21)
- A rise (10 % or greater increase) of hCG lasting for at least three measurements over a period of 2 weeks or longer (days 0, 7 and 14)
- GTN is diagnosed if there is a histological diagnosis of gestational choriocarcinoma

Spontaneous remission of hydatidiform mole is characterized by a slow decrease of hCG, which implies that GTN should not be routinely diagnosed in woman with an elevated but falling hCG 6 months following uterine evacuation of a hydatidiform mole. Moreover, a histological diagnosis of invasive mole is not enough to diagnose a GTN as long as hCG levels spontaneously decrease.

Once the diagnosis of neoplasia is made, investigation for metastasis of GTN is mandatory to give information on prognosis and treatment. Loco regional investigation includes at least a pelvic examination with ultrasonography. Distant investigation includes at least a chest X-ray, even if lung computed tomography (CT) may also be used. Lung metastases should be counted with chest X-ray but not with CT to calculate the FIGO score. In case of lung metastases, investigation for abdominal and brain metastases is recommended. Liver metastases should be sought by ultrasonography or CT. For brain metastases, magnetic resonance imaging is superior to computed tomography.

EOTTD experts agree with the use of the WHO / FIGO prognostic scoring system for GTN as reported by FIGO[12] which allows the definition of :

- low-risk patients as having a 0 to 6 FIGO score, with or without metastases
- high-risk patients as having a 7 or higher FIGO score, with or without metastases

Therapeutic indications for GTN should be based according to FIGO score. Single agent chemotherapy is the recommended treatment for low risk GTN with an overall cure rate close to 100 %. Among EOTTD countries, methotrexate is the recommended first line single agent treatment of low risk GTN. Surgery is not recommended as first line treatment of low risk GTN for reproductive age women wishing to conceive. For high-risk GTN, combination chemotherapy is the recommended medical treatment and surgery of metastases is not routinely indicated. Total hysterectomy is the reference treatment for placental site trophoblastic tumour and epithelioid trophoblastic tumour confined to the uterus.

14.3.5 Post-chemotherapy follow-up

The duration of hCG follow-up after gestational trophoblastic neoplasia depends on the FIGO score and should be at least maintained for 12 or 18 months in case of low- or high-risk disease, respectively. No pregnancy should be initiated during this follow-up.

14.4 Conclusion

There are few published randomized trials on which to base evidenced recommendations about management of GTD. Centralised management of patients with gestational trophoblastic diseases is then a safe way to proceed as every gynaecologist, oncologist or pathologist is expected to see very few cases in a lifetime. Kohorn et al. recently confirmed this long-standing concept, highlighting the decreased mortality of patients managed by expert centres[13]. Experienced centres from EOTTD then play a key role in the establishment of new European national centres. International collaborative research projects are also more likely to include a high

number of patients. EOTTD has to move forward on that basis following the International Society for the Study and Treatment of Trophoblastic diseases, which has always been a leader in this field by bringing together the knowledge of countries with different resources and epidemiology.

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