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Formalised consensus of the European Organisation for Treatment of Trophoblastic Diseases on management of gestational trophoblastic diseases

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KEYWORDS
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Hydatidiform mole
Molar pregnancy
Rare cancers
Human chorionic gonadotropin
Choriocarcinoma
Placental site

Abstract Gestational trophoblastic disease (GTD) is a spectrum of cellular proliferations arising from trophoblast. Their invasive and metastatic potential sometimes requires chemotherapy and/or surgery. Current management is generally associated with favourable prognosis. Therefore, treatments must be chosen according to the desire for further childbearing of each patient. The European Organisation for Treatment of Trophoblastic Diseases (EOTTD) is dedicated to optimise diagnosis, treatment, follow-up and research in GTD by bringing together knowledge of clinicians and researchers from 29 countries working in the field of GTD in Europe. This study assessed the level of agreement among an expert panel of the EOTTD in order to rationalise the management of patients in Europe. The RAND/UCLA Appropriateness Method was used to combine the best available scientific

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trophoblastic tumour
Epithelioid trophoblastic tumour

evidence with the collective judgment of experts to yield a statement regarding the appropriateness of performing a procedure at the level of patient-specific symptoms, medical history and test results. There was an agreement for 54 statements while the experts showed a disagreement for two statements. As there is little evidence from randomised trials on which to base recommendations about management of GTD, many of these recommendations are based on expert opinion derived from changes in management fact that have improved outcomes from nearly 100% fatality to nearly 100% cure rates. However, a large agreement among experts is invaluable to the individual clinician who is struggling to decide whether a fertility-sparing treatment of hydatidiform mole or a low-risk GTN can be chosen and how it must be conducted.

1. Introduction

Gestational trophoblastic disease (GTD) is a spectrum of cellular proliferations arising from the different types of trophoblast encompassing five main clinicopathologic forms: hydatidiform mole (complete and partial), invasive mole (IM), choriocarcinoma (CC), placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour [1,2]. These diseases are predominantly found in women of reproductive age from all ethnic groups and their invasive and metastatic potential sometimes requires chemotherapy and/or surgery. Current management is generally associated with favourable prognosis. Therefore, treatments must be chosen according to the desire for further childbearing of each patient.

The European Organisation for Treatment of Trophoblastic Diseases (EOTTD) is dedicated to optimise diagnosis, treatment, follow-up and research in GTD by bringing together knowledge of clinicians and researchers from 29 countries working in the field of GTD in Europe. European countries included in the EOTTD have much in common, of which the incidence of gestational trophoblastic diseases, general health care system organisation, and availability of medical and paramedical examinations. The following recommendations have been established by an expert panel of the EOTTD in order to rationalise the management of patients in Europe. Randomised 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. Therefore, the RAND/UCLA Appropriateness Method (RAM) was used to combine the best available scientific evidence with the collective judgment of experts to yield a statement regarding the appropriateness of performing a procedure at the level of patient-specific symptoms, medical history and test results.

Forty-five experts from 16 countries of EOTTD were asked to rate 56 statements twice according to how appropriate they felt each statement was in properly managing patients with GTD.

2. Material and methods

According to the RAM [3], an 8-member steering group of the EOTTD critically reviewed the literature to summarise the scientific evidence available on GTD management and developed a list of 56 statements to be rated by an expert panel. The main selection criteria for the constitution of the expert panel were acknowledged leadership in the field of GTD, absence of conflicts of interest, geographic diversity and a multidisciplinary practice setting. Forty-five experts from 16 countries of EOTTD were selected and sent the list of statements along with the literature review and instructions (Table 1). The experts were asked to rate each statement using a 7-point scale according to how appropriate they felt each statement was in properly managing patients with GTD. A score of 1 indicates that the statement is highly inappropriate and 7 that it is highly appropriate. The experts rated each of the statements twice, in a two-round 'modified Delphi' process [4]. In the first round, the ratings were made individually at home, with no interaction among experts. In the second round, the experts met face-to-face for 1 day under the leadership of a moderator, discussed the rating focusing on the areas of disagreement, modified the original list of statements if needed and rerated each statement individually.

The definition of agreement and disagreement among experts was defined according to the number of experts rating each statement [4] (Table 2). Agreement was defined by a number of experts rating outside the region containing the median value (1–2, 3–5, 6–7) of $\leqslant$12, $\leqslant$13 and $\leqslant$13 for a total number of experts of 39, 41 and 42, respectively. Disagreement was defined by a number of experts rating in each extreme (1–2 and 6–7) of $\geqslant$13, $\geqslant$14 and $\geqslant$14 for a total number of experts of 39, 41 and 42, respectively.

3. Results

Each of the 45 experts responded to the first questionnaire and 42 out of 45 participated in the second (93% response rate). Finally, 17 statements were rated by 42

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Table 1
The expert panel of European Organisation for Treatment of Trophoblastic Diseases (EOTTD).

Name	Country	Speciality
Frédéric Goffin	Belgium	Gynaecologic oncology
Filip Hron	Czech Republic	Gynaecology obstetrics
Petr Šafář	Czech Republic	Gynaecologic oncology
Lars O. Vejerslev	Denmark	Gynaecology obstetrics
Jocelyne Attia*	France	Medical gynaecology
Lucien Frappart	France	Pathology
François Golfier*	France	Gynaecology obstetrics
Jean-Pierre Lotz	France	Medical oncology
Jérôme Massardier*	France	Gynaecology obstetrics
Sophie Patrier	France	Pathology
Benoit You	France	Medical oncology
Eva Maria Grischke	Germany	Gynaecology obstetrics
Vilmos Fülöp	Hungary	Gynaecology obstetrics
Maria Grazia Cantu	Italy	Gynaecology obstetrics
Ezio Fulcheri	Italy	Pathology
Angela Salerno	Italy	Pathology
Antonella Villa	Italy	Gynaecologic oncology
Simonetta Rimondini	Italy	Medical oncology
Christianne Lok	Netherlands	Gynaecologic oncology
Leon Massuger*	Netherlands	Gynaecologic oncology
Nienke van Trommel*	Netherlands	Gynaecologic oncology
René Verheijen	Netherlands	Medical gynaecology
Janne Kaern	Norway	Gynaecologic oncology
Rita Steen	Norway	Gynaecologic oncology
Ewa Nowak Markwitz	Poland	Gynaecologic oncology
Jozef Sufliarsky	Slovakia	Medical oncology
Miroslav Korbel	Slovakia	Gynaecology obstetrics
Ulrika Joneborg	Sweden	Gynaecologic oncology
Thomas Hogberg	Sweden	Gynaecologic oncology
Alexandre Rozenholc	Switzerland	Gynaecologic oncology
Vildana Finci	Switzerland	Pathology
Sinan Berkman	Turkey	Gynaecologic oncology
Mehmet Harma	Turkey	Gynaecologic oncology
Muge Harma	Turkey	Gynaecologic oncology
Cem Iyibozkurt	Turkey	Gynaecologic oncology
S. Sinan Ozalp	Turkey	Gynaecologic oncology
Muzaffer Sanci	Turkey	Gynaecologic oncology
Nataly Tsip	Ukraine	Gynaecologic oncology
Robert Coleman	United Kingdom	Medical oncology
Janet Everard	United Kingdom	Nurse specialist
Philip M Savage	United Kingdom	Medical oncology
Michael J Seckl*	United Kingdom	Medical oncology
J. Richard Smith	United Kingdom	Gynaecologic oncology
John A Tidy	United Kingdom	Gynaecologic oncology
Matthew C Winter	United Kingdom	Medical oncology

* This expert was a member of the steering group.

experts, 37 statements by 41 experts and two statements were rated by 39 experts (Fig. 1). After completion of the two rounds, the analysis method revealed that there was an agreement for 54 statements while the experts showed a disagreement for two statements (Table 3).

4. Discussion

Guidelines are a relevant way of summarising the evidence sustaining high-quality health care. Internationally accepted tools for assessing the evidence are sometimes not suitable, particularly in the case of rare diseases. As few contributory randomised clinical trials have been published in the field of gestational trophoblastic diseases, we decided to use the most appropriate group judgement method (RAND/UCLA

Table 2
Definitions of agreement and disagreement for different panel sizes. The number of panellists rating in extreme regions and outside the region containing the median value depends on the panel size [4].

Panel Size	Disagreement	Agreement
	Number of panellists rating in each extreme (1–2 and 6–7)	Number of panellists rating outside the region containing the median (1–2; 3–5; 6–7)
38–39-40	$\geqslant 13$	$\leqslant 12$
41–42-43	$\geqslant 14$	$\leqslant 13$

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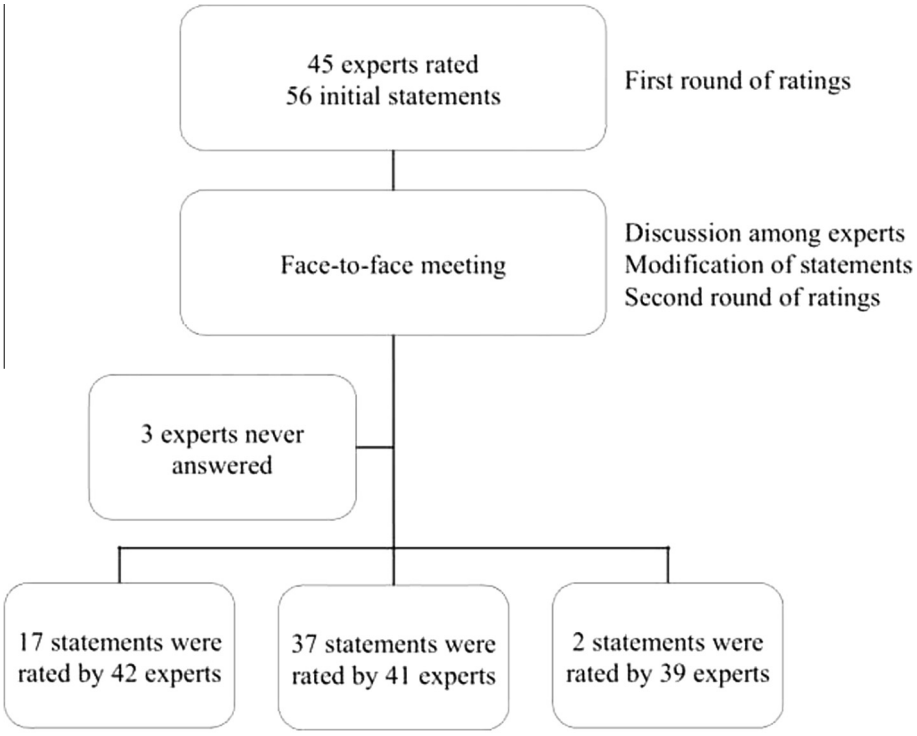

Fig. 1. Rating process of statements by European Organisation for Treatment of Trophoblastic Diseases (EOTTD) experts.

Appropriateness Method) [4]. The objective was not to reach a 100% consensus but rather to assess the level of agreement among EOTTD experts. The strength of these recommendations is that it is truly multidisciplinary with a broad representation from 16 European countries across dedicated organisations among which some have been internationally recognised for decades. The panel included people with expertise in gestational trophoblastic diseases who were thought to have credibility with the target audience.

There are potential weaknesses in a group judgement method such as this. Even if generally drawn from national reference centres, most of the statements cannot be strongly based on research evidence [8–14]. Moreover, the level of experience will vary between centres and experts with some having managed thousands of cases and others only hundreds or less. However, such statements could still be associated with a strong level of agreement among numerous international experts. We will inevitably have overlooked some infrequent clinical situations, in spite of the methodology and feedback from all experts. It is therefore intended that these recommendations will be updated regularly in response to feedback and, hopefully, increasing evidence in our field.

Encouragingly, there were only two statements for which no agreement could be reached after two rounds of rating. Five experts out of 41 did not agree with the uselessness of investigations to diagnose metastases in case of hydatidiform mole. This statement is still a matter of debate among International Society for Study of Trophoblastic 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 [10,13], while the Royal College of Obstetricians and Gynaecologists and the French Reference Centre for Trophoblastic Diseases do not [9,12]. However, since the literature review prior to the first rating round, international recommendations on the management of trophoblastic diseases have been published and do not mention the need for baseline chest X-ray [15].

Four experts out of 41 did not agree with the statement that a new pregnancy is allowed immediately after normalisation of human chorionic gonadotropin (hCG) levels in case of PHM and 15 experts considered that this statement did not meet full agreement criteria. The delay to allow a new pregnancy after HM depends on the duration of hCG monitoring after return to normal. As post molar GTN is usually diagnosed during the first year after HM, hCG monitoring may be compromised and relapse treatment may be delayed by a new pregnancy started too early. The main reason why some of the European experts did not fully agree with this statement is the low number of published studies on the risk of post-normalisation GTN after PHM [16–18]. However, these three studies included more than 800 patients with confirmed PHM and reported no GTN diagnosis after hCG normalisation. It is though reasonable to admit that a new pregnancy can be safely started once hCG returned to normal after a PHM [18].

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Table 3
Level of agreement among experts for each statement after the second round of ratings.

Statements	Experts ratings				Median	Level of agreement
	Total	Rating regions				
		1–2	3–5	6–7		
Diagnosis of gestational trophoblastic diseases						
(1) To improve the management of Gestational Trophoblastic Diseases (GTD), it is essential to have a reference structure within or between European countries	42	0	2	40	7	Agreement
(2) GTD include premalignant entities namely partial and complete hydatidiform moles (PHM, CHM)	42	3	0	39	7	Agreement
(3) GTD include histological malignant entities called malignant gestational trophoblastic neoplasia (GTN) which encompass: - invasive moles, - gestational choriocarcinoma, - placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT)	42	5	3	34	7	Agreement
(4) It is desirable to strive for the diagnosis of HM during first trimester of pregnancy	41	1	0	40	7	Agreement
(5) Pelvic ultrasonography is important for the suspicion of HM	41	0	0	41	7	Agreement
(5bis) Normal ultrasonography does not exclude the diagnosis of a mole	41	2	5	34	7	Agreement
(6) A quantitative determination of serum human chorionic gonadotropin (hCG) is recommended in any ultrasound suspicion of HM	41	0	1	40	7	Agreement
(7) No investigations to diagnose metastases are needed when diagnosing an HM	41	5	11	25	6	Disagreement
(8) Histology is mandatory to achieve a correct diagnosis of HM	42	1	3	38	7	Agreement
(9) It is desirable to have a reference pathologist available for reviewing HM	42	0	3	39	7	Agreement
(10) Gold standard histological criteria for diagnosis of PHM and CHM are listed by Sebire et al. [5] and Genest et al. [6]	42	0	1	41	7	Agreement
(11) The use of ancillary techniques is desirable in difficult cases of HM	42	1	5	36	7	Agreement
Treatment of HM						
(12) An uterine evacuation with sonographic control is desirable to ensure completeness in the standard treatment of an HM	41	1	3	37	7	Agreement
(13) There is no justification to operate on functional cysts associated with HM in the absence of complications (cyst rupture and haemorrhage, adnexal torsion)	41	0	1	40	7	Agreement
(14) An injection of anti-D immunoglobulin is recommended in rhesus D negative women with PHM	39	1	3	35	7	Agreement
(15) An injection of anti-D immunoglobulin is recommended in rhesus D negative women with CHM	39	9	3	27	7	Agreement
(16) Hysterectomy might be considered for a confirmed HM when childbearing considerations have been fulfilled	41	2	3	36	7	Agreement
(17) A second uterine evacuation can be considered in case of persistent sonographic abnormalities suspicious of residual molar tissue	41	2	9	30	6	Agreement
(18) A third uterine evacuation is not recommended for an HM (increased risk of synechia)	41	1	1	39	7	Agreement
Follow-up after HM						
(19) hCG follow-up is recommended for HM at least until the values are within the normal range	41	0	1	40	7	Agreement
(20) After normalisation, hCG follow-up of HM should be done on a monthly basis	41	1	3	37	7	Agreement
(21) After normalisation, hCG follow-up of CHM should be done on a monthly basis for at least 6 months	41	2	3	36	7	Agreement
(22) No routine imaging is recommended if hCG decrease spontaneously in HM	41	0	3	38	7	Agreement
(23) A quantitative determination of hCG is recommended in the follow-up of HM to diagnose a GTN	42	0	0	42	7	Agreement
Diagnosis of GTN						
(24) 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	41	0	0	41	7	Agreement
(25) A quantitative determination of hCG is recommended in reproductive age women with metastasis (lung, liver, brain, renal or vaginal) of unknown primary cancer	42	0	0	42	7	Agreement

(*continued on next page*)

Table 3 (*continued*)

Statements	Experts ratings					
	Total	Rating regions			Median	Level of agreement
		1–2	3–5	6–7		
(26) 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) enables for the diagnosis of GTN	41	0	3	38	7	Agreement
(27) 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) enables for the diagnosis of GTN	41	0	2	39	7	Agreement
(28) GTN should not be routinely diagnosed in woman with an elevated but falling hCG 6 months following uterine evacuation of an HM	41	1	3	37	7	Agreement
(29) GTN is diagnosed if there is a histological diagnosis of gestational choriocarcinoma	42	1	0	41	7	Agreement
(30) A histological diagnosis of invasive mole is not enough to diagnose a GTN as long as hCG levels spontaneously decrease	42	5	5	32	7	Agreement
(31) Investigation for metastasis of GTN is mandatory to give information on prognosis and treatment	42	0	0	42	7	Agreement
(32) Loco regional investigation includes at least a pelvic examination with sonography	42	1	0	41	7	Agreement
(33) Distant investigation includes at least a chest X-ray, even if lung computed tomography (CT) may be used	42	1	1	40	7	Agreement
(34) Chest X-rays are used for counting the number of metastases, not lung CT	41	0	3	38	7	Agreement
(35) In case of lung metastases, investigation for abdominal and brain metastases is recommended	41	0	1	40	7	Agreement
(36) Liver metastases may be diagnosed by ultrasound or CT scanning	41	0	1	40	7	Agreement
(37) For brain metastases magnetic resonance imaging is superior to CT scanning	41	0	3	38	7	Agreement
Treatment and follow-up of GTN						
(38) WHO/FIGO scoring system as reported by FIGO [7] allows to define low risk and high-risk patients with GTN	42	0	2	40	7	Agreement
(39) - Low risk GTN patients have a FIGO score of 6 or lower, with or without metastases - High-risk GTN patients have a FIGO score of 7 or higher, with or without metastases	41	0	0	41	7	Agreement
(40) Therapeutic indications for GTN should be based according to FIGO score	41	1	2	38	7	Agreement
(41) Do you agree with the use of the WHO/FIGO prognostic scoring system for GTN as reported by FIGO [7]	41	0	3	38	7	Agreement
(42) Single agent chemotherapy is the recommended treatment for low risk GTN with a overall cure rate close to 100%	41	0	0	41	7	Agreement
(43) Methotrexate (MTX) is the recommended first line single agent treatment of low risk GTN	41	0	1	40	7	Agreement
(44) Surgery is not recommended as first line treatment of low risk GTN for reproductive age women wishing to conceive	41	0	0	41	7	Agreement
(45) Combination chemotherapy is the recommended medical treatment for high risk GTN	41	0	0	41	7	Agreement
(46) Surgery of metastases is not routinely indicated for high risk GTN	41	0	0	41	7	Agreement
(47) Surgery of persistent lung images is not indicated after hCG normalisation	41	1	2	38	7	Agreement
(48) hCG follow-up is recommended for at least 12 months after normalisation in low risk GTN	41	0	0	41	7	Agreement
(49) hCG follow-up is recommended for at least 18 months after normalisation in a high risk GTN	41	0	1	40	7	Agreement
Appropriate time to allow pregnancy after HM and GTN						
(50) Contraception is recommended after evacuation of an HM	41	3	1	37	7	Agreement
(51) After a CHM, it is advised to delay a new pregnancy for 6 months after hCG normalisation	41	1	5	35	7	Agreement
(52) After a PHM, a new pregnancy is allowed immediately after normalisation of hCG levels.	41	4	15	22	6	Disagreement
(53) After a chemotherapy for a GTN, the advice is to delay a new pregnancy for 12 (low risk) to 18 (high-risk) months after hCG normalisation	41	2	3	36	7	Agreement
Management of PSTT and ETT						
(54) Total hysterectomy is the reference treatment for PSTT and ETT confined to the uterus	42	0	2	40	7	Agreement
(55) Histologic diagnosis of PSTT or ETT should be reviewed by a referent pathologist before implementing treatment	42	0	0	42	7	Agreement

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As there is little evidence from randomised trials on which to base recommendations about management of GTD, many of these recommendations are based on expert opinion derived from changes in management fact that have improved outcomes from nearly 100% fatality to nearly 100% cure rates. However, a large agreement among experts is invaluable to the individual clinician who is struggling to decide whether a fertility-sparing treatment of HM or a low-risk GTN can be chosen and how it must be conducted. Such recommendations are also arguably particularly important for surgical and medical gynaecologic oncology teams. Centralised management of GTD, which is associated with a decreased mortality, is not yet structured in each EOTTD country [19]. These recommendations provide the best evidence available on the majority of practical clinical situations as a framework of the main concerns a newly created reference centre should consider. Not all physicians will agree with these recommendations of EOTTD experts, but for the vast majority, they will be a valuable reference to guide clinical practice for patients with GTD.

Conflict of interest statement

None declared.

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