Brazilian Network for Gestational Trophoblastic Disease Study Group Consensus on Management of Gestational Trophoblastic Disease

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OBJECTIVE: To present the Brazilian Network for Gestational Trophoblastic Disease Study Group consensus on management of gestational trophoblastic disease (GTD).

STUDY DESIGN: The modified Delphi technique was used in this study to obtain a consensus among Brazilian specialists on the treatment of GTD. For the 64 statements listed, each participant was asked to assign a Likert scale value according to their agreement. The RAND/UCLA method was used to define the level of consensus among the specialists.

There is great similarity between the European and Brazilian guidelines for GTD treatment.

RESULTS: The response rate of the potential study participants after the 2 rounds was 40/47 (85%). Of the 64 statements presented, there was an agreement on 54/64 (84%). The situations of disagreement were as follows: 1/12 (8%) statements in the section on diagnosis of GTD, 5/10 (50%) statements in the section on treatment of hydatidiform mole (HM), 2/16 (12.5%) statements in the section on diagnosis of gestational trophoblastic neoplasia (GTN), 1/14 (7%) statements in the section on treatment and follow-up of GTN, and 1/5 (20%) statements in the section on

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appropriate time to allow pregnancy after HM and GTN. CONCLUSION: This guideline will serve to standardize the conduct among the Brazilian GTD reference centers as well as to guide the new specialized services that may arise and eventually to physicians who may need to treat cases of GTD. (J Reprod Med 2018;63:261–270)

Keywords: Brazil, hydatidiform mole, gestational trophoblastic disease, rare cancers.

Gestational trophoblastic disease (GTD) refers to a spectrum of placental abnormalities that range from benign forms, represented by hydatidiform mole (HM) (complete [CHM] and partial [PHM]), to malignant and sometimes metastatic entities, namely gestational trophoblastic neoplasia (GTN), which includes invasive mole (IM), choriocarcinoma (CCA), placental site trophoblastic tumor, and epithelioid trophoblastic tumor.[1-3]

In Brazil it is estimated that there is 1 case of GTD in every 200–400 gestations, an incidence 5 to 10 times more frequent than that seen in Europe and North America. Despite over a half century of well-established treatment, there are still reported cases of near-miss and maternal death caused by this condition.[4-6]

In the last 5 years, with the support of the International Society for the Study of Trophoblastic Disease, the Brazilian Network for Gestational Trophoblastic Disease Study Group was created under the auspices of the Brazilian Association of Gestational Trophoblastic Disease in order to diffuse the importance of GTD reference centers throughout the country.[7] It is important to emphasize that Brazil is the fifth most populated country in the world, with 203,657,210 inhabitants, the fifth largest country in territorial extension, with 8,515,767 km^2, and the largest country in the southern hemisphere. In addition, it is worth mentioning that the Brazilian public health system provides free care to all people who seek it.[7] As a result, Brazil has gone from 12 GTD reference centers in 2012 to 47 in 2018, present in all the states of Brazil, especially in its capitals. Although this represents a great advance in the treatment of GTD, we observed a heterogeneity in the care in the different Brazilian GTD reference centers, notably among the most recently created specialized services.

It should not be ignored that, due to the absolute low frequency of GTD cases, making it a rare disease, there is little robust scientific evidence, and the majority of GTD treatment is based on expert opinion.[8] In order to consolidate and disseminate the opinion of specialists in the treatment of GTD, the European Organization for Treatment of Trophoblastic Diseases (EOTTD) presented in 2015 the formalized consensus on management of GTD, combining 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.[9] This was of great value to European physicians and helped the reference centers created later.

The purpose of this paper is to present the Brazilian Network for Gestational Trophoblastic Disease Study Group consensus on management of GTD. This guideline will serve to standardize the conduct among the Brazilian GTD reference centers, as well as to guide the new specialized services that may arise and eventually to physicians who may need to treat cases of GTD.

Materials and Methods

The first 7 authors of this paper reviewed the 57 statements made in the consensus of EOTTD[9] and concluded that they were pertinent to the Brazilian medical reality. In addition, 7 new statements were included that were judged appropriate by the 7-member steering group of the Brazilian Network for GTD Study Group.

The modified Delphi technique was used in this study to obtain a consensus among Brazilian specialists on the treatment of GTD.[10,11] An email invitation was sent to 47 Brazilian physicians who were recognized for treating GTD cases and who treated at least 50 new GTD patients per year. This invitation introduced the research proposal, ensured the confidentiality of the identity in the evaluation of the answers, and presented a form with 64 statements about the treatment of GTD. The 40 Brazilian physicians who agreed to participate in this study are listed in Table I.

For the 64 statements listed, each participant was asked to assign a value according to their agreement. The Likert scale was used, with a score set from 1 to 7 (disagrees totally - fully agrees).

Using the RAND/UCLA method to define categories of scores,[10] the median score of each item on the statement form was used to establish the level of consensus (Table II). Agreement was defined by ≤11 experts giving a rating outside the region containing the median value (1–2; 3–5; 6–7), and disagreement was defined by ≥12 experts giving a

Table I *Expert Panel of the Brazilian Network for Gestational Trophoblastic Disease Study Group*

Name	State	Specialty
Elaine do Azevedo Soares Leal	Acre	Obstetrics and Gynecology
Manoel Calheiros Silva	Alagoas	Obstetrics and Gynecology
Ione Rodrigues Brum	Amazonas	Obstetrics and Gynecology
Nirce Carvalho da Silva	Amapá	Obstetrics and Gynecology
Olivia Lúcia Nunes Costa	Bahia	Obstetrics and Gynecology
Valéria Cristina Gonçalves	Brasília	Obstetrics and Gynecology
Henrique Zacharias Borges Filho	Espírito Santo	Obstetrics and Gynecology
Antonio Chambo Filho	Espírito Santo	Gynecologic Oncology
Mauricio Guilherme de Campos Viggiano	Goiás	Obstetrics and Gynecology
Marília da Glória Martins	Maranhão	Obstetrics and Gynecology
Regiane Martins Ribeiro Itaborahy	Mato Grosso	Obstetrics and Gynecology
Suely de Souza Resende	Mato Grosso do Sul	Obstetrics and Gynecology
Gabriel Costa Osanan	Minas Gerais	Obstetrics and Gynecology
Maríla Gabriela Queiroz da Luz	Pará	Obstetrics and Gynecology
Cláudio Sérgio Medeiros Paiva	Paraíba	Obstetrics and Gynecology
Melania Maria Ramos de Amorin	Paraíba	Obstetrics and Gynecology
Bruno Maurizio Grillo	Paraná	Obstetrics and Gynecology
Aurélio Costa	Pernambuco	Obstetrics and Gynecology
José Arimatéa dos Santos Júnior	Piauí	Obstetrics and Gynecology
Antonio Rodrigues Braga Neto	Rio de Janeiro	Obstetrics and Gynecology
Bruna Obeica Vasconcelos	Rio de Janeiro	Obstetrics and Gynecology
Fernanda Freitas Oliveira Cardoso	Rio de Janeiro	Obstetrics and Gynecology
Flavia Tarabini Castellani Asmar	Rio de Janeiro	Obstetrics and Gynecology
Rodrigo Rocco Pires Pesce	Rio de Janeiro	Obstetrics and Gynecology
Maria do Carmo Lopes de Melo	Rio Grande do Norte	Obstetrics and Gynecology
Elza Maria Hartmann Uberti	Rio Grande do Sul	Obstetrics and Gynecology
José Mauro Madi	Rio Grande do Sul	Obstetrics and Gynecology
Rita de Cássia Alves Ferreira Silva	Rondonia	Obstetrics and Gynecology
Cynthia Dantas de Macedo Lins	Roramia	Obstetrics and Gynecology
Fabiana Rebelo Pereira Costa	Santa Catarina	Obstetrics and Gynecology
Daniela Angerame Yelà Gomes	São Paulo	Obstetrics and Gynecology
Eduarda Silveira	São Paulo	Clinical Oncology
Izildinha Maesta	São Paulo	Obstetrics and Gynecology
Jurandyr Moreira de Andrade	São Paulo	Obstetrics and Gynecology
Karayna Gil Fernandes	São Paulo	Obstetrics and Gynecology
Lawrence Hsu Lin	São Paulo	Obstetrics and Gynecology
Alexandre Pitorri	São Paulo	Obstetrics and Gynecology
Sue Yazaki Sun	São Paulo	Obstetrics and Gynecology
Marina de Pádua Nogueira Menezes	Sergipe	Obstetrics and Gynecology
João de Deus	Tocantins	Obstetrics and Gynecology

rating in each extreme (1–2 and 6–7), both for a total number of experts of 40 (Table II).

This study was approved by the local Institutional Review Board of the Maternity School of Rio de Janeiro Federal University, associated with the Brazilian Research Ethics Committee, under protocol number 2.299.887 (CAAE 74862317.3.0000.5275).

Results

The response rate of the potential study participants

Table II *Definitions of Agreement and Disagreement According to the Panel Size*

	Disagreement	Agreement
Panel size	No. of panelists rating in each extreme (1–2 and 6–7)	No. of panelists rating outside the region containing the median (1–2; 3–5; 6–7)
40	≥12	≤11

after the 2 rounds was 40/47 (85%), and while in the first round 36/40 (90%) experts answered all the assessments, after being specially advised to respond to all sentences, in the second round 100% of statements were analyzed by the participants of this study (Figure 1).

Of the 64 statements presented, there was an agreement of 54/64 (84%) (Table III). Among the areas of disagreement, it was observed in 1 of 12 (8%) statements in the section on diagnosis of GTD, 5 of 10 (50%) statements in the section on treatment of HM, 2 of 16 (12.5%) statements in the section on diagnosis of GTN, 1 of 14 (7%) statements in the section on treatment and follow-up of GTN, and 1 of 5 (20%) statements in the section on appropriate time to allow pregnancy after HM and GTN.

Discussion

The consensus is a scientific method, within intersubjectivity, which aims to bring together the practices, behaviors, and knowledge carried out by professionals specialized in a certain field of knowledge in order to present the best clinical practice for the user.[11] The achievement of the Brazilian consensus on the treatment of GTD is extremely relevant for the care and management of GTD in Brazil, as well as promoting the knowledge of health professionals on how they have treated patients, yet it encourages the establishment of protocols and the restructuring of workflows in order to provide the highest quality of health care.

One of the great challenges in the creation of a consensus is to synthesize methodologically the opinion of several experts. One of the strategies for this is the application of the Delphi exercise, which began to be more widely used in the 1960s, through researchers at Rand Corporation whose

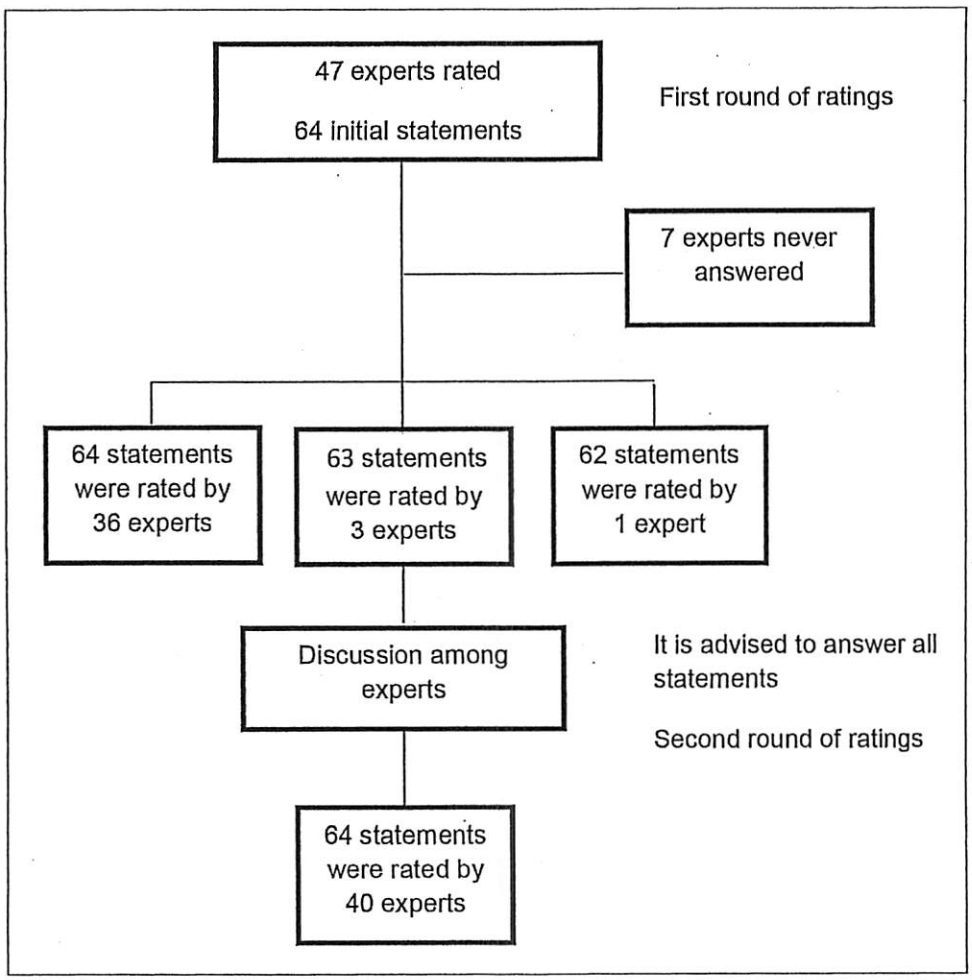

Figure 1
Rating process of statements by Brazilian Network for Gestational Trophoblastic Disease Study Group experts.

Table III *Level of Agreement Among Experts from the Brazilian Network for Gestational Trophoblastic Disease Study Group for Each Statement After the Second Round of Ratings*

Statement	Expert ratings					
		Rating regions				
	Total	1–2	3–5	6–7	Median	Level of agreement
Diagnosis of GTD						
1. To improve the management of patients with GTD in Brazil, the working of the Reference Centers is essential	40	0	0	40	7	Agreement
2. GTD includes premalignant entities, namely PHM and CHM	40	1	3	36	7	Agreement
3. GTD includes histological malignant entities, called malignant GTN, which encompass invasive moles, gestational choriocarcinoma, PSTT, and ETT	40	1	1	38	7	Agreement
4. It is desirable to strive for the diagnosis of HM during the first trimester of pregnancy	40	0	0	40	7	Agreement
5. Pelvic ultrasonography is important for the suspicion of HM	40	0	0	40	7	Agreement
6. Normal ultrasonography does not exclude the diagnosis of a mole	40	3	6	31	7	Agreement
7. A quantitative determination of serum hCG is recommended in any ultrasound with a suspicion of HM	40	0	3	37	7	Agreement
8. No investigations to diagnose metastases are needed when diagnosing HM	40	26	5	9	1	Disagreement
9. Histology is mandatory to achieve a correct diagnosis of HM	40	5	2	33	7	Agreement
10. It is desirable to have a reference pathologist available for reviewing HM	40	0	5	35	7	Agreement
11. Gold standard histological criteria for diagnosis of PHM and CHM must be updated to allow the diagnosis of molar pregnancy at early gestational age	40	0	3	37	7	Agreement
12. The use of ancillary techniques is desirable in difficult cases of HM	40	0	0	40	7	Agreement
Treatment of HM						
13. Uterine evacuation with sonographic guidance is desirable to ensure complete uterine evacuation in the standard treatment of an HM	40	3	11	26	6	Disagreement
14. There is no justification to operate on functional cysts associated with HM in the absence of complications (cyst rupture and hemorrhage, adnexal torsion)	40	1	0	39	7	Agreement
15. An injection of anti-D immunoglobulin is recommended in rhesus D negative women with PHM	40	0	0	40	7	Agreement
16. An injection of anti-D immunoglobulin is recommended in rhesus D negative women with CHM	40	6	4	30	7	Agreement
17. The use of misoprostol for cervical ripening before uterine evacuation is permissible	40	18	11	11	1	Disagreement
18. The use of oxytocin during uterine evacuation is permissible	40	12	6	22	7	Disagreement
19. Hysterectomy might be considered for a confirmed HM when childbearing considerations have been fulfilled	40	13	14	13	5	Disagreement
20. A second uterine evacuation can be considered in case of persistent sonographic abnormalities suspicious of residual molar tissue	40	5	15	20	7	Disagreement
21. A third uterine evacuation is not recommended for an HM (increased risk of synechia)	40	4	7	29	7	Agreement
22. Prophylactic chemotherapy is indicated for patients with high-risk HM and is a good strategy for the treatment of those patients	40	36	2	2	1	Agreement
Follow-up after HM						
23. hCG follow-up is recommended for HM at least until the values are within the normal range	40	0	1	39	7	Agreement
24. After normalization, hCG follow-up of HM should be done on a monthly basis	40	3	6	31	7	Agreement
25. After normalization, hCG follow-up of CHM should be done on a monthly basis for at least 6 months	40	3	6	31	7	Agreement
26. No routine imaging is recommended for hCG levels that regress spontaneously after hydatidiform mole (not developed in the clinical routine: ultrasonography or chest X-ray)	40	4	4	32	7	Agreement
27. A quantitative determination of hCG is recommended in the follow-up of HM to diagnose a GTN	40	0	0	40	7	Agreement

Table III *Level of Agreement Among Experts from the Brazilian Network for Gestational Trophoblastic Disease Study Group for Each Statement After the Second Round of Ratings (Cont'd.)*

Statement	Expert ratings					
		Rating regions				
	Total	1–2	3–5	6–7	Median	Level of Agreement
Diagnosis of GTN						
28. A quantitative hCG is recommended in cases of persistent bleeding after pregnancy (regardless of its outcome, whether abortion, ectopic pregnancy, or childbirth) if no material has been submitted for histology	40	0	2	38	7	Agreement
29. A quantitative determination of hCG is recommended in reproductive age women with metastasis (lung, liver, brain, renal, or vaginal) of unknown primary cancer	40	0	1	39	7	Agreement
30. A plateau of hCG (<10% variation) lasting for at least 4 measurements over a period of ≥3 weeks (days 0, 7, 14, and 21) establishes the diagnosis of GTN	40	0	1	39	7	Agreement
31. A rise (≥10% increase) of hCG lasting for at least 3 measurements over a period of ≥2 weeks (days 0, 7, and 14) establishes the diagnosis of GTN	40	1	4	35	7	Agreement
32. GTN should not be routinely diagnosed in woman with an elevated but falling hCG 6 months following molar evacuation	40	1	3	36	7	Agreement
33. GTN is diagnosed if there is a histological diagnosis of gestational choriocarcinoma	40	1	2	37	6	Agreement
34. A histological diagnosis of invasive mole is not enough to diagnose a GTN as long as hCG levels spontaneously decrease	40	0	5	35	7	Agreement
35. Patients with hCG ≥20,000 IU/L 4 weeks after molar evacuation have an indication for chemotherapy for the treatment of GTN	40	10	6	24	7	Disagreement
36. Patients with a histopathological diagnosis of choriocarcinoma with nonmetastatic GTN have an indication for chemotherapy for the treatment of GTN	40	10	6	24	7	Disagreement
37. Investigation for metastasis of GTN is mandatory to give information on prognosis and treatment	40	0	0	40	7	Agreement
38. Locoregional investigation includes at least a pelvic examination with sonography	40	0	2	38	7	Agreement
39. Distant investigation includes at least a chest X-ray, even if lung CT may be used	40	0	5	35	7	Agreement
40. Chest X-rays are used for counting the number of metastases, not lung CT	40	2	4	34	7	Agreement
41. In case of lung metastases, investigation for abdominal and brain metastases is recommended	40	0	1	39	7	Agreement
42. Liver metastases may be diagnosed by ultrasound or CT scanning	40	0	5	35	7	Agreement
43. For brain metastases magnetic resonance imaging is superior to CT scanning	40	0	4	36	7	Agreement
Treatment and follow-up of GTN						
44. The WHO/FIGO scoring system as reported by FIGO defines low-risk and high-risk patients with GTN	40	1	8	31	7	Agreement
45. Low-risk GTN patients have a FIGO score of ≤6, with or without metastases	40	0	0	40	7	Agreement
46. High-risk GTN patients have a FIGO score of ≥7, with or without metastases	40	3	4	33	7	Agreement
47. Therapeutic indications for GTN should be based according to FIGO score	40	1	4	35	7	Agreement
48. Do you agree with the use of the WHO/FIGO prognostic scoring system for GTN as reported by FIGO?	40	0	3	37	7	Agreement
49. Single-agent chemotherapy is the recommended treatment for low-risk GTN, with an overall cure rate close to 100%	40	1	7	32	7	Agreement
50. MTX is the recommended first-line single-agent treatment of low-risk GTN	40	0	1	39	7	Agreement
51. Patients on the first cycle of treatment with MTX must be hospitalized due the high risk of transvaginal bleeding	40	25	8	7	1	Disagreement
52. Hysterectomy is not recommended as first-line treatment for patients with low-risk GTN for women of reproductive age wishing to conceive	40	0	0	40	7	Agreement
53. Combination chemotherapy is the recommended medical treatment for high-risk GTN	40	0	2	38	7	Agreement
54. Surgery of metastases is not routinely indicated for high-risk GTN	40	1	4	35	7	Agreement
55. Surgery of persistent lung lesions is not indicated after hCG normalization	40	3	4	33	7	Agreement

Table III *Level of Agreement Among Experts from the Brazilian Network for Gestational Trophoblastic Disease Study Group for Each Statement After the Second Round of Ratings (Cont'd.)*

Statement	Expert ratings					
		Rating regions				
	Total	1–2	3–5	6–7	Median	Level of Agreement
56. hCG follow-up is recommended for at least 12 months after normalization in low-risk GTN	40	2	5	33	7	Agreement
57. hCG follow-up is recommended for at least 18 months after normalization in a high-risk GTN	40	4	5	31	7	Agreement
Appropriate time to allow pregnancy after HM and GTN						
58. Contraception is recommended after evacuation of HM	40	2	0	38	7	Agreement
59. Hormonal contraception is safe for patients with HM and can be started immediately after uterine evacuation of molar pregnancy	40	1	0	39	7	Agreement
60. After a CHM it is advised to delay a new pregnancy for 6 months after hCG normalization	40	6	1	33	7	Agreement
61. After a PHM a new pregnancy is allowed immediately after normalization of hCG levels	40	28	8	4	1	Disagreement
62. After chemotherapy for a GTN the advice is to delay a new pregnancy for 12 (low risk) to 18 (high risk) months after hCG normalization	40	0	6	34	7	Agreement
Management of PSTT and ETT						
63. Total hysterectomy is the preferred treatment for PSTT and ETT confined to the uterus	40	1	6	33	7	Agreement
64. Histologic diagnosis of PSTT or ETT should be reviewed by a referent pathologist before implementing treatment	40	0	4	36	7	Agreement

GTD = gestational trophoblastic disease, PHM = partial hydatidiform mole, CHM = complete hydatidiform mole, GTN = gestational trophoblastic neoplasia, PSTT = placental site trophoblastic tumor, ETT = epithelioid trophoblastic tumor, HM = hydatidiform mole, hCG = human chorionic gonadotropin, CT = computed tomography, WHO = World Health Organization, FIGO = International Federation of Gynecology and Obstetrics, MTX = methotrexate.

goal was to establish a strategy to enhance the use of expert opinion.[10] The methodology developed established 3 basic conditions: the anonymity of the respondents, the statistical representation of the distribution of results, and the feedback of the group's responses for reevaluation in the subsequent rounds. The modified Delphi exercise used in this study was innovative because it performed the rounds in a query without face-to-face interaction, through electronic means of communication.[10,11]

Interestingly, of the 57 statements shared between the EOTTD study and this investigation, there were disagreements on the same issues. Considering the statement that recommends against investigating metastases in the diagnosis of HM, both European (5/41 [12%], median 6) and Brazilian (26/40 [56%], median 1) GTD specialists disagree with this statement.[9] This possibly represents the influence of the North American guidelines[12,13] among the Brazilian physicians, as opposed to that of the Royal College of Obstetricians and Gynaecologists[14] that no longer recommended a chest X-ray for patients with a diagnosis of HM. Current international recommendations indicate that there is no need to perform lung metastasis screening for patients diagnosed with HM.[1] Similarly, European and Brazilian GTD specialists disagree with the timing of a new pregnancy after PHM. In response to the statement that pregnancy is allowed immediately after normalization of serum human chorionic gonadotropin (hCG) levels, 4/41 (9%, median 6) Europeans disagree totally, while 28/40 (70%, median 1) Brazilians disagree totally with this statement. Although there are few studies showing the safety of pregnancy soon after hCG normalization in cases of PHM,[15-17] a Brazilian study has shown that the chance of GTN occurring after PHM remission is negligible, and there is no reason to maintain hormonal vigilance or delay pregnancy in this population.[18]

We had 3 differences from the European opinion on the statements presented by the EOTTD. The first was a disagreement that uterine evacuation with sonographic guidance is desirable to ensure

completeness in the standard treatment of HM. Although there is a tendency to agree with this statement among the Brazilian specialists in GTD, some physicians consider, even based on a Brazilian study on this subject, that there is no difference in the rate of complete molar evacuation when sonographic guidance is used.[19] The second was a disagreement that hysterectomy might be considered for confirmed HM in a patient who no longer desires future childbearing. It is important to note that women with HM in advanced maternal age, without future reproductive desire, benefit from prophylactic hysterectomy, not only because it reduces the time to hCG remission, but it also decreases the occurrence of postmolar GTN.[20] The third was a disagreement that a second uterine evacuation can be considered in case of persistent sonographic abnormalities suspicious of residual molar tissue. The second curettage seems to prevent the onset of chemotherapy in 9–60% of patients and could be considered in selected cases.[21-23]

Interestingly, among the 7 questions that were included in addition to those proposed by the EOTTD, only 2 had agreement among Brazilian GTD specialists. The first one says that hormonal contraception is safe for patients with HM and can be immediately indicated after uterine evacuation of molar pregnancy, which was fully agreed upon by the Brazilian GTD experts. Although there are still questions about safety in the use of hormonal contraception in the postmolar follow-up,[24] studies with European and Brazilian populations show that these hormonal contraceptive methods do not promote the development of postmolar GTN and do not increase the time to hCG remission.[25,26] The other statement for which there was consensus among Brazilian GTD experts was the lack of indications for prophylactic chemotherapy, even for cases of high-risk HM. Although Brazilian publications on prophylactic chemotherapy show encouraging results,[27,28] only 1 Brazilian GTD reference center currently employs this strategy.[29]

The other 5 statements included showed disagreement among the Brazilian GTD specialists. Regarding the treatment of molar pregnancy, there was disagreement among Brazilian GTD experts about the appropriateness of using misoprostol for cervical ripening before uterine evacuation and oxytocin during uterine evacuation. Although safe, the use of misoprostol for cervical ripening was associated with trophoblastic embolization when prolonged cervical preparation was used as well as with the development of postmolar GTN among patients with enlarged uterus for gestational age.[14] In the same way, the use of oxytocin should be avoided prior to completion of the evacuation due to the risk of trophoblastic embolization.[14] Regarding the diagnosis of GTN, there was disagreement among Brazilian GTD experts about the indication of chemotherapy for the treatment of GTN in patients with hCG ≥20,000 IU/L 4 weeks after molar evacuation or those with a histopathological diagnosis of choriocarcinoma with nonmetastatic GTN. A recent Brazilian publication showed safety in the hormonal surveillance of patients with nonmetastatic GTN and histopathological diagnosis of choriocarcinoma, notably when hCG levels are falling or normal.[30] Similarly, although hCG level ≥20,000 IU/L 4 weeks after molar evacuation was very predictive of development of postmolar GTN, delay in treatment until hCG plateau or increase did not affect outcomes, with no uterine perforations or treatment failures.[31] Regarding the treatment of GTN, there was disagreement among Brazilian GTD experts on the necessity that the patient on the first cycle of treatment with methotrexate must be hospitalized due to the high risk of transvaginal bleeding. In the Brazilian experience there was no copious hemorrhage during the first cycle of methotrexate.[32] All patients, however, are advised to seek the emergency department of the GTD reference center in case of any abnormality during chemotherapy. In addition, the occupation of a hospital bed for 7 days to give immediate treatment to an uncommon complication in our population seems inappropriate.

The strength of this study lies in its broad representation of the Brazilian specialists in the treatment of GTD. All physicians involved in this study treat at least 50 new GTD patients per year. There are potential weaknesses in this type of study: the first one is that, although it deals with currently accepted clinical principles, its level of evidence evaluated is the opinion of specialists, subject to biases. Although we have a cutoff point in the minimum number of patients with GTD treated per year to include the participant in this study, there is a great heterogeneity in the number of new patients attended to at the different reference centers (ranging from 50 to 300 new patients per year), as well as in the experience of these specialists treating GTD (ranging from 5 to 50 years). Lastly, despite the fact that this consensus has been supplemented with more statements

than EOTTD, it is still evident that some clinical situations were not contemplated, suggesting that it is essential to broaden this consensus and keep it updated.

We conclude from this study that there is great similarity between the European and Brazilian guidelines for GTD treatment. Despite a large socioeconomic difference between these 2 populations, this agreement reflects that the best practices currently available for the treatment of GTD can be applied not only in developed countries but also in developing countries. Finally, as has been widely repeated about the advantages of these women being treated in GTD reference centers, the stimulus for these new centers of referral should be accompanied by a previous familiarization of the team with the local guidelines for the treatment of GTD. That is why it is essential to have quality consensus, with the best evidence available, for the qualified treatment of GTD.

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