PEER REVIEW HISTORY

BMJ Medicine publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Advances in the Diagnosis and Early Management of Gestational Trophoblastic Disease
AUTHORS	Joyce, Caroline; Fitzgerald, Brendan; McCarthy, Tommie; Coulter, John; Odonoghue, Keelin

VERSION 1 - REVIEW

REVIEWER 1	Branco-Silva, Mariza; Sao Paulo State University Julio de Mesquita Filho, Gynecology and Obstetrics. Competing Interest: None
REVIEW RETURNED	10-Aug-2022

GENERAL COMMENTS	This is a very interesting study and the authors have provided valuable information. The manuscript is clear, concise, and well-written. The data chosen is up to date and relevant. There are just a few points the authors could address for greater clarity and comprehensiveness 1- Although GTD diagnosis is very well discussed, the manuscript should be more informative on the management of GTD to be consistent with its title. Otherwise, I suggest changing the title. 2- Page 2, lines 46-48. Consider moving " The incidence of GTD in the United Kingdom (UK) is 1 in 714 live births but incidence varies according to ethnicity with the highest incidence reported in women of Asian descent" to the incidence section. 3- Page 10, lines 8, Persistent low-level elevated hCG section. Consider rephrasing the first paragraph to inform that, beyond pregnancy, not only raised pituitary hCG or false positive elevation (caused by circulating heterophile antibodies), but also quiescent gestational trophoblastic disease (QTD) may be associated 4- Page 13, line 18 – "uncertainly" should be "uncertainty"

REVIEWER 2	Elias, Kevin. Competing Interest: None
REVIEW RETURNED	15-Aug-2022

GENERAL COMMENTS	The authors have presented a comprehensive review on the diagnosis and management of GTD. The manuscript highlights the major points regarding the disease and will serve as a useful review for experts and novices alike. The micrographs are well-chosen and the tables easy to read. In reviewing the points, I would suggest some minor additions would improve the utility to readers: 1) In the section on scoring GTN, it is important to emphasize that the score is based on the post-evacuation hCG level, nor prior to curettage. This is a common mistake among generalists. Similarly, one should emphasize the importance of obtaining a pelvic ultrasound to ascertain the size of any intrauterine tumor as well as using chest xray rather than CT to evaluate for metastases.

	2) The authors should discuss the role of contraception during post-molar follow-up, especially with regards to being safe and avoiding the risk of a false elevation in hCG from normal gestation. 3) The manuscript focuses on diagnosis of GTD but does not delve into management of GTN as there are no discussions of chemotherapy regimens or complications. I would advise changing the title to diagnosis and initial management of GTD and clarify in the introduction that chemotherapy will not be discussed.

REVIEWER 3	Seckl, Michael; Imperial College London - Charing Cross Campus, Medical Oncology. Competing Interest: I receive funding from the MRC and Cancer Treatment and Research Trust to support research into trophoblastic disease
REVIEW RETURNED	16-Aug-2022

GENERAL COMMENTS	The authors have written a comprehensive review on advances in the diagnosis and management of gestational trophoblastic disease but not covered the chemotherapeutic treatment of gestational trophoblastic neoplasia in any detail. They might like to make this clear in their introduction where they also point out that they do not cover the management of placental site and epithelioid trophoblastic tumours. If they do wish to cover the management of GTN following molar pregnancies then this area will need expanding with sections on low risk, high risk and ultra-high risk as there have a number of advances in each of these areas. With regards to the rest of this review I have a few suggestions for how it could be enhanced which are detailed in the order of the manuscript and not in order of importance: 1) In the abstract the word 'respectively' could be added at the end of the sentence on line 16 following the words 'maternal genome'. 2) In the section on 'Incidence' the sentence ending on line 39 that 30% of choriocarcinomas have metastasis at the time o diagnosis (Ref14). This figure seems very low to me and indeed, others have reported metastasis in more than 50% of patients with non-molar choriocarcinomas eg see Savage et al BJOG '20 PMID: 32146729. The authors might like to modify the sentence to reflect this. 3) In the section on 'Clinical Presentation' the authors describe the presentation of molar pregnancies and in the second sentence refer to ultrasound detgection of molar pregnancies. A number of individuals believe ultrasound is diagnostic but there is plenty of evidence that this is not the case and I would encourage the insertion of a sentence to indicate that whilst ultraouns may be suggestive it is not diagnostic and that histology is the way to make the diagnosis more firmly. eg PMID: 16273594 4) In the section on Clinical Guidelines on page 10, sentence beginning on line 6 and ending on line 8 discusses length of hCG monitoring following uterine evacuation of a complete mole. This has missed the data on time to normalisation of hCG from the date of uterine evacuation and how this influences recurrence although the authors have referenced the paper (Ref 104). They migt like to include this data as it has impacted on the RCOG guidelines where we still adjust duration of monitoring depending on whether the hCG normalises within or beyond 56 days (8 weeks). Women normalises within 8 weeks have hCG monitoring for a total of 6 months from the date of uterine evacuation whereas those normalising beyond 56 days require 6 months of normal hCG values before discontinuing hCG monitoring.

	5) In the same section paragraph beginning line 25 the words score < 6 should be changed to score ≤ 6. In the same para on line 30 the score ≥ 12 should be changed to > 12 6) In the same section on page 10 in line 39 the Ref110 seems incorrect and might be better replaced with Balachandran et al Gynae Oncol '19 PMID 31375268 7) In the section Advances in Daignostics and Therapeutics the authors have written briefly about immunotherapy using pembrolizumab but have omitted to include data on avelumab following single agent chemotherapy failure (You et al JCO '20 PMID 33104436) or the combination of Camrelizumab plus apatinib (Cheng et al Lancet Oncol '21 PMID: 34624252). They might also like to include reference to how we might refine stratification of low risk patients to combination agent chemotherapy quoting the Braga et al Lancet Oncol '21 PMID: 34181884 and moving forwards whether there may be potential for ATR or CDK 4/6 inhibitors quoting Georgiou et al Oncogene '22 PMID 33104436. 8) In the conclusion the last word 'curative' might be best replaced with the word 'curable'

VERSION 1 – AUTHOR RESPONSE

Reviewer 1	**Response to Reviewer 1**
Comments to the Author: This is a very interesting study and the authors have provided valuable information. The manuscript is clear, concise, and well-written. The data chosen is up to date and relevant. There are just a few points the authors could address for greater clarity and comprehensiveness	Thank you for your helpful reviewer's comments on our manuscript. We have responded to the comments of reviewer 1 below.
1. Although GTD diagnosis is very well discussed, the manuscript should be more informative on the management of GTD to be consistent with its title. Otherwise, I suggest changing the title.	We have revised the title of the manuscript to read as follows: "Advances in the Diagnosis and Early Management of Gestational Trophoblastic Disease" We have also included the following sentence in the last paragraph of the introduction: "This review focusses on the diagnosis and early management of GTD and the reader is directed to other publications for expert opinion on the chemotherapeutic management of GTN."
2. Page 2, lines 46-48. Consider moving "The incidence of GTD in the United Kingdom (UK) is 1 in 714 live births but incidence varies according to ethnicity with the highest incidence reported in women of Asian descent" to the incidence section.	We have moved this line to the second paragraph of the incidence section (page 2, Line 27-29).
3. Page 10, lines 8, Persistent low-level elevated hCG section. Consider rephrasing the first paragraph to inform	We have modified the section entitled persistent low-level elevated hCG as follows:

that, beyond pregnancy, not only raised pituitary hCG or false positive elevation (caused by circulating heterophile antibodies), but also quiescent gestational trophoblastic disease (QTD) may be associated.	(Page 9, Line 29-30) In addition, some women with quiescent GTD have persistently low levels of hCG without clinical or radiological evidence of disease. Diagnostic interpretation may also be complicated by a pregnancy or the presence of pituitary derived-hCG in post-menopausal women (Page 9, Line 42-45) Concurrent testing of serum and urine hCG in a GTD reference centre resolved all cases with false positives results due to circulating heterophilic antibodies.
4. Page 13, line 18 – "uncertainly" should be "uncertainty"	This misspelling is now corrected.
Reviewer 2	**Response to Reviewer 2**
Comments to the Author: The authors have presented a comprehensive review on the diagnosis and management of GTD. The manuscript highlights the major points regarding the disease and will serve as a useful review for experts and novices alike. The micrographs are well-chosen and the tables easy to read. In reviewing the points, I would suggest some minor additions would improve the utility to readers:	Thank you for your helpful reviewer's comments on our manuscript. We have responded to the comments of reviewer 2 below.
1. In the section on scoring GTN, it is important to emphasize that the score is based on the post-evacuation hCG level, nor prior to curettage. This is a common mistake among generalists. Similarly, one should emphasize the importance of obtaining a pelvic ultrasound to ascertain the size of any intrauterine tumor as well as using chest xray rather than CT to evaluate for metastases.	In line with these comments, we have modified the clinical guidelines section as follows: 5th Paragraph (Page 10, Line 26-29): The FIGO scoring system is endorsed by all international GTD guidelines and revolves around three main measures: post-evacuation hCG concentration, presence of metastatic disease and histopathological diagnosis. (Page 10, Line 29-32): A doppler pelvic ultrasound should be performed to confirm the absence of a pregnancy and ascertain the size of any intrauterine tumour. Chest X-ray (CXR) as opposed to computed tomography (CT) is the preferred imaging modality for detection of pulmonary metastases.
2. The authors should discuss the role of contraception during post-molar follow-up, especially with regards to being safe and avoiding the risk of a false elevation in hCG from normal gestation.	We have added an additional sentence to the second last paragraph in the clinical guidelines section as follows: Page 11 (line 16): "Advice on safe contraception after a molar pregnancy can be found in national fertility guidelines. A systematic review found no evidence for an association between oral

	contraceptive use during post-molar follow up and the incidence of GTN. Moreover, a Brazilian study found no association between hormonal contraception use during molar pregnancy follow-up or GTN treatment and the risk or severity of GTN, nor did it postpone the normalisation of hCG levels.
3. The manuscript focuses on diagnosis of GTD but does not delve into management of GTN as there are no discussions of chemotherapy regimens or complications. I would advise changing the title to diagnosis and initial management of GTD and clarify in the introduction that chemotherapy will not be discussed.	As mentioned in response to reviewer 1, we have modified the title of the manuscript to read as follows: "Advances in the Diagnosis and Early Management of Gestational Trophoblastic Disease" We have also clearly stated in the introduction that chemotherapy will not be discussed: Page 1, Line 42-44: "This review focusses on the diagnosis and early management of GTD and the reader is directed to other publications for expert opinion on the chemotherapeutic management of GTN."
Reviewer 3	**Response to Reviewer 3**
Comments to the Author: The authors have written a comprehensive review on advances in the diagnosis and management of gestational trophoblastic disease but not covered the chemotherapeutic treatment of gestational trophoblastic neoplasia in any detail. They might like to make this clear in their introduction where they also point out that they do not cover the management of placental site and epithelioid trophoblastic tumours. If they do wish to cover the management of GTN following molar pregnancies then this area will need expanding with sections on low risk, high risk and ultra-high risk as there have a number of advances in each of these areas. With regards to the rest of this review I have a few suggestions for how it could be enhanced which are detailed in the order of the manuscript and not in order of importance:	Thank you for your helpful reviewer's comments on our manuscript. We have responded to the comments of reviewer 3 below. As mentioned above, we have modified the title as follows: "Advances in the Diagnosis and Early Management of Gestational Trophoblastic Disease" We have also clearly stated in the introduction that chemotherapy will not be discussed: Page 1, Line 42-44: "This review focusses on the diagnosis and early management of GTD and the reader is directed to other publications for expert opinion on the chemotherapeutic management of GTN."
1. In the abstract the word 'respectively' could be added at the end of the sentence on line 16 following the words 'maternal genome'.	We have added "respectively" to this sentence.

2. In the section on 'Incidence' the sentence ending on line 39 that 30% of choriocarcinomas have metastasis at the time of diagnosis (Ref14). This figure seems very low to me and indeed, others have reported metastasis in more than 50% of patients with non-molar choriocarcinomas eg see Savage et al BJOG '20 PMID: 32146729. The authors might like to modify the sentence to reflect this.	We have added an additional sentence to reflect the higher incidence reported in non-molar choriocarcinoma as follows: "More recently, a UK study reported metastasis in more than 50% of women with non-molar choriocarcinoma."
3. In the section on 'Clinical Presentation' the authors describe the presentation of molar pregnancies and in the second sentence refer to ultrasound detection of molar pregnancies. A number of individuals believe ultrasound is diagnostic but there is plenty of evidence that this is not the case and I would encourage the insertion of a sentence to indicate that whilst ultrasound may be suggestive it is not diagnostic and that histology is the way to make the diagnosis more firmly. eg PMID: 16273594	We have added the following sentence: "Although ultrasound may be suggestive of a molar pregnancy, histopathological examination of the products of conception remains the gold standard for the diagnosis of molar pregnancy."
4. In the section on Clinical Guidelines on page 10, sentence beginning on line 6 and ending on line 8 discusses length of hCG monitoring following uterine evacuation of a complete mole. This has missed the data on time to normalisation of hCG from the date of uterine evacuation and how this influences recurrence although the authors have referenced the paper (Ref 104). They might like to include this data as it has impacted on the RCOG guidelines where we still adjust duration of monitoring depending on whether the hCG normalises within or beyond 56 days (8 weeks). Women normalises within 8 weeks have hCG monitoring for a total of 6 months from the date of uterine evacuation whereas those normalising beyond 56 days require 6 months of normal hCG values before discontinuing hCG monitoring.	In response to this comment, we agree that although we showed the different follow-up required for hCG normalisation pre and post 8 weeks in Figure 7, we did not describe this in the body of the manuscript. We have updated the sentence on hCG monitoring in CHM to address this comment as follows: "In CHM cases where hCG normalisation occurs within 56 days (8 weeks), women have hCG monitoring for a total of 6 months post uterine evacuation. However, when hCG normalisation occurs beyond 56 days, women have hCG monitoring for 6 months post normalisation. (fig 7)."
5. In the same section paragraph beginning line 25 the words score < 6 should be changed to score ≤ 6. 6. In the same para on line 30 the score ≥ 12 should be changed to > 12	5./6. The FIGO scores are now corrected on page 11, lines 5 and 9 respectively.

7. In the same section on page 10 in line 39 the Ref110 seems incorrect and might be better replaced with Balachandran et al Gynae Oncol '19 PMID 31375268	We agree and have replaced Powles et al. with Balachandran et al. in page 10, last paragraph as follows: "Women treated with chemotherapy post-molar pregnancy are advised to avoid pregnancy for at least a year when the risk of relapse is greatest (3%) and a rising hCG may prevent early detection of disease recurrence."
8. In the section Advances in Diagnostics and Therapeutics the authors have written briefly about immunotherapy using pembrolizumab but have omitted to include data on avelumab following single agent chemotherapy failure (You et al JCO '20 PMID 33104436) or the combination of Camrelizumab plus apatinib (Cheng et al Lancet Oncol '21 PMID: 34624252). They might also like to include reference to how we might refine stratification of low risk patients to combination agent chemotherapy quoting the Braga et al Lancet Oncol '21 PMID: 34181884 and moving forwards whether there may be potential for ATR or CDK 4/6 inhibitors quoting Georgiou et al Oncogene '22 PMID 33104436.	In response to these recommendations, these studies have been included in the last two paragraphs of this section as follows: "Another PD-L1 inhibitor, Avelumab is safe and effective in GTN cases resistant to single-agent chemotherapy. An alternative salvage therapy for chemo resistant GTN involves use of Camrelizumab plus apatinib" "Women with low-risk GTN (FIGO score 5-6) who have a high chance of resistance to first line therapy (Methotrexate or Actinomycin-D) could be risk stratified to combination therapy based on prognostic factors (pre-treatment hCG, metastatic disease status and choriocarcinoma histopathology). In particular, women with Methotrexate resistance could be treated with ATR or CDK4/6 inhibitors."
9. In the conclusion the last word 'curative' might be best replaced with the word 'curable'	We agree with this change and have amended the word.