BJOG An International Journal of Obstetrics and Gynaecology

Royal College of Obstetricians & Gynaecologists

Management of Gestational Trophoblastic Disease

Green-top Guideline No. 38

September 2020

Please cite this paper as: Tidy J, Seckl M, Hancock BW, on behalf of the Royal College of Obstetricians and Gynaecologists. Management of Gestational Trophoblastic Disease. BJOG 2020; https://doi.org/10.1111/1471-0528.16266.

NICE accredited
www.nice.org.uk/accreditation

DOI: 10.1111/1471-0528.16266

Management of Gestational Trophoblastic Disease

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This is the fourth edition of this guideline. The third edition was published in 2010 under the same title. The second edition was published in 2004 titled *The Management of Gestational Trophoblastic Neoplasia*, which replaced *The Management of Gestational Trophoblastic Disease*, published in April 1999.

Executive summary

How do molar pregnancies present to the clinician?

Clinicians should be aware of the symptoms and signs of molar pregnancy. The most common presentation is irregular vaginal bleeding, a positive pregnancy test and supporting ultrasonographic evidence. C

Less common presentations of molar pregnancies include hyperemesis, excessive uterine enlargement, hyperthyroidism, early-onset pre-eclampsia and abdominal distension due to theca lutein cysts. *[New 2020]* ✓

Very rarely women can present with haemoptysis or seizures due to metastatic disease affecting the lungs or brain. *[New 2020]* ✓

How are molar pregnancies diagnosed?

The definitive diagnosis of a molar pregnancy is made by histological examination. D

Removal of a molar pregnancy

What is the best method for removal of a molar pregnancy?

Suction curettage is the method of choice for removal of complete molar pregnancies. ✓

Ultrasound guidance during removal and curettage may be of use to minimise the chance of perforation and to ensure that as much tissue as possible is removed. ✓

Suction curettage is the method of choice for removal of partial molar pregnancies except when the size of fetal parts deters the use of suction curettage and then medical removal can be used. ✓

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Anti-D prophylaxis is recommended following removal of a molar pregnancy. ✓

Is it safe to prepare the cervix prior to surgical removal?

Preparation of the cervix immediately prior to uterine removal is safe. D

Can oxytocic infusions be used during surgical removal?

Excessive vaginal bleeding can be associated with surgical management of molar pregnancy and the involvement of an experienced clinician is advised. ✓

The use of oxytocic infusion prior to completion of the removal is not recommended. ✓

If the woman is experiencing significant haemorrhage prior to or during removal, surgical removal should be expedited and the need for oxytocin infusion weighed up against the risk of tissue embolisation. ✓

In what circumstances should a repeat surgical removal be indicated and what is the timing?

There is almost always a role for urgent surgical management for the woman who is experiencing heavy or persistent vaginal bleeding causing acute haemodynamic compromise, particularly in the presence of retained pregnancy tissue on ultrasound. ***[New 2020]*** ✓

Outside the context of acute compromise, there should be consultation with the relevant GTD referral centre before performing surgical management for the second time in the same pregnancy. D

Histological examination of pregnancy tissue in the diagnosis of GTD

Should pregnancy tissue from all miscarriages be examined histologically?

The histological assessment of material obtained from the medical or surgical management of all miscarriages is recommended to exclude trophoblastic neoplasia if no fetal parts are identified at any stage of the pregnancy. D

Women who receive care for a miscarriage should be recommended to do a urinary pregnancy test 3 weeks after miscarriage. ***[New 2020]*** ✓

Should pregnancy tissue be sent for examination after abortion?

There is no need to routinely send pregnancy tissue for histological examination following therapeutic abortion, provided that fetal parts have been identified at the time of surgical abortion or on prior ultrasound examination. D

Women who undergo medical abortion should be recommended to do a urinary pregnancy test 3 weeks after the procedure. ***[New 2020]*** ✓

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How should women with an elevated human chorionic gonadotrophin after a possible pregnancy event be managed?

Referral to a GTD centre should be considered for all women with persistently elevated human chorionic gonadotrophin (hCG) either after an ectopic pregnancy has been excluded, or after two consecutive treatments with methotrexate for a pregnancy of unknown location. *[New 2020]*

✓

Which women should be investigated for GTN after a non-molar pregnancy?

Any woman who develops persistent vaginal bleeding after a pregnancy event is at risk of having GTN.

D

A urine hCG test should be performed in all cases of persistent or irregular vaginal bleeding lasting more than 8 weeks after a pregnancy event.

✓

Symptoms from metastatic disease, such as dyspnoea and haemoptysis, or new onset of seizures or paralysis, can occur very rarely.

D

Biopsy of secondary deposits in the vagina can cause major haemorrhage and is not recommended.

✓

How should suspected ectopic molar pregnancy in women be managed?

Cases of women with ectopic pregnancy suspected to be molar in nature should be managed as any other case of ectopic pregnancy. If there is a local tissue diagnosis of ectopic molar pregnancy, the tissue should be sent to a centre with appropriate expertise for pathological review. *[New 2020]*

✓

How is twin pregnancy of a viable fetus and presumptive coexistent molar pregnancy managed?

Women diagnosed with a combined molar pregnancy and viable twin, or where there is diagnostic doubt, should be referred to a regional fetal medicine centre and GTD centre.

✓

In the situation of a twin pregnancy where there is one viable fetus and the other pregnancy is molar, the woman should be counselled about the potential increased risk of perinatal morbidity and the outcome for GTN.

D

Prenatal invasive testing for fetal karyotype should be considered in cases where it is unclear if the pregnancy is a complete mole with a coexisting normal twin or a possible singleton partial molar pregnancy. Prenatal invasive testing for fetal karyotype should also be considered in cases of abnormal placenta, such as suspected mesenchymal hyperplasia of the placenta.

D

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How should a placental site trophoblastic tumour or epithelioid trophoblastic tumour be managed?

All women with placental site trophoblastic tumour (PSTT) or epithelioid trophoblastic tumour (ETT) should be registered with and cared for within a GTD centre. *[New 2020]* D

How should a placental site nodule or atypical placental site nodule be managed?

Women with an atypical placental site nodule (PSN) or where the local pathology is uncertain should have their histology reviewed centrally. All women with atypical PSN will then be called up for central review to discuss the existing data, perform staging investigations and to determine further management. Women with typical PSN do not currently require further investigation or review. *[New 2020]* ✓

Which women should be registered at GTD centres?

All women diagnosed with GTD should be provided with written information about the condition and the need for referral for follow-up by a GTD centre should be explained. D

Clinicians should be aware that outcomes for women with GTN and GTD are better with ongoing care from GTD centres. The registration of affected women with a GTD centre represents a minimum standard of care. *[New 2020]* ✓

Women with the following diagnoses should be registered and require follow-up as determined by the screening centre: D

- **complete molar pregnancy/partial molar pregnancy**
- **twin pregnancy with complete or partial molar pregnancy**
- **limited macroscopic or microscopic molar change suggesting possible early complete or partial molar pregnancy/choriocarcinoma**
- **PSTT or ETT**
- **atypical PSN. *[New 2020]***

What is the optimum follow-up following a diagnosis of GTD?

For complete molar pregnancy, if hCG has reverted to normal within 56 days of the pregnancy event then follow-up will be for 6 months from the date of uterine removal. C

If hCG has not reverted to normal within 56 days of the pregnancy event then follow-up will be for 6 months from normalisation of the hCG level. C

Follow-up for partial molar pregnancy is concluded once the hCG has returned to normal on two samples, at least 4 weeks apart. *[New 2020]* C

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Women who have not received chemotherapy no longer need to have hCG measured after any subsequent pregnancy event. *[New 2020]* C

What is the optimum treatment for GTN?

Women with GTN may be treated with single-agent or multi-agent chemotherapy. B

Treatment used is based on the FIGO 2000 scoring system for GTN following assessment at the treatment centre. *[New 2020]* B

PSTT and ETT are now recognised as variants of GTN. They may be treated with surgery because they are less sensitive to chemotherapy. D

What is the recommended interval between a complete or partial molar pregnancy and trying to conceive in the future, what is the monitoring of women following a successful pregnancy after a previous molar pregnancy and what is the outcome of subsequent pregnancies?

Women are advised not to conceive until their follow-up is complete. C

Women who undergo chemotherapy are advised not to conceive for 1 year after completion of treatment, as a precautionary measure. C

Women who have a pregnancy following a previous molar pregnancy, which has not required treatment for GTN, do not need to send a post-pregnancy hCG sample. Histological examination of placental tissue from any normal pregnancy, after a molar pregnancy, is not indicated. *[New 2020]* D

What is the long-term outcome of women treated for GTN?

The outlook for women treated for GTN is generally excellent with an overall cure rate close to 100%. *[New 2020]* B

Further pregnancies are achieved in approximately 80% of women following treatment for GTN with either methotrexate alone or multi-agent chemotherapy. *[New 2020]* B

There is an increased risk of premature menopause for women treated with combination agent chemotherapy. Women, especially those approaching the age of 40 years, should be warned of the potential negative impact on fertility, particularly when treated with high-dose chemotherapy. B

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What is safe contraception following treatment of GTD and when should it be commenced?

It is important that women who have had a removal of a molar pregnancy are advised not to become pregnant until they have completed their hCG follow-up. *[New 2020]* D

Advice on contraception after a molar pregnancy can be found in the Faculty of Sexual and Reproductive Health Guideline Executive Summary *Contraception After Pregnancy. [New 2020]* D

Is the use of exogenous estrogens and other fertility drugs safe for women undergoing assisted reproductive treatment after a molar pregnancy?

The use of exogenous estrogens and other fertility drugs may be used once hCG levels have returned to normal. *[New 2020]* ✓

Is hormone replacement therapy safe for women to use after GTD?

Hormone replacement therapy may be used once hCG levels have returned to normal. ✓

Impact of diagnosis on women and their families

GTD centres now provide individualised support to women and their families throughout their GTD journey, through dedicated GTD nurse specialists and advisors, who can be accessed either through attending a GTD centre or via phone, or both. Online support groups are available (molarpregnancy.co.uk) alongside regular drop-in support groups at Charing Cross Hospital, London and Weston Park Hospital, Sheffield. Further information is available from each centre. *[New 2020]* ✓

1. Definitions

Gestational trophoblastic disease (GTD) comprises a group of disorders spanning the premalignant conditions of complete and partial molar pregnancies (also known as hydatidiform moles) through to the malignant conditions of invasive mole, choriocarcinoma and the very rare placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). The malignant potential of atypical placental site nodules (PSNs) remains unclear.

If there is any evidence of persistence of GTD after primary treatment, most commonly defined as a persistent elevation of human chorionic gonadotrophin (hCG), the condition is referred to as gestational trophoblastic neoplasia (GTN). The diagnosis of GTN does not require histological confirmation. The diagnosis of complete mole, partial mole, atypical PSN and PSTT/ETT does require histological confirmation.

2. Purpose and scope

The purpose of this guideline is to describe the presentation, diagnosis, management, treatment and follow-up of GTD and GTN. It also provides advice on future pregnancy outcomes and the use of contraception.

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3. Introduction and background epidemiology

Molar pregnancies can be subdivided into complete and partial molar pregnancies based on genetic and histopathological features. Complete molar pregnancies are diploid and androgenic in origin, with no evidence of fetal tissue. Complete molar pregnancies usually (75–80%) arise as a consequence of duplication of a single sperm following fertilisation of an 'empty' ovum. Some complete moles (20–25%) can arise after dispermic fertilisation of an 'empty' ovum. Partial molar pregnancies are usually (90%) triploid in origin, with two sets of paternal haploid chromosomes and one set of maternal haploid chromosomes. Partial molar pregnancies occur, in almost all cases, following dispermic fertilisation of an ovum. Occasionally molar pregnancies represent tetraploid or mosaic conceptions. In a partial mole, there is usually evidence of a fetus or fetal red blood cells. Not all triploid or tetraploid pregnancies are partial moles. For the diagnosis of a partial mole, there must be histopathological evidence of trophoblast hyperplasia.

GTD (hydatidiform mole, invasive mole, choriocarcinoma, PSTT) is an uncommon occurrence in the UK, with a calculated incidence of 1 in 714 live births. There is evidence of ethnic variation in the incidence of GTD in the UK, with women from Asia having a higher incidence compared with non-Asian women (1 in 387 versus 1 in 752 live births, respectively).[1] The incidence of GTD is associated with age at conception, being higher in the extremes of age (women aged less than 15 years, 1 in 500 pregnancies; women aged more than 50 years, 1 in 8 pregnancies).[2,3] However, these figures may under-represent the true incidence of the disease because of problems with reporting, particularly in regard to partial moles. GTN may develop after a molar pregnancy, a non-molar pregnancy or a live birth. The incidence after a live birth is estimated at 1 in 50 000. On average, a consultant obstetrician and gynaecologist may only deal with one new case every 2 years.

In the UK, there exists an effective registration and treatment programme. The programme has a cure rate of 98–100%, and a chemotherapy rate of 0.5–1.0% for GTN after partial molar pregnancy and 13–16% after complete molar pregnancy.[2,4–6] Clinicians should be aware that outcomes for women with GTN and GTD are better with ongoing management from GTD centres. The registration of affected women with a GTD centre represents a minimum standard of care.

4. Identification and assessment of evidence

This guideline was developed using standard methodology for developing RCOG Green-top Guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects [DARE] and the Cochrane Central Register of Controlled Trials [CENTRAL]), EMBASE, MEDLINE and Trip were searched for relevant papers. The search was inclusive of all relevant articles published between January 2008 and June 2019. The databases were searched using the relevant Medical Subject Headings (MeSH) terms, including all subheadings and synonyms, and this was combined with a keyword search. Search terms included 'trophoblastic neoplasms', 'trophoblastic disease', 'trophoblastic tumour', 'hydatidiform' and 'molar pregnancy'. The search was limited to studies on humans and papers in the English language. Relevant guidelines were also searched for using the same criteria in the National Guideline Clearinghouse and the National Institute for Health and Care Excellence (NICE) Evidence Search. The full search strategy is available to view online as supporting information (Appendix S1 and S2).

Where possible, recommendations are based on available evidence. Areas lacking evidence are highlighted and annotated as 'good practice points'. Further information about the assessment of evidence and the grading of recommendations may be found in Appendix 1.

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5. How do molar pregnancies present to the clinician?

Clinicians should be aware of the symptoms and signs of molar pregnancy. The most common presentation is irregular vaginal bleeding, a positive pregnancy test and supporting ultrasonographic evidence. C

Less common presentations of molar pregnancies include hyperemesis, excessive uterine enlargement, hyperthyroidism, early-onset pre-eclampsia and abdominal distension due to theca lutein cysts. ✓

Very rarely women can present with haemoptysis or seizures due to metastatic disease affecting the lungs or brain. ✓

Vaginal bleeding remains the most common presenting symptom of molar pregnancy and is associated with approximately 60% of presentations. This symptom has not changed despite a reduction in the gestation at presentation (from 11 to 10 weeks) between 1996 and 2006. The percentage of women presenting with an abnormal ultrasound result, as the only presenting feature, increased from 1% to 12% over the same time period.[7] Evidence level 2+

The use of ultrasound in early pregnancy has led to the earlier diagnosis of molar pregnancy. Soto-Wright et al.[8] demonstrated a reduction in the mean gestation at presentation, from 16 weeks of gestation between 1965 and 1975 to 12 weeks of gestation between 1988 and 1993. There has been a further reduction in gestational age at diagnosis to 9 weeks of gestation between 1994 and 2013.[9] The majority of histologically proven molar pregnancies are associated with an ultrasound diagnosis of delayed miscarriage or anembryonic pregnancy.[10] In one study, the pre-removal diagnosis of molar pregnancy increased with gestational age: 35–40% correctly identified before 14 weeks of gestation, increasing to 60% after 14 weeks of gestation.[11] A further study reported that ultrasound examination correctly identified 56% of molar pregnancies in women with suspected missed miscarriage.[12] When pregnancy tissue was routinely examined after surgical removal, the incidence of molar pregnancy and atypical PSNs, unrecognised prior to removal, was 2.7%.[13] Evidence level 2+

Ultrasound features suggestive of a complete molar pregnancy include a polypoid mass between 5 and 7 weeks of gestation and thickened cystic appearance of the villous tissue after 8 weeks of gestation with no identifiable gestational sac.[14,15] Partial molar pregnancies are associated with an enlarged placenta or cystic changes within the decidual reaction in association with either an empty sac or a delayed miscarriage. Using these criteria, a reasonable sensitivity for complete mole is 95% and 20% for partial mole. The positive predictive value is low for both complete (40%) and partial (22%) moles.[16] A review of the ultrasound features of partial and complete molar pregnancies found the ultrasound diagnosis of a partial molar pregnancy to be more subtle, reporting the finding of multiple soft markers, including cystic spaces in the placenta, and ratio of transverse to anteroposterior dimension of the gestational sac greater than 1:1.5. These features may be of help in the diagnosis of a partial molar pregnancy.[17,18] Using these extra criteria, 41.4% of partial molar pregnancies are correctly diagnosed prior to removal compared with 86.4% of complete molar pregnancies.[18] A study of women presenting to an early pregnancy unit reported ultrasound correctly identified 88.2% of complete molar pregnancies and 56% of partial molar pregnancies.[19] Evidence level 2+

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The estimation of hCG levels may be of value in diagnosing molar pregnancies: in a small study of 51 suspected cases of molar pregnancy hCG levels were significantly higher for both complete and partial molar pregnancies.[12]

Evidence level 2+

Rarer presentations include hyperthyroidism, early-onset pre-eclampsia or abdominal distension due to theca lutein cysts.[20] Very rarely, women can present with haemoptysis, acute respiratory failure or neurological symptoms, such as seizures, likely to be due to metastatic disease.[21]

Evidence level 4

6. How are molar pregnancies diagnosed?

The definitive diagnosis of a molar pregnancy is made by histological examination.

D

Pathological features consistent with the diagnosis of complete molar pregnancies include: absence of fetal tissue; extensive hydropic change to the villi; and excess trophoblast proliferation. Features of a partial molar pregnancy include: presence of fetal tissue; focal hydropic change to the villi; and some excess trophoblast proliferation. Ploidy status and immunohistochemistry staining for *p57*, a paternally imprinted gene, may help in distinguishing partial from complete molar pregnancies.[22,23]

Evidence level 2+

7. Removal of a molar pregnancy

7.1. What is the best method for removal of a molar pregnancy?

Suction curettage is the method of choice for removal of complete molar pregnancies.

✓

Ultrasound guidance during removal and curettage may be of use to minimise the chance of perforation and to ensure that as much tissue as possible is removed.

✓

Suction curettage is the method of choice for removal of partial molar pregnancies except when the size of fetal parts deters the use of suction curettage and then medical removal can be used.

✓

Anti-D prophylaxis is recommended following removal of a molar pregnancy.

✓

Complete molar pregnancies are not associated with fetal parts, and therefore, suction removal is the method of choice for uterine removal irrespective of uterine size. Medical removal of a complete molar pregnancy should be avoided if possible, irrespective of the agents used.[24] In a review of 4247 women with GTD, the risk of developing GTN and requiring chemotherapy was 16-fold higher when medical methods of removal were used compared with surgical removal.[25] In addition, there is theoretical concern, supported by clinical experience, over the routine use

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of potent oxytocic agents because of the potential to embolise and disseminate trophoblastic tissue through the venous system leading to adult respiratory distress syndrome, similar in presentation to amniotic fluid embolism.[26]

For twin pregnancies where there is a non-molar pregnancy alongside a molar pregnancy and the woman has decided to terminate the pregnancy (or there has been demise of the coexisting twin) and the size of the fetal parts deters the use of suction curettage, medical removal can be used.

Evidence level 2+

There is a higher rate of incomplete removal with medical methods. The risk of this increasing the need for treatment for GTN is 13–16% with complete molar pregnancies and 0.5–1.0% with partial molar pregnancies.[2–4]

Evidence level 2+

A review of the literature found no published evidence examining the use of ultrasound at the time of uterine removal for GTN. There is a consensus view, however, that this may be the preferred surgical option.[27]

Women who have an unrecognised molar pregnancy and undergo medical or surgical abortion of the pregnancy are at increased risk of life-threatening complications of GTN, require more surgical intervention and chemotherapy.[28]

Evidence level 3

Poor vascularisation of the chorionic villi and absence of the D antigen by trophoblast cells means that anti-D prophylaxis is not required for complete molar pregnancies.[29] However, it is required for partial molar pregnancies. Confirmation of the diagnosis of complete molar pregnancy may not occur for some time after removal, which could delay administration of anti-D. If the diagnosis of complete molar pregnancy cannot be established within 72 hours, anti-D prophylaxis can be administered for practical reasons.

Evidence level 4

7.2. *Is it safe to prepare the cervix prior to surgical removal?*

Preparation of the cervix immediately prior to uterine removal is safe. D

Ripening of the cervix with either physical dilators or prostaglandins prior to uterine removal is not associated with an increased risk of developing GTN. In a case–control study of 219 patients, there was no evidence that the ripening of the cervix prior to uterine removal is linked to a higher risk of needing chemotherapy.[30]

Evidence level 2+

7.3. *Can oxytocic infusions be used during surgical removal?*

Excessive vaginal bleeding can be associated with surgical management of molar pregnancy and the involvement of an experienced clinician is advised. ✓

The use of oxytocic infusion prior to completion of the removal is not recommended. ✓

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If the woman is experiencing significant haemorrhage prior to or during removal, surgical removal should be expedited and the need for oxytocin infusion weighed up against the risk of tissue embolisation. ✓

Excessive vaginal bleeding can be associated with surgical management of molar pregnancy. There is theoretical concern over the routine use of oxytocic agents, including ergometrine and misoprostol, because of the potential to embolise and disseminate trophoblastic tissue through the venous system.[26] This is known to occur in normal pregnancy, especially when uterine activity is increased, such as with placental abruption. The contraction of the myometrium may force tissue into the venous spaces at the site of the placental bed. The dissemination of this tissue may lead to profound deterioration in the patient, with embolic and metastatic disease occurring in the lungs. In the event of life-threatening haemorrhage or ongoing bleeding, oxytocic infusions may be used.

Evidence level 4

7.4. *In what circumstances should a repeat surgical removal be indicated and what is the timing?*

There is almost always a role for urgent surgical management for the woman who is experiencing heavy or persistent vaginal bleeding causing acute haemodynamic compromise, particularly in the presence of retained pregnancy tissue on ultrasound. ✓

Outside the context of acute compromise, there should be consultation with the relevant GTD referral centre before performing surgical management for the second time in the same pregnancy. D

Women with persistent heavy vaginal bleeding and evidence of retained pregnancy tissue on ultrasound examination may need a repeat surgical removal. This remains true when a woman has had a prior surgical removal for suspected GTD. Expediting surgical management in the case of acute haemodynamic compromise is the priority and delay can be harmful. Consideration should be given to balloon tamponade and to uterine artery embolisation to reduce the risk of hysterectomy for women who wish to preserve fertility. Embolisation will not always stop the bleeding but will permit management of blood loss. Bleeding from vaginal metastases can be reduced by compression from a vaginal pack.

Evidence level 4

Several case series have found there may be a role for second removal in selected cases when the hCG is less than 5000 units/l.[31–34] A prospective phase II trial of second removal for GTN reported 40% of women avoided chemotherapy as a consequence of undergoing second removal with low complication rates. In three out of 34 cases in which primary treatment failed, the histological findings on second removal were significantly different (PSTT) when compared with initial diagnosis (molar pregnancy).[34]

Evidence level 3

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8. Histological examination of pregnancy tissue in the diagnosis of GTD

8.1 Should pregnancy tissue from all miscarriages be examined histologically?

The histological assessment of material obtained from the medical or surgical management of all miscarriages is recommended to exclude trophoblastic neoplasia if no fetal parts are identified at any stage of the pregnancy. D

Women who receive care for a miscarriage should be recommended to do a urinary pregnancy test 3 weeks after miscarriage. ✓

As GTD can be difficult to recognise at the time of miscarriage it is recommended that either:

- All material obtained from the medical or surgical management of miscarriage be sent to pathology.

or

- If no tissue has been sent to pathology, a pregnancy test should be carried out 3 weeks after the miscarriage. If this is still positive, serum levels should be tracked to ensure that the level is falling and, if not, an ultrasound is arranged to look for further pregnancy tissue. All tissue obtained in this situation should be sent to pathology. The incidence of GTD, unrecognised prior to removal, is 2.7%.[13]

Evidence level 2+

8.2. Should pregnancy tissue be sent for examination after abortion?

There is no need to routinely send pregnancy tissue for histological examination following therapeutic abortion, provided that fetal parts have been identified at the time of surgical abortion or on prior ultrasound examination. D

Women who undergo medical abortion should be recommended to do a urinary pregnancy test 3 weeks after the procedure. ✓

Seckl et al.[28] reviewed the risk of GTN developing after confirmed therapeutic abortion. The rate is estimated to be 1 in 20 000. However, the failure to diagnose GTD at the time of abortion leads to adverse outcomes, with a significantly higher risk of life-threatening complications, surgical intervention, including hysterectomy, and multi-agent chemotherapy.

Evidence level 3

9. How should women with an elevated hCG after a possible pregnancy event be managed?

Referral to a GTD centre should be considered for all women with persistently elevated hCG either after an ectopic pregnancy has been excluded, or after two consecutive treatments with methotrexate for a pregnancy of unknown location. ✓

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GTN can develop after any pregnancy event and failure to treat GTN can be fatal. GTN requires more intensive chemotherapy than treatment of a pregnancy of unknown location. Very rarely, some women will have familial raised hCG with hCG levels between 10 IU/l and 200 IU/l. These women have menstrual cycles and can conceive.[35,36] Low levels of hCG elevation are also associated with malignant female germ cell tumours and any epithelial cancers including bladder, breast, lung, gastric and colorectal cancers.[37] Low levels of hCG elevation can also be caused by the presence of pituitary hCG or the presence of human anti-mouse antibodies.[38]

Evidence level 4

The hCG glyco-protein can be present in many forms, in both serum and urine, including intact hCG, free hCGβ subunit, nicked hCG and hCG β-core fragment. Molar pregnancies and GTN can produce all these variants of hCG. Most commercial hCG assays for routine laboratory use do not measure all hCG variants. The three UK GTD centres use specialised in-house hCG assays to detect all forms of hCG.[39]

10. Which women should be investigated for GTN after a non-molar pregnancy?

Any woman who develops persistent vaginal bleeding after a pregnancy event is at risk of having GTN. D

A urine hCG test should be performed in all cases of persistent or irregular vaginal bleeding lasting more than 8 weeks after a pregnancy event. ✓

Symptoms from metastatic disease, such as dyspnoea and haemoptysis, or new onset of seizures or paralysis, can occur very rarely. D

Biopsy of secondary deposits in the vagina can cause major haemorrhage and is not recommended. ✓

GTN can develop after miscarriage, therapeutic abortion and term pregnancy. Choriocarcinoma is estimated to occur after approximately 1 in 50 000 pregnancies.[40,41] It is uncommon (less than 1%) for GTN to develop in women who have had a normal hCG urine or serum level within 8 weeks of removal of a molar pregnancy.[42–44]

Evidence level 3

Several case series have shown that vaginal bleeding is the most common presenting symptom of GTN diagnosed after miscarriage, therapeutic abortion or postpartum.[40,41,45–48]

Evidence level 2+

The prognosis for a woman with GTN after a non-molar pregnancy may be worse owing to delay in diagnosis or advanced disease, such as liver or central nervous system disease, at presentation.[41,42,45–48]

Evidence level 2+

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11. How should suspected ectopic molar pregnancy in women be managed?

Cases of women with ectopic pregnancy suspected to be molar in nature should be managed as any other case of ectopic pregnancy. If there is a local tissue diagnosis of ectopic molar pregnancy, the tissue should be sent to a centre with appropriate expertise for pathological review. ✓

Ectopic molar pregnancy is a rare event. Symptoms and signs are the same as any other ectopic pregnancy. The histopathological features of an early complete ectopic molar pregnancy can be confused with choriocarcinoma.[49–51] Evidence level 4

12. How is twin pregnancy of a viable fetus and presumptive coexistent molar pregnancy managed?

Women diagnosed with a combined molar pregnancy and viable twin, or where there is diagnostic doubt, should be referred to a regional fetal medicine centre and GTD centre. ✓

In the situation of a twin pregnancy where there is one viable fetus and the other pregnancy is molar, the woman should be counselled about the potential increased risk of perinatal morbidity and the outcome for GTN. D

Prenatal invasive testing for fetal karyotype should be considered in cases where it is unclear if the pregnancy is a complete mole with a coexisting normal twin or a possible singleton partial molar pregnancy. Prenatal invasive testing for fetal karyotype should also be considered in cases of abnormal placenta, such as suspected mesenchymal hyperplasia of the placenta. D

There is an increased risk of early fetal loss (40%) and premature birth (36%) in a twin pregnancy of a viable fetus and coexisting molar pregnancy. The incidence of pre-eclampsia is variable, with rates as high as 20% reported. However, in a large UK series, the incidence was only 4% and there were no maternal deaths.[52,53] In the same UK series, there was no increase in the risk of developing GTN after such a twin pregnancy and outcome after chemotherapy was unaffected. Analysis of a further 153 UK cases confirmed the earlier experience, with a slightly higher rate of babies surviving (51%), no maternal deaths and no increase in the need for chemotherapy (15%) in the women who gave birth after 26 weeks of gestation.[52,53] Evidence level 2+

Some women may wish to continue with their pregnancy. Increased monitoring for pre-eclampsia, and fetal and maternal wellbeing during such ongoing pregnancies is sensible. Histological examination of the placenta is recommended and all confirmed cases of GTD registered with a GTD centre. Evidence level 4

13. How should a placental site trophoblastic tumour or epithelioid trophoblastic tumour be managed?

All women with PSTT or ETT should be registered with and cared for within a GTD centre. D

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PSTTs and ETTs are rare forms of GTD diagnosed by histological examination of retained pregnancy tissue. Their presentation and behaviour are different and less predictable. Hysterectomy is curative in many cases with localised disease. In women with a long time period since the antecedent pregnancy and/or with distant and/or extensive metastatic disease, intensive chemotherapy plays a major role.[54,55]

Evidence level 2+

14. How should a placental site nodule or atypical placental site nodule be managed?

Women with an atypical PSN or where the local pathology is uncertain should have their histology reviewed centrally. All women with atypical PSN will then be called up for central review to discuss the existing data, perform staging investigations and to determine further management. Women with typical PSN do not currently require further investigation or review.

✓

PSNs have been, for many years, regarded as a benign finding of little clinical significance. There have been reports of PSNs with or without atypical features, which have either been admixed with PSTTs or ETTs, or that have subsequently progressed over time to PSTTs or ETTs. This link to cancer appears strongest with atypical PSNs and may occur in 10–15% of women.[56] The condition often presents with vaginal bleeding resulting in endometrial biopsy, or because of a hysteroscopic biopsy performed for other reasons. Those women who have completed their families may wish to consider a hysterectomy in the absence of metastatic disease. Women who desire more children require careful counselling and further testing.

Evidence level 3

15. Which women should be registered at GTD centres?

All women diagnosed with GTD should be provided with written information about the condition and the need for referral for follow-up by a GTD centre should be explained.

D

Clinicians should be aware that outcomes for women with GTN and GTD are better with ongoing care from GTD centres. The registration of affected women with a GTD centre represents a minimum standard of care.

✓

Women with the following diagnoses should be registered and require follow-up as determined by the screening centre:

D

- **complete molar pregnancy/partial molar pregnancy**
- **twin pregnancy with complete or partial molar pregnancy**
- **limited macroscopic or microscopic molar change suggesting possible early complete or partial molar pregnancy/choriocarcinoma**
- **PSTT or ETT**
- **atypical PSN.**

The overall risk of requiring chemotherapy for GTN is around 13–16% for complete molar pregnancy and 0.5–1.0% for partial molar pregnancy,[2,4,5] hence the need for registration and follow-up, which consists of

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serial estimations of hCG levels, either in blood or urine. Choriocarcinoma, if not treated early, is potentially lethal and requires immediate registration, specialist assessment and treatment. PSTTs and ETTs are rare and unpredictable tumours that need specialist assessment and treatment.[54] Atypical PSNs may transform into PSTT/ETT so all women with this condition should be registered.[56]

Evidence level 2+

16. What is the optimum follow-up following a diagnosis of GTD?

For complete molar pregnancy, if hCG has reverted to normal within 56 days of the pregnancy event then follow-up will be for 6 months from the date of uterine removal. C

If hCG has not reverted to normal within 56 days of the pregnancy event then follow-up will be for 6 months from normalisation of the hCG level. C

Follow-up for partial molar pregnancy is concluded once the hCG has returned to normal on two samples, at least 4 weeks apart. C

Women who have not received chemotherapy no longer need to have hCG measured after any subsequent pregnancy event. C

Several large case series have shown that once the hCG reverts to normal the possibility of GTN developing is very low.[42–44,57] The incidence of GTD in a subsequent pregnancy event is very low (1:4011) in women who have not received chemotherapy for a prior molar pregnancy.[58]

Evidence level 2+

17. What is the optimum treatment for GTN?

Women with GTN may be treated with single-agent or multi-agent chemotherapy. B

Treatment used is based on the International Federation of Gynecology and Obstetrics (FIGO) 2000 scoring system for GTN following assessment at the treatment centre. B

PSTT and ETT are now recognised as variants of GTN. They may be treated with surgery because they are less sensitive to chemotherapy. D

Women are assessed before chemotherapy using the FIGO 2000 scoring system (Table 1).[27,59] Women with scores of 6 or less are at low risk and are treated with single-agent intramuscular methotrexate, alternating daily with folinic acid for 1 week followed by 6 rest days. Women with scores of 7 or greater are at high risk and are treated with intravenous multi-agent chemotherapy, which includes combinations of methotrexate, dactinomycin, etoposide, cyclophosphamide and vincristine. Treatment is continued, in all cases, until the hCG level has returned to normal and then for a further 6 consecutive weeks. Women suspected of choriocarcinoma

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Table 1. FIGO scoring system

FIGO scoring	0	1	2	4
Age (years)	< 40	≥ 40	—	—
Antecedent pregnancy	Mole	Abortion (including miscarriage)	Birth	—
Interval months from end of index pregnancy to treatment	< 4	4 to < 7	7 to < 13	≥ 13
Pretreatment serum hCG (IU/l)	$< 10^3$	10^3 to $< 10^4$	10^4 to $< 10^5$	$\geq 10^5$
Largest tumour size, including uterus (cm)	< 3	3 to < 5	≥ 5	–
Size of metastases	Lung	Spleen, kidney	Gastrointestinal	Liver, brain
Number of metastases	—	1–4	5–8	> 8
Previous failed chemotherapy	—	—	Single drug	Two or more drugs

require more extensive investigation in the specialist centre, including computed tomography of the chest and abdomen, or magnetic resonance imaging of the head and pelvis, all with contrast in addition to the serum hCG and a Doppler ultrasound of the pelvis. Any woman with a score of 13 or greater is now recognised to have a higher risk of early death (within 4 weeks), often due to bleeding into organs, or late death due to multi-drug-resistant disease.

The cure rate for women with a score of 6 or less is almost 100%, while the rate for women with a score of 7 or greater is 94%. Rarely, women with multi-relapsed disease will require high-dose chemotherapy with stem cell recovery.[6,55]

Evidence level 2++

PSTT and ETT are the rarest forms of GTN comprising about 0.2% of all GTD. They tend to produce less hCG, are confined to the uterus for longer, more often involve lymphatics and are more chemoresistant than other forms of GTN. For these reasons, they are not managed according to their FIGO score. Evidence shows that the most important prognostic factor for adverse outcome is the interval to presentation from the last known and presumed causative pregnancy. An interval of more than 48 months previously has been associated with a 100% death rate regardless of stage and despite initial favourable responses to treatments. In contrast, women presenting within 48 months are nearly all long-term survivors. A more recent series where more intensive treatments were given to PSTT/ETT patients with a long interval from their causative pregnancy reported improved survival, but still over 50% died in this group. Stage IV disease has also now emerged as an independent poor prognostic factor.[55] Surgery plays a very important role in the management of PSTT and ETT, which is tailored around stage and risk factors. Thus, for women with stage I disease, hysterectomy is the mainstay of management and intensive platinum-based combination agent chemotherapy is only required if the interval is more than 48 months. Rarely, women with multi-relapsed disease will require high-dose chemotherapy with stem cell recovery, or treatment with immunotherapy which has been approved by NHS England for GTN cases in this situation.[54,55,60]

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18. What is the recommended interval between a complete or partial molar pregnancy and trying to conceive in the future, what is the monitoring of women following a successful pregnancy after a previous molar pregnancy and what is the outcome of subsequent pregnancies?

Women are advised not to conceive until their follow-up is complete. C

Women who undergo chemotherapy are advised not to conceive for 1 year after completion of treatment, as a precautionary measure. C

Women who have a pregnancy following a previous molar pregnancy, which has not required treatment for GTN, do not need to send a post-pregnancy hCG sample. Histological examination of placental tissue from any normal pregnancy, after a molar pregnancy, is not indicated. D

The risk of a further molar pregnancy is low (approximately 1%) and is associated more with complete than partial molar pregnancy.[61] Women who become pregnant following a molar pregnancy are not at increased risk of maternal complications. However, women exposed to a molar pregnancy prior to the index birth were at an almost 25% increased risk of preterm birth (OR 1.23, 95% CI 1.06–1.43), whereas women with at least one birth between the molar pregnancy and the index birth were at an increased risk of a large-for-gestational-age birth and stillbirth (OR 1.35, 95% CI 1.10–1.67 and OR 1.81, 95% CI 1.11–2.96, respectively).[62] Evidence level 2+

In a study of 230 women who conceived within 12 months of completing chemotherapy, there was an increased risk of miscarriage and higher rate of abortion in women who received multi-agent chemotherapy compared with women who received single-agent chemotherapy. The increased rate of abortion may, in part, reflect an increase in concern relating to teratogenicity after receiving multi-agent chemotherapy. The rate of congenital abnormality was low (1.8%), irrespective of the type of chemotherapy used.[63] The rate of stillbirth was elevated compared with the normal population (18.6 in 1000 births).[64] However, in another UK study of 241 treated patients who had a pregnancy within 12 months of chemotherapy, there was no significant increased risk of miscarriage, ectopic pregnancy, second molar pregnancy or stillbirth compared to the general UK population. There was no increase in the risk of relapse in women who conceived early compared to those who conceived after 12 months.[65] Evidence level 2+

A UK national retrospective evaluation has concluded that the 'pick-up' rate for recurrent GTD on routine post-pregnancy screening of previously uncomplicated molar pregnancy is extremely low and may be safely discontinued.[57] However, those that have required chemotherapy for GTN do still need to have hCG levels checked following subsequent pregnancies. Moreover, another UK retrospective evaluation of over 4000 patients treated with chemotherapy for low- or high-risk GTN concluded that hCG follow-up can be safely stopped after 10 years.[66] Evidence level 2+

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19. What is the long-term outcome of women treated for GTN?

The outlook for women treated for GTN is generally excellent with an overall cure rate close to 100%. B

Further pregnancies are achieved in approximately 80% of women following treatment for GTN with either methotrexate alone or multi-agent chemotherapy. B

There is an increased risk of premature menopause for women treated with combination agent chemotherapy. Women, especially those approaching the age of 40 years, should be warned of the potential negative impact on fertility, particularly when treated with high-dose chemotherapy. B

Although it is common for periods to stop during treatment, they nearly always restart within a few weeks to months after completing chemotherapy. Indeed, the chances of having a pregnancy appear to be equally good, at around 83%, after either methotrexate alone or multi-agent chemotherapy, such as EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine [oncovin]). However, menopause can occur earlier than expected for women treated with combination agent chemotherapy; 13% will have had premature menopause by the age of 40 years and 36% by the age of 45 years.[67] Therefore, women approaching 40 years of age should be counselled regarding the possible negative impact on fertility. Moreover, women who receive high-dose chemotherapy are unlikely to regain ovarian function. Those seeking a fertility review after chemotherapy for GTN should be advised that the anti-müllerian hormone test can give misleading low results that do not reflect the true ability to conceive. Evidence level 3

The potential risk of second cancers induced by chemotherapeutic drugs is very low. The largest GTN study to date, with over 30 000 patient-years of follow-up, reported no overall increased risk of second cancers for women treated with methotrexate alone or EMA/CO.[67] Evidence level 2+

20. What is safe contraception following treatment of GTD and when should it be commenced?

It is important that women who have had a removal of a molar pregnancy are advised not to become pregnant until they have completed their hCG follow-up. D

Advice on contraception after a molar pregnancy can be found in the Faculty of Sexual and Reproductive Health (FSRH) Guideline Executive Summary *Contraception After Pregnancy.* D

Elevated hCG during the follow-up period may indicate recurrence. Pregnancy is best avoided during the follow-up period until the success of treatment has been established. Evidence level 3

Please refer to the FSRH Guideline *Contraception After Pregnancy* for information on contraception after a molar pregnancy.[68] Evidence level 4

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21. Is the use of exogenous estrogens and other fertility drugs safe for women undergoing assisted reproductive treatment after a molar pregnancy?

The use of exogenous estrogens and other fertility drugs may be used once hCG levels have returned to normal. ✓

There appears to be no evidence of risk that the use of exogenous estrogens and other fertility drugs affects the outcome of GTN. Evidence level 4

22. Is hormone replacement therapy safe for women to use after GTD?

Hormone replacement therapy may be used once hCG levels have returned to normal. ✓

There appears to be no evidence that the use of hormone replacement therapy affects the outcome of GTN. Evidence level 4

23. Impact of diagnosis on women and their families

GTD centres now provide individualised support to women and their families throughout their GTD journey, through dedicated GTD nurse specialists and advisors, who can be accessed either through attending a GTD centre or via phone, or both. Online support groups are available (molarpregnancy.co.uk) alongside regular drop-in support groups at Charing Cross Hospital, London and Weston Park Hospital, Sheffield. Further information is available from each centre. ✓

Evidence suggests GTD can be an isolating and frightening experience where women are affected physically, emotionally and socially by their experience.[69] A systematic review of patient-reported outcomes found GTD had a negative effect on short-term health-related quality of life, including clinically significant levels of anxiety, depression, sexual dysfunction and fertility-related distress relating to the condition.[69] For long-term survivors of GTD, quality of life was at or above population norms. Evidence level 3

24. GTD treatment centres (UK)

The following treatment centres are recommended:

Trophoblastic Tumour Screening and Treatment Centre
Department of Medical Oncology
Charing Cross Hospital
Fulham Palace Road
London W6 8RF
Tel: +44 (20) 8846 1409
Fax: +44 (20) 8748 5665
Website: hmole-chorio.org.uk

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Sheffield Trophoblastic Disease Centre
Weston Park Hospital
Whitham Road
Sheffield S10 2SJ
Tel: +44 (0) 114 226 5205
Fax: +44 (0) 114 226 5511
Website: stdc.group.shef.ac.uk

Hydatidiform Mole Follow-up (Scotland)
Department of Obstetrics and Gynaecology
Ninewells Hospital
Dundee DD1 9SY
Tel: +44 (0) 1382 632748
Fax: +44 (0) 1382 632096
Website: www.nsd.scot.nhs.uk/services/specserv/hydmole

25. Recommendations for future research

- Investigations to identify role of tumour vascularity, Doppler ultrasound pulsatility index and the biology and molecular mechanisms in predicting which molar pregnancies will resolve spontaneously, persist as GTN or transform into choriocarcinoma, PSTT or ETT.
- Evaluation of the use of ultrasound at the time of uterine removal for molar pregnancies in the reduction of persistent gynaecological symptoms, second removal for persistent gynaecological symptoms and the need for chemotherapy.
- The aetiology of atypical PSN, do all PSNs progress to atypical PSNs?
- Research in refining the FIGO scoring system to predict resistance to single-agent chemotherapy. Currently, 70% of women with a low-risk mole that scores 5 or 6 can expect to end up needing multi-agent chemotherapy to eliminate their disease.
- Evaluation of checkpoint immunotherapies, such as pembrolizumab, in the management of multi-relapsed disease.[27]
- Improved understanding of the impact of GTD on women, their partners and families, and how they may suffer. Problems identified include psychosexual issues and increased anxiety and further work is required to better understand how we can help women to overcome these by developing and utilising patient-reported outcomes.[69]

26. Auditable topics

- Proportion of women with GTN registered with the relevant screening centre (100%), including:
  - complete molar pregnancy/partial molar pregnancy
  - twin pregnancy with complete or partial molar pregnancy
  - limited macroscopic or microscopic molar change suggesting possible complete or partial molar pregnancy/choriocarcinoma
  - PSTT or ETT
  - atypical PSNs.
- Proportion of women with a histological diagnosis of complete molar pregnancy who have an ultrasound diagnosis of molar pregnancy prior to uterine removal.

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- Proportion of women who undergo medical management for removal of pregnancy tissue with an ultrasound diagnosis of complete molar pregnancy.

27. Useful links and support groups

- Royal College of Obstetricians and Gynaecologists. *Gestational trophoblastic disease. Information for you.* London: RCOG; 2011.
- Molar Pregnancy – Support & Information [http://www.molarpregnancy.co.uk].
- Charing Cross Gestational Trophoblast Disease Service [www.hmole-chorio.org.uk/].
- The Sheffield Trophoblastic Disease Centre [http://stdc.group.shef.ac.uk/].
- Tommy's – Molar pregnancy stories [https://www.tommys.org/pregnancy-information/pregnancy-complications/pregnancy-loss/molar-pregnancy/molar-pregnancy-stories].
- Miscarriage Association [www.miscarriageassociation.org.uk/information/molar-pregnancy/].

Disclosures of interest

JT has declared no conflicts of interest. BWH has declared no conflicts of interest. MS has declared no conflicts of interest. Full disclosures of interest for the developers, Guidelines Committee and peer reviewers are available to view online as supporting information.

Funding

All those involved in the development of the Green-top Guidelines, including the Guidelines Committee, Guidelines Committee co-chairs, guideline developers, peer reviewers and other reviewers, are unpaid volunteers and receive no direct funding for their involvement in producing the guideline. The only exception to this are the Guidelines Committee members who receive reimbursement for the expenses for attending the Guidelines Committee meetings for standard RCOG activities; this is standard as per RCOG rules.

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Appendix 1: Explanation of guidelines and evidence levels

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1 *Development of RCOG Green-top Guidelines* (available on the RCOG website at http://www.rcog.org.uk/green-top-development). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

A	At least one meta-analysis, systematic reviews or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good Practice Points

✓	Recommended best practice based on the clinical experience of the guideline development group

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All RCOG guidance developers are asked to declare any conflicts of interest. A statement summarising any conflicts of interest for this guideline is available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg38/.

The final version is the responsibility of the Guidelines Committee of the RCOG.

The guideline will be considered for update 3 years after publication, with an intermediate assessment of the need to update 2 years after publication.

DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

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