The Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Excellence in Women's Health

Management of gestational trophoblastic disease

This statement has been developed by the principal authors, reviewed by the Women's Health Committee and approved by the RANZCOG Board and Council.

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A list of Women's Health Committee Members can be found in Appendix B.

Declarations of interest have been received from all principal authors and Women's Health Committee.

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Objectives: To provide advice on the management of gestational trophoblastic disease.

Target audience: All health practitioners providing maternity care, and patients.

Values: The evidence was reviewed by the Women's Health Committee (RANZCOG), and applied to local factors relating to Australia and New Zealand.

Validation: This statement was compared with RCOG[1] and ACOG[2] guidelines on this topic.

Funding: The development of this statement was funded by RANZCOG.

Table of Contents

1. Patient summary

Gestational trophoblastic disease (GTD) is the name given to some uncommon tumours of placental tissue. There are a number of different types of GTD. The commonest types of GTD are usually diagnosed in early pregnancy and are commonly referred to as molar pregnancies. These are almost always successfully treated by evacuating the contents of the uterus. In most cases, the woman can have further normal pregnancies.

Occasionally, the abnormal placental tissue may persist, either in the muscle layer of uterus, or elsewhere in the body. This can be detected by a pregnancy test. For this reason, it is important, following an initial diagnosis of a molar pregnancy, that the woman has regular pregnancy blood tests under the care of a specialist obstetrician and gynaecologist.

In the rare cases where GTD persists in the body, management by doctors (subspecialists) with special expertise in this condition is required. Depending on individual circumstances, this may require transfer of the woman's care to a major centre. Fortunately, most cases of persistent GTD are successfully treated by chemotherapy. In all cases, it is very important for the woman not to get pregnant again until her follow-up is complete and she receives the "all clear" from her specialist. Options for contraception should always be discussed with the specialist.

The risk of recurrent GTD with future pregnancies is slightly higher than the general population. Therefore a pregnancy blood test should be performed six weeks after the completion of any future pregnancy regardless of the outcome of that future pregnancy.

2. Introduction

Gestational trophoblastic disease (GTD) is a group of placental related disorders derived from a pregnancy. The incidence of GTD is 1:200-1000 pregnancies, with evidence of ethnic variation; Women from Asia have a higher incidence than non-Asian women (1/390 and 1/750 respectively). The incidence after a live birth is 1/50,000. Incidence is higher at both ends of the reproductive spectrum, i.e. in women younger than 15 and older than 45.

3. Definition

Gestational Trophoblastic Disease includes hydatidiform mole (complete and partial moles), invasive mole, gestational choriocarcinoma, placental site trophoblastic tumour (PSTT) and Epithelioid Trophoblast Tumour (ETT).

Gestational trophoblastic neoplasia (GTN) is a term used to describe GTD requiring chemotherapy or excisional treatment because of persistence of HCG or presence of metastases. GTN follows hydatidiform mole (60 per cent), previous miscarriage/abortion (30 per cent), normal pregnancy or ectopic gestation (10 per cent). GTN most commonly follows hydatidiform mole as a persistently elevated hCG titre.

4. Evidence summary and basis for recommendations

Given the rarity of this condition, there are no randomised controlled trials comparing interventions (except that of first-line chemotherapy for low risk GTN).[1] However, there are a large number of case-controlled studies, case series and case reports.

4.1 What are the clinicopathological features?

4.1.1 Hydatidiform moles

Hydatidiform moles are separated into complete and partial moles based on genetic and histopathological features. In early pregnancy (less than 8 -12 weeks gestation), it may be difficult to separate complete and partial moles on H&E microscopy, and other tests (e.g. ploidy, p57) will often be required to make the diagnosis.[3]

Complete mole usually occurs when the ovum contains no maternal genetic material and is fertilised by one sperm that replicates (75 per cent), or, less commonly, by two sperm (dispermy) (25 per cent). Twin pregnancies, in which a single molar pregnancy is suspected, create special diagnostic and management dilemmas, and are best referred to a specialist centre.

Partial moles are usually triploid (dispermy), but may be tetraploid or mosaic. Partial molar pregnancies usually contain embryonic or fetal material such as fetal red blood cells. As it may take some time to get a definitive diagnosis of partial or complete mole, it is recommended that all patients who are Rhesus negative receive Anti-D prophylaxis.

Most molar pregnancies spontaneously remit after evacuation; however persistence or change into malignant disease requiring chemotherapy occurs in 0.5 – 4 per cent of partial moles and 15 – 25 per cent of complete moles.

4.1.2 Persistent GTD

Persistent GTD usually presents with βhCG elevation following a molar pregnancy, however clinical features can include PV bleeding, abdominal pain or swelling.

4.1.3 Gestational choriocarcinoma

Gestational choriocarcinoma most commonly follows a complete molar pregnancy (25-50 per cent), within 12 months of a non-molar abortion (25 per cent), or after a term pregnancy (25-50 per cent). Symptoms may include PV bleeding, pelvic mass, or symptoms from distant metastases such as liver, lung and brain metastases. HCG is always elevated. It may be a difficult pathological diagnosis because of the frequent haemorrhage and necrosis that accompany it. This is a tumour that crosses the placenta so the newborn of a mother newly diagnosed with choriocarcinoma must be investigated to exclude disease (urinary Bhcg).

4.1.4 Placental Site Trophoblastic Tumour

Placental Site Trophoblastic Tumour (PSTT) is very rare. This frequently presents as a slow growing tumour a number of years after a molar pregnancy, non-molar abortion or term pregnancy. Usually PSTT presents with gynaecologic symptoms, as metastases are later and rarer than in Choriocarcinoma. Rarely, patients can present with hyperprolactinaemia or nephrotic syndrome. Usually the hCG levels are relatively low in PSTT relative to the volume of the disease.

PSTT is increasingly thought of as a separate entity, as its behaviour differs from other GTDs. PSTT should be considered in cases of relapse. Treatment for PSTT is usually hysterectomy.

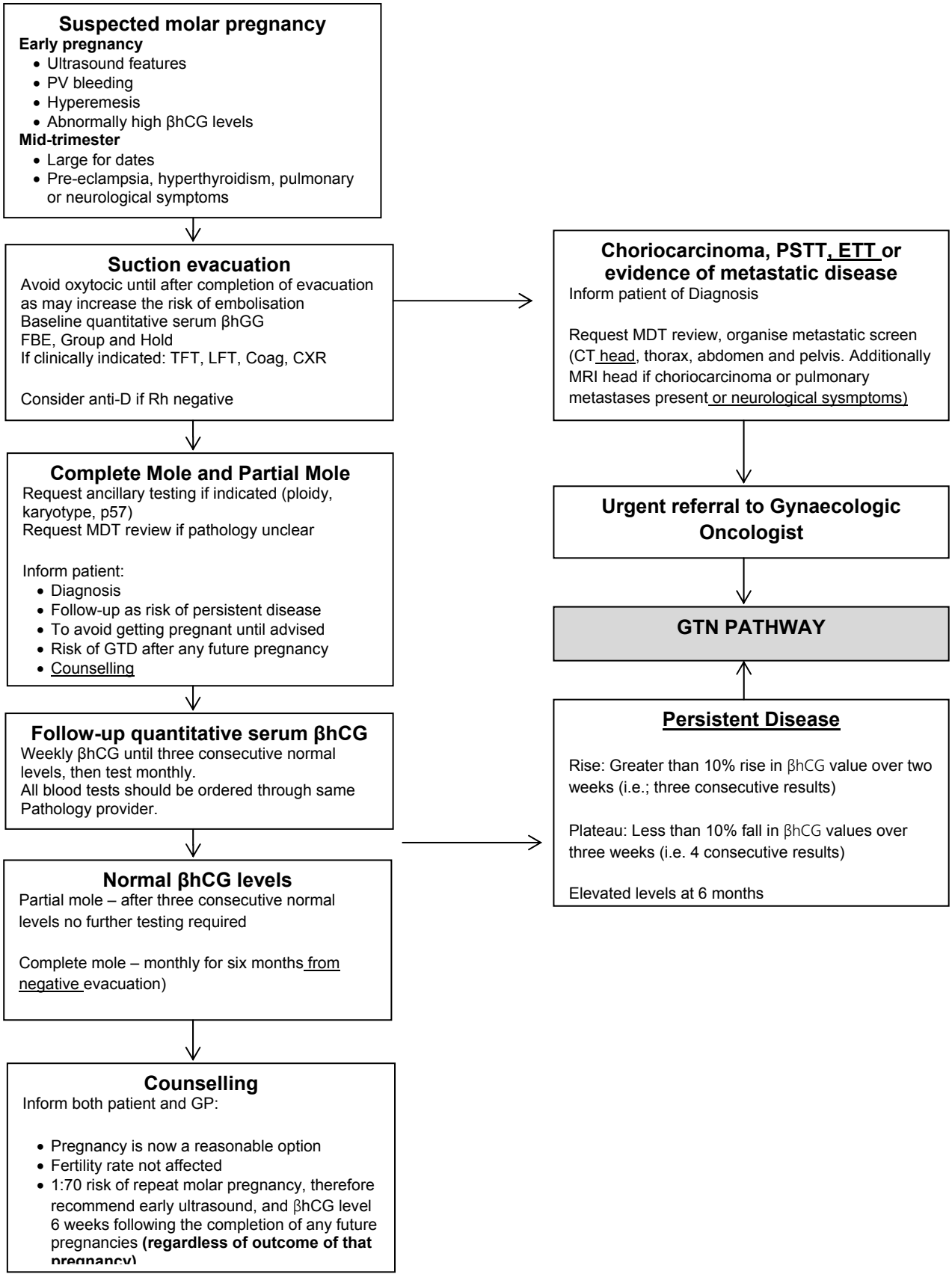
4.1.5 Epithelioid Trophoblast Tumour (ETT)

Epithelioid Trophoblast Tumour (ETT) is a distinctive but rare form of GTN. It is a disease of intermediate trophoblast cells. Pathological diagnosis is often difficult and differential diagnoses include Choriocarcinoma, PSTT and SCC of the cervix. Histology specimens should be reviewed by specialist pathologists familiar with this condition. ETT is typically characterised by a long interval from the antecedent pregnancy and more commonly follows a term pregnancy. βhCG levels are generally much lower than with a molar pregnancy. The biological behaviour of ETT is less aggressive than choriocarcinoma, but its metastatic potential is similar to PSTT. Primary treatment is hysterectomy as these tumours are resistant to chemotherapy. High mitotic index, atypia and vascular invasion confer a poorer prognosis.[4, 5]

4.2 Do Australia and New Zealand have GTD Registries?

In Australia, there is no nationally coordinated program for the registration or management of gestational trophoblast disease (GTD), but there are State-based registries in South Australia, Victoria and Queensland. New Zealand also has a national GTD registry. Fellows should check with their State's Gynaecologic Oncology service regarding GTD registries.

4.3 How should GTD be managed?



5. Recommendations

5.1 Clinical presentation

Recommendation 1	Grade and reference
A pregnancy test should be performed in all cases of persistent or irregular vaginal bleeding after a pregnancy event.	Consensus-based recommendation 6, 7
Recommendation 2	**Grade**
Vaginal gestational trophoblastic neoplasia (GTN) is most commonly located in the fornices or suburethrally. Due to their highly vascular nature biopsy should be avoided.	Consensus-based recommendation

5.2 Surgical management

Recommendation 3	Grade and reference
Suction evacuation is the preferred initial management regardless of uterine size. Ideally this should be performed by an experienced Obstetrician/Gynaecologist.	Consensus-based recommendation 1, 8
Recommendation 4	**Grade and reference**
In selected cases, a second evacuation may be necessary because of problematic bleeding but it has been shown that there is still a 70 per cent chance of requiring chemotherapy, and an 8 per cent chance of uterine perforation.[9-11] If considering a second surgical evacuation, liaise with your local GTD registry. Consider hysteroscopy in order to locate persistent focus, if a second evacuation is performed. Repeat evacuation is not recommended if βhCG >5000 or in the presence of metastases. All products of conception obtained at evacuation for suspected GTN should be sent for histology. Ploidy status and immunohistochemistry staining for P57 may be useful for differentiation between partial or complete mole.[3]	Consensus-based recommendation 3, 9-11
Recommendation 5	**Grade and reference**
Use of prostaglandins to ripen the cervix is appropriate.[12] Data is lacking in prolonged use or late gestation and should be used with caution. Avoid oxytocic use until after evacuation. It is recommended that all patients who are Rhesus negative receive Anti-D prophylaxis.	Consensus-based recommendation 12

Recommendation 6	Grade
To minimise the risk of perforation of the uterus, insertion of an intrauterine device should be delayed for at least six weeks after evacuation of the uterus and hCG levels have returned to normal.	Consensus-based recommendation

5.3 Monitoring

Recommendation 7	Grade
Report case to GTD Registry (in 2017 applies to South Australia, Victoria, Queensland and New Zealand only).	Consensus-based recommendation
Recommendation 8	**Grade**
One person or team should be made responsible for the patient regarding monitoring βhCG. The use of the GTD graph may be of assistance (see Appendix A).	Consensus-based recommendation
Recommendation 9	**Grade**
Monitoring of post-evacuation βhCG levels and counselling should be undertaken by the Obstetrician/Gynaecologist as outlined in the flow chart.	Consensus-based recommendation
Recommendation 10	**Grade**
Weekly quantitative βhCG levels should be undertaken until three consecutive normal levels are seen. For Partial Moles, no further testing is recommended. For Complete moles monthly levels should continue until cleared of ongoing monitoring (6 months).	Consensus-based recommendation
Recommendation 11	**Grade**
A rise of greater than 10 per cent over two weeks (3 weekly βhCG levels) or a fall of less than 10 per cent over three weeks (4 weekly βhCG levels) confirms a diagnosis of persistent GTD. Should this occur, a metastatic screen and WHO risk score is performed. Patients should be referred to a specialist centre / Gynaecologic Oncologist for further management.	Consensus-based recommendation
Recommendation 12	**Grade and reference**
Pregnancy should be avoided during follow-up. The oral contraceptive pill may be prescribed.*	Consensus-based recommendation [13,14, 15]
Recommendation 13	**Grade**
A diagnosis of a gestational choriocarcinoma and PSTT warrants referral to a Gynaecologic Oncologist. Management of PSTT may require hysterectomy. PSTT should be considered in cases of relapse.	Consensus-based recommendation

*The largest dataset of 1384 patients from the Charing Cross Hospital receiving oral contraceptives found that only 1 patient of the 1049 patients who took the OC after normalisation of βhCG went on to need chemotherapy, in contrast 103 of the 335 (31%) of those women who took the OC before normalisation of their βhCG required chemotherapy. The US figures were 57% vs. 33% in patients using, versus not using OCs after evacuation respectively. [14, 15]

5.4 Follow-up

Recommendation14	Grade and reference
Women who receive multi-agent chemotherapy for invasive mole may be at increased risk of early pregnancy complications if conception occurs within 12 months of completion of treatment. Long-term outcomes in women having had chemotherapy are not affected.	Consensus-based recommendation [1]
Recommendation 15	**Grade**
For women who conceive again, there is a low chance (about 1:70) of having a subsequent GTD event. Therefore obtain βhCG 6 weeks after conclusion of any future pregnancy regardless of the pregnancy outcome.	Consensus-based recommendation
Recommendation 16	**Grade and reference**
In circumstances where patients have completed their family, hysterectomy may be an appropriate treatment for GTN confined to the uterus to reduce the need for chemotherapy. Two small American studies have shown that the chances of needing chemotherapy after hysterectomy for molar pregnancy are 3-10 per cent, i.e. about halved, but certainly not eliminated.[16, 17] The need for careful surveillance remains after hysterectomy.	Consensus-based recommendation [16, 17]

5.5 Technical information

- The serum half-life of hCG is ~24-36 hours. The level is roughly linked to the number of tumour cells; 5IU/l ~104 – 105 tumour cells.
- Phantom hCG is a false positive result for serum hCG. This is due to human heterophilic antibodies (antibodies that can bind to non-human immunoglobulins present in commercial hCG assays).
- False positive serum hCG results can be excluded if the urine hCG is negative (heterophilic antibodies are not present in urine) or by serial dilution of the serum (no parallel dilution in results observed). [2]

6. Links to other College statements

Evidence-based Medicine, Obstetrics and Gynaecology (C-Gen 15)
http://www.ranzcog.edu.au/component/docman/doc_download/894-c-gen-15-evidence-based-medicine-obstetrics-and-gynaecology.html?Itemid=341

7. References

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6. Nugent D, Hassadia A, Everard J, Hancock BW, Tidy JA. Postpartum choriocarcinoma presentation, management and survival. J Reprod Med. 2006;51(10):819-24.
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12. Flam F, Lundstrom V, Pettersson F. Medical induction prior to surgical evacuation of hydatidiform mole: is there a greater risk of persistent trophoblastic disease? Eur J Obstet Gynecol Reprod Biol. 1991;42(1):57-60.
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17. Moodley M, Moodley J. Evaluation of chest X-ray findings to determine metastatic gestational trophoblastic disease according to the proposed new staging system: a case series. J Obstet Gynaecol. 2004;24(3):287-8.
18. National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra. 2009.

8. Further reading

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2. Kerkmeijer L *et al.* Guidelines following hydatidiform mole: a reappraisal. Aust NZ J Obstet Gyanecol. 2006 Apr;46(2):112-8.

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4. International Federation of Obstetrics and Gynecology Oncology Committee. FIGO staging for gestational trophoblastic neoplasia 2000. Int J Gynecol Obstet 2002;77:285–7.

Appendices

Appendix A GTD Follow-up form (Source: Western Australian Gyneacologic Cancer Service)

GESTATIONAL TROPHOBLASTIC DISEASE FOLLOW-UP

Med Rec No _____

Surname _____

Forename _____

Sex _____ DOB _____

Following a diagnosis of a molar (complete or partial) pregnancy, weekly quantitative serum bHCG levels should be taken and recorded on the graph below.
This form is not to be used when a diagnosis of persistent gestational trophoblastic disease has been established (see below).

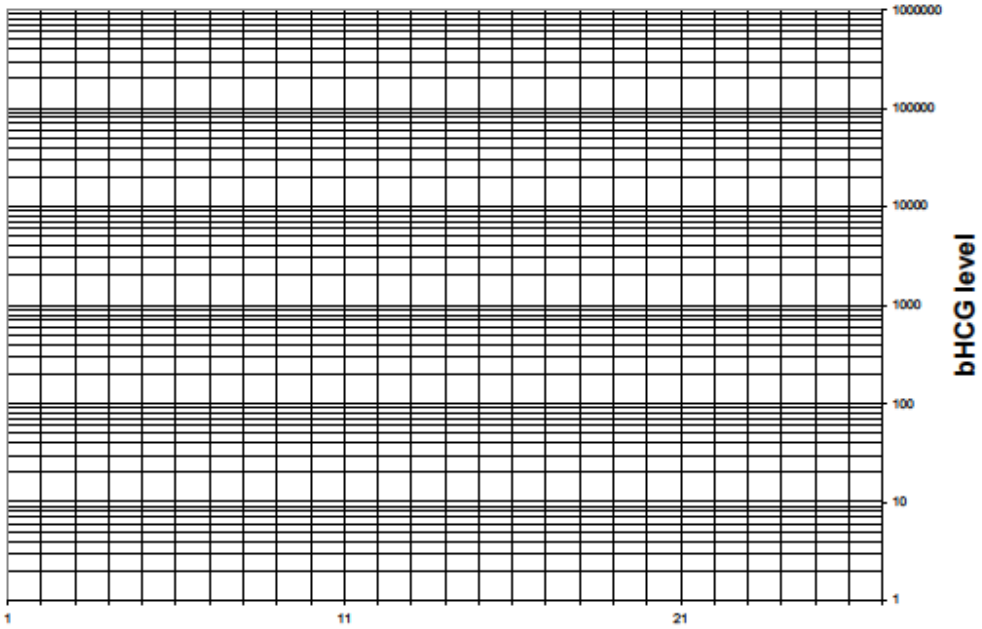
Refer to Gynaecologic Oncology if
- Serum bHCG level >20,000 more than four weeks post evacuation
- Progressively rising serum bHCG post evacuation (>10% rise over two weeks)
- Plateau of serum bHCG for three consecutive weeks (<10% fall over three weeks)
- Any detectable serum bHCG 4 – 6 months post evacuation
- Evidence of metastatic disease

Please contact the on-call Gynaecologic Oncologist if there are any questions.

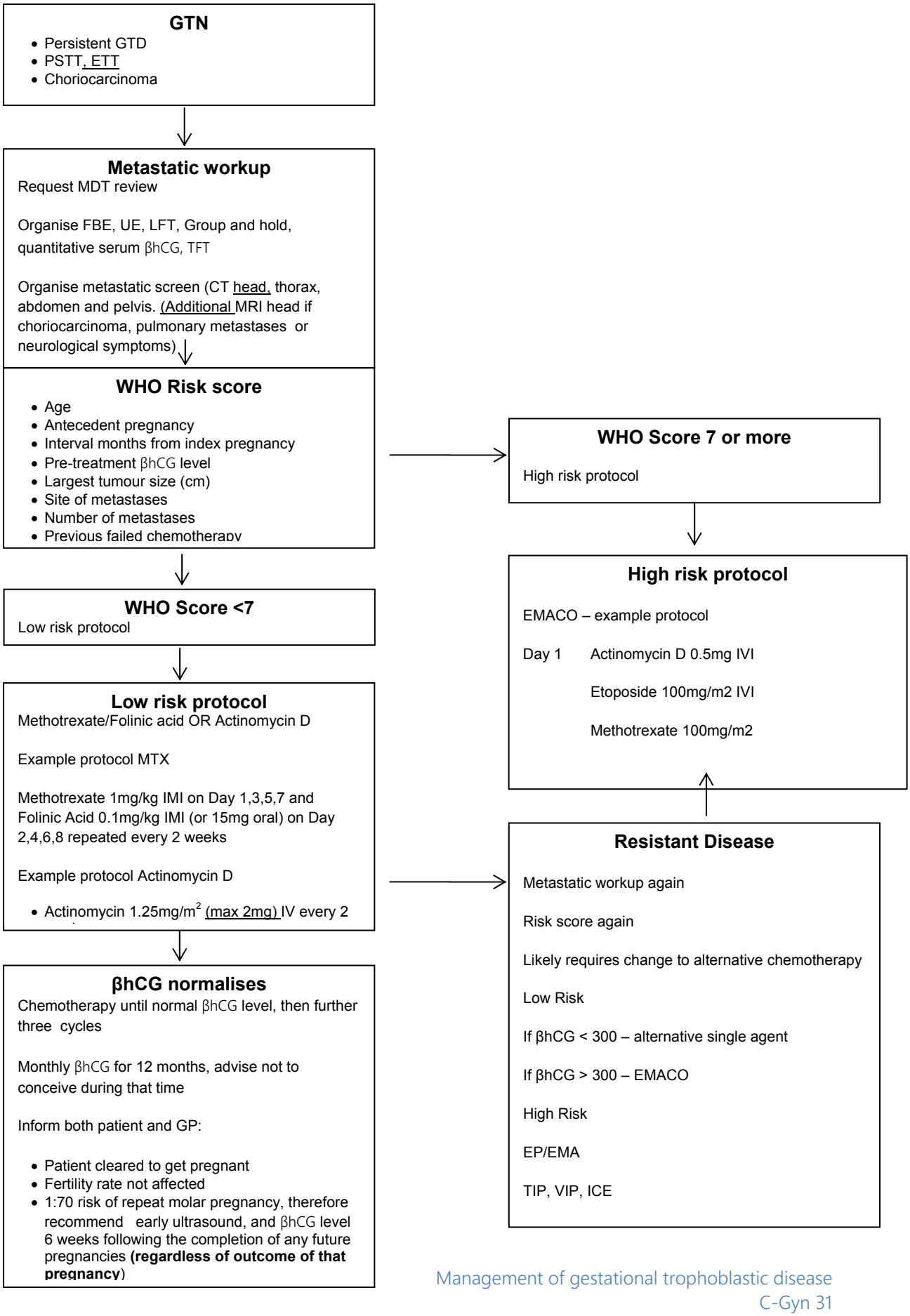
Ensure adequate contraceptive advice is provided for six months from the date the level became negative.

If the levels fall appropriately and are negative at six months, patient can be referred back to their family doctor.
Provide advice regarding bHCG testing after any future pregnancy

Gestational Trophoblastic Disease
Follow-up bHCG levels



Appendix B How should GTN be managed?



Appendix C Women's Health Committee Membership

Name	Position on Committee
Professor Yee Leung	Chair
Dr Joseph Sgroi	Deputy Chair, Gynaecology
Associate Professor Janet Vaughan	Deputy Chair, Obstetrics
Professor Susan Walker	Member
Associate Professor Ian Pettigrew	Member
Dr Tal Jacobson	Member
Dr Ian Page	Member
Dr John Regan	Member
Dr Craig Skidmore	Member
Dr Lisa Hui	Member
Dr Bernadette White	Member
Dr Scott White	Member
Associate Professor Kirsten Black	Member
Dr Greg Fox	College Medical Officer
Dr Marilyn Clarke	Chair of the A&TSI WHC
Dr Martin Byrne	GPOAC Representative
Ms Catherine Whitby	Community Representative
Ms Sherryn Elworthy	Midwifery Representative
Dr Amelia Ryan	Trainee Representative

Appendix D Overview of the development and review process for this statement

i. Steps in developing and updating this statement

This statement was developed during 2013 and most recently reviewed in March 2017. The principle authors carried out the following steps in developing this statement:

- Declarations of interest were received from all principal authors and Women's Health Committee members prior to reviewing this statement.
- Structured clinical questions were developed and agreed upon.
- A literature search to answer the clinical questions was undertaken and a draft was developed.
- This draft was compared with the current RCOG[1] and ACOG[2] guidelines on this topic. Recommendations were graded as set out below in Appendix D part iii).
- All principal authors reviewed the draft and provided comments which were incorporated.
- The draft was submitted to Women's Health Committee for approval at the November 2013 Women's Health Committee meeting. This draft statement was reviewed (where

appropriate) based on the body of evidence and clinical expertise of Women's Health Committee.

ii. Declaration of interest process and management

Declaring interests is essential in order to prevent any potential conflict between the private interests of members, and their duties as part of the Women's Health Committee.

A declaration of interest form specific to guidelines and statements was developed by RANZCOG and approved by the RANZCOG Board in September 2012. The Women's Health Committee members were required to declare their relevant interests in writing on this form prior to participating in the review of this statement.

Members were required to update their information as soon as they become aware of any changes to their interests and there was also a standing agenda item at each meeting where declarations of interest were called for and recorded as part of the meeting minutes.

There were no significant real or perceived conflicts of interest that required management during the process of updating this statement.

iii. Grading of recommendations

Each recommendation in this College statement is given an overall grade as per the table below, based on the National Health and Medical Research Council (NHMRC) Levels of Evidence and Grades of Recommendations for Developers of Guidelines.[18] Where no robust evidence was available but there was sufficient consensus within the writing group, consensus-based recommendations were developed and are identifiable as such. Consensus-based recommendations were agreed to by the entire committee. Good Practice Notes are highlighted throughout and provide practical guidance to facilitate implementation. These were also developed through consensus.

Recommendation category		Description
Evidence-based	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
	D	The body of evidence is weak and the recommendation must be applied with caution
Consensus-based		Recommendation based on clinical opinion and expertise as insufficient evidence available

Good Practice Note	Practical advice and information based on clinical opinion and expertise

Appendix E Full Disclaimer

This information is intended to provide general advice to practitioners, and should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any patient.

This information has been prepared having regard to general circumstances. It is the responsibility of each practitioner to have regard to the particular circumstances of each case. Clinical management should be responsive to the needs of the individual patient and the particular circumstances of each case.

This information has been prepared having regard to the information available at the time of its preparation, and each practitioner should have regard to relevant information, research or material which may have been published or become available subsequently.

Whilst the College endeavours to ensure that information is accurate and current at the time of preparation, it takes no responsibility for matters arising from changed circumstances or information or material that may have become subsequently available.