Management of gestational trophoblastic disease

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 RCOG1 and ACOG2 guidelines on this topic.

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

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.

Disclaimer: This information is intended to provide general advice to practitioners. This information 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 document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The document has been prepared having regard to general circumstances.

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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). 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.

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 \( \beta \text{hCG} \) 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?

**Suction evacuation**
Avoid oxytocin until after completion of evacuation as may increase the risk of embolisation
Baseline quantitative serum βhGG
FBE, Group and Hold
If clinically indicated: TFT, LFT, Coag, CXR
Consider anti-D if Rh negative

**Suspected molar pregnancy**

**Early pregnancy**
- Ultrasound features
- PV bleeding
- Hyperemesis
- Abnormally high βhCG levels

**Mid-trimester**
- Large for dates
- Pre-eclampsia, hyperthyroidism, pulmonary or neurological symptoms

**Choriocarcinoma, PSTT, ETT or evidence of metastatic disease**
Inform patient of Diagnosis
Request MDT review, organise metastatic screen (CT head, thorax, abdomen and pelvis. Additionally MRI head if choriocarcinoma or pulmonary metastases present or neurological symptoms)

**Urgent referral to Gynaecologic Oncologist**

**GTN PATHWAY**

**Persistent Disease**
Rise: Greater than 10% rise in βhCG value over two weeks (i.e.; three consecutive results)
Plateau: Less than 10% fall in βhCG values over three weeks (i.e. 4 consecutive results)
Elevated levels at 6 months

**Complete Mole and Partial Mole**
Request ancillary testing if indicated (ploidy, karyotype, p57)
Request MDT review if pathology unclear
Inform patient:
- Diagnosis
- Follow-up as risk of persistent disease
- To avoid getting pregnant until advised
- Risk of GTD after any future pregnancy
- Counselling

**Follow-up quantitative serum βhCG**
Weekly βhCG until three consecutive normal levels, then test monthly.
All blood tests should be ordered through same Pathology provider.

**Normal βhCG levels**
Partial mole – after three consecutive normal levels no further testing required
Complete mole – monthly for six months from negative evacuation

**Counselling**
Inform both patient and GP:
- Pregnancy is now a reasonable option
- Fertility rate not affected
- 1:70 risk of repeat molar pregnancy, therefore recommend early ultrasound, and βhCG level 6 weeks following the completion of any future pregnancies (regardless of outcome of that pregnancy)
5. Recommendations

5.1 Clinical presentation

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

5.2 Surgical management

<table>
<thead>
<tr>
<th>Recommendation 3</th>
<th>Grade and reference</th>
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</thead>
<tbody>
<tr>
<td>Suction evacuation is the preferred initial management regardless of uterine size. Ideally this should be performed by an experienced Obstetrician/Gynaecologist.</td>
<td>Consensus-based recommendation 1, 8</td>
</tr>
</tbody>
</table>

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<tr>
<th>Recommendation 4</th>
<th>Grade and reference</th>
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<tbody>
<tr>
<td>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. 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 &gt;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.</td>
<td>Consensus-based recommendation 3, 9-11</td>
</tr>
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<tr>
<th>Recommendation 5</th>
<th>Grade and reference</th>
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<tr>
<td>Use of prostaglandins to ripen the cervix is appropriate. 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.</td>
<td>Consensus-based recommendation 12</td>
</tr>
</tbody>
</table>
### 5.3 Monitoring

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
<th>Recommendation Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation 6</td>
<td>Consensus-based recommendation</td>
<td>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.</td>
</tr>
<tr>
<td>Recommendation 7</td>
<td>Consensus-based recommendation</td>
<td>Report case to GTD Registry (in 2017 applies to South Australia, Victoria, Queensland and New Zealand only).</td>
</tr>
<tr>
<td>Recommendation 8</td>
<td>Consensus-based recommendation</td>
<td>One person or team should be made responsible for the patient regarding monitoring βhCG. The use of the GTD graph may be of assistance (<em>see Appendix A</em>).</td>
</tr>
<tr>
<td>Recommendation 9</td>
<td>Consensus-based recommendation</td>
<td>Monitoring of post-evacuation βhCG levels and counselling should be undertaken by the Obstetrician/Gynaecologist as outlined in the flow chart.</td>
</tr>
<tr>
<td>Recommendation 10</td>
<td>Consensus-based recommendation</td>
<td>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).</td>
</tr>
<tr>
<td>Recommendation 11</td>
<td>Consensus-based recommendation</td>
<td>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.</td>
</tr>
<tr>
<td>Recommendation 12</td>
<td>Consensus-based recommendation</td>
<td>Pregnancy should be avoided during follow-up. The oral contraceptive pill may be prescribed.*</td>
</tr>
<tr>
<td>Recommendation 13</td>
<td>Consensus-based recommendation</td>
<td>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.</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Recommendation 14</th>
<th>Grade and reference</th>
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<tbody>
<tr>
<td>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.</td>
<td>Consensus-based recommendation 1</td>
</tr>
<tr>
<td>Long-term outcomes in women having had chemotherapy are not affected.</td>
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<tr>
<th>Recommendation 15</th>
<th>Grade</th>
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<tbody>
<tr>
<td>For women who conceive again, there is a low chance (about 1:70) of having a subsequent GTD event. Therefore obtain $\beta$hCG 6 weeks after conclusion of any future pregnancy regardless of the pregnancy outcome.</td>
<td>Consensus-based recommendation</td>
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<tr>
<th>Recommendation 16</th>
<th>Grade and reference</th>
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<tbody>
<tr>
<td>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.</td>
<td>Consensus-based recommendation</td>
</tr>
<tr>
<td>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.</td>
<td>16, 17</td>
</tr>
<tr>
<td>The need for careful surveillance remains after hysterectomy.</td>
<td></td>
</tr>
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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 ~10^4 – 10^5 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)
7. References

8. Further reading


Appendices

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

GESTATIONAL TROPHOBLASTIC DISEASE FOLLOW-UP

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

Weeks (start with FIRST available titre and INSERT DATE)

[Graph showing bHCG levels over time]
Appendix B How should GTN be managed?

**GTN**
- Persistent GTD
- PSTT, ETT
- Choriocarcinoma

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**Metastatic workup**
Request MDT review
Organise FBE, UE, LFT, Group and hold, quantitative serum βhCG, TFT
Organise metastatic screen (CT head, thorax, abdomen and pelvis. (Additional MRI head if choriocarcinoma, pulmonary metastases or neurological symptoms)

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**WHO Risk score**
- Age
- Antecedent pregnancy
- Interval months from index pregnancy
- Pre-treatment βhCG level
- Largest tumour size (cm)
- Site of metastases
- Number of metastases
- Previous failed chemotherapy

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**WHO Score <7**
Low risk protocol

**Low risk protocol**
Methotrexate/Folinic acid OR Actinomycin D

Example protocol MTX
Methotrexate 1mg/kg IMI on Day 1,3,5,7 and Folinic Acid 0.1mg/kg IMI (or 15mg oral) on Day 2,4,6,8 repeated every 2 weeks

Example protocol Actinomycin D
- Actinomycin 1.25mg/m² (max 2mg) IV every 2

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**βhCG normalises**
Chemotherapy until normal βhCG level, then further three cycles
Monthly βhCG for 12 months, advise not to conceive during that time
Inform both patient and GP:
- Patient cleared to get pregnant
- Fertility rate not affected
- 1:70 risk of repeat molar pregnancy, therefore recommend early ultrasound, and βhCG level 6 weeks following the completion of any future pregnancies (regardless of outcome of that pregnancy)

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**WHO Score 7 or more**
High risk protocol

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**High risk protocol**
EMACO – example protocol
Day 1  Actinomycin D 0.5mg IVI
Etoposide 100mg/m² IVI
Methotrexate 100mg/m²

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**Resistant Disease**
Metastatic workup again
Risk score again
Likely requires change to alternative chemotherapy
Low Risk
If βhCG < 300 – alternative single agent
If βhCG > 300 – EMACO
High Risk
EP/EMA
TIP, VIP, ICE
Appendix C Women’s Health Committee Membership

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

<table>
<thead>
<tr>
<th>Recommendation category</th>
<th>Description</th>
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<tbody>
<tr>
<td>Evidence-based</td>
<td>A Body of evidence can be trusted to guide practice</td>
</tr>
<tr>
<td></td>
<td>B Body of evidence can be trusted to guide practice in most situations</td>
</tr>
<tr>
<td></td>
<td>C Body of evidence provides some support for recommendation(s) but care should be taken in its application</td>
</tr>
<tr>
<td></td>
<td>D The body of evidence is weak and the recommendation must be applied with caution</td>
</tr>
<tr>
<td>Consensus-based</td>
<td>Recommendation based on clinical opinion and expertise as insufficient evidence available</td>
</tr>
<tr>
<td>Good Practice Note</td>
<td>Practical advice and information based on clinical opinion and expertise</td>
</tr>
</tbody>
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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.