Management of gestational trophoblastic disease: a survey of New Zealand O&G practice

Maria Kladnitski, Diane Kenwright

ABSTRACT

AIM: The aim of the study was to obtain information on pathways for diagnosis and management of molar pregnancy/gestational trophoblastic disease (GTD) across New Zealand, the protocols used, and, in addition, to consider the view of O&G Specialists on a national GTD reference centre.

METHOD: An electronic survey approved by the RANZCOG Continues Professional Development Committee was distributed amongst registered O&G Specialists currently working in New Zealand. Data were analysed using Microsoft Excel 2011. Frequency distributions were used to determine the percentage of participants responding to the listed alternatives for each question.

RESULTS: There were 234 potential responders, but only 68 complete questionnaires were received and available for analysis. The diagnosis of GTD requires histopathological analysis of pregnancy tissue, however only 79.7% of participants request this test routinely. Sixty-five percent of Fellows thought that a number of molar pregnancies can be missed with increasing proportion of medically-managed miscarriages, reliance on ultrasound and appearance of the tissue being contributing factors. Sixty-six percent of specialists were directly involved in the management of patients with GTD to various degrees. Follow-up responsibilities were divided between designated O&G specialists (52.3%), specialised gynaecology clinics (29.2%), acute assessment units (13.8%), nurse specialists (12%), O&G registrars (10.8%), GPs (6.2%), and others (6.2%). NZGCG guidelines were used by the majority of responders (54.8%), followed by local (29%) and RCOG (27.4%) guidelines. Seventy-two percent of specialists felt that some form of centralisation in the management of GTD is needed.

CONCLUSION: In spite of the low response rate, our research demonstrates existing practice heterogeneity at every level of care. It also confirms that there is a desire for some form of centralisation in diagnosis and management of GTD, and a definite need for data collection in the form of a national register.

Background

Gestational trophoblastic disease (GTD) comprises a spectrum of interrelated conditions originating from the placenta. Histologically distinct disease entities include complete and partial mole, invasive mole, gestational choriocarcinoma, and placental site trophoblastic tumours.

Although estimates for the incidence of various forms of GTD vary, molar pregnancy is the most common subtype. For example, in the US, hydatidiform moles are observed in approximately 1:600 therapeutic abortions and 1:1,500 pregnancies. Data from the UK are slightly different. The incidence of complete hydatidiform mole is around 1:1,000 pregnancies and 3:1,000 for partial hydatidiform mole. There is also evidence of ethnic variation. Women from Asia, for instance, have a higher incidence than non-Asian women; 1:125 pregnancies in Taiwan versus 0.6–1.1:1,000 pregnancies in Europe. Furthermore, incidence is higher at the extremes of the reproductive spectrum; in women younger than 15, and older than 40.

Estimates for the incidence of hydatidiform moles/GTD in New Zealand are not currently available as the entity is not registered, but it was not always the case. The Trophoblastic Disease Register was established in New Zealand in late 1979,
and since 1982 it was under the auspice of the Royal New Zealand College of Obstetricians and Gynaecologists. The aims of the register were to collect epidemiological data on trophoblastic disease, to facilitate early detection of malignant trophoblastic disease, and thus to optimise management.

Two studies conducted in New Zealand shortly after introduction of the register, gave the incidence of trophoblastic disease between 1:1,497 pregnancies and 1:400 deliveries. According to Duff, 70% of cases were reported to the register (notification from some smaller centres in both the North and South Islands were below average at 42–58%). The clinical information obtained at the time revealed no difference in incidence of GTD between the three main ethnic groups, which make up the New Zealand population: New Zealand European, Māori and Asian.

Unfortunately the register no longer exists, and the incidence of GTD in New Zealand at present is not known. However, the indication that the Asian population is rising and maternal age at conception is increasing in New Zealand (in 1962, 26.5 years; in 2009, 32.1 years) suggests that New Zealand incidence may currently be higher compared with European countries.

Most women with GTD can be cured and their reproductive function can be preserved, but it is important that the initial management and follow-up of a patient be timely and appropriate. Currently, there is no information regarding the mode of referral, the initial assessment, and the management of patients with molar pregnancies or GTD in New Zealand. Although there are guidelines available, it is not known if they are used across the country as a single source of information.

Where there is variation in clinical practice or concerns about ineffective practice, guidelines can be a useful way to improve the quality of health care, and assist clinicians in the management of specific conditions. Moreover, the advantages of centralisation of cases have long been recognised as essential to improve the management of patients with rare diseases.

In the UK, there are three National Centres for Trophoblastic Disease, which has been functioning for many years now. Thorough follow-up and centralised management have achieved impressive results with cure rate of 98–100%, and low chemotherapy rates.

Brewer reported as far back as 1971, that both the morbidity and mortality of GTD patients was nine times lower at a centre staffed by physicians experienced in the management of trophoblastic disease compared with the ‘occasional’ physician treating this entity.

Countries such as France, the US, Sweden, the Netherlands, Norway and Hungary have the registration and management of GTD centralised.

### Table 1: Survey Questions.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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<tbody>
<tr>
<td>1. Do you routinely send products of conception for histopathological analysis?</td>
<td></td>
</tr>
<tr>
<td>2. What influence your decision on sending obtained products of conception to histopathological analysis?</td>
<td></td>
</tr>
<tr>
<td>3. Do you think that some number of molar pregnancies are missed and, if so, why?</td>
<td></td>
</tr>
<tr>
<td>4. Are you involved in the management of molar pregnancies /GTD in your hospital /practice and, if YES, to what degree?</td>
<td></td>
</tr>
<tr>
<td>5. What guidelines do you follow in your DHB?</td>
<td></td>
</tr>
<tr>
<td>6. Do you agree with your local guidelines? If you disagree, is there anything you would like to change?</td>
<td></td>
</tr>
<tr>
<td>7. In your hospital/region/practice who is responsible for follow up of the patients with molar pregnancies?</td>
<td></td>
</tr>
<tr>
<td>8. There is some evidence that creation of a Trophoblastic Disease Reference centre is desirable to improve treatment of patients with GTD. Do you agree?</td>
<td></td>
</tr>
<tr>
<td>9. There is no such centre in New Zealand at present. Do you think that the diagnosis and treatment of GTD should be centralised?</td>
<td></td>
</tr>
<tr>
<td>10. In your opinion, what would be the best option?</td>
<td></td>
</tr>
</tbody>
</table>
The Philippines, and some parts of India, also try to implement centralised management. It appears to be a good time to consider reviving the National GTD Register in New Zealand, and a creation of a reference centre as a next step.

The overarching aim of the present study was to better understand how New Zealand O&G specialists currently approach GTD management with the view to initiate improvement in the assessment, diagnosis, and treatment of this condition in New Zealand.

**Method**

In May 2013, a link to an electronic survey was sent via email to registered O&G Specialists currently working in New Zealand, using the RANZCOG mailing list. A reminder email was sent 2 weeks later.

The survey was comprised of ten questions examining current clinical practice related to the diagnosis and management of patients with GTD (Table 1).

There were also sections allowing responders to explain their answers.

A total of 244 surveys were distributed. Nine surveys failed to be delivered; one responder was no longer practicing, leaving 234 potential responders.

The RANZCOG’s Continuing Professional Development Committee approved the survey for distribution. Ethical approval was not sought, as this was a survey of practice and opinions.

**Results**

Data were analysed using Microsoft Excel 2011. Frequency distributions were used to determine the percentage of participants responding to the listed alternatives for each question. Descriptive statistics are presented in Tables 2 through 4 below.

In total, 75 responses were received (32% response rate). Of those, 29% (68) responses were completed questionnaires available for analysis, and 2.9% (7) responses were from participants opting out, indicating that they were not involved in the care of patients with GTD.

Specialists were asked: a) if they routinely submit obtained products of conception for histopathological analysis; b) what influences their decision; and c) their opinion regarding missed molar pregnancies.

Survey showed that 79.7% (51) of specialists always send tissue, irrespective of the results of pre-operative investigations, 7.8% (5) do not, 12.5% (8) do it sometimes, and 5.8% (4) skipped the question. Out of those who do not submit tissue for histological analysis, 80% of specialists base their decision on the ultrasound scan (USS) report, 80% on the appearance of the tissue, and 60% on clinical presentation. Out of those who submit tissue sometimes, 87% rely on USS report, 62% on the appearance, and 75% on clinical presentation. Other factors mentioned included previous molar pregnancy. The percentages add up to more than 100%, as responders were able to choose more than one response.

As can be seen from the above data, 20% of products of conception are not always sent to histology, and various methods are used to determine if histology is required. Sixty-five percent (41) of Fellows thought that GTD is being missed through current referral practices. 69.8% (44) of specialists mentioned an increasing number of medically-managed miscarriages was the main reason GTD had been missed. 20.6% (13) and 12.7% (8) respectively think that reliance on USS and gross appearance of the tissue contributes to missed diagnosis.

We were interested in the extent to which O&G specialists are involved in the care of patients with GTD once it is diagnosed. Among the responders, there were 10% (7) gynaecologists or oncologists who provide consultations and treatment of persistent GTD. Involvement of generalists includes performing D&C and following hHCG levels post procedure, supervision of junior staff, clinical advice and signing histology reports. Overall, 66% (45) of generalists were directly involved in patient’s care. The data from question seven are summarised in Table 2.

In order to obtain an accurate diagnosis and provide appropriate treatment to patients with GTD, one must use current, evidence-based guidelines. At the time of the survey there were several guidelines available and Fellows were asked what guidelines they use in their decision making, and whether they agree with the guidelines or would like some changes to be made.
made. Responders were given five options, including RCOG, ACOG, NZGCG Guidelines, NSW Gynaecological Cancer Guidelines and local DHB’s guidelines (Table 3) Of note, the RANZCOG statement for the management of GTD was not included at the time as it had become available only in November 2013.

Majority of the responders 93% (54) agreed with the guidelines, and 8.6% (5) of specialists indicated that they would like some changes to be introduced, including the use of unified national guidelines by all involved.

The view of O&G specialists on a Trophoblastic Disease Reference Centre is presented in Table 4.

**Table 4: View of O&G specialists on a Trophoblastic Disease Reference Centre.**

<table>
<thead>
<tr>
<th>Opinion</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centralisation needed</td>
<td>48</td>
<td>72.7</td>
</tr>
<tr>
<td>Centralisation not needed</td>
<td>18</td>
<td>26.4</td>
</tr>
<tr>
<td>Few named centres</td>
<td>35</td>
<td>53</td>
</tr>
<tr>
<td>Single national centre</td>
<td>26</td>
<td>39.4</td>
</tr>
<tr>
<td>Joined Australian &amp; New Zealand centre</td>
<td>6</td>
<td>9.1</td>
</tr>
</tbody>
</table>

**Table 2: Follow-up responsibilities.**

<table>
<thead>
<tr>
<th>Clinical role</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurse specialist</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Acute assessment unit</td>
<td>9</td>
<td>13.8</td>
</tr>
<tr>
<td>Specialised gynaecology clinic</td>
<td>19</td>
<td>29.2</td>
</tr>
<tr>
<td>Designated O&amp;G specialist</td>
<td>34</td>
<td>52.3</td>
</tr>
<tr>
<td>O&amp;G registrar</td>
<td>7</td>
<td>10.8</td>
</tr>
<tr>
<td>GP</td>
<td>4</td>
<td>6.2</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>6.2</td>
</tr>
</tbody>
</table>

The designation of ‘other’ has not been specified.

**Table 3: Guidelines used in the management of GTD in New Zealand.**

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCOG</td>
<td>17</td>
<td>27.4</td>
</tr>
<tr>
<td>ACOG</td>
<td>3</td>
<td>4.8</td>
</tr>
<tr>
<td>NZGCG</td>
<td>34</td>
<td>54.8</td>
</tr>
<tr>
<td>Local guidelines</td>
<td>18</td>
<td>29</td>
</tr>
<tr>
<td>NSWGTD</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Discussion**

GTD is a type of neoplasia derived from a pregnancy. Approximately 10–20% of patients will develop malignant sequela, requiring administration of chemotherapy after evacuation of hydatidiform moles.

In New Zealand, generalist obstetrician-gynaecologists are the most likely practitioners to be involved in the care of women with hydatidiform moles, which comprise nearly 70% of all GTD. O&G consultants are expected to diagnose, follow-up, and evaluate a patient’s risk status to allow appropriate referrals and treatment. Currently in New Zealand, 66.1% (45) of specialists indicated that they are directly involved in the management of patients with GTD, of them 10% (7) were gynaecologists/ oncologists.

As with any other medical condition, a patient’s journey begins when the diagnosis is made. GTD is diagnosed much earlier now than 20 years ago. The most common presenting symptom is abnormal bleeding. Ultrasound examination has replaced all other non-invasive means of establishing the diagnosis. Molar tissue is typically identified as a mixed echogenic pattern replacing the placenta, the appearance produced by expanded villi and intrauterine blood clots.

Multiple soft USS markers, including cystic spaces in the placenta, and a ratio of transverse to anterior-posterior dimension of the gestational sac of greater than 1.5 are required for the reliable diagnosis of a partial molar pregnancy. However, according to the several retrospective studies, when USS is used in the first and early second trimester, only 40–60% molar...
pregnancies are correctly identified as such, with the rest being mislabelled as miscarriages.\textsuperscript{11,12} The combination of USS findings with elevation of \textit{b}HCG above expected for gestational age and clinical presentation with vaginal bleeding are highly suggestive of a molar pregnancy, but not diagnostic.

In our survey, the appearance and amount of tissue play some role in the decision making, but the majority of responders, who do not perform routine histopathological exam, rely mainly on the preoperative USS report and clinical presentation.

As there are difficulties in making a diagnosis of a molar pregnancy before evacuation, the histopathological assessment of material obtained from the surgical management of incomplete/missed miscarriage is recommended by all major guidelines on GTD and early pregnancy loss.\textsuperscript{6,10,16,17} Yasemin Tasci evaluated the histopathological findings related to tissue samples obtained via surgical evacuation in patients who were admitted to the early pregnancy clinic with the diagnosis of incomplete/missed miscarriage, or anembryonic pregnancy.\textsuperscript{13} Histology revealed RPOC in 69.7%; partial molar pregnancy in 2.1%; complete molar pregnancy in 0.43%; exaggerated placental site and placental site trophoblastic nodule in 0.12%; and decidual tissue in 16.9%.

Of note, all the patients had an USS and \textit{b}HCG prior to evacuation, but not a single one had a diagnosis of GTD prior to the operation.

Another study looked at the value of histological examination of product of conception. In a retrospective review of case notes of 23 patients diagnosed with molar pregnancy in Birmingham City Hospital, in 11/23 (48%) of cases there was no suspicion at having molar pregnancy before histological diagnosis.\textsuperscript{14}

In our survey, 79.7% of responders routinely send products of conception to histology, 12.5% do it sometimes and 7.8% do not send obtained tissue to histology. It was very reassuring to learn that majority of RANZCOG Fellows routinely sent tissue to histology and some commented on importance of histopathological analysis.

However, it is concerning that in about 20% of cases, products of conception are not examined routinely, with reasons why not being stated. Both lack of submission of tissue and medical management of non-viable pregnancies are considered to contribute to missing GTD. 69.8% (44) of specialists thought increasing number of medically-managed miscarriages was the main reason.

El-Refaey states that as many as 20% of women expressed a strong preference for medical management, in order to avoid general anaesthesia and to feel being more in control.\textsuperscript{15} Women who miscarried at home should be strongly advised to take any tissue passed to the hospital, so that histological examination can be arranged.\textsuperscript{16} However, it is a difficult task, as some tissue passed cannot be recognised as such, and women are not willing to retrieve and transport blood clots and tissue. Alternative management can include measurement of \textit{b}HCG 3 weeks after completion of treatment, or at least urine pregnancy test.\textsuperscript{17} 20.6% (13) and 12.7% (8) of Fellows respectively think that rely on USS and gross appearance of the tissue contributes to missed diagnosis.

Once GTD is diagnosed, appropriate counselling and follow-up should be arranged. The question of follow-up is an important one, because it is time when persistent GTD is unmasked and decision on further treatment and referral to a gynaecologist/oncologist is to be made. Different hospitals have different modes of follow-up, with various health professionals with different level of training, being involved in the process. The majority of patients are seen either by an O&G specialist or in the specialised clinic (52.3% and 29.2% respectively). The rest were divided between nurse specialists, registrars, GPs and others. Once again, practice heterogeneity becomes obvious when health professionals with different level of training and experience are involved in the care of patients with GTD.

One way to avoid mistakes when managing patients with rare conditions is to use guidelines and follow protocols. Various guidelines are used around the country. The majority of participants (54.8%) are using NZGCC guidelines on management of trophoblastic disease, which were updated and published online in January 2014.\textsuperscript{6} Out of the remaining participants, 29% use local guidelines, and 27.4% use the RCOG guide-
A small number of specialists are using the ACOG guidelines (4.8%). The use of RANZCOG Guidelines was not questioned, as it was not available at the time of the survey.

The lack of information or any form of registration of patients with GTD in New Zealand makes it impossible to collect data or conduct an audit to determine standards of care. This is a serious deficiency in care in New Zealand.

Available literature suggests that a national approach to registration and treatment of GTD in the form of a Register or a National Reference Centre can improve the quality of care delivered to patients with GTD, and majority of participants surveyed (92.5% (62)) agree with the statement. However, opinions on the creation of such a centre in New Zealand were divided. 72.7% (48) of Fellows indicated that some form of centralisation, or at least registration of patients with GTD, is desirable. On the other hand, 27.3% (18) of specialists expressed an opinion that centralisation is not necessary, or is not possible, at present. Among the arguments were comments about small population size, remoteness of some rural areas associated with transport issues, and lack of data on adverse outcomes, which make it difficult to implement improvements. Table 5 shows some comments.

Table 5: Comments.

<table>
<thead>
<tr>
<th>Comment</th>
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<tbody>
<tr>
<td>“GTD should be managed via an oncology service with clear guidance on follow up via a local clinic. Centralisation makes access for some people very difficult secondary to transport issues”</td>
</tr>
<tr>
<td>“Very rural areas in NZ. Perhaps follow-up and treatment management in consultation with centralised centre”</td>
</tr>
<tr>
<td>“Not practical a present, but national approach should be considered”</td>
</tr>
<tr>
<td>“Population too small and too widespread”</td>
</tr>
<tr>
<td>“If there is evidence of poor treatment/outcomes then that should be addressed by education. If a national service could be shown to be cost effective then it could be considered”</td>
</tr>
<tr>
<td>“I think the diagnosis should be recorded in the national register for audit and quality control purposes”</td>
</tr>
<tr>
<td>Nevertheless some form of advice and guidance from a local gynaecology oncology services or MDT appears to be necessary in majority of cases. The following comments support the statement:</td>
</tr>
<tr>
<td>“MDT management by off-site conferencing could be helpful”</td>
</tr>
<tr>
<td>“The current medical oncologist in Christchurch provides a useful reference source of information and advice. May be her role should be formalised?”</td>
</tr>
<tr>
<td>“Central case discussion with submission of all cases would be good and an annual report on number of cases and outcomes”</td>
</tr>
</tbody>
</table>

Nevertheless some form of advice and guidance from a local gynaecology oncology services or MDT appears to be necessary in majority of cases. The following comments support the statement:

“MDT management by off-site conferencing could be helpful”

“The current medical oncologist in Christchurch provides a useful reference source of information and advice. May be her role should be formalised?”

“Central case discussion with submission of all cases would be good and an annual report on number of cases and outcomes”

Conclusions

The most recent literature on the incidence of trophoblastic disease in New Zealand dates back to 1986. It appears that the pathways for the initial diagnosis and the follow-up arrangements vary widely between specialists, hospitals, and DHBs. This may impact on detection and management of GTD. Moreover, a lack of data at the national level makes it impossible to monitor quality of care and improve outcomes.

Therefore, the first step to the unified management of GTD should be the use of a single guideline across all DHBs. The majority of Fellows already use NZGCC guidelines, which were recently updated and are now easily available on the Ministry of Health website. We suggest that it can be used as a National guideline.

The second step should be the establishment of a national registry. The RANZCOG Statement for the management of Gestational Trophoblastic Disease, which became available at the end of 2013, mentions a New Zealand Registry, but to our knowledge one does not exist at present.
The NZGCG guidelines recommend the establishment of local registries to capture all GTD patients, but it is not known how many are in use at present. Furthermore, creation of multiple registries may lead to fragmentation of care.

In contrast, the establishment of only a few registries with shared database under the supervision of regional gynaecology-oncology services will aid in the collection of reliable data on GTD in New Zealand and provision of quality care.

One notable limitation of the present study was a modest response rate of 32%. It is therefore likely that the results represent only a small snapshot of the knowledge and experiences of O&G specialists. While a higher participation rate would have been desirable, it is rarely achieved in surveys of medical practitioners. Participation bias by those most interested in the topic cannot be excluded. A possible explanation for the low response rate is the degree of involvement of O&G specialists in GTD care. It may be the case that the specialists who are not involved in the care opted not to complete the survey. Therefore, future research should consider a survey of O&G registrars, who tend to be more actively involved in the management of early pregnancy complications.

In conclusion, our research shows existing practice heterogeneity, and practitioner’s call for re-establishing national data collection in the form of a registry/registries, and some degree of consistency in the diagnosis and management of GTD under the supervision of the oncology services. Although the results should be interpreted with caution, we believe that the survey reflects current practice in the management of trophoblastic disease.

**Competing interests:** Nil

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