Molar pregnancy

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Review Molar pregnancy

Author Philip Savage

Key content:

- Molar pregnancies are rare, occurring at a rate of approximately 1 for every 700 live births.
- Most cases of molar pregnancy are diagnosed in the first trimester by ultrasound or as early pregnancy losses.
- The initial management is by evacuation and registration with one of the follow-up services, which are based in Sheffield, Dundee and at Charing Cross Hospital, London.
- Approximately 15% of cases of complete moles and 0.5% of cases of partial moles require further treatment with chemotherapy: second evacuations are generally unhelpful.
- The cure rate for molar pregnancies, including for those women requiring chemotherapy, is >99%.

Learning objectives:

- To learn about the aetiology and diagnosis of molar pregnancy.
- To be aware of the initial management and importance of patient registration.
- To be able to discuss the diagnosis with women, including an outline of indications and practicalities of chemotherapy.

Ethical issues:

- Calling the condition 'persistent trophoblast disease' rather than 'cancer' is appropriate, given the near 100% cure rate.

Keywords choriocarcinoma / gestational tumours / molar pregnancy / trophoblast

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Author details

Philip Savage PhD FRCP
Consultant in Medical Oncology
Department of Medical Oncology,
Charing Cross Hospital, Fulham Palace Road,
London W6 8RF, UK
Email: philip.savage@imperial.nhs.uk
(corresponding author)

Introduction

Molar pregnancies are rare, occurring at a rate of approximately 1 for every 700 live births. With only 1600 cases registered in the UK each year, most individual obstetric or gynaecology teams are only likely to see a case every few years.

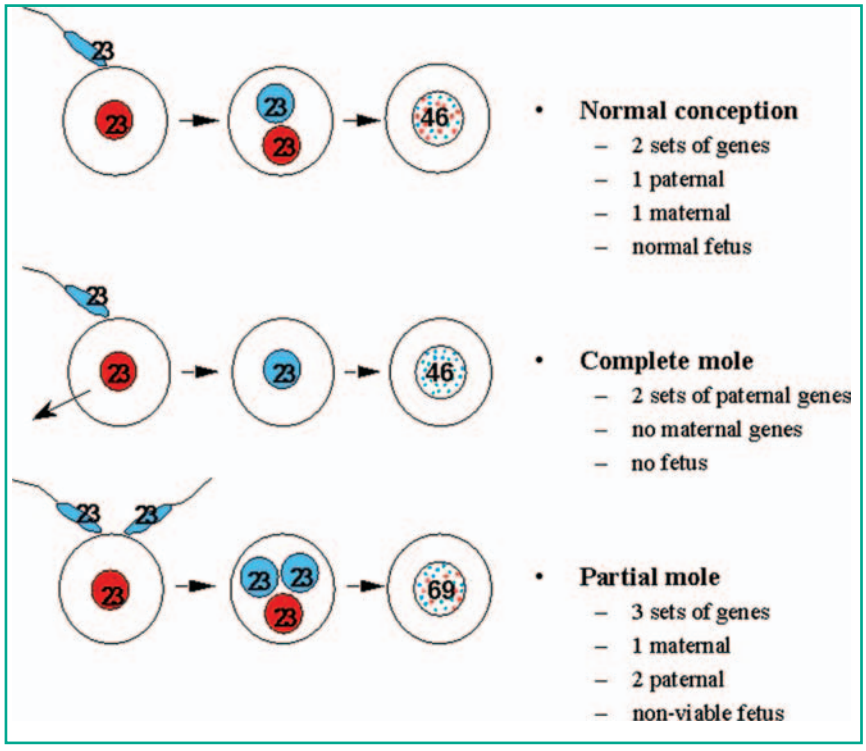
The time of diagnosis is usually very difficult for women: they have to cope with the loss of a pregnancy, the details of follow-up, potential chemotherapy and the increased risks in future pregnancies. As a result of the rarity of the condition and the lack of family and, sometimes, general practitioners' knowledge of the disease, women often feel unsupported and depend on their local hospital team as their initial source of information. This review aims to introduce the aetiology, clinical presentation and management of molar pregnancy, which should be of value to all involved with the care of these women.

Genetics

Molar pregnancies are the premalignant forms of gestational trophoblastic neoplasia, a group of illnesses that also includes the rare but aggressive malignancies of choriocarcinoma and placental site trophoblastic tumours. Fortunately, in the absence of any indication for additional treatment, women with simple molar pregnancies should be reassured that they have not had cancer but will just need close monitoring.

The genetic events occurring in normal conception and in complete and partial molar pregnancies are shown in **Figure 1**. In a normal conception, 23 chromosomes are derived from the mother and 23 from the father, but in complete molar pregnancies the genetic material of the trophoblast cells is entirely of male origin following the loss of the maternal chromosomes from the oocyte. Usually the chromosome count is 46XX, which results from a single sperm duplicating within an empty oocyte. Less often, a 46XY genotype can occur when an empty ovum is fertilised by two sperm. In partial molar pregnancies, the trophoblast cells have three sets of chromosomes: two from the father and one from the mother. Partial molar pregnancy is believed to occur as a result of two sperm entering the oocyte at the same time: this leads to fertilisation but with twice the normal complement of genetic material from the father.

Figure 1
Genetic events occurring in normal conceptions and complete and partial molar pregnancies



Risk factors

Whilst the diagnosis of molar pregnancy is rare, there are two groups of women who have significantly elevated risks of developing a molar pregnancy. At the extremes of the reproductive age, girls under the age of 15 years have a risk approximately 20 times higher than women aged 20–40, whilst women aged over 45 have a several hundred-fold higher risk than those aged 20–40.[1] The increased risk for these groups is mainly for complete molar pregnancy, with the incidence of partial molar pregnancy changing less across the age groups.

The second group of women with an increased risk of molar pregnancy are those who have had a molar pregnancy previously. In this group, the risk appears to be approximately 1 in 55 for those with one previous molar pregnancy and 1 in 10 for those with two.[2]

Primary management of molar pregnancy

Diagnosis

In the first few months of pregnancy, molar pregnancy is associated with a higher incidence of vaginal bleeding or discharge, abdominal pain and morning sickness. However, as these symptoms are relatively nonspecific, they rarely lead to the diagnosis being made prior to the routine first ultrasound scan.

In complete molar pregnancy, the ultrasound characteristically shows an absent gestational sac and a complex echogenic intrauterine mass with cystic spaces. In contrast, the ultrasound of a partial molar pregnancy may resemble a normal conception with an embryo visible. As the diagnosis of a partial molar pregnancy is frequently difficult to make on the initial ultrasound, a significant proportion of these women present later with early pregnancy loss, with the diagnosis achieved histologically.

Gynaecological management

The initial gynaecological management of molar pregnancy is by uterine evacuation. The Royal College of Obstetricians and Gynaecologists has published practical guidelines on management.[3] They recommend that suspected complete molar pregnancies should be removed by suction evacuation, while suspected partial molar pregnancies should generally be removed via medical termination, as the fetal parts can present an obstacle to suction evacuation. Usually, evacuation is straightforward; however, haemorrhage is a potential risk and oxytocic infusions can be of value, preferably after the completion of the evacuation.

Histopathology

The evacuation specimen from women with suspected molar pregnancy should always be sent for histological analysis. In the UK, all specimens from cases of suspected molar pregnancy are also sent for central review. The final diagnosis is frequently altered between the types of molar pregnancy and sometimes to or from non-molar diagnoses.[4]

Typically, in a complete molar pregnancy the pathology shows hydropic villi with trophoblastic hyperplasia, while in partial molar pregnancy it frequently shows only focal changes and it is usually far less florid than a complete mole. Newer diagnostic tests, such as immunostaining with p57KIP2, are available at specialist centres and help confirm the diagnosis of complete moles.[5]

Registration and follow-up

Since 1973, the UK has had a national molar pregnancy registration, follow-up and treatment service. All women with a documented or suspected molar pregnancy should be registered at one of the three follow-up centres in London, Sheffield and Dundee for the human chorionic gonadotrophin (hCG)-based follow-up. Women can be registered by phone, fax or by using the online registration service.[6]

Follow-up practicalities and the importance of hCG measurement

Trophoblast cells constitutively make hCG, which is readily measured by immunoassay. After evacuation, in the majority of cases the residual trophoblast cells are unable to continue to proliferate for long and the fall in serum hCG levels is a very accurate indication of their declining activity. In most cases, after evacuation of a molar pregnancy the hCG level falls to normal (<4 iu/l) within 2–3 months, after which relapse of the molar pregnancy is extremely rare.

In approximately 15% of cases of complete molar pregnancies and 0.5% of cases of partial molar pregnancies, the abnormal trophoblast cells continue to proliferate and invade into the uterine wall; they can then metastasise to other organs, particularly the lungs. This development of invasive behaviour is believed to be linked to abnormal patterns of gene silencing and expression in trophoblast cells.

At present there is no reliable method to determine how any individual molar pregnancy will behave after evacuation and whether further treatment will be required. Fortunately, a change in hCG level gives a very accurate assessment of the level of disease activity and this forms the basis of the follow-up protocol.

After registration, new patients are sent information on the diagnosis, along with contact information for their follow-up centre. Additionally, they are supplied with a kit to allow hCG samples to be posted back to the follow-up team. Checking of the hCG levels is done every 2 weeks and allows early identification of women who will need further treatment.

Indications for treatment

The change in diagnosis from a premalignant molar pregnancy to a malignant form of gestational trophoblastic neoplasia that requires chemotherapy is usually made clinically. This decision is based on the medical assessment and, in particular, the pattern of change of hCG levels. Additional biopsies are rarely performed as they are clinically unhelpful and these highly vascular tumours can bleed heavily. Analysis of data from women previously in the surveillance programme has identified indications for initiating treatment in the post-molar pregnancy surveillance programme (**Box 1**).

A small minority of women with disease limited to the uterus can be cured by a second uterine evacuation; however, the majority require chemotherapy. Historically, an hCG cut-off value of under 20 000 iu/l for women with disease limited to the uterus had been used when considering further evacuation. However, recent analysis of data from Sheffield and from Charing Cross Hospital[7,8] indicates that a second uterine evacuation is rarely of benefit when the hCG level is greater than 5000 iu/l. In this situation, our preference at Charing Cross Hospital is now generally to move directly to chemotherapy.

- Brain, liver, gastrointestinal or lung metastases >2 cm on chest X-ray
- Histological evidence of choriocarcinoma
- Heavy vaginal bleeding or gastrointestinal/intraperitoneal bleeding
- Pulmonary, vulval or vaginal metastases, unless the hCG level is falling
- Rising hCG in two consecutive serum samples
- hCG >20 000 iu/l more than 4 weeks after evacuation
- hCG plateau in three consecutive serum samples
- Raised hCG level 6 months after evacuation

Box 1
Indications for initiating chemotherapy following molar pregnancy

Table 1
Prognostic scoring system for initial chemotherapy treatment of persistent trophoblast disease.[18] (Reproduced with permission from the International Federation of Gynecology and Obstetrics.)

Score	0	1	2	4
Age	<40	>40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Months from index pregnancy	<4	4–6	7–13	>13
Pretreatment hCG	<1000	1000–10 000	10 000–100 000	>100 000
Largest tumour size (cm)	–	3–5	≥5	–
Site of metastases	Lung	Spleen, kidney	Gastrointestinal	Brain, liver
Number of metastases	–	1–4	5–8	>8
Previous chemotherapy	–	–	Single agent	Two or more drugs

Treatment of persistent trophoblast disease

At the Trophoblast Unit at Charing Cross Hospital, we generally refer to women who require chemotherapy after molar pregnancies as having *persistent trophoblast disease*. Although medically and legally this is a diagnosis of malignancy, we try to avoid using the word 'cancer' for these women, particularly as there is a near 100% cure rate.

Pretreatment investigations

For the majority of women with persistent trophoblast disease after a recent molar pregnancy, the investigations performed prior to chemotherapy are limited to a Doppler ultrasound scan of the pelvis and a chest X-ray. The ultrasound allows the formal exclusion of a new pregnancy as the cause of the hCG elevation and measurement of the size of the uterine tumour, while the chest X-ray gives an indication of any pulmonary metastases. This information is used as part of the prognostic scoring system shown in **Table 1**, which determines the intensity of the initial chemotherapy treatment. The low-risk group includes women scoring 0–6, while women scoring 7 or higher fall into the high-risk treatment group.

Low-risk disease management

The majority of women with persistent trophoblast disease after a molar pregnancy will fall into the low-risk treatment group and start chemotherapy with intramuscular methotrexate combined with oral folinic acid rescue as shown in **Box 2**. The first cycle of treatment is given as an inpatient, with the following cycles administered closer to home. Women with an initial pretreatment hCG of >1000 iu/l may stay as inpatients for longer as they have a higher risk of bleeding: the larger tumours shrink rapidly with the initiation of chemotherapy.

The low-risk methotrexate treatment is usually well tolerated without major toxicity. Methotrexate does not cause hair loss or significant nausea and bone marrow suppression is rare. The most common side effects are pleural inflammation, mucositis and hepatic toxicity but each of these is relatively rare.[9] For low-risk women with lung metastases on their chest X-ray, we add central nervous system prophylaxis with intrathecal methotrexate, which is administered on three occasions, 2 weeks apart.

All women have their hCG levels checked twice a week while undergoing treatment and, following hCG normalisation, chemotherapy is continued for another three cycles (over 6 weeks) to ensure eradication of any residual disease present below the level of hCG detection. Overall, two-thirds of the low-risk group will successfully complete treatment with methotrexate alone. However, for those who have an inadequate response to methotrexate, as shown by an hCG plateau or rise, treatment is changed to second-line chemotherapy. For this, single agent dactinomycin (Actinomycin-D) is given intravenously at 0.5 mg on days 1–5 every 2 weeks if the hCG is under 300 iu/l, or combination chemotherapy is used if the hCG is greater than 300 iu/l at the time of the treatment change.

Box 2
Chemotherapy regimens used in the treatment of persistent trophoblast disease

a) Methotrexate/folinic acid treatment schedule

Day 1 methotrexate 50 mg IM at noon
Day 2 folinic acid 15 mg orally at 6 p.m.
Day 3 methotrexate 50 mg IM at noon
Day 4 folinic acid 15 mg orally at 6 p.m.
Day 5 methotrexate 50 mg IM at noon
Day 6 folinic acid 15 mg orally at 6 p.m.
Day 7 methotrexate 50 mg IM at noon
Day 8 folinic acid 15 mg orally at 6 p.m.

b) EMA/CO chemotherapy

Week 1

Day 1 dactinomycin 0.5 mg IV
etoposide 100 mg/m^2 IV
methotrexate 300 mg/m^2 IV

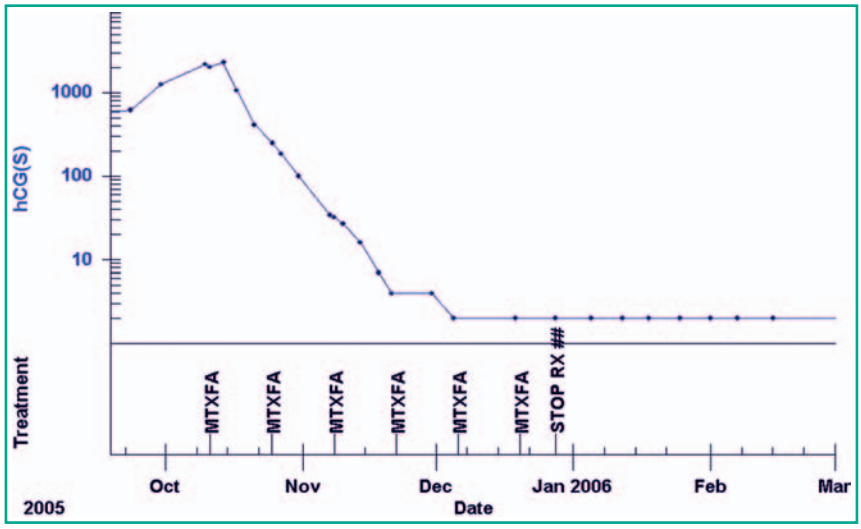
Day 2 dactinomycin 0.5 mg IV
etoposide 100 mg/m^2 IV
folinic acid 15 mg orally 12 hourly × 4 doses, starting 24 hours after commencing methotrexate

Week 2

Day 8 vincristine 1.4 mg/m^2 (maximum 2 mg)
cyclophosphamide 600 mg/m^2

IM = intramuscularly; IV = intravenously

Figure 2a
Human chorionic gonadotrophin and treatment graph of a low-risk woman during treatment with methotrexate following complete molar pregnancy
MTXFA = methotrexate/folinic acid



Figures 2a and **2b** show the treatment graphs of two low-risk women who required chemotherapy following complete molar pregnancies. The first woman was rapidly cured with methotrexate treatment alone, while the second, despite an initial response to methotrexate, required a change to combination chemotherapy with EMA/CO to complete treatment successfully.

The overall cure rate of the low-risk treatment group is nearly 100% and the stepwise introduction of more toxic chemotherapy as necessary minimises the long-term toxicity resulting from treatment in the majority of women.

High-risk disease management

Relatively few women with persistent trophoblast disease after a molar pregnancy fall into the high-risk prognostic group. However, the historical data indicates that only 10% of this group of women would be cured with single-agent methotrexate therapy.[10] Fortunately, the introduction of combination chemotherapy treatments in the 1970s transformed this situation. Modern treatment, primarily with EMA/CO chemotherapy, as used at Charing Cross Hospital, or MEA, as used at Sheffield, produces cure rates in excess of 90%.[11–13]

The EMA/CO combination of etoposide/methotrexate/dactinomycin and cyclophosphamide/vincristine gives an intense treatment, with the five chemotherapy agents delivered as 2 groups, 1 week apart, as shown in **Box 2**. The combination treatment has considerable side effects, including bone marrow suppression, and support with granulocyte-colony stimulating factor (G-CSF) injections is frequently helpful in keeping the treatment on schedule. Fortunately, other serious toxicity is rare with EMA/CO and the majority of women tolerate treatment well. Similarly to the low-risk women, chemotherapy treatment is continued for 6 weeks after the normalisation of the hCG level. **Figure 2c** shows the treatment graph of a high-risk woman, who presented 3 weeks after an evacuation of a molar pregnancy with a rapidly rising hCG level and was successfully treated with EMA/CO chemotherapy.

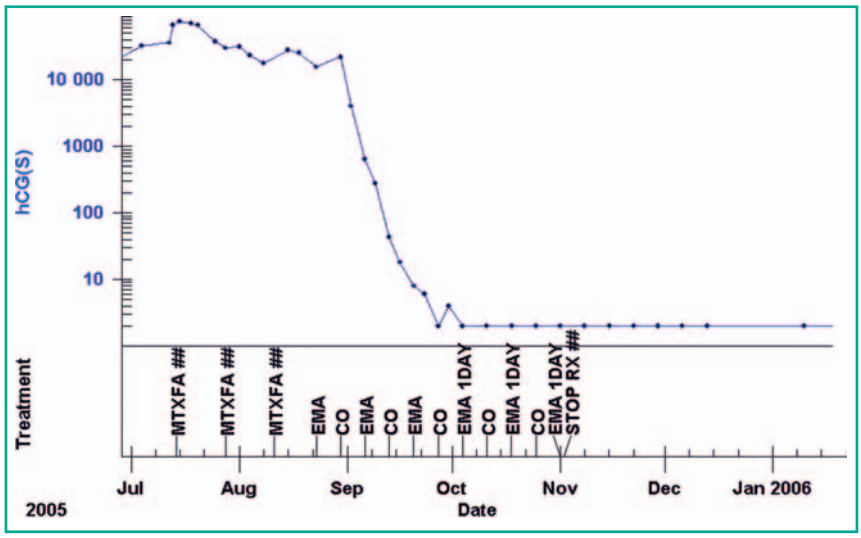


Figure 2b
Human chorionic gonadotrophin and treatment graph of a low-risk woman during treatment with methotrexate and combination chemotherapy following complete molar pregnancy. CO = cyclophosphamide/vincristine; EMA = etoposide/methotrexate/dactinomycin; MTXFA = methotrexate/folinic acid

Outcome of treatment

After the serum hCG level has fallen to normal, the outlook is very good for women with all forms of trophoblast disease. The risk of relapse is approximately 2% for women treated for low-risk disease and only 3% for high-risk women treated with EMA/CO. If they occur, recurrences usually happen within the first 12 months and we advise women to avoid becoming pregnant during that time in case the hCG from the new pregnancy masks the hCG production caused by the relapse.

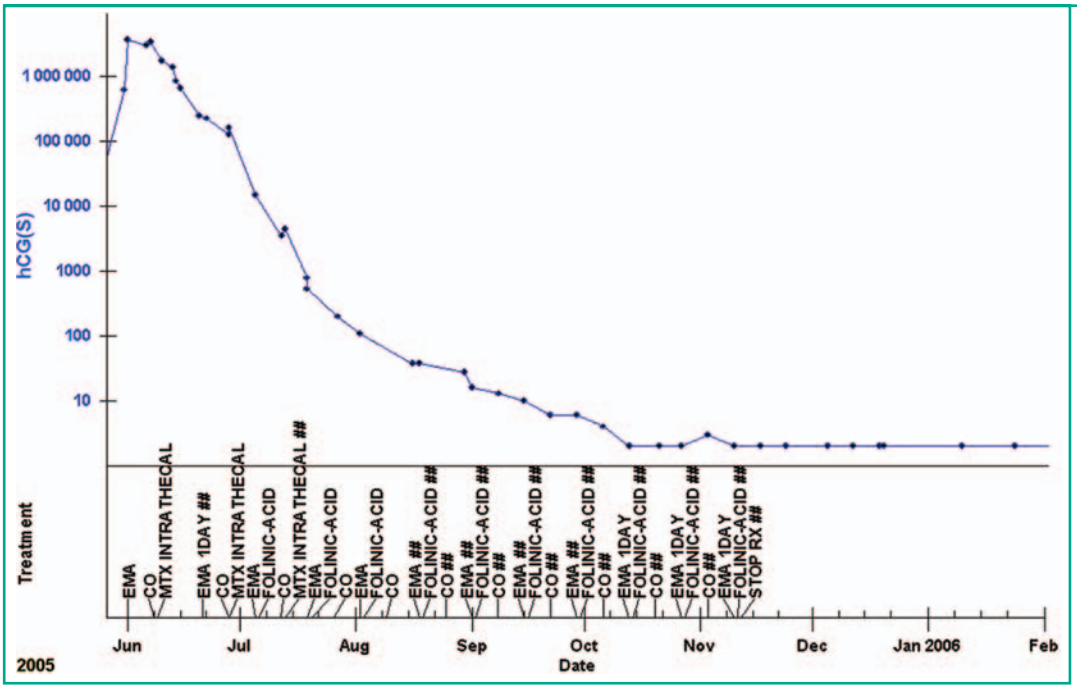


Figure 2c
Treatment graph of a high-risk woman, who presented 3 weeks after evacuation of a molar pregnancy with a rapidly rising hCG level and was successfully treated with EMA/CO chemotherapy. CO = cyclophosphamide/vincristine; EMA = etoposide/methotrexate/dactinomycin; MTX = methotrexate

Fortunately, even on relapse, trophoblast tumours remain highly curable. A recent analysis[14] indicated that 100% of women who were originally in the low-risk category were cured on relapse, with a cure rate of 85% for those initially presenting with high-risk disease.

Subsequent fertility after chemotherapy treatment

Despite exposure to cytotoxic drugs, the fertility of most women is maintained after low- or high-risk chemotherapy treatment and menstruation resumes within 6 months of completing chemotherapy. Chemotherapy does cause some damage to ovarian function, as indicated by the menopause being brought forward by approximately 1 year for low-risk methotrexate and 5 years for high-risk EMA/CO.[15] After completion of chemotherapy, we recommend that pregnancy is avoided for 12 months to minimise any damaging effects on developing oocytes and to minimise the confusion over disease relapse from hCG produced in pregnancy. Despite the exposure to cytotoxic chemotherapy, particularly in the high-risk group, there does not appear to be any significant increase in fetal abnormalities and most women wishing to conceive are successful.

With the increasing number of long-term survivors after chemotherapy for gestational trophoblast tumours, it has become clear that intensive chemotherapy treatment with the EMA/CO and EP/EMA regimens results in an increased risk of second malignancies. An analysis of the gestational trophoblast tumours patient database[16] indicates that the lifetime risk of further malignancy is increased approximately 1.5-fold, with the largest increase being found for myeloid leukaemia. In contrast, single-agent methotrexate does not appear to produce any increased risk of future malignancy or other serious health issues.

Summary

Molar pregnancy is rare and its aetiology, biology and responsiveness to treatment are very different from those of any other form of malignancy. Fortunately, the majority of cases can be cured by simple surgical intervention and those that require chemotherapy are generally cured with very low toxicity treatment.

The UK's centralised surveillance and treatment service is a model that is widely admired around the world.[17] This service links together all the obstetric and gynaecology teams in the UK with an effective registration, follow-up and expert treatment service. Molar pregnancy and the overtly malignant forms of gestational trophoblastic neoplasia are rare and can present unusual clinical challenges. At both Charing Cross Hospital in London and Weston Park in Sheffield there is a 24-hour emergency advice and treatment service and both centres are always willing to give advice on any UK and overseas patients on request.

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