Università degli Studi di Padova
Dipartimento di Scienze Ginecologiche e della Riproduzione Umana
Scuola di Specializzazione in Ginecologia e Ostetricia
Direttore Prof. Giovanni Battista Nardelli

Mola vescicolare

Dott.ssa Stefania Di Gangi

Mola Idatiforme (parziale o totale):

- ✓ *gravidanza a decorso anomala*
- ✓ *proliferazione trofoblastica con vari gradi di degenerazione idropica dei villi coriali*

Clinicopathologic features of gestational trophoblastic disease

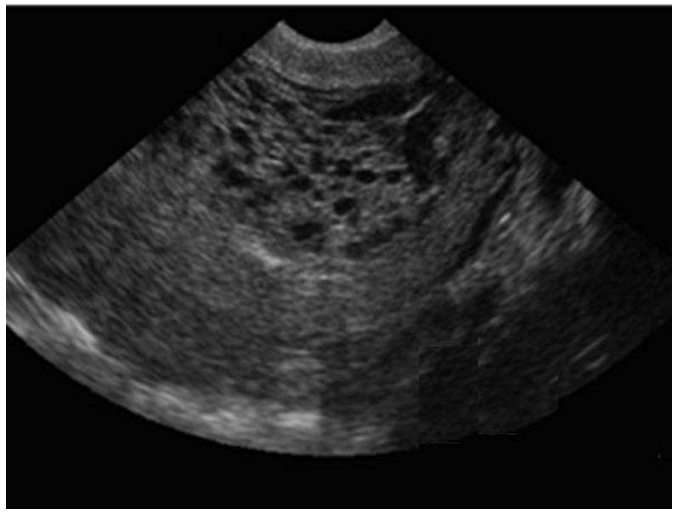
Gestational trophoblastic disease	Pathologic features	Clinical features
Hydatidiform mole, complete	46,XX (mainly); 46,XY Absent fetus/embryo Diffuse swelling of villi Diffuse trophoblastic hyperplasia	15-20% trophoblastic sequelae hCG often >100,000 mIU/mL Medical complications
Hydatidiform mole, partial	Triploid (69, XXY; 69, XYY; 69 XXX) Abnormal fetus/embryo Focal swelling of villi Focal trophoblastic hyperplasia	<5% trophoblastic sequelae hCG usually <100,000 mIU/mL Rare medical complications

Incidenza: *0.57–1.1 /1000* *(North America, Australia, New Zealand, and Europe)*

2.0 /1000 *(American Indians, Eskimos, Hispanics, and African Americans)*

VARIABILITA' ETNICA

Lurain JR. Am J Obstet Gynecol. 2010 Dec;203(6):531-9.
RCOG - Gestational Trophoblastic Disease (Green-top 38). 2010, Feb.



Anamnesi

Paziente 35 AA – Africana –

Para 2022 – 2 PS – 2 RCU –

Emo-Gruppo B Rh + –

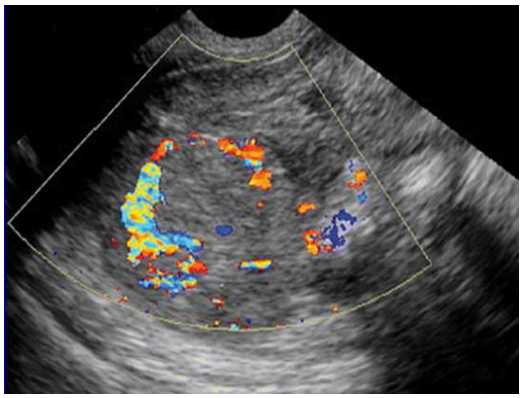
Spotting ultimi 30 gg – Metrorragia ultimi 3 gg –

UM: non nota – βhCG Pos:128.130 **UI** *– Hb: 110 g/L –*

Visita + ECO Office

Reperto obiettivo: *nei limiti di norma*
modeste perdite ematiche in atto rosso vivo

Eco TV: *contenuto endocavitario disomogeneo (mm 21) ad aspetto cistico ed intensa vascolarizzazione al Doppler. Non immagini in cavità riferibili a camera ovulare. Campi annessiali liberi. Ovaio destro regolare, Ovaio sinistro con immagine riferibile a corpo luteo. Non free fluid nel Douglas.*

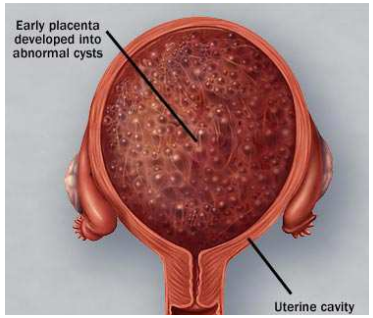


Management

RX Torace: neg. – RCU ecoguidata – No profilassi Anti-D

Follow-up βhCG: caduta dei valori senza azzeramento a 3 settimane (128.130 **UI** → *8470* **UI***)*

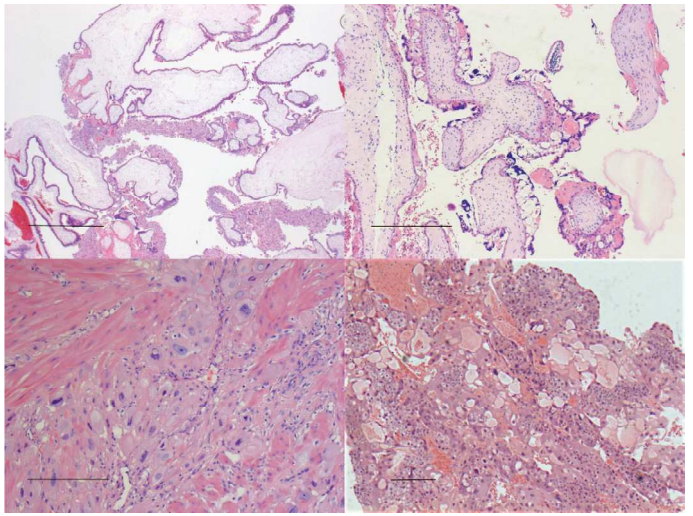
Peristenza perdite ematiche, No dispenea, No alterazioni neurologiche



Eco TV: materiale riferibile a trofoblasto

Istologia:

<u>materiale trofoblastico con alterazioni compatibili con quadro di mola vescicolare completa</u>



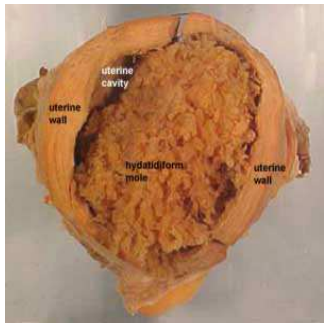
Management

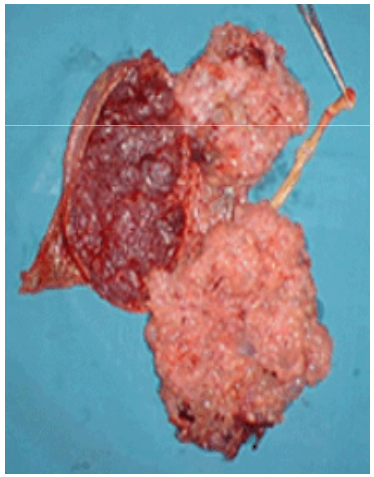
Stadiazione mediante RM : non lesioni riferibili a localizzazioni extrauterine

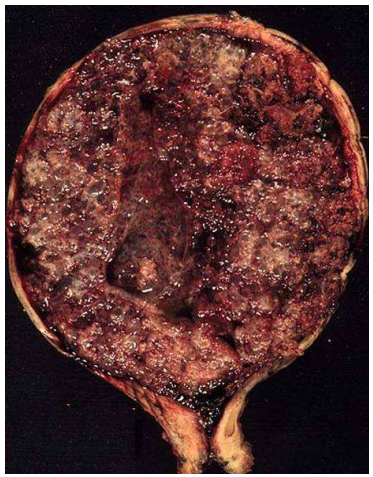
Persistenza perdite ematiche Anemizzazione (Hb 71 g/L)

Isterectomia totale con conservazione degli annessi

Esame Istologico (utero): Mola vescicolare completa, con minima invasione dello strato miometriale







Follow-up βhCG:

dosaggi settimanali fino ad azzeramento (< 5 UI);

bisettimanali fino mensilmente per 6 mesi con valori < 5 UI

PAZIENTE LIBERA DA MALATTIA

Soper JT, et al.ACOG Practice Bulletin No. 53. Gynecol Oncol. 2004 Jun;93(3):575-85.
RCOG - Gestational Trophoblastic Disease (Green-top 38). 2010, Feb.

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No. 38
February 2010

1. Definitions

Gestational trophoblastic disease (GTD) forms a group of disorders spanning the conditions of complete and partial molar pregnancies through to the malignant conditions of invasive mole, choriocarcinoma and the very rare placental site trophoblastic tumour (PSTT). There are reports of neoplastic transformation of atypical placental site nodules to placental site trophoblastic tumour.

Lancet 2010; 376: 717–29

Published Online
July 28, 2010
DOI:10.1016/S0140-6736(10)60280-2

Gestational trophoblastic disease

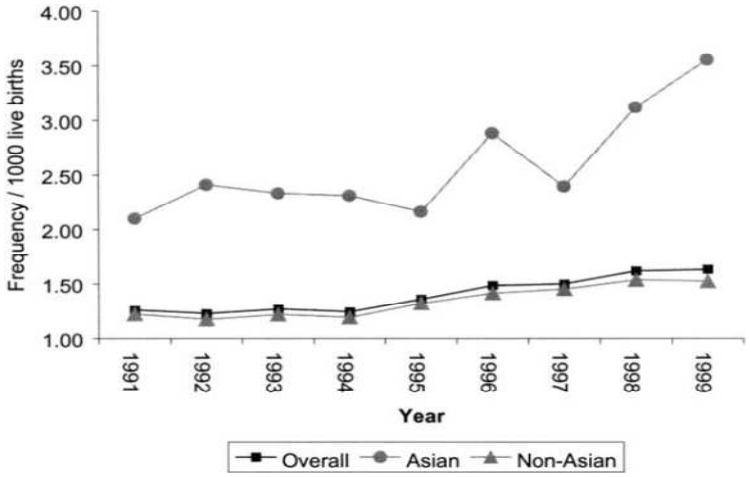
Michael J Seckl, Neil J Sebire, Ross S Berkowitz

Gestational trophoblastic disease encompasses a range of pregnancy-related disorders, consisting of the premalignant disorders of complete and partial hydatidiform mole, and the malignant disorders of invasive mole, choriocarcinoma, and the rare placental-site trophoblastic tumour. These malignant forms are termed gestational trophoblastic tumours or neoplasia. Improvements in management and follow-up protocols mean that overall cure rates can exceed 98% with fertility retention, whereas most women would have died from malignant disease 60 years ago. This success can be explained by the development of effective treatments, the use of human chorionic gonadotropin as a biomarker, and centralisation of care. We summarise strategies for management of gestational trophoblastic disease and address some of the controversies and future research directions.

BJOG: an International Journal of Obstetrics and Gynaecology
June 2003, Vol. 110, pp. 555–559

Gestational trophoblastic disease in the Asian population of Northern England and North Wales

B.W.L. Tham[a], J.E. Everard[b], J.A. Tidy[c,*], D. Drew[d], B.W. Hancock[b]



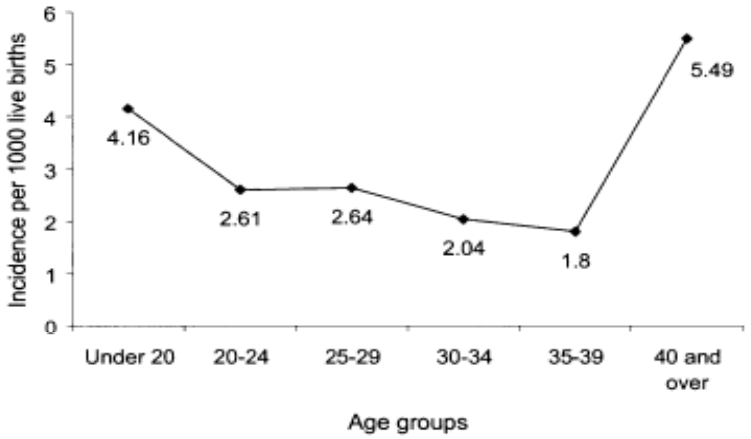


Table 3. Frequency of types of molar pregnancies.

Types of gestational trophoblastic disease	Age group (years)						Total
	0–19	20–24	25–29	30–34	35–39	>40	
Partial mole	12	53	56	27	13	8	169
Complete mole	13	41	29	13	5	7	108
Choriocarcinoma	0	1	2	0	0	0	3
Placental site trophoblastic tumour	0	0	0	1	0	0	1
Unspecified mole	2	13	15	7	2	2	41
Total	27	108	102	48	20	17	322
Ratio of partial mole to complete mole	0.92	1.29	1.93	2.08	2.60	1.14	1.56

Case-control study of risk factors for partial molar pregnancy

AJOG American Journal of Obstetrics & Gynecology

Ross S. Berkowitz, MD, Marilyn R. Bernstein, MHP, Bernard L. Harlow, PhD, Laurel W. Rice, MD, Janice M. Lage, MD, Donald P. Goldstein, MD, and Daniel W. Cramer, MD, ScD

Boston, Massachusetts

Variable	*Cases (n = 65)*	*Controls (n = 130)*	*Odds ratio and 95% confidence interval*	*Significance (Wald test)*
Prior gravidity				
None	11	43	1	
1-2	39	66	2.31 (1.07-4.50)	$p = 0.033$
≥3	15	21	2.79 (1.09-7.13)	$p = 0.032$
Abortion or miscarriage*				
None	41	82	1	
Abortion only	10	27	0.74 (0.33-1.68)	$p = 0.471$
Any miscarriage	14	21	1.33 (0.62-2.89)	$p = 0.466$
Two or more miscarriages	4	0	—	$p = 0.006$
Prior live birth				
No	26	76	1	
Yes†	39	54	2.11 (1.15-3.87)	$p = 0.016$
Only male	23	25	2.69 (1.31-5.53)	$p = 0.007$
Only female	16	27	1.73 (0.81-3.71)	$p = 0.158$

Variable	*Mean*	*SE*	*t test*	*Significance*
Carotene (IU, ×1000)				
Cases	11.20	1.24	−0.144	$p = 0.886$
Controls	11.40	0.78		
Vitamin A (IU, ×1000)				
Cases	14.50	1.35	−0.022	$p = 0.983$
Controls	14.53	0.89		
Vitamin E (mg)				
Cases	16.18	2.22	−1.842	$p = 0.067$
Controls	30.93	7.69		

Variable	*Adjusted odds ratio and 95% confidence interval*	*Significance (Wald test)*
Irregular cycles (yes vs no)	2.52 (1.00-6.35)	$p = 0.051$
Prior male live birth (yes vs no)	2.11 (1.07-4.16)	$p = 0.032$
Length of oral contraceptive use (>48 mo vs ≤48 mo or none)	2.52 (1.24-5.12)	$p = 0.011$

RESEARCH COMMUNICATION

Prevention of Post-Mole Malignant Trophoblastic Disease with Vitamin A

Andri Andrijono[1*], M Muhilal[2]

Original article SWISS MED WKLY 2003;133:563–566 · www.smw.ch 563

Peer reviewed article

The low level of vitamin A or retinol might be one of the causal factors in the proliferation of hydatidiform mole trophoblastic cells. The prolonged low level of retinol and might be responsible for the proliferation of trophoblastic cells after the evacuation. The proliferation of trophoblastic cells occurring after the evacuation could clinically develop into MTD.

Increased oxidative stress in patients with hydatidiform mole

Muge Harma[a], Mehmet Harma[a], Ozcan Erel[b]

[a] Departments of Gynaecology and Obstetrics, University of Harran, Faculty of Medicine, Sanliurfa, Turkey

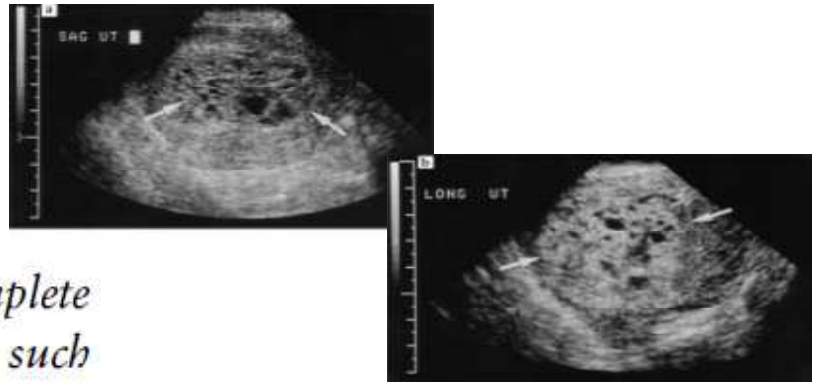
[b] Biochemistry Department, University of Harran, Faculty of Medicine, Sanliurfa, Turkey

mole found in the current study. The data of this study showed that as high as 73.21% (71.43%-75%) of patients with hydatidiform mole had decreased retinol deposit in the liver. This goes to demonstrate that these patients with hydatidiform mole had suffered from vitamin A deficiency in a relatively long period of time.

Ultrasound Obstet Gynecol 2000; **16:** 188–191.

Sonographic appearance of first trimester complete hydatidiform moles

C. B. BENSON*, D. R. GENEST†, M. R. BERNSTEIN‡, V. SOTO-WRIGHT‡, D. P. GOLDSTEIN‡ and R. S. BERKOWITZ‡



Conclusion *The majority of first trimester complete moles demonstrate a typical ultrasound appearance such that the diagnosis can be made with ultrasound in most cases.*

Ultrasound Obstet Gynecol 2007; **29:** 70–75
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.3875

The accuracy of first trimester ultrasound in the diagnosis of hydatidiform mole

E. KIRK*, A. T. PAPAGEORGHIOU†, G. CONDOUS*, C. BOTTOMLEY* and T. BOURNE*
**Early Pregnancy Unit and †Fetal Medicine Unit, St George's, University of London, London, UK*

Conclusion *Ultrasonography is more reliable for diagnosing CHMs than for PHMs. Overall, the sensitivity of ultrasound for accurately predicting hydatidiform mole is 44%, and one in two women with an abnormal scan will have the disease confirmed on histology.*

Year	First author	n	Hydatidiform mole (n (%))	CHM (n (%))	PHM (n (%))	Ultrasound detection of CHM (n/n (%))	Ultrasound detection of PHM (n/n (%))	Overall ultrasound detection rate (%)
2001	Sebire[5]	194	155 (80)	64 (41)	91 (59)	37/64 (58)	16/91 (18)	34
2005	Johns[10]	51	44 (86)	11 (25)	33 (75)	10/11 (90)	16/33 (49)	56
2006	Fowler[6]	1053	859 (82)	253 (29)	606 (71)	200/253 (79)	178/606 (29)	44
Current study		90	61 (68)	20 (33)	41 (67)	19/20 (95)	8/41 (20)	44

CHM, complete hydatidiform mole; PHM, partial hydatidiform mole.

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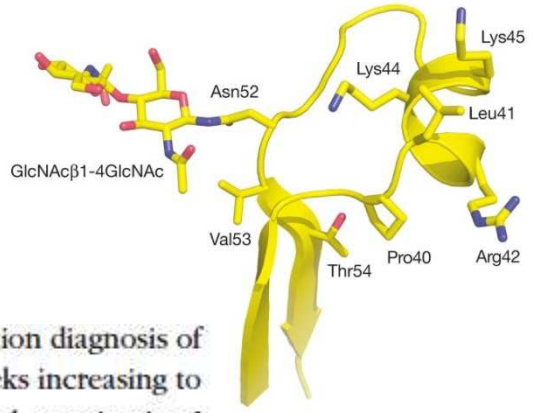

6. How are molar pregnancies diagnosed?

In one study, the accuracy of pre-evacuation diagnosis of molar pregnancy increased with increasing gestational age, 35–40 % before 14 weeks increasing to 60% after 14 weeks.[4] A further study suggested a 56% detection rate for ultrasound examination.[5]

Estimation of hCG levels may be of value in diagnosing molar pregnancies: hCG levels greater than two multiples of the median may help.[5]

Ultrasound examination is helpful in making a pre-evacuation diagnosis but the definitive diagnosis is made by histological examination of the products of conception.

7. Evacuation of a molar pregnancy

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

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

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Gynecologic Oncology
www.elsevier.com/locate/ygyno

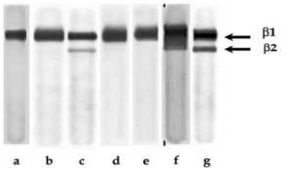
Diagnosis and treatment of gestational trophoblastic disease:
ACOG Practice Bulletin No. 53☆

John T. Soper, David G. Mutch, and Julian C. Schink
For the American College of Obstetricians and Gynecologists*
The American College of Obstetricians and Gynecologists, 409 12th Street, SW, PO Box 96920, Washington, DC 20090-6920, USA

Management after evacuation of hydatidiform mole

As long as hCG values are decreasing after molar evacuation, there is no role for chemotherapy. However, if hCG levels increase or plateau over several weeks, immediate evaluation and treatment for malignant postmolar gestational trophoblastic disease are indicated. Occasionally, the plateauing or increasing hCG levels are a result of a false-positive laboratory test result caused by heterophilic antibodies cross-reacting with the hCG test. Such false-positive test results, also known as "phantom hCG", are discussed later.

False-Negative Pregnancy Test in Hydatidiform Mole



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The NEW ENGLAND JOURNAL of MEDICINE

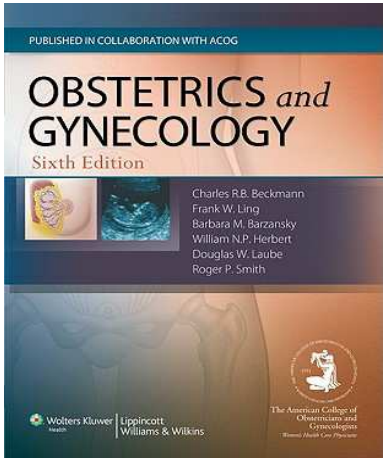
CLINICAL PRACTICE

A False Negative Pregnancy Test in a Patient with a Hydatidiform Molar Pregnancy

Falsely low or false negative results can occur when an extremely high level of substrate overwhelms the assay system. This high-dose hook effect has been documented with immunoassays for β-hCG, ferritin, prostate-specific antigen, prolactin, thyrotropin, and CA-125.[5] These inaccurate results can be overcome by diluting the serum or urine sample.[4]

Er TK, Jong et al. Clin Chem. 2006 Aug;52(8):1616-8.

The diagnosis of malignant sequelae as indicated by the need for chemotherapy includes the plateau or increase of hCG levels after evacuation of hydatidiform moles as mentioned previously, the histologic diagnosis of choriocarcinoma or invasive mole from findings from uterine curettage, or the identification of clinical or radiographic evidence of metastases. Repeat curettage is not recommended because it does not often induce remission or influence treatment and may result in uterine perforation and hemorrhage



The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Molar Pregnancy

Ross S. Berkowitz. M.D.. and Donald P. Goldstein. M.D.

Patients who have completed or do not have an interest in childbearing may undergo hysterectomy. Although hysterectomy prevents the development of local invasion, it does not eliminate metastatic disease. Therefore, careful monitoring of hCG levels is still required to ensure that persistent neoplasia does not develop.

The Australian and New Zealand Journal of Obstetrics and Gynaecology ANZJOG

Original Article

Persistence and malignant sequelae of gestational trophoblastic disease: Clinical presentation, diagnosis, treatment and outcome

Soo-Keat KHOO,[1] Mukhtiar SIDHU,[2] David BAARTZ,[3] Wai-Lum YIP[3] and Lee TRIPCONY[3]
[1]*Betty Byrne Henderson Women's Health Research Centre, University of Queensland, Brisbane, Queensland,* [2]*Queen Elizabeth II Hospital, and* [3]*Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia*

	n (%)
First-line chemotherapy (methotrexate, folinic acid)	73 (75.2)
Second-line chemotherapy (actinomycin-D, multi-drug)	17 (17.5)
Multi-drug chemotherapy	
Triple regimen MAC	10 (10.3)
CHAMOMA regimen	5 (5.1)
EMA-CO regimen	12 (12.4)
Cisplatinum/etoposide	3 (3.1)
Surgery	
Hysterectomy	27 (27.8)
Resection of metastases	4 (4.1)
Radiotherapy	0

She was disease-free and HCG-negative after hysterectomy for localised disease in the uterus.

Table 1 – FIGO Scoring system[32]

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

Panel 2: Indications for chemotherapy for gestational trophoblastic disease in the UK

- Plateaued or rising hCG concentration after evacuation*
- Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage
- Histological evidence of choriocarcinoma
- Evidence of metastases in brain, liver, or gastrointestinal tract, or radiological opacities larger than 2 cm on chest radiograph
- Serum hCG concentration of 20 000 IU/L or more, 4 weeks or more after evacuation, because of the risk of uterine perforation
- Raised hCG concentration 6 months after evacuation, even when still decreasing

hCG=human chorionic gonadotropin. *A plateaued hCG concentration is defined as four or more equivalent values of hCG for at least 3 weeks (days 1, 7, 14, and 21), and rising as two consecutive increases in hCG concentration of 10% or more for at least 2 weeks (days 1, 7, and 14).

Lancet 2010; 376: 717–29
Published Online July 28, 2010
DOI:10.1016/S0140-6736(10)60280-2

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A prospective phase II trial by the Gynecologic Oncology Group reported a 70–80% primary remission rate for patients with nonmetastatic gestational trophoblastic disease treated with weekly intramuscular methotrexate at a dose of 30–50 mg/m^2 [37]. There was no apparent benefit of increasing the dose to 50 mg/m^2. It was concluded that the weekly methotrexate regimen was the preferred choice of several methotrexate or dactinomycin schedules when efficacy, toxicity, and cost were taken into consideration [37,38].

Primary remission rates of patients treated with a variety of chemotherapy regimens for nonmetastatic gestational trophoblastic disease are similar [4]. Essentially

How is nonmetastatic gestational trophoblastic disease treated? In a patient with nonmetastatic gestational trophoblastic disease, which is better: hysterectomy alone or in combination with chemotherapy?

In patients with nonmetastatic gestational trophoblastic disease, early hysterectomy will shorten the duration and amount of chemotherapy required to produce remission [34,40]. Therefore, each patient's desire for future fertility should be evaluated at the onset of treatment.

The overall cure rate for patients with nonmetastatic disease is nearly 100% [1,33,34,37,42]. When chemotherapy is given for an additional 1–2 cycles after the first normal hCG value, recurrence rates are less than 5% [39].

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

If hCG has reverted to normal within 56 days of the pregnancy event then follow up will be for 6 months from the date of uterine evacuation.

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

All women should notify the screening centre at the end of any future pregnancy, whatever the outcome of the pregnancy. hCG levels are measured 6-8 weeks after the end of the pregnancy to exclude disease recurrence.

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

Women who receive chemotherapy for GTN are likely to have an earlier menopause.

Women with high-risk GTN who require multi-agent chemotherapy which includes etoposide should be advised that they may be at increased risk of developing secondary cancers.

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When can women whose last pregnancy was a complete or partial hydatidiform molar pregnancy try to conceive in the future and what is the outcome of subsequent pregnancies?

Women should be advised not to conceive until their follow-up is complete.

Women who undergo chemotherapy are advised not to conceive for 1 year after completion of treatment.

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

Women with GTD should be advised to use barrier methods of contraception until hCG levels revert to normal.

Once hCG level have normalised, the combined oral contraceptive pill may be used. There is no evidence as to whether single-agent progestogens have any effect on GTN.

If oral contraception has been started before the diagnosis of GTD was made, the woman can be advised to remain on oral contraception but she should be advised that there is a potential but low increased risk of developing GTN.

Intrauterine contraceptive devices should not be used until hCG levels are normal to reduce the risk of uterine perforation.