Current Management of Gestational Trofoblastic Diseases (GTD)

X. International Turkish – German Gynecology Congress

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TAJEV (Turkish - German Gynecological Education and Research Foundation)

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GTD

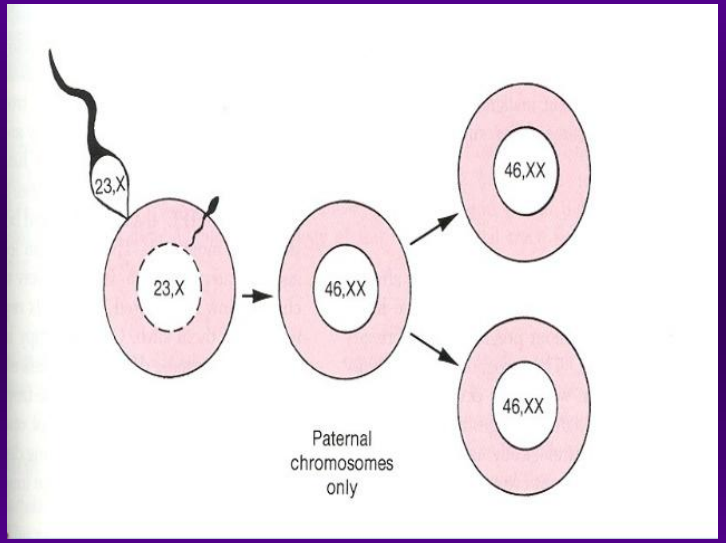
- Hydatidiform mole (HM) (complete and partial)
- Gestational trophoblastic neoplasia (GTN)
  - Invasive mole
  - Choriocarcinoma
  - Placental site trophoblastic tumor
  - Epithelioid trophoblastic tumor

Etiologic risk factors - HM

- Advanced or very young maternal age
- Prior HM
- Familial biparental complete HM associated with NLRP7 gene

Morphologic and cytogenetic criteria, CHM

- Uniform hydatid enlargement of villi, absence of fetus or embryo, hyperplastic trophoblast with varying degrees of atypia, absent villous capillaries
- 90% of CHM are 46, XX, originating from duplication of the chromosomes of a haploid sperm

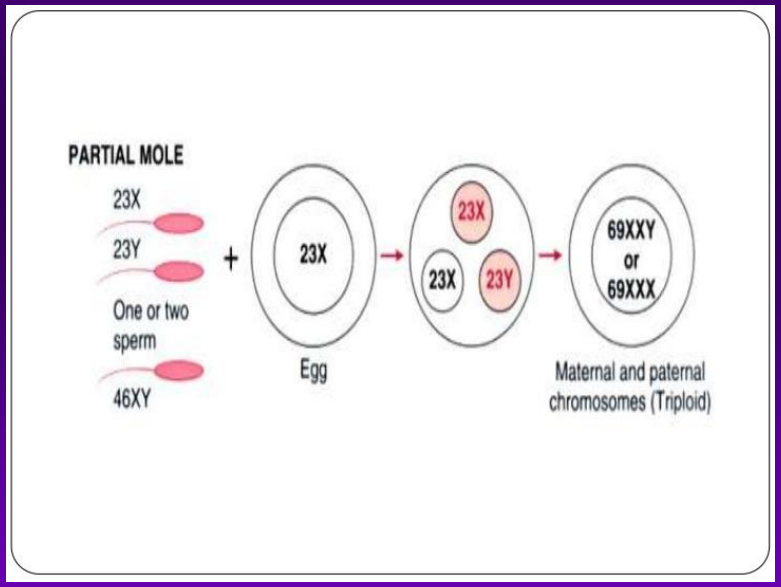


- 10% of CHM are 46, XY, or 46, XX, as a result of fertilization of an empty ovum by 2 sperm (dispermy)

Morphologic and cytogenetic criteria partial HM

- Identifiable fetal or embryonic tissue, chorionic villi with focal edema, functioning villous circulation, focal trophoblastic hyperplasia with mild atypia only
- Most partial moles

Have a triploid karyotype (usually 69, XXY), resulting from the fertilization of an apparently normal ovum by 2 sperm



Changing clinical presentation of complete HM New England Trophoblastic Disease Center

Symptoms/signs	1965–1975 (N = 306)	1988–1993 (N = 74)
Vaginal bleeding	97%	84%
Anemia (Hb < 10.0 g/dl)	54%	5%
Uterine size > dates	51%	28%
Preeclampsia	27%	1%
Hyperemesis	26%	8%
Hyperthyroidism	7%	0
Respiratory distress	2%	0

Partial HM, clinical presentation

- 90% of patients with partial HM have symptoms of incomplete or missed abortion, and the diagnosis is usually made after histologic review of curettage specimens
- The main presenting symptom is vaginal bleeding in 75% of patients
- Other symptoms are infrequent
- Preevacuation hCG levels are >100,000 mIU/mL in <10% of patients

- B. Czernobilsky, A. Barash, M. Lancet Partial moles: a clinicopathologic study of 25 cases Obstet Gynecol, 59 (1982), pp. 75–77
- A.E. Szulman, U. Surti The clinicopathologic profile of the partial hydatidiform mole Obstet Gynecol, 59 (1982), pp. 597–602
- R.S. Berkowitz, D.P. Goldstein, M.R. Bernstein Natural history of partial molar pregnancy Obstet Gynecol, 66 (1985), pp. 677–681

Diagnosis, US

- **US plays a critical role in the diagnosis of both complete and partial HM**
  - Because the chorionic villi of complete HM exhibit diffuse hydropic swelling, vesicular US pattern can be observed, consisting of multiples echoes (holes) within the placental mass and usually no fetus
  - V. Soto-Wright, M.R. Bernstein, D.P. Goldstein *et al.* The changing clinical presentation of complete molar pregnancy Obstet Gynecol, 86 (1995), pp. 775–779
  - R. Santos-Ramos, J.P. Forney, B.E. Schwarz Sonographic findings and clinical correlations in molar pregnancy Obstet Gynecol, 56 (1980), pp. 186–192
  - C.B. Benson, D.R. Genest, M.R. Bernstein *et al.* Sonographic appearance of first trimester complete hydatidiform moles Ultrasound Obstet Gynecol, 16 (2000), pp. 188–191
  - C. Fine, A.L. Bundy, R.S. Berkowitz *et al.* Sonographic diagnosis of partial hydatidiform mole Obstet Gynecol, 73 (1989), pp. 414–418
- **US facilitate the early diagnosis of a partial HM by demonstrating focal cystic spaces within the placenta and an increase in the transverse diameter of the gestational sac**
  - C. Fine, A.L. Bundy, R.S. Berkowitz *et al.* Sonographic diagnosis of partial hydatidiform mole Obstet Gynecol, 73 (1989), pp. 414–418

HCG

- HCG is a disease-specific tumor marker produced by HM and GTN
- HCG levels have been shown to correlate with the burden of disease

- L.A. Cole hCG, its free subunits and its metabolites: roles in pregnancy and trophoblastic disease J Reprod Med, 43 (1998), pp. 3–10
- R.S. Berkowitz, M. Ozturk, D. Goldstein *et al.* Human chorionic gonadotropin and free subunits' serum levels in patients with partial and complete hydatidiform moles Obstet Gynecol, 74 (1989), pp. 212–216
- M. Ozturk, R. Berkowitz, D. Goldstein *et al.* Differential production of human chorionic gonadotropin and free subunits in gestational trophoblastic disease Am J Obstet Gynecol, 158 (1988), pp. 193–198

False-positive hCG (phantom hCG)

- Some assays may yield false-positive hCG results, with levels as high as 800 mIU/mL, have led to treatment of healthy patients with unnecessary surgery and chemotherapy
- These antibodies are found in 3-4% of healthy people and can mimic hCG immunoreactivity

- S. Rotmensch, L.A. Cole False diagnosis and needless therapy of presumed malignant disease in women with false-positive human chorionic gonadotropin concentrations Lancet, 355 (2000), pp. 712–715

False-positive hCG (phantom hCG)

- There are 3 ways to determine whether hCG assays are falsely positive
  - Determine a urine hCG level, which should be negative
  - Request serial dilution of the serum, which should not show a parallel decrease with dilution
  - Send the serum and urine of the patient to an hCG reference laboratory
- Additionally, there is some cross-reactivity of hCG with LH, which may lead to falsely elevated low levels of hCG. Measurement of LH to identify this possibility and suppression of LH with COC pills will prevent this problem

- S. Rotmensch, L.A. Cole False diagnosis and needless therapy of presumed malignant disease in women with false-positive human chorionic gonadotropin concentrations Lancet, 355 (2000), pp. 712–715

Quiescent GTD

- Inactive form of GTN that is characterized by persistent, unchanging low levels (<200 mIU/mL) of "real" hCG for at least 3 months associated with a history of GTD or spontaneous abortion, but without clinically detectable disease
- The hCG levels do not change with chemotherapy or surgery
- No hyperglycosylated hCG
- Follow-up of patients with quiescent GTD reveals subsequent development of active GTN in about one-quarter, which is heralded by an increase in both hyperglycosylated hCG and total hCG

- L.A. Cole, S.A. Butler, S.A. Khanlian *et al.* Gestational trophoblastic diseases, 2: hyperglycosylated hCG as a tumor marker of active neoplasia Gynecol Oncol, 102 (2006), pp. 151–159
- S.A. Khanlian, L.A. Cole Management of gestational trophoblastic disease and other cases with low serum levels of human chorionic gonadotropin J Reprod Med, 51 (2006), pp. 812–818

Quiescent GTD - recommendations

- False-positive hCG resulting from heterophile antibodies or LH interference should be excluded
- The patient should be thoroughly investigated for evidence of disease, immediate chemotherapy or surgery should be avoided
- The patient should be monitored long term with periodic hCG testing while avoiding pregnancy
- Treatment should be undertaken only when there is a sustained rise in hCG or the appearance of overt clinical disease

- B.W. Hancock hCG measurement in gestational trophoblastic neoplasia: a critical appraisal J Reprod Med, 51 (2006), pp. 859–860

Pathologic diagnosis

- Pathologic diagnosis of CHM and PHM is made by examination of curettage specimens
- IH staining for p57 (a paternally imprinted, maternally expressed gene) can differentiate absent immunostaining CHM from positively staining hydropic abortuses and PHM
- Flow cytometry can distinguish diploid CHM from triploid PHM

- D.H. Castrillon, D. Sun, S. Weremowicz *et al.* Discrimination of complete hydatidiform mole from its mimics by immunohistochemistry of the paternally imprinted gene product p57K1P2 Am J Surg Pathol, 25 (2001), pp. 1225–1230
- H.M. Thaker, A. Berlin, B. Tycko *et al.* Immunohistochemistry for the imprinted gene product IPL/PHLDA2 for facilitating the differential diagnosis of complete hydatidiform mole J Reprod Med, 49 (2004), pp. 630–636

Pathologic diagnosis

- Additionally, pathologic diagnosis of invasive mole, choriocarcinoma, PSTT, and ETT can sometimes be made by curettage, biopsy of metastatic lesions, or examination of hysterectomy specimens or placentas
- Biopsy of a vaginal lesion suggestive of a GTN is dangerous because of the massive bleeding that may occur
  - E. Berry, G.S. Hagopian, J.R. Lurain Vaginal metastases in gestational trophoblastic neoplasia J Reprod Med, 53 (2008), pp. 487–492

HM treatment

- Suction evacuation (SE) is the preferred method of evacuation of a HM
- IV oxytocin infusion be started at the onset of SE and continued for several hours postop to enhance uterine contractability
- SE should be followed by gentle sharp curettage
- At least 2 U of blood should be available
- Patients who are Rh negative should receive Rh immune globulin at the time of evacuation, as Rh D factor is expressed on trophoblastic cells

HM treatment

- Hysterectomy provides permanent sterilization and eliminates the risk of local myometrial invasion as a cause of persistent disease
- Because of the potential for metastatic disease even after hysterectomy, the risk of postmolar GTN still remains at 3-5%, thereby requiring continued hCG follow-up

- J.T. Soper Surgical therapy for gestational trophoblastic disease J Reprod Med, 39 (1994), pp. 168–174

Follow-up after molar evacuation

- **Trophoblastic sequelae (invasive mole or choriocarcinoma), which develop in approximately 15-20% with complete mole and 1-5% with partial mole**

- S. Goto, A. Yamada, T. Ishizuka, Y. Tomodo Development of postmolar trophoblastic disease after partial molar pregnancy Gynecol Oncol, 48 (1993), pp. 165–170
- R.S. Berkowitz, D.S. Goldstein Clinical practice: molar pregnancy N Engl J Med, 360 (2009), pp. 1639–1645
- J.R. Lurain, J.I. Brewer, E. Torok, B. Halpern Natural history of hydatidiform mole after primary evacuation Am J Obstet Gynecol, 145 (1983), pp. 591–595
- C.M. Feltmate, J. Batorfi, V. Fulop *et al.* Human chorionic gonadotropin follow-up in patients with molar pregnancy: a time for reevaluation Obstet Gynecol, 101 (2003), pp. 732–736
- B.W. Hancock, K. Nazir, J.E. Everard Persistent gestational trophoblastic neoplasia after partial hydatidiform mole: incidence and outcome J Reprod Med, 51 (2006), pp. 764–766
- C.M. Feltmate, W.B. Growdon, A.J. Wolfberg *et al.* Clinical characteristics of persistent gestational trophoblastic neoplasia after partial hydatidiform molar pregnancy J Reprod Med, 51 (2006), pp. 902–906

Follow-up after molar evacuation

- Clinical + hCG
- Every week until 3 consecutive tests show normal levels
- After which hCG levels should be determined at 3-month intervals for 6 months after the spontaneous return to normal
- Contraception is recommended for 6 months after the first normal hCG result
- The use of COC pills is preferable

- R.S. Berkowitz, D.S. Goldstein Clinical practice: molar pregnancy N Engl J Med, 360 (2009), pp. 1639–1645

Diagnose of postmolar GTN

- Include at least 1 of the following
  - HCG plateau for 4 consecutive values over 3 weeks
  - HCG rise of ≥10% for 3 values over 2 weeks
  - HCG persistence 6 months after molar evacuation
  - Histopathologic diagnosis of CoCa
  - Presence of metastatic disease
  - The FIGO stage is designated by a Roman numeral followed by the modified WHO score designated by an Arabic numeral, separated by a colon
- PSTTs and ETTs are classified separately

GTN

- Varied presentation depending on the antecedent pregnancy event, extent of disease, histopathology
- Postmolar GTN (invasive mole or CoCa) mostly presents as irregular bleeding after evacuation of HM
- Signs suggestive of postmolar GTN are an enlarged, irregular uterus and persistent bilateral ovarian enlargement
- Occasionally, a metastatic vaginal lesion may be noted on evacuation, disruption of which may cause uncontrolled bleeding
- CoCa associated with nonmolar gestation has no characteristic symptoms or signs, which are mostly related to invasion of tumor in the uterus or at metastatic sites

Classification/staging

- Metastatic workup and an evaluation for risk factors
- Complete history and physical examination
- Blood cell count, coagulation studies, serum chemistries, blood type and antibody screen, and hCG level
- Chest x-ray, if the chest x-ray is negative, CT scans of the abdomen and pelvis, and CT scan or magnetic resonance imaging of the brain
- HCG in cerebrospinal fluid may be helpful in detecting brain involvement

Stage

I. Disease confined to uterus

II. Disease extends outside uterus but is limited to genital structures (adnexa, vagina, broad ligament)

III. Disease extends to lungs with or without genital tract involvement

IV. Disease involves other metastatic sites

Modified WHO prognostic scoring system as adapted by FIGO

Scores	0	1	2	4
Age	< 40	> 40	–	–
Antecedent pregnancy	Mole	Abortion	Term	
Interval months from index pregnancy	< 4	4–7	7–13	> 13
Pretreatment serum hCG (IU/L)	< 1000	< 10,000	< 100,000	> 100,000
Largest tumor size (including uterus)	–	3–< 5 cm	> 5 cm	
Site of metastases	Lung	Spleen/kidney	GI	Liver/brain
Number of metastases	–	1–4	5–8	> 8
Previous failed chemotherapy			Single drug	2 or more drugs

Treatment of GTN

- Patients with nonmetastatic (stage I) and low-risk metastatic (stages II and III, score <7) GTN can be treated with single-agent chemotherapy, with resulting survival rates approaching 100%
- Patients classified as having high-risk metastatic disease (stage IV and stages II-III, score ≥7) should be treated with multiagent chemotherapy ± adjuvant radiation or surgery to achieve cure rates of 80-90%

Chemotherapy for low-risk gestational trophoblastic neoplasia

Chemotherapy regimen	Remission rate, %
1. MTX 0.4 mg/kg (maximum 25 mg)/d IV or IM for 5 d; repeat every 14 d	87–93
2. MTX 30-50 mg/m^2 IM weekly	49–74
3. MTX 1 mg/kg IM d 1, 3, 5, 7; folinic acid 0.1 mg/kg IM d 2, 4, 6, 8; repeat every 15-18 d, or as needed	74–90
4. MTX 100 mg/m^2 IVP, then 200 mg/m^2 in 500 mL D5W over 12 h; folinic acid 15 mg IM or PO q 12 h for 4 doses beginning 24 h after start of MTX; repeat every 18 d, or as needed	69–90
5. Act-D 10-13 µg/kg IV qd for 5 d; repeat every 14 d	77–94
6. Act-D 1.25 mg/m^2 IV every 2 wk	69–90
7. Alternating MTX/Act-D regimens 1 and 5	100

Lurain. Gestational trophoblastic disease II. Am J Obstet Gynecol 2011.

Low-risk disease

- Hysterectomy for low-risk GTN may be performed as adjuvant treatment with the initiation of chemotherapy to shorten the duration of treatment if fertility preservation is not desired
- Hysterectomy may also become necessary to eradicate persistent, chemotherapy-resistant disease in the uterus or to remedy uterine hemorrhage from tumor.
- Hysterectomy is the treatment of choice for PSTT and ETT

High-risk metastatic disease

- Treated initially with multiagent chemotherapy with or without adjuvant surgery or radiation therapy
- EMA-CO is the initial treatment of choice for high-risk metastatic GTN

EMA-CO regimen

- In 2 reported series, the complete response rates were 71% and 67%, and the overall survival rates were 91% and 93%, respectively.
- The only patients who died had FIGO stage IV disease with scores >12

- P.F. Escobar, J.R. Lurain, D.K. Singh *et al.* Treatment of high-risk gestational trophoblastic neoplasia with etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine chemotherapy Gynecol Oncol, 91 (2003), pp. 552–557
- J.R. Lurain, D.K. Singh, J.C. Schink Primary treatment of metastatic high-risk gestational trophoblastic neoplasia with EMA-CO chemotherapy J Reprod Med, 51 (2006), pp. 767–772

High-risk metastatic disease who failed primary therapy with EMA-CO

- Of the 10 patients who failed primary therapy with EMA-CO, 9 (90%) had complete clinical responses to EMA-EP or bleomycin, etoposide, cisplatin, but only 6 (60%) subsequently achieved a lasting remission
- J.R. Lurain, B. Nejad Secondary chemotherapy for high-risk gestational trophoblastic neoplasia Gynecol Oncol, 97 (2005), pp. 618–623

GTN

- The overall cure rate in treating these tumors is currently >90%
- Nonmetastatic (stage I) and low-risk metastatic (stages II and III, score <7) GTN can be treated with single-agent chemotherapy resulting in a survival rate approaching 100%.
- High-risk GTN (stages II-IV, score ≥7) requires initial multiagent chemotherapy with or without adjuvant radiation and surgery to achieve a survival rate of 80-90%

Summary

- Centralisation of care is necessary
- Treatment of HM is suction D&C
- Anti-D prophylaxis is recommended following suction D&C
- The FIGO scoring system should be used to determine the risk of GTN becoming resistant to single-agent chemotherapy
- Patients with a FIGO score of 0–6 and / or stage I-III can be treated with either single-agent MTX or ActD

Summary

- Patients with a FIGO score of ≥7 or stage IV should receive multi-agent chemotherapy EMA/CO
- High-risk failures can be frequently salvaged with further chemotherapy with EP/EMA or TE/TP
- Surgery alone can effectively salvage some patients with isolated foci of chemoresistant disease
- Cure for low and high risk disease is 100% and 80-90% respectively

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High-risk metastatic disease