Definitions and Management of Mole Hidatidiform

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GTD -

- GTD represents the result of an aberrant human pregnancy with an abnormal karyotype due to an incorrect fertilisation and, finally, abnormal proliferation of placental villi
- Hydatidiform mole (HM)
- Molar pregnancy,
- Bunch of grapes

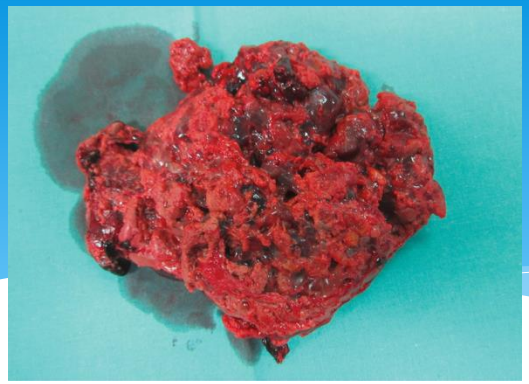
- Fonseca EKUN, Rodrigues MAS, Yamauchi FI, et al., "Bunch of grapes" in complete hydatidiform mole. Abdom Radiol (NY). 2017;42(5):1606

GTD - Histopathologically

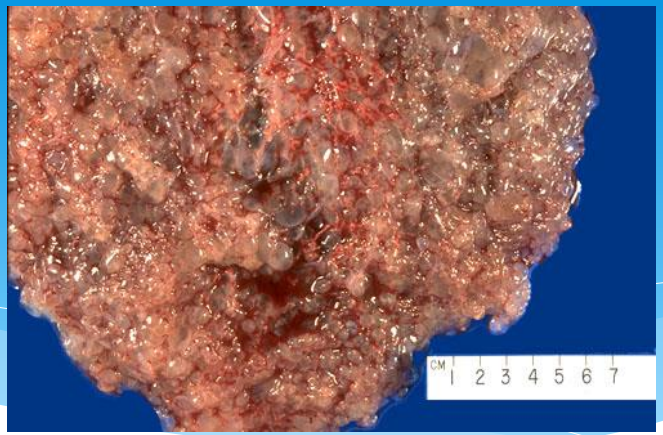
- HM
  - CHM
  - PHM
- Malignant sequelae
  - Partial: less than 5%
  - Complete: approximately 20%
- GTN, GTT
  - Invasive mole
  - Choriocarcinoma
  - PSTT
  - ETT

GTN - Definitions

- The term GTN replaces the terms invasive mole, metastasizing mole and choriocarcinoma which are histopathologic diagnoses
- While histopathologic verification is desirable, it is not essential for the classification that is currently used
- PSTT and ETT, are variant of GTD but should be classified separately as they have a distinct clinical presentation and its course and management differs from other GTDs

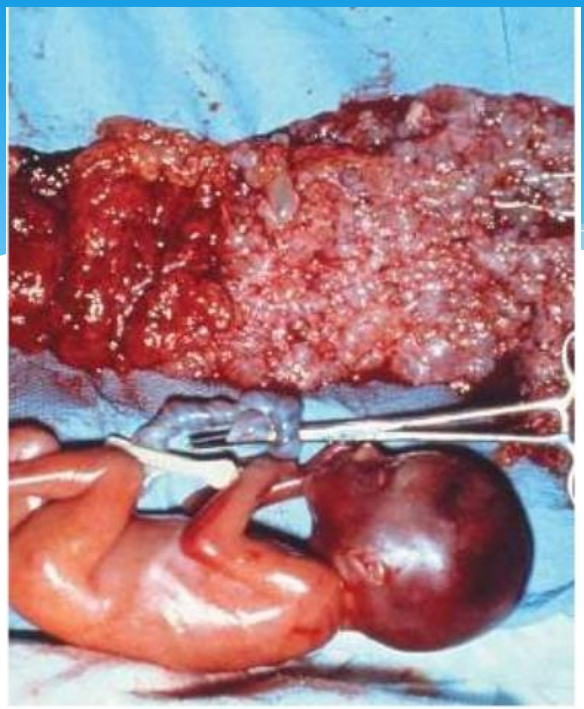


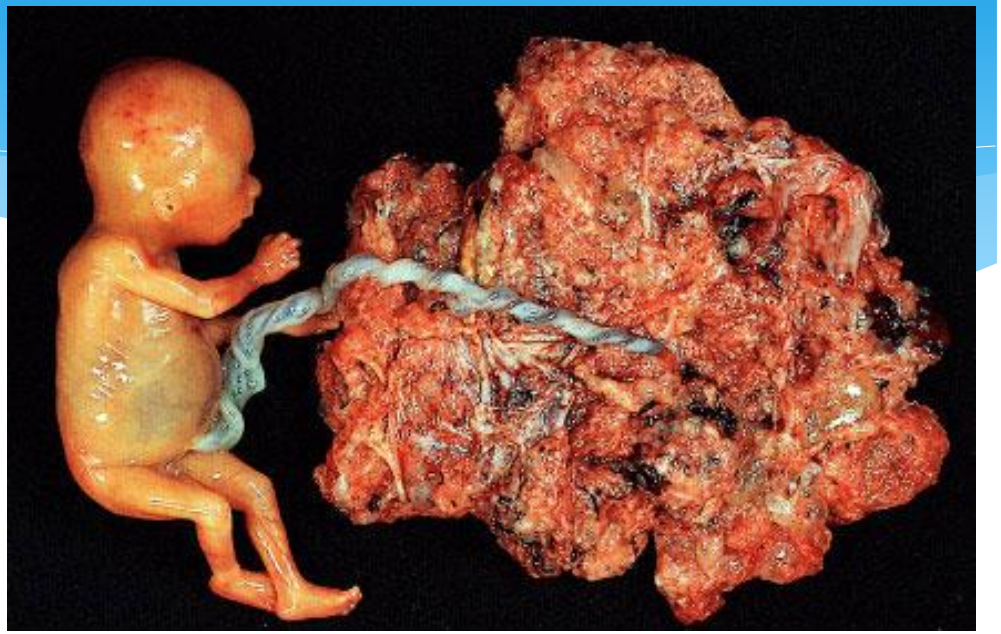
CHM



- CHM, ovum is lacking a maternal complement of chromosomes
- It is fertilized by a haploid sperm, containing an X chromosome
- Duplication of this chromosome set typically yields a 46, XX karyotype that is paternally derived
- Fertilized by 2 sperm, resulting 46XX or 46XY chromosome
- No fetus develops

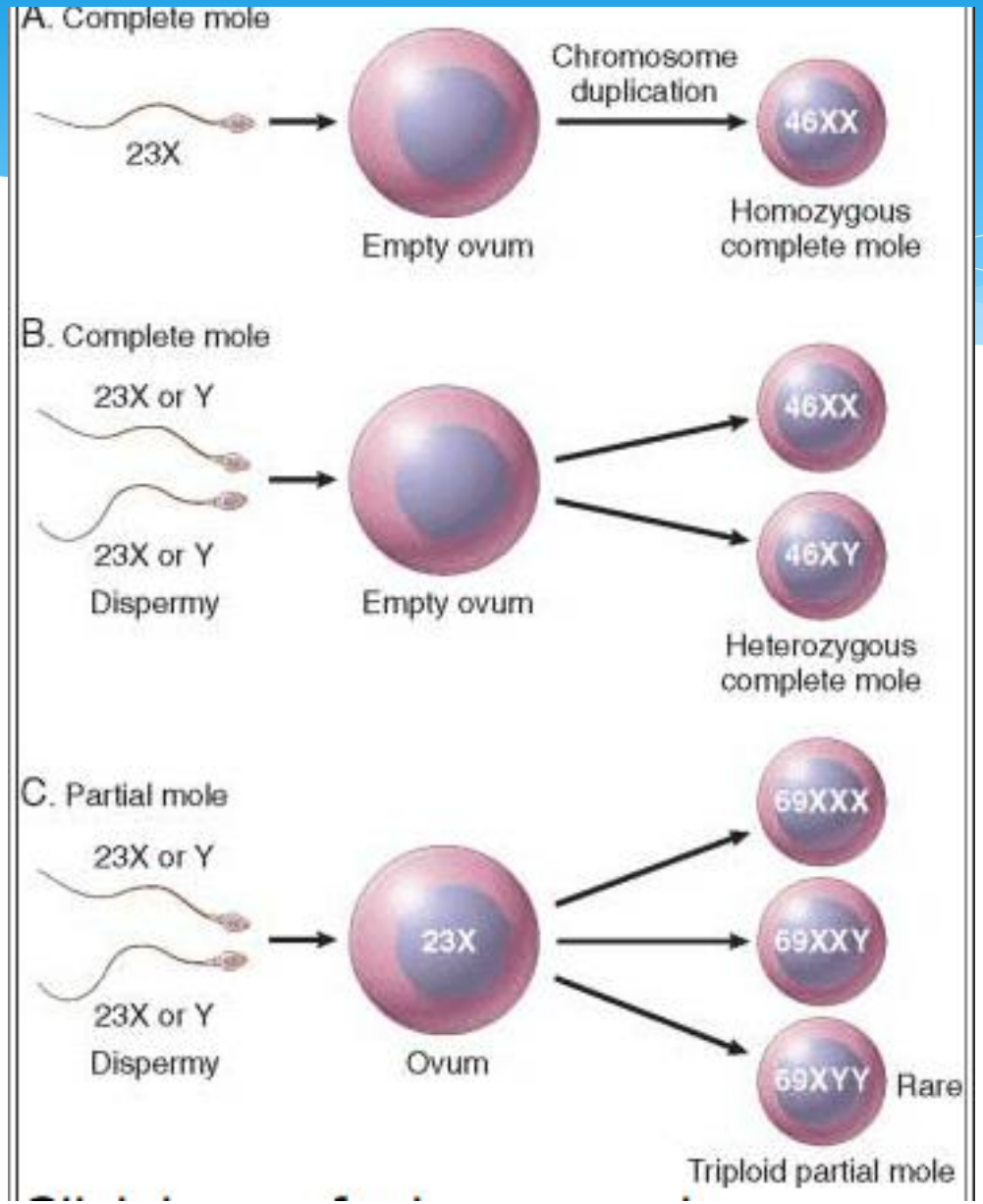
PHM





- **PHM is caused by the fertilisation of an ovum by two sperms, leading to a triploid karyotype**

CHMs and PHMs



Familial recurrent HM

- The occurrence of two or more molar pregnancies in the same patient.
- Rare autosomal recessive condition
- Usually associated with mutations of the NLRP7 or KHDC3L gene
- Genotyping demonstrated that they are diploid and biparental
- These women in general are unable to conceive naturally, the only way to become pregnant is by oocyte donation

Recurrent CHM and familial HMs

- Nguyen NMP, Khawajkie Y, Mechtouf N, Rezaei M, Breguet M, Kurvinen E, Jagadeesh S, Solmaz AE, Aguinaga M, Hemida R, Harma MI, Rittore C, Rahimi K, Arseneau J, Hovanes K, Clisham R, Lenzi T, Scurry B, Addor MC, Bagga R, Nendaz GG, Finci V, Poke G, Grimes L, Gregersen N, York K, Bolze PA, Patel C, Mozdarani H, Puechberty J, Scotchie J, Fardaei M, Harma M, Gardner RJM, Sahoo T, Dudding-Byth T, Srinivasan R, Sauthier P, Slim R. The genetics of recurrent hydatidiform moles: new insights and lessons from a comprehensive analysis of 113 patients. Mod Pathol. 2018;31(7):1116-1130

- Reddy R, Nguyen NM, Sarrabay G, Rezaei M, Rivas MC, Kavasoglu A, Berkil H, Elshafey A, Abdalla E, Nunez KP, Dreyfus H, Philippe M, Hadipour Z, Durmaz A, Eaton EE, Schubert B, Ulker V, Hadipour F, Ahmadpour F, Touitou I, Fardaei M, Slim R. The genomic architecture of NLRP7 is Alu rich and predisposes to disease-associated large deletions. Eur J Hum Genet. 2016;24(10):1445-52

- Ulker V, Gurkan H, Tozkir H, Karaman V, Ozgur H, Numanoglu C, Gedikbasi A, Akbayir O, Uyguner ZO. Novel NLRP7 mutations in familial recurrent hydatidiform mole: are NLRP7 mutations a risk for recurrent reproductive wastage? Eur J Obstet Gynecol Reprod Biol. 2013;170(1):188-92

- Buyukkurt S(1), Fisher RA, Vardar MA, Evruke C. Heterogeneity in recurrent complete hydatidiform mole: presentation of two new Turkish families with different genetic characteristics. Placenta. 2010;31(11):1023-5

- Wang CM, Dixon PH, Decordova S, Hodges MD, Sebire NJ, Ozalp S, Fallahian M, Sensi A, Ashrafi F, Repiska V, Zhao J, Xiang Y, Savage PM, Seckl MJ, Fisher RA. Identification of 13 novel NLRP7 mutations in 20 families with recurrent hydatidiform mole; missense mutations cluster in the leucine-rich region. J Med Genet. 2009;46(8):569-75

Clinical presentation of GTD

Clinical presentation of HM

- Vaginal bleeding (VB) %49
- VB + pain %21
- VB + Pre-eclampsi %14
- VB + acute abdomen % 2
- VB + Hyperthyroidism % 1
- Total with bleeding %85

- Ayhan A, Özalp S.: Benign trofoblastik hastalıklar (Hydatidiform mole) 100 olgunun klinik incelenmesi. Hacettepe Tıp/Cerrahi Bülteni. 15:56-62,1982.

Changing presentation of CHM over the past three decades

- **In the current cohort (1994 to 2013) the median gestational age at diagnosis continued to decline compared to our prior cohort (1988-1993) (9 weeks versus 12 weeks)**
- **Patients in the current cohort were also significantly less likely to present with vaginal bleeding (46 versus 84%, $p<0.001$)**

* **Sun SY, Melamed A, Goldstein DP, et al, Changing presentation of complete hydatidiform mole at the New England Trophoblastic Disease Center over the past three decades: does early diagnosis alter risk for gestational trophoblastic neoplasia? Gynecol Oncol. 2015;138(1):46**

Clinical presentation of HM

- **Vaginal bleeding % 93.2**
- **US findings % 6.8**
- **Total % 100.0**

- **Özalp, S., Hassa, H., Şener, T.Minsin, H.:Elli dokuz hidatidiform olgusunun değerlendirilmesi. Jinekoloji ve Obstetrik Bülteni, 7:51-56, 1998**

Pelvic US diagnosis of HM

- **CHM**
  - **Heterogeneous mass in the uterine cavity with multiple anechoic spaces, "snowstorm" appearance**
  - **Absence of an embryo or fetus, and no amniotic fluid is present**
- **PHM**
  - **Typically is the finding of a fetus which may be viable**
  - **Presence of amniotic fluid, and the placenta appears to have enlarged, cystic spaces, "Swiss cheese" appearance**
  - **PHMs are diagnosed as a missed or incomplete abortion up to %60 of cases**

US diagnosis of PHM versus CHM

- CHM had larger gestational sacs (612 versus 44 mm, p = 0.005)
- More often
  - Avascular on color Doppler imaging (45.5% versus 18.8%, p = 0.02)
  - Abnormal tissue in the uterus (82.6% versus 20.8%, p < 0.0001)
  - Placental masses (86.9% versus 16.7%, p < 0.0001)
  - Diagnosed prospectively (86.4% versus 41.7%, p = 0.0005)
- Improved US equipment

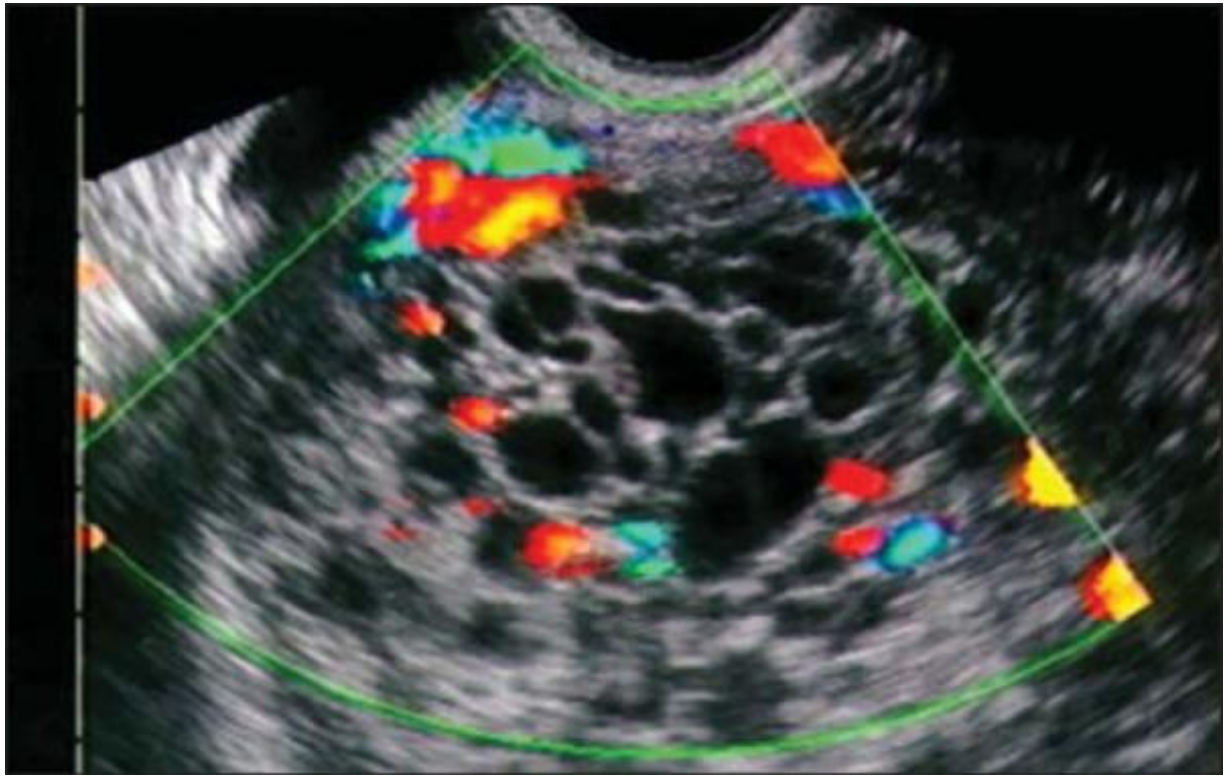
- Savage JL, Maturen K, Mowers EL, Pasque KB, Wasnik AP. Sonographic diagnosis of partial versus complete molar pregnancy: A reappraisal. J Clin Ultrasound. 2017;45(2):72-7

US diagnosis of HM

- Of cases suspected on US as GTD, 58.2%, had histologically confirmed GTD
- HMs were suspected on pre-op US; 88.2% of CHM and 56.0% of PHM cases
- Detecting HMs by US remains a diagnostic challenge, particularly for PHMs
- Ross JA, Unipan A, Clarke J, et al, Ultrasound diagnosis of molar pregnancy. Ultrasound. 2018;26(3):153

TVUS, patient with bleeding at 14 weeks of pregnancy, endometrial cavity filled with amorphous material with multiple anechoic areas, suggestive of CHM, no embryonic tissue, in the Doppler flow study, there was no vascular flow among the vesicles

Lima, LLA et al, Clinical and radiological correlations in patients with gestational trophoblastic disease, Radial Bras. 2016; 49(4): 241



Early diagnosis of HM and the rate of GTN development

- **The rate of postmolar GTN did not improve despite earlier diagnosis**
  - Lertkhachonsuk AA, Israngura N, Tangtrakul S, Chittithaworn S, Complete Hydatidiform Mole Change in Clinical Profile over Three Decades, Conference Paper in JRM, 57(11):470-474, 2012
- **Earlier diagnosis of CHM did not result in a decrease in the rate of postmolar GTN (19 and 23%)**
  - Sun SY, Melamed A, Goldstein DP, Bernstein MR, Horowitz NS, Moron AF, Maestá), Braga A, Berkowitz R. Changing presentation of complete hydatidiform mole at the New England Trophoblastic Disease Center over the past three decades: does early diagnosis alter risk for gestational trophoblastic neoplasia? Gynecol Oncol. 2015 Jul;138(1):46-9
- **Early diagnosis has not resulted in a reduction in the development of GTN, a dilemma that still challenges professionals working with GTD**
  - Braga A, Moraes V, Maestá I, Amim Júnior J, Rezende-Filho Jd, Elias K, Berkowitz R. Changing Trends in the Clinical Presentation and Management of Complete Hydatidiform Mole Among Brazilian Women. Int J Gynecol Cancer. 2016 Jun;26(5):984-90

Twin pregnancies consisting of a normal fetus and a co-existing HM

- In one of 20000 to 100000 pregnancies

Twin pregnancies, comprising CHM and healthy co-twin

- 77 cases
- 24 women decided to have a termination
- 53 women continued with their pregnancies
- 2 had terminations because of severe pre-eclampsia
- 23 spontaneously aborted
- 28 pregnancies resulting in 20 livebirths
- About 40% result in livebirths, without increasing the risk of persistent GTD

- Sebire NJ, Foskett M, Paradinas FJ, Fisher RA, Francis RJ, Short D, Newlands ES, Seckl MJ. Outcome of twin pregnancies with complete hydatidiform mole and healthy co-twin. Lancet. 2002, 22;359(9324):2165-6

CHM with a coexisting live fetus

- So far, approximately 177 cases have been documented in the literature with consequent 66 live births
- An individualistic approach and an informed doctor patient consensus may improve the likely outcome

- Rohilla M, Singh P, Kaur J, et al, Individualistic approach to the management of complete hydatidiform mole with coexisting live fetus. Eur J Obstet Gynecol Reprod Biol. 2015;191:39-42

Accuracy of p57KIP2 immunostaining compared with molecular genotyping for the diagnosis of CHM
A systematic review and meta-analysis

- **p57KIP2 immunostaining is accurate when diagnosing CHM**
- **It can be used as an adjunct test in a combination algorithmic approach**

- **Madi JM, Braga A, Paganella MP, et al, Accuracy of p57KIP2 compared with genotyping to diagnose complete hydatidiform mole: a systematic review and meta-analysis. BJOG. 2018;125(10):1226**

Approach to HMs after diagnosis

- First stabilize the patient
- The gold standard in treating HM is suction dilation and curettage performed under US vision to avoid uterus perforation
- Hysterectomy
- All rhesus D-negative patients should obtain prophylactic anti-D rhesus immunglobulin

Factors for persistent disease in women with HM

- 82 patients with HM
- 38% developed persistent trophoblastic neoplasia
- Elevated hCG level, advanced age, history of HM, presence of hyperplasia, marked nuclear atypia and necrosis, and hemorrhage were significant risk factors for persistent neoplasia after univariate analysis
- Trophoblastic hyperplasia, age and history of HM were identified as the most powerful indicators of persistent disease after multivariate analysis

- Ayhan A, Tuncer ZS, Halilzade H, Küçükali T.. Predictors of persistent disease in women with complete hydatidiform mole. J Reprod Med. 1996;41(8):591-4

The risk factors for developing GTN

- CHM
- Uterine size greater than gestational age
- Serum hCG levels more than 100,000 mIU/mL
- Ovarian theca lutein cysts greater than 6 cm in diameter
- Age greater than 35 to 40 years

Comparison of different therapeutic strategies for CHM in women at least 40 years old

- **Patients treated by expectant management, who received prophylactic chemotherapy, and treated by prophylactic total hysterectomy, the incidence of post-molar GTN was 37.1%, 41.7% and 11.4% respectively**
- **Prophylactic total hysterectomy is the most effective therapeutic strategy**

- Zhao P, Chen Q, Lu W. Comparison of different therapeutic strategies for complete hydatidiform mole in women at least 40 years old: a retrospective cohort study. BMC Cancer. 2017;17(1):733

CHM, associated complications

- **Hyperthyroidism**
- **Pre-eclampsia**
- **Ovarian theca lutein cysts**

Clinical profile of GTD in Turkey, data from 6 centers

- 351,650 deliveries, and 263 cases of HMs
- Incidence 0.7/1,000 deliveries
- 1.1% patients had repeat HMs
- 66.5% CHM
- 6.4% had prophylactic chemo
- 2.2% had hysterectomy

- Oge T, Ozalp SS, Güngör T, Yildirim Y, Sanci M, Dogan A, Ertas IE, Yetimalar H, Dilek S, Celik C. Hydatidiform mole in Turkey: results from six centers. Reprod Med. 2012;57(5-6):259-61

Follow-up of HMs

	CHM	PHM
Duration of serum/urine β-hCG controls	1 year	3–6 months
Frequency of β-hCG measurement	weekly until 3× negative, then monthly	weekly until 2–3× negative, then monthly
Prophylactic chemotherapy	no	no
Risk of subsequent GTD	1–2% following one previous mole15–18% following two previous moles	
Chance for GTN	15–20%	0.5–2%

The optimal duration of hCG surveillance following evacuation of a HM

- For CHM the risk of persistant GTN after hCG normalisation was 1 in 406
- For PHM the risk of persistant GTN after hCG normalisation was 1 in 3195
- The current UK hCG surveillance protocol for PHM to a single additional confirmatory normal urine hCG measurement one month after first normalisation
- The protocol for CHM remains unchanged

- Coyle C, Short D, Jackson L, et al, What is the optimal duration of human chorionic gonadotrophin surveillance following evacuation of a molar pregnancy? A retrospective analysis on over 20,000 consecutive patients, Gynecol Oncol. 2018;148(2):254

Hormonal contraceptive (HC) use before hCG remission and the risk of GTN following CHM

- 2423 women with CHM of whom 154 commenced HC while hCG was still elevated,
- No relationship was observed between HC use with mean time to hCG remission and GTN development
- HC can be safely used to prevent a new conception following CHM before hCG remission

- Braga A, Maestá I, Short D, Savage P, Harvey R, Seckl MJ. Hormonal contraceptive use before hCG remission does not increase the risk of gestational trophoblastic neoplasia following complete hydatidiform mole: a historical database review. BJOG. 2016 Jul;123(8):1330-5.

Thanks for your attention