Gestational trophoblastic disease

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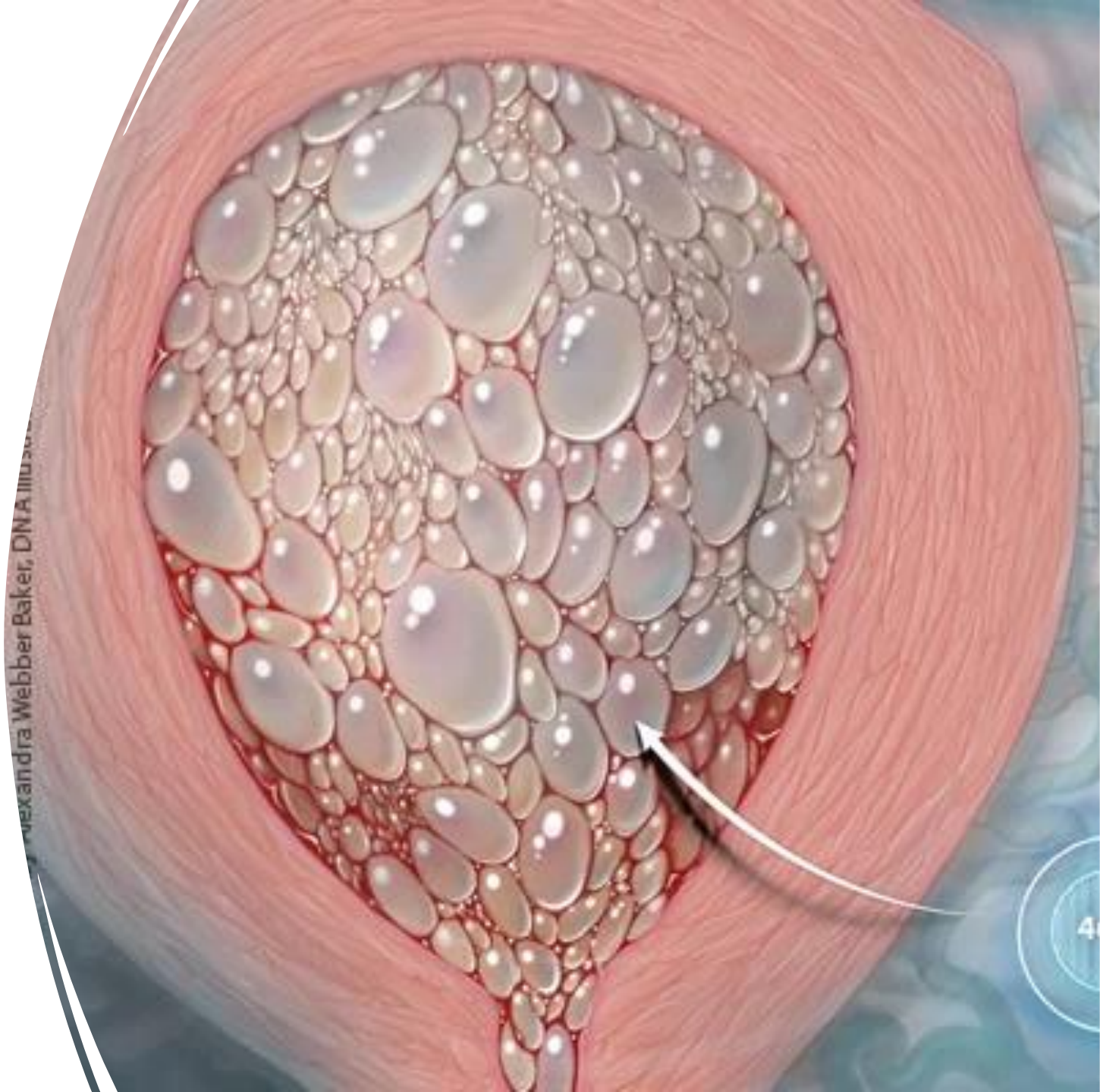


- Gestational trophoblastic disease (GTD) comprises a group of disorders spanning the hydatidiform moles (molar pregnancies) through to the malignant conditions of invasive mole, choriocarcinoma and the very rare placental site trophoblastic tumour (PSTT) and epithelioid trophobastic tumour (ETT).

- GTN: persistence of GTD, defined as a persistent elevation of beta human chorionic gonadotrophin (□hCG)

- The diagnosis of GTN does not require histological confirmation.

- The diagnosis of complete mole, partial mole, atypical PSN and PSTT/ETT does require histological confirmation.

- Molar pregnancies can be subdivided into complete and partial molar pregnancies based on genetic and histopathological features

Complete molar pregnancies

- diploid and androgenic in origin, with no evidence of fetal tissue
- 75–80% arise as a consequence of duplication of a single sperm following fertilisation of an ‘empty’ ovum.
- Some complete moles (20–25%) can arise after dispermic fertilisation of an ‘empty’ ovum.

Partial molar pregnancy

- 90% triploid in origin, with two sets of paternal haploid chromosomes and one

  set of maternal haploid chromosomes.

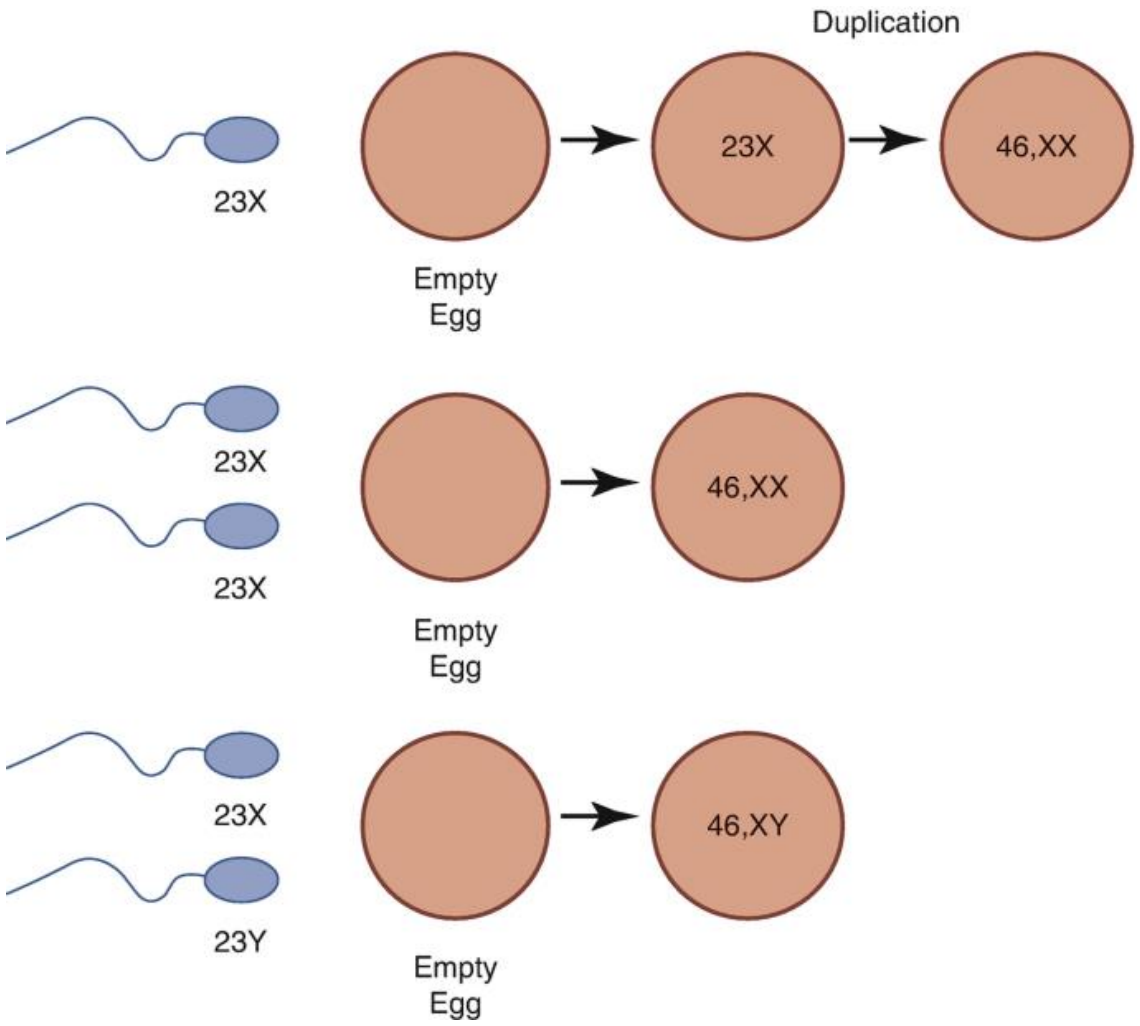
- Occasionally molar pregnancies represent tetraploid or mosaic conceptions.

- there is usually evidence of a fetus or fetal red blood cells.

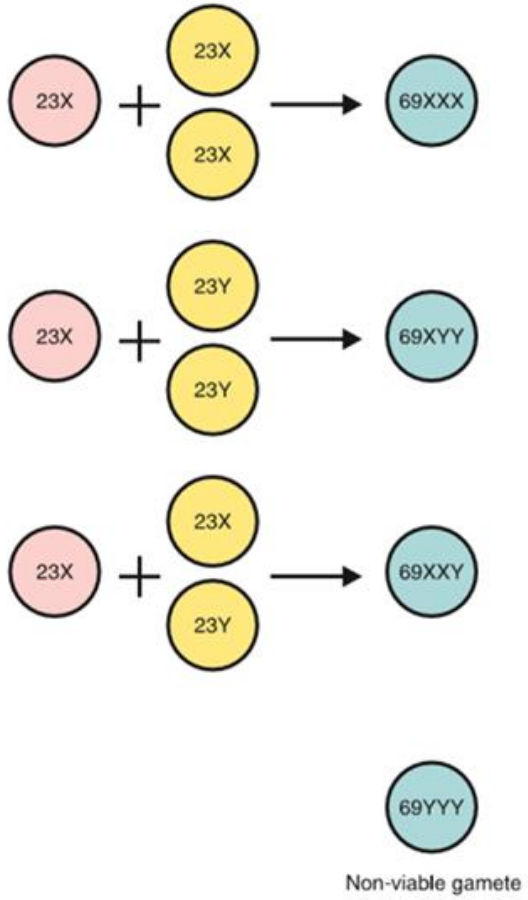
- Not all triploid or tetraploid pregnancies are partial moles.

- For the diagnosis of a partial mole, there must be histopathological evidence of trophoblast hyperplasia.

Complete mole ..



Partial mole..



Incidence

There is evidence of ethnic variation in the incidence of GTD in the UK, with women from Asia having a higher incidence compared with non-Asian women (1 in 387 versus 1 in 752 live births, respectively).

incidence of GTD is associated with age at conception, being higher in the extremes of age (women aged less than 15 years, 1 in 500 pregnancies; women aged more than 50 years, 1 in 8 pregnancies).

GTN may develop after a molar pregnancy, a non-molar pregnancy or a live birth.

The incidence after a live birth is estimated at 1 in 50 000.

- Previous molar pregnancy (risk of recurrence after one or two moles is 2% and 20% respectively; recurrence risk is not altered if there is a change in male partner).

- Familial/sporadic clusters of biparental complete hydatidiform mole (autosomal recessive); associated with chromosome
- 19q: *NLRP7* mutation

presentation

- The most common presentation is irregular vaginal bleeding, a positive pregnancy test and supporting ultrasonographic evidence.
- Less common presentations of molar pregnancies include hyperemesis, excessive uterine enlargement, hyperthyroidism, early-onset pre-eclampsia and abdominal distension due to theca lutein cysts.
- Very rarely women can present with haemoptysis or seizures due to metastatic disease affecting the lungs or brain.

- mean age at diagnosis is 9 weeks of gestation
- The majority of histologically proven molar pregnancies are associated with an ultrasound diagnosis of delayed miscarriage or anembryonic pregnancy

Physical examination

- Enlarged uterus Bilateral ovarian cysts.
- Vaginal metastases in about 30 percent of cases; these lesions are very vascular and prone to bleeding; they may also become infected

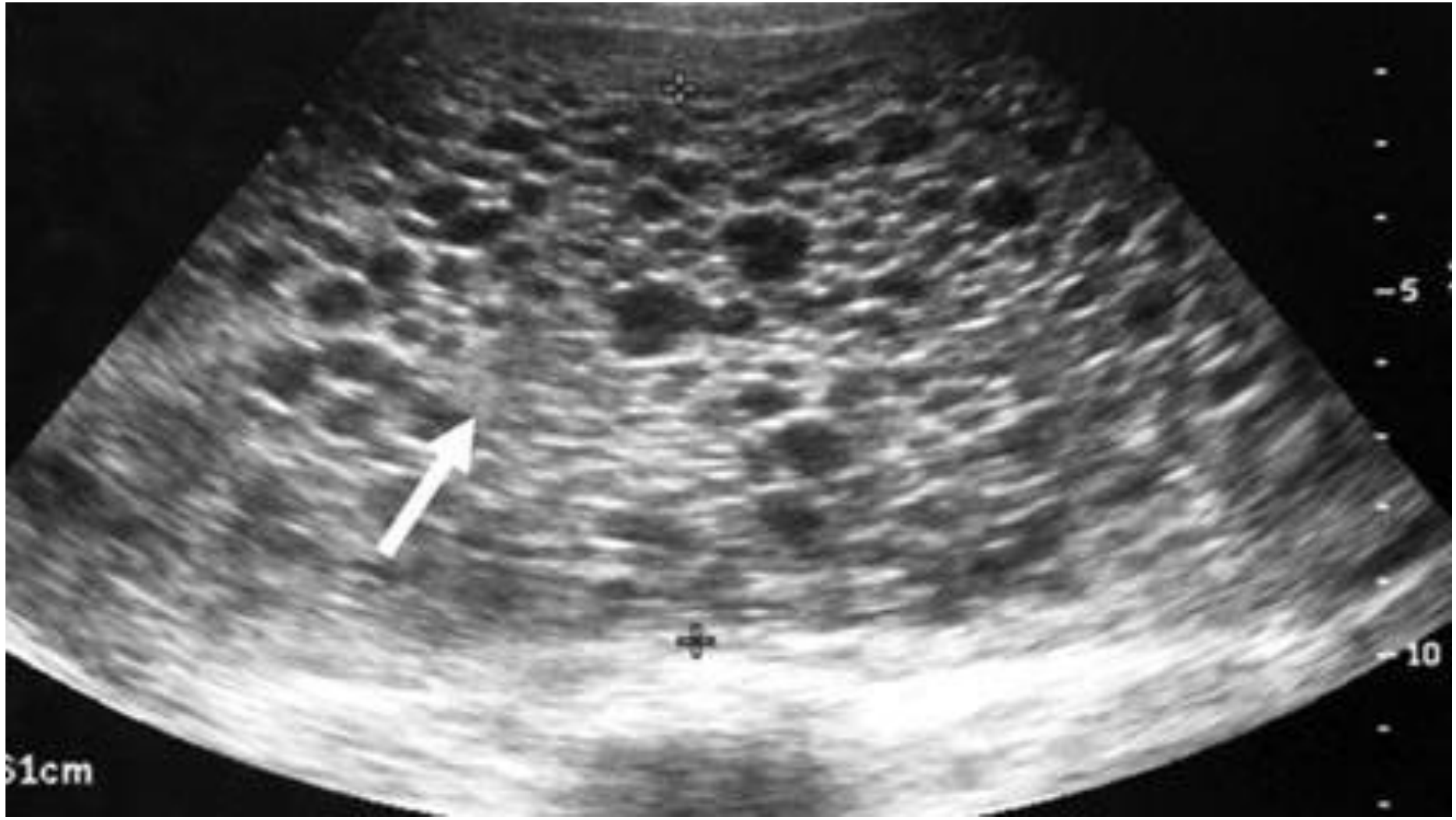
Ultrasound features

- complete molar pregnancy:
  - 5-7 weeks of gestation : central heterogenous polypoid mass
  - after after 8 weeks : thickened cystic appearance of the villous tissue

“ snow storm appearance “

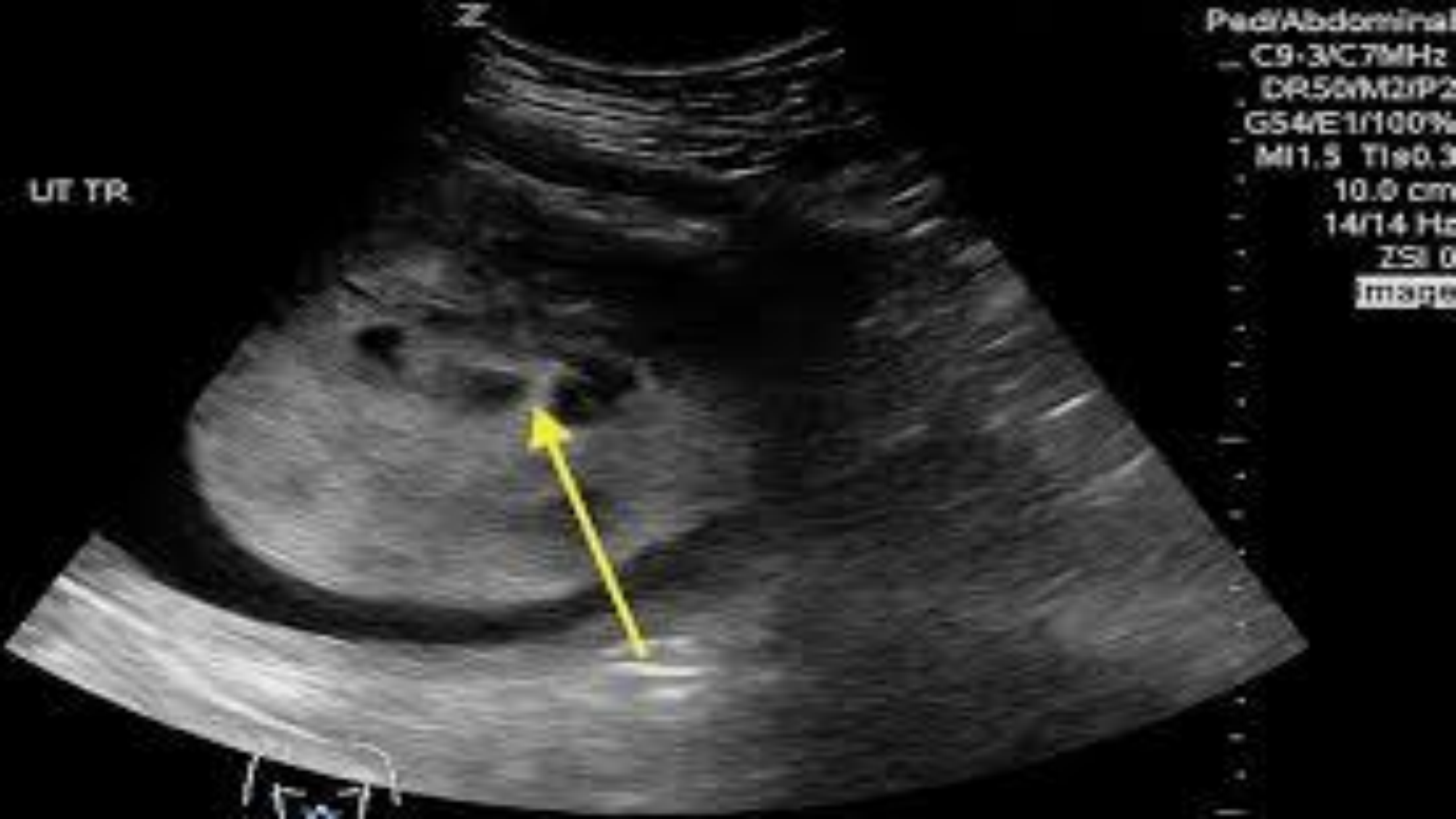
- no identifiable gestational sac.

- Theca lutein cysts


-5
-10
61cm

partial molar pregnancies

- ✓an enlarged placenta or cystic changes within the decidual reaction in association with either an empty sac or a delayed miscarriage
- ✓If more advanced GA : fetus is present, may be viable, and is often Agrowth restricted
- ✓cystic spaces in the placenta
- ✓ratio of transverse to anteroposterior dimension of the gestational sac greater than 1:1.5


UT TR
Ped/Abdominal
C9-3/C7MHz
10.0 cm

- hCG levels were significantly higher for both complete and partial molar pregnancies

- Usually, hCG levels greater than 100,000 mIU/mL

hCG levels during pregnancy (in weeks sincelast menstrual period)	
3 weeks LMP	5 - 50 mIU/ml
4 weeks LMP	5 - 426 mIU/ml
5 weeks LMP	18 - 7,340 mIU/ml
6 weeks LMP	1,080 - 56,500 mIU/ml
7 - 8 weeks LMP	7, 650 - 229,000 mIU/ml
9 - 12 weeks LMP	25,700 - 288,000 mIU/ml
13 - 16 weeks LMP	13,300 - 254,000 mIU/ml
17 - 24 weeks LMP	4,060 - 165,400 mIU/ml
25 - 40 weeks LMP	3,640 - 117,000 mIU/ml
non pregnant	55-200 ng/ml

Definitive diagnosis is by histopathology

complete molar pregnancies :

absence of fetal tissue;

extensive hydropic change to the villi; and

excess trophoblast proliferation

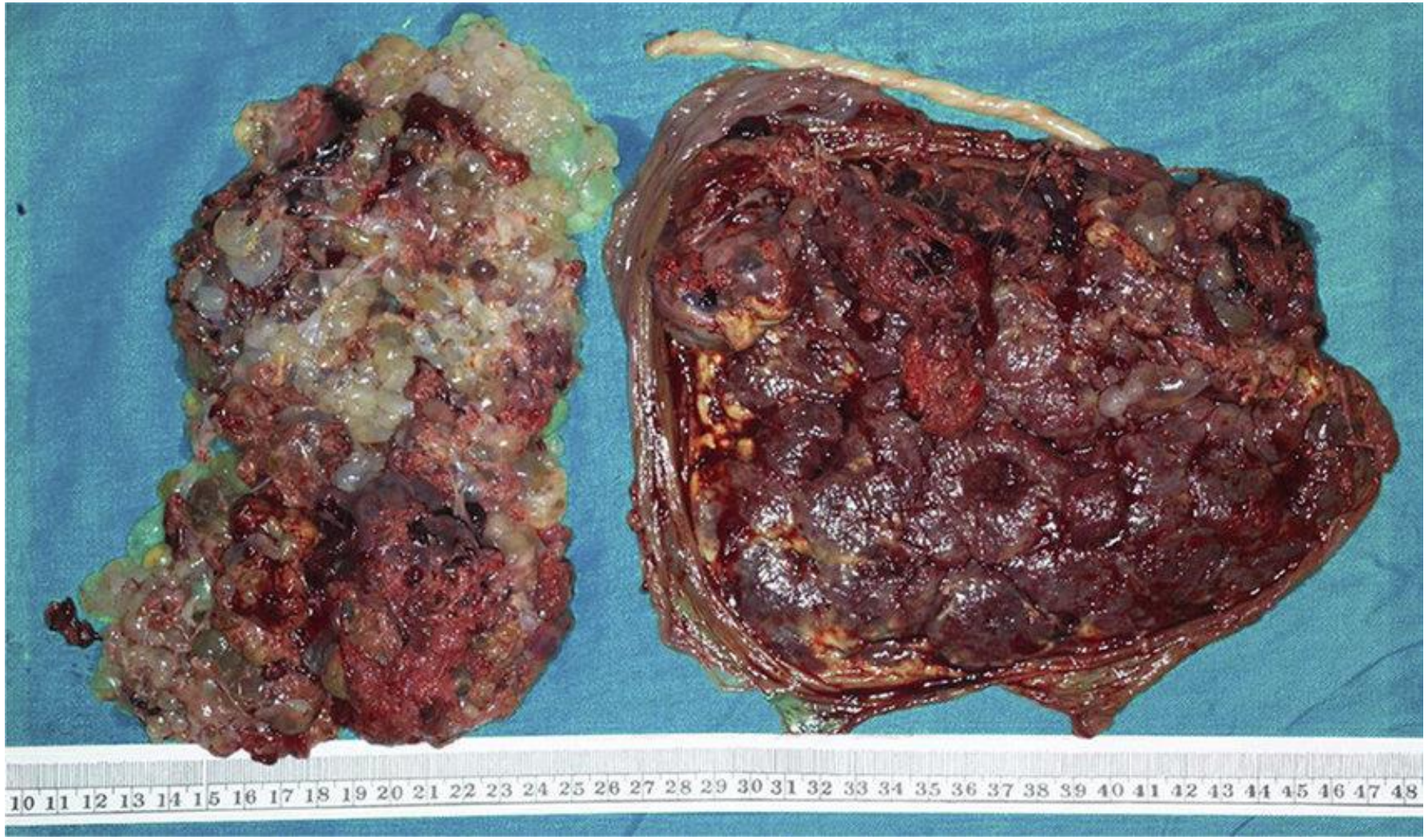
partial molar pregnancy :

presence of fetal tissue;

focal hydropic change to the villi; and

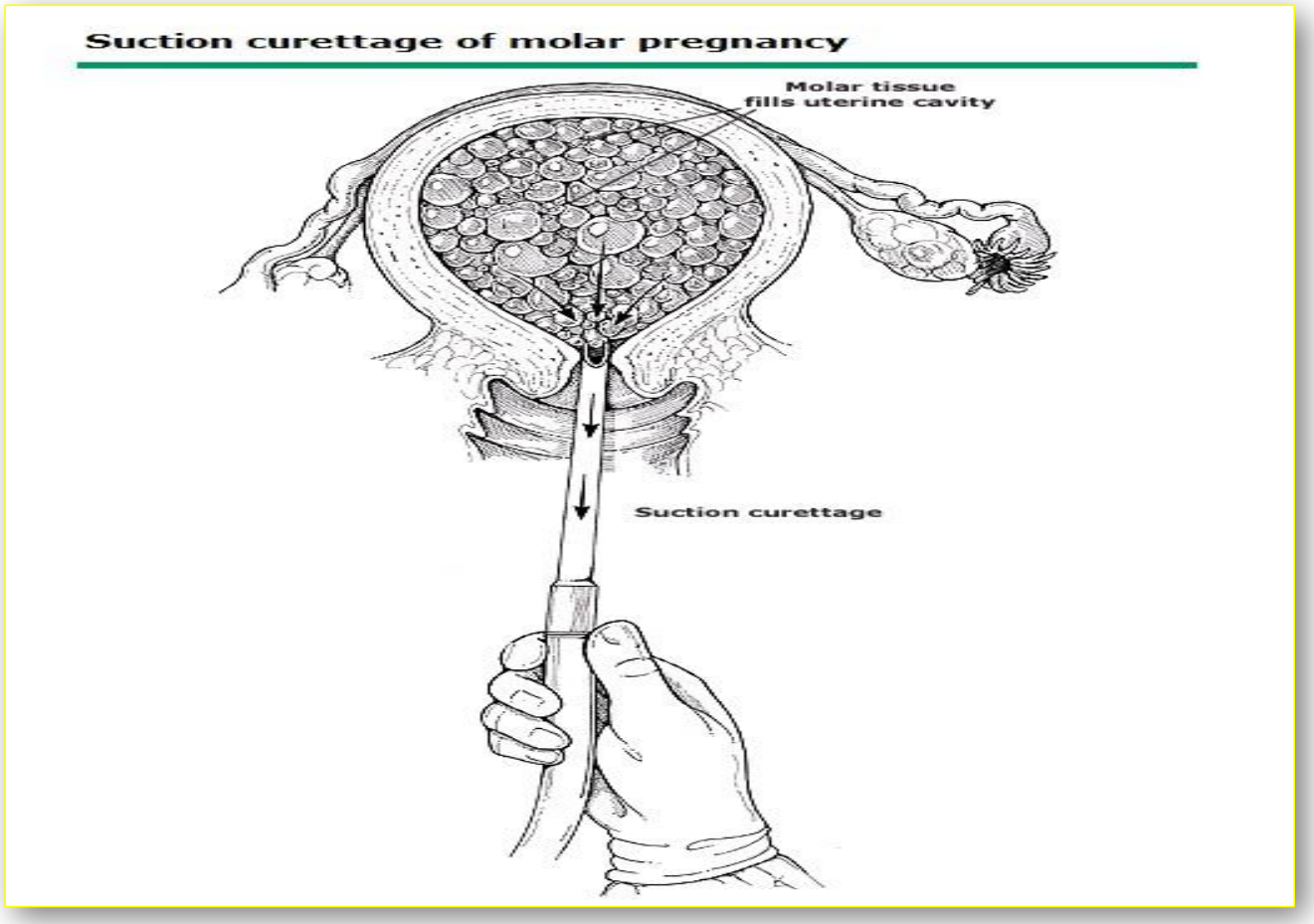
some excess trophoblast proliferation.

Ploidy status and immunohistochemistry staining for *p57*, a paternally imprinted gene, may help in distinguishing partial from complete molar pregnancies


10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48

Treatment

- Complete molar pregnancies: suction curettage is the method of choice
- Medical termination of a complete molar pregnancy should be avoided if possible, irrespective of the agents used due to the increased risk of developing GTN and requiring chemotherapy
- In addition, there is theoretical concern, supported by clinical experience, over the routine use of potent oxytocic agents because of the potential to embolise and disseminate trophoblastic tissue through the venous system leading to adult respiratory distress syndrome, similar in presentation to amniotic fluid embolism.


Suction curettage of molar pregnancy
Molar tissue
fills uterine cavity
Suction curettage

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

- Anti-D prophylaxis is recommended following removal of a molar pregnancy.

- All material obtained from the medical or surgical management of miscarriage be sent to pathology

- If no tissue has been sent to pathology, a pregnancy test should be carried out 3 weeks after the miscarriage.

- If still positive, serum levels should be tracked to ensure that the level is falling and, if not, an ultrasound is arranged to look for further pregnancy tissue. All tissue obtained in this situation should be sent to pathology

follow-up following a diagnosis of complete mole

- Patients are monitored with weekly hCG levels until three consecutive normal values are obtained

- Once HCG is normalised:
  - If ≤56 days after evacuation, measure monthly for 6 month from the date of evacuation.
  - If >56 days after evacuation, measure monthly for 6/12 from the date hCG became normalised

- Follow-up for partial molar pregnancy is concluded once the hCG has returned to normal on two samples, at least 4 weeks apart.

Diagnosis of persistence disease

1.A plateau in the serum hCG concentration for at least four values over three weeks(days 1,7,14, and 21)

2. A serum hCG concentration that rises (by 10 percent or greater) for three values or more over at least two consecutive weeks(days 1,7, 14)

3. Persistence of detectable serum hCG for more than six months after molar evacuation

4. Histologic confirmation of choriocarcinoma

- GTN can develop after miscarriage, therapeutic abortion and term pregnancy.
  - Rates of persistent disease are 15-20 % after a complete, and 3-5 % after a partial mole.
- Choriocarcinoma is estimated to occur after approximately 1 in 50 000 pregnancies
- It is uncommon (less than 1%) for GTN to develop in women who have had a normal hCG urine or serum level within 8 weeks of removal of a molar

- vaginal bleeding is the most common presenting symptom of GTN diagnosed after miscarriage, therapeutic abortion or postpartum

- The prognosis for a woman with GTN after a non-molar pregnancy may be worse owing to delay in diagnosis or advanced disease, such as liver or central nervous system disease, at presentation

Indications for chemotherapy for GTD

- Plateaued or rising hCG concentration after evacuation (most common indication for chemotherapy)
- Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage
- Histological diagnosis of choriocarcinoma
- Evidence of metastases in the brain, liver, gastrointestinal tract or lung (radiological opacities >2 cm on chest radiograph)
- Serum hCG concentration of 20 000 IU/l or more, 4 weeks or more after evacuation
- Raised hCG concentration 6 months after evacuation, even when still decreasing.

Treatment

- Women with GTN may be treated with single-agent or multi-agent chemotherapy.

Treatment used is based on the International Federation of Gynecology and Obstetrics (FIGO) 2000 scoring system for GTN following assessment at the treatment centre.

FIGO prognostic scoring system

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

FIGO anatomical staging for GTN	
Stage I	GTN confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures (adnexae, vagina, broad ligament)
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	GTN extends to all other metastatic sites including liver, kidney, spleen and brain

- Women with scores of 6 or less are at low risk and are treated with single-agent intramuscular methotrexate, alternating daily with folinic acid for 1 week followed by 6 rest day

- with scores of 7 or greater are at high risk and are treated with intravenous multi-agent chemotherapy, which includes combinations of methotrexate, dactinomycin, etoposide, cyclophosphamide and vincristine(EMA-CO)

- Treatment is continued, in all cases, until remessioon (three consecuative normal hCG level) and then for a further 6 consecutive weeks.

- After remission is achieved, serum beta-hCG should be measured monthly until monitoring has shown one year of normal hCG levels.

- Women suspected of choriocarcinoma require more extensive investigation in the specialist centre, including computed tomography of the chest and abdomen, or magnetic resonance imaging of the head and pelvis, all with contrast in addition to the serum hCG and a Doppler ultrasound of the pelvis.

- Any woman with a score of 13 or greater is recognised to have a higher risk of early death (within 4 weeks), often due to bleeding into organs, or late death due to multihyphenate drug-resistant disease.

- Women are 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, as a precautionary measure.

long-term outcome of women treated for GTN?

- The outlook for women treated for GTN is generally excellent with an overall cure rate close to 100%.
- Further pregnancies are achieved in approximately 80% of women following treatment for GTN with either methotrexate alone or multi-agent chemotherapy.
- There is an increased risk of premature menopause for women treated with combination agent chemotherapy.

Choriocarcinoma

- Pathology:
- The macroscopic appearance is a soft, purple, largely haemorrhagic mass.
- Tumour metastases to distant sites occurs by vascular spread; common sites include the lungs, brain, liver, pelvis and vagina, kidney, intestines and spleen.

choriocarcinoma

- Epidemiology:
- Highly malignant, can arise following any type of pregnancy event.
- May complicate 1/ 50 000 pregnancies & 1/ 40 (3%) of HM
- The most aggressive GTN.

Pathology

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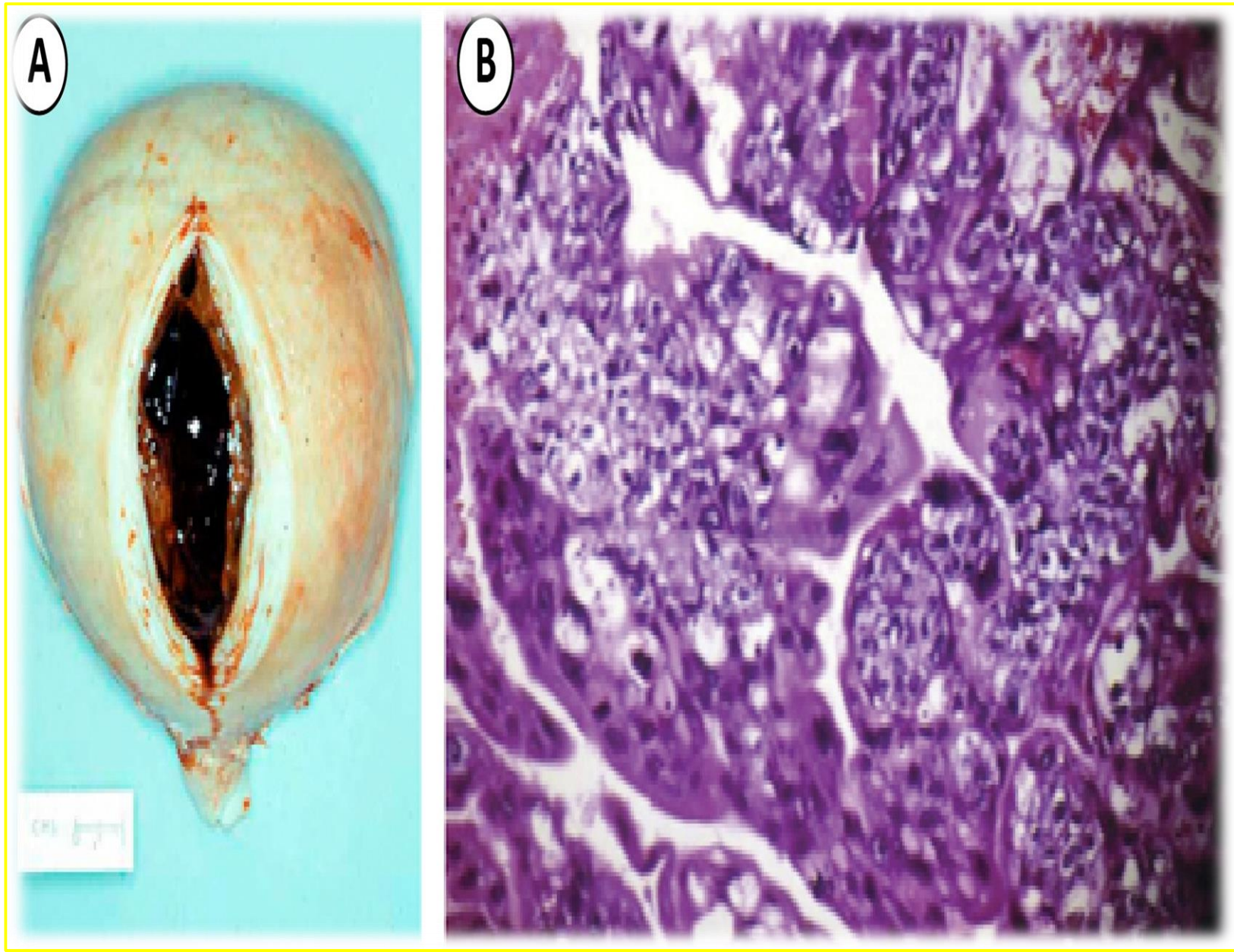
A
B

Clinical presentation

- vaginal bleeding, abdominal pain, a pelvic mass & symptoms due to a high serum hCG.
- 1/3 of women present without gynaecological features but with features of metastases.
- PPH
- AUB may develop a year or more after an antecedent pregnancy
- Severe Hemorrhage if tumor erodes through myometrium or uterine vessels.

How should a placental site trophoblastic tumour or epithelioid trophoblastic tumour be managed?

- PSTTs and ETTs are rare forms of GTD diagnosed by histological examination of retained pregnancy tissue.
- Their presentation and behaviour are different and less predictable.
- Hysterectomy is curative in many cases with localised disease.
- In women with a long time period since the antecedent pregnancy and/or with distant and/or extensive metastatic disease, intensive chemotherapy plays a major role

- PSTT and ETT are the rarest forms of GTN comprising about 0.2% of all GTD. They tend to produce less hCG, are confined to the uterus for longer, more often involve lymphatics and are more chemoresistant than other forms of GTN. For these reasons, they are not managed according to their FIGO score

- Compared to choriocarcinoma, PSTT is associated with less vascular invasion and necrosis and greater tendency for lymphatic spread.

- PSTT are relatively insensitive to chemotherapy and hysterectomy and pelvic lymphadenectomy remains the mainstay of treatment if there is residual disease confined to the uterus.

- Since hCG is not a reliable marker in these patients, long-term (>5 years) clinical follow-up is recommended.