

# GESTATIONAL TROPHOBLAST DISEASE

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# DEFINITION

- Partial and Complete Mole are precancers
- **Gestational Trophoblast Neoplasia** is defined as persistent HCG levels requiring excisional surgery or chemotherapy = cancer
- Heterogenous group of inter-related conditions representing an aberrant fertilisation event  
Origin from placental tissue  
Paternal genetic origin

# GTD = GTN

- GTD has gone from one of the most fatal cancers in young women to one of the most curable due to advances in chemotherapy, ultrasound and HCG assays
- Rare tumours which are usually curable even if metastatic



# HISTOLOGICAL TYPES

- Premalignant: Hydatidiform Mole
  - 1. Complete Mole = 12% risk GTD
  - 2. Partial Mole = 0.5% risk GTD
- Malignant (persistent GTN):
  - 1. Invasive mole
  - 2. Choriocarcinoma
  - 3. Placental Site Trophoblast Tumours
    - Very rare

# RISK FACTORS FOR GTD

- **Age:** Extremes of maternal age
  - 2x risk >35
  - 5x risk >40
  - ?increased risk in adolescents
- **Asian ethnicity**
  - Indonesia 10/1000
  - Taiwan 8.3/1000
  - Philippines 5.2/1000
  - Mexico 4.6/1000
- **Previous GTD**
- ??ART / insemination
- ??Blood group
- ?? environmental or dietary (Vitamin A) deficiency of carotene
- Protective: previous term live births

# EPIDEMIOLOGY

- In Australia 1 in 1200 pregnancies are molar pregnancies
- Persistent disease requiring treatment 12%
  - 8% non-metastatic
  - 4% metastatic
- Choriocarcinoma 1 in 20 000 pregnancies



# PARTIAL MOLES

- Triploid origin, thus karyotyping allows correct diagnosis: 69XXX, 69XXY, 69XYY
  - 2 sets of paternal chromosomes
  - 1 set of maternal chromosome
    - NB. triploidy occurs in 1-3% of conceptions and 20% of spont Ab with abn karyotype, but only P.M. if 2 paternal sets of chromosomes
- Results from fertilisation of 1 ovum with 2 sperm
- Associated fetal tissue

# PARTIAL MOLES

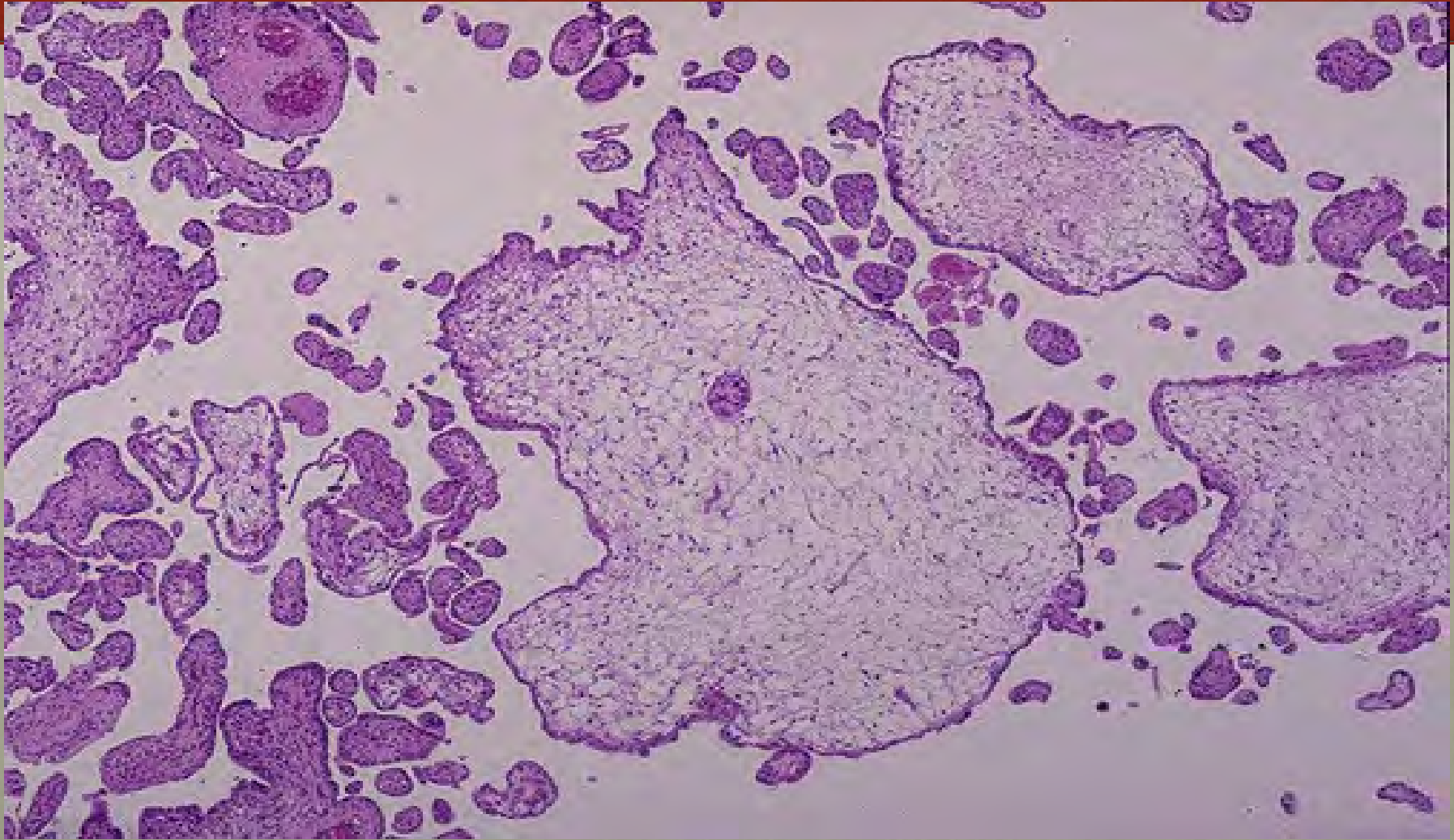
- 4% persistent disease quoted, but <0.5%
- In some Australian states, centralised process to allow confirmation of the diagnosis and all tissue is reviewed by one pathologist, and karyotyping is routinely performed
- Choriocarcinoma has been described after a partial mole
- HCG should be normal **within 8 weeks** of curette



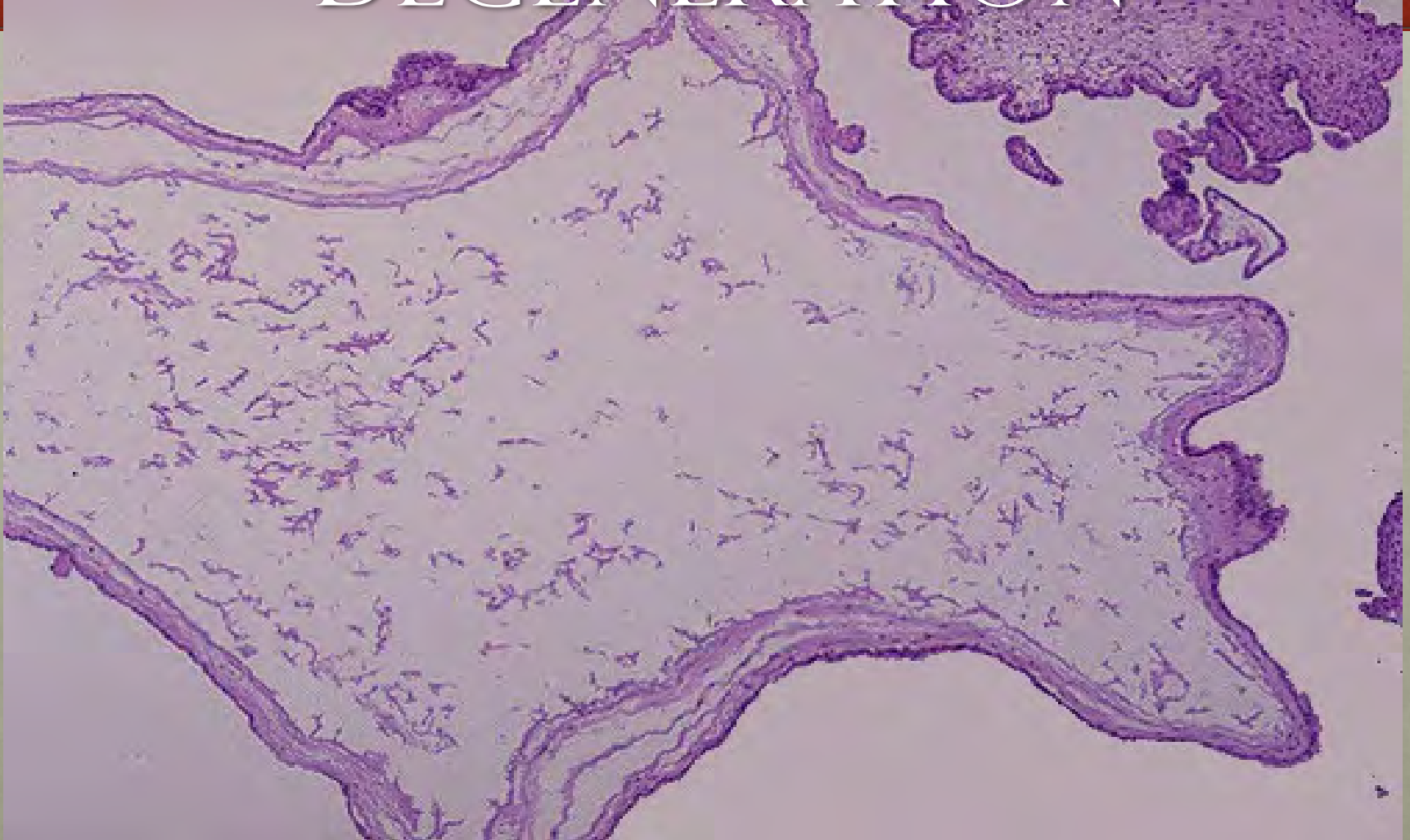
# PARTIAL MOLES

- Clinical Presentation:
  - Early pregnancy bleeding
  - Ultrasound features
  - Histopath on POC
  - Miscarriage or Missed AB
  - Uterus small for dates

# PARTIAL MOLE



# CFVS HYDROPIC DEGENERATION





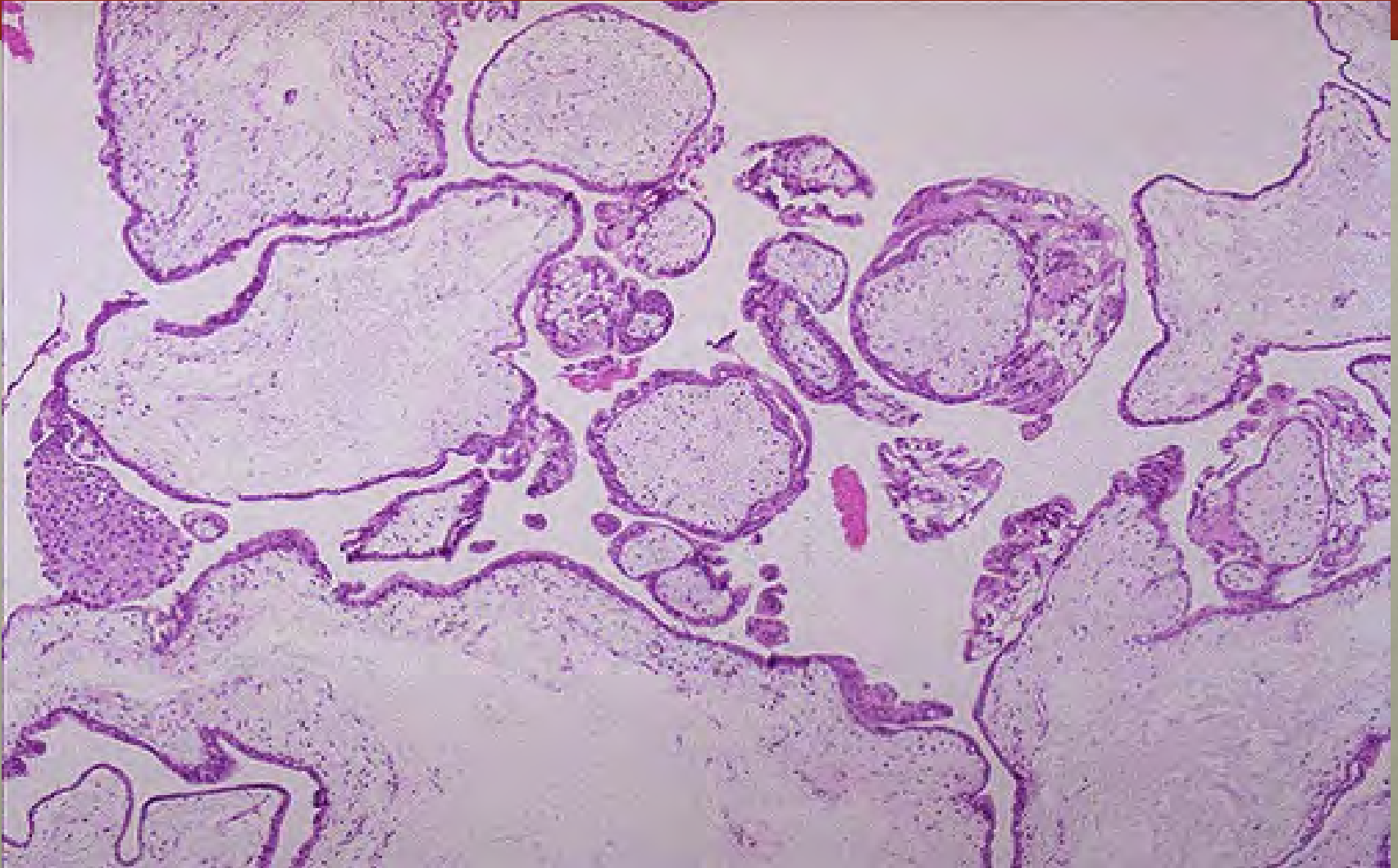
# COMPLETE MOLES

- Diploid
- All **paternally** derived chromosomal material 46XX or 46XY(10%) (androgenetic)
- May be caused by loss of normal genomic imprinting expressed from 1 parent only eg. H19, KIP-2 (tumour suppressors) from mo or IGF2 (growth factor) from father
- Usually derived from fertilisation of an empty ovum by 1 or 2 sperm
- No foetal tissue, unless in twin pregnancy -  
1 in 20 000 to 100 000 pregnancies
- 12% risk of subsequent persistent disease

# COMPLETE MOLES

- Clinical Presentation:
  - Threatened miscarriage: “prune juice” or grape-like vesicles, often anaemic due to XS bleeding
  - Ultrasound features –old “snowstorm”
  - POC histopathology
  - Uterus > dates in 50%
  - Hyperthyroidism -7%
  - Hyperemesis – 25%
  - Pre-eclampsia < 20/40 - 27% of those with excessive uterine size and high HCG
  - Respiratory distress due to pulm mets, anaemia, emboli

# COMPLETE MOLE





# COMPLETE MOLE



# COMPLETE VS PARTIAL MOLES

	<u>Complete</u>	<u>Partial</u>
<b>Karyotype</b>	46 XX, 46XY	Triploid xxx, xxy, xyy
<b>Foetal Tissue</b>	Absent occas foetal RBC and embr elements	Present
<b>Villi</b>	Round, Swollen, All villi involved	Scalloped, Less swollen, Focal changes
<b>Trophoblast Proliferation</b>	Circumferential	Focal, minimal
<b>Trophoblast Atypia</b>	Often present	None

# MANAGEMENT OF MOLAR PREGNANCY

- If diagnosis made prior to curettage:
  - 1. Gp and hold (X-M if  $>12/40$  size uterus)
  - 2. FBE, U&E, LFTs, TFTs
  - 3. Suction curettage
    - 10-12 size suction curette, no place for sharp curette
    - Initially place just within internal os
    - Syntocinon bolus 10U after starting procedure
    - Syntocinon infusion 40U over 12 hours
    - Anti-D required for both complete and partial
      - although CM does not normally have any foetal red cells



# MANAGEMENT OF MOLAR PREGNANCY

- If diagnosis made after curettage:
  1. Register with Mole Registry at RWH
  2. C X-Ray mets to lungs may regress after suction
  3. Vaginal Examination
    - to exclude metastatic disease
  4. Follow up:
    - Quantitative HCG measured weekly until normal then monthly for 9-12/12
    - No benefit in rpt D&C, particularly as risk of perforation is high and risk of chemo after 2 curettes is 18% and after 4 curettes is 81%, so only if major h# to empty uterus

# FOLLOW UP OF MOLAR PREGNANCY

- If follow up of complete moles is performed by the EPAU at TCH
  - Serial HCG measured weekly until normal x 3, then monthly for 12 months
  - Bloods assays preferred, but urine assays acceptable, (but beware “phantom HCG”, usually due to HAMA antibodies, and may be distinguished by absence in urine)
  - Sensitive RIA necessary
  - HCG usually normal by 12/52

# FOLLOW-UP

- Avoid pregnancy for 9-12/12, depending on speed of return of HCG to normal. If normal within 8 weeks no chemo has been required.
- Adequate contraception
  - Condoms initially
  - OCP once HCG normal – (some evidence that OCP may increase risk of persistent trophoblast if used prior to HCG being normal)



# FOLLOW-UP

## Subsequent Pregnancy:

- 1. Early US to exclude 1% risk of recurrence
- 2. Placenta for histology
- 3. HCG 6/52 post partum to exclude persistent trophoblast

# GTN = GTD

- =Persistent Trophoblast Disease:
- =Malignant:
- 1. Invasive mole = chorioadenoma destruens
  - locally invasive, rarely metastatic
- 2. Choriocarcinoma
  - always malignant, high metastatic potential
- 3. Placental Site Trophoblast Tumour

# GTN = GTD

- Persistent Trophoblast Disease:
- Diagnosis is usually made on persistently elevated HCG without tissue diagnosis
- HCG  $t_{1/2}$  is 24-36 hours
- Gold standard RIA using polyclonal AB recognising all forms of HCG sensitive to 1 IU/L in serum and 20 IU/l in urine not prone to false positives but time consuming, serial dilutions required and only as good as Ab used
- 5 IU/l = 10 000-100 000 viable tumour cells



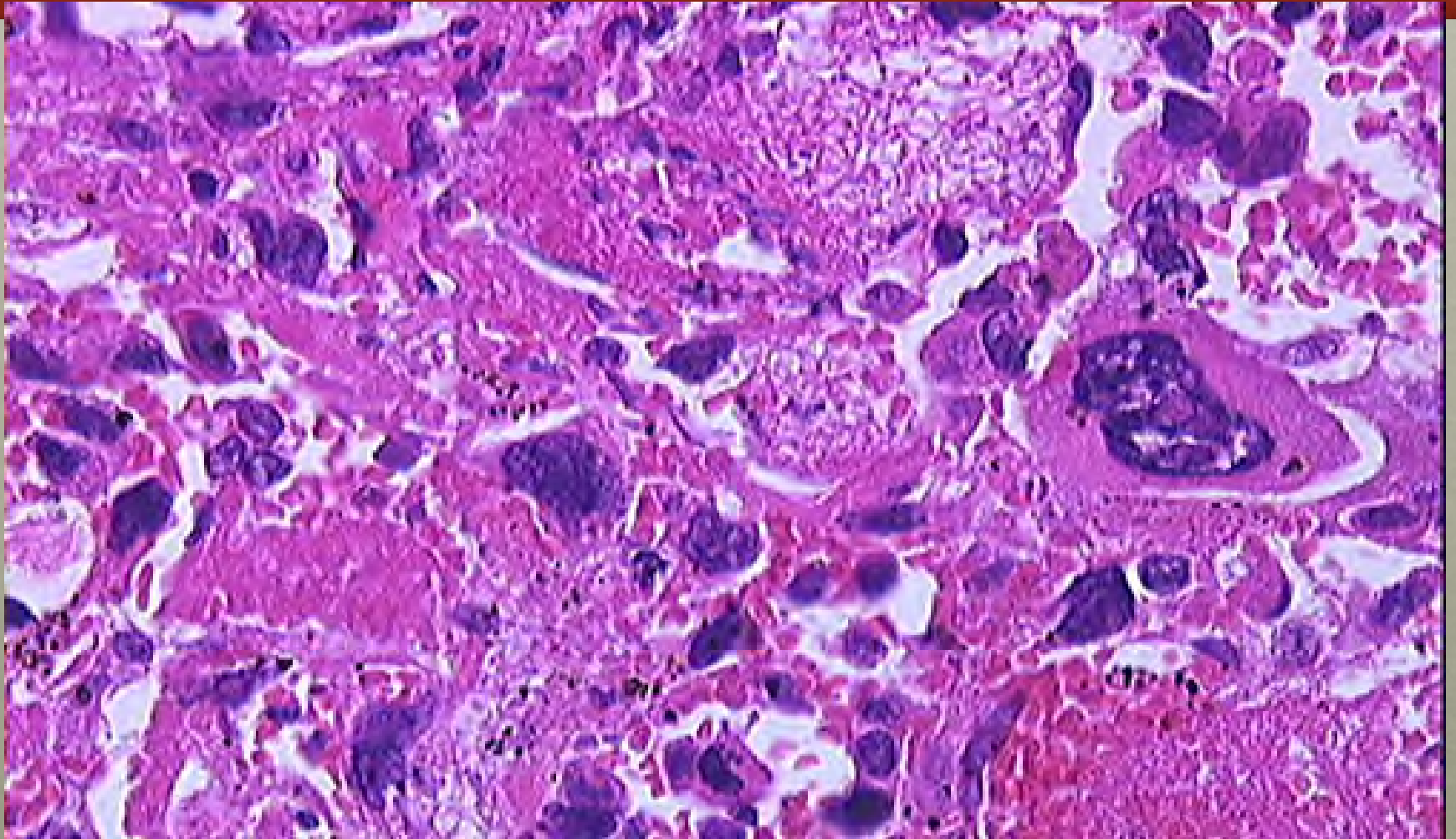
# INVASIVE MOLE

- Defined by persistent HCG
- Locally invasive
- Rarely metastatic
- Villi still identified
- Invasion of myometrium by trophoblast
- Hyperplasia of trophoblast
  - Cytotrophoblast
  - Syncytiotrophoblast

# CHORIOCARCINOMA

- Malignant tumour of trophoblastic epithelium
  - Cytotrophoblast
  - Syncytiotrophoblast
- No villi
- Characterised by haemorrhage and necrosis
- Extremely vascular so avoid biopsy
- Early metastatic potential
  - Lungs – 80% cannonball, miliary, pleural effusions ddx P-E
  - Vagina – 30%
  - Pelvis – 20%
  - Brain – 10%
  - Liver – 10%
  - Spleen, Intestines, Kidney

# CHORIOCARCINOMA





# CHORIOCARCINOMA

- Origin from any gestation, not necessarily the immediate preceding one, up to 17 years post pregnancy
  - Hydatidiform mole 45%
  - Term pregnancy 25%
  - Spontaneous Ab 25%
  - Ectopic 5%
- Karyotype is variable

# CHORIOCARCINOMA

- **Presentation:**
  - Follow up of complete mole
  - Abdo pain
  - Pelvic mass
  - Vaginal bleeding
  - Metastatic disease in 1/3 with lungs, brain, liver most common
  - Neonatal – 26 cases documented

# PLACENTAL SITE TROPHOBLAST TUMOUR

- Extremely rare
- Derived from Intermediate trophoblast invading myometrium
- Slow growing, late metastasising
- Minimal HCG production so levels relatively low with >50% <500
- HPL – human placental lactogen stains +ve



# PLACENTAL SITE TROPHOBLAST TUMOUR

- HPL – human placental lactogen stains +ve
- Differentiate from placental nodule via increased ki67 levels
- hPL can cause increased prolactin
- Present with
  - Amenorrhoea
  - Galactorrhoea
  - Rarely nephrotic syndrome  
haematuria  
DIC

# PLACENTAL SITE TROPHOBLAST TUMOUR

- Origin – 95% post term pregnancy
- Karyotype variable

- Unpredictable behaviour
  - 90% benign
  - 10% metastatic
- Resistant to chemotherapy

- Indication for hysterectomy

# ASSESSMENT OF PERSISTENT TROPHOBLAST DISEASE

- **Diagnosis:**

Usually made on rising levels of HCG in absence of viable pregnancy often during follow up of molar pregnancy. Histology not required for diagnosis.

**FIGO Definition:**

1. Rising HCG  $>10\%$  over 2 weeks, 3 titres
2. Plateau of HCG over 3 weeks, 4 titres
3. Increase in HCG 6/12 after evacuation of mole
4. Histology of choriocarcinoma
5. Metastatic Disease

All GTN requires chemotherapy



# ASSESSMENT OF PERSISTENT TROPHOBLAST DISEASE

- History
- Examination including PV to exclude mets
- Investigations including:
  - FBE, U&E&C, LFTs, TFTs, Quant HCG
  - CxR or CT chest
  - If +ve for chest metastases, then CT brain, chest, abdo, pelvis
  - If metastatic disease and CT brain normal, LP for CSF HCG - ratio 60 (serum)>1 (CSF)

# FIGO CLASSIFICATION 2000

- Stage 1: Disease confined to the uterus
  - Stage 2: Disease confined to Genital Tract
  - Stage 3: Lung metastases
  - Stage 4: All other metastatic sites
- 
- Previously subclassified according to other risk factors, these have now been discarded



# FIGO SCORING

## USED TO DECIDE INITIAL CHEMO REGIMEN

	<u>0</u>	<u>1</u>	<u>2</u>	<u>4</u>
Age	<40	40+		
Preceding Preg	Hydat	Ab	Term	
Interval -months	<4	4-6	7-12	>12
Pretx HCG	<1000	<10 000	<100 000	>100 000
Largest tumour	3-4cm	5cm		
Site of mets		Spleen, kid	GIT	Brain, liver
No of mets	0	1-3	4-8	>8
Previous chemo			Single	2 or more



# FIGO 2000

- Low risk: 6 or less
- High risk: 7 or more
- Anatomic staging
- +
- Risk factor scoring system of WHO
  - Modified from Bagshawe: excludes ABO and promotes liver mets to score of 4
- Placental site tumours not included

# PERSISTENT GTD

- Risk of persistent GTD after molar pregnancy 40-50% if:
  - HCG >100 000 at diagnosis
  - Ovarian thecomas >6cm
  - Pre-eclampsia
  - Hyperthyroidism
  - Tumour embolisation
- If VE and Chest X-ray normal, very low risk of metastases elsewhere

# TREATMENT OF LOW RISK GTD

- Single agent chemo using MTX or Actinomycin-D
- Usual regime:
  - Methotrexate 1mg/kg alt days
  - Folinic acid rescue 30 hours after each dose of MTX
  - Repeat cycles every 14 days until HCG normal  $<1$  for 2-3 cycles
  - Monitor FBE, LFTs
  - Side Effects: minimal
    - Mouth ulcers
    - Alopecia rare
    - Liver dysfunction
    - Haematological rare
    - Pleuritic chest pain



# TREATMENT OF HIGH RISK GTD

- EMACO
- 14 day cycle
- Part A Day 1
  - Etoposide 100mg/sq m IV
  - MTX 100mg/sq m stat then 200mg/sq m over 12/24
  - Actinomycin D 0.5mg/sq m IV
- Part A Day 2
  - Actinomycin D 0.5mg/sq m IV
  - Etoposide 100mg/sq m
  - Folinic acid 15mg 6/24 x 8 starting 24/24 post MTX
- Part B Day 8
  - Vincristine (Oncovin) 1mg/sq m IV
  - Cyclophosphamide 600mg/sq m IV
  - +/- Intrathecal MTX if high risk

# TREATMENT OF ULTRA-HIGH RISK GTD

- EMAPE
- Part A: Day 1: EMA as before
- Part B: Day 8: Cisplatin 80mg/sq m  
Etoposide 100mg/sq m
- Other active agents include Taxol

# TREATMENT FOR HIGH RISK GTD

- Treatment continues for 3 cycles beyond normal HCG
- Side effects
  - Alopecia
  - Haematological
  - Nausea, vomiting, mucositis
  - Infertility
  - Neuropathy via vincristine
- Pregnancy avoided for 12 months
- HCG monitored weekly for 4 weeks then monthly for the remainder of the year
- If high risk metastatic disease, then monitor for 2 years
- 70% require G-CSF support



# PREGNANCY AFTER GTD

- Fertility after chemotherapy
  - 68% live births after complete mole
  - 74% live births after partial mole
  - 68% live births after persistent GTD
- Risk of subsequent molar pregnancy
  - 1% after 1 mole
  - 15-30% after 2 molar pregnancies
  - Increased risk of GTD after repeat mole 3x
- Infertility rate no different to general population – 4%

# PROGNOSIS AFTER GTD

- 5 year survival 86%
- If liver mets 30% 5 year survival (see scoring)
- If brain mets 70% 5 year survival, but if survive initial presentation, then survival 85%
- Long term 2<sup>nd</sup> tumours
  - AML (etoposide) 16x risk
  - Ca colon 4.6x risk
  - Melanoma 3.4x risk
  - Breast ca 5.8x risk
- No change in fertility under 35years
- Increased risk premature menopause >35, generally menopause occurs 3 years earlier after EMACO

# CASE 1

- 45 year old requiring chemo post evacuation of mole with HCG 900, disease confined to uterus
- Stage:
- Prognostic score:
- Treat with



# CASE 1

- 45 year old requiring chemo post evacuation of mole with HCG 900, disease confined to uterus
- Stage: 1
- Prognostic score: 1 =low risk
- Treat with MTX

# CASE 2

- 40 year old 15 months post term delivery with 4 lung mets, largest 4cm, 1 brain met and 1 kidney met, with HCG 42 000
- Stage:
- Score:
- Treat with

# CASE 2

- 40 year old 15 months post term delivery with 4 lung mets, largest 4cm, 1 brain met and 1 kidney met, with HCG 42 000
- Stage: 4
- Score: 15 =high risk
- Treat with EMACO



# CASE 3

- 44 year old post miscarriage, with a 9cm uterine mass, a 5cm vaginal nodule, with an HCG of 18 000, having failed MTX monotherapy
- Stage:
- Score:
- Treat with

# CASE 3

- 44 year old post miscarriage, with a 9cm uterine mass, a 5cm vaginal nodule, with an HCG of 18 000, having failed MTX monotherapy
- Stage: 2
- Score: 10 =high risk
- Treat with EMACO

# CASE 4

- 38 year old with HCG 40 000 4 months post evacuation of molar pregnancy with 2 lung lesions largest 4cm but no other mets
- Stage:
- Score:
- Treat with



# CASE 4

- 38 year old with HCG 40 000 4 months post evacuation of molar pregnancy with 2 lung lesions largest 4cm but no other mets
- Stage: 3
- Score: 4 =low risk
- Treat with MTX