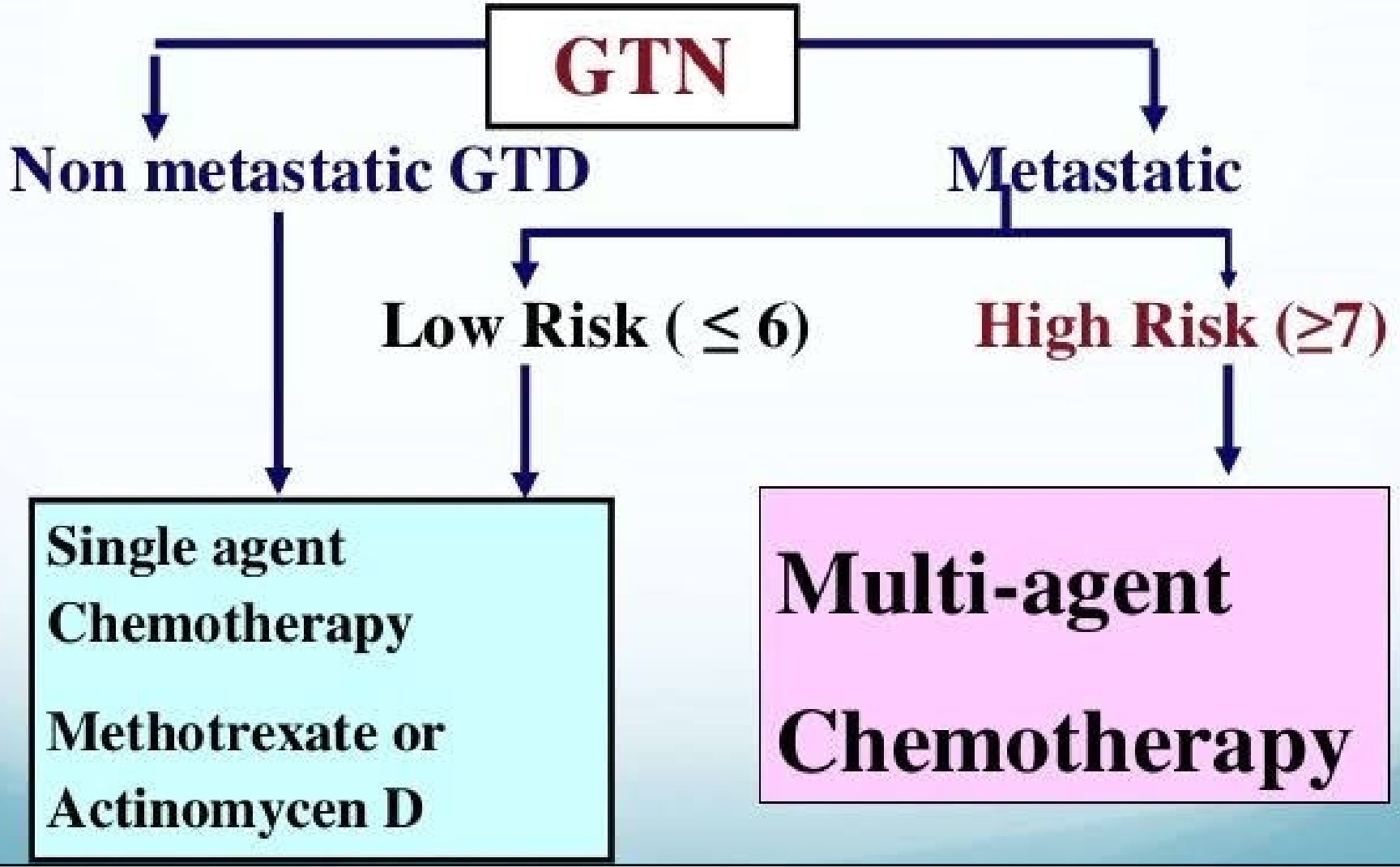
MANAGEMENT OF GESTATIONAL TROPHOBLASTIC NEOPLASIA

What Is The Optimum Treatment For GTN?

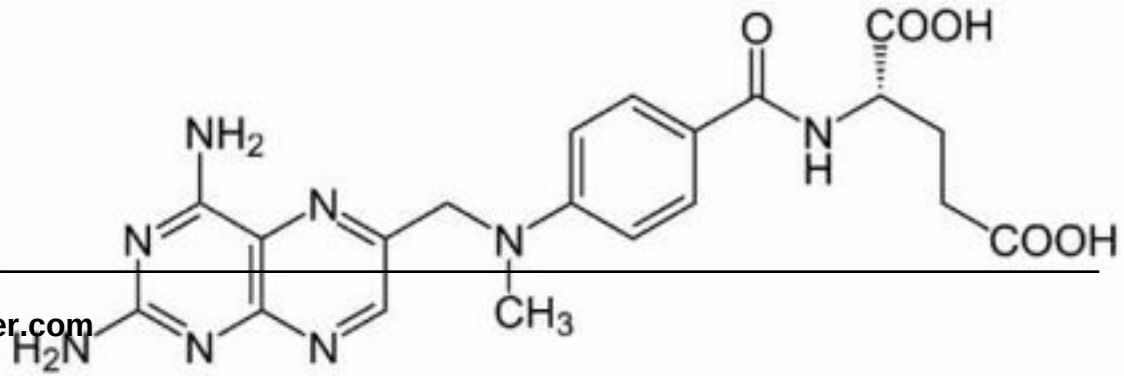


PRE TREATMENT EVALUATION

- History and clinical examination
- Serum βhCG
- Lab evaluation – RFT, LFT, WBC count, DLC, Platelet count, clotting profile
- USG pelvis- excludes pregnancy
- Chest X-Ray/CT scan
- CT Abdomen and Pelvis
- CT/MRI Head – Brain metastases
- Thyroid function test

LOW RISK GTN

- **METHOTREXATE**
  - Most common treatment – single agent Mtx
  - Recommended 8 day regimen – Mtx alternating with Folinic acid
  - Mtx **50mg/kg** bodyweight I.M - on day **1,3,5,7** and oral folinic acid **7.5 –15 mg** orally on days **2,4,6,8**
  - Treatment repeated every 2 weeks.



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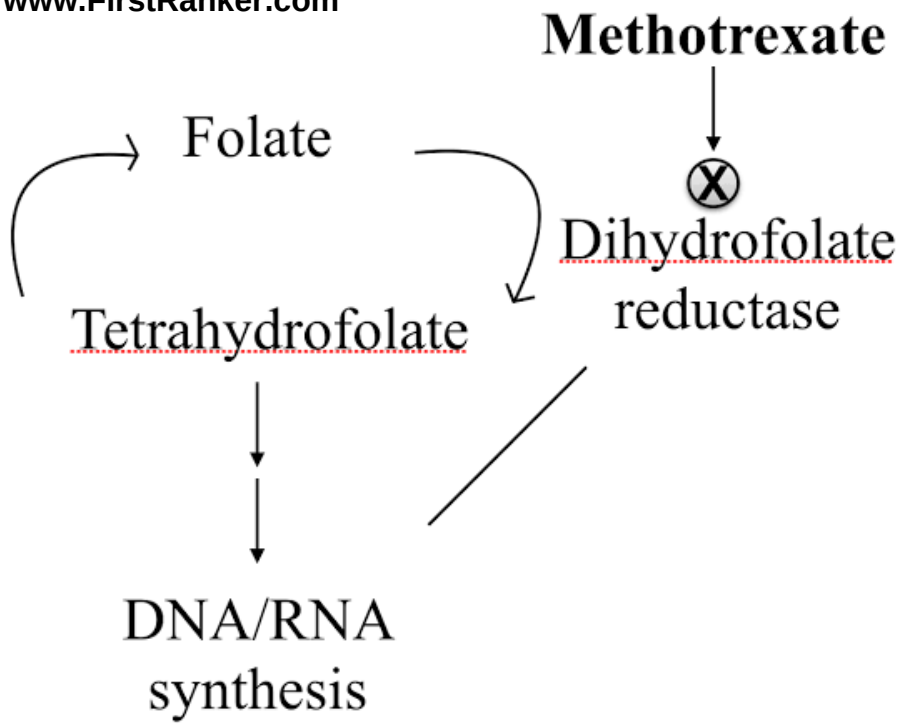
Folinic Acid Rescue



- Mtx – Folinic acid antagonist – inhibit DNA synthesis

- Side effects of Mtx-
  - Mild stomatitis
  - Pleurisy
  - Infrequently pericarditis,peritonitis,pneumonitis

- Hence folinic acid- Mtx ALTERNATE regimen :Protect normal mucosal and serosal cells.

- Before each Mtx course – CBC, RFT, LFT mandatory.
- Courses repeated every 14 days.
- Remission – 3 normal consecutive weekly titers ----- hence weekly serum βhCG, done till normal x 3 weeks
- One more course – after normalization of βhCG
- Pregnancy avoided for atleast one year after cessation of chemotherapy.

Drug Resistance

- 19 – 33 % women develop Mtx resistance.
- Detection – increasing or plateauing levels of serum β hCG
- Second line drug – Actinomycin D [Dactinomycin]
- Etoposide may also be effective
- If still no response – high risk protocol

DACTINOMYCIN

- Superior efficacy as a single agent.
- Pulse I.V Dactinomycin 1.25-2 mg /sq.m repeated every 14 days.
- Side effects : alopecia, grade 4 toxicity.
- Mtx resistant GTN often responds to dactinomycin.

HIGH RISK GTN

- More likely to develop drug resistance to single agent – hence combination chemotherapy.
- Highly effective regimen – ETOPOSIDE + MTX+ DACTINOMYCIN alternating with CYCLOPHOSPHAMIDE + VINCRISTINE [ONCOVIN] --- ***EMA-CO REGIMEN***
- Cycle repeated every 2 weeks until serum βhCG normal – then 3 more cycles given
- Overall survival – 86%

TABLE 1. EMACO Regimen*

EMA	
Day 1	
Dactinomycin	0.5 mg IV bolus
Etoposide	100 mg/m^2 in 250 mL NS over 1 h
Methotrexate	100 mg/m^2 in 100 mL NS over 15 min
Methotrexate	200 mg/m^2 in 500 mL NS over 12 h
Day 2	
Dactinomycin	0.5 mg IV bolus
Etoposide	100 mg/m^2 in 250 mL NS over 1 h
Folinic acid	25 mg orally every 6 h for 8 administrations starting 24 h after start of methotrexate
CO	
Day 8	
Vincristine	1 mg/m^2 (maximum 2 mg)
Cyclophosphamide	600 mg/m^2 in 250 mL NS over 30 min

*Every 21 days.
NS indicates normal saline.

- 1 Quarter patients become refractory to or relapse.

- Secondary treatment –

  Platinum based chemotherapy + possible surgical excision of resistance site

  - ✓ *EMA/EP regimen [etoposide – cisplatin]*
  - ✓ *paclitaxel + cisplatin alternating with paclitaxel + etoposide*
  - ✓ *BEP regimen : bleomycin + etoposide +cisplatin*

Day	Drug	Dose
		Protocol for EMA/CO Regimen
1	Etoposide actD MTX	100 mg/m^2 by infusion in 200 ml saline over 30 min 0.5 mg IV push 100 mg/m^2 IV push 200 mg/m^2 by infusion over 12 h
2	Etoposide actD Folinic acid	100 mg/m^2 by infusion in 200 ml saline over 30 min 0.5 mg IV push 15 mg q 12 h × four doses IM or PO beginning 24 h after starting MTX
8	Cyclophosphamide Vincristine	600 mg/m^2 by infusion in saline over 30 min 1.0 mg/m^2 IV push
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8	Cisplatin Etoposide	60 mg/m^2 with prehydration 100 mg/m^2 by infusion in 200 ml saline over 30 min

HYSTERECTOMY

- **INDICATIONS**

✓ Invasive mole perforating the serosa causing an intraperitoneal bleed

✓ Uncontrollable vaginal bleeding

✓ Extensive uterine tumor to reduce burden and limit chemotherapy.

BRAIN METASTASES

Why EMA-CO + Whole-brain Irradiation?

The concurrent use of EMA/CO and whole-brain irradiation will lessen the risk of :

- **Spontaneous cerebral hemorrhage**
- **Cerebral hemorrhage at emergency craniotomy (if the patient displays rapidly deteriorating signs)**

Methotrexate 15 mg intrathecal injection may be given instead of brain irradiation adjuvant to EMA/CO regimen.

- Presenting features - seizures / headaches /hemiparesis
- Whole brain irradiation + combination chemotherapy
- Other choice – intrathecal Mtx, fortnightly
- Moribund circumstances –IC bleed – emergency craniotomy + critical care support

VAGINAL METASTASES

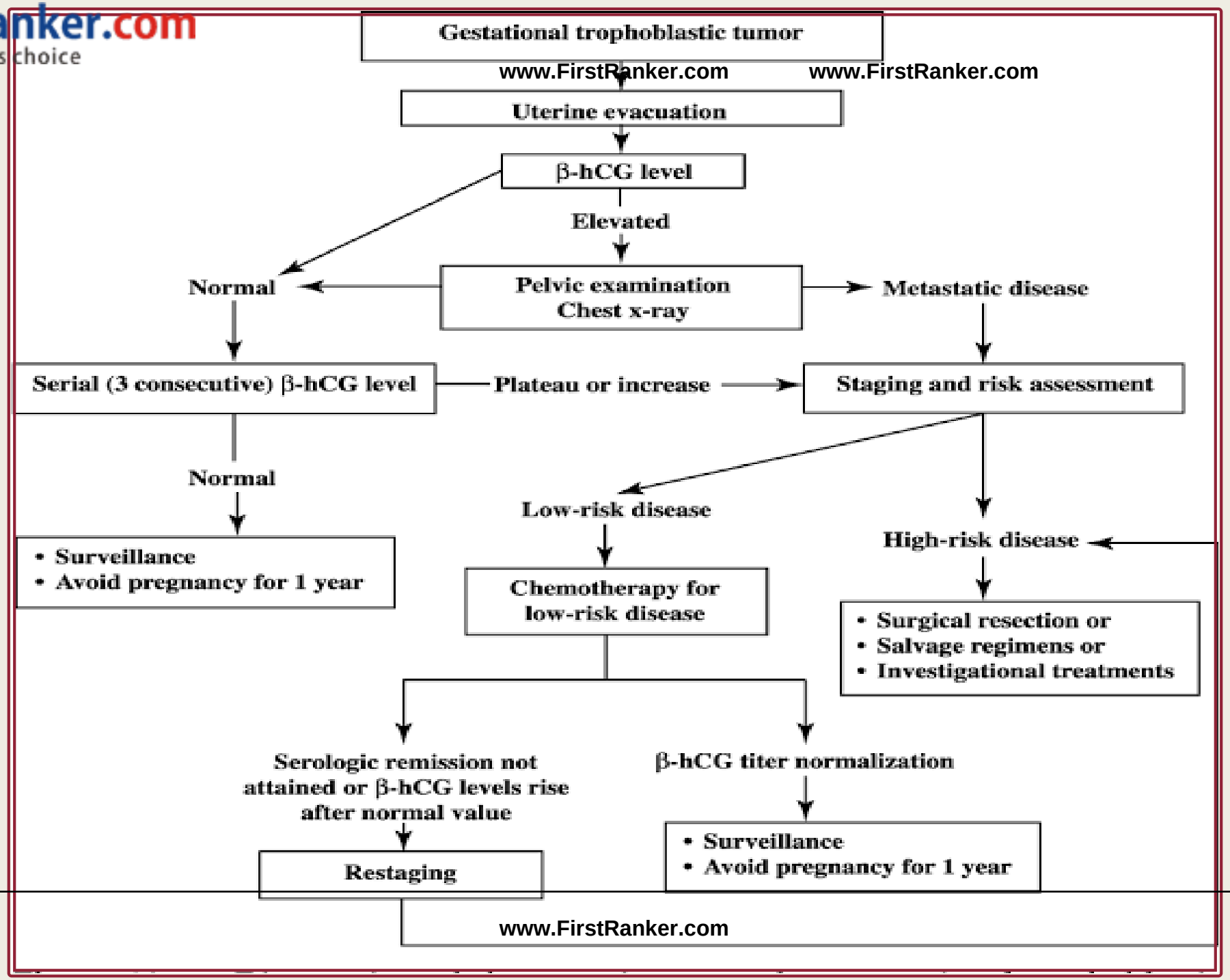
- Profuse bleeding – managed by packing/ wide local excision
- Rarely, embolization of hypogastric arteries.

PULMONARY METASTASES

- 90% - remission with chemotherapy
- Rarely – thoracotomy and excision needed.

LIVER METASTASES

- Difficult to treat with chemotherapy
- Rarely need hepatic resection and arterial embolisation



POST TREATMENT SURVEILLANCE

- Low risk GTN --- weekly βhCG – until titers undetectable for 3 consecutive weeks.
  --- then monthly titers until level undetectable for 12 months
- High risk GTN --- followed for 24 months, since chance of late relapse
- Effective contraception during surveillance period.

Surveillance During And After Therapy Of GTN

Monitor serum quantitative hCG levels every week during chemotherapy:

1. **Response**: >10% decline in hCG at one cycle
2. **Plateau**: ±10% change in hCG at one cycle
3. **Resistance**: >10% rise in hCG at one cycle or **Plateau for two cycles** of chemotherapy

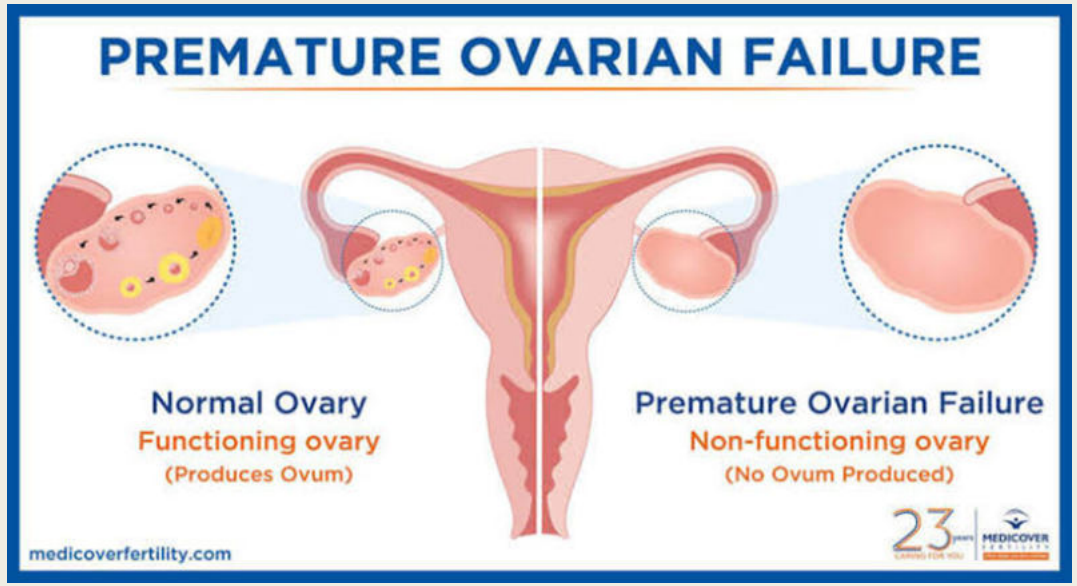
- Evaluate for new metastases
- Consider alternative chemotherapy
- Consider extirpation of drug-resistant sites of disease

Disaia &Creasman Clinical Gynecological Oncology 2007

PROGNOSIS

- Overall cure rate for GTN – 90%
- Non and low risk mets – excellent prognosis – 100% survival rate with single agent therapy
- High risk disease – 86% with multiple agent therapy

POST TREATMENT SEQUELAE



- PREMATURE OVARIAN FAILURE
- PSYCHOSOCIAL PROBLEMS
- RISK OF SECONDARY MALIGNANCY

SUBSEQUENT PREGNANCY

- Advised not to become pregnant atleast for 1 year after chemotherapy
- Send placenta for histological examination
- Do serum β hCG test 6 and 10 weeks after delivery
- Lifelong followup

hCG - H

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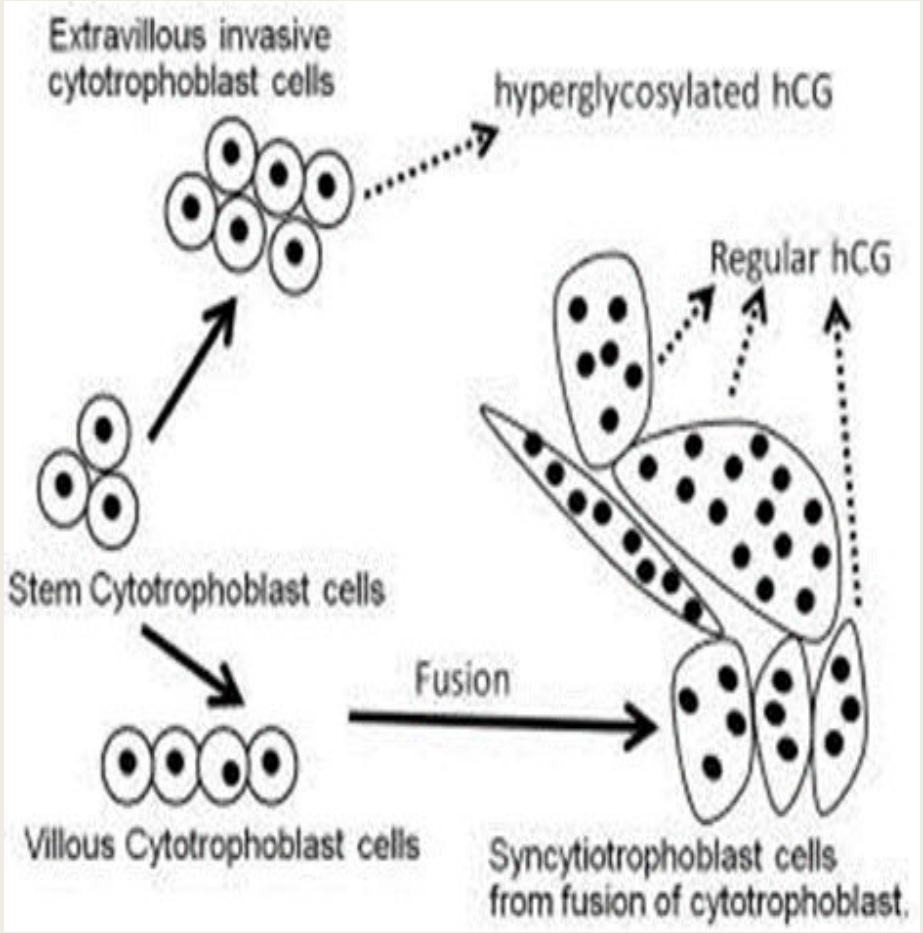
[Hyperglycosylated Hcg]

- Variant of βhCG – produced by invasive trophoblasts – has double sized oligosaccharides
- Presence only in implantation phases of normal pregnancy
- Seen mainly in GTN
- Action autocrine.
- Main action – promote trophoblast growth and invasion



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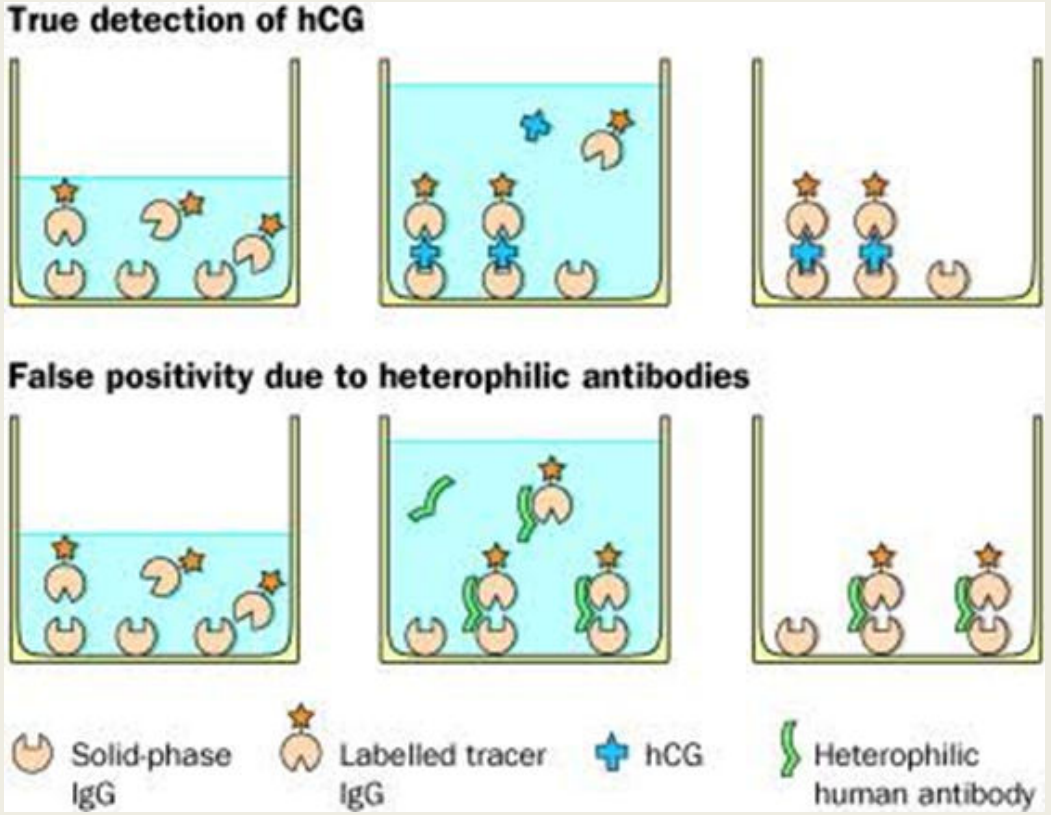
Phantom βhCG

- Due to presence of heterophile Abs in serum
- Interfere with immunoassay – cause false + result
- This cause mild elevation of βhCG
  - clinicians erroneously treat with chemotherapy
- Clarification :
  - *UTP : negative*
  - *Serial dilations of serum sample : phantom βhCG unchanged*
  - *Different βhCG assay by alternate method : absence of true βhCG*



DIAGNOSIS OF PSTT

- ✓ Presenting symptom – 90% with bleeding
- ✓ Only mild elevation of serum β Hcg

  - due to predominance of intermediate trophoblast and lack of syncytiotrophoblast

- ✓ Radiological evidence of uterine tumour
- ✓ Tumours stain intensively with antibodies to hPL
- ✓ However serum hPL not elevated hence hPL not for followup.

TREATMENT OF PSTT

- Chemoresistant tumors.
- Primary modality – surgery
- Simple hysterectomy + pelvic lymphadenectomy + ovary preservation
- Lifelong follow up
- Advanced disease or distant mets – adjuvant chemotherapy

THANKYOU