BIOMARKERS IN GTN

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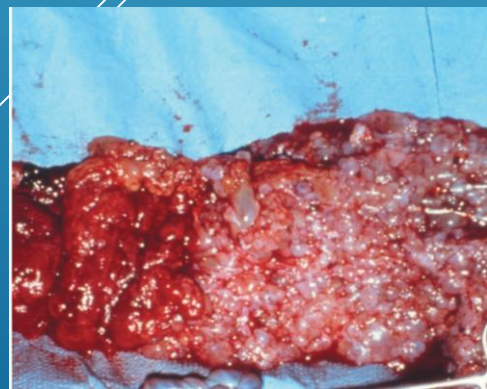
GESTATIONAL TROPHOBLASTIC DISEASE (GTD) :

- heterogeneous group of lesions that arise from abnormal proliferation of placental trophoblasts.
  - **Benign**
    - complete hydatidiform moles
    - Partial hydatidiform moles
    - placental site nodule
    - exaggerated placental site
  - **malignant**



GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN):

- malignant neoplasms of abnormal proliferation of trophoblastic tissue
- **may follow :**
  - **hydatidiform mole**

or

  - **nonmolar pregnancy**
- GTN is the most curable gynecologic malignancy

- **histologic types:**
- Invasive mole
- Choriocarcinoma

} high levels of HCG

- Placental site trophoblastic tumor (PSTT)
- Epithelioid trophoblastic tumor (ETT)

} low levels of hCG

SIGNS & SYMPTOM

- enlarged uterus,
- abnormal uterine bleeding (AUB)
- persistent bilateral enlarged ovaries
- Bleeding from uterine perforation or abdominal pain, hemoptysis, or melena.
- metastatic nodule

DIAGNOSIS

- plateaued
- rising
- Prolonged persistence of elevated hCG values after molar evacuation;
- histologic diagnosis:
  - choriocarcinoma,
  - invasive mole,
  - PSTT, or ETT
  - metastatic disease.

- The level of serum hCG varies across histologic types of GTN
- hCG serves as:
  - tumor marker for diagnosis (even in the absence of histologic confirmation)
  - monitoring treatment response
  - posttreatment surveillance


HCG
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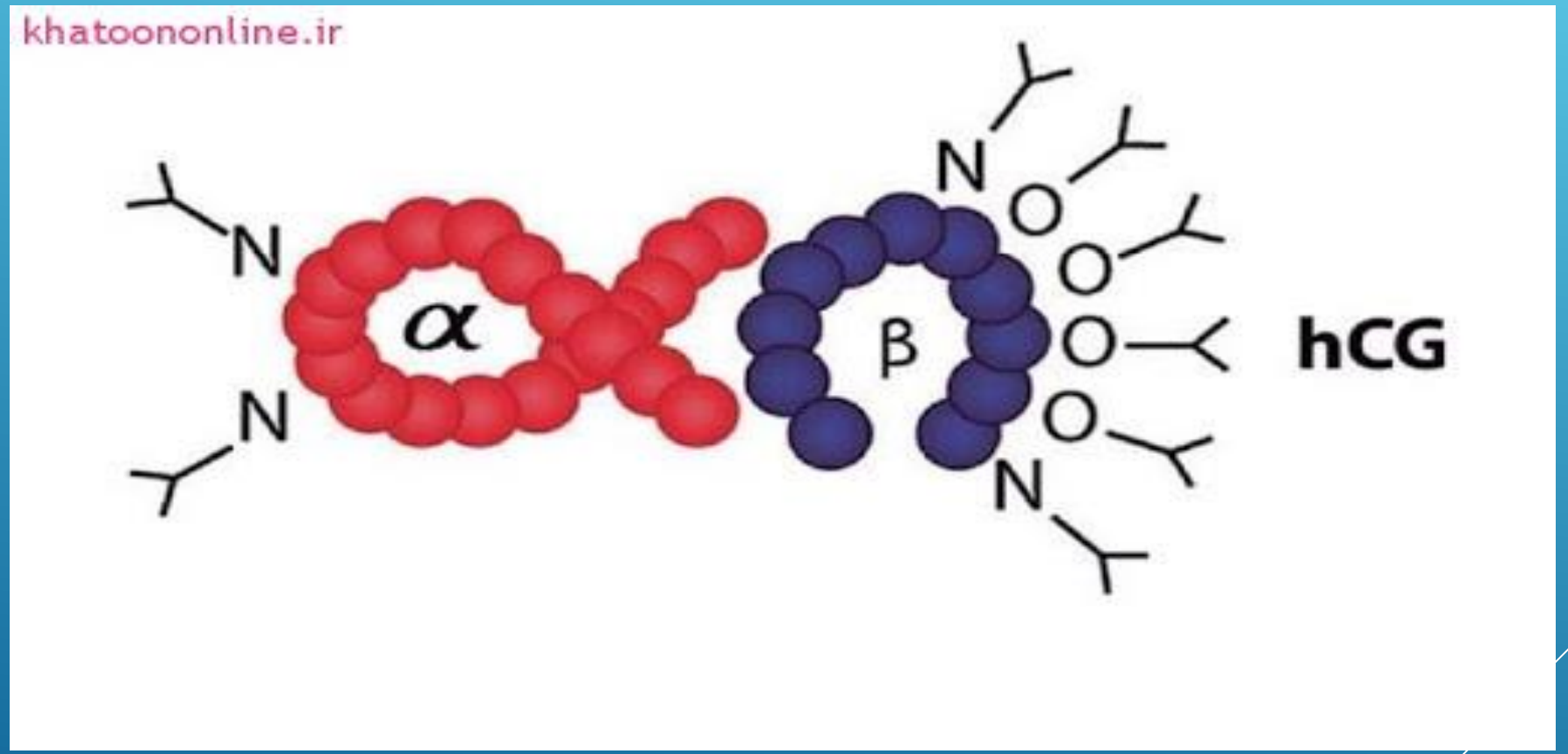
- part of the **glycoprotein** hormone family.
- common alpha-subunit and varying degrees of homology in their beta-subunits
- beta-subunit of hCG is very similar to that of LH
- produced almost exclusively by cytotrophoblast &syncytiotrophoblast

- important **biomarker** :
  - detection of pregnancy and pregnancy-related disorders.
- useful **tumor marker** :
  - management of trophoblastic disease and germ cell neoplasias.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N
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hCG

- most serum hCG immunoassays available today detect:
  - intact hCG
  - free beta-subunit of hCG
- Routine serum hCG or pregnancy immunoassay tests :
- simply "hCG assays" or for clarity "total hCG assays" to prevent confusion.

- serum **free beta-subunit** of hCG:

- percentage free beta-subunit of hCG -compared with of total hCG alone.
- 3 to 5 % is typical of low-risk postmolar invasive GTN.
- choriocarcinoma have a higher proportion, at approximately 10 %
- most aggressive form of GTN: PSTT, has the highest proportion of the free beta-subunit of hCG, approximately 20%

POSTOPERATIVE MONITORING OF MOLAR PREGNANCY

- Persistent hCG elevation :
  - molar tissue that invaded the myometrium
  - not completely removed
  - metastatic invasive mole

PROTOCOL FOR SERIAL HCG MEASUREMENTS AFTER MOLAR PREGNANCY

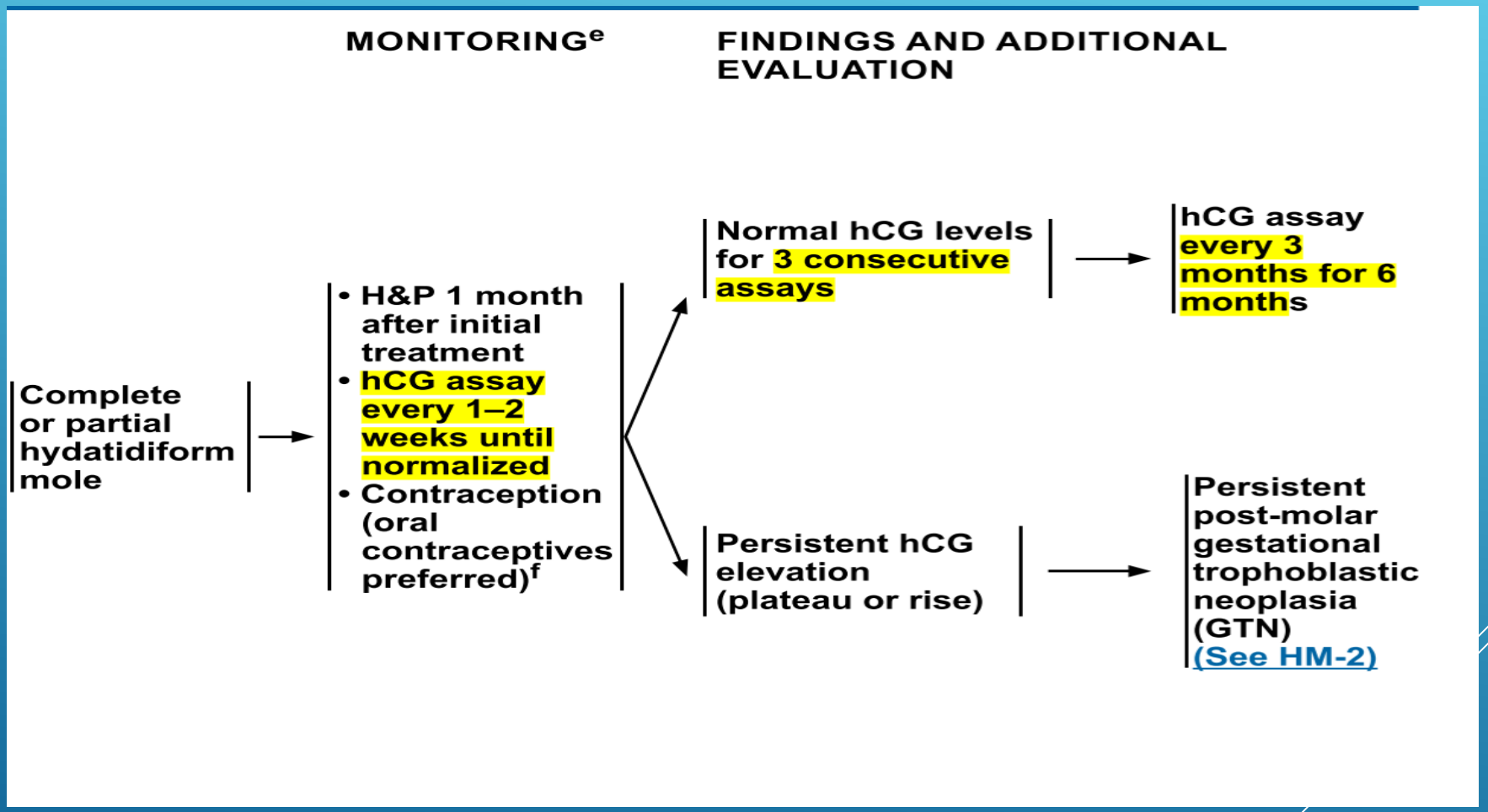
- hCG assay should measure the intact hCG dimer
- After 3 negative test, risk of GTN in partial mole or complete mole is much less than 1% and is lower for partial mole than complete mole.
- progressively decreases >10 % across 4 values during a 3 week period (days 1, 7, 14, and 21).

FIGO RECOMMENDS FOLLOWING PATIENTS WITH MOLAR PREGNANCIES

- hCG levels every 1 to 2 weeks until hCG normalization and then monthly
- **partial mole**:
- if a normal hCG is confirmed 1 month after the hCG normalized, then hCG monitoring can be discontinued
- **complete mole**:
- confirmatory normal hCG levels are needed for six months before discontinuing hCG monitoring

NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES

- following hCG levels every 1 to 2 weeks.
- When 3 consecutive hCG levels are normal, 2 additional hCG assays should be obtained at 3 month intervals, with discontinuation of hCG monitoring if the hCG remains normal


MONITORING[e]
FINDINGS AND ADDITIONAL EVALUATION
Complete or partial hydatidiform mole
• H&P 1 month after initial treatment
• hCG assay every 1–2 weeks until normalized
• Contraception (oral contraceptives preferred)[f]
Normal hCG levels for 3 consecutive assays
hCG assay every 3 months for 6 months
Persistent hCG elevation (plateau or rise)
Persistent post-molar gestational trophoblastic neoplasia (GTN)
(See HM-2)

UPTUDATE RECOMENDETION

- **complete mole**, after hCG normalizes:
- monthly hCG values for 3 additional months and then discontinue monitoring if the level remains undetectable.
- **partial mole**, after hCG normalizes:
- single additional hCG measurement one month later and then discontinue monitoring if the level remains undetectable.

PREDICTION:

- pre-evacuation uterine size is larger than gestational age
- serum hCG >100,000 mIu/mL, are a marker for high risk of development of GTN.
- combination of markedly elevated hCG levels >175,000 mIu/mL and older age appears to constitute an "ultra high-risk" group

PREDICTION:

- **rapidity** of hCG normalization was predictive of the likelihood of resolution versus development of GTN.
  - In complete mole:normalization within 56 days of evacuation reduced the risk of GTN to approximately 1 in 1159 versus 1 in 308 when normalization occurred after 56 days.
- **Level** of HCG
  - hCG level >2000 mIu/mL in the 4 week was associated with a 64 % risk of persistency

FOLLOWING A MOLAR PREGNANCY

DECREASE IN HCG LEVEL IS SLOW

- hCG levels remain detectable 6 months or more after evacuation.
  - (decreasing hCG but still detectable at six months) used to be considered diagnostic of GTN,
- FIGO removed this criterion in 2018 due to findings in the following studies conducted in the United Kingdom and Brazil.
- managed conservatively (continued hCG monitoring until levels meet criteria for undetectable, rising, or plateaued).

INCREASING HCG LEVELS

- level that progressively increases >10 % across3 values during at least a 2 week period (on days 1, 7, and 14)
- meet criteria for postmolar GTN and typically require chemotherapy to achieve remission.

PLATEAUED HCG LEVELS

- 4 measurements that remain within ±10 % over at least a 3 week period (days 1, 7, 14, and 21)
- meet criteria for postmolar GTN and typically require chemotherapy to achieve remission.

LOW-LEVEL PLATEAUED HCG (QUIESCENT GTN)

- low level (<200) of hCG persists for at least 3 months after evacuation of HM in the absence of any clinical or radiologic evidence of GTN.
- due to presence of a small focus of highly diff-noninvasive syncytiotrophoblast cells that produce small amounts of hCG
  - usually do not progress to invasive disease as long as cytotrophoblast or intermediate cells are absent.
- do not require therapy but do require close follow-up
- monitored with monthly hCG testing and advised to avoid pregnancy

RISK ASSESSMENT

- For patients with GTN:
  - both a stage and a risk score are assigned prior to treatment.
- FIGO staging system
- WHO Prognostic Scoring System.

- Stage I: Persistently elevated hCG levels; tumor confined to uterine corpus
- Stage II: Tumors extending to adnexa or vagina, but limited to the genital tract
- Stage III: Pulmonary metastases on CXR, ± uterine, pelvic, or vaginal involvement
- Stage IV: Metastatic disease outside of lungs and pelvis and/or vagina

WHO PROGNOSTIC SCORING SYSTEM

- Age
- Antecedent pregnancy
- Interval from last pregnancy
- Pretreatment serum hCG level
  - at the time of treatment for GTN and not at the time of diagnosis or evacuation of a molar pregnancy.
- Largest tumor (including uterine)
- Site of metastases
- Number of metastases
- Prior chemotherapy treatment

FIGO Staging of Gestational Trophoblastic Neoplasia (GTN) and modified WHO Prognostic Scoring System as adapted by FIGO

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures (adnexa, vagina)
Stage III	GTN extends to the lungs, with or without genital tract involvement
Stage IV	All other metastatic sites
The stage should be followed by the sum of the risk factors (eg, III:5)	

Risk factor	Score			
	0	**1**	**2**	**4**
Age (years)	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval (months)*	4	4 to 6	7 to 12	>12
Pretreatment serum hCG (mIU/mL)	$<10^3$	10^3 to 10^4	10^4 to 10^5	$>10^5$
Largest tumor (including uterus)	<3 cm	3 to 4 cm	≥5 cm	–
Site of metastases	Lung	Spleen, kidney	GI tract	Brain, liver
Number of metastases	–	1 to 4	5 to 8	>8
Prior failed chemotherapy	–	–	Single drug	≥2 drugs

FIGO: International Federation of Gynecology and Obstetrics; WHO: World Health Organization; hCG: human chorionic gonadotropin; GI: gastrointestinal.

* Interval (in months) between end of antecedent pregnancy and start of chemotherapy.

- A score of 0 to 6 :
  - low risk of resistance to single-agent chemotherapy.
- A score of ≥7 :
  - high risk of resistance to monotherapy and requires combination chemotherapy.
- A score ≥12 :
  - ultra high risk ,associated with nonmolar antecedent pregnancy, brain metastases, and failed prior multi-agent chemotherapy.
    - Kong et al reported that the five-year overall survival in this group was 68 %

MONITORING DURING TREATMENT IN LOW RISK

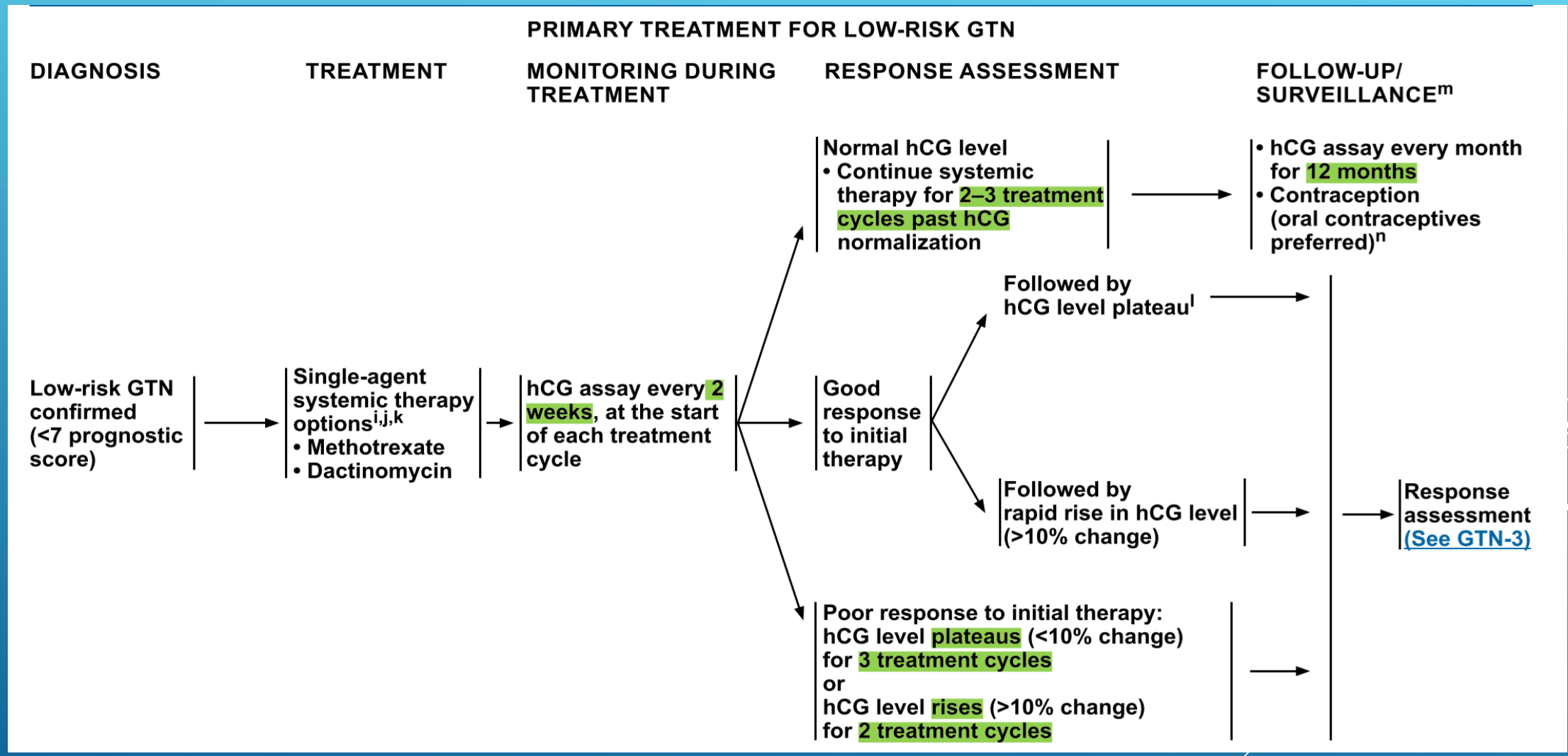
- All patients with GTN should be monitored with serial measurements of serum hCG at the start of treatment and then at weekly intervals during therapy.

DEFINING REMISSION

- 3 consecutive weekly normal hCG values (less than 5 mIU/mL).
- Treatment should then be continued for 3 consecutive courses of the last effective regimen to reduce the risk of relapse.

POSTTREATMENT SURVEILLANCE

- After remission :
- serum hCG should be measured monthly in asymptomatic patients until one year of normal hCG levels has been documented.


PRIMARY TREATMENT FOR LOW-RISK GTN
DIAGNOSIS
TREATMENT
MONITORING DURING TREATMENT
RESPONSE ASSESSMENT
FOLLOW-UP/ SURVEILLANCE[m]
Low-risk GTN confirmed (<7 prognostic score)
Single-agent systemic therapy options[i,j,k]
• Methotrexate
• Dactinomycin
hCG assay every 2 weeks, at the start of each treatment cycle
Normal hCG level
• Continue systemic therapy for 2–3 treatment cycles past hCG normalization
• hCG assay every month for 12 months
• Contraception (oral contraceptives preferred)[n]
Good response to initial therapy
Followed by hCG level plateau[l]
Followed by rapid rise in hCG level (>10% change)
Poor response to initial therapy:
hCG level plateaus (<10% change) for 3 treatment cycles
or
hCG level rises (>10% change) for 2 treatment cycles
Response assessment
(See GTN-3)

PERSISTENT OR PROGRESSIVE DISEASE

- increase or a plateau in 2 consecutive hCG values over a 2 week interval.
- half-life of hCG is 1.5 to 3 days, and serum levels should fall

  (at least one log within 18 days)
- A slower rate of decline suggests the possibility of chemoresistance,
- no consensus or clear guideline to:
  - optimal cutoff for determining chemoresistance
  - management of patients with a slower than expected tumor marker decline.

DIAGNOSIS OF RECURRENT DISEASE

- 1.This is usually marked as a rise in the HCG level at a median time of 6 months since end of therapy
- 2. following completion of one year of hCG surveillance the patient develops new symptoms, such as AUB:
    - recurrence should be considered
    - hCG value should be obtained.
- diagnosed with relapse:
    - re-imaging with chest, abdominal, and pelvic CT scans and brain MRI should be performed.

MONITORING DURING TREATMENT IN HIGH RISK

- high-risk GTN:
- serial measurements of serum hCG at the start of treatment and then at weekly intervals during therapy.
- serum levels should fall exponentially (by at least one log within 18 days).
- A slower rate of decline suggests the possibility of chemoresistance,

DEFINITION OF REMISSION

- quantitative hCG level becomes undetectable for 3 consecutive weeks.
- no imaging is required if levels are consistent with remission
- abnormalities on imaging can persist despite the attainment of undetectable hCG levels, representing fibrosis rather than active tumor.

PERSISTENT OR PROGRESSIVE DISEASE

- increase or a plateau in 2 consecutive hCG values over a 2 week interval
- other generally accepted criteria include detection of new metastases

POST-TREATMENT SURVEILLANCE

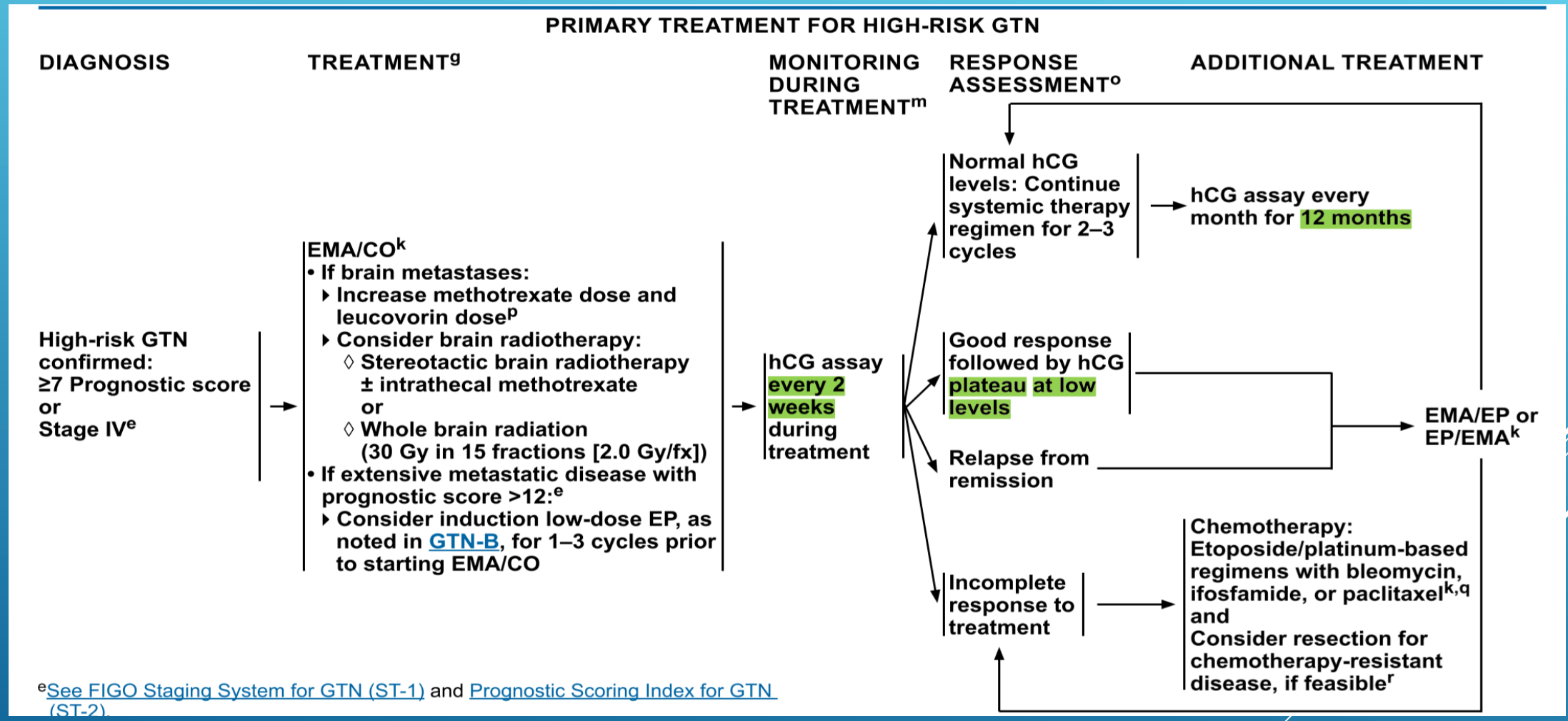
- hCG should be measured monthly until there have been undetectable for 12 months.
- rising hCG after remission:
  - consider alternative sources for this elevation

- Assays :
- should measure hCG at least down to 5 mIu/mL
- should measure not only intact hCG but also hCG fragments and subunits.
- When assays measure hCG to very low levels (<1 mIu/mL):
- suppress pituitary production of LH and hCG with strong, OCP to facilitate reliable monitoring of disease status.

DIAGNOSIS OF RECURRENT OR RESISTANT DISEASE

- **Recurrent:**
  - hCG level re-elevates after becoming undetectable for 3 consecutive weeks .

- **resistant** :
  - hCG level remains elevated despite treatment are considered to have disease.



eSee FIGO Staging System for GTN (ST-1) and Prognostic Scoring Index for GTN (ST-2).

ETT &PSTT

- develop from extravillous, intermediate trophoblast , show no chorionic villi
- after a nonmolar abortion or pregnancy
- A key difference:
  - secretes very low levels of hCG
- The clinical behavior of ETT is similar to PSTT.
- Diagnosis is typically late
  - slow growth, paucity of symptoms, and low or absent hCG production
- ETT cells show :
  - diffuse expression of IHC cytokeratin and inhibin a
- hCG are usually <1000 mIu/mL and are infrequently undetectable.
- In PSTT, measurement of the free beta hCG may be useful