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Review Article

Gestational Trophoblastic Disease

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Introduction

It is over 100 years since Felix Marchand identified choriocarcinoma as a tumor arising from placental villous trophoblast. In 1956, Hertz etal [1] first reported the cure of a patient with metastatic choriocarcinoma using chemotherapy. The next decade saw Hertz and colleagues at the National Institute of Health, Brewer in Chicago and Bagshawe in London develop the chemotherapeutic approach to gestational trophoblastic neoplasia that would cure the majority of patients with this fatal disease. Trophoblastic tumors are fetal allograft in maternal tissues and present unique biological, immunological and pathological problems. The screening programs for persistent trophoblastic disease following evacuation of hydatidiform mole have been instrumental in the near elimination of fatalities from sequelae following mole [2]. Most patients with metastatic diseases are now cured and usually retain reproductive function. This is achieved with the development of sensitive assay systems to precisely measure human chorionic gonadotrophin (hCG) and with the availability of effective chemotherapy.

Gestational trophoblastic diseases

Gestational trophoblastic disease (GTD) is the terminology now used to span the spectrum of cellular proliferation ranging from the various forms of hydatidiform mole, through invasive mole and choriocarcinoma (CC) to placental site trophoblastic tumors (PSTT). It is now well recognized that molar pregnancy comprises two distinct entities, complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM), which differ on the bases of chromosomal pattern, gross and microscopic pathology and clinical presentation. PSTT is a rare neoplastic subtype of gestational trophoblastic disease. Epithelioid trophoblastic tumor (ETT) is the most recently described and rarest of the trophoblastic tumors. Nongestational trophoblastic tumors are the primary choriocarcinoma of the ovary and testes.

CHM and PHM differ in their invasive potential and propensity for malignant transformation. Approximately 9 to 20% of patients with CHM may be at the risk of developing GTD following molar evacuation while PHM leads to GTN in less than 3% of cases.

Genetics of hydatidiform mole

The male and female gametes are unique cell types in having a haploid set of chromosomes. At fertilization the complete complement of 23 pairs is restored.

Vassilakos and Kajii [3], Szulman and Surti [5,6] and Lawler [7-9] have clearly demonstrated that complete hydatidiform mole and partial hydatidiform mole are separate syndromes with different genetic background.

With complete mole, the chromosomal material from the ovum is lost and this empty egg is fertilized by a sperm containing 23X which duplicates to form 46XX (90%); fertilization may also be by two sperms giving a 46XX or 46XY (10%) androgenic conceptus. 46YY fertilization is incompatible with life. Although the

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embryo usually disappears at a very early stage, fetal RBCs may be formed which may necessitate administration of anti-D immunoglobulin. Trophoblastic hyperplasia is more marked in complete mole.

Partial moles are triploid; an ovum with 23X fertilized by two sperms of 23X leading to 69XXX. It is possible to have 69XXY and rarely 69XYY, but not 69YYY. The fetus may develop to varying stages with focal hydropic changes of the placenta with less trophoblastic activity compared to complete mole.

Diagnosis of hydatidiform mole

Patients usually present with vaginal bleeding; hyperemesis is a common complaint. The classical findings of a large uterus with early onset pre-eclampsia and the presence of big lutein cysts are rare to see now thanks to the routine use of ultrasonography for the evaluation of early pregnancy. The classical snow-storm appearance is evident if the ultrasound study is done in late first trimester. Partial moles may be misdiagnosed as missed abortion. Hence it is mandatory to perform histopathological analysis of products of conception after evacuation. Histopathological differentiation of molar pregnancy maybe challenging. Differentiation of complete and partial mole may require DNA polymorphic markers and study of imprinted genes; complete mole will not have maternally expressed imprinted gene TSSC3 [10]. It is important to check urinary hCG 10 weeks after evacuation of all miscarriages including medical terminations of pregnancy, as GTN has been reported after such events [11].

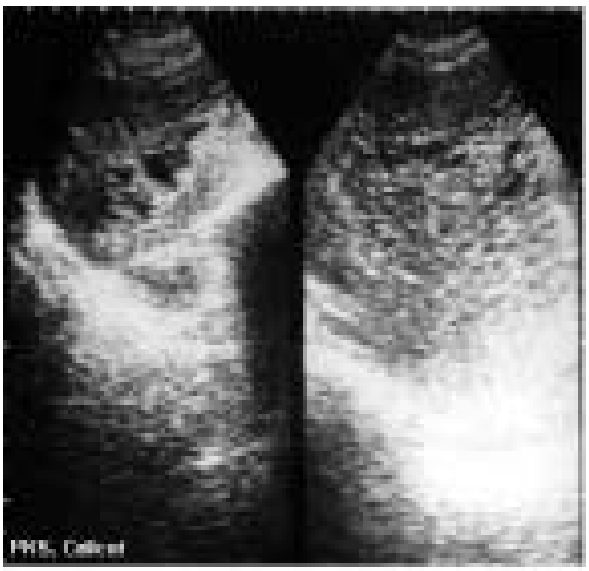

Figure 1. Snowstorm appearance on USG in complete hydatidiform mole

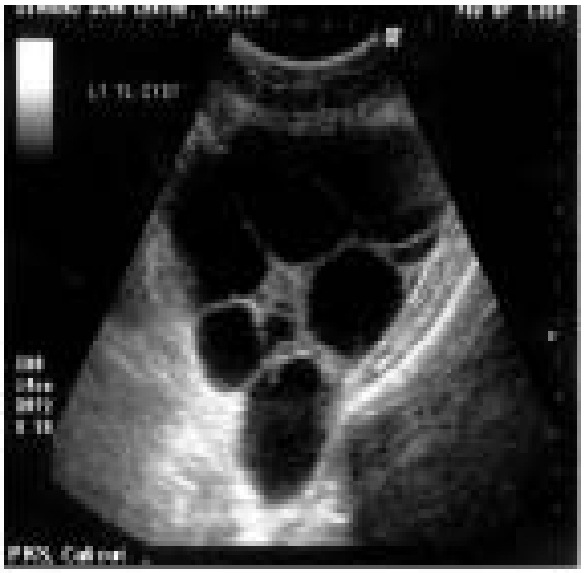

Figure 2.USG theca lutein cysts in hydatidiform mole

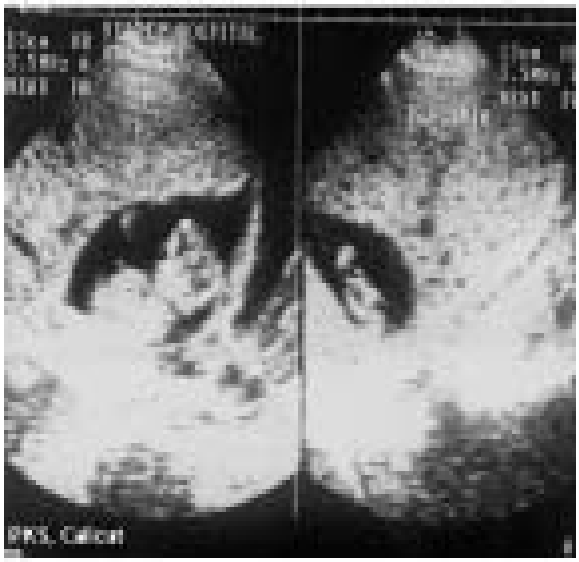

Figure 3. USG of partial mole with focal molar changes and fetus

Evacuation of hydatidiform mole

Suction evacuation under anesthesia is the procedure of choice. Vaginal PGE_1 may be used for cervical priming. Oxytocin during evacuation helps to minimize bleeding without increased risk of persistent disease. A careful curettage should be performed following

evacuation to ensure the uterus has been emptied of molar tissue. Hysterectomy with mole in situ with regular follow up is an option in elderly multiparous women. Routine prophylactic chemotherapy is not recommended as it exposes 80% of patients to unnecessary chemotherapy. If at all it is used in high risk patients who may not have appropriate follow up, several courses of prophylactic or adjuvant chemotherapy may have to be given till the hCG titre becomes negative[12]. Anti-D immunoglobulin should be given to Rh-negative women.

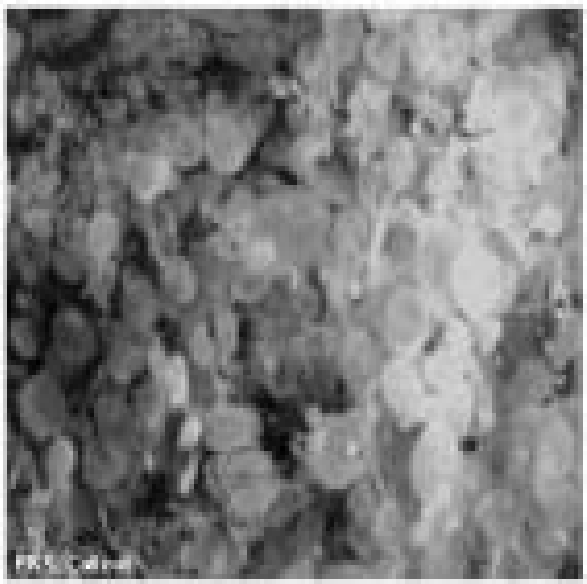

Figure 4. Typical appearance of complete hydatidiform mole following evacuation

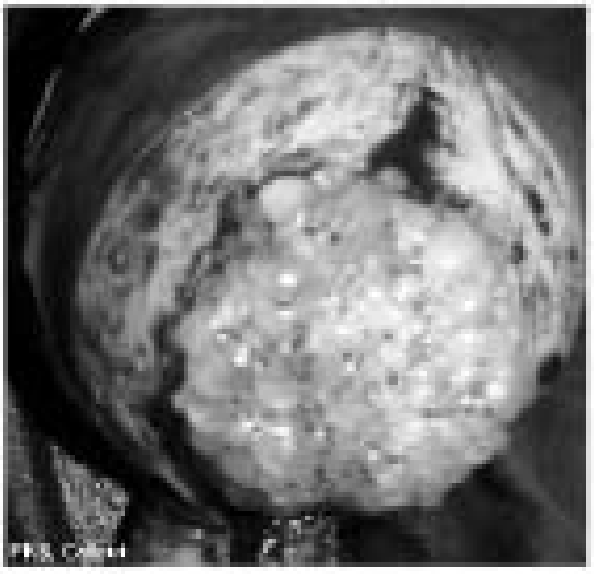

Figure 5. Hysterectomy specimen with mole in situ

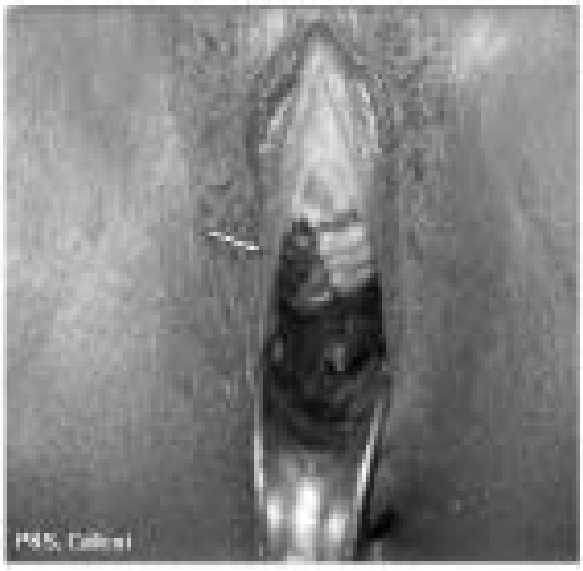

Figure6. Typical appearance of sub-urethral nodule (arrow)

Follow-up

Serum hCG at 24 hours following evacuation serves as the initial level. Supportive measures including correction of anemia by blood transfusion and treatment of any concurrent infection maybe required. An ultrasound evaluation is done after one week of evacuation to ensure the completeness of the procedure. A second curettage is done only if there is evidence of incomplete evacuation on ultrasound. The patient is initially followed up till three consecutive weekly serum hCG assays become negative subsequent monthly follow up with hCG estimation is undertaken for 6 months and then once in two months for an additional 6 months to ensure that hCG remains undetectable. Barrier contraception is advised till hCG assays is negative followed by low dose oral contraceptive pills.

Patients with partial mole also require regular follow up as GTN following partial mole (albeit rare) is also reported[13,14].

If hCG falls by one log value every week and becomes negative by 8 weeks, pregnancy is permissible after an additional 6 months follow up. If the fall in hCG is slow and takes more than 8 weeks, then the patient requires a total of 2 years follow up. An ultrasound evaluation of the subsequent pregnancy should be

done to rule out recurrent mole. After termination of the subsequent normal pregnancy, hCG should be measured at 6 and 10 weeks.

It may be noted that patients with uterine size 4 weeks larger than date with theca lutein cyst of >6cm have a 50% risk of persistent disease.

hCG assays

A reliable assay for total hCG is central to the management of patients with trophoblastic disease. Human chorionic gonadotrophin (hCG) is a glycoprotein composed of two dissimilar subunits; a (92 amino acids) and ß (45 amino acids), with 8 sugar side chains (oligosaccharides). In addition to regular hCG, 4 major variants of hCG are present in serum samples: hyperglycosylated hCG (hCG-H), nicked hCG, hCG missing the ß-subunit C-terminal peptide and free ß-subunit[15]. In addition variants such as hyperglycosylated free ß-subunit and nicked hCG missing the C-terminal peptide have been reported. These variants are more common in neoplasia than regular hCG. The assay must measure all variants of hCG, especially hCG-H. It is recommended to use DPC Immulite® system to detect the various hCG related molecules [15].

False positive or phantom hCG is reported in recent years where the patient does not have GTD or pregnancy related events, and maybe inappropriately advised unnecessary chemotherapy or surgery[16]. This occurs due to the presence of heterophilic antibodies in the patient's serum. To differentiate 'real' hCG from false, (1) repeat the test in serial dilutions (2) use different assay kits to replicate the results and (3) test urine for hCG which will be absent in cases of phantom hCG as heterophilic antibodies will not be present in urine. For clarification, consult Laurance A Cole, US hCG Reference Laboratory (larry@hcglab.com).

Quiescent GTD

In the recent past clinicians have encountered patients with elevated hCG, usually in the range of 50 to 100 IU/L that either follows a molar pregnancy or is an incidental finding. The elevated hCG titre may persist in spite of chemotherapy or surgery. The first step is to exclude heterophilic antibodies (see above). Patients do not have abnormal clinical findings and imaging studies are negative. In 20% of such cases, hCG becomes re-elevated after several weeks to several years and overt tumor becomes detectable. During the quiescent period the patient has no detectable hCG-H and chemotherapy in this instance is ineffective as there are no actively dividing cells. With the onset of active cell replication, hCG rises, of which, a significant proportion is hCG-H. This biochemical change occurs frequently prior to clinical findings. At this stage chemotherapy is effective. Therefore, all patients with low levels of real hCG need follow up, possibly even for years [17].

Diagnosis of post-molar GTN

It is not essential to have histological conformation for diagnosis of gestational trophoblastic neoplasia (GTN). The diagnosis is based on the rise or plateauing of hCG and the duration of the molar disease. GTN may follow hydatidiform mole (60%), abortion (30%) and normal or ectopic pregnancy (10%).

Postmolar GTN is diagnosed by -

1. Plateau of serum hCG level(±10%) for four measurements during a period of 3 weeks or longer – days 1,7,14,21
2. Rise of serum hCG>10% during three weekly consecutive measurements or longer, during a period of 2 weeks or more-days 1,7,14.
3. Serum hCG remains detectable for 6 months or more
4. Histological criteria for choriocarcinoma are present

Criteria for methods used to diagnose metastasis in Trophoblastic Neoplasia are -

1. Chest X-ray is adequate to diagnose lung metastasis and is used for counting the number of lung metastases to evaluate the risk factor score. Alternatively, CT thorax may be used.
2. Liver metastases may be diagnosed by CT or ultrasound imaging.
3. Brain metastases may be diagnosed by MRI or CT scanning.
4. To diagnose intraabdominal metastases, CT scanning is preferred.

The new FIGO staging and Risk Factor Scoring System [18]

In March 2002, the FIGO council accepted the FIGO classification of trophoblastic neoplasia combining the anatomic FIGO staging with the modified WHO scoring system.

A prognostic scoring system giving different weightage to different prognostic factors was first developed by Bagshawe [19] in 1976; based on this score patients were assigned high, medium, or low risk to select the patients for chemotherapy. In 1983, the WHO working group proposed modifications to the Bagshawe system and issued the WHO scoring system [20].

In the new FIGO risk scoring system introduced in 2002, the risk score for ABO blood groups has been eliminated and the risk score for liver metastases was upgraded from 2 to the highest risk score of 4. The 'medium risk' group of WHO classification was eliminated in the new FIGO risk score. Instead a score of 6 or less is classified as low risk and a score of 7 or greater as high risk.

Placental Site Trophoblastic Tumor (PSTT) will be categorized separately from other gestational trophoblastic neoplasia. Table I gives FIGO staging of GTN and Table II gives FIGO risk factors scoring System

Table 1. FIGO Staging of GTN.

Stage I	Disease confined to the uterus.
Stage II	GTN extends outside the uterus but is limited to the genital structures (adnexa, vagina, broad ligament).
Stage III	GTN extends to the lungs with or without genital tract involvement.
Stage IV	All other metastatic sites.

Tabe 2. FIGO Risk Factor Scoring System.

FIGO scoring	0	1	2	4
Age	<40	>40		
Antecedent pregnancy	Mole	Abortion	Term	
Months from index pregnancy	<4	4 - <7	7 - <13	³13
Pre-treatment serum hCG (IU/l)	$<10^3$	10^3 - $<10^4$	10^4 - $<10^5$	³$10^5$
Largest tumor size (cm)	<3	3 - <5	³5	
Site of metastasis	Lung	Spleen, Kidney	GIT	Liver, Brain
Number of metastasis	—	1- 4	5 - 8	>8
Previous failed chemotherapy	—	—	Single drug	2 or more drugs

Treatment of GTN

Selection of patients for treatment with single agent or multi agent chemotherapy is based on the stage and risk score. Low risk cases are treated with single agent chemotherapy and high risk cases are treated with multiagent chemotherapy.

Low risk GTN are -

- Non metastatic gestational trophoblastic neoplasia
- Low risk metastatic neoplasia-metastases to lungs only
- Duration less than 4 months from the index

pregnancy

- hCG less than 40,000 IU/L
- Risk score 6 or less
- FIGO stage I, II and III

High Risk GTN are -

- FIGO stage I, II, and III with risk score of 7 or more.
- FIGO stage IV

Drug schedule

Single agent chemotherapy for low risk GTN

1. Methotrexate with Leucovorin (Folinic acid) rescue - complete blood count with liver function and renal function tests should be normal before starting each course. Injection methotrexate 1mg/kg body weight IM is given on alternate days with injection folinic acid 0.1mg IM 24 hrs after each injection of methotrexate. This is a widely used regimen in United Kingdom and United States with a cure rate of 80 to 90%. We found it to be an effective regimen for low-risk GTN and could achieve a remission rate of 92.9% [21]. All patients tolerated the drug with only mild toxicity. The largest experience with methotrexate–folinic acid was reported by Bagshawe and associates with a sustained remission rate of over 90% in low-risk cases[22]. Berkowitz el al also reported a similar remission rate [23].
2. Injection methotrexate 0.4mg/kg Im for 5 days, repeated every 2 weeks. This is one of the original protocols used to treat GTN and is being followed even today in some centers in the US.
3. Injection methotrexate 50mg/m^2 Im every week. This regimen is associated with a primary failure rate of 20% and such cases can be treated with daily methotrexate or actinomycin.
4. Actinomycin-D 9-12 µgm/kg IV daily for 5 days, repeated every two weeks. This regimen is useful in patients with hepatic dysfunction where methotrexate is contraindicated. Actinomycin-D can cause severe sloughing of the tissues if extravasation occurs. To avoid this, the drug should be given via a large bore cannula in a free running intravenous infusion. In case of extravasation, infiltrate the area with 100mg of hydrocortisone and 2ml of 1% xylocaine.

At least one course and usually two to three courses of chemotherapy should be given beyond the first negative hCG level, especially if the fall in hCG is slow.

Multi-agent chemotherapy for high risk GTN

1. EMA-CO Regimen for High-Risk GTN: patients with high risk GTN are treated with combination chemotherapy, EMA-CO being the primary regimen. EMA-CO consists of etoposide, methotrexate with leucovorin rescue and actinomycin, given on days 1&2 and cyclophosphamide and vincristine (Oncovin) given on day 8. The number of courses of EMA-CO is limited to 6 due to the risk of leukemia and other malignancies in rare instances[24]. Even in high risk metastatic cases, a cure rate of 65-85% is reported with EMA-CO regimen[24,25]. (Table III).

Table 3. EMA-CO regimen.

Day	Drug	Dose
1	Etoposide	100mg/m^2 IV over 30 min
	Actinomycin-D	0.5mg IV push
	Methotrexate	100mg/ m^2 infusion in 1000 ml 5% dextrose in 12 h
2	Etoposide	100mg/m^2 IV over 30 min
	Actinomycin-D	0.5mg IV push
	Folinic Acid	15mg IM every 12 h for 4 doses beginning 24 h after start of methotrexate
8	Cyclophosphamide	600mg/m^2 IV infusion
	Vincristine	1.0mg/m^2 IV push

Repeat cycles on days 15, 16 and 22 (every 2 weeks)

2. In EMA-CO resistant cases or following relapse, 75% of patients may achieve remission by substituting etoposide and cisplatin for cyclophosphamide and vincristine (EMA-EP) with or without surgery [26].

3. For EMA-EP resistant cases (1) paclitaxel (Taxol) with cisplatin alternating with taxol-etoposide or (2) iphosphamide, cisplatin etoposide regimen (ICE) maybe used. Intensive chemotherapy for high risk GTN carries a small risk of inducing malignancies such as leukemia.

Three further courses of chemotherapy should be given after hCG has become negative in high-risk cases. A negative hCG value implies that the number of malignant cells is $<10^7$. It does not mean that the disease is completely eradicated.

Metastases to lung, liver, brain or other sites that do not regress with chemotherapy may be amenable to surgical extirpation. Brain and liver metastases may require radiation.

Patients requiring chemotherapy for metastatic disease should be advised to delay pregnancy by 12 months following treatment.

Placental Site Trophoblastic Tumor – PSTT

PSTT originates from intermediate cytotrophoblast from the placental implantation site. It can develop following normal pregnancy, abortion or molar pregnancy. The tumor invades the myometrium by dissecting between the smooth muscle fibers with extensive invasion of vessel walls. Since syncytiotrophoblast formation is limited, the production of hCG is low and is not a reliable tumor marker; instead hPL (human placental lactogen) may be demonstrated by immunohistochemical staining. Patients frequently present with irregular vaginal bleeding or amenorrhea. Most patients with non metastatic disease are cured by surgery, metastatic disease is relatively insensitive to chemotherapy and aggressive multi-drug regimens are needed (such as EMA-EP).

Epithelioid Trophoblastic Tumor – ETT

This is the most recently described and rarest of trophoblastic tumors. It is composed of chorionic-type intermediate trophoblast and is distinct from both CC and PSTT although mixed tumors with two or three of these trophoblastic tumors together have been reported [27]. ETT usually presents as a discreet uterine mass and stains diffusely positive with PLAP (placental specific alkaline phosphatase) and cytokeratin, whereas hCG and hPL positivity is weak and scattered. It would seem from recent literature that ETT is truly a rare but distinct trophoblastic tumor rather than just a morphological variant of longstanding PSTT, although the biological behavior appears similar [28].

Multiple pregnancies with mole and coexisting fetus

A twin molar pregnancy is a rare dizygotic gestation with a normal fetus and complete mole. The clinical presentation is that of hydatidiform mole or twin gestation with rapid enlargement of uterus. Careful ultrasound examination will reveal a normal fetus, amniotic sac and placenta with separate molar tissue elsewhere. Partial moles may have a fetus, but have diffuse molar changes throughout the single placenta. However the correct diagnosis is made in only 70% of cases. They are often diagnosed late and associated with a live birth rate of around 25%. These patients are at a higher risk of developing pre-eclampsia and hemorrhage. The subsequent need for chemotherapy for persistent disease is greater than other molar pregnancies. The present policy is to allow the pregnancy to go to term according to the patient's choice following proper counseling. Patients are counseled regarding the substantial risk of fetal loss, pregnancy induced hypertension, hemorrhage and increased risk of GTN [29]. They are followed up after pregnancy as in other cases of hydatidiform mole. Conservative management of these patients allowing the pregnancy to go ahead unless there are clear cut medical grounds for termination such as pre-eclampsia or hemorrhage appears to be the treatment of choice.

Pregnancy outcome after molar pregnancy

Following molar pregnancy, patients can expect to have normal reproductive outcome in most instances, though there is an increase in the incidence of recurrent mole. Patients after chemotherapy can also expect a normal outcome, but are advised to wait for 12 months after the last course of chemotherapy.

Our experience at Calicut [21]

During the fifteen year period from 1990 to 2005, 1569

cases of hydatidiform mole were diagnosed and managed at Medical College, Calicut. Regular follow up of these cases helped to diagnose GTN at an early stage where single agent chemotherapy is curative. The incidence of GTN in our series is 20.4% and single agent chemotherapy with methotrexate and folinic acid was curative in 92.9%. Rest of the cases required multiagent chemotherapy. The overall outcome of the 413 pregnancies following hydatidiform mole, including 157 pregnancies following chemotherapy for GTN, was comparable to the general population.

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