18 Establishment of Regional Centers for Gestational Trophoblastic Disease Follow-Up and Referral and Gestational Trophoblastic Disease Registry

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18.1 Introduction

Gestational Trophoblastic Disease (GTD) develops as a result of abnormal proliferation of placental trophoblast and includes the benign complete and partial hydatidiform moles (CHM and PHM) as well as the malignant versions such as Choriocarcinoma (CC), invasive mole (IM), Placental Site Trophoblastic Tumor (PSTT), and Epithelioid Trophoblastic Tumor (ETT). The malignant forms of the condition are collectively referred to as Gestational Trophoblastic Neoplasia (GTN).

Regular surveillance following hydatidiform mole is crucial for the timely detection and management of the potentially fatal gestational trophoblastic neoplasia. Such fatalities are avoidable if there is a system of regular follow-up using highly sensitive and validated hCG assay platforms. Regional GTD referral centers play a key role in ensuring optimum diagnosis and management of Gestational Trophoblastic Neoplasia.

GTD centers should have a standardized evidence-based protocol to diagnose and manage cases of gestational trophoblastic disease and in addition foster research by facilitating prospective studies. Clinical datasets should be stored in a secure electronic format and made accessible for future analyses.

18.2 The Setting

GTD referral centers and the associated registries can be started in Government/Private teaching hospitals with the aim of developing a network of expertise including the departments of Obstetrics and Gynecology, Gynecologic oncology, Medical,

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B. Nayak, U. Singh (eds.), *Gestational Trophoblastic Disease*,
https://doi.org/10.1007/978-981-33-4878-3_18

Surgical and Radiation oncology, clinical imaging facilities (including ultrasonography [USG], CT, and MRI scanning), pathologists with expertise in the diagnosis of GTD and a clinical chemistry laboratory service with facilities for hormonal assays. These centers should set up outpatient GTD referral clinics on fixed days of the week with standardized pathways accessible to all referring physicians that should stipulate the minimum dataset required to make a referral to GTD centers. Oversight and supervision will be the responsibility of a group of clinicians who wish to develop a special interest in GTD within the department of Obstetrics and Gynecology and led by senior faculty members with expertise in GTD management. All referred cases should be streamlined for registration and review in this clinic. The services should include counseling and psychological support for the patient and her family. Funding for such GTD centers may be collaboratively secured from state and central government departments as well as charitable organizations. GTD centers should register, monitor, and treat women with gestational trophoblastic disease as well as audit treatment outcomes and maintain prospective clinical datasets for education and research. They should also host a website that provides relevant information to referring physicians and patients. A network of communication including appropriate use of electronic and social media should be set up to foster long-term relationships between GTD centers, referring physicians, and patients.

18.3 The Registry

The protocol-based prospective analysis and treatment results of GTD cases should be recorded and maintained in electronic format for future research and evaluation of treatment results. This should also allow effective communication with patients to ensure engagement with their care, monitoring, and education. Treatment results of various regimens should be collated with details of USG findings, β-hCG values, and histopathological results along with epidemiological data (Data collection sheet is attached as Appendix).

18.4 The Key Ingredients

1. Diagnosis of molar pregnancy
2. Sensitive hCG assay
3. The expert clinical team
4. Protocol-based management

18.5 Diagnosis: Ultrasonography and Histopathological Evaluation

The classical presentation of a molar pregnancy with uterine size disproportionately larger than the period of amenorrhea, associated with hyperemesis, bleeding, bilateral lutein cysts, early-onset preeclampsia, and thyrotoxicosis is rare

nowadays, thanks to the availability of USG in the early evaluation of pregnancy [1]. Molar changes may be evident on ultrasonography beyond 10 weeks, and pathological confirmation is usually straightforward in the late first trimester or in the early second trimester. However, it may be difficult to make a diagnosis of hydatidiform mole if a USG is performed for vaginal bleeding in early pregnancy at ≤8 weeks and reported as a failing pregnancy. Hence, all products of conception should be sent for histopathological evaluation in such instances. The services of an expert pathologist are essential for the diagnosis of molar pregnancy in the first trimester. Facilities for immunohistochemistry for imprinted genes such as $p57^{kip2}$ [2] may be necessary in certain cases. The timely diagnosis of a molar pregnancy is crucial for such patients to be registered for regular follow-up. Further clarification of the diagnosis as complete or partial mole is also important given the differences in the risk of malignant transformation (15–20% in complete mole versus 1–5% in partial mole).

18.6 Expert Pathologist

The classical pathological appearance of late first trimester or early second-trimester hydatidiform mole may not be present in early first trimester hydatidiform mole, and therefore, the input of an expert pathologist is necessary to establish the diagnosis. Development of GTN is not dependent on gestational age at evacuation but on the type of abnormal pregnancy, i.e., complete versus partial mole [3]. Such differentiation is a key step in ensuring regular follow-up for the patient group at high risk of GTN.

18.7 hCG Assay

Human Chorionic Gonadotrophin (hCG) is a highly sensitive tumor marker for the follow-up and management of GTD. All types of trophoblastic cells secrete hCG; however, in GTN, there is a higher incidence of abnormal hCG molecules compared to normal pregnancy. Routine hCG assay systems used for the confirmation of pregnancy may not pick up abnormal types of hCG seen in GTN. Assay platforms that reliably detect and quantify all types of hCG, including hyperglycosylated hCG, nicked hCG, free β-hCG, and hCG without C-terminal should be used in GTD centers for surveillance of GTD patients. The Siemens IMMULITE system has been validated for accurate detection of such abnormal hCG types seen in malignant trophoblastic disease [4]. Whenever the hCG level does not correlate with the clinical scenario, alternative assays should be used to rule out false-positive results. Phantom hCG due to heterophilic antibodies can be excluded by testing for the presence of hCG in the urine which will be absent in cases of spurious assay results.

18.8 The Clinical Team

The head of the department of Obstetrics and Gynecology should have operational oversight of GTD centers. The department should run a specialist clinic, "The Trophoblastic Disease Clinic" on a fixed day of the week, separate from the routine OP day of the unit. A senior member of the faculty, preferably from the unit of the head of the department, will be responsible for running the clinic. They will be assisted by other junior faculty members and postgraduate students. All patients will be registered in the GTD center and prospectively followed up according to the standard operating protocol. The patients diagnosed with Gestational Trophoblastic Neoplasia (GTN) should be assessed by the tumor board to decide on the indications for chemotherapy and the particular regimen for each patient.

18.9 The Tumor Board

The board will be chaired by the head of the department of obstetrics and gynecology and consist of the faculty member in charge of the GTD clinic, gynecological oncologist, medical oncologist, surgical oncologist, radiation oncologist, and the pathologist. The board should schedule regular meetings at least on a fortnightly basis to recommend individualized management plans for patients including the appropriate chemotherapeutic regimen.

18.10 Ultrasonography

The classic ultrasonographic appearance of "snowstorm" appearance of CHM is rarely seen nowadays as ultrasonography is performed early for evaluation of pregnancy [5] especially if they present with bleeding or other symptoms in the first trimester. Suspicious cases should undergo evacuation under general anesthesia after preliminary evaluation and the products should be submitted for histopathological examination by the expert pathologist. The typical histopathological features will not be evident in the early stages (≤8 weeks), and therefore, this requires input from such experts.

Early-stage molar pregnancy may be misdiagnosed as anembryonic pregnancy, blighted ovum, or missed abortion and managed by medical abortion. Such patients may expel the products of conception at home, and it is likely that no histopathological examination will be made. Therefore, all products of conception in early pregnancy loss should be submitted for histopathological analysis even if USG does not suggest typical molar pregnancy [6, 7]. Early evacuation of a molar pregnancy alone does not reduce the risk of subsequent development of GTN. It is advisable to perform a urine pregnancy test 4 weeks after any abortion to confirm regression of hCG levels to baseline. Any persistent elevation in hCG levels at this stage warrants further evaluation.

18.11 Registration

All patients with a diagnosis of Gestational Trophoblastic Disease should be registered in the specialist referral centers. Patients should sign a form after informed consent confirming their willingness to have the necessary follow-up as per the management protocol including the relevant investigations and treatment and consent for the use of their anonymized clinical data for research purposes. Patients should be assigned a unique ID for the retrieval of their data. Contact details should be stored separately to encourage adherence to follow-up visits.

18.12 The Protocol

All patients with suspected molar pregnancy should undergo suction evacuation under general anesthesia, preferably with ultrasound guidance. Pre-evacuation hCG assay and complete blood count are mandatory. With a larger uterine size and a higher risk of heavy bleeding, oxytocin infusion may be considered to reduce the bleeding during evacuation. Gentle curettage of the uterine cavity will help to ensure complete evacuation. The specimen should be submitted for histopathological examination to confirm the diagnosis and type of molar pregnancy—especially to differentiate complete from partial hydatidiform mole. Rh-negative patients should receive anti-D immunoglobulin. Following evacuation, patients are advised to use low-dose COC pills for contraception.

Patients are then asked to report 1 week after evacuation for ultrasonographic evaluation to ensure complete evacuation of the products of conception. Repeat curettage is not indicated if there is no USG evidence of retained tissue.

18.13 Prophylactic Chemotherapy

Routine use of prophylactic chemotherapy at the time of the evacuation of the mole is not recommended. Patients with high-risk features such as uterine size 4 weeks more than period of amenorrhea, pre-evacuation hCG of 100,000 IU/L and above, bilateral theca lutein cysts, elderly multiparas, and those who may not have reliable follow-up may benefit from prophylactic chemotherapy. A proportion of these patients may develop GTN and have resistant disease.

18.14 Follow-Up

All patients after evacuation of a molar pregnancy should have regular follow-up with weekly serum β-hCG assay until negative, to enable early diagnosis of GTN and ensure complete cure.

In complete mole, if β-hCG becomes negative within 8 weeks of evacuation, only six more months' follow-up is required from the date of evacuation. If more

than 8 weeks are required for β-hCG to normalize, then six additional months' follow-up is required from the date of normalization of hCG with monthly β-hCG measurements. In cases of partial hydatidiform mole, following hCG normalization, a repeat hCG evaluation is done after 1 month and if negative, no further follow-up is required [8, 9].

18.15 Diagnosis of GTN

- Rising trend (>10% increase) in hCG across three values over two consecutive weeks
- Plateauing of four consecutive values over 3 weeks (<10% fall from the previous week)
- Persistence of hCG more than 6 months following evacuation
- Histological diagnosis of choriocarcinoma

Once the diagnosis of GTN is made, the patient is managed by the gynecologic oncology/medical oncology team. In our institution (Government Medical College, Calicut, Kerala), low-risk cases requiring single-agent chemotherapy are managed by the gynecology team running the follow-up clinics with expert input from the tumor board.

18.16 Evaluation of Metastases in GTN

Once the diagnosis of GTN is confirmed, further imaging must be arranged to detect metastases and for staging and risk scoring. Chest X-ray may be adequate for the detection of lung metastasis. Pelvic ultrasonography with Doppler study will help to identify localized growth in the uterus. If chest X-ray confirms secondaries, then CT abdomen and MRI brain should also be performed [10].

18.17 Staging and Risk Score to Determine Choice of Chemotherapy

FIGO 2000 Anatomical staging and the modified WHO scoring adopted by FIGO in 2000 [11] are used worldwide to determine the type of chemotherapy and is recommended for risk stratification.

GTN with FIGO stage I, II, and III and a risk score of ≤6 are treated with single-agent chemotherapy.

GTN with FIGO stage I, II, and III risk with a risk score of ≥7 or stage IV are treated with multi-agent chemotherapy.

18.18 Choice of Single-Agent Chemotherapy for Low-Risk GTN

Based on our experience [12] of achieving 92.9% cure with a Methotrexate and Folinic rescue regimen (MTX/FA) in the management low-risk GTN, this is the treatment of choice in low-risk patients.

18.18.1 MTX/FA Rescue Regimen

Inj. methotrexate 1 mg/kg on days 1, 3, 5, and 7 and inj. Folinic acid on days 2, 4, 6, and 8 by intramuscular route. Folinic acid is given 24 h after methotrexate. The course is repeated every 2 weeks and two to three additional courses are recommended after hCG assays become negative. Complete blood count, LFT, and RFT are done before starting every course. Anemia, infection, and impaired liver and renal function will aggravate the toxicity of methotrexate.

18.18.2 Actinomycin-D

Actinomycin-D is an effective single agent for low-risk GTN, and the usual regimen is 0.5 mg I/V for 5 days, repeated every 2 weeks. Extravasation of Actinomycin will result in sloughing of the local area with severe pain (local infiltration with 100 mg Hydrocortisone and 2 ml of 1% Xylocaine will reduce the severity of such local reaction).

18.19 Low-Risk GTN with Score 5 and 6

It is reported that low-risk GTN with scores of 5 and 6 may not respond well to single-agent chemotherapy. In order to reduce the toxicity, such patients may also be treated using single-agent chemotherapy and the majority may respond. For those who are showing poor response with hCG levels between 100 and 300 IU/L, a second agent such as Actinomycin-D following MTX/FA regimen may achieve cure. The patients with a risk score of 5 and 6 showing poor response to a single agent with hCG levels above 300 IU/L will require multi-agent therapy.

18.20 High-Risk GTN

High-risk GTN is managed by EMA-CO regimen (etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine). Patients who fail to respond to EMA-CO can be managed with salvage therapies such as EP-EMA, TP/TE, MBE, ICE, or BEP regimens achieving a cure rate of 95%.

18.21 Ultrahigh-Risk GTN

Patients with a risk score of 13 and above and with massive liver and brain metastases do poorly when treated with first-line multi-agent chemotherapy. Standard chemotherapy may cause sudden tumor collapse with bleeding, metabolic acidosis, myelosuppression, septicemia, and multiorgan failure which may be fatal. They are best managed by induction therapy with etoposide 100 mg/m^2 and Cisplatin 20 mg/m^2 on days 1 and 2, repeated weekly for 1–3 weeks before starting the full regimen.

18.22 Follow-Up After GTN

After treatment of GTN, follow-up with monthly hCG assays is required for 1 year for identification of relapses. Patients should be advised of reliable contraception during follow-up. Future fertility, pregnancy, and babies are not affected. Patients who had molar pregnancy without development of GTN need not have any follow-up after subsequent pregnancy.

18.23 Twin Pregnancy with Mole and Baby

There is no extra risk of malignancy in twins with normal fetus and pregnancy may be allowed to continue after counseling regarding the risk of bleeding and need for surgical management, after confirming the normality of the baby by amniocentesis and karyotyping.

18.24 Role of Surgery

Emergency laparotomy and hysterectomy may be required in cases of invasive mole leading to perforation of uterus with severe intraperitoneal bleeding. Neurosurgery may be required in cases of intracranial bleeding or raised intracranial pressure. Resection of localized drug-resistant tumor may also be curative.

18.25 Our Experience

The author's group has started a trophoblastic disease follow-up and referral center at Government Medical College, Calicut, Kerala, in 1990. Calicut Medical College serves as the tertiary care teaching hospital catering to the four northern districts of Kerala with an annual delivery rate of more than 25,000 deliveries during this period. From 1990 to 2005, we had 1569 cases of hydatidiform mole, and 321 cases were diagnosed as GTN (20.4%). By ensuring regular follow-up of cases, GTN was diagnosed at a very early stage and 92.9% had complete cure with Methotrexate and Folinic Acid. Patients needing single-agent chemotherapy

were treated in the Gynecology department. Only 7.1% needed multi-agent chemotherapy [12]. There were no fatalities and many patients subsequently conceived and had normal deliveries. The center continues to function well as a leading center for trophoblastic diseases.

Appendix

Data collection for GTD register

Name ——————— Age ———————

Address ———————

Mail ID ——————— Phone no. ———————

Parity——————— LMP ———————

Period of gestation in weeks ———————

Clinical presentation

Hyperemesis ——————— Bleeding P/V ———————

Passing of vesicles ———————

USG findings ———————

Complete mole/partial mole ———————

Blood gp. CBC, TSH, Pre-evacuation hCG

Method of evacuation ———————

Histopathology

USG after 1 week- residual products- repeat curettage.

Weekly serum hCG hCG after 4 weeks (> 20,000 IU/L—Chemotherapy)

Post evacuation bleeding

Persistence of lutein cysts Sub-urethral nodule

Plateauing/rise in hCG GTN

Metastatic workup X-ray chest, USG abdomen, CT abdomen, MRI brain

Chemotherapy regimen

No. of courses—Response

Follow-up

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