MEDWIN PUBLISHERS
Committed to Create Value for researchers

Open Access Journal of Gynecology
ISSN: 2474-9230

Gestational Trophoblastic Neoplasia

Wanjari S*

Professor, Department of Obstetrics & Gynaecology, Mahatma Gandhi Institute of Medical Sciences, India

***Corresponding author:** Sanjivani Wanjari, Professor, Department of Obstetrics & Gynaecology, Mahatma Gandhi Institute of Medical Sciences, Sewagram, India, Tel: 9822573624; Email: sanjivaniwanjari@yahoo.com

Review Article

Volume 5 Issue 1

Received Date: April 27, 2020

Published Date: June 04, 2020

DOI: 10.23880/oajg-16000193

Abstract

Introduction: Gestational trophoblastic neoplasia (GTN) account for less than 1% of cancers of the female reproductive system. Nearly 50% of gestational choriocarcinomas are seen after molar pregnancies. About 25% after abortions or ectopic pregnancy and another 25% after a normal pregnancy. FIGO staging and prognostic scoring index of modified WHO classification is used. Serum β-HCG assay is an important factor in the diagnosis and management of GTN. It is a sensitive tumour marker for GTN and its level is directly related to the number of viable tumour cells. Serial measurement of β-hCG levels is useful for follow-up of women diagnosed with complete or partial mole. An increasing level or plateauing of serum β-hCG is diagnostic of invasive disease which can be invasive mole or choriocarcinoma.

Case Report: Patient A-was a 22 year old lady, para1, two year old child which was a normal delivery. She was asymptomatic and reported to the hospital for missed periods. Urine pregnancy test was positive. Ultrasound scan did not find any pregnancy. Beta HCG levels were very high. Then MRI was done which showed no abnormality, other than a bulky uterus. Curettage was done and the report came as trophoblastic tissue seen with possibility of choriocarcinoma. This patient was given 2 cycles of methotrexate with folinic acid after which the patient was lost to follow up.

Patient B-was a 27 year old lady, para1, three year old child delivered by caesarean section. She also gave history of two subsequent abortions. She presented with menorrhagia and on examination a cervical polyp was detected. The polyp was resected and sent for histo-pathology and the report suggested choriocarcinoma. Her beta HCG was 30,000. This patient was given three cycles of multi-agent chemotherapy, MAC (Methotrexate, Actinomycin-D and Cyclophosphamide) regime and responded to treatment.

Discussion: The main stay of treatment is chemotherapy. Mostly single agent chemotherapy is used methotrexate being the drug of choice. Methotrexate in the dose of 0.4 mg/kg IM or IV daily for 5 days, appears to be the most effective treatment protocol. Another widely used regimen is using folinic acid along with methotrexate. Some of the more commonly used multi-agent chemotherapy combinations are – MAC, EMA-CO, EMA-EP, VBP and BEP.

Conclusion: GTN can be treated with appropriate chemotherapy and supportive management, after correct staging and scoring of the disease. They are also the most curable of all cancers in women.

Keywords: Gestational Trophoblastic Neoplasia; Chemotherapy; Methotrexate; Prognostic Scoring Index

Introduction

Gestational trophoblastic neoplasia (GTN) account for less than 1% of cancers of the female reproductive system. They are also the most curable of all cancers in women. Most of the gestational trophoblastic tumours are hydatidiform moles and they are mostly benign. The malignant form of gestational trophoblastic disease (GTD) is known as Choriocarcinoma. It is rare, affecting only about 2 to 7 of every 100,000 pregnancies. Nearly 50% of gestational choriocarcinomas are seen after molar pregnancies. About 25% develop in after spontaneous or induced abortions or

ectopic pregnancy. Another 25% may develop after a normal pregnancy.

The World Health Organization WHO has classified gestational trophoblastic disease as follows:

Hydatidform moles

- Hydatidiform mole
- Complete and
- Partial
- Invasive mole

Trophobastic tumours

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

Staging and Prognostic Scoring

The official International Federation of Gynaecology and Obstetrics staging of gestational trophoblastic neoplasia is as follows.

Stage I – Confined to the uterus

Stage II – Limited to the genital structures (adnexa, vagina, and broad ligaments)

Stage III – Lung metastases

Stage IV – Other metastases

The currently used prognostic scoring index is a modification of the World Health Organization (WHO) classification. Scores are determined by adding up points from a list of 19 prognostic factors.

FIGO Scoring	0	1	2	3
Age	<40	>40	-	-
Antecedent Pregnancy	Mole	Absorption	Term	-
Interval months from index Pregnancy	<4	4-7	7-13	>13
Pre-treatment Serum hCG IU/L	$<10^3$	10^3-10^4	10^4-10^5	10^5-10^6
Largest tumour size cm	<3	3-5	>5	-
Site of metastasis	Lung	Spleen, Kidney	GIT	Liver, brain
Number of metastasis	-	1- 4	5- 8	>8
Previous Failed Chemotheraphy	-	-	Single, drug	2 or more drugs

Table 1: Modified WHO Prognostic Scoring System as Adapted by FIGO.

Treatment of Low-risk disease - Patients with non-metastatic (stage I) and low-risk metastatic (stages II and III, score < 7) disease should be treated with single-agent therapy in the form of methotrexate or actinomycin D chemotherapy. Stage IV and high risk (Stage II & III with risk score of >=7) GTN should be treated with multi-agent chemotherapy and/or adjuvant radiotherapy or surgery to achieve clinical response rate of 80-90 %.

Serum β-HCG assay is an important factor in the diagnosis and management of GTN. It is a sensitive tumour marker for GTN and its level is directly related to the number of viable tumour cells. Serial measurement of β-hCG levels is useful for follow-up of women diagnosed with complete or partial mole. The serum hCG levels steadily drop to normal within 8-12 weeks post-evacuation, in 80% of the patients with a benign hydatidiform mole. An increasing level or plateauing of serum β-hCG is diagnostic of invasive disease which can be invasive mole or choriocarcinoma.

Case Report

Recently we has two patients with GTN, both with atypical presentation -

Patient A: was a 22 year old lady who had a two year old child which was a normal delivery. She was asymptomatic and reported to the hospital for missed periods. Her urine pregnancy test was done which came positive. She was then sent for a routine ultrasound scan, which showed no pregnancy. Repeat scan was done to search for intrauterine or extra-uterine pregnancy and also to rule out molar pregnancy. Again the scan did not show any pregnancy. Serum β-hCG levels were done which were very high, 7000 initially. MRI was done which showed no abnormality, other than a bulky uterus. Dilatation and curettage was done and the report came as trophoblastic tissue seen with possibility of choriocarcinoma. This patient was given 2 cycles of methotrexate with folinic acid after which the patient went home and was lost to follow up.

Patient B: was a 27 year old lady, who had a three year old child delivered by caesarean section. She also gave history of two subsequent abortions, no history of dilatation and evacuation. She presented with menorrhagia and on examination a cervical polyp was detected. The polyp was resected and sent for histo-pathology and the report suggested choriocarcinoma. X-ray chest and x-ray skull were done and they were normal. Her β-hCG was 30,000. This patient was given three cycles of multi-agent chemotherapy, MAC (Methotrexate, Actinomycin-D and Cyclophosphamide) regime. After third cycle the β-hCG levels came to < 10mg/dl.

She will now be kept for further follow up [1-10].

Gestational Trophoblastic Neoplasia Includes

Invasive mole: This is when the molar villi are found in the myometrium and rarely in other places. Most invasive moles show marked trophoblastic activity, invasion of myometrium and persistence of villous structures. It is not necessary to make histo-pathological diagnosis of invasive mole, as it is difficult to diagnose from curettings and hysterectomy is rarely done for invasive mole. Chemotherapy can be started on basis of rising β-hCG levels. Invasive mole can be diagnosed because of post-molar bleeding, sub-involution of the uterus and rising HCG levels.

Choriocarcinoma is the malignant transformation of a molar pregnancy or a de novo lesion arising after term pregnancy or abortion. It produces human chorionic gonadotropin (β-hCG) and hence can be diagnosed by increasing or plateauing level of serum β-hCG. The tumour occurs because of abnormality of syncytiotrophoblast and cytotrophoblasts, which lack chorionic villi. It has the potential to invade pelvic structures and metastasize to distant sites like lungs, brain and other sites.

Non-gestational choriocarcinoma have a less favourable prognosis as compared to gestational choriocarcinoma and also they can be less responsive to chemotherapy.

Placental-site trophoblastic tumor (PSTT) is a very rare form of GTN. This tumour can develop after a normal pregnancy or abortion, or may also develop after evacuation of complete or partial mole. These tumours are locally invasive and have a tendency to invade the myometrium of the uterus. Mostly they do not spread to other sites in the body. Placental-site trophoblastic tumours represent neoplastic proliferation of intermediate cytotrophoblasts. Hence they produce more of hPL as compared to HCG (as there are less number of syncitiotrophoblast) and hence HCG may not serve as a tumour marker for follow up of these tumours. PSTTs are not sensitive to chemotherapy drugs. Hence they are usually treated with surgery in the form of hysterectomy in order to completely remove the disease.

Epithelioid trophoblastic tumor (ETT) is an extremely rare type of GTN that can be difficult to diagnose. Epithelioid trophoblastic tumours occur more commomnly after a full-term pregnancy. Also, like placental-site trophoblastic tumours, epithelioid trophoblastic tumours, do not respond very well to chemotherapy. Hence the main treatment of the disease is surgery in the form of hysterectomy. Metastasis are common and hence they have a poor prognosis.

Management of GTN

Surgery for GTN: Suction evacuation is done as a primary measure to remove the complete or partial mole. Repeat dilatation and curettage can be done in patients with persistent disease as found on pelvic ultrasonography. Repeat D&C can help reduce the number of chemotherapy cycles needed to achieve remission.

Hysterectomy: Hysterectomy can be done for several reasons. Hysterectomy reduces the dose of chemotherapy needed to achieve complete remission in women with low risk GTN. A hysterectomy is the treatment of choice for PSTT, but the ovaries need not be removed if the patient is premenopausal. Also hysterectomy can be performed for epitheloid trophoblastic tumours ETT or other types of chemo-resistant disease. Emergency hysterectomy may be necessary in case of uncontrolled haemorrhage.

Chemotherapy: Patients with non-metastatic GTN and those with metastatic low-risk GTN can be treated with single-agent chemotherapy. For single agent chemotherapy, methotrexate is the drug of choice. Methotrexate in the dose of 0.4 mg/kg IM or IV daily for 5 days, appears to be the most effective treatment protocol. Another widely used regimen is using folinic acid along with methotrexate (Bagshawe & Wilde). The folinic acid rescue allows higher doses of methotrexate to be used. This regimen includes giving injection Methotrexate 1mg/kg body weight on days 1, 3, 5 & 7 and injection Folinic acid 0.01mg/kg body weight in day 2, 4, 6 & 8. The cycle can be repeated if necessary to achieve complete remission in non-metastatic and low risk metastatic GTD. Each cycle consists of eight days of chemotherapy, followed by 7-day rest period and then the cycle is repeated again. Methotrexate cycles are continued until levels of serum β-hCG remain normal for a few weeks [11-20].

Some of the more commonly used multi-agent chemotherapy combinations are -

- MAC - methotrexate/leucovorin, actinomycin-D, and cyclophosphamide or chlorambucil
- EMA-CO - etoposide, methotrexate/leucovorin, and actinomycin-D, followed a week later by cyclophosphamide and vincristine (Oncovin)
- EMA-EP - etoposide, methotrexate/leucovorin, and actinomycin-D, followed a week later by etoposide and cisplatin ("platinum")
- VBP - vinblastine, bleomycin, and cisplatin
- BEP - bleomycin, etoposide, cisplatin

Radiotherapy is not used very often to treat gestational trophoblastic disease (GTN). It is used when the disease has spread widely and is not responding to chemotherapy.

Cure rates for GTD: Cure rates are nearly 100% for women with complete or partial moles and low-risk GTD. For high-risk GTD cure rates are good and can be as high as 80% to 90%. But they will probably require more intensive treatment in the form of combination chemotherapy and sometimes radiotherapy and/or surgery [21-30].

References

1. Seckl MJ, Sebire NJ, Berkowitz RS (2010) Gestational trophoblastic disease. Lancet 376(9742): 717-729.

2. Altieri A, Franceschi S, Ferlay J, Smith J, La Vecchia C (2003) Epidemiology and aetiology of gestational trophoblastic diseases. Lancet Oncol 4(11): 670-678.

3. Ngan HY, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, et al. (2015) Update on the diagnosis and management of gestational trophoblastic disease. Int J Gynaecol Obstet 131(S2): S123-S126.

4. Lurain JR (2010) Gestational trophoblastic disease. I. Epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. Am J Obstet Gynecol 203(6): 531-539.

5. Stevens FT, Katzorke N, Tempfer C, Kreimer U, Bizjak GI, et al. (2015) Gestational trophoblastic disorders: an update in 2015. Geburtshilfe Frauenheilkd 75(10): 1043-1050.

6. Garrett LA, Garner EIO, Feltmate CM, Goldstein DP, Berkowitz RS (2008) Subsequent pregnancy outcomes in patients with molar pregnancy and persistent gestational trophoblastic neoplasia. J Reprod Med 53(7): 481-486.

7. Garavaglia E, Gentile C, Cavoretto P, Spagnolo D, Valsecchi L, et al. (2009) Ultrasound imaging after evacuation as an adjunct to beta-hCG monitoring in posthydatidiform molar gestational trophoblastic neoplasia. Am J Obstet Gynecol 200(4): 417.e1-5.

8. Agarwal R, Harding V, Short D, Fisher RA, Sebire NJ, et al. (2012) Uterine artery pulsatility index: a predictor of methotrexate resistance in gestational trophoblastic neoplasia. Br J Cancer 106(6): 1089-1094.

9. Berkowitz RS, Goldstein DP (2009) Current management of gestational trophoblastic diseases. Gynecol Oncol 112(3): 654-662.

10. Darby S, Jolley I, Pennington S, Hancock BW (2009) Does chest CT matter in the staging of GTN? Gynecol Oncol 112(1): 155-160.

11. FIGO Oncology Committee (2002) FIGO staging for gestational trophoblastic neoplasia 2000, FIGO Oncology Committee. International Journal of Gynecology & Obstetrics 77(3): 285-287.

12. Lurain JR (2003) Pharmacotherapy of gestational trophoblastic disease. Expert Opin Pharmacother 4(11): 1-13.

13. Alazzam M, Tidy J, Hancock BW, Osborne R (2009) First line chemotherapy in low risk gestational trophoblastic neoplasia. Cochrane Database Syst Rev 1: CD007102.

14. RCOG (2010) The Management of Gestational Trophoblastic Disease Green–top Guideline No. 38. Royal college of Obstetricians and Gynaecologists.

15. Foulmann K, Guastalla JP, Caminet N, Trillet-Lenoir V, Raudrant D, et al. (2006) What is the best protocol of single-agent methotrexate chemotherapy in nonmetastatic or low-risk metastatic gestational trophoblastic tumors? A review of the evidence. Gynecol Oncol 102(1): 103-110.

16. Roberts JP, Lurain JR (1996) Treatment of low-risk metastatic gestational trophoblastic tumors with single-agent chemotherapy. Am J Obstet Gynecol 174(6): 1917-1923.

17. Matsui H, Suzuka K, Yamazawa K, Tanaka N, Mitsuhashi A, et al. (2005) Relapse rate of patients with low-risk gestational trophoblastic tumor initially treated with single-agent chemotherapy. Gynecol Oncol 96(3): 616-620.

18. Kohorn EI (2002) Is lack of response to single-agent chemotherapy in gestational trophoblastic disease associated with dose scheduling or chemotherapy resistance. Gynecol Oncol 85(1): 36-39.

19. Ngan HY, Odicino F, Maisonneuve P, Creasman WT, Beller U, et al. (2006) Gestational trophoblastic neoplasia. FIGO 6th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet 95(S1): S193-S203.

20. Li MC, Hertz R, Spencer DB (1956) Effect of methotrexate therapy on choriocarcinoma and chorioadinoma. Proc Soc Exp Biol Med 93(2): 361-366.

21. Hammond CB, Hertz R, Ross GT, Lipsett MB, Odell WD (1967) Primary chemotherapy for nonmetastatic gestational trophoblastic neoplasms. Am J Obstet Gynecol 98(1): 71-78.

22. Hammond CB, Borchert LG, Tyrey L, Creasman WT, Parker RT (1973) Treatment of metastatic trophoblastic disease: good and poor prognosis. Am J Obstet Gynecol 115(4): 451-457.

23. Lurain JR, Elfstrand EP (1995) Single-agent methotrexate chemotherapy for the treatment of non-metastatic gestational trophoblastic tumors. Am J Obstet Gynecol 172(2): 574-579.

24. Bagshawe KD, Dent J, Newlands ES, Begent RH, Rustin GJ (1989) The role of low-dose methotrexate and folinic acid in gestational trophoblastic tumours (GTT). Br J Obstet Gynaecol 96(7): 795-802.

25. Berkowitz RS, Goldstein DP, Bernstein MR (1986) Ten years' experience with methotrexate and folinic acid as primary therapy for gestational trophoblastic disease. Gynecol Oncol 23(1): 111-1118.

26. Osborne RJ, Filiaci V, Schink JC, Mannel RS, Alvarez Secord A, et al. (2011) Phase III trial of weekly methotrexate or pulsed dactinomycin for low-risk gestational trophoblastic neoplasia: a gynecologic oncology group study. J Clin Oncol 29(7): 825-831.

27. Newlands ES, Mulholland PJ, Holden L, Seckl MJ, Rustin GJ (2000) Etoposide and cisplatin/etoposide, methotrexate, and actinomycin D (EMA) chemotherapy for patients with high-risk gestational trophoblastic tumors refractory to EMA/cyclophosphamide and vincristine chemotherapy and patients presenting with metastatic placental site trophoblastic tumors. J Clin Onco 18(4): 854-859.

28. Van Trommel NE, Massuger LF, Verheijen RH, et al. (2005) The curative effect of a second curettage in persistent trophoblastic disease: a retrospective cohort survey. Gynecol Oncol 99(1): 6-13.

29. Suzuka K, Matsui H, Iitsuka Y, Yamazawa K, Seki K, et al. (2001) Adjuvant hysterectomy in low-risk gestational trophoblastic disease. Obstet Gynecol 97(3): 431-434.

30. Berkowitz BJ, Jones JG, Merkatz IR, Runowicz CD (1990) Ovarian conservation in placental site trophoblastic tumor. Gynecol Oncol 37(2): 239-243.