GESTASYONEL TROFOBLASTİK TÜMÖRLER

26. BÖLÜM

Ezgi Ceren DALLI ALPER [1]

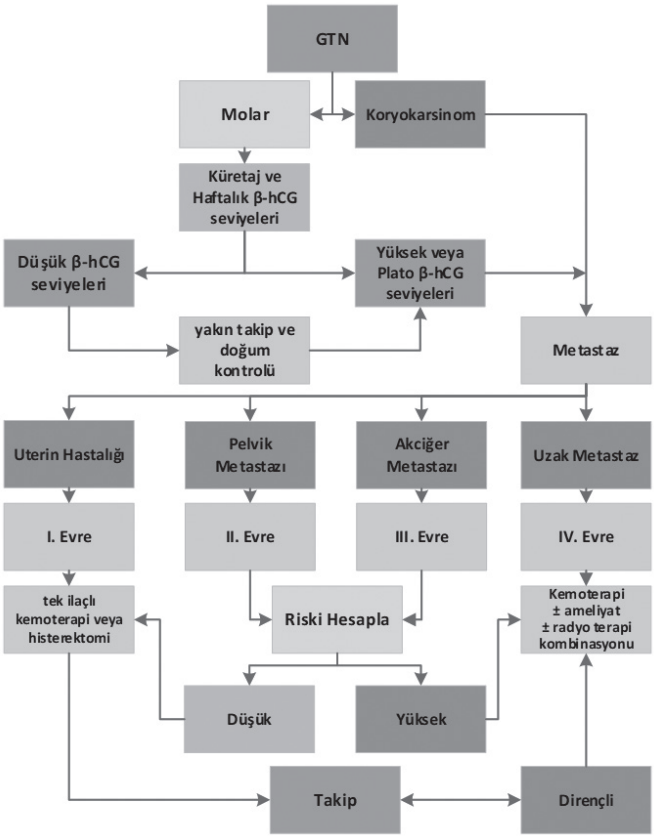
GİRİŞ

Gestasyonel trofoblastik hastalıklar, plasental trofoblastların anormal proliferasyonundan kaynaklanan heterojen bir lezyon grubunu içerir. Gestasyonel trofoblastik hastalıkların patogenezi benzersizdir çünkü lezyonlar fetal dokudan kaynaklanır, maternal kaynaklı değildir. Gestasyonel Trofoblastik Neoplazi (GTN), trofoblastik dokuların anormal proliferasyonundan oluşan bir grup malign neoplazmı ifade etmektedir. Hidatiform mol veya molar olmayan bir gebeliği takiben oluşabilir. Histolojik tiplendirme; İnvazif mol, Koryokarsinom, Plasental Yerleşimli Trofoblastik Tümörler, Epiteloid Trofoblastik Tümörler olmak üzere 4 gruba ayrılır. (1)

GTN molar olmayan gebelik veya canlı doğumdan sonra gerçekleşebilir. (2) GTN insidansını kesin olarak saptamak zordur çünkü çoğu ülkeden yeterli veri toplanamamaktadır. GTN vakalarının yaklaşık %50' si molar gebelik kaynaklı, %25' i düşük veya tubal gebelikten ve yüzde %25' i de term veya preterm gebelikten kaynaklanmaktadır. (3) GTN molar gebelikten sonra geliştiğinde çoğunlukla molar doku veya koryokarsinoma rastlanır, nadiren plasental yerleşimli trofoblastik tümörler ya da epiteloid trofoplastik tümörler görülebilir. Komplet hidatiform sonrası hastaların %15' inde lokal invazyon, %5' inde metastatik hastalık gelişmesi beklenmektedir. Genellikle metastatik olmayan GTN, parsiyel mol hidatiform sonrası hastaların %1-4' ünde görülür. (4)

Molar olmayan gebelik sonrası gelişen GTN, genellikle koryokarsinom, nadiren plasental yerleşimli trofoblastik tümörler veya epiteloid trofoblastik tümörler olarak görülebilir. Avrupa ve Kuzey Amerika'da yaklaşık 2-7/100.000 oranında ortaya çıkarken, Güneydoğu Asya ve Japonya'da insidans sırasıyla 100.000

[1] Op. Dr., Sağlık Bilimleri Üniversitesi, Ümraniye Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum ezgicerendalli@gmail.com



Şekil-1: Gestasyonel trofoblastik tümörün yönetimi. GTN, gestasyonel trofoblastik neoplazi; hCG, insan koryonik gonadotropini; RT, radyoterapi.

KAYNAKÇA

1. Ngan HYS, Seckl MJ, Berkowitz RS, et al. Update on the diagnosis and management of gestational trophoblastic disease. *Int J Gynecol Obstet*. 2018;143:79-85. doi:10.1002/ijgo.12615
2. Management of Gestational Trophoblastic Disease: Green-top Guideline No. 38 – September 2020. *BJOG An Int J Obstet Gynaecol*. 2020. doi:10.1111/1471-0528.16266
3. Ngan S, Seckl MJ. Gestational trophoblastic neoplasia management: an update. *Curr Opin Oncol*. 2007;19(5):486-491. doi:10.1097/CCO.0b013e3282dc94e5
4. Goldstein DP, Berkowitz RS. Current Management of Gestational Trophoblastic Neoplasia. *Hematol Oncol Clin North Am*. 2012;26(1):111-131. doi:10.1016/j.hoc.2011.10.007
5. BRINTON LA, BRACKEN MB, CONNELLY RR. CHORIOCARCINOMA INCIDENCE IN THE UNITED STATES. *Am J Epidemiol*. 1986;123(6):1094-1100. doi:10.1093/oxfordjournals.aje.a114337
6. Smith HO. Gestational trophoblastic disease epidemiology and trends. *Clin Obstet Gynecol*. 2003;46(3):541-556. doi:10.1097/00003081-200309000-00006
7. Sebire NJ, Foskett M, Fisher RA, Lindsay I, Seckl MJ. Persistent gestational trophoblastic disease is rarely, if ever, derived from non-molar first-trimester miscarriage. *Med Hypotheses*. 2005;64(4):689-693. doi:10.1016/j.mehy.2004.11.032

8. Ngan HYS, Seckl MJ, Berkowitz RS, et al. Update on the diagnosis and management of gestational trophoblastic disease. *Int J Gynecol Obstet*. 2018;143:79-85. doi:10.1002/ijgo.12615
9. Berkowitz RS, Goldstein DP. Molar Pregnancy. *N Engl J Med*. 2009;360(16):1639-1645. doi:10.1056/NEJMcp0900696
10. Seckl MJ, Fisher RA, Salerno G, et al. Choriocarcinoma and partial hydatidiform moles. *Lancet*. 2000;356(9223):36-39. doi:10.1016/S0140-6736(00)02432-6
11. Berkowitz RS, Goldstein DP. Chorionic Tumors. *N Engl J Med*. 1996;335(23):1740-1748. doi:10.1056/NEJM199612053352306
12. Niemann I, Petersen LK, Hansen ES, Sunde L. Predictors of Low Risk of Persistent Trophoblastic Disease in Molar Pregnancies. *Obstet Gynecol*. 2006;107(5):1006-1011. doi:10.1097/01.AOG.0000210635.24543.3b
13. Lurain JR. Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. *Am J Obstet Gynecol*. 2010;203(6):531-539. doi:10.1016/j.ajog.2010.06.073
14. Butler LACSA. *Human Chorionic Gonadotropin (HGC)*. 2nd ed. Elsevier; 2015. doi:10.1016/C2013-0-18593-5
15. Lok CA, Ansink AC, Grootfaam D, van der Velden J, Verheijen RH, ten Kate-Booij MJ. Treatment and prognosis of post term choriocarcinoma in The Netherlands. *Gynecol Oncol*. 2006;103(2):698-702. doi:10.1016/j.ygyno.2006.05.011
16. Diver E, May T, Vargas R, Bernstein M, Goldstein D, Berkowitz R. Changes in clinical presentation of postterm choriocarcinoma at the New England Trophoblastic Disease Center in recent years. *Gynecol Oncol*. 2013;130(3):483-486. doi:10.1016/j.ygyno.2013.06.014
17. Rodabaugh KJ, Bernstein MR, Goldstein DP, Berkowitz RS. Natural history of postterm choriocarcinoma. *J Reprod Med*. 1998;43(1):75-80. http://www.ncbi.nlm.nih.gov/pubmed/9475153.
18. Tidy JA, Rustin GJS, Newlands ES, et al. Presentation and management of choriocarcinoma after nonmolar pregnancy. *BJOG An Int J Obstet Gynaecol*. 1995;102(9):715-719. doi:10.1111/j.1471-0528.1995.tb11429.x
19. van Trommel NE, Lok CAR, Bulten H, Thomas CMG, Massuger LFAG. Long-term outcome of placental site trophoblastic tumor in The Netherlands. *J Reprod Med*. 58(5-6):224-228. http://www.ncbi.nlm.nih.gov/pubmed/23763007.
20. Zhao J, Lv WG, Feng FZ, et al. Placental site trophoblastic tumor: A review of 108 cases and their implications for prognosis and treatment. *Gynecol Oncol*. 2016;142(1):102-108. doi:10.1016/j.ygyno.2016.05.006
21. Baergen RN, Rutgers JL, Young RH, Osann K, Scully RE. Placental site trophoblastic tumor: A study of 55 cases and review of the literature emphasizing factors of prognostic significance. *Gynecol Oncol*. 2006;100(3):511-520. doi:10.1016/j.ygyno.2005.08.058
22. Taylor JS, Viera L, Caputo TA, et al. Unsuccessful planned conservative resection of placental site trophoblastic tumor. *Obstet Gynecol*. 2013;121(2 Pt 2 Suppl 1):465-468. doi:10.1097/aog.0b013e31826d7da6
23. Lan C, Li Y, He J, Liu J. Placental site trophoblastic tumor: lymphatic spread and possible target markers. *Gynecol Oncol*. 2010;116(3):430-437. doi:10.1016/j.ygyno.2009.10.056
24. Newlands ES, Mulholland PJ, Holden L, Seckl MJ, Rustin GJS. 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 Plac. *J Clin Oncol*. 2000;18(4):854-854. doi:10.1200/JCO.2000.18.4.854
25. HASSADIA A, GILLESPIE A, TIDY J, et al. Placental site trophoblastic tumour: Clinical features and management. *Gynecol Oncol*. 2005;99(3):603-607. doi:10.1016/j.ygyno.2005.06.054
26. Hyman DM, Bakios L, Gualtiere G, et al. Placental site trophoblastic tumor: Analysis of presentation, treatment, and outcome. *Gynecol Oncol*. 2013;129(1):58-62. doi:10.1016/j.ygyno.2012.12.029

27. Schmid P, Nagai Y, Agarwal R, et al. Prognostic markers and long-term outcome of placental-site trophoblastic tumours: a retrospective observational study. *Lancet*. 2009;374(9683):48-55. doi:10.1016/S0140-6736(09)60618-8
28. Shih I-M, Kurman RJ. Epithelioid Trophoblastic Tumor. *Am J Surg Pathol*. 1998;22(11):1393-1403. doi:10.1097/00000478-199811000-00010
29. Palmer JE, Macdonald M, Wells M, Hancock BW, Tidy JA. Epithelioid trophoblastic tumor: a review of the literature. *J Reprod Med*. 2008;53(7):465-475. http://www.ncbi.nlm.nih.gov/pubmed/18720920.
30. Horowitz NS, Goldstein DP, Berkowitz RS. Placental site trophoblastic tumors and epithelioid trophoblastic tumors: Biology, natural history, and treatment modalities. *Gynecol Oncol*. 2017;144(1):208-214. doi:10.1016/j.ygyno.2016.10.024
31. Davis MR, Howitt BE, Quade BJ, et al. Epithelioid trophoblastic tumor: A single institution case series at the New England Trophoblastic Disease Center. *Gynecol Oncol*. 2015;137(3):456-461. doi:10.1016/j.ygyno.2015.03.006
32. Frijstein MM, Lok CAR, van Trommel NE, et al. Management and prognostic factors of epithelioid trophoblastic tumors: Results from the International Society for the Study of Trophoblastic Diseases database. *Gynecol Oncol*. 2019;152(2):361-367. doi:10.1016/j.ygyno.2018.11.015
33. Ngan H, Bender H, Benedet JL, et al. Gestational trophoblastic neoplasia, FIGO 2000 staging and classification. *Int J Gynecol Obstet*. 2003;83:175-177. doi:10.1016/S0020-7292(03)90120-2
34. Allen SD, Lim AK, Seckl MJ, Blunt DM, Mitchell AW. Radiology of gestational trophoblastic neoplasia. *Clin Radiol*. 2006;61(4):301-313. doi:10.1016/j.crad.2005.12.003
35. Ng T., Wong L. Diagnosis and management of gestational trophoblastic neoplasia. *Best Pract Res Clin Obstet Gynaecol*. 2003;17(6):893-903. doi:10.1016/S1521-6934(03)00098-1
36. Darby S, Jolley I, Pennington S, Hancock BW. Does chest CT matter in the staging of GTN? *Gynecol Oncol*. 2009;112(1):155-160. doi:10.1016/j.ygyno.2008.10.003
37. Gamer EIO, Garrett A, Goldstein DP, Berkowitz RS. Significance of chest computed tomography findings in the evaluation and treatment of persistent gestational trophoblastic neoplasia. *J Reprod Med*. 2004;49(6):411-414. http://www.ncbi.nlm.nih.gov/pubmed/15283046.
38. Price JM, Hancock BW, Tidy J, Everard J, Coleman RE. Screening for central nervous system disease in metastatic gestational trophoblastic neoplasia. *J Reprod Med*. 55(7-8):301-304. http://www.ncbi.nlm.nih.gov/pubmed/20795342.
39. Dhillon T, Palmieri C, Sebire NJ, et al. Value of whole body 18FDG-PET to identify the active site of gestational trophoblastic neoplasia. *J Reprod Med*. 2006;51(11):879-887. http://www.ncbi.nlm.nih.gov/pubmed/17165434.
40. Numnum TM, Leath CA, Straughn JM, Conner MG, Barnes MN. Occult choriocarcinoma discovered by positron emission tomography/computed tomography imaging following a successful pregnancy. *Gynecol Oncol*. 2005;97(2):713-715. doi:10.1016/j.ygyno.2005.01.049
41. Agarwal R, Teoh S, Short D, Harvey R, Savage PM, Seckl MJ. Chemotherapy and human chorionic gonadotropin concentrations 6 months after uterine evacuation of molar pregnancy: a retrospective cohort study. *Lancet*. 2012;379(9811):130-135. doi:10.1016/S0140-6736(11)61265-8
42. Braga A, Torres B, Burlá M, et al. Is chemotherapy necessary for patients with molar pregnancy and human chorionic gonadotropin serum levels raised but falling at 6months after uterine evacuation? *Gynecol Oncol*. 2016;143(3):558-564. doi:10.1016/j.ygyno.2016.09.012
43. Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. Cham: Springer International Publishing; 2017. doi:10.1007/978-3-319-40618-3
44. Sita-Lumsden A, Short D, Lindsay I, et al. Treatment outcomes for 618 women with gestational trophoblastic tumours following a molar pregnancy at the Charing Cross Hospital, 2000–2009. *Br J Cancer*. 2012;107(11):1810-1814. doi:10.1038/bjc.2012.462

45. Ngan HYS. The practicability of FIGO 2000 staging for gestational trophoblastic neoplasia. *Int J Gynecol Cancer*. 2004;14(2):202-205. doi:10.1111/j.1048-891X.2004.014236.x
46. Lurain JR, Singh DK, Schink JC. Management of metastatic high-risk gestational trophoblastic neoplasia: FIGO stages II-IV: risk factor score > or = 7. *J Reprod Med*. 55(5-6):199-207. http://www.ncbi.nlm.nih.gov/pubmed/20626175.
47. Mackenzie F, Mathers A, Kennedy J. Invasive hydatidiform mole presenting as an acute primary haemoperitoneum. *BJOG An Int J Obstet Gynaecol*. 1993;100(10):953-954. doi:10.1111/j.1471-0528.1993.tb15116.x
48. Lurain JR, Brewer JI, Torok EE, Halpern B. Gestational trophoblastic disease: treatment results at the Brewer Trophoblastic Disease Center. *Obstet Gynecol*. 1982;60(3):354-360. http://www.ncbi.nlm.nih.gov/pubmed/6289207.
49. Braga A, Campos V, Filho JR, et al. Is chemotherapy always necessary for patients with nonmetastatic gestational trophoblastic neoplasia with histopathological diagnosis of choriocarcinoma? *Gynecol Oncol*. 2018;148(2):239-246. doi:10.1016/j.ygyno.2017.12.007
50. Seckl MJ, Rustin GJS, Newlands ES, Gwyther SJ, Bomanji J. Pulmonary embolism, pulmonary hypertension, and choriocarcinoma. *Lancet*. 1991;338(8778):1313-1315. doi:10.1016/0140-6736(91)92603-Y
51. Newlands ES, Holden L, Seckl MJ, McNeish I, Strickland S, Rustin GJS. Management of brain metastases in patients with high-risk gestational trophoblastic tumors. *J Reprod Med*. 2002;47(6):465-471. http://www.ncbi.nlm.nih.gov/pubmed/12092015.
52. Savage P, Kelpanides I, Tuthill M, Short D, Seckl MJ. Brain metastases in gestational trophoblast neoplasia: An update on incidence, management and outcome. *Gynecol Oncol*. 2015;137(1):73-76. doi:10.1016/j.ygyno.2015.01.530
53. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. *Lancet*. 2010;376(9742):717-729. doi:10.1016/S0140-6736(10)60280-2
54. Ross S. Berkowitz, Neil S. Horowitz DPG. Gestational Trophoblastic Neoplasia. In: *Berek and Novak's Gynecology*. 16th ed. Wolters Kluwer; 2020:2756-2794.
55. Nguyen CP. Gestational Trophoblastic Neoplasia. In: Bankowski BJ, Hearne AE, Lambrou NC, Fox HE WE, ed. *The John's Hopkins Manual of Gynecology and Obstetrics*. 2nd ed. Lippincott Williams; 2002.
56. Osborne RJ, Filiaci VL, Schink JC, et al. Second Curettage for Low-Risk Nonmetastatic Gestational Trophoblastic Neoplasia. *Obstet Gynecol*. 2016;128(3):535-542. doi:10.1097/AOG.0000000000001554
57. Hemida R, Vos EL, El-Deek B, et al. Second Uterine Curettage and the Number of Chemotherapy Courses in Postmolar Gestational Trophoblastic Neoplasia. *Obstet Gynecol*. 2019;133(5):1024-1031. doi:10.1097/AOG.0000000000003232
58. Massad L. Poor compliance with postmolar surveillance and treatment protocols by indigent women. *Obstet Gynecol*. 2000;96(6):940-944. doi:10.1016/S0029-7844(00)01064-4
59. Clark RM, Nevadunsky NS, Ghosh S, Goldstein DP, Berkowitz RS. The evolving role of hysterectomy in gestational trophoblastic neoplasia at the New England Trophoblastic Disease Center. *J Reprod Med*. 55(5-6):194-198. http://www.ncbi.nlm.nih.gov/pubmed/20626174.
60. Bolze P-A, Mathe M, Hajri T, et al. First-line hysterectomy for women with low-risk non-metastatic gestational trophoblastic neoplasia no longer wishing to conceive. *Gynecol Oncol*. 2018;150(2):282-287. doi:10.1016/j.ygyno.2018.05.030
61. Eysbouts YK, Bulten J, Ottevanger PB, et al. Trends in incidence for gestational trophoblastic disease over the last 20years in a population-based study. *Gynecol Oncol*. 2016;140(1):70-75. doi:10.1016/j.ygyno.2015.11.014
62. Soper JT. Gestational Trophoblastic Disease. *Obstet Gynecol*. 2021;Publish Ah. doi:10.1097/AOG.0000000000004240
63. Powles T, Savage P, Short D, Young A, Pappin C, Seckl MJ. Residual lung lesions after completion of chemotherapy for gestational trophoblastic neoplasia: should we operate? *Br J Cancer*. 2006;94(1):51-54. doi:10.1038/sj.bjc.6602899

64. Cao Y, Xiang Y, Feng F, Wan X, Yang X. Surgical Resection in the Management of Pulmonary Metastatic Disease of Gestational Trophoblastic Neoplasia. *Int J Gynecol Cancer*. 2009;19(4):798-801. doi:10.1111/IGC.0b013e3181a3d014
65. Fleming EL, Garrett L, Growdon WB, et al. The changing role of thoracotomy in gestational trophoblastic neoplasia at the New England Trophoblastic Disease Center. *J Reprod Med*. 2008;53(7):493-498. http://www.ncbi.nlm.nih.gov/pubmed/18720924.
66. Lurain JR. Pharmacotherapy of gestational trophoblastic disease. *Expert Opin Pharmacother*. 2003;4(11):2005-2017. doi:10.1517/14656566.4.11.2005
67. Lawrie TA, Alazzam M, Tidy J, Hancock BW, Osborne R. First-line chemotherapy in low-risk gestational trophoblastic neoplasia. *Cochrane Database Syst Rev*. June 2016. doi:10.1002/14651858.CD007102.pub4
68. Taylor F, Grew T, Everard J, et al. The outcome of patients with low risk gestational trophoblastic neoplasia treated with single agent intramuscular methotrexate and oral folinic acid. *Eur J Cancer*. 2013;49(15):3184-3190. doi:10.1016/j.ejca.2013.06.004
69. Yashar KA-RBBCCCCCCCDDEFFGHHLMMNNFRRTUW. *NCCN Clinical Practice Guidelines in Oncology: Gestational Trophoblastic Neoplasia, Version 1.2019*.; 2018.
70. Lybol C, Sweep FCGJ, Harvey R, et al. Relapse rates after two versus three consolidation courses of methotrexate in the treatment of low-risk gestational trophoblastic neoplasia. *Gynecol Oncol*. 2012;125(3):576-579. doi:10.1016/j.ygyno.2012.03.003
71. Sharma S, Jagdev S, Coleman RE, Hancock BW, Lorigan PC. Serosal complications of single-agent low-dose methotrexate used in gestational trophoblastic diseases: first reported case of methotrexate-induced peritonitis. *Br J Cancer*. 1999;81(6):1037-1041. doi:10.1038/sj.bjc.6690804
72. Maestá I, Nitecki R, Horowitz NS, et al. Effectiveness and toxicity of first-line methotrexate chemotherapy in low-risk postmolar gestational trophoblastic neoplasia: The New England Trophoblastic Disease Center experience. *Gynecol Oncol*. 2018;148(1):161-167. doi:10.1016/j.ygyno.2017.10.028
73. Alazzam M, Tidy J, Osborne R, Coleman R, Hancock BW, Lawrie TA. Chemotherapy for resistant or recurrent gestational trophoblastic neoplasia. *Cochrane Database Syst Rev*. January 2016. doi:10.1002/14651858.CD008891.pub3
74. Yarandi F, Eftekhar Z, Shojaei H, Kanani S, Sharifi A, Hanjani P. Pulse methotrexate versus pulse actinomycin D in the treatment of low-risk gestational trophoblastic neoplasia. *Int J Gynecol Obstet*. 2008;103(1):33-37. doi:10.1016/j.ijgo.2008.05.013
75. Osborne RJ, Filiaci V, Schink JC, et al. Phase III Trial of Weekly Methotrexate or Pulsed Dactinomycin for Low-Risk Gestational Trophoblastic Neoplasia: A Gynecologic Oncology Group Study. *J Clin Oncol*. 2011;29(7):825-831. doi:10.1200/JCO.2010.30.4386
76. Li L, Wan X, Feng F, et al. Pulse actinomycin D as first-line treatment of low-risk post-molar non-choriocarcinoma gestational trophoblastic neoplasia. *BMC Cancer*. 2018;18(1):585. doi:10.1186/s12885-018-4512-5
77. Covens A, Filiaci VL, Burger RA, Osborne R, Chen MD. Phase II trial of pulse dactinomycin as salvage therapy for failed low-risk gestational trophoblastic neoplasia. *Cancer*. 2006;107(6):1280-1286. doi:10.1002/cncr.22118
78. Kohorn EI. Persistent Low-Level "Real" Human Chorionic Gonadotropin: A Clinical Challenge and a Therapeutic Dilemma. *Gynecol Oncol*. 2002;85(2):315-320. doi:10.1006/gyno.2002.6622
79. Escobar PF, Lurain JR, Singh DK, Bozorgi K, Fishman DA. Treatment of high-risk gestational trophoblastic neoplasia with etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine chemotherapy. *Gynecol Oncol*. 2003;91(3):552-557. doi:10.1016/j.ygyno.2003.08.028
80. Lu W-G, Ye F, Shen Y-M, et al. EMA-CO chemotherapy for high-risk gestational trophoblastic neoplasia: a clinical analysis of 54 patients. *Int J Gynecol Cancer*. 2008;18(2):357-362. doi:10.1111/j.1525-1438.2007.00999.x

81. Patel SM, Desai A. Management of drug resistant gestational trophoblastic neoplasia. *J Reprod Med*. 55(7-8):296-300. http://www.ncbi.nlm.nih.gov/pubmed/20795341.
82. Wang J, Short D, Sebire NJ, et al. Salvage chemotherapy of relapsed or high-risk gestational trophoblastic neoplasia (GTN) with paclitaxel/cisplatin alternating with paclitaxel/etoposide (TP/TE). *Ann Oncol*. 2008;19(9):1578-1583. doi:10.1093/annonc/mdn181
83. Essel KG, Bruegl A, Gershenson DM, Ramondetta LM, Naumann RW, Brown J. Salvage chemotherapy for gestational trophoblastic neoplasia: Utility or futility? *Gynecol Oncol*. 2017;146(1):74-80. doi:10.1016/j.ygyno.2017.04.017
84. Alifrangis C, Agarwal R, Short D, et al. EMA/CO for High-Risk Gestational Trophoblastic Neoplasia: Good Outcomes With Induction Low-Dose Etoposide-Cisplatin and Genetic Analysis. *J Clin Oncol*. 2013;31(2):280-286. doi:10.1200/JCO.2012.43.1817
85. Ahamed E, Short D, North B, Savage PM, Seckl MJ. Survival of women with gestational trophoblastic neoplasia and liver metastases: is it improving? *J Reprod Med*. 57(5-6):262-269. http://www.ncbi.nlm.nih.gov/pubmed/22696824.
86. Berkowitz, RS; Goldstein D. Gestational Trophoblastic Neoplasia. In: *Berek and Hacker's Gynecologic Oncology*. ; 2005:603-628.
87. Bolze P-A, Riedl C, Massardier J, et al. Mortality rate of gestational trophoblastic neoplasia with a FIGO score of ≥13. *Am J Obstet Gynecol*. 2016;214(3):390.e1-390.e8. doi:10.1016/j.ajog.2015.09.083
88. Schorge JO. Williams Gynecology. In: *Williams Gynecology*. 4th ed. ; 2020:774.
89. Ghaemmaghami F, Behtash N, Memarpour N, Soleimani K, Hanjani P, Hashemi FA. Evaluation and management of brain metastatic patients with high-risk gestational trophoblastic tumors. *Int J Gynecol Cancer*. 2004;14(5):966-971. doi:10.1111/j.1048-891X.2004.14536.x
90. Weed JC, Hammond CB. Cerebral metastatic choriocarcinoma: intensive therapy and prognosis. *Obstet Gynecol*. 1980;55(1):89-94. http://www.ncbi.nlm.nih.gov/pubmed/6243407.
91. Jones WB, Wagner-Reiss KM, Lewis JL. Intracerebral choriocarcinoma. *Gynecol Oncol*. 1990;38(2):234-243. doi:10.1016/0090-8258(90)90048-P
92. Small W, Lurain JR, Shetty RM, Huang CF, Applegate GL, Brand WN. Gestational trophoblastic disease metastatic to the brain. *Radiology*. 1996;200(1):277-280. doi:10.1148/radiology.200.1.8657926
93. Cagayan MSFS, Lu-Lasala LR. Management of gestational trophoblastic neoplasia with metastasis to the central nervous system: A 12-year review at the Philippine General Hospital. *J Reprod Med*. 2006;51(10):785-792. http://www.ncbi.nlm.nih.gov/pubmed/17086807.
94. Schechter NR, Mychalczak B, Jones W, Spriggs D. Prognosis of Patients Treated with Whole-Brain Radiation Therapy for Metastatic Gestational Trophoblastic Disease. *Gynecol Oncol*. 1998;68(2):183-192. doi:10.1006/gyno.1997.4920
95. GHAEMMAGHAMI F, ASHRAF-GANJOOIE T. Gestational trophoblastic neoplasia. *Asia Pac J Clin Oncol*. 2006;2(1):9-21. doi:10.1111/j.1743-7563.2006.00035.x
96. Balachandran K, Salawu A, Ghorani E, et al. When to stop human chorionic gonadotrophin (hCG) surveillance after treatment with chemotherapy for gestational trophoblastic neoplasia (GTN): A national analysis on over 4,000 patients. *Gynecol Oncol*. 2019;155(1):8-12. doi:10.1016/j.ygyno.2019.07.024
97. Cagayan MSFS. Sexual dysfunction as a complication of treatment of gestational trophoblastic neoplasia. *J Reprod Med*. 2008;53(8):595-599. http://www.ncbi.nlm.nih.gov/pubmed/18773624.
98. Williams J, Short D, Dayal L, et al. Effect of early pregnancy following chemotherapy on disease relapse and fetal outcome in women treated for gestational trophoblastic neoplasia. *J Reprod Med*. 59(5-6):248-254. doi:24937965
99. Lok CAR, van der Houwen C, ten Kate-Booij MJ, van Eijkeren MA, Ansink AC. Pregnancy after EMA/CO for gestational trophoblastic disease: a report from The Netherlands. *BJOG*. 2003;110(6):560-566. http://www.ncbi.nlm.nih.gov/pubmed/12798472.

100. Cioffi R, Bergamini A, Gadducci A, et al. Reproductive Outcomes After Gestational Trophoblastic Neoplasia. A Comparison Between Single-Agent and Multiagent Chemotherapy. *Int J Gynecol Cancer*. 2018;28(2):332-337. doi:10.1097/IGC.0000000000001175
101. Savage P, Cooke R, O'Nions J, et al. Effects of Single-Agent and Combination Chemotherapy for Gestational Trophoblastic Tumors on Risks of Second Malignancy and Early Menopause. *J Clin Oncol*. 2015;33(5):472-478. doi:10.1200/JCO.2014.57.5332
102. Rustin GJ, Newlands ES, Lutz JM, et al. Combination but not single-agent methotrexate chemotherapy for gestational trophoblastic tumors increases the incidence of second tumors. *J Clin Oncol*. 1996;14(10):2769-2773. doi:10.1200/JCO.1996.14.10.2769
103. Schorge JO, Goldstein DP, Bernstein MR, Berkowitz RS. Recent advances in gestational trophoblastic disease. *J Reprod Med*. 2000;45(9):692-700. http://www.ncbi.nlm.nih.gov/pubmed/11027078.
104. Khanlian SA, Smith HO, Cole LA. Persistent low levels of human chorionic gonadotropin: A premalignant gestational trophoblastic disease. *Am J Obstet Gynecol*. 2003;188(5):1254-1259. doi:10.1067/mob.2003.271
105. Palmieri C, Dhillon T, Fisher RA, et al. Management and outcome of healthy women with a persistently elevated β-hCG. *Gynecol Oncol*. 2007;106(1):35-43. doi:10.1016/j.ygyno.2007.01.053
106. Cole LA. Phantom hCG and Phantom Choriocarcinoma. *Gynecol Oncol*. 1998;71(2):325-329. doi:10.1006/gyno.1998.5181
107. Rotmensch S, Cole LA. False diagnosis and needless therapy of presumed malignant disease in women with false-positive human chorionic gonadotropin concentrations. *Lancet*. 2000;355(9205):712-715. doi:10.1016/S0140-6736(00)01324-6
108. OLSEN T. Falsely elevated human chorionic gonadotropin leading to unnecessary therapy1. *Obstet Gynecol*. 2001;98(5):843-845. doi:10.1016/S0029-7844(01)01585-X