Case Report

Methotrexate Toxicity & Dactinomycin Resistance During Treatment for Benign Gestational Trophoblastic Disease: Case Report and Management with Combination Therapy

Nafeesa Zamurd *

Posted Date: 26 January 2026

doi: 10.20944/preprints202601.1987.v1

Keywords: methotrexate toxicity; hypersensitivity reactions; benign gestational trophoblastic disease; combination therapy; dactinomycin resistance; case report; chemotherapy regimen

 doi:10.20944/preprints202601.1987.v1

Case Report

Methotrexate Toxicity & Dactinomycin Resistance During Treatment for Benign Gestational Trophoblastic Disease: Case Report and Management with Combination Therapy

Nafeesa Zamurd

Safia Hafeez Hospital Jhelum, Jhelum, Pakistan; nafeesazamurd93@gmail.com

Abstract

Background: Gestational trophoblastic disease GTD is a rare group of malignant and benign tumors that results from the abnormal proliferation of placental tissue after conception in women. In the United States, GTD occurs in 1 in 1000 pregnancies. **Case:** A 35-year-old female presented to the emergency room due to concerns about a rise in bHCG levels three times. The patient was pregnant, and an evacuation due to suspicion of a bladder mole was performed at 8 weeks and 5 days of pregnancy. There was cramp-like pain in the lower abdomen and dizziness. Tatts-hCG showed an increase from 279,000 to 426,000 IU/L. Ultrasound before the evacuation confirmed a morphologically spotted hydatidiform mole. **Intervention:** The patient was initiated on a four-day regimen of low-dose methotrexate administered every 2 weeks, as per National Comprehensive Cancer Network guidelines. It is the first case ever reported in Norway in which the patient's voice was affected due to methotrexate hypersensitivity. Due to persistent reaction to methotrexate patient was switched to a 4-day regimen of dactinomycin. Due to dactinomycin resistance, the patient was switched to combination therapy, which includes EMA-CO etoposide, dactinomycin, cyclophosphamide, and vincristine without methotrexate. **Outcome:** Patient completely recovered from benign gestational trophoblastic disease and her bHCG levels normalized (<0.2 IU/L) within five months. **Conclusion:** This study concluded that proper monitoring of bHCG levels and early detection of methotrexate toxicity and dactinomycin resistance are important to achieve complete recovery in GTD with reduced risk of morbidity. This study also determined that EMA-CO is the best choice of combination therapy regimen in case of methotrexate toxicity/dactinomycin resistance, low-risk GTD, and high-risk GTD.

Keywords: methotrexate toxicity; hypersensitivity reactions; benign gestational trophoblastic disease; combination therapy**;** dactinomycin resistance; case report; chemotherapy regimen

Introduction

Gestational trophoblastic disease GTD is a rare group of malignant and benign tumors that results from the abnormal proliferation of placental tissue after conception in women. In the United States, GTD occurs in 1 in 1000 pregnancies. Benign tumors include hydatidiform mole, also known as a molar pregnancy, which is the most common type and can be malignant in some cases, accounting for 80% of all GTD. Malignant forms of GTD, also known as gestational trophoblastic neoplasia GTN include choriocarcinoma, invasive moles, and placental site trophoblastic tumors. Invasive mole in GTN accounts for 15% of all GTD[1]. Hydatidiform mole (molar pregnancy) is classified into two types —complete or partial —based on histopathology and its potential for

 doi:10.20944/preprints202601.1987.v1

malignant transformation. Lorain reported in 2010 that the incidence rate of gestational trophoblastic neoplasia after hydatidiform mole is 18 to 29%[2].

Complete molar pregnancy occurs when a fertilized egg does not contain maternal genes. The pregnancy that results from it does not have fetal tissue; it only has a grape-like cyst (hyper-echoic foci) that fills the uterine cavity. In case of a hydatidiform mole ultrasound shows the absence of a fetus without amniotic fluid in an enlarged uterus. Partial molar pregnancy occurs when fertilization of a normal egg occurs by normal sperm, which results in a pregnancy in which both the placenta and fetus are abnormal. The uterine cavity contains both normal tissue and a grape-like cyst (hyper-echoic foci)[3]. Gestational trophoblastic disease is curable in 90 % of cases, making it one of the most curable gynecological diseases[4]. The most common symptoms of benign gestational trophoblastic disease are feeling pregnant and bright red or watery brown vaginal bleeding. Other symptoms includes: abdominal bloating, nausea and vomiting more severe than normal pregnancy, fatigue, breathlessness, and anemia[5].

Cariocarcinoma is a highly malignant form of gestational trophoblastic disease occurring in 1 in 20-30,000 pregnancies, that spreads throughout the body and requires rigorous treatment. It may begin as a hydatidiform mole and become malignant later following the miscarriage or childbirth[6]. Lung and vagina are the most common sites of metastasis in gestational trophoblastic disease, brain, liver and other areas of the body are less frequently involved. Placental site trophoblastic tumor is a rare form of GTD that occurs at the placental site in the uterus. This tumor doesn't spread to other parts of the body; it usually penetrates the muscle layer in uterus[7].

Most molar pregnancies are cured by evacuation (dilatation and curettage, D&C) of the womb. If bHCG levels still continue to rise then chemotherapy is required with or without surgery. First line of treatment with anti-cancer drugs for low-risk GTN is methotrexate or dactinomycin after evacuation of the uterus. Methotrexate and dactinomycin are the two most commonly used drugs in Europe and North America. If methotrexate is the first-line treatment for low-risk GTN then dactinomycin is the second option or vice versa. Sometimes, first-line treatment fails to cure the disease or has side effects that require the treatment regimen to be changed[8].

Side effects associated with dactinomycin are considered to be more severe than methotrexate; major side effects of dactinomycin include alopecia, nausea, or vomiting. When on methotrexate, >10% of patients experience gastrointestinal problems (e.g., nausea, vomiting, diarrhea or constipation), dizziness, renal or hepatotoxicity and headache[9]. Adverse side effects of methotrexate occur due to hypersensitivity reaction, type I reaction is immediate and IgE mediated that occur due to the release of vasoactive mediators by basophils and mast cells. Type II-IV reactions are delayed and IgG or T-cells mediated cell destruction or immune complex deposition and complement activation, respectively[9]. Methotrexate toxicity is rare and there are few cases reported in the literature that showed the low or high dose treatment regimens for non-gynecologic[10] and gynecologic pathologies. It is important to understand what factors increase the risk of hypersensitivity reactions and how to manage methotrexate toxicity.

In case of first-line treatment failure or high-risk GTN combination therapy is used. The most favored initial combination chemotherapy regimen is EMA-CO (etoposide, methotrexate and actinomycin (EMA) along with cyclophosphamide and vincristine (CO))[11]. Alternative intensive combination chemotherapy regimens includes MAC (methotrexate, dactinomycin, plus cyclophamid[12]/chlorambucil[13]), TP/TE[14](paclitaxel, cisplatin/paclitaxel, etoposide), BEP[15] (bleomycin, etoposide, cisplatin), FAEV[16] (floxuridine, dactinomycin, etoposide, vincristine), which may be as effective as EMA/CO with fewer side effects but its not clear with the available evidence and CHAMOCA[17] (methotrexate, dactinomycin, cyclophosphamide, doxorubicin, melphalan, hydroxyurea and vincristine) which was found to be less effective and more toxic[18] than MAC.

 doi:10.20944/preprints202601.1987.v1

We present a case of a 35-years-old female who had a complete hydatidiform mole with a progression to benign gestational trophoblastic disease (BGTN) who developed toxicity to methotrexate and resistance to dactinomycin. Informed consent was taken from the patient to present her case.

Case Study

Patient Information and Diagnosis:

A 35-year-old female presented to the emergency room at the Department of Oncology at Radium Hospital as a transfer from Akershus University Hospital, Norway, due to concerns about a rise in bHCG levels three times. The patient was pregnant, and an evacuation due to suspicion of bladder mole was performed at Akershus University Hospital at 8 weeks and 5 days of pregnancy. bHCG levels before evacuation increased from 279,000 to 426,000 and 1 week after evacuation, bHCG levels fell from 426,000 to 7390 IU/L. Ultrasound before EVAC showed intrauterine hyper-echoic filling approximately 6×7 cm with small scattered anechoic vesicles. It confirmed a morphologically spotted hydatidiform mole. The patient underwent EVAC due to suspicion of a bladder mole, and was at PPG due to vaginal bleeding, and a lot of nausea occurred during pregnancy. A TVUL described a 35mm diastasis intrauterine without a fetus. 14 days after the evacuation, there was an increase in vaginal discharge, sudden worsening at night with a clot, and spotting (the size of an egg). There was cramp-like pain in the lower abdomen and dizziness. Tatts-hCG showed an increase from 279,000 to 426,000 IU/L. CT chest revealed 14 micro nodules. Abdomen/pelvis was normal without extra uterine pathology; CT brain and chest X-ray were normal, MRI head showed no signs of bleeding, Ischemia or metastases, but the patient had multiple lung metastases, consistent with Benign gestational trophoblastic disease.

Treatment Course:

- **Initial Therapy and Adverse Events:**

The patient was then started on a four-day regimen of low-dose methotrexate every 2 weeks as per National Comprehensive Cancer Network guidelines, and tolerated the first four days of the first cycle well. bHCG levels were assessed every 14 days for 6 weeks. On day 1 of the second cycle, the patient developed chest pain, lightheadedness, and drowsiness during the infusion, but vital signs remained stable throughout the treatment cycle. There was a significant decrease in bHCG level after two cycles of methotrexate. On day 1 of the third cycle, the patient's voice is affected (sudden aphasia occurred). The patient was evaluated in the emergency room, and there was no edema, cyanosis, or jaundice except dysphasia and blood tests were normal. The patient was then prescribed Vitamin A, her voice returned but she was able to speak in a hoarse voice. After observation, it was determined that the patient symptoms were related to methotrexate hypersensitivity. The treatment was not well tolerated and methotrexate was discontinued. It is the first case ever reported in Norway in which the patient's voice was affected.

- **Switch to Dactinomycin:**

Due to persistent reaction to methotrexate patient was then switched to a 4-day regimen of dactinomycin. After the first cycle of dactinomycin, patients' bHCG levels got elevated again. After evaluation, they determined that the patient was resistant to dactinomycin, so dactinomycin was stopped.

Combination Therapy:

The patient was switched to combination therapy, which includes EMA-CO etoposide, dactinomycin, cyclophosphamide, and vincristine without methotrexate. A chemo port was inserted under the patient's chest 1 week before the start of combination therapy. 12 mg dexamethasone and 1 capsule netupitant/ palonosetron 300 mg/0.5 mg was given to the patient in the morning at least 1 hour before the treatment. On days 1 and 2 of the EMA-CO Course No. 1, etoposide and dactinomycin were injected via chemo port, on day 8, cyclophosphamide and vincristine were injected, which she

 doi:10.20944/preprints202601.1987.v1

tolerated well. Patient experienced night sweats without fever, no cough or wheezing, pink discharge, slight headache and no burning sensation when urinating or stools. bHCG levels were assessed every 8th day, for 8 weeks.

At the start of EMA-CO Course No. 2, alopecia started to occur, and other side effects that occur in patients include lightheadedness, soft palpation tenderness in the abdomen, gastrointestinal issues (diarrhea, constipation), decreased blood count, rashes, joint pain, and fatigue. Due to low neutrophil count patient received an immunity booster Filgastrim for 3 days from day 3 of EMA-CO Course No. 3. Patient was injected with Filgastrim, every 2 weeks to boost immunity until the end of chemotherapy. bHCG levels continued to decrease and became normal after Course No. 6, bHCG levels <0.2. Patient completed six cycles of combination therapy EMA-CO without Methotrexate, two cycles past normalization of her bHCG levels.

Table 1. bHCG Levels Before the Treatment for Benign Gestational Trophoblastic Disease.

Before Chemotherapy Treatment	BHCG levels IU/L
Before Evacuation	426000
1 Week After Evacuation	7390
3 Weeks After Evacuation	23500

Table 2. bHCG Levels During the Treatment for Benign Gestational Trophoblastic Disease:.

Chemotherapy Treatment Course	BHCG Levels IU/L
Before Methotrexate Course	21858
Methotrexate Course No. 1	7742
Methotrexate Course No. 2	2009
Methotrexate Course No. 3	1041
Dactinomycin Course No. 1	1544
EMA-CO Course No. 1	137
EMA-CO Course No. 2	12
EMA-CO Course No. 3	2.6
EMA-CO Course No. 4	0.5
EMA-CO Course No. 5	<0.2
EMA-CO Course No. 6	<0.2

Assessment after normalization of bHCG levels:

The bHCG levels will be measured every two weeks for the first three months after the end of the treatment, then monthly until the last check up which will take place one year after the diagnosis, regular physical examination will be conducted during follow up to check any signs of recurrence e.g., abnormal uterine bleeding or vaginal mass, and patient is advised to use reliable contraceptives through out the follow up period. The chemo port will be removed 3 months after the last combination therapy. Menstrual recovery will take 3 to 6 months to recover completely.

Discussion

Gestational trophoblastic disease is extremely sensitive to chemotherapy drugs and typically GTD is treated with single-agent chemotherapy like methotrexate or dactinomycin. Methotrexate is an antifolate drug used to inhibit the proliferation of tumor cells by binding it to dihydrofolate reductase, thus interfering with the DNA synthesis[19]. Methotrexate is specific to cell cycle and trophoblasts are sensitive to it, thus inhibiting the proliferation of trophoblasts and preventing embryonic development in patients[20]. Dactinomycin is an anticancer drug[21], it inhibits the synthesis of RNA by impairing the function of RNA polymerase thus inhibiting the proliferation of tumor cells[22].

 doi:10.20944/preprints202601.1987.v1

Izildinha Maestá assessed the outcomes and toxicity of methotrexate in low-risk GTD patients receiving 8-day methotrexate or 1-day methotrexate infusion regimens and determined that the side effects such as Urinary tract infection, eye disorders, respiratory infections, anemia, and gastrointestinal disorders, etc., were self-limited and resolved with no long term issues[23]. Previous studies reported that Asian patients show more resistance to first-line MTX chemotherapy than non-Asian patients[24]. 90 % of the patients who experienced methotrexate failure were treated with dactinomycin, and the success rate was 80 %. Ayesha Kar reported that a female patient experienced severe methotrexate hypersensitivity during the treatment of gestational trophoblastic neoplasia. Patient experienced dizziness, headache, alopecia, difficulty to opening the eyes, diaphoresis and two episodes of stuttering. Due to persistent methotrexate hypersensitivity, the patient was switched to dactinomycin which was well tolerated and she completely recovered[25].

Hoeijmakers YM et al., carried out a retrospective study to find risk factors for dactinomycin resistance after failure of methotrexate treatment in low-risk gestational trophoblastic disease. Selected studies included patients treated with second-line dactinomycin after methotrexate toxicity. He determined that the type of antecedent pregnancy and bHcg levels pre-dactinomycin were the major risk factors for dactinomycin failure[26]. Hextan Y. S. Ngan et al.; determined that low risk GTD is mostly treated with single-agent chemotherapy (methotrexate or actinomycin D) but may require additional agents and high-risk GTD is treated with combination therapy (e.g., EMA-CO or EP/EMA regimen) with or without surgery for resistant foci of the disease or radiotherapy in case of metastasis[27]. Ghaemmaghami F et al., determined that EMA-EP combination therapy was used as a first-line chemotherapy regimen in cases of high-risk GTD and it resulted in remission in all the patients who received this treatment[28].

Linyu Deng et al., compared the effects of the MAC (methotrexate, dactinomycin and chlorambucil) regimen versus the CHAMOCA (methotrexate, dactinomycin, cyclophosphamide, doxorubicin, melphalan, hydroxyurea, and vincristine) regimen in high-risk GTD and determined that the MAC regimen was more effective and less toxic than the CHAMOCA. Six patients who received the CHAMOCA died as compared to one in MAC group and the study was stopped due to high level of toxicity in the CHAMOCA group[29]. Newland et al., conducted a cohort study to see the efficacy of the EMA-CO regimen on high-risk gestational trophoblastic disease and determined that remission occurred in 90.5 % of the patients. Twenty patients who completely recovered from GTD relapsed (sixteen who achieved remission due to EMA-CO and four who switched combination therapy due to resistance to EMA-CO)[30].

Currently, EMA-CO is the first line of combination therapy for GTD with a high success rate and less toxicity. GTD is one of the first cancers that was highly responsive to chemotherapy. There is a need of properly planned prospective and comparative studies to determine the clinically effective, less toxic and cost effective combination therapy regimen for low-risk and high-risk GTD. The possible treatment options that could be compared with EMA-CO include CHAMOCA, MAC, FAEV, BEP, TP/TE, EMA-EP, and EMA.

Conclusion

This study concluded that proper monitoring of bHCG levels and early detection of methotrexate toxicity and dactinomycin resistance are important to achieve complete recovery in GTD with reduced risk of morbidity. This study also determined that EMA-CO is the best choice of combination therapy regimen in case of methotrexate toxicity/dactinomycin resistance, low-risk GTD, and high-risk GTD.

Ethics approval: Not applicable.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are cited in Reference section.

Competing interests: Not applicable.

Funding: Not applicable.

Ethical publication statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Acknowledgments: Not applicable.

References

1. Joychan, S., Patel, B., Mayer, J., Sriaroon, P., 2017. P038 A case of anaphylaxis to methotrexate and successful desensitization. Ann. Allergy Asthma Immunol. 119 (5), S29.
2. Lurain, J.R., 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.
3. Stevens FT, Katzorke N, Tempfer C, Kreimer U, Bizjak GI, Fleisch MC, Fehm TN. Gestational trophoblastic disorders: an update in 2015. Geburtshilfe und Frauenheilkunde. 2015 Oct;75(10):1043-50.
4. Seckl, M.J., Sebire, N.J., Berkowitz, R.S., 2010. Gestational trophoblastic disease. Lancet 376 (9742), 717–729.
5. Twice BT, Clement OO, Kosoko AA. Gestational Trophoblastic Disease. Emergency Medicine Case-Based Guide: Obstetric Emergencies. 2024 Dec 21:23.
6. Somashekhar SS. Clinico Pathological Study of Gestational Trophoblastic Disease–A Three Years Study (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)).
7. Istrate-Ofiţeru AM, Vrabie SC, Zorilă GL, Zorilă et, Căpitănescu RG, Berbecaru EI, Liliac AI, Iovan L, Andreiana BC, Mateescu VO, Busuioc CJ. Gestational trophoblastic diseases–literature review and atypical case reports. Romanian Journal of Morphology and Embryology. 2025 Mar 31;66(1):7.
8. Alazzam MI, Tidy J, Hancock BW, Osborne R, Lawrie TA. First-line chemotherapy in low-risk gestational trophoblastic neoplasia. Cochrane Database of Systematic Reviews. 2012(7).
9. Solomon, D.H., Glynn, R.J., Karlson, E.W., Lu, F., Corrigan, C., Colls, J., Xu, C., MacFadyen, J., Barbhaiya, M., Berliner, N., Dellaripa, P.F., 2020. Adverse effects of low-dose methotrexate: a randomized trial. Ann. Intern. Med. 172 (6), 369–380.
10. Dilley, M.A., Lee, J.P., Broyles, A.D., 2017. Methotrexate hypersensitivity reactions in pediatrics: evaluation and management. Pediatr. Blood Cancer 64 (5), e26306.
11. Schorge JO. Contemporary therapy in obstetrics and gynecology. China: Ren-ming Wei-sheng Chu-banshe, 2003.
12. Goldstein DP, Berkowitz RS. Current management of gestational trophoblastic neoplasia. Hematology and Oncology Clinics of North America 2012;26:111-131.
13. Hammond CB, Borchert LG, Tyrey L, Creaman WT, Parker RT. Treatment of metastatic trophoblastic disease: good and poor prognosis. American Journal of Obstetrics and Gynecology 1973;115(4):451-7.
14. WangJ, ShortD, SebireNJ, LindsayI, NewlandsES, SchmidP, et al. Salvage chemotherapy of relapsed or high-risk gestational trophoblastic neoplasia (GTN) with paclitaxel/cisplatin alternating with paclitaxel/etoposide (TP/TE). Annals of Oncology 2008;19:1578-3.
15. SoperJT, EvansAC, RodriguezG, BerchuckA, Clarke- PearsonDL, HammondCB. Etoposide-platin combination therapy for chemorefractory gestational trophoblastic disease. Gynecologic Oncology 1995;56(3):421-4.
16. FengF, XiangY, WanX, GengS, WangT. Salvage combination chemotherapy with floxuridine, dactinomycin, etoposide and vincristine (FAEV) for patients with relapsed/chemoresistant gestational trophoblastic neoplasia. Annals of Oncology 2011;22:1588-94.
17. Bagshawe KD. Risk and prognostic factors in trophoblastic neoplasia. Cancer 1976;38(3):1373-85.
18. CurrySL, BlessingJA, DiSaiaPJ, SoperJT, TwiggsLB. A prospective randomised comparison of methotrexate, dactinomycin and chlorambucil versus methotrexate, dactinomycin, cyclophosphamide,

 doi:10.20944/preprints202601.1987.v1

doxorubicin, melphalan, hydroxyurea and vincristine in 'poor prognosis' metastatic gestational trophoblastic disease: a Gynaecologic Oncology Group study. Obstetrics & Gynecology 1989;73(3, Part 1):357-62.

19. Claxton L, Taylor M, Soonasra A, Bourret JA, Gerber RA. 2018. An economic evaluation of tofacitinib treatment in rheumatoid arthritis after methotrexate or after 1 or 2 TNF inhibitors from a U.S. payer perspective. Eur J Med Chem. 138:170–181.
20. Elias KM, Harvey RA, Hasselblatt KT, Seckl MJ, Berkowitz RS. 2014. Type I interferons modulate methotrexate resistance in gestational trophoblastic neoplasia. Gynecol Oncol. 133(6):190–191.
21. Wang Y, Miao JW, Wang T, Wang Y, Wu YM, Kong WM, Su L, Duan W. 2016. Comparison of MACT and 5Fu+ACT chemotherapy regimens in the treatment of low-risk gestational trophoblastic neoplasia. J Chemother. 28(2):135–139.
22. Cortes CL, Veiga SR, Almacellas E, Hernándezlosa J, Ferreres JC, KozmaSC, AmbrosioS, ThomasG, TaulerA. 2016. Effect of low doses of actinomycin D on neuroblastoma cell lines. Mol Cancer. 15(1):1–13.
23. Maestá I, Nitecki R, Horowitz NS, Goldstein DP, Moreira MD, Elias KM, Berkowitz RS. Effectiveness and toxicity of first-line methotrexate chemotherapy in low-risk postmolar gestational trophoblastic neoplasia: The New England Trophoblastic Disease Center experience. Gynecologic oncology. 2018 Jan 1;148(1):161-7.
24. I. Maestá, R.S. Berkowitz, D.P. Goldstein, M.R. Bernstein, L.A. Ramírez, N.S. Horowitz, Relationship between race and clinical characteristics, extent of disease, and response to chemotherapy in patients with low-risk gestational trophoblastic neoplasia, Gynecol. Oncol. 138 (2015) 50–54.
25. Kar A, Mills KA. Severe methotrexate hypersensitivity during treatment for Gestational trophoblastic Neoplasia: Case Report and considerations for management. Gynecologic Oncology Reports. 2024 Apr 1;52:101364.
26. Hoeijmakers YM, Sweep FC, Lok CA, Ottevanger PB. Risk factors for second-line dactinomycin failure after methotrexate treatment for low-risk gestational trophoblastic neoplasia: a retrospective study. BJOG: An International Journal of Obstetrics & Gynaecology. 2020 Aug;127(9):1139-45.
27. Ngan HY, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, Lurain JR, Massuger L. Diagnosis and management of gestational trophoblastic disease: 2021 update. International Journal of Gynecology & Obstetrics. 2021 Oct;155:86-93.
28. Ghaemmaghami F, Modares M, Arab M, Behtash N, Moosavi AZ, Khanafshar N, Hanjani P. EMA-EP regimen, as firstline multiple agent chemotherapy in high-risk GTT patients (stage II-IV). International Journal of Gynecological Cancer. 2004 Feb 1;14(2):360-5.
29. Deng L, Zhang J, Wu T, Lawrie TA. Combination chemotherapy for primary treatment of high-risk gestational trophoblastic tumour. Cochrane Database of Systematic Reviews. 2013(1).
30. NewlandsES, BowerM, HoldenL, ShortD, SecklMJ, RustinGJ, et al. Management of resistant gestational trophoblastic tumors. Journal of Reproductive Medicine 1998;43(2):111-8.