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Third time recurrent invasive mole with an intervening viable gestation

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Abstract

Background: Invasive mole is a subtype of Gestational Trophoblastic Neoplasms (GTNs) that develop from malignant transformation of trophoblastic tissue after molar evacuation. The occurrence of hydatidiform mole in more than two conceptions is known as recurrent hydatidiform mole. Recurrent molar pregnancy is very rare, its incidence being less than 2 %, but it may progress to invasive mole or choriocarcinoma.

Case presentation: In this case report, we highlight a case of a patient who experienced three recurrent invasive molar pregnancies with an intervening normal viable pregnancy. A 21 year old patient, G4P1L1D1A2, was admitted to our hospital with a third invasive molar pregnancy. The patient underwent suction and evacuation and was followed up with serial serum Human Chorionic Gonadotropin (β-hCG) estimation. The patient required chemotherapy. The couple was counselled to use a reliable method of contraception during the period of follow up until serum β-hCG levels become undetectable.

Despite having an invasive mole for the third time, the patient achieved remission each time with an appropriately selected chemotherapy regimen and also experienced a good reproductive outcome in the intervening period.

Keywords: Gestational Trophoblastic Disease, Gestational Trophoblastic Neoplasms, Invasive mole, Hydatidiform mole, Recurrent molar pregnancy, Human Chorionic Gonadotropin, Chemotherapy.

Introduction

Gestational Trophoblastic Disease (GTD) is unique, as it originates from the gestational tissue rather than from the maternal tissue. GTD is divided into 2 major groups: benign, which consists of complete and partial hydatidiform moles, and malignant, referred to as Gestational Trophoblastic Neoplasia (GTN), which consists of invasive moles, choriocarcinomas, placental site trophoblastic tumours (PSTTs), and epithelioid trophoblastic tumours (ETTs). These malignancies can occur weeks or years following any pregnancy (molar pregnancy, abortion, ectopic pregnancy or normal

pregnancy) but occur most commonly after a molar pregnancy.

In India and the Middle East, the incidence of molar pregnancy is estimated as 1 in 160 pregnancies.[1] Following one molar pregnancy, the risk of a hydatidiform mole in a subsequent pregnancy increases to ~1–2%.[2] After a complete molar pregnancy, the risk of a hydatidiform mole in a subsequent pregnancy has been reported as 0.91% whereas after a partial molar pregnancy, the risk is lower, at 0.28%. The risk is further lowered if a molar pregnancy is followed by an intervening normal viable gestation. Following two consecutive molar pregnancies, the risk increases to 23%.[2] Approximately 80% of the second Hydatidiform moles are of the same histopathological type as the index mole. Invasive mole is defined as the presence of oedematous trophoblastic tissue and hydropic chorionic villi invading the myometrium with or without extra-uterine metastasis, which arises from myometrial invasion of Hydatidiform mole via direct extension through tissue or venous channels. Invasive moles occur mostly in women of reproductive age. Herein we report a unique and challenging case of third time recurrence of an invasive mole with an intervening viable gestation treated successfully with single-agent chemotherapy (Methotrexate).

Case Report

We report the case of a 21 year old female, G4P1L1D1A2, married since 6 years who presented to Gynaecology OPD at NKPSIMS and LMH, Nagpur with chief complaint of amenorrhoea of 3 months. Patient had history of intake of MTP pills 10 days back, after pregnancy was confirmed by a urine pregnancy test. Obstetric ultrasound was not done. Following intake of MTP pills, patient experienced vaginal bleeding for 1 day with passage of a mass and clots. Serum β-hCG was done 3 days back, which was >10,000 mIU/ml. Serum β-hCG was repeated on admission and was determined to be > 60,000 mIU/ml which raised the suspicion of hydatidiform mole.

On admission, there was no history of vaginal bleeding, abdominal pain, passage of grape like vesicles, nausea, vomiting, tachycardia, tremors, raised BP readings, pallor, palpitations, cough, breathlessness, chest pain, epigastric or right upper quadrant pain. She had no history of contraceptive drug use. The vital signs were normal. On per abdomen examination, uterus was just palpable (12 – 14 weeks size). Speculum examination showed no bleeding and no mass infiltration in the vagina. On bimanual examination, uterus size was corresponding to 12 to 14 weeks of gestation. There was no adnexal mass. Patient had history of invasive mole in first pregnancy 5 years back. Ultrasound report was suggestive of invasion of trophoblastic tissue into the anterior myometrium. Suction and evacuation was done. Histopathology report of the tissue obtained was complete Hydatidiform mole. Post procedure, patient received 7 cycles of single-agent chemotherapy with Methotrexate and serial serum β-hCG monitoring was done. She was advised not to conceive during the period of follow up, until serum β-hCG levels become undetectable.

On serial monitoring, serum β-hCG levels displayed a rising trend. It was assumed that the patient had conceived during the period of follow up against medical advice. On subsequent evaluation, it was rather diagnosed as a case of recurrent invasive mole. Suction and evacuation was done and the patient was then given 6 cycles of multi-agent chemotherapy with EMA-CO (Etoposide, Methotrexate, Actinomycin-D,

Cyclophosphamide and Vincristine). Unfortunately, the diagnosis was not histopathologically confirmed. Serial monitoring of serum β-hCG was done until β-hCG levels became undetectable. Patient was then advised to conceive.

A year later, patient conceived spontaneously and it was a Monochorionic Diamniotic twin gestation. She had history of preeclampsia in that pregnancy. Elective LSCS was done at 37 weeks of gestation. The twins had discordant growth due to Twin to Twin Transfusion Syndrome (TTTS). Male child, birth weight 2.5 kg survived and female child, birth weight 600 grams was admitted to NICU and succumbed on postnatal day 1.

There was no family history of recurrent molar pregnancy. Patient's blood group was B positive. All pre-operative blood investigations were done – Blood group, Rh antibody, Complete blood count, Thyroid function test, Renal function test, Serum electrolytes, Liver function test, urine analysis and Coagulation profile. Laboratory results revealed haemoglobin 9.8 g/dL, leucocytes 7370/mm^3, platelets 2.5 lakh/mm^3, and a quantitative β-hCG level of 60,000 mIU/mL. The patient's thyroid function was within normal limits, with a slight decrease in TSH 0.18 mIU/L. Chest X-ray revealed no significant abnormality.

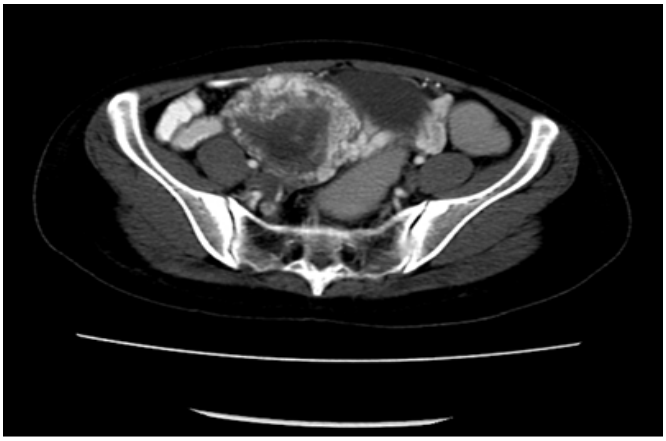

Figure 1

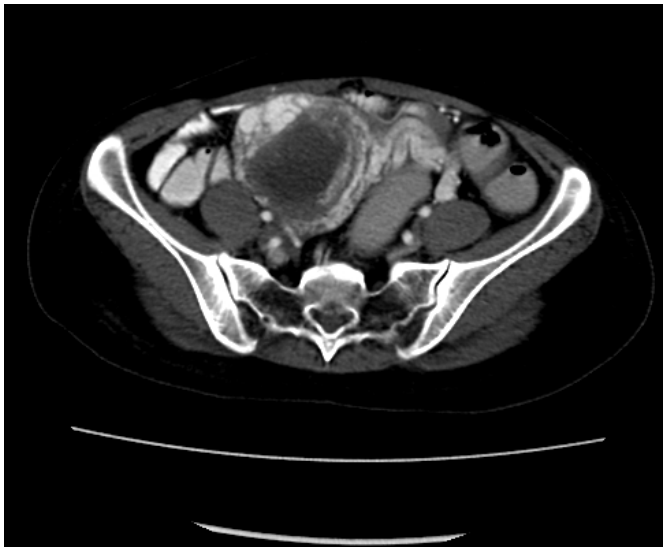

Figure 2

CT (Abdomen + Pelvis) - a well-defined hypodense collection in the endometrium (red arrow); and cystic areas along with multiple dilated vascular channels in the anterior myometrium replacing 50% of anterior myometrium. (blue arrow)

Pelvic ultrasonography demonstrated a heterogeneous mass obliterating the endometrial cavity, with a vesicular appearance and normal ovaries. Computed tomography (CT) scan of the abdominopelvic region was done. After informed consent and arrangement for adequate blood, the patient underwent an uneventful suction and evacuation. Intraoperative blood loss was approximately 500 cc. Intraoperatively 1 unit of packed red cells was transfused. Post procedure, the patient was scheduled for single agent chemotherapy with Methotrexate (1 mg/kg) and Folinic acid. Serial monitoring of serum β-hCG was done. Post-operative period was uneventful. The serum β-hCG level showed a decreasing trend.

Table 1: Serial monitoring of Serum β-hCG and Chemotherapy regimen (Methotrexate)

Day	Serum β-hCG value in mIU/ml
9/7/21(Preoperative)	10,000
12/7/21(Preoperative)	60,000
15/7/21 (day 0)	35770 Methotrexate given on 16/07/21 (day 1) and 18/07/21 (day 3)
19/7/21 (day 4)	4428 Methotrexate given on 20/07/21 (day 5)
22/7/21 (day 7)	960 Methotrexate given on 24/07/21 (day 9)
26/7/21 (day 11)	434
Week 1	< 2
Week 2	< 2
Week 3	< 2

The final histopathologic diagnosis was complete hydatidiform mole. Karyotyping of the products of conception and karyotype of parents was not done due to affordability issues. Immunohistochemical examination of the tissue specimen was not done. Since serum β- hCG levels revealed a declining trend implying a good response to Methotrexate, patient was discharged and advised to follow up with serum β-hCG, on outpatient basis, weekly. Serum β-hCG levels became undetectable at the end of first week and remained so in the subsequent 2 weeks. As serum β-hCG levels were undetectable for 3 consecutive weeks, the patient is advised monthly follow up with serum β-hCG for 12 consecutive months. Patient was encouraged to use oral contraceptive pills during the entire interval of follow up.

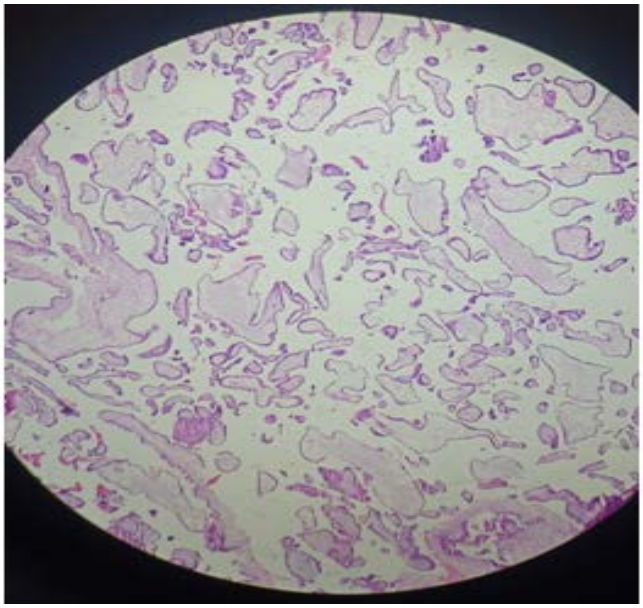

Figure 3: original magnification ×10

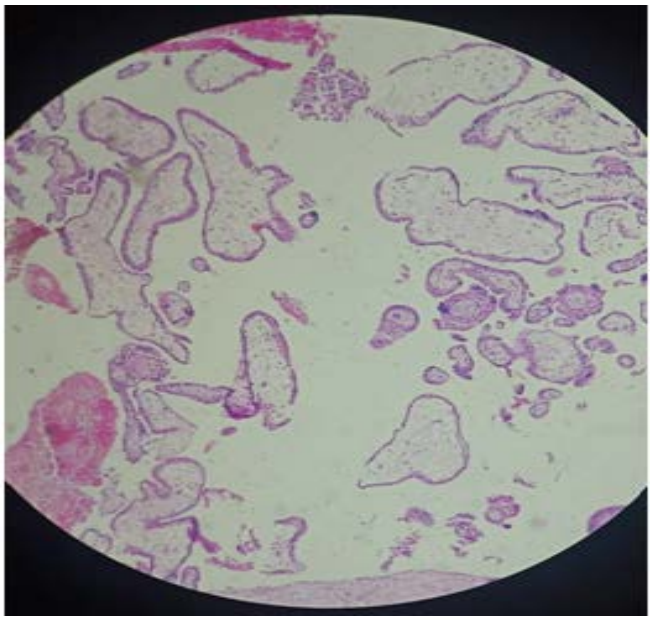

Figure 4: original magnification ×40

A microscopic image demonstrating a circumferential proliferation of cytotrophoblasts and syncytiotrophoblasts surrounding chorionic villi with cystic dilatation (hematoxylin and eosin [H&E] stain). Based on clinical, laboratory and radiological correlation, the diagnosis was confirmed as an invasive mole, stage I GTN according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system. Single-agent chemotherapy is the

preferred treatment in patients with stage I GTN. In resistant cases, combination chemotherapy should be administered. The distinction between low risk and high risk according to World Health Organization (WHO) prognostic scoring system. applies mainly to patients with stage II and stage III GTN.

Discussion

Hydatidiform mole are due to abnormal proliferation of trophoblastic tissue. Complete mole is the most common type. Complete moles are typically diploid (46 XX – 90%, 46 XY – 10%), do not contain embryonic or foetal tissue, have diffuse trophoblastic proliferation and produce high levels of Human Chronic Gonadotropin. In complete moles, only paternal DNA is expressed with only mitochondrial DNA of maternal origin. Whereas, partial moles are triploid (69 XXX, 69 XXY, 69 XYY - the extra haploid set of chromosomes is paternal), contain identifiable foetal residues and have focal trophoblastic proliferation. In partial moles, paternal DNA as well as maternal DNA is expressed.[3] Hydatidiform mole is characterized by chromosomal abnormalities. The dysfunction of oncogenes and anti-oncogenes and the alteration of telomerase regulation might contribute to the malignant transformation of the trophoblasts into invasive mole.

Patients with complete molar pregnancies have a 5% risk of Persistent Trophoblastic Gestational Disease (PTD); whereas in patients with partial molar pregnancies, this risk is <1%.[4] Patients with a uterine size that is larger than the gestational age and presence of theca lutein cyst more than 6 cm in diameter, have a 50% risk of PTD. Recurrent complete moles have significant implications, including a risk of malignant transformation and a poor reproductive future for the woman.[5]

Invasive moles are preceded by hydatidiform moles in approximately 95% of the cases. The risk of invasive disease in a complete molar pregnancy is around 15% to 20%, and in a partial molar pregnancy is 1% to 5%.[6,7,8] Invasive mole is often clinically diagnosed based on persistent elevation of serum β-hCG levels after evacuation of molar pregnancy. Irregular vaginal bleeding and subinvolution of uterus may be present. Invasive moles have the same histopathological characteristics as that of a non-invasive hydatidiform mole except for the infiltration of trophoblasts into the myometrium and necrotic changes associated with it. Invasive mole is generally confined to uterine myometrial invasion and extrauterine metastasis occurs in approximately 5% of complete moles and rarely in partial moles.[8,9] Invasive mole has a high rate of metastasis, approximately 30%, at the time of initial presentation. Metastasis mainly develops via the haematogenous route. Lung is the most common site of metastasis (80%) followed by vagina (30%), pelvis (20%), liver (10%), brain (10%), and others (<5%).[8,10] Thus, imaging of the lungs is recommended for all patients. Patients with pulmonary metastasis have a high risk of developing central nervous system and abdominal metastasis, highlighting the role of abdominal CT and cerebral MRI for staging of the disease.[11] Invasive moles have a high risk of transformation into choriocarcinoma.

Familial recurrent hydatidiform mole (FRHM) are extremely rare, reported only among 21 families in medical literature so far. In these cases, complete moles are diploid but biparental unlike sporadic complete moles. The pathological features are similar to that of a sporadic complete mole. It is an autosomal recessive condition and causes patients to have recurrent molar

pregnancies and a rare chance of a successful pregnancy. At present, mutation in two genes, NLRP7[12] and KHDC3L[13] account for ~75% and 5% of the affected cases, respectively. In women with three or more molar pregnancies, genotyping should be advised for the diagnosis of FRHM. Recurrent molar pregnancy does not always warrant chemotherapy unlike PTD and GTN. Our patient had no family history of recurrent molar pregnancies.

Despite the aggressive behaviour and high metastatic rate of invasive moles, they are highly sensitive to chemotherapy, which is considered the treatment of choice. Surgical procedures might be recommended in specific cases including postmenopausal patients and invasive moles with uncontrolled vaginal bleeding.[14,15,16]

Weekly serum β-hCG levels are done after surgery for evacuation of molar pregnancies until an undetectable level of β-hCG is obtained. Patients with previous molar pregnancy are advised to use reliable contraception to avoid a new pregnancy. It could conflict with weekly serum β-hCG level testing, as in our case, and make it impossible to determine the occurrence of invasive molar disease.

GTN should be suspected if a patient's β-hCG levels increase or remain high for several weeks after evacuation of molar pregnancy. The post-molar diagnosis of GTN can be made based on criteria from FIGO.[17]

1. A β-hCG level that does not change (±10% of the previous result) on 4 measurements made over ≥3 weeks.
2. A β-hCG level that increases by more than 10% on 3 consecutive weekly measurements made over ≥2 weeks.
3. Persistence of β-hCG in the serum for >6 months after mole evacuation.

High-risk factors for developing post molar GTN are age >40 years, multiparity, uterus size greater than gestational age, β-hCG >1,00,000 mIU/mL, theca lutein cyst greater than 6 cm in diameter on ultrasound, and histopathology that shows excessive trophoblastic proliferation.[18,19,20] Offering prophylactic chemotherapy for high risk women with complete moles may decrease the incidence of GTN.

Primary therapy for GTN should be chemotherapy. The chemotherapy regimen is designed according to FIGO anatomic staging system and WHO prognostic scoring system. Low-risk patients, with scores less than 7, are administered a single agent (Methotrexate) as first-line chemotherapy. Actinomycin D can be added in cases of poor response to Methotrexate. High-risk patients, with scores more than 7, are administered a multi-agent regimen - EMA-CO (Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide and Vincristine) followed a week later by cyclophosphamide and vincristine or MAC regimen (Methotrexate, Actinomycin D, Cyclophosphamide). Regular monitoring of serum β-hCG levels for 1 year in low risk cases and 2 years in high risk cases is mandatory.[15,21]

Our case was a rare presentation of a third time recurrence of an invasive mole with an intervening viable gestation. The final diagnosis was FIGO stage 1 GTN. Despite having an invasive mole for the third time, the patient achieved remission each time with an appropriately selected chemotherapy regimen and also achieved a good reproductive outcome in the intervening period. Complete remission was achieved in our case. In our case, the antecedent pregnancy was a

term pregnancy and the interval to transformation into GTN was 3 years. Whether her stage I GTN followed her previous normal term pregnancy rather than representing early transformation into GTN of her current molar pregnancy is a question.

Conclusion

Despite the aggressive behaviour and high metastatic rate of invasive moles, they are highly sensitive to chemotherapy. Single-agent chemotherapy achieves a high remission rate in nonmetastatic and low risk metastatic GTN. Most of the patients can preserve their fertility and anticipate normal reproduction in the future. Inspite of third time recurrence of invasive mole, complete remission was achieved in our case with Methotrexate. Counselling on future pregnancies poses a real obstetric dilemma.

Acknowledgement

All authors have made a substantial contribution to the conception and design, gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Abbreviations

GTD - Gestational Trophoblastic Disease

GTN - Gestational Trophoblastic Neoplasms

HCG - Human Chorionic Gonadotropin

PSTT - Placental site trophoblastic tumours

ETT - Epithelioid trophoblastic tumours

OPD – Outpatient department

MTP – Medical termination of pregnancy

BP – Blood pressure

EMA-CO - Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide and Vincristine

LSCS – Lower segment caesarean section

TTTS - Twin to Twin Transfusion Syndrome

NICU – Neonatal Intensive care unit

TSH – Thyroid stimulating hormone

FIGO - International Federation of Gynaecology and Obstetrics

WHO - World Health Organization

PTD - Persistent Trophoblastic Gestational Disease

CT -Computed Tomography

MRI – Magnetic Resonance Imaging

FRHM - Familial recurrent hydatidiform mole

References

1. Daftary SN, Padubidri VG. Trophoblastic diseases. In: Padubidri VG, Daftary SN, editors. Shaw's Textbook of Gynaecology. 13th ed. New Delhi: Elsevier India, Ltd.; 2004:248–259.
2. Bagshawe KD, Dent J, Webb J. Hydatidiform mole in England and Wales 1973-83. Lancet. 1986;2:673–677.
3. Kar A, Mishra C, Biswal P, Kar T, Panda S, Naik S. Differential expression of cyclin E, p63, and Ki-67 in gestational trophoblastic disease and its role in diagnosis and management: A prospective case-control study. Indian J Pathol Microbiol. 2019 Jan-Mar;62(1):54-60.
4. Sebire NJ, Foskett RA, Fisher RA, Rees H, Seckl M, Newlands E. Risk of partial and complete hydatidiform molar pregnancy in relationship to age. BJOG. 2002;109:99–102.
5. Madhudas C, Khursheed F, Srichand P. Analysis of patients with recurrent molar pregnancy. Eur J Biol Sci. 2011;3:102–104.
6. El-Helw LM, Hancock BW. Treatment of metastatic gestational trophoblastic neoplasia. LancetOncol. 2007;8(8):715–724.
7. Shih IM. Gestational trophoblastic neoplasia—pathogenesis and potential therapeutic targets. LancetOncol. 2007;8(7):642–650. doi:

10.1016/S1470-2045(07)70204-8. [PubMed] [CrossRef][Google Scholar]

8. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. Lancet. 2010;376:717–729.doi: 10.1016/S0140-6736(10)60280-2. [PubMed] [CrossRef] [Google Scholar]
9. Brown J, Naumann RW, Seckl MJ, Schink J. 15years of progress in gestational trophoblastic disease: scoring, standardization, and salvage. Gynecol Oncol. 2017;144(1):200–207.doi: 10.1016/j.ygyno.2016.08.330. [PubMed] [CrossRef] [Google Scholar]
10. Seckl MJ, Sebire NJ, Fisher RA, Golfier F, Massuger L, Sessa C, ESMO Guidelines Working Group Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi39–vi50. doi: 10.1093/annonc/mdt345. [PubMed][CrossRef] [Google Scholar]
11. Dudiak KM, Maturen KE, Akin EA, et al. ACR appropriateness criteria® Gestational trophoblastic disease. J Am Coll Radiol. 2019;16(11):S348–S363. doi: 10.1016/j.jacr.2019.05.015. [PubMed][CrossRef] [Google Scholar]
12. Murdoch S, Djuric U, Mazhar B, et al. Mutations in NALP7 cause recurrent hydatidiform moles and reproductive wastage in humans. Nat Genet. 2006;38:300–302. doi:10.1038/ng1740
13. Parry DA, Logan CV, Hayward BE, et al. Mutations causing familial biparental hydatidiform mole implicate c6orf221 as a possible regulator of genomic imprinting in the human oocyte. Am J Hum Genet. 2011 ; 89:451–458.
14. Von Welser SF, Grube M, Ortmann O. Invasive mole in a perimenopausal woman: a case report and systematic review. Arch Gynecol Obstet. 2015;292(6):1193–1199. doi: 10.1007/s00404-015-3777-z.[PubMed] [CrossRef] [Google Scholar]
15. Nakashima A, Miyoshi A, Miyatake T, et al. Perimenopausal invasive hydatidiform mole treated by total abdominal hysterectomy followed by chemotherapy. J Surg Case Rep. 2016doi: 10.1093/jscr/rjw142. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
16. Braga A, Mora P, de Melo AC, et al. Challenges in the diagnosis and treatment of gestational trophoblastic neoplasia worldwide. World J Clin Oncol. 2019;10(2):28–37.doi: 10.5306/wjco.v10.i2.28. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
17. Bruce S, Sorosky J. StatPearls. Treasure Island (FL): StatPearls Publishing; 2021. Gestational trophoblastic disease. [Updated 2020 Aug 26] https://www.ncbi.nlm.nih.gov/books/NBK470267/[Google Scholar]
18. Hidayat YM. Faktor-Faktor Risiko Terjadinya Keganasan Pasca Mola Secara Klinikopatologis. MolaHidatidosa dan Deteksi Dini Keganasan Pasca Evakuasi Mola Hidatidosa. 2020:31–38. [in Indonesian] [Google Scholar]
19. Vargas R, Barroilhet LM, Esselen K, et al. Subsequent pregnancy outcomes after complete and partial molar pregnancy, recurrent molar pregnancy, and gestational trophoblastic neoplasia: An update from the New England Trophoblastic Disease Center. J Reprod Med. 2014;59(5–6):188–94. [PubMed][Google Scholar]

20. Ning F, Hou H, Morse AN, Lash GE. Understanding and management of gestational trophoblastic disease. F1000Res. 2019;8:F1000. Faculty Rev-428. [PMC free article] [PubMed] [Google Scholar]
21. Kohorn EI. Scoring system for gestational trophoblastic disease. Update and critical discussion :2015. Published online 2015:1-10.