



New Management of Gestational trophoblastic diseases; A Continuum of Moles to Choriocarcinoma: A Review Article

ARTICLE INFO

Article Type

Analytical Review

Authors

Soheila Aminimoghaddam¹ MD,
Nastaran Abolghasem¹ MD,
Tahereh Ashraf- Ganjooie^{2*} MD, PhD

How to cite this article

Soheila Aminimoghaddam, Nastaran Abolghasem, Tahereh Ashraf-Ganjooie. New Management of Gestational trophoblastic diseases; A Continuum of Moles to Choriocarcinoma: A Review Article. Journal of Obstetrics, Gynecology and Cancer Research. 2018 ;3(3):123-128.

ABSTRACT

Introduction Gestational trophoblastic diseases (GTD) is the only group of female reproductive neoplasms derived from paternal genetic material (Androgenic origin). GTD is a continuum from benign to malignant; molar pregnancy is benign, but choriocarcinoma is malignant. Approximately 45% of patients have metastatic disease when Gestational trophoblastic neoplasia (GTN) is diagnosed. GTN is unique in women malignancies because it arises from trophoblast but not from genital organs. It is curable with chemotherapy, low-risk GTN completely response to single-agent chemotherapy and does not require histological confirmation. In persistent GTN, clinical staging and workup of metastasis should be performed. The aim of the present study was to review the new management of GTD.

Conclusion In the case of brain, liver, or renal metastases, any woman of reproductive age who presents with an apparent metastatic malignancy of unknown primary site should be screened for the possibility of GTN with a serum HCG level. Excisional biopsy is not indicated to histologically confirm the diagnosis of malignant GTN if the patient is not pregnant and has a high HCG value. Given the vascular nature of these lesions, a biopsy can have significant morbidity. In every woman with abnormal bleeding or neurologic symptom without documented reason, the probability of malignant GTN should be in mind and determination of HCG titer is recommended. In selected cases with low-risk GTN, repeat curettage is done to reduce the need for chemotherapy courses. In recent years personalized medicine is encouraged for treatment of GTN.

Keywords Gestational trophoblastic neoplasia; Hydatidiform mole; Chemotherapy; Pregnancy

¹Obstetrics & Gynecology Department, Medical Faculty, Iran University of Medical Sciences, Tehran, Iran

²Obstetrics & Gynecology Department, Medical Faculty, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*Correspondence

Address: Obstetrics & Gynaecology Ward, 2nd Floor, Emam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Madani Street, Tehran, Iran. Postal Code: 1617763141

Phone: +98 (21) 77558081

Fax: +98 (21) 77557079

tashrafganjooie@yahoo.com

Article History

Received: March 13, 2018

Accepted: April 29, 2018

ePublished: September 22, 2018

CITATION LINKS

[1] Unusual presentation of invasive mole: A case report [2] A review of recent findings for obstetricians about combined oral contraceptive pills [3] Ovarian malignant mixed germ cell tumor: A case of unusual presentation as molar pregnancy [4] Clinical gynecologic oncology [5] OC27. 01: Role of imaging in assessment of gestational trophoblastic neoplasia and transvaginal Doppler ultrasound versus pelvic dynamic contrast enhanced MRI [6] Williams Obstetrics [7] Berek and Novak's gynecology [8] Outcome of treatment with EMA/EP (etoposide methotrexate and actinomycin-D/etoposide and cisplatin) regimen in gestational trophoblastic neoplasia [9] Human chorionic gonadotrophin as an indicator of persistent gestational trophoblastic neoplasia [10] Gestational trophoblastic disorders: an update in 2015 [11] Gestational trophoblastic neoplasia [12] Five-day intravascular methotrexate versus biweekly actinomycin-d in the treatment of low-risk gestational trophoblastic neoplasia: a clinical randomized trial [13] Using ultrasound for diagnosing remnants of pregnancy after second-trimester abortion: is it practical? [14] Patients with presenting unusual manifestations with gestational trophoblastic neoplasm: case series and review of literatures [15] Major surgeries performed for gestational trophoblastic neoplasms in a teaching hospital in Tehran, Iran [16] Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up [17] Assessment of the response to chemotherapy in gestational trophoblastic neoplasia with vaginal metastases [18] Telinde's operative gynecology [19] Six-Month Follow-Up After Mole Evacuation

Introduction

Gestational trophoblastic neoplasia (GTN) is unique in women's malignancies because of reasons. This malignancy arises from trophoblast but not from genital organs, it is curable with chemotherapy, in low-risk GTN single-agent chemotherapy is enough for treatment, and does not require histological confirmation for diagnoses.

Epidemiology of women's malignancies show that incidence rate has declined over past 30 years (In Southeast Asia and Japan 2 per 1000 pregnancy, in Europe 0.57 to 1.1 per 1000 pregnancy).

Gestational trophoblastic disease (GTD) is the only group of female reproductive neoplasms derived from paternal genetic material (Androgenic origin). GTD is a continuum from benign to malignant, molar pregnancy is benign, but choriocarcinoma is malignant. Molar pregnancy is a histologic description of proliferating trophoblast that could be completed or partial. Due to aberrant chromosomal distribution in the fertilized egg, in placental development, angiogenesis is not done, so tertiary placenta with cytotrophoblast, syncytiotrophoblast and villous formation without vessels developed. Mole proliferation of trophoblast is diffuse, but in a partial mole, it is sparse.

GTD describes a spectrum of neoplastic conditions derived from placenta including hydatidiform mole, post molar gestational trophoblastic neoplasia (GTN), gestational choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). Gestational trophoblastic disease is another name for complete mole and partial mole. Cytotrophoblast and syncytiotrophoblast with the villous formation in myometrium are called invasive mole [1], documentation of which are by hysterectomy. In rare cases with sharp curettage diagnosed. In choriocarcinoma without villous formation, syncytiotrophoblast proliferation and necrosis with bleeding would be seen.

The risk factors of this aberrant fertilization have not been fully understood but the most common are [2]:

- 1) Extreme of reproductive age (Risk Ratio 1-5)
- 2) History of prior molar pregnancy (Risk Ratio 10-40)
- 3) Only consistent environmental association between Beta-carotene and dietary animal fat intake
- 4) Oral Contraceptive pill and previous abortion are risk factors for partial mole.
- 5) Choriocarcinoma risk factor is, prior complete mole, ethnicity and advanced maternal age

The aim of the present study was to review the new management of gestational trophoblastic diseases.

Presentation

The most common presentation of molar pregnancy is first trimester bleeding. Due to the advancement of sonography, many of molar pregnancies can be

diagnosed earlier and so, difficulty in histopathologic diagnosis of earlier mole exists [3]. The uterus that is larger than gestational age is another presentation of that. This sign is typical for complete mole rather incomplete. Due to the high serum level of Human Chorionic Gonadotropin (HCG) in blood, hyperemesis gravidarum is present and large theca lutein cyst could be seen, hyperthyroidism is another sign due to HCG rise and after the evacuation of molar pregnancy, the normal range of thyroid hormone in blood could be seen [3].

Diagnosis

Molar pregnancy diagnoses via sonography. The vesicular pattern is a typical sign for complete mole. In partial mole, the gestational sac is wider than normal pregnancy and in advanced pregnancy age, an abnormal fetus with polydactyly or other abnormalities could be seen. Definite diagnosis is with pathology report. Immunohistochemistry (IHC) for a p57 distinguished partial from the complete mole. Ten percent of suspected complete mole and partial mole based on ultrasound turn out to be non-molar hydropic abortions on histological review. Therefore, a histological review of the material of any non-viable pregnancy is mandatory [4]. A combined algorithm using Human chorionic gonadotropin (HCG), clinical history, examination, and imaging is required to make the diagnosis of hydatidiform mole [4].

Treatment

The best route of termination of this abnormal pregnancy is suction curettage due to low risk of perforation of the uterus in women older than 40 years, and no desire to have another pregnancy, hysterectomy should be done. Ovaries must be preserved. The molar pregnancy should be evacuated as soon as possible after stabilization of any medical complications [4].

Before surgery, we need [5] pelvic exam, sonography (and if needed pelvic Doppler sonography), HCG titer, CBC, platelet count, liver, kidney, and thyroid function test, Clotting function studies, blood type antibody screen, and Chest x-ray as baseline.

Many experts prefer prophylactic chemotherapy in the high-risk mole, but the evidence is weak. Of note, despite the earlier diagnosis and decreasing symptom burden among patients in the modern era with molar pregnancies, there has not been a decrease in the incidence of postmolar GTN [4]. So, due to curable nature of GTN and complications of chemotherapy, some gynecologic oncologist do not recommend chemotherapy before the evacuation of mole. The best regimen is not well documented but actinomycin D or methotrexate could be used [6-8].

High-risk mole defined as:

- 1) Uterus larger than gestational age
- 2) HCG is greater than 100000IU/L
- 3) Age of mother older than 40 years
- 4) Coexistence of theca lutein cyst bigger than 6cm

In twin pregnancy with a mole, management is

individualized [1, 3]

If continuation of pregnancy is desired, a fetal karyotype should be obtained, chest radiography needs to be performed to screen for metastases, and serial serum HCG values must be followed. If fetal karyotype is normal, major fetal malformations are excluded by ultrasonography, and there is no evidence of metastatic disease. It is reasonable to allow the pregnancy to continue unless pregnancy-related complications force delivery. After delivery, the placenta should be histologically evaluated, and the patient should be followed closely with serial HCG values, as one would with a singleton hydatidiform mole [4].

Follow up

After the evacuation of molar pregnancy, the patient is followed with HCG titer after 48 hours that can be used as a pilot titer and after it with weekly titer. For definite contraception, Oral Contraceptive Pill (OCP) usage is recommended. When the titer is reached to lower than 5, and persist for two weeks, another pregnancy is allowed. Continued allow molar evacuation with HCG monitoring for 6 months is recommended after normalization of HCG values. However, it should be noted that the risk of postmolar GTN is quite low [5]. The mean time for normalization of HCG titer in a complete mole is nine weeks and in partial mole 7 week. The HCG titer in two weeks after termination of molar pregnancy is very important for detecting persistent GTN in recent research [9].

Patients with a history of molar pregnancy would be with an elevated risk of GTN after all future pregnancies. Thus, pathologic examination of all future pregnancies is recommended, including placental examination and examination of the products of conception. Patients should also obtain a serum HCG value at 6 weeks after any pregnancy event (Delivery or spontaneous or therapeutic abortion) [4, 6, 7].

The criteria of malignant persistent GTN

The current International Federation of Gynecology and Obstetrics (FIGO) requirements for making a diagnosis of postmolar GTN are [4]:

- 1) Four values or more of plateaued HCG ($\pm 10\%$) over at least 3 weeks: Days 1, 7, 14, and 21
- 2) A rise of HCG of 10% or greater for 3 values or more over, At least 2 weeks: Days 1, 7, and 14
- 3) Histologic diagnosis of choriocarcinoma
- 4) Persistence of HCG beyond 6 months after mole evacuation

Approximately 45% of patients have metastatic disease when GTN is diagnosed [4]. After documentation of persistent GTN, clinical staging would be done. For confirmation of non-metastatic GTN, workup of metastasis should be done:

- 1) Taking history of cough, headache, vaginal or rectal bleeding
- 2) Pelvic examination and determination of vaginal metastasis

3) Chest x-ray or Computed Tomography (CT) scan of the chest

4) Sonography, Magnetic Resonance Imaging (MRI) or CT scan of pelvis and abdomen

5) Contrast MRI of the brain [4]

6) HCG titer (HCG level obtained immediately before instituting treatment for malignant GTN is the one used for staging-not the HCG level obtained at the time of molar evacuation)

7) CBC, liver and kidney and thyroid function test

8) Stool exam for guaiac test

Although the majority of patients with high-risk metastatic sites have pulmonary metastases on chest radiography or symptoms of metastatic, a full metastatic evaluation is recommended for all patients rather than relying on a negative chest radiograph alone to make a determination of nonmetastatic GTN [4].

Sonography with color Doppler is very useful in detection of mass in myometrium and confirmation of stage 1 GTN. Myoma could be considered in differential diagnosis. Operative procedures for confirming the diagnosis or staging are rare [4].

After metastatic workup, 4 stage for GTN is diagnosed [10], they are:

Stage 1: Confined to the uterus

Stage 2: Metastasis to the vagina, pelvic organ, parametrium

Stage 3: Metastasis to the lung with or without pelvic metastasis

Stage 4: Metastasis to brain, liver, kidney and gastrointestinal (GI)

The current International Federation of Gynecology and Obstetrics (FIGO) system counts and measures pulmonary metastases only if they are visible on chest radiograph. Liver metastases are the most common intra-abdominal metastases [4].

Ordinary, stage 1 is low risk and treatment with single-agent chemotherapy is done, and stage 4 is high risk, so multiple agent chemotherapies are needed. In stage 2 and 3, the scoring system is done. In world health organization (WHO) revising the scoring system, the age of the patient, previous pregnancy, HCG titer, duration of disease, size of metastasis, the location of metastasis, previous failure chemotherapy scored. In score lower than seven single-agent chemotherapies are done and in the score, ≥ 7 multiple agent chemotherapy used.

Because the clinical classification system is relatively simple, it may be the best system for use by the general gynecologist for the purpose of appropriate referral [4]. The prognosis and treatment of a patient are dependent on stage and score. For example, with HCG > 100000, after 12 months from term previous pregnancy, multiple agent chemotherapy needed. The recommendation of the recent article is about change in the scoring system, for example, HCG > 400000 is a very high risk and need for multiple chemotherapies. Patients with metastatic disease and one or more of the clinical

classification system risk factors or a FIGO risk score of 7 or greater have high-risk disease. They require multi-agent chemotherapy [4, 11].

The individual prognosis of a patient with GTN can be calculated by using FIGO prognostic score in combination with an anatomical staging system. The anatomical staging system can also be applied to patients with PSTT and ETT. Patients having less than 7 points based on the FIGO scoring system, belong to the low-risk group. In this group, nearly 100% cure rate is achieved by single-agent systemic chemotherapy. Patients with a FIGO score higher than six points have a high risk to develop resistance to single-agent systemic chemotherapy. Overall survival rates of 95 to 100% can be retained despite raising drug-resistant diseases. Nevertheless, some patients may develop a malignant disease resulting in death. Who presents with an apparent metastatic malignancy of unknown primary site should be screened with serum HCG level (Table 1).

Table 1) FIGO risk score for Gestational Trophoblastic Neoplasia

Factors	0	1	2	4
Age (years)	<40	≥40		
Antecedent Pregnancy	Mole	Abortion	Term	
Interval from Antecedent Pregnancy to Chemotherapy (months)	<4	4-6	7-12	>12
HCG (IU/l)	<10 ³	10 ³ -10 ⁴	10 ⁴ -10 ⁵	>10 ⁵
Number of Metastases	0	1-4	5-8	>8
Site of Metastases	Lung	Spleen/Kidney	Gastrointestinal Tract	Brain/Liver
Largest Tumor Mass (cm)		3-5	>5	
Previous Chemotherapy		Monotherapy		Combined Therapy

Calculation of patients risk score by adding single factors: 0-6 points → low-risk group, ≥7 points → high-risk group; FIGO anatomical staging used for PSTT/ETT; Stage Description: I- Disease confined to the uterus; II- Disease extending into the pelvis; III- Disease spread to lungs with or without known genital involvement; IV- All other metastatic sites (Liver, Kidney, Spleen, Brain)

The best single agent chemotherapy for the low-risk patient is actinomycin D due to the following factors [12];

- 1) The courses to obtain normal HCG is lower than methotrexate (4 courses)
- 2) The complication is lower than methotrexate (MTX) except for alopecia that is significant.

Actinomycin D can be used 1.25mg/m² every two weeks or 12µg/kg daily for five days every other week and treatment is continued until HCG<5IU/ml. Methotrexate can be used via 50mg/M²/day every week or 0.4mg/m²/day for 5 days or 1mg/m² alternate with leukotriene 0.1mg/kg/day. Treatment is continued until HCG level lower than 5, and then two additional courses are used as

consolidation chemotherapy to prevent recurrence. The efficacy of any route is good and in low-risk patient in tertiary center cure rate is 100%. The patient will be followed for one year with HCG titer and then in the absence of recurrence, it will be allowed to be pregnant.

Unresponsiveness to a single agent means that another agent should be used after radiographic restaging. In cases that HCG level rise or plateau in two types of single-agent therapy, multiple agent chemotherapies is used. Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, Vincristine (EMA-CO) is standard regimen in high-risk patients and failure of single-agent chemotherapy in low risk. Etoposide and MTX and actinomycin in days 1 and 2, cyclophosphamide and vincristine (CO) in days 8 is given. These courses are continued until the level of HCG reach to <5, and then add three courses is used as maintenance therapy. When chemotherapy is given for an additional one to two cycles after the first normal HCG value, recurrence rates are less than 5% [4]. In unresponsiveness to standard regimen, Etoposide and Cisplatin with Etoposide, Methotrexate, and Dactinomycin (EMA-EP) is used that on day 8, etoposide and cisplatin substituted instead CO.

Regardless of the regimen selected, aggressive recycling of multi-agent therapy is the cornerstone for management of patients with high-risk disease. Despite using sensitive HCG assays and maintenance chemotherapy, up to 13% of patients with the high-risk disease will develop recurrence after achieving an initial remission [4].

In many centers, score >12 is treated with EMA-EP primarily. The responsiveness to treatment in high-risk GTN is 86%. The patient is followed with HCG titer for detection of relapse until two years and then with HCG<5, allowed to conceive. In some center continuous long life follows up is recommended.

Placental Site Trophoblastic Tumor (PSTT) and Epithelioid Trophoblastic Tumor (ETT)

In placental site trophoblastic Tumor and Epithelioid trophoblastic tumor, hysterectomy is the method of choice for treatment (Unless there are widespread metastases). The intermediate trophoblast is the most abnormal cell in this entity, so is against syncytiotrophoblast responsiveness in choriocarcinoma to chemotherapy [13, 14]. Ovarian removal is not required because GTN rarely metastasizes to the ovaries, and these tumors are not hormonally influenced [4].

The staging system is used the same as another GTN but scoring system is not used. Chemotherapy with EMA-EP regimen is used in advanced stages. ETT is similar to PSTT that grows slowly, is resistant to chemotherapy, and produces low levels of HCG. The tumors often present in the lower uterine segment and often have positive staining for p63 and cytokeratin, causing them to be confused with

squamous cell carcinoma of the squamous cell carcinoma lower uterine segment^[4, 15].

The role of surgery in management of malignant GTN

Chemotherapy is a choice method for treatment of malignant GTN but hysterectomy is indicated for treatment in the following:

- 1) Stage 1 and no desire for another pregnancy
- 2) The uterus is nidus for sepsis
- 3) Heavy vaginal bleeding
- 4) PSTT and ETT

In contrast to patients with non-metastatic or low-risk metastatic GTN, early hysterectomy does not appear to improve the outcome in women with high-risk metastatic disease^[4]. However, further chemotherapy after hysterectomy is mandatory until HCG values are normal^[4].

Each patient considered for local myometrial tumor resections should be carefully evaluated for systemic metastases, and the uterine lesion should be localized using a combination of color-flow ultrasonography, MRI, and hysteroscopy^[5, 10]. Intraoperative frozen sections should be used to assess surgical margins. Small lesions associated with low levels HCG are more likely to be completely excised with a conservative myometrial tumor resection than lesions larger than 2 to 3cm in diameter^[4].

Other modalities include options below^[16-18]:

- 1) If the vagina is the only site of metastasis, the majority of these lesions respond to chemotherapy. Vaginal metastases of malignant GTN are highly vascular, originating from submucosal venous plexus of the vagina. A few patients require vaginal packing or selective embolization using interventional radiology to control active hemorrhage.
- 2) In isolated chest metastasis, after chemotherapy, surgery is recommended for removal of it. HCG level remission within 1 to 2 weeks of surgery portends a favorable outcome. The most frequently used surgical procedure for removal of extrauterine metastases is thoracotomy with pulmonary wedge resection^[4].
- 3) In brain metastasis, in concordance with chemotherapy, radiotherapy to the whole brain is recommended (Consider gamma knife radiation if isolated brain lesion) for hemostatic action of it. Chemotherapy in brain metastasis would be with induction low dose etoposide and cisplatin. Specialized center is recommended in this situation. In sharp contrast to the outlook for women with brain metastases from other solid tumors, up to 85% of women with brain metastases presenting for primary therapy from malignant GTN will sometimes be cured craniotomy is required for women who require acute decompression of CNS hemorrhagic lesions to allow stabilization and institution of therapy^[4].
- 4) In liver metastasis that can be fatal, intra-arterial

chemotherapy is recommended. Even with intense chemotherapy, additional surgery may be necessary to control hemorrhage from metastases, remove chemoresistant disease, or treat other complications to stabilize high-risk patients during therapy^[4].

5) Metastasis to Gastrointestinal (GI) tract is rare but case report of GI bleeding exists. Mortality rate in this situation is high.

6) The overall efficacy of radiation therapy to sites other than the brain is unclear. Most of the successes probably reflect the summation of an aggressive multimodality approach to individual patients with high-risk metastatic GTN^[4, 19].

Future childbearing

After effective treatment for malignant GTN, molar pregnancies occur in only about 1% to 2% of subsequent pregnancies, so; it is reasonable to evaluate subsequent pregnancies with first trimester ultrasonography^[4]. These patients have occasionally developed repeated hydatidiform moles or malignant GTN subsequent to the implementation of assisted reproductive technologies, therefore; the use of intracytoplasmic sperm injection (ICSI) with preimplantation genetic diagnosis or donor oocyte IVF are therapeutic alternatives in these cases.

Limitations of this study were frequency dependency of molar pregnancy and GTN to race and geographical area; so, it was suggested to conduct research in different races and areas to get a better result in the next studies. Another suggestion is that repeat curettage will be the standard treatment of low-risk molar pregnancy in future.

Conclusion

In the case of brain, liver, or renal metastases, any woman of reproductive age who presents with an apparent metastatic malignancy of unknown primary site should be screened for the possibility of GTN with a serum HCG level. Excisional biopsy is not indicated to histologically confirm the diagnosis of malignant GTN if the patient is not pregnant and has a high HCG value. Given the vascular nature of these lesions, a biopsy can have significant morbidity. In every woman with abnormal bleeding or neurologic symptom without documented reason, the probability of malignant GTN should be in mind and determination of HCG titer is recommended. In selected cases with low-risk GTN, repeat curettage is done to reduce the need for chemotherapy courses. In recent years personalized medicine is encouraged for treatment of GTN. Tertiary center and gynecologist oncologist are an essential part of treatment. In recurrent or relapse cases, another regimen such as Bleomycin, Etoposide, Cisplatin (BEP) or encourage to participate in the research protocol is advised.

Acknowledgments: The authors wish to thank the dear staff of the central library of the Iran University

of medical sciences for cooperating with us for easy access to references.

Ethical permissions: This article is written in compliance with ethical rules.

Conflicts of interests: The authors declare that there are no Conflicts of interests.

Authors' Contribution: Soheila Aminimoghaddam (First author), Introduction author/ Methodologist/ Original researcher (70%); Nastaran Abolghasem (Second author), Assistant researcher (10%); Tahereh Ashraf-Ganjooie (Third author), Assistant researcher (20%)

Funding/Support: There were no sources of funding or support for this study.

References

- 1- Aminimoghaddam S, Maghsoudnia A. Unusual presentation of invasive mole: A case report. *J Reprod Infertil.* 2017;18(1):205-9.
- 2- Aminimoghaddam S. A review of recent findings for obstetricians about combined oral contraceptive pills. *J Obstet Gynecol Cancer Res.* 2017;2(2):e11200.
- 3- Aminimoghaddam S, Mohseni I, Afzalzadeh A, Esmaeeli S. Ovarian malignant mixed germ cell tumor: A case of unusual presentation as molar pregnancy. *J Reprod Infertil.* 2016;17(2):133-6.
- 4- DiSaia P, Creasman W, Mannel R, McMeekin DS, Mutch D. *Clinical gynecologic oncology.* 9th Edition. Amsterdam: Elsevier Health Sciences; 2017.
- 5- Rahmani M, Foroozi S, Akhavan S, Yarandi F, Aminimoghaddam S. OC27. 01: Role of imaging in assessment of gestational trophoblastic neoplasia and transvaginal Doppler ultrasound versus pelvic dynamic contrast enhanced MRI. *Ultrasound Obstet Gynecol.* 2016;48(S1):49-50.
- 6- Gary Cunningham F, Leveno J, Bloom L, Spong Y, Dashe S, Hoffman L, et al. *Williams Obstetrics.* 25th Edition. New York: McGraw-Hill Education; 2018.
- 7- Berek JS. *Berek and Novak's gynecology.* 15th Edition. Philadelphia: Lippincott Williams & Wilkins; 2011.
- 8- Aminimoghaddam S, Nezhadislami F, Anjidani S, Tond SB. Outcome of treatment with EMA/EP (etoposide methotrexate and actinomycin-D/etoposide and cisplatin) regimen in gestational trophoblastic neoplasia. *Med J Islam Repub Iran.* 2018;32:36.
- 9- Aminimoghaddam S, Yarandi F, Nejadslami F, Taftachi F. Human chorionic gonadotrophin as an indicator of persistent gestational trophoblastic neoplasia. *Med J Islam Repub Iran.* 2014;28:44.
- 10- Stevens F, Katzorke N, Tempfer C, Kreimer U, Bizjak G, Fleisch M, et al. Gestational trophoblastic disorders: An update in 2015. *Geburtshilfe Frauenheilkd.* 2015;75(10):1043-50.
- 11- Ghaemmaghami F, Ashraf-Ganjooei T. Gestational trophoblastic neoplasia. *Asia-Pacific J Clinic Oncol.* 2006;2(1):9-21.
- 12- Yarandi F, Mousavi A, Abbaslu F, Aminimoghaddam S, Nekuie S, Adabi K, et al. Five-day intravascular methotrexate versus biweekly actinomycin-d in the treatment of low-risk gestational trophoblastic neoplasia: A clinical randomized trial. *Int J Gynecol Cancer.* 2016;26(5):971-6.
- 13- Rahimi Sharbaf F, Nekuie S, Mohseni M, Esmaili A, Khansari N, Moinfar Z, et al. Using ultrasound for diagnosing remnants of pregnancy after second-trimester abortion: is it practical?. *Elixir Gynaecol.* 2017;111:769-72.
- 14- Ashraf-Ganjooei T, Ghaemmaghami F. Patients with presenting unusual manifestations with gestational trophoblastic neoplasm: Case series and review of literatures. *Arch Gynecol Obstet.* 2008;277(5):465-70.
- 15- Ghaemmaghami F, Ashrafgangooei T, Gillani MM, Mosavi A, Behtash N. Major surgeries performed for gestational trophoblastic neoplasms in a teaching hospital in Tehran, Iran. *J Gynecol Oncol.* 2011;22(2):97-102.
- 16- Seckl M, Sebire N, Fisher R, Golfier F, Massuger L, Sessa C, et al. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013;24(suppl_6):vi39-vi50.
- 17- Fatemeh G, Shohreh B, Azamolsadat M, Tahereh A, Mitra MG, Nadereh B, et al. Assessment of the response to chemotherapy in gestational trophoblastic neoplasia with vaginal metastases. *Arch Gynecol Obstet.* 2008;278(4):315-8.
- 18- Jones HW, Rock JA. *Telinde's operative gynecology.* 11th Edition. Philadelphia: Lippincott Williams & Wilkins; 2015.
- 19- Farzaneh F, Vahedpour Z, Ashrafganjoei T, Rafizadeh M, Al e Bouyeh H, Hosseini M. Six-Month Follow-Up After Mole Evacuation. *Obstet Gynecol cancer res.* 2016;1(1):e7331.