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Review Article

A systematic review on molar pregnancy

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ABSTRACT

Molar pregnancy is a non cancerous benign tumour that develops in the uterus. Molar pregnancy is the most common type of gestational trophoblatic disease. Molar pregnancies are most common in Asian countries, such as Taiwan, the Philippines and Japan, and also among Native Americans. Complete molar pregnancies are more common in teenage women and women over 45 years old. Most cases of molar pregnancy are diagnosed in the first trimester by ultrasound or as early pregnancy losses. The cure rate for molar pregnancies, including for those women requiring chemotherapy, is 99%. Trans-vaginal ultrasound, routinary dosage of beta – hcG and current approaches to chemotherapy, let most women with malignant gestational trophoblatic disease to be cured and their reproductive function preserved.

Key Words: Molar pregnancy, Gestational-trophoblatic disease, Human chorionic gonadotrophin, Chemotherapy.

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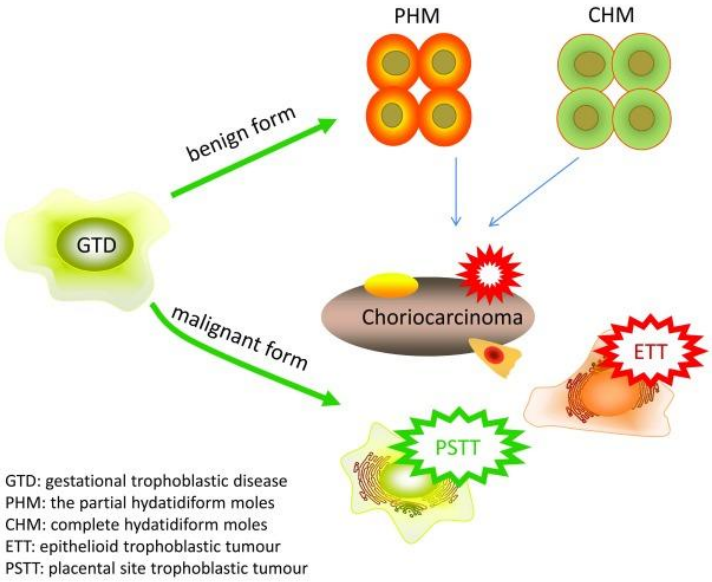
INTRODUCTION

Gestational trophoblatic disease is a term covering pregnancy conditions that involve placental tissue turning like cancer. Placental trophoblatic cells possess the ability to proliferate, invade host tissue, avoid the host's immune response and even metastasize. GTD is defined as heterogeneous group of interrelated lesions arising from the trophoblatic epithelium of the placenta after abnormal fertilization [1]. It includes various lesions such as pre-malignant lesions including hydatidiform mole (partial and complete type), while malignant lesions (gestational trophoblatic neoplasm) comprise invasive mole, Choriocarcinoma, placental-site trophoblatic tumour, and epithelioid trophoblatic tumour [2].

Figure: 1



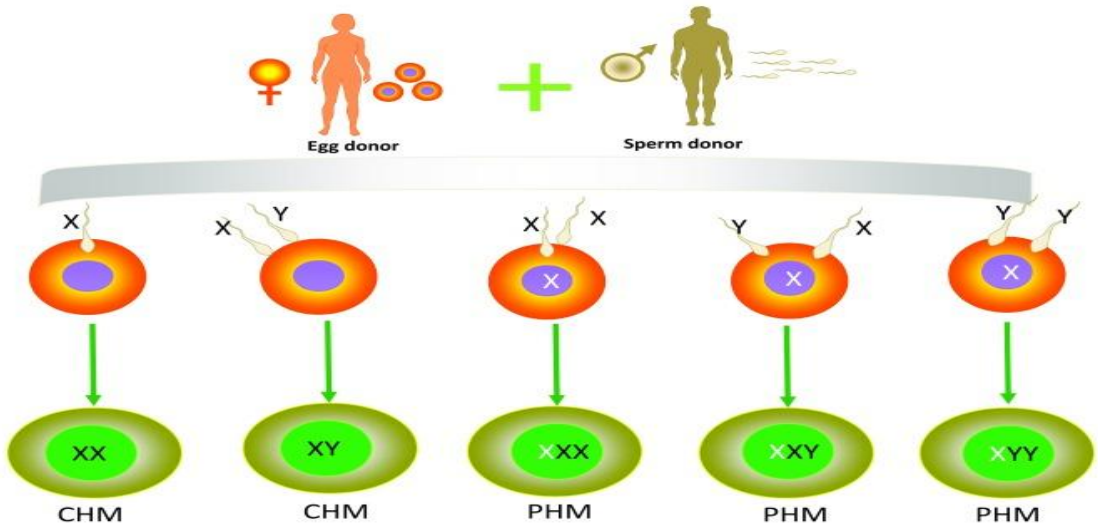
A molar pregnancy also known as hydatidiform mole is a non cancerous benign tumour that develops in the uterus. Molar pregnancy is the most common type of GTD. A molar pregnancy starts when an egg is fertilized, but instead of a normal, viable pregnancy resulting, the placenta develops into an abnormal mass of cyst. In a complete molar pregnancy, there's no embryo or normal placental tissue [3]. In a partial molar pregnancy, there is an abnormal embryo and possibly some normal placental tissue. The embryo begins to develop but is malformed and can't survive. A molar pregnancy can have serious complications including a rare form of cancer [4].

Types of gestational trophoblastic disease: The main types of GTD are:

1. Hydatidiform mole (complete or partial mole)
2. Invasive mole
3. Choriocarcinoma
4. Placental – site trophoblatic tumour
5. Epithelioid trophoblatic tumour.

Hydatidiform moles: Hydatidiform moles are oedematous immature placentas which are broken down into complete and partial moles. A complete mole occurs when an empty ovum is fertilized by a sperm, about 90% of complete hydatidiform moles are 46XX which originate from the duplication of chromosomes of a haploid sperm and the other 10% are 46XY (figure:2)[5] and the chromosomes are paternally derived. Complete hydatidiform moles take on the appearance of a "bunch of grapes" which undergo diffuse villous (capillaries are absent. Foetal tissue or the embryo is absent in complete moles) enlargement with hydropic changes. In complete hydatidiform moles, the uterus is typically significantly enlarged for gestational age, and patients always have an elevated human chorionic gonadotrophin (hcG) level of gestational age. Often, there can be early onset of medical complications such as pregnancy induced hypertension, hyperthyroid, hyper emesis gravidarium [5-6].The most common presentation of molar pregnancy is abnormal vaginal bleeding during the first trimester and ovarian theca-lutein cysts greater than 6cm in diameter [7-8]. A partial mole occurs when an empty ovum is fertilized by two sperm, the normal karyotype being 69XXX, 69XXY, or 69XYY, although a diploid karyotype may also exist (figure: 2) [5]. In PHM's placental villi have focal oedema and denatured areas of varying size and shape and pathological trophoblatic cell proliferation. Foetal tissue or a recognizable embryo will be present. Rarely, a term infant will be born.

Figure: 2



CHM=complete hydatidiform mole
PHM=partial hydatidiform mole
Paternal (black) and maternal (white) derived genes are shown

Invasive mole: Invasive mole is common manifestation of gestational trophoblatic neoplasia characterised by the presence of whole chorionic villi that accompany excessive trophoblatic over growth and invasion. These tissues penetrate deep into the myometrium sometimes involving the peritoneum or vaginal vault. Such moles are locally invasive but generally lack the pronounced tendency to develop wide spread metastases typical of Choriocarcinoma. Invasive mole originates exclusively from complete or partial mole [9 -10].

Choriocarcinoma: Choriocarcinoma is a germ cell tumour containing cells of trophoblatic origin. It is usually associated with gestational event like molar pregnancy and secretes human chorionic gonadotrophin (b- hcG) [11]. Primary pulmonary Choriocarcinoma (pcc) is a rare tumour that generally affects young individuals [12]. It is rarely in the post menopausal women [13].

Placental site trophoblatic tumour: Placental site trophoblatic tumour is a rare tumour, representing from 0.23[14] to 3% [15] of gestational trophoblatic disease (GTD). It mainly affects women of childbearing age, after pregnancy. PSTT differs from other GTD by a slow growth and a relative resistance to chemotherapy.

Epithelioid trophoblatic tumour: Epithelioid trophoblatic tumour is an extremely rare type of gestational trophoblatic disease that can be hard to diagnose. ETT used to be called atypical Choriocarcinoma because the cells look like Choriocarcinoma cells under the microscope, but it is now thought to be a spate disease. ETT is most often occurs after a full- term pregnancy [16].

ETIOLOGY:

As described previously, hydatiform moles are divided into complete and partial moles. Complete mole is the more common type and does not contain a foetus, whereas in a partial mole are typically diploid, where as partial moles are triploid. complete moles tend to causes higher levels of the human chronic gonadotrophin (hcG), which is one of the main clinical features of this process .in incomplete moles , the karyotype is 46,XX90% of time and 46,XY10% of the time. It arises when an enucleated egg is fertilized either by two sperms or by a haploid sperm that then duplicates and therefore only parental DNA is expressed. On other hand In partial moles, the karyotype is 90% of the time triploid and either by two sperm subsequently fertilizes a haploid ovum duplicate and or when two sperms fertilize a haploid ovum .in partial moles, both maternal and paternal DNA is expressed[17,18,19]

PATHOPHYSIOLOGY:

Molar gestations are increased in older and very young females of reproductive age in those with a history of prior molar pregnancy. Advanced paternal age may be a risk factor for complete molar pregnancy[20]. Molar pregnancies and gestational trophoblatic neoplasm all take their origin from the placental trophoblast. Normal trophoblast is composed of cytotrophoblast, Syncytiotrophoblast and intermediate trophoblast. Syncytiotrophoblast invades the endometrial stroma with implantation of the blastocyst and is the cell type that produces human chorionic gonadotrophin (hcG). Cytotrophoblast functions to supply the syncytium with cells in addition to forming outpunching that become the chorionic

villi covering the chorionic sac. The villousnchorion adjacent to the endometrial and basal layer of endometrium together forms the functional placenta for maternal foetal nutrient and waste exchange. Intermediate trophoblast is located in the villi, the implantation site, and the chorionic sac. All three types of trophoblast may result in gestational trophoblatic disease when they proliferate[21-22].

Risk Factors:

- Whilst the diagnosis of molar pregnancy is rare , there are two group of women who have significantly elevated risk of developing a molar pregnancy. At the extremes of the reproductive age of 15 years have a risk approximately 20 times higher than women aged 20-40 , whilst women aged over 45 years have a several hundred –fold higher risk than those aged 20-40[23].
- Age – complete molar pregnancies are common in teenage women and women over 45 years old. Age has little or no effect on the risk of partial molar pregnancy[24].
- Previous molar pregnancy –if you have had one molar pregnancy before, your chance of having another one is around one to two in 100, compared with one in 600 for women who haven't had a molar pregnancy. If you had two or more molar pregnancies, your risk of having another is around15-20 in 100[25].
- Ethnicity- molar pregnancies are most common in Asian countries, such as Taiwan, the Philippines and Japan, and also among Native Americans. However, in recent years, the differences in the incidence of molar pregnancy between these communities and the general population have less marked[25].
- A low intake of carotene (a form of vitamin A).
- Prior history of gestational trophoblatic disease – the recurrence rate is one in 100.
- Ovulatory disorders, such as polycystic ovary syndrome (PCOS).
- Living in, or coming from certain geographical areas (as mentioned before women from southeast Asian [26].

Signs and Symptoms: A molar pregnancy may seem like a molar pregnancy at first, but most molar pregnancies cause specific signs and symptoms, including:

- Dark brown to bright red vaginal bleeding during the first trimester
- Severe nausea and vomiting
- Sometimes vaginal passage of grape – like cysts
- Rarely pelvic pressure or pain[27].
- In many cases there may be no signs that patient is having a molar pregnancy and it may go undetected until routine early pregnancy scan at 10-12 weeks. If patient experience any signs or symptoms of a molar pregnancy, she should consult physician or pregnancy care provider[28].He or she may detect other signs of molar pregnancy, such as:
    1. Rapid uterine growth – the uterus is too large for the stage of pregnancy
    2. High blood pressure
    3. Preeclampsia-a condition that causes high blood pressure and protein in the urine after 20 weeks of pregnancy[29].
    4. No foetal movement
    5. Abnormal appearance of the uterine cavity at the first ultrasound (called a 'snowstorm' pattern).
    6. No foetal heart beat
    7. Ovarian cysts
    8. Anaemia
    9. Overactive thyroid(hyperthyroidism) [29]

Diagnosis:

- The diagnosis of a molar pregnancy might be suspected based on a number of clinical features: abnormal vaginal bleeding in early pregnancy is the most common presentation;[30] uterus large for dates (25%); pain from large benign theca-lutein cysts (20%); vaginal passage grape- like vesicles(10%); exaggerated pregnancy symptoms including hyper emesis (10%), hyperthyroidism(5%), early preeclampsia(5%).
- Now a day's ultrasound scan often permits diagnose molar pregnancy before 12 weeks, showing a fine vascular or honeycomb appearance. Later a complete mole is characteristically described as snowstorm appearance of mixed echogenicity, representing hydropic villi and intrauterine haemorrhage. The ovaries often contain multiple large theca- lutein cysts as a result of increased ovarian stimulation by excessive beta- hcG [31].
- Ultrasound diagnosis of partial mole difficult: the foetus may show signs consistent of triploid, such as unusually early growth restriction or developmental abnormalities. There may be only scattered cystic spaces within the placenta, and ovarian cystic changes as usually much less pronounced. In case of doubt, the scan should be repeated in 1 to 2 weeks.
- In women with a complete mole, the quantitative serum beta- hcG level is higher than expected, often exceeding 100,000IU/L. In case of partial mole, the level of beta-hcG is often within the wide range associated with

normal pregnancy are usually less pronounced. For these reasons the diagnosis of partial mole is often missed clinically and made from subsequent histological assessment of the abortive material [32].

Imaging:

- The diagnosis of molar pregnancy can nearly always be made by ultrasound, because the chorionic villi of a typical complete mole proliferate with vacuolar swelling and produce a characteristic vesicular sonographic pattern [33].
- Previously when the diagnosis was made at a later stage, the classical 'snowstorm' pattern of the uterus was described; however this is not commonly seen now.
- The majority of the first trimester complete moles demonstrated a typical sonographic appearance of a complex and echogenic intrauterine mass containing many small cystic spaces.
- One may see a large, central fluid collection that mimics an embryonic gestation or abortion [34].
- Occasionally, there is merely a central mass of variable echogenicity, presumably because the villi are too small to be seen with sonography at that time.
- Transverse sonogram of the uterus demonstrates the heterogeneous mass within the endometrial cavity. The visualized anterior and posterior myometrium appear to be normal and uninvolved.
- The sagittal view of the uterus demonstrating that the endometrial cavity is filled with an echogenic cavity is filled with an echogenic mass containing cystic spaces.
- Non- invasive GTD may appear avascular and contain many cystic spaces within, which correspond to the swollen chorionic villi. Invasive GTD including Choriocarcinoma however show increased intratumoral blood flow, and focal areas of increased flow in the myometriumas well, if there is local invasion[35-36].
- Studies have concluded that it is not always possible to make a diagnosis of early molar pregnancy by ultrasound and therefore, histological examination of the aborted/ evacuated specimens remains important and DNA analysis should be carried out for the final diagnosis, if the histology is inconclusive [37].
- The present data indicates that ultrasound can correctly identify molar changes in early pregnancy and together with HCG levels and uterine Doppler measurements may establish the differential diagnosis in uterus of the various forms of placental molar transformations [38].
- Patients are often counselled to avoid pregnancy for at least one year to minimize the risk of missing persistent trophoblatic neoplasia.
- With a standard ultrasound, high frequency sound waves are directed at the tissues in the abdominal and pelvic area.
- During early pregnancy, however, the uterus and fallopian tubes are closer to the vagina than to the abdominal surface, so the ultrasound may be done through a wand like device placed in patient's vagina [39].

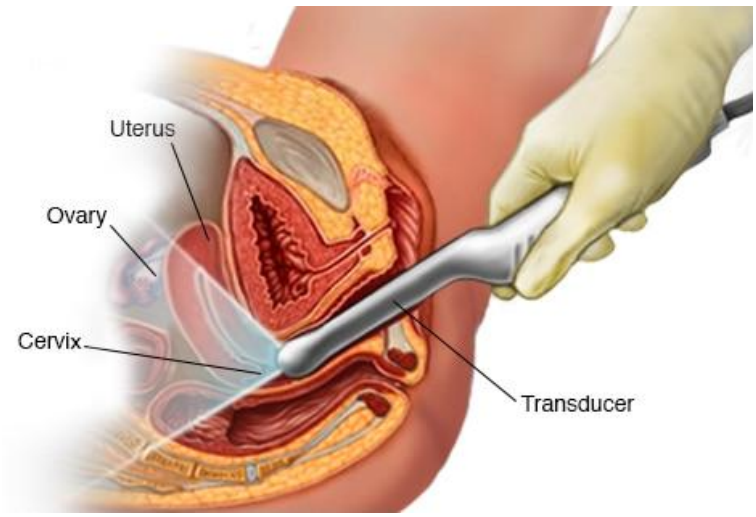


Figure: 3

Trans-vaginal ultrasound:

An ultrasound of a complete molar pregnancy- which can be detected as early as eight or nine weeks of pregnancy- may show: [40]

- No embryo or foetus
- No amniotic fluid
- A thick cystic placenta nearly filling the uterus
- Ovarian cysts

An ultrasound of a partial molar pregnancy may show:

- A growth- restricted foetus
- Low amniotic fluid
- A thick cystic placenta [40]

If health care provider detects a molar pregnancy, he or she may check for the other medical problems, including:

- Preeclampsia
- Hyperthyroidism
- Anaemia

TREATMENT

A molar pregnancy can't continue as a normal viable pregnancy. To prevent complications, the molar tissue must be removed. Treatment usually consists of one or more of the following:

Dilation and Curettage (D&C): To treat a molar pregnancy, doctor removes the molar tissue from patient's uterus during a procedure called dilation and curettage (D&C). A D&C usually done as an outpatient procedure in a hospital [41]. During the procedure, patient receives a local or general anaesthetic and lie on her back with legs in stirrups. Doctor inserts a speculum into patient's vagina, as in a pelvic exam, to see his or her cervix. Doctor then dilates his or her cervix and removes uterine tissue with a vacuum device. A D&C usually takes about 15 to 30 minutes.

Hysterectomy: The molar tissue is extensive and there's no desire for future pregnancies, patient might have surgery to remove her uterus (hysterectomy).

HCG monitoring: After the molar tissue is removed, doctor repeats measurement of your HCG level until it returns to normal. If patient continue to have HCG in her blood, she may need additional. Once treatment for the molar pregnancy is complete, doctor may continue to monitor her HCG levels for six months to one year to make sure there's no remaining molar tissue. Because pregnancy makes it difficult to monitor HCG levels, doctor may recommend waiting until after follow up before trying to become pregnant again [42].

After treatment: Following the mole's removal, some cells will be left in the womb. The cells usually die off over time in around 90% of women. To check the cells have died, all women who have had a molar pregnancy in the UK undergo monitoring of the hormone HCG via the National Trophoblastic Screening Centre's surveillance programme [43- 44]. hcG is the pregnancy test hormone produced by a normal placenta, but also by the mole cells, and is the hormone detected in a pregnancy test. It can also be detected in blood and urine tests. Women on the surveillance programme send in blood or urine samples every two weeks. This is so they can be monitored for signs of persistent trophoblastic disease, which is a risk after molar pregnancy [44]. Persistent trophoblastic disease needs further treatment with chemotherapy.

Chemotherapy: Complete molar pregnancy is well recognized to have the potential for local invasion and distant spread. After evacuation, local uterine invasion occurs in about 15% and metastasis in 4%. Complete molar pregnancy is usually divided into low and high risk for persistent based on signs and symptoms of marked trophoblastic proliferation at the time of evacuation, i.e., hcG >100,000 mIU/ML; excessive uterine enlargement; theca-lutein ovarian cyst>6cm in diameter; older maternal age; a previous molar pregnancy. The risk of post molar GTD is significant less with partial molar pregnancy and is seen in approximately 1-6% [45]. Unfortunately there are no distinguishing clinical or pathologic features for predicting persistence after a complete molar pregnancy. Although controversial, the use of chemoprophylaxis at the time of evacuation of high-risk complete molar pregnancy has been shown to significantly decrease the development of GTD from approximately 50% to 10-15%. A number of chemotherapy regimens are used for treating the disease, but the best seems to be the association between methotrexate, actinomycin D and cyclophosphamide [46].

CONCLUSION

Molar pregnancy is rare and its aetiology, biology and responsiveness to treatment are very different from those of any other form of malignancy. Fortunately, the majority of cases can be cured by simple surgical intervention and those that require chemotherapy are generally cured with very low toxicity treatment. The general understanding of the natural history and management of ***Molar Pregnancy*** has advanced considerably in recent years. The frequency of hydatidiform mole is common in our setting. Complete mole was more frequent and present mainly with vaginal bleeding. The clinical presentation of partial mole was similar to incomplete and/or missed miscarriage. The outcome of pregnancy in women with previous

hydatidiform mole was uneventful except for a slight increased risk of a repeat mole. The key- role in obtaining a high cure rate becomes an early diagnosis and the subsequent strictly follow-up. Efforts are still necessary to develop effective new second- line therapies for patients with drug-resistant disease.

REFERENCES

1. Deep JP, Sedhai LB, et al. Gestational trophoblastic disease. J chitwan Medical college 2013; 3(4):4-11.
2. Seckl M J, Sebire NJ, et al. Gestational trophoblastic disease. Lancet.2010; 376(9742): 717-29.
3. Petignat P, Billieux MH, et al. Is genetic analysis useful in the routine management of hydatidiform mole. Hum Reprod, 2003; 18(2): 243-9.
4. Fryns JP, Vande Kerckhove A, et al. Unusually long survival in a case of full triploidy of maternal origin. Hum Genet. 1977; 38(2): 147-55.
5. Seckl MJ, Sebire NJ, Berkowitz RS: Gestational trophoblastic disease. Lancet. 2010; 376(9742): 717-29.
6. Higgins HP, Hershman JM, Kenimer JG, et al. The thyro- toxicosis of hydatidiform mole. Ann Intern Med. 1975; 83(3): 307-11.
7. Bruce S, Sorosky J: Gestational trophoblastic Disease. Stat Pearls Publishing. 2017.
8. Monchek K, Wiedasecks S: Gestational trophoblastic disease. an overview.J Midwifery Womens Health. 2012;57(3):255-9.
9. A. Ilancheran Optimal treatment in gestational trophoblastic disease. Ann Acad Med Singapore, 27(1998), pp. 698-704.
10. M. Alazzam, J. Tidy, B.W. Hancock, et al. First line chemotherapy in low risk gestational trophoblastic neoplasia. 21(1)(2009),10.
11. V. Di Crescenzo, P. Laperuta, et al. An unusual case of primary Choriocarcinoma of the lung. BMC Surgery, vol.13, no.2, article no.S33, 2013.
12. U.B.M. Kanni, primary pulmonary Choriocarcinoma. is it still an enigma. Indian journal of chest diseases and allied sciences , vol -47, PP- 216-226, 2007.
13. Snoj, Z., Kocijancic, I., & Skof, E. (2016). Primary pulmonary Choriocarcinoma . Radiology and oncology, 51(1), 1–7.
14. Hassadia A, Gillesepie A, et al. placental site trophoblastic tumour: clinical features and management gynecol oncol (2005) 99:603-607.
15. Cole ME, Broaddus R, et al. placental site thropoblstic tumours,a case of resistant pulmonary metastasis. Nat clin prat oncol (2008) 5(3): 171-5.
16. Shin IM Gestational trophoblastic neoplasia-pathogenesis and potential therapeutic. Lancet Oncol.2007:8:642-650.et al. Epithelioid trophoblastic tumour: a case report &review of the literature. J Clin pathol. 2006; 59(12):1307-8.
17. Lec D, Contreras M.Robson SC, et al. Recommendations for the use of anti –D immunoglobulin for Rh Prophylaxsis. British Blood Transfusion Society and the royal college of obstetricians and Gynaecologists. Transfus Med, 1999; 9(1):93-7.
18. Moore, K L, Persaud, T.V.N et al. The developing human – clinically oriented embryology. WB Saunders, Philadelphia (PA); 1993 e10.
19. Bentley, R.C. Pathology of gestational trophoblastic disease. Clin obstet Gynecol.2003; 46:513-522.
20. Braga A, Mora P, de Melo AL, Nogueira, et al. Challenges in the diagnosis and treartment of gestational tropoblastic neoplasia worldwide. World J Clin Oncol. 2019 Feb 24; 10 (2): 28 – 37.
21. Yuk JS, Baek JC, et al. Incidence of gestational trophoblastic disease in South korea: a longitudinal, population – based study. Peer J. 2019; 7: e6490.
22. Lix, XUY, Liu Y, et al. the management of hydantiform mole with lung nodule. a retrospective analysis in 53 patients. J. Gynecol Oncol. 2019; 30 (2) : e16
23. Scoper JT, Clerke-Person DL et al. 5 days methotrexate for women with metastatic gestational trophobalstic disease. Gyneocol Oncol, 1994; 54:76-9.
24. Serbire NJ, Foskett M, Fisher RA, et al. Risk of partial and complete hydatidiform moalr pregnancy in relation to maternal age. BJOG. an International Journal of Obstetrics and Gynaecology 2002, Vol. 109, pp. 99– 102.
25. Sebire NJ, Foskett M, et al. Risk of recurrent hydatidiform mole and subsequent pregnancy outcome following complete or partial hydatidiform molar pregnancy. BJOG. an International Journal of Obstetrics and Gynaecology 2003, Vol. 110, pp. 22–26.

26. Royal college of Obstetricians and Gynaecologist. The management of gestational Trophoblastic neoplasia. Green-top Guideline NO.38. RCOG;2004
27. Paradinas FJ et al. The diagnosis and prognosis of molar pregnancy. the experience of the National Referral Centre in London. Int J Gynoecol Obstet, 1998; 60(1):S57-S64.
28. Castrillon DH, Sun D, Weremowiezs, et al. Discrimination of Complete hydatidiform mole from its mimics by immune histochemistry of the paternally impainted gene product p57kip2. Am J Surg Pathol, 2001; 25:1225-30.
29. Bower M, Rustin GJ, Newlands ES, et al.chemotherapy for gestational trophoblastic tumours hastens menopause by 3 years. Eurj Cencer, 1998; 34:1204-7.
30. Rustin GJ, Newlands ES, et al. combination but not single –agent methotrexate chemotherapy for gestational trophoblastic tumors increases the incidence of second tumor. J Clin Oncol, 1996; 14: 2769-73.
31. Goldstein DP, Garner EI, et al. The role of repeat uterine evacuation in the management of persistent gestational trophoblastic disease. Gynecol Oncol. 2004; 95:421-2.
32. FIGO Oncology Committee. FIGO Staging for gestational trophoblastic neoplasia 2000 FIGO Oncology Committee. Int J Gynecol Obstet, 2002; 77:285-7.dio:10.1016/S0020- 7292(02)00063-2.
33. Aghajanian P, AH decherney et al. Gestational trophoblastic disease . Current Diagnosis and treatment Obstetrics and Gynecology. 10th ed., 2007; 885-895.
34. Li AJ. Gestational trophoblastic neoplasms.In RS Gibbs et al.eds. Danforth's Obstetrics and Gynaecology. Philadelphia: Lippincott Williams and Wilkins. 10th ed., 2008; 1073-1085.
35. Shigeru Sasaki. Clinical presentation and management of molar pregnancy. Best Practice and Research clinical Obstetrics and Gynecology. 2003; 17(6):885-892.
36. Batorfi J, Vegh G, et al. How long should patient be followed after molar pregnancy. Analysis of serum hcg follow-up data. Eur J Obstet Gynecol Reprod Biol., 2004; 112(1):95-7.
37. Benson C, et al. Sonographic appearance of first trimester complete hydatidiform moles. Ultrasound in Obstetrics and Gynecology.2000;16: 188-191.
38. Lazarus E, et al. Sonographic appearance of early complete molar pregnancy. Journal in the medicine, 1999; 18:589-593.
39. Sebire N, et al. The diagnostic implications of routine ultrasound examination in histologically confirmed early molar pregnancy. Ultrasound in Obestetrics and Gynecology, 2001; 18:662-665.
40. Wagner B, et al. Gestational trophoblastic disease: radiologic-Pathologic correlation. Radiographics., 1996;16(1).
41. Benson C, et al. Sonographic appearance of first trimester complete hydatidiform moles. Ultrasound in Obstetrics and Gynecology. 2000;16:188-191.
42. Kawano M, et al. Transvaginal color Doppler studies in gestational trophoblastic disease. Ultrasound Obstet Gynecol., 1996; 7(3):197-200.
43. Yalcin OT, Ozalp SS, Tanir HM et al. Assessment of gestational trophoblastic disease by Doppler ultrasonography. Eur J Obstet Gynecol Reprod Biol., 2002; 103(1):83-7.
44. Bidzinski M, et al. Clinical usefulness of color Doppler flow examination during treatment of gestational trophoblastic disease. Ginekol Pol., 1999; 70(2):88-92.
45. Soper JT, Clarke – Pearson DL, et al. 5- day methotrexate for women with metastatic gestational trophoblastic disease. Gynecol Oncol. 1994; 54:76-9.
46. Deng L, Zhang J, Wu T, Lawrie TA et al. Combination chemotherapy for primary treatment of high-risk gestational trophoblastic tumour. Cochrane Database of Systematic Reviews 2013, Issue 1.