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Molar pregnancy and maternal age

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بسم الله الرحمن الرحيم

(نَرْفَعُ دَرَجَاتٍ مَّن نَّشَاءُ وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ..)

صدق الله العظيم

سورة يوسف آية (٧٦)

الاهداء

من علَّمني كيف أقف بكل ثبات فوق الأرض إلى

أبي المحترم

إلى نبع المحبة والإيثار والكرم

أمي المو ّقرة

إلى أقرب الناس إلى نفسي

أخواني وأخواتي

إلى جميع الشهداء رحمهم الله

إلى جميع من تلقَّيتُ منهم النصح والدعم من الاقارب والأصدقاء

أهديكم خلاصة جهدي العملي

ألشكر والتقدير

الحمدلله ألذي هدانا وأعدنا وأمدنا والهمنا الصبر على المشاق

ووفقنا لما نحن عليه فله الحمد والشكر ابتداءاً وانتهاءاً

وارفع كلمة الشكر الى الأستاذة الدكتورة ايناس جليل وفقها

الله فقد كانت سندا لي على طول الطريق

والى كل من مد يد العون لي من قريب أو بعيد

وقبل أن أمضي اقدم اسمى ايات الشكر والامتنان والتقدير

والمحبة

الى الذين مهدوا لي طريق العلم والمعرفة

الى جميع اساتذتي الافاضل

Abstract

Molar pregnancy is composed of two separate entities, partial (PHM) and complete (CHM), which are distinct in terms of epidemiology, genetics, histopathology, clinical presentation and risk of persistent gestational trophoblastic tumor (GTT).**(1)**The most common presenting symptom in patients with CHM is vaginal bleeding. Approximately half the patients with CHM show signs of exuberant trophoblastic growth, with uterine enlargement and high levels of human chorionic gonadotropin (hCG). In contrast, patients with PHM usually present as though they have an incomplete or missed abortion, with bleeding, small uteri and low hCG levels. **(2)**Cytogenetically, all chromosomal material in CHM is derived from the male. Hence, no fetal parts are identified. In PHM, dispermy results in a triploid conceptus, in which an abnormal fetus is present and ultimately dies. The diagnosis of CHM is usually confirmed by sonography when a vesicular pattern is noted. The ultrasound pattern in PHM is less consistent and depends on careful measurement of the gestational sac. Patients with CHM with marked trophoblastic hyperplasia, elevated hCG levels and enlarged uteri can develop significant medical complications, which should be recognized early and treated aggressively.**(3)** These include acute respiratory distress syndrome, hyperthyroidism, preeclampsia and theca lutein cysts. All molar pregnancies should be evacuated promptly following a definitive diagnosis. If the patient no longer wishes to preserve her fertility, a hysterectomy will reduce the risk of developing nonmetastatic GTT. Following evacuation, careful hCG monitoring is mandatory since it is the most reliable and sensitive method for the early detection of GTT.**(2)(3)**

Introduction

- molar pregnancy is a gestational trophoblastic disease which grow into a mass in the uterus that have swollen chorionic villi (it is defined as a products of conception that does not contain an intact fetus and show gross cyst-like swelling of the chorionic villi due to the accumulation of fluid).**(3)**
- These result in the formation of clusters of small cysts of varying sizes. Because of its superficial resemblance to hydatid cyst, it is named as hydatidiform mole .The name Hydatidiform stems from the Greek word hydatis , meaning droplet of water is best regarded as a benign neoplasia of the chorion with malignant potential.**(3)(4)**
- Incidence :- There is a wide range of geographical and ethnic variation of the prevalence of the condition. The molar pregnancy is common in Oriental countries—Philippines, China, Indonesia, Japan, India, Central and Latin America and Africa. The highest incidence is in the Philippines being 1 in 80 pregnancies and lowest in European countries 1 in 752 and the USA being about 1 in 2000. The incidence, in India, is about 1 in 400. **(5)**

ETIOLOGY

The cause is not definitely known,but :-

1- Its prevalence is highest in teenage pregnancies and in those women over 35 years of age.**(5)(6)**

2- The prevalence appears to vary with race and ethnic origin.

3- Faulty nutrition caused by inadequate intake of protein, animal fat could partly explain itspreva-lence in the Oriental Countries. Low Dietary intake of carotene is associated with increased risk.

4- Increased association with AB blood group which possesses no ABO antibody.**(6)**

5- Cytogenetic abnormality In general,complete moles have a 46, XX karyotype (85%)the molar chromosomes are derived.**(6)(7)**

6- History of prior hydatidiform mole increases the chance of recurrence (1 to 4%).**(7)**

7- familial syndrome of recurrent complete hydatidiform mole (inherited in autosomal recessive pattern) but it is extremely rare .**(8)**

Age-related molar pregnancy risks:-

The overall risk for the whole population is 1:607 and throughout the usual reproductive age range, the risks are low with the lowest risk 1:792, occurring at the age of 24. Slightly higher risks are seen for younger women; at age 18, the risk is 1:597 and for teenagers aged 14–17 the risk is slighter higher at 1:378–563, and at the extreme of the reproductive range, girls who become pregnant at the age of 13 have a risk of 1:208. For older women, the overall risk of molar pregnancy rises significantly with age, reaching 1:423 at 40, 1:101 at 45 and 1:8 for women aged >50.

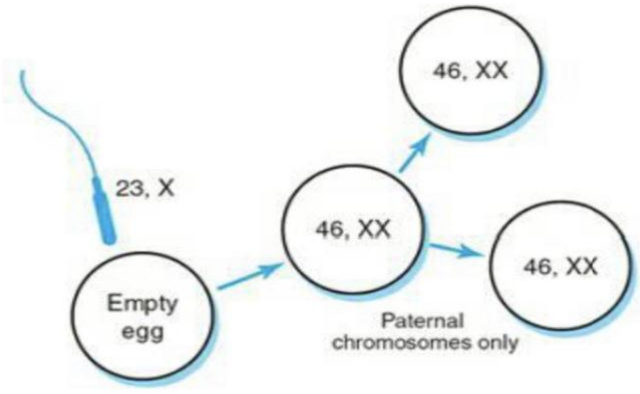
Types of molar pregnancy

The types are categorized on the basis of gross morphology, histopathology and karyotype that are:-**(9)**

1. Complete.
2. Incomplete (partial).

1-Complete mole

In 90% of cases, an empty ovum containing no genomic DNA is fertilized by one sperm, which duplicates its DNA, leading to an abnormal 46,XX karyotype, with all DNA paternal in origin. In the remaining 10% of cases, the empty ovum is fertilized by two sperm, resulting in an abnormal 46,XX or 46,XY karyotype ,again with all DNA of paternal origin. Thus, in a complete mole all the chromosomes are paternally derived**(9)**



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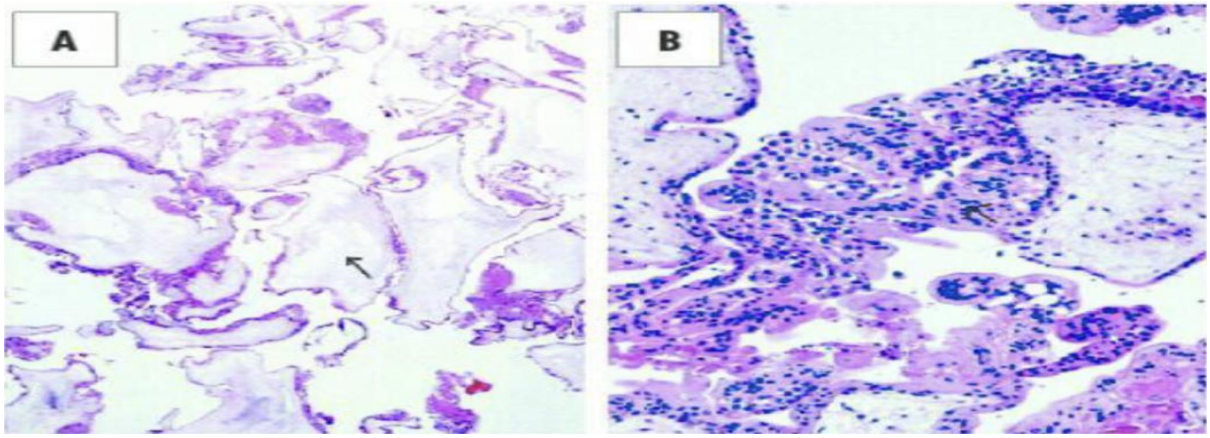
Chromosomal origin of a diploid complete hydatidiform Mole

Histologic features

- Marked edema and enlargement of the villi (hydropic villi)
- Disappearance of the villous blood vessels
- Diffuse proliferation of the trophoblastic lining
- Absence of fetal tissue.**(10)**



Complete hydatidiform mole. (A) Histological low power view showing numerous edematous villi with frequent cistern formation (arrow); (B) histological high power view showing hyperplastic trophoblast (arrow).**(10)**

Clinical features of complete moles :

1. History of amenorrhoea of 8-12 weeks.
2. Irregular Vaginal bleeding-is the commonest one and varies from spotting to profuse haemorrhage. **(11)**
3. Expulsion of grapes like vesicles from vagina (50%) -Lower abdominal pain may be caused by the following:-
    - overstretching of the uterus.
    - concealed(internal) haemorrhage.
    - uterine contraction to expel out the content.
    - infection.
    - perforation of the uterus by invasive mole**(12)**.

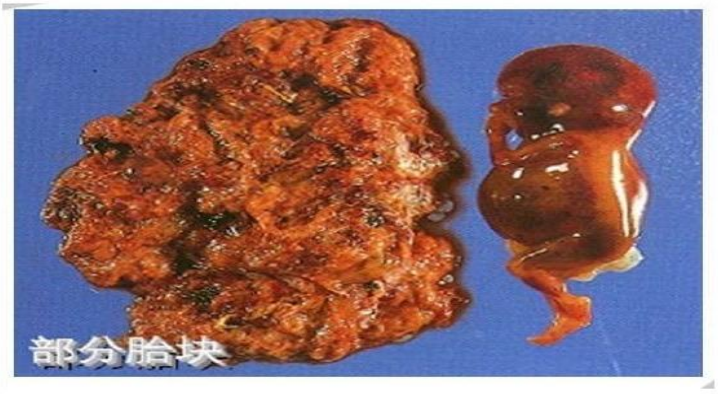
The risk of complete mole in relation to age

shown in Table I, teenagers have a moderately enhanced risk of a complete mole with a risk of 1:234 at the age of 13, 1:699 at the age of 16 and 1:1,012 at 18. From 19–40 the risk remains <1:1,000 with a lowest value of 1:1,741 at age 24. After the age of 40, the risks increase rapidly with values of 1:157 at 45, 1:30 at 48 and 1:8 for women aged >50.

Age-related risk for a complete molar pregnancy in England and Wales 2000–09

Age	Risk
13	1:234
14	1:515
15	1:463
16	1:699
17	1:914
18	1:1,012
19	1:1,165
20	1:1,423
21	1:1,419
22	1:1,509
23	1:1,643
24	1:1,741
25	1:1,592
26	1:1,469
27	1:1,649
28	1:1,727
29	1:1,681
30	1:1,852
31	1:1,812
32	1:1,931
33	1:1,647
34	1:1,923
35	1:2,151
36	1:2,244
37	1:1,740
38	1:1,446
39	1:1,454
40	1:1,248
41	1:993
42	1:589
43	1:350
44	1:320
45	1:157
46	1:80
47	1:56
48	1:30
49	1:19
≥ 50	1:8
Overall	1:1,423

2-Incomplete mole or partial mole (less common) results from fertilization of a normal egg with 2 sperm resulting in triploid 69,XXY karyotype. A fetus, umbilical cord, and amniotic fluid is seen, which ultimately cause fetal demise. Progression to malignancy is 10%.**(11)(12)**



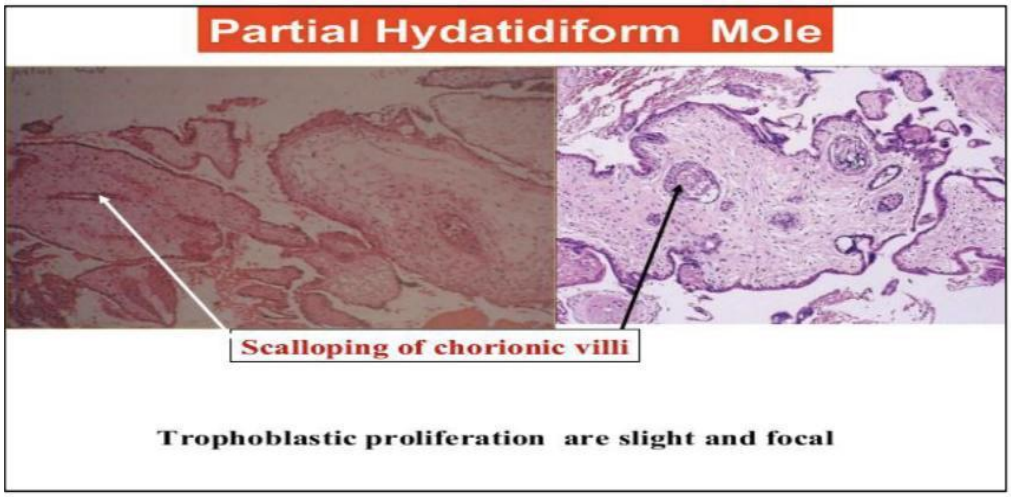
Partial hydatidiform mole with fetus

*Microscopically,enlarged and edematous villi with abnormal trophoblastic proliferation are slight and focal and don't involve the entire villi.**(12)(13)**

There is scalloping of chorionic villi with a wave-like border.

*Macroscopically, The molar pattern doesn't involve the entire placenta. Uterine enlargement above that expected for gestational age. Theca-lutein cysts are rare in comparison with complete mole.

Fetal and embryonic tissue or amnion are seen.**(13)**



Clinical features of partial moles :

- Vaginal bleeding
- Usually diagnosed as missed or incomplete abortion(91%).**(14)**

Physical :

1. A uterus is small for gestational age
2. Excessive uterine size noted in (4%)
3. Toxemia of pregnancy noted in (4%).**(15)**

The risks of partial mole according to age

In Table II the risks for a partial molar pregnancy compared with the number of viable conceptions are demonstrated. This shows that there is only a modest effect of maternal age on risk across the age range of 13–29, as the risk throughout this period is in the range 1:1,063–1,876, with no apparent increase risk for teenagers. From the age of 30 onwards, the risk increases relatively gently with age, with risks of 1:903 at age 35; 1:650 at 40; 1:286 at 45 and the highest value of 1:113 for women aged >50.

Table II. Age-related risk for a partial molar pregnancy in England and Wales 2000–09.

Age	Risk
13	1:1,876
14	1:1,417
15	1:1,424
16	1:1,266
17	1:1,466
18	1:1,455
19	1:1,566
20	1:1,638
21	1:1,488
22	1:1,342
23	1:1,317
24	1:1,453
25	1:1,113
26	1:1,217
27	1:1,152
28	1:1,064
29	1:1,063
30	1:959
31	1:991
32	1:980
33	1:924
34	1:992
35	1:903
36	1:778
37	1:880
38	1:770
39	1:794
40	1:639
41	1:650
42	1:496
43	1:459
44	1:491
45	1:286
46	1:281
47	1:307
48	1:472
49	1:192
≥ 50	1:113
Overall	1:1,058

Table 1. Genetic and Histopathologic Features of Molar Pregnancy

	Complete	Partial
Karyotype	Generally diploid or tetraploid; generally all chromosomes paternal	Generally triploid; extra set of chromosomes is paternal
Hydropic villi	Diffuse	Focal
Trophoblastic hyperplasia	Diffuse	Focal
Scalloping of villi	Absent	Present
Fetal or embryonic tissue	Absent	Present
p57 expression	Negative	Positive

Management

-History

- Vaginal bleeding.
- Abdominal pain & discomfort
- History of previous abortion
- History of previous moles
- Family history of any gestational trophoblastic diseases.**(16)**

-Examination

1-General examination

- Patient looks ill and Pallor is out of proportion of bleeding.
- Pulse rate-tachycardia, Respiratory rate- tachypnea /dyspnoea
- Features of pre eclampsia ,usually there is early onset of pre eclampsia.**(17)**

2-Abdominal examination

1. Uterine enlargement more than expected GA.
2. The uterus is soft and doughy due to the absence of the amniotic fluid sac.
3. Fetal parts are not felt
4. Fetal heart sound cannot be detected.
5. Cervical os may be open or close.
6. Vulval or vaginal metastasis may appear as purple nodule.
7. Unilateral or bilateral theca lutein cyst of ovary palpable in 25-35% of cases.**(16)(17)**

Investigations

- Ultrasound ،the diagnosis of complete mole is characteristically described as having a(snowstorm)appearance, although many will be diagnosed as an incomplete or an embryonic pregnancy.
- Partial mole may show a coexisting live fetus, with only scattered cystic spaces in the placenta.**(18)**

- Characteristically the diagnosis of partial mole is made after histological review of curettage specimens from presumed incomplete or missed abortions.**(19)**
- Quantitative serum β-HCG is elevated, usually >100 000 IU/L in the complete mole.
- Full blood count and liver and renal function tests & thyroxin level should be obtained.
- Chest radiography, CT scan, or an MRI may be required to exclude metastatic spread.
- ECG if tachycardia is present or the patient is older than 40 years of age.**(19)**

*What Is The Plan of Management ?

There are 2 important basic lines :-

1. Evacuation of the mole
2. Regular follow-up to detect persistent trophoblastic disease **(20)**
3. If these measures are done appropriately, mortality rates will reduce to zero.

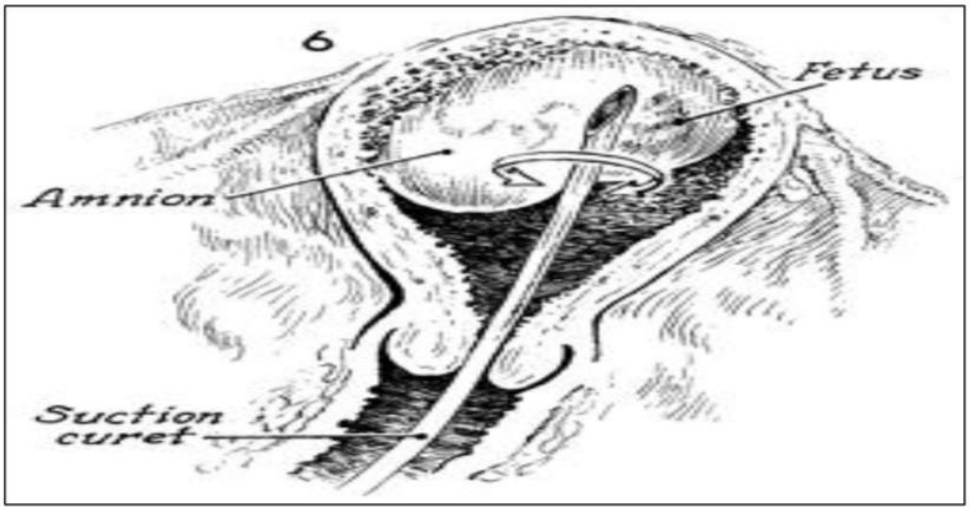
If these measures are done appropriately, mortality rates will reduce to zero.**(20)**

Prior to evacuation , correct :

- Any metabolic abnormality , stabilize the patient.
- Transfuse for anemia & correct coagulopathy.
- Treat medical diseases which include pre-eclampsia , thyrotoxicosis and dehydration.**(21)**

1-Suction evacuation : Is the method of choice even for large mole.Under general anesthesia dilate the cervix carefully to avoid damage to 12mm with oxytocin infusion and introduce suction curettage with negative pressure 60-70mmHg , then after evacuation gentle curation to avoid Asherman syndrome .Oxytocin continued postoperatively to reduce the likelihood of hemorrhage.

*If the uterus is less than 10 weeks dilatation and curettage is (un dx of Moler pregnancy – abortion)) primary treatment .**(21)**



(Suction evacuation)

2-Hysterectomy :-Suitable in older patients who completed their families because the risk of post molar trophoblastic disease increases with maternal age . care must be taken to do little manipulation to avoid embolization of trophoblastic tissue .**(22)**

****Follow up**

Following primary treatment, patients are followed
up with serial β-HCG assays every 2 weeks until beta HCG <5mlU/ml .
After normalization occur monthly beta HCG surveillance is recommended for 3-6 months in partial moles & 12 months in complete moles to exclude residual disease.
* Where suction curettage is performed for a suspected molar pregnancy, it is advised to avoid prostaglandin cervical preparation, oxytocic drugs, sharp curettage, or medical evacuation due to concerns that this may lead to dissemination of disease.**(23)**

****Post molar pregnancy surveillance patients**

(Indications for chemotherapy)
1- Raised HCG level 6 months after evacuation (even if falling)
2- HCG plateau in three consecutive serum samples
3- HCG >20,000 IU/l > 4 weeks following evacuation.
4-Increased HCG in two consecutive serum samples
5- Pulmonary, vulval or vaginal metastases unless the HCG level is
falling
6- Heavy PV bleeding or GI or intraperitoneal bleeding
7- Histological evidence of choriocarcinoma
8- Brain, liver, GI metastases or lung metastases >2 cm on CXR **(24)**

****What Is Safe Contraception Following ,GTD?**

1-Barrier methods — most preferred method.
2-Oral contraceptive method-Once ß-HCG level have normalized: COC pill may be used.(as it may acts as growth factor for trophoblastic tissue)
Low dose OCP is preferred.

If oral COC was started before the diagnosis of GTD ,COC can be continue as its potential to increase risk of GTN is very low **(25)**

3-IUCD should not be used until HCG levels are normal to reduce uterine perforation.**(26)**

4-Permanent sterilization- preferred in those couples whose family has been completed.

When Anti-D Is Required ?

•It is required in Partial due to the presence of fetal RBCs

• In Complete mole because of poor vascularization of the chorionic villi and absence of the anti-D antigen, anti-D prophylaxis is not required.

• Although ACOG recommends giving Anti-D in all cases.**(27)**

Complication

1. Perforation of uterus during suction curettage due to increase size of uterus . If perforation is present , do the procedure under laparoscopic guidance.
2. Hemorrhage during evacuation .
3. Molar metastasis : Respiratory distress during surgery because of trophoblastic embolization to the lung leads to respiratory compromise and hypoxemia with pulmonary edema , the high risk factor is a uterus large than expected gestational age.
4. heart failure caused by anemia or iatrogenic fluid overload
5. Choriocarcinoma : Malignant trophoblastic disease develops in 10-20% of molar pregnancy, quantitative HCG should be monitored carefully for 1 year , after complete mole the risk 1:10 ,partial mole 1:200 , therefore careful follow up of HCG is essential.**(26)(27)**

Prognosis

Due to early diagnosis and appropriate treatment , mortality rate from hydatidiform mole is essentially zero. Approximately 20% of women with a complete mole develop a trophoblastic neoplasm. Gestational trophoblastic malignancies (ie, gestational trophoblastic neoplasia) are almost 100% curable.**(28)**

Discussion

Accurate data on the population incidence of molar pregnancies is relatively limited, however most modern series in Europe, Asia and North America report overall incidences in the range of 2–3 cases per 1,000 live births, the study done in England and wales during (2000-2009)based on registfor molar pregnancies,this study show that the overall risk for a molar pregnancy is shown to be slightly increased, above average for young teenagers with a risk of 1:450 aged 16; relatively unchanged at <1:500 for women of the majority of the reproductive age group and then increases significantly for those aged >40, with a risk of 1:101 at age 45 and 1:8 for women aged >50. **(29)**

The differing patterns of contributions of partial and complete molar pregnancies to these statistics are shown in Tables I And II for partial moles, there is no excess risk at the younger age and the increasing risk that starts at age 25 years does so at a slow rate reaching only 1:630 at 40, 1:286 at 45 and 1:113 at 50. In contrast, in complete moles there is a slightly increased risk for the young with a values of 1:699 at age 16, while at older ages, the increased risk rises much more rapidly from 1:1,248 at 40, to 1:157 at 45 and 1:8 for >50.

As a result of these differing changes with age, the ratio of complete mole to partial mole changes significantly with age, while the overall figure is 42% for those aged 13–18 years, 63% are complete mole; aged 18–40 years 39%; aged 41–49 54% and aged >50, 93%.

(30) Another study was done by Hourieh Shamshiri Milani In Asia show no significant association was found between molar pregnancy and mothers' age and parity. In other studies there were found relations between mole with mother's age especially age-groups of less than 15and more than 35, like study was done at Trophoblastic Disease Registration Centre that show a positive relationship was found between the risk of molar pregnancy and both upper and lower extremes of maternal age (≥35years and ≤15 years, respectively). This association, although present for both complete and partial moles, is much greater for complete moles at all maternal ages, and the degree of risk is much greater with older (≥35 years) rather than younger (≤15 years) maternal age. This study provides, for the first time, data regarding specific risk of partial versus complete hydatidiform mole with maternal age.**(31)**

The result however, showed that there's significant relationships between molar pregnancy and maternal age so maternal age is considered one of the risk factors for molar pregnancy **(32)**.

Conclusion

In the light of the present studies,aged older than 35 and below than 15 years seems a risk factor and vaginal bleeding is the commonest presenting symptom. Early booking of pregnant women to antenatal care clinics and routine first trimester ultrasound made diagnosis easier and earlier before complications appear.**(33)**

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