Recurrent Molar Pregnancy

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Molar pregnancy is a gestational trophoblastic disorder as a result of abnormal fertilisation and gametogenesis, characterised by hydropic swelling of the placental villi, hyperplasia of villous trophoblast and absent, or abnormal, faetal development. It is potentially a malignant pregnancy condition, broadly grouped under gestational trophoblastic disease (GTD). The commonest molar pregnancy is complete hydatidiform mole (CHM) and the next common is partial hydatidiform mole (PHM). The malignant form of GTD is otherwise called gestational trophoblastic neoplasia (GTN) which encompasses: Invasive mole (IM), Choriocarcinoma (CCA), Placental site trophoblastic tumour (PSTT) and Epitheloid trophoblastic tumour (ETT). More than 80% of molar pregnancies are cured with usual suction and evacuation with regular follow-up with clinical and β-hCG estimation. About 15–20% of CHM and 3–5% of PHM will require chemotherapy depending upon the WHO score for GTN with normal pregnancy outcome thereafter. However, it is typical that once molar pregnancy, there is a high risk of molar events in subsequent pregnancy. By definition, recurrent hydatidiform mole is characterised by the occurrences of at least two abnormal pregnancies that have resulted in hydatidiform mole.

15.1 Recurrence Rate in Complete and Partial Molar Pregnancy

The incidence of molar pregnancy varies widely from country to country, even from one part of the same country to other parts. It is estimated that 1 in 1000 pregnancies in most parts of the world [1] and 2 in 1000 pregnancies in the Asian population do have molar pregnancy events [2]. Savage et al. observed recurrent HM in 1 in 68 in a 10 years survey of over 5000 post-molar pregnancies and concluded that there is

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almost tenfold (incidence of molar pregnancy in the UK is 1 in 600 pregnancies) increased chance of repeat mole in subsequent pregnancies following a molar event [3]. Sebire et al. in 2003 also had a similar opinion. They observed an increase of about 1–2% incidence of repeat mole and an increase up to 23% after two consecutive molar pregnancies [4].

Retrospective observation of 16,523 women with first molar pregnancy at Charing Cross Hospital, UK, revealed incidence of second molar pregnancy to be 1% and more common with CHM than PHM (0.91% vs. 0.28%, respectively). The risk of further molar event after one or more non-molar intervening pregnancy was also more in CHM than in PHM (0.65% vs. 0.37%). More than 80% of recurrent moles were of the same histological type as of previous pregnancy. In a study, of 8553 women with histological PHM, only 11 (0.13%) had CHM while of the 7037 with CHM, 21 (0.3%) experienced a subsequent PHM in the same patients in their reproductive life [5]. Vegas et al. observed that 50% of complete and 30% of partial moles are at an increased risk of second HM [6]. Amongst the women having second molar pregnancy, 13% were found to have subsequent third molar pregnancy and most of them had previous two pregnancies with CHM and this rarely did happen with PHM. It was also observed that recurrence of third molar does occur within the first 1–2 years of second molar event, regardless of whether a CHM or PHM [5].

15.2 Familial Recurrent Hydatidiform Mole

It is now recognised that women with recurrent molar pregnancies do have a number of patients included under "the familial recurrent hydatidiform mole (FRHM)". This is a rare autosomal recessive condition, where the woman has an inherited predisposition to have recurrent molar pregnancy, most of which are CHM [7]. Two mutant genes, NLRP7 and KHDC 3 L have been recognised to be responsible for 75 and 5% of cases of FRHM, respectively. Genotyping of the complete mole (CM) can be of value for the identification of the women affected by familial recurrent hydatidiform mole. It is well known that CHM is androgenic (AnCHM), while those affected with FRHM are diploid but biparental in origin (BiCHM) [7].

15.2.1 Incidence

Familial recurrent HM is considered an exceedingly rare condition. In medical literature, only 21 families have been reported to date. According to the report of Charing Cross Hospital, UK, the risk of a third HM is mostly associated with CHM, while 1 in 640 women with third recurrence had FRHM. This condition accounted for most, though not all cases of three or more CHM. It is usually recommended to have a genetic evaluation of molar tissue in women with three or more recurrent molar events, to diagnose FRHM, and fertility counselling can be offered [5].

15.2.2 Diagnosis

Recurrent molar pregnancy can be diagnosed by a thorough evaluation of previous pregnancy losses. Among previous pregnancy losses, molar pregnancy is most important as the outcome of this may be life-threatening and it may be recurrent and may recur in families. In this regard, evaluation of confirmatory evidence of previous molar pregnancies like ultrasonography report, serum β-hCG report, surgical note of molar pregnancy, histopathological report, immune-histochemistry report and finally genotyping report if available are very informative. Every gynaecologist or gynaecological oncologist should be careful about keeping all the records and should counsel the patients and her attendants about the importance of keeping all these records. Recurrent second HM can easily be diagnosed by evaluation of the above records.

15.3 Development of Gestational Trophoblastic Neoplasia (GTN)

After the second mole, the incidence of recurrent molar pregnancy increases to between 10 and 23% [4]. It is associated with an increasing risk of development of GTN. The risk of development to GTN is similar both in AnCHM and BiCHM and is 22% after first molar pregnancy, increases to 50% after the second molar event [8]. Management of such a situation does not differ from GTN developing from molar pregnancy.

15.4 Fertility Issue

Though there is a moderate increased risk of second and third molar event after HM, the pregnancy outcome after one or two molar event does not differ, and so also after chemotherapy when given for GTN. It is observed that most patients with two repeat CHM do have Aan CHM and can have normal pregnancy outcome. Women with FRHM usually do have BiCHM and do have little chance of successful pregnancy [4]. However, as suggested earlier, genetic typing of molar tissue should be advised in cases of three or more repeat molar events to differentiate between CHM and FRHM. If detected to have AnCHM, IVF (ICSI) and preimplantation genetic diagnosis (PGD) can reduce recurrence of CHM and successful pregnancy outcome [9, 10]. Women with FRHM need to be treated by IVF with ovum donation to achieve normal pregnancy [10, 11].

15.4.1 A Case Report

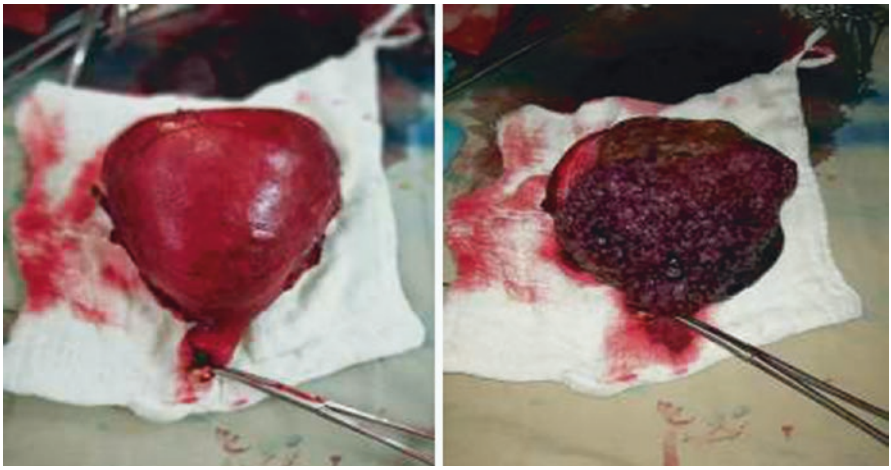
A 40-year-old woman reported to me on 29.9.2018 with the complain of amenorrhea for 2 months. She came from a district town of Dhaka division with a report of

transabdominal ultrasonography done on 23.9.18, repeated on 26.9.18. Both reports showed molar pregnancies. Her β-hCG done on 23.9.18 was 225,000 mIU/ml. She had a X-ray Chest report which was normal. Her X-ray Chest, CBC, fasting and 2 h after breakfast blood sugar level, serum electrolytes, SGPT, creatinine level, albumin, all were within normal limit. Her cardiac status was normal.

As a mandatory test for evaluation of thyroid status, she had serum TSH and FT4 level measurement on 3.10.18. Her TSH level was 0.02 nmol/L (N-0.55–4.78 nmol/L) and FT4 level was 359.1 pmol/L (N-58.1–140.6 nmol/L).

Regarding her obstetric history, she is married for 20 years but no normal pregnancy. Unfortunately, she became pregnant four times. Each time it was a molar pregnancy and each time she had suction evacuation for molar pregnancy. This was her fifth pregnancy and it was also molar pregnancy. Her first molar pregnancy was in 2005, second in 2006, third in 2007, fourth in 2014 and this was her fifth pregnancy in 2018.

She consulted with me after her fourth pregnancy to know whether she should be pregnant or not and whether her fifth pregnancy will be molar or not. There was no scope for genotyping, as molar tissue was not available at that time. So, she was advised to take a chance. Now, she came with her fifth molar pregnancy and she does not intend to preserve her uterus. So, the decision was taken to do a total abdominal hysterectomy for her. Her hyperthyroidism was managed conservatively by β blocker agent. She underwent TAH with left-sided salpingo-ophorectomy with right salpingectomy with preservation of right ovary on 11.10.18. On the cut section, the endometrial cavity was found distorted by vesicular grape-like structures. The total volume of the vesicular structure was 100 cc. The size of the biggest vesicle was 0.5 cm.



Histopathological report showed complete hydatidiform mole. Serum β-hCG 13.10.18, 48 hours after hysterectomy sharply fell down to 163,541.70 mIU/ml. She was advised to do weekly β-hCG but was reluctant to do so; ultimately she had serum β-hCG on 31.10.18 and it was 267.90 mIU/ml. Her thyroid status

become normal and on 16.10.18 serum FT4, FT3 and TSH levels were 27.93 pmol/L, 8.10 p.mol/l and 0.01 mIU/L, respectively. On 7.10.18 it was 19.86, 2.14 and 0.01.

She needs β-hCG done weekly up to three normal levels, then monthly β-hCG done up to 6 months.

15.5 Conclusion

Recurrence of molar pregnancy is a major concern. The recurrence chance of a molar pregnancy to subsequent molar pregnancy is about 1.5–2%, increased to 23% after two or more molar events. Though repeat molar pregnancy does have more chance of development to GTN, treatment and result of treatment do not differ. For better pregnancy outcome, genotyping is recommended in cases of three or more repeat molar events, and ICSI and PGD are employed in androgenic CHM and IVF with ovum donation in biparental CHM may prevent further recurrence and a desirable pregnancy outcome.

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