Recurrent GTD and GTD co-existing with normal twin pregnancy

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Abstract

Hydatidiform mole (HM) affects around 1/1000 pregnancies, and in such cases the recurrence risk is around 1%, being greater for those with complete hydatidiform mole (CHM). Whilst most cases appear sporadic with unknown mechanisms, there is a distinct subgroup of patients who suffer recurrent pregnancy loss including multiple recurrent CHM (familial recurrent biparental hydatidiform mole syndrome). The majority of these cases are related to maternal genetic mutations in genes related to control of imprinting, specifically NALP7 and KHDC3L. Oocyte donation is an effective treatment allowing these patients to have successful pregnancies.

Approximately 1 in 50,000 pregnancies are complicated by twin pregnancy comprising normal fetus and HM, the majority of reported cases being CHM. Such pregnancies are at significantly increased risk of complications including pregnancy loss, early-onset preeclampsia and severe preterm delivery, but when managed conservatively delivery of liveborn healthy infant occurs in around one third of cases. Regardless of management, the risk of persistent GTD in such cases appears similar to that following singleton CHM. Rarely, other conditions mimic prenatal ultrasound appearances of twin pregnancy with HM, CHM mosaicism and placental mesenchymal dysplasia, both of which have distinctive histological and genetic features.

191 words

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Introduction

Hydatidiform moles (HM) represent a spectrum of genetically abnormal conceptions, which usually result in pregnancy loss and have potential to be associated with subsequent persistent gestational trophoblastic disease (pGTD) requiring chemotherapy. Two distinct major subtypes of HM are described, based on genetic and characteristic histological findings, with all HM demonstrating abnormal trophoblast proliferation and villous dysmorphism as their hallmarks. HM represent abnormalities of imprinting with relative overexpression of paternal genes in the placenta; complete hydatidiform mole (CHM) being diploid conceptions in which all genetic material is paternally derived whereas partial hydatidiform mole (PHM) are triploid with two sets of paternal chromosomes.

The histological features of CHM and PHM are now well described including those cases evacuated in early pregnancy and in most cases the diagnosis can be made reliably on histopathological evaluation. In some cases however, distinguishing PHM in particular from other chromosomal abnormalities can be difficult on morphological features alone and ancillary diagnostic tests may be required for definitive diagnosis, including molecular genetic testing. Whilst this is not carried out in most straightforward cases in many centres, for the reliable and specific diagnosis of some of the conditions discussed in this chapter, ancillary investigations including immunohistochemical staining and genetic testing are often required for definitive diagnosis.

Recurrent Hydatidiform Mole

HM affect around 1/1000-1/2000 pregnancies, with rates varying geographically and with ethnic background,[1–3] although some regions have reported increased rates, such as Japan[4,5] with most European countries consistently reporting around 1/1000 pregnancies).[6,7]

Data from large registries have demonstrated that within a population, patients with a history of a previous HM have increased risk of another HM in a subsequent pregnancy, this rate generally being about 10x greater than the background risk, or

around 1/100.[8,9] However, other than the increased HM recurrence risk any future pregnancy outcome appears otherwise unaffected by the history of previous HM.[10] Interestingly, patients who have had multiple HM demonstrate greater risk of subsequent HM, likely since any predisposing factors will remain, suggesting that the overall described 1% recurrence risk probably in reality represents a bimodal distribution, with most patients having sporadic HM with very low recurrence risk but including a small number with underlying predisposing conditions with significantly increased risk of multiple HM.

In order to understand recurrent risk in more detail it is necessary to have data from a relatively representative geographic population with high levels of ascertainment, hence the largest and most detailed information in this regard is derived from the national trophoblastic disease service in England and Wales. The most recent data using patients following centralised national/regional recruitment to a specialist trophoblastic disease service with high ascertainment of cases, provided information on 5,793 CHM and 7,790 PHM from a total population of 8,242,511 pregnancies. The overall frequency was therefore around 1/600 pregnancies for all HM (1/1,400 for CHM and 1/1,000 for PHM, with a slight excess of PHM). In this population, the rates of pGTD development requiring chemotherapy were around 15% and 1% respectively for CHM and PHM.[11] Importantly in the present context, the risk of subsequent HM was 1/70 overall (1.4%). Most cases of recuurence were CHM, with CHM recurrence risk being 1/100 (1%) after one CHM and 1/4 (25%) after two CHM, whereas PHM cases were associated with minimal increased HM rates.[9]

Familial Recurrent Biparental Hydatidiform Moles

As noted above, within the group of women with recurrent HM there are some with especially increased risk, typically having multiple pregnancies affected by CHM and few or no livebirths.[10,12–15] Largely based on genetic investigation, it is now understood that these patients represent a group of familial recurrent biparental HM (FRBHM) in which the molar conceptus is diploid, (as with typical sporadic CHM), but in contrast to sporadic CHM, is biparental, therefore superficially appearing to have an apparently normal genotype. [12,16,17][18,19]

CHM in patients with FRBHM are histopathologically indistinguishable from sporadic androgenetic CHM, both in terms of morphological features and the abnormal $p57^{KIP2}$ expression pattern seen as a marker of loss of maternal allele expression.[20] These features suggest that the CHM phenotype is therefore a consequence of abnormal imprinting control resulting in only paternal allele expression, and can be manifest either secondary to complete absence of maternal genetic material, as with androgenetic sporadic CHM, or with non-expression of the maternal genetic material present present, as with impaired imprinting in FRBHM syndrome.

Initial studies examined inheritance patterns and clearly reported a likely maternal autosomal recessive condition, with early studies suggesting a defect at 19q13.3-13.4[18] in a gene subsequently identified as *NLRP7 (NALP7).* This was rapidly confirmed as the likely responsible gene, with many different mutations being reported. Initial studies suggested that around 80% of women with FRBHM may have *NLRP7* mutations of some kind.[21–25] *NLRP7* is involved in immunological and inflammatory pathways but the precise mechanisms by which mutations cause the disruption of imprinting and hence CHM remained uncertain.

Further studies reported mutations in other genes in women with FRBHM including the C6orf221/KHDC3L gene in around 5%, with the remaining 15% having no detectable mutations.[26] Interestingly, these initially described mutations are not reported in association with other pregnancy complications either in HM or recurrent miscarriages.[27],[28]

A large review of published data which included >150 pregnancies from around 40 women with FRBHM, 113 conceptions (74%) were CHM, 26 (17%) were non-molar miscarriages, six (4%) were apparent PHM and seven (5%) were phenotypically normal pregnancies.[10] Whilst a range of pregnancy outcomes are possible, the vast majority, around 70% of pregnancies in such cases represent CHM and without treatment there is a low chance (<5%) off having a pregnancy resulting in a healthy livebirth. Despite the difference in underlying genetic constitution, the risk of subsequent pGTD development appears similar to that of sporadic androgenetic CHM,

being around 10% in this series. [10] Further recent data supports that there is no significant difference in the risk of developing pGTN in sporadic compared to FRBHM, suggesting that it is the CHM phenotype rather than the underlying genetic constitution that is the main risk for pGTD development.[9]

With increasing recognition of this condition and further data and investigations it appears that there are three main maternal genes associated with FRBHM, including NLRP7, KHDC3L, and PADI6.[29] Furthermore, the precise mechanism is beginning to be understood. Using single-cell bisulphite sequencing and methylation analysis, oocytes from mothers with KHDC3Lc mutation demonstrate genome-wide abnormalities in DNA methylation compared to normal oocytes with methylation defects of imprinted genes persisting post fertilisation, although most non-imprinted regions recovered normal methylation status.[30] In molar tissue, sporadic androgenetic CHM show methylation at paternally methylated loci but lack of methylation at maternally methylated regions, whereas in FRBHM there is only lack of methylation in maternal regions, but with variation between HM, confirming defective placenta-specific imprinting and over-expression of paternally expressed gene transcripts in CHM.[31]

In a series of >100 patients, 50-80% of those with recurrent HM showed biallelic pathogenic variants in *NLRP7* or *KHDC3L* genes, all of these HM being diploid biparental.[32] However, the HM from those patients without identifiable mutations are more heterogeneous, with <10% being diploid biparental (8%). Other mechanisms reported in these patients without mutations included diploid androgenetic monospermic (24%) and triploid dispermic (32%) HM; these patients are generally non-familial, with fewer reproductive losses, and more live births. These results suggest that patients with recurrent HM are divided into those with mutations in known FRBHM genes, and those without, representing different clinical and genetic mechanisms. In those with known gene mutations, there are an increasing number of novel mutations continuing to be reported, including some specific to particular cases or families.[33][34][35][36] In patients with FRBHM and mutations in genes involved

in control of imprinting, the only described successful therapy includes use of oocyte donation.[37]

Pregnancy with combination of apparent hydatidiform mole and normal fetus

The clinical setting of antenatal ultrasound examinations demonstrating the coexistence of an apparently structurally normal fetus in a uterus in combination with placental sonographic changes suggestive of hydatidiform mole represents a particular management challenge. There are several pathologic processes which may result in similar antenatal imaging features, which are usually easily resolved following histological examination after delivery.

Hydatidiform mole with normal cotwin

HM represents a genetically abnormal conception and therefore, based on probability alone, may of course comprise part of a polyzygotic multiple pregnancy, most usually a dizygotic, dichorionic twin pregnancy consisting of HM and non-molar cotwin. This occurrence is now well-reported, but rare, affecting around 1 in 200 pregnancies with histologically confirmed CHM.[38] For reasons that are unclear, the combination of a PHM and normal gestation appears to be much less commonly described, but this may simply be because distinction of twin/PHM from PHM alone may be difficult/impossible morphologicaly, particularly in early miscarriages.

Theoretically, the coexistence of a CHM and a non-molar gestation may cause diagnostic confusion with PHM both on antenatal ultrasonographic examination and histological evaluation of the products of conception, but in practice this is rarely the case since in PHM, the fetus is almost never morphologically normal, usually resulting in pregnancy failure or with multiple structural abnormalities, and in cases that fail early, histological findings of CHM are distinctive.

On imaging examination, cases with CHM and normal cotwin usually demonstrate clearly demarcated, but adjacent, areas of cystic abnormal HM, and normal placental parenchyma, with clear visualisation of the umbilical cord insertion into the

apparently normal placental tissue. Following delivery, similar features are observed with areas of macroscopically normal placenta adjacent to an area of apparently molar placenta. On histological examination these geographically distinct areas of chorionic villi with normal histologic features and villi with typical diagnostic features of CHM are observed. Even in cases evacuated in early pregnancy, in which there may be more mixing of the normal and molar tissue due to the evacuation process, distinct populations of normal and CHM villi are usually easily identified. $P57^{KIP2}$ immunostaining may also be used for further confirmation to highlight the distinctive geographical populations of villi if required.

The outcome of pregnancies with histologically confirmed CHM and co-twin was initially regarded as poor, since this was based on anecdotal reports of cases with complications.[39] However, with increasing recognition of this condition, more recent data, which includes complete ascertainment of unselected cases diagnosis in early pregnancy, has demonstrated that risk of pGTD is similar to that following singleton CHM. Furthermore, risk of pGTD development is not significantly different for patients managed by early elective termination of pregnancy versus those that continue pregnancy, consistent with data in singletons suggesting that pGTD risk is likely to be related to an intrinsic characteristic of the HM rather than the duration of the pregnancy.

However, whilst risk of pGTD development may not be significantly increased with continuation of pregnancy, there is clearly increased risk of several pregnancy complications in these patients, including fetal loss before 24 weeks' gestation in around 50%, later intrauterine death in around 25% and early preterm delivery in 40%. Other complications of pregnancy continuation include vaginal bleeding / antepartum haemorrhage and severe pre-eclampsia, with around one third of the total cases choosing to continue the pregnancy resulting in a healthy live birth.[38] Similarly, a recent review identified 14 studies including series with CHM and cotwin outcomes and reported that 80% of ongoing pregnancies encountered complications included vaginal bleeding, hyperthyroidism and pre-eclampsia, with an overall 50% livebirth rate. In this review around 30% of total cases subsequently developed pGTN, which is

greater than singleton CHM, although this may be a consequence of inclusion bias.[40] Triplets with coexistent HM are also reported with anecdotal good outcome [41]

MOSAIC HYDATIDIFORM MOLE

Rarely, the placental tissue, both sonographically and on histological examination after delivery, demonstrates an admixture of normal and molar chorionic villi, without clear geographic distinction, which represents genetically mosaic CHM. These cases are very rare but have now been well-reported and confirmed since the introduction of more widespread genetic testing (it is estimated that mosaic moles may represent around 1% of CHM). On placental histological examination, there are abnormal molar villi scattered throughout the placental parenchyma, with the abnormal villi having the typical morphological features of CHM, but surrounded by a dominant population of completely normal, non-molar villi.

Mosaic HM have been described in both second and third trimesters, based on initially abnormal antenatal sonographic features. Importantly, and typically, these patchy molar changes in the placenta are associated with an apparently structurally normal fetus. Confirmation of definitive diagnosis requires ancillary testing including immunostaining with p57KIP2 to highlight the distribution of affected and normal villi, and molecular genetic studies to confirm the diagnosis with molar tissue showing typical monospermic androgenetic diploidy and the normal villi showing biparental diploidy, with the same androgenetic markers present throughout. These changes represent a form of confined placental mosaicism. [42] There are now also case reports of mosaic PHM.[43][44]

PLACENTAL MESENCHYMAL DYSPLASIA

Placental mesenchymal dysplasia (PMD) was initially described as a sonographic ‘mimic’ of PHM, but without the typical genetic changes of HM, associated with an apparently normal fetus and with characteristic histopathological placental features post delivery of dilated chorionic plate vessels and marked stem villous hydrops in te absence of abnormal trophoblast hyperplasia. Such cases almost always clinically present as apparent diffuse ‘molar’ hydropic change of the placenta detected on

routine antenatal sonographic examination in the mid and late trimester. Initially, cases of PMD were reported in association with Beckwith-Wiedemann syndrome but it is now apparent that the majority of cases are unrelated.

In reality, PMD is not a subtype of GTD, but rather represents a form of abnormal imprinting associated with biparental/androgenetic placental mosaicism. Whilst HM are characterised by overexpression of paternal genes in both mesenchymal elements and trophoblast, PMD is characterised by normal biparental trophoblast but abnormal placental stroma/mesenchyme due to localised overexpression of paternal genes within the stromal component.[45–48] This understanding of the condition as an imprinting disorder also explains the reported association with Beckwith-Wiedemann syndrome.[46,49]

On histological examination, there is no trophoblast hyperplasia with PMD but instead the abnormal stromal tissue is associated with hydrops of stem villi, often with chorionic vascular abnormalities and/or angiomatoid villous stromal changes.[50][46] It is important to distinguish PMD from HM, since PMD is not associated with increased risk of pGTD and hence maternal hCG surveillance is not required.

The potential infant associations remain to be fully determined but cases of PMD may be associated with pregnancy complications such as pre-eclampsia, which may be early onset.[51] In a review of >20 cases, preterm delivery was common, half of cases were growth restricted and fetal death occurred ion 20%; antenatal maternal biochemical screening was abnormal in around 40%. In addition, an increasing number of conditions are reported affecting the infants, including developmental syndromes and infantile/paediatric tumours.[52][53][54] Similarly a literature review of >100 published PMD cases reported a 30% rate of stillbirth and 70% preterm birth rate of liveborns, although optimal approaches to improve these outcomes have not been established.[55] Discordance for PMD in twin pregnancies, both monochorionic and dichorionic has been reported.[56][57]

SUMMARY

The majority of cases of HM are sporadic with minimal recurrence risk. Overall recurrence risk is around 1% following an HM, with most of the risk associated with patients having a previous CHM. In patients who have had two consecutive CHM, the recurrence risk in future pregnancies increases to around 25% since this group contains those with familial recurrent biparental hydatidiform mole, who are at significantly increased risk of multiple HM. In the clinical setting of antenatal detection of an apparently normal fetus with the placenta showing patchy hydropic change suggestive of HM, there are several possibilities including twin pregnancy with CHM and cotwin, mosaic CHM and placental mesenchymal dysplasia, all of which can be readily distinguished on histological examination and have different implications for future management.

PRACTICE POINTS

- Patients with more than one CHM should be considered for further investigation regarding familial recurrent biparental hydatidiform mole, since these patients may have multiple molar pregnancies and require specific management
- Overall recurrence risk for any patient having HM is around 1%, with very low risk for those having PHM
- Pregnancies antenatally suspected of having molar change in the placenta in association with an apparently normal fetus, should be investigated after delivery since this may represent twin pregnancy with CHM, mosaic CHM or placental mesenchymal dysplasia

RESEARCH AGENDA

- At present patients with familial recurrent biparental hydatidiform mole are often only diagnosed following multiple molar pregnancies. No distinctive histopathological features allow a reliable differentiation of biparental from androgenetic CHM, but detection at the time of the initial mole would allow improved management of such cases and further research is required to identify characteristic features.
- Patients with twin pregnancies containing CHM are at risk of persistent GTD following delivery, although even in this group the majority of cases will require no subsequent intervention; at present there is no reliable mechanism to identify cases of CHM at particular risk of persistent GTD development. Further research is required to better risk stratify such patients to allow earlier intervention for those that require it and reduced surveillance for those that do not.
- Placental mesenchymal dysplasia (PMD) is being increasingly recognised and reported and whilst the association with pregnancy complications is now established it remains uncertain as to whether children of such pregnancies are increased risk of longer term complications, hence further follow-up

studies are required to understand the risk and spectrum of potential associations affecting the infant and child

Conflicts of interest

The author has no conflicts of interest.

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MCQs

1. A patient presents in her first pregnancy with late 1st trimester miscarriage and histological examination reveals atypical complete hydatidiform mole. Which of the following statements are correct:
    a. She is not at increased risk of subsequent molar pregnancies (F)
    b. There is around a 1 in 100 chance that her next pregnancy will also be a complete hydatidiform mole (T)
    c. She could be affected by familial recurrent biparental hydatidiform mole syndrome due to maternal genetic mutations (T)
    d. She is at much great increased risk of further recurrence if the next pregnancy is also a complete hydatidiform mole (T)

2. A patient presents at 26 weeks of gestation with a fetus which appears small for gestational age but otherwise normal and a placenta showing some normal areas and some areas suggestive of hydropic change indicating hydatidiform mole. Which of the following are true:
    a. This pregnancy is at increased risk of pregnancy complications including preeclampsia and stillbirth (T)
    b. There is no need to exam and the placenta histologically following delivery if the baby appears normal (F)
    c. These features indicate hydatidiform mole and the patient must undergo hCG follow-up after delivery in any indication (F)
    d. These features may be due to several different underlying pathologies relating to imprinting disorders (T)