Gestational trophoblastic disease

Michael J Seckl, Neil J Sebire, Ross S Berkowitz

Gestational trophoblastic disease encompasses a range of pregnancy-related disorders, consisting of the premalignant disorders of complete and partial hydatidiform mole, and the malignant disorders of invasive mole, choriocarcinoma, and the rare placental-site trophoblastic tumour. These malignant forms are termed gestational trophoblastic tumours or neoplasia. Improvements in management and follow-up protocols mean that overall cure rates can exceed 98% with fertility retention, whereas most women would have died from malignant disease 60 years ago. This success can be explained by the development of effective treatments, the use of human chorionic gonadotropin as a biomarker, and centralisation of care. We summarise strategies for management of gestational trophoblastic disease and address some of the controversies and future research directions.

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Department of Cancer Medicine (Prof M J Seckl FRCP) **and Department of Histopathology** (N J Sebire FRCPath), **Charing Cross Gestational Trophoblastic Disease Centre, Charing Cross Hospital Campus of Imperial College London, London, UK; and New England Trophoblastic Disease Center, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Harvard Medical School, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Boston, MA, USA** (R S Berkowitz MD)

Correspondence to: Prof Michael J Seckl, Department of Cancer Medicine, Charing Cross Gestational Trophoblastic Disease Centre, Charing Cross Hospital Campus of Imperial College London, London W6 8RF, UK **m.seckl@imperial.ac.uk**

Introduction

Hippocrates was probably the first to describe gestational trophoblastic disease around 400 BC in his description of dropsy of the uterus.[1] Although other observations have been made since, Marchand first associated hydatidiform mole with pregnancy in 1895.[1] Healthy trophoblastic tissue aggressively invades the endometrium and develops a rich uterine vasculature, generating an intimate connection between the fetus and the mother known as the placenta. Invasion is one of the distinct features of malignant disease, and healthy trophoblast can be detected by PCR in the maternal circulation.[2] Fortunately, malignant-like behaviour is tightly controlled in healthy trophoblast. However, in gestational trophoblastic disease the regulatory mechanisms fail, resulting in tumours that are highly invasive, metastatic, and very vascular. In this Seminar we discuss the epidemiology, origins, pathological changes, and clinical behaviour of the various forms of gestational trophoblastic disease.

Epidemiology

Gestational trophoblastic disease arises more frequently in Asia than in North America or Europe,[3,4] which could be due to differences in prevalence, discrepancies between hospital-based and population-based data, or disparity in availability of central pathology review. In the UK, all patients are included on a national register, with central pathology review; and the incidence of complete hydatidiform mole is around one per 1000 pregnancies and three per 1000 for partial hydatidiform mole.[5] Other developed countries report similar data.[6]

The incidence of molar pregnancy has decreased in South Korea from 4·4 cases per 1000 births in the 1960s to 1·6 cases per 1000 births in the 1990s,[7] possibly because of improved socioeconomic conditions and dietary changes—especially since findings from studies in animals show that diet can reset the genetic imprint.[8] Additionally, an increased risk of molar pregnancy is associated with reduced consumption of dietary carotene[9,10] and animal fat,[9] and advanced maternal age.[3,11–13] Ova from older women are more susceptible to abnormal fertilisations than are those from younger women.

After a molar pregnancy, the risk of further complete and partial mole rises to 1–2%.[11,14,15] After two molar gestations, the risk of a third mole is 15–20%,[11,14,15] and the risk is not decreased by change of partner.[16] Some repeat molar pregnancies are due to familial or sporadic biparental molar disease (figure 1).

The frequency of choriocarcinoma or placental-site trophoblastic tumour is less well known, since these diseases can arise after any type of pregnancy.[17,18] Choriocarcinoma develops in around one in 50 000 deliveries,[19] and placental-site trophoblastic tumour accounts for about 0·2% of cases of gestational trophoblastic disease in the UK.[20] The risk of gestational trophoblastic neoplasia might also be linked to hormonal factors, since women with menarche after 12 years of age, light menstrual flow, and previous use of oral contraceptives are at increased risk.[21,22] Additionally, risk of malignant disease after hydatidiform mole has been associated with oral contraceptive use (if started when human chorionic gonadotropin [hCG] concentrations are raised) in some[23] but not all[24] studies.

Causes and genetics

In most cases, complete hydatidiform mole usually arises when an ovum without maternal chromosomes

Search strategy and selection criteria

We searched the Cochrane Library, Medline (via PubMed, Internet Grateful Med, OVID, and Knowledgefinder), for meta-analyses, previous systematic reviews, cohort studies (and when appropriate comparison groups), and case-control studies published in English between 1980 and 2010, with the keywords "trophoblastic disease", "GTD", "GTN", "choriocarcinoma", "molar pregnancy", "hydatidiform mole", "placental site trophoblastic tumor", "genetics", "epidemiology", "pathology", "treatment", "chemotherapy", "methotrexate", "actinomycin D", "dactinomycin", "cisplatin", "paclitaxel", "high-dose", "management", "risk factors", "hCG", "imaging", "ultrasound", "PET", "CT", "MRI", "prognosis", and "staging". We included results presented at the 15th International Society for the Study of Trophoblastic Diseases meeting in November, 2009, in Cochin, India. Reference lists from all previous publications were scanned to find any publications not already identified by our electronic search strategy.

is fertilised by one sperm that then duplicates its DNA, resulting in a 46XX androgenetic karyotype, in which all chromosomes are paternally derived.[25–27] About 10% of complete moles are 46XY,[28] arising from fertilisation by two sperm (figure 1). Although nuclear DNA is entirely paternal, mitochondrial DNA remains maternal in origin.[29] Findings from some studies[30] show that patients with recurrent disease can have biparental molar rather than typical androgenetic disease, which might be familial or sporadic. Genetic studies in such families showed that the related genes are at chromosome 19q13.3–13.4,[31] and subsequent analysis noted *NLRP7* mutations in this region.[32] The function of the normal protein and the mechanism by which mutations are associated with imprinting abnormalities and gestational trophoblastic disease are unknown.[33] Data show clustering of mutations in the leucine-rich region of *NLRP7* (figure 2), suggesting that this region is crucial for normal function.[34] Some androgenetic diploid complete moles and possibly even triploid partial hydatidiform moles might also carry *NLRP7* mutations,[35] but confirmation from large studies is needed.

Partial hydatidiform moles are almost always triploid (figure 1), and they result from fertilisation of a seemingly healthy ovum by two sperm;[36–38] diploid partial moles probably do not exist, with most reported cases being misdiagnosed complete moles.[39]

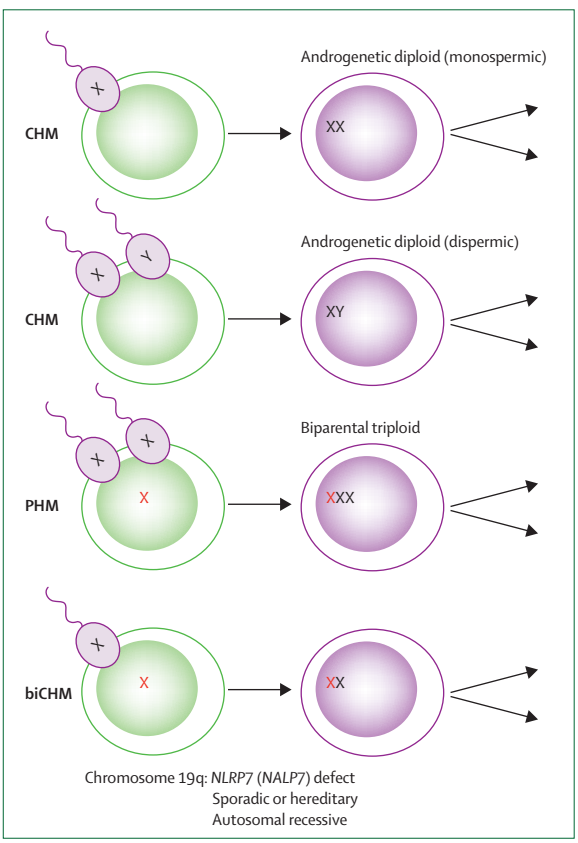

Figure 1: **Karyotype derivation of complete and partial hydatidiform moles and rare biparental repetitive complete hydatidiform mole**
CHM=complete hydatidiform mole. PHM=partial hydatidiform mole. biCHM=rare biparental complete hydatidiform mole. Paternal (black) and maternal (red) derived genes are shown.

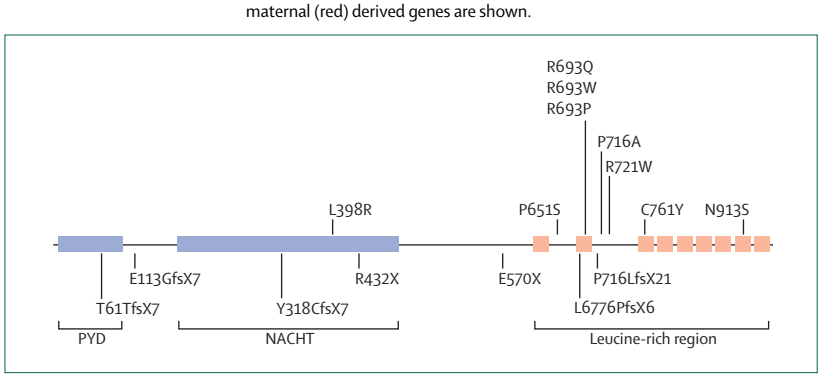

Figure 2: **Domain structure of *NLRP7* and identified mutations noted in 17 families with biparental repetitive hydaditiform moles**
Predicted protein domains include PYRIN (PYD), NACHT, and a leucine-rich region. The nine missense aminoacid substitutions or mutations are shown above the protein and seven nonsense mutations are shown below the protein. There seems to be some clustering of mutations in the leucine-rich region.

Pathology

All gestational trophoblastic disease is derived from the placenta. Hydatidiform moles and choriocarcinoma arise from villous trophoblast and placental-site trophoblastic tumours from interstitial trophoblast. Most complete and partial hydatidiform moles have distinctive morphological characteristics, although diagnostic criteria have changed because evacuation is done earlier in gestation (median 8–9 weeks in the UK). First-trimester complete moles show a characteristic abnormal budding villous structure with trophoblast hyperplasia, stromal karyorrhectic debris, and collapsed villous blood vessels. By contrast, early partial moles show patchy villous hydrops with scattered abnormally shaped irregular villi, trophoblastic pseudoinclusions, and patchy trophoblast hyperplasia (figure 3).[40–42]

Morphological distinction of non-molar miscarriage from partial hydatidiform mole can be difficult, since villous dysmorphism can be present but without the characteristic trophoblast hyperplasia that is noted in partial mole. Ancillary techniques are needed in some cases to differentiate non-molar miscarriage from hydatidiform mole, including immunostaining for $P57^{kip2}$, the product of CDKN1C. $P57^{kip2}$ is expressed by the maternal allele and is visible on histology as nuclear staining of cytotrophoblast and villous mesenchyme in placenta of all gestations apart from androgenetic complete mole.[43,44] Additionally, ploidy analysis by in-situ hybridisation or flow cytometry can distinguish diploid from triploid conceptions, helping to diagnose partial mole, but is unable to distinguish complete mole from diploid non-molar miscarriage, or molar versus non-molar triploidy, which necessitate molecular investigations.[18,45–47]

Choriocarcinomas are malignant hCG-producing epithelial tumours with central necrosis and a characteristic biphasic architecture recapitulating cytotrophoblast-like