10
CLINICAL FEATURES OF MOLAR PREGNANCIES AND GESTATIONAL TROPHOBLASTIC NEOPLASIA

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10.1 INTRODUCTION

Gestational trophoblastic disease (GTD) is comprised of a spectrum of conditions, each of which is characterised by low incidence and high cure rates. The diagnoses range from the generally benign but best viewed as pre-malignant partial and complete molar pregnancies to the malignant invasive mole, choriocarcinoma, placental site trophoblastic and epithelioid trophoblastic tumours (PSTT/ETT). The malignant forms are often referred to as gestational trophoblastic neoplasia (GTN)[1] . In addition, we have recently become aware of atypical placental site nodules as being a new premalignant addition to the GTD family [2]. The optimal care of patients with these rare conditions relies on effective team working between obstetricians, gynaecologists, radiologists, pathologists, oncologists, nurses and an effective post molar pregnancy follow-up team.

Patients with molar pregnancies make up the large majority of the cases of GTD and approximately 8% of them will require additional therapy following uterine evacuation [3]. The patients who develop malignancy after a molar pregnancy should rarely prove difficult to treat and in areas with well organised care overall cure rates approaching 100% are reported [4–7]. In contrast the GTN patients with choriocarcinoma or PSTT/ETT occurring after a non-molar pregnancy can present with a wide variety of symptoms which may lead to treatment delays whilst the diagnosis is made [8,9]. Fortunately the majority of these patients should also have the expectation of curative treatment, although this is likely to be relatively more complex and toxic [1,10–12].

The focus of this chapter is the clinical characteristics and presentations of the differing forms of GTD. The more common presenting features as well as some of the unusual cases will be reviewed and the value of the established and newer diagnostic procedures discussed.

10.2 CLASSIFICATION AND GENETIC ORIGINS OF GTD

10.2.1 **Pre-malignant forms of GTD**

10.2.1.2 Partial and complete molar pregnancies

The differing forms of GTD develop from the trophoblast cells of the conception via two separate genetic pathways. The most common forms of GTD, partial and complete molar pregnancies, arise from trophoblast cells derived from aberrant fertilizations in which there are imbalances in the genetic inputs from the ovum and the sperm. In a partial molar pregnancy (PHM) there are 3 sets of chromosomes, two of paternal origin and one maternal, that follow the fertilization of the egg by two sperm [13,14] In a complete molar pregnancy (CHM) there are 46 chromosomes but all are derived from the father, with the maternal chromosomes in the nucleus of the ovum lost either at the point of conception or earlier in ovum development [15]. The result of both processes is to produce trophoblast cells that can divide rapidly, make human chorionic gonadotrophin (hCG) and are unable to produce a viable fetus but have the potential to become malignant.

Complete moles and partial moles differ significantly in their invasive potential and risk for malignant transformation. Approximately 15% of patients with CHM will develop persistent trophoblastic disease following uterine evacuation [3,16] whilst 1% or less of PHMs will require additional treatment [3] Despite their different genetic make-up there appears to be no significant difference in the need for further therapy or the response to chemotherapy treatment for patients with CHM derived from either the duplication of a single sperm or those resulting from dispermic fertilization [17]. Similarly the rare cases of malignancy occurring after a PHM appear equally as sensitive to chemotherapy treatment as the cases arising from CHM [3].

10.2.2 **Malignant forms of GTN**

10.2.2.1 Invasive mole (chorioadenoma destruens)

The microscopic appearance of an invasive mole (IM) appears histologically benign having a similar appearance to complete molar pregnancy [18]. Despite this appearance, the clinical course of an invasive mole is a malignant one, with predominantly invasion of the trophoblast tissue into the myometrium and spread of molar tissue through pelvic veins. If left untreated, invasive moles can result in heavy bleeding, uterine rupture or other symptoms from local invasion.

10.2.2.2 Choriocarcinoma and PSTT/ETT

In contrast to molar pregnancies, many cases of gestational choriocarcinoma and the majority of cases of PSTT/ETT arise from a malignant transformation within previously healthy trophoblast cells that have the usual complement of 46 chromosomes with 23 from each parent

[19] Rarer histologically identical cases of choriocarcinoma and PSTT can also arise from each type of molar pregnancy [20] and all of these gestational tumours, irrespective of their individual genetic origin, share similar clinical characteristics including the marked sensitivity to chemotherapy [21].

Placental site trophoblastic tumours and ETT are the rarest form of GTN and can complicate any form of conception but most frequently follow a normal pregnancy [22–24]. Frequently PSTT is localised within the uterus and these cases can be cured with surgery alone [25]. In contrast advanced cases of PSTT have a variable response to chemotherapy, with success closely linked to the length of the interval from the causative pregnancy [24].

10.2.2.3 Atypical placental site nodules

Placental site nodules (PSN) are often an incidental finding discovered months or years after the end of a pregnancy as a consequence of investigation into for example intermenstrual bleeding. PSN represent persisting nodules of placental tissue in the uterine wall. A proportion of these display atypical features and we have recently become aware that they may be associated with and/or develop into either PSTT or ETT. Our current small data set of about 23 cases suggests that about 15% will be associated with such a tumour and so suspected cases require careful investigation and monitoring over time [2]

10.3 CLINICAL AND PATHOLOGICAL REQUIREMENTS FOR DIAGNOSIS OF GTN

As nearly all forms of GTD constitutively make hCG, most cases of GTN can be clinically diagnosed without the need for a potentially hazardous biopsy [3].

The requirement for combination chemotherapy to provide curative therapy for the majority of patients with a pathological diagnosis of choriocarcinoma has been confirmed in a number of publications [7,12] However the scoring systems that determine the intensity of initial chemotherapy for GTN are based on clinical parameters with little distinction between cases following a molar pregnancy, invasive mole and choriocarcinoma in treatment planning. The widely used FIGO prognostic system does not include an assessment of the histology for determining the intensity of therapy but employs their common clinical characteristics as surrogate factors for the pathology [26]. The majority of patients with post molar pregnancy GTN will fall into the low risk group, whilst those with metastatic disease following a normal pregnancy, which if biopsied would be most likely to demonstrate choriocarcinoma, will almost always fall into the high risk group.

Generally it is more important that treatment is administered promptly

prior to the development of organ compromise or a high risk of bleeding or uterine rupture, than the specific histological type of GTN is formally identified. The main exception is for patients with suspected PSTT/ETT, which is often suggested by a relatively low hCG level for the bulk of the disease, a longer interval from the last pregnancy and frequently a relatively indolent course. In these cases pathological confirmation can be very helpful, as the management of PSTT/ETT differs significantly from the other forms of GTN, with the use of more intensive chemotherapy and a larger role for surgery [22,24]

10.4 THE EPIDEMIOLOGY OF GTD

10.4.1 Incidence Rates and Risk Factors for Molar Pregnancies

Most modern series suggest that the incidence of molar pregnancies is increasingly uniform in the various racial and geographical groupings at around 2-3 cases per 1000 live births [27,28]. The relative incidence of complete and partial molar pregnancies still remain subject to some debate, perhaps due to the difficulty in making the correct diagnosis in first trimester specimens. However a number of published series with expert pathological review suggest a comparable incidence for the two forms [29].

Historical series with significantly higher incidence rates of molar pregnancy have been reported from Korea, the Philippines, Japan and other countries from that region [30]. Interestingly, more recent studies from these countries have demonstrated over the past 30 years their rates to have fallen to figures very similar to the 2-3 per 1000 live births as those seen in Europe and North America [27,31]. In contrast to this rapid reduction in incidence, high rates of up to 20 cases per 1000 are still reported from a few countries in Asia and Africa [32,33].

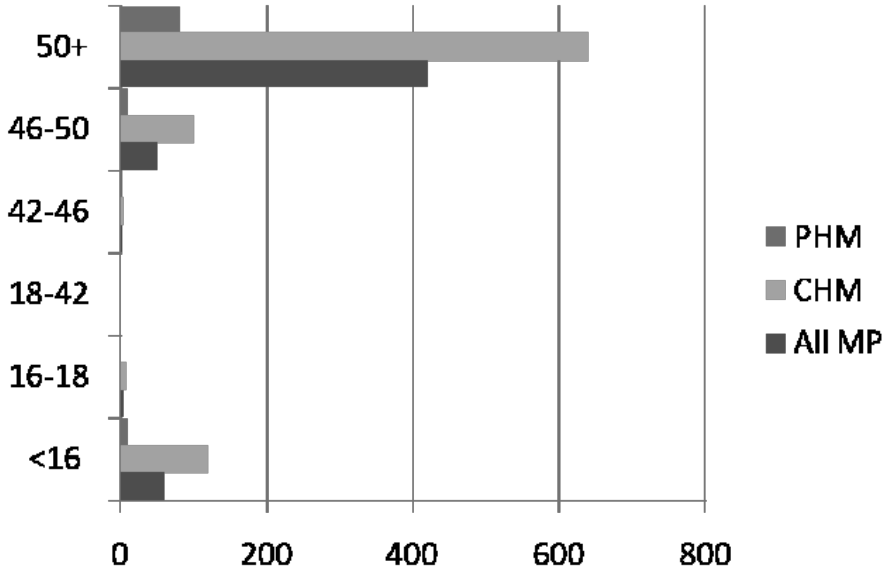
The relative impact of changes in diagnostic accuracy, reporting variations or reductions in real incidence due to dietary, maternal age or other factors is difficult to ascertain. An increased risk of molar pregnancy is associated with a reduced consumption of dietary carotene and animal fat [34,35].

Aside from these potential effects of diet, ethnicity and location, there are two clear risk factors that result in an increased risk of a molar pregnancy. Conceptions occurring at the extremes of the reproductive age groups carry considerably higher risks of molar pregnancy than for pregnancies in women aged 20-40 as shown in Fig 10.1. Girls under 15 have a 10-20 fold higher incidence of a molar pregnancy whilst women aged 45-50 have a 20-fold increased risk and those over 50 have a 200 fold relative risk [30,36,37]. The age related increased risk is more marked for complete molar pregnancies where the risk in women conceiving in their late forties or early fifties is more than 500 fold increased. The risks for

partial molar pregnancies and also for non-molar hydropic abortions are also increased but at considerably lower rates [38]. Interestingly advanced paternal age may also yield a modestly higher risk of CHM but has not been linked to elevated risk of PHM [39].

Figure 10.1

Maternal Age and the Relative Risk of Molar Pregnancy

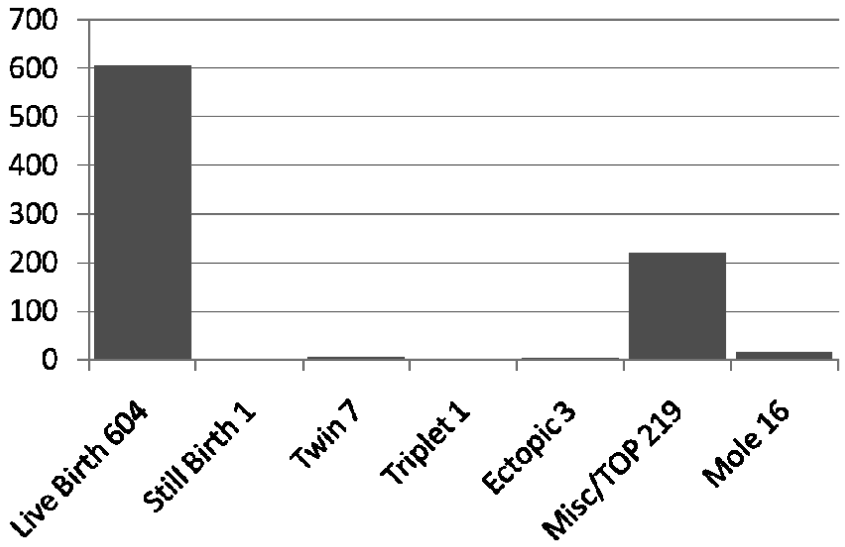


Adapted from Sebire et al

After a molar pregnancy, the risk of further complete and partial mole rises to 1-2% [29,40,41]. After two molar gestations, the risk of a third mole is 15-20% [29,41]. The data in Fig 10.2 shows the subsequent pregnancy outcome for a cohort of 851 women, with a previous molar pregnancy, from the Charing Cross Hospital database, who become pregnant in 2005 and in keeping with the published data confirms a second molar pregnancy rate of 1.8%.

Figure 10.2

Charing Cross Hospital unpublished data



In patients with a second molar pregnancy the pathological type is not necessarily the same type as the first. Of the women who have a complete molar pregnancy who have another molar pregnancy, 81% had another CHM whilst 19% had a PHM with their next molar pregnancy. Similarly of those who had a PHM for their first molar pregnancy and then went on to have another molar pregnancy, 68% had another PHM and 32% a CHM [29].

As a prior molar pregnancy results in an increased risk of a subsequent molar pregnancy it is unsurprising that the occurrence of earlier normal healthy pregnancies results in a decreased statistical risk of having a molar pregnancy. In contrast a history of repeated miscarriage may lead to an enhanced risk [42]. Women who have repetitive molar pregnancies may have a familial biparental hydatidiform mole syndrome which is characterized by recurrent complete hydatidiform moles of biparental, rather than the more usual androgenetic, origin [43]. Patients who have had a molar pregnancy do not appear to have an increased risk of developing other malignancies [44]. However, there is some data to suggest a slight excess risk of childhood malignancies in the children of women who have had molar pregnancies [45].

10.4.2 Choriocarcinoma

The incidence of gestational choriocarcinoma is approximately one case

for every 50,000 pregnancies [1]. Whilst some of the cases arise from previous molar pregnancies and so presumably share the same risk factors, the majority of cases arise from genetically normal placental tissue. An increased incidence of choriocarcinoma occurs at the upper and lower extremes of the reproductive years and it has been suggested that non-Caucasian populations have an increased risk [46]. Certain parental ABO blood groups may also be linked to an increased risk of choriocarcinoma but do not increase the risk for hydatidiform mole [47] No other epidemiological variables have been consistently linked with choriocarcinoma, probably owing to the rarity of the disease.

10.4.3 Placental site and epithelioid trophoblastic tumours (PSTT/ETT)

Placental site trophoblastic tumours are extremely rare making up 0.2% of all registered GTD in the UK [24]. With this rarity any potential associations with risk factors, even if present, are unlikely to be established. The diagnosis appears to occur fairly evenly across the child bearing age range [48] but of interest some data suggests that PSTT occur either predominantly or can only follow a pregnancy with a female conception [49]. ETT is assumed to behave like PSTT but data are really too sparse thus far to be sure [50].

10.5 Clinical Manifestations of Gestational Trophoblastic Neoplasia

10.5.1 Molar pregnancies

A number of clinical features including, vaginal bleeding or discharge, abdominal pain and excessive morning sickness are reported with an increased incidence by patients who are later diagnosed with molar pregnancies [36,51]. However as these symptoms also occur not infrequently in women with normal conceptions they are of limited value in making the diagnosis of molar pregnancy prior to ultrasound assessment.

The measurement of serum hCG levels in the early stages of pregnancy can also give information on the potential diagnosis of a molar pregnancy. A number of studies have demonstrated that hCG levels are generally higher in complete molar pregnancies than in normal pregnancies but there is a considerable overlap and can frequently be lower in partial molar pregnancies [52]. As these findings are not of high specificity and early evacuations of molar pregnancies brings only a relatively small decrease in the risk of developing malignancy it is conventional to wait until the diagnosis becomes clear on ultrasound to avoid the risk of evacuating a healthy pregnancy [53].

More recently, detailed research has indicated that the absolute level of hCG beta and the ratio of hCG beta to total hCG can distinguish between the diagnosis of molar pregnancy and a normal gestation with 100% specificity and 90% sensitivity [54]. However the logistics of performing and financing this relatively complex testing as a screening procedure for an illness with a low incidence and near 100% cure rate may prove an obstacle to routine application.

The introduction of routine first trimester ultrasound has significantly altered the presentation and natural history of molar pregnancies all over the world [55,56]. This data summarised in Table 10.1 confirms that the classical findings of molar pregnancy of excessive uterine enlargement, hyperemesis and pre-eclampsia are now unusual where routine ultrasound is available.

Table 10.1

Routine 1st Trimester Ultrasound and the symptoms of complete molar pregnancies.

Routine Ultrasound	No routine Ultrasound
PV bleeding 84% Anaemia 5% Uterine enlargement 28% Hyperemesis 8% Pre-eclampsia 1%	PV bleeding 97% Anaemia 54% Uterine enlargement 51% Hyperemesis 26% Pre-eclampsia 27%

Adapted from reference 74

Characteristic ultra-sonographic scans of CHM show a uterine cavity filled with a heterogeneous mass (so-called snowstorm), without associated fetal development and with theca lutein ovarian cysts [57,58]. However, these features are not visible in the first trimester and, although some investigators [59] have suggested that ultrasound can be diagnostic of complete mole in early pregnancy, large studies [60,61] have shown that only 40-60% of cases are detected by sonography in routine clinical practice. Moreover, 10% of cases that are thought to be molar on sonography were diagnosed as non-molar hydropic abortions on histological review [61]. Findings from other reports [62] are similar and emphasise the false-positive and false-negative rates are high with ultrasonagraphy-especially for PHM- and histological examination is necessary to achieve a correct diagnosis. All products of conception from non-viable pregnancies should undergo histological examination irrespective of ultrasonographic findings.

10.5.2 Clinical features of molar pregnancies with routine first trimester ultrasound

In centres who carry out a routine first trimester ultrasound, the majority of complete molar pregnancies are diagnosed by 8-12 weeks gestation [61]. Compared to studies performed prior to routine ultrasound it is apparent that the routine imaging has resulted in a significant reduction in the median gestational age at evacuation decreasing from the previously documented 17 weeks [63].

In contrast, partial moles are less commonly diagnosed by ultrasound or prior to uterine evacuation. Most patients with partial moles present with signs and symptoms suggesting incomplete or missed abortion and the ultrasound most frequently demonstrates a non-viable pregnancy rather than an obvious molar pregnancy [64,65].

As a result of the earlier diagnosis, the classical molar pregnancy clinical findings of excessive uterine enlargement, pre-eclampsia and hCG values greater than 100,000 U/I are rarely observed and hyperthyroidism, hyperemesis and pre-eclampsia are now exceedingly rare [56].

Very rarely a twin pregnancy comprising a normal conception in combination with a molar pregnancy can occur. The Charing Cross database with 126 cases of molar pregnancy combined with a viable twin pregnancy during a twenty-year period suggests an incidence in the order of 1 per 100,000 live births [66].

10.5.3 Clinical features of molar pregnancy without routine first trimester ultrasound

In areas where routine first trimester ultrasound is not routinely available the patterns of presentation of molar pregnancies are significantly different. In this situation that we will term advanced molar pregnancy, vaginal bleeding remains the most common presenting symptom experienced by 89-97% of patients and when severe can result in symptomatic anaemia [56].

The majority of patients with advanced molar pregnancy will present by 20 weeks gestation, and liquefaction of intrauterine clots may lead to leakage of fluid with the colour and consistency of prune juice. If left undiagnosed some patients may pass molar vesicles or even miscarry the entire molar tissue [67].

Approximately 40-50% of women with advanced molar pregnancy experience uterine enlargement in excess of four weeks greater than that expected for their dates [68] as a result of the trophoblast hyperplasia and haemorrhage. Although uterine size greater than dates is regarded as a classic manifestation of advanced molar pregnancy, approximately 15-

40% of patients will have a 'small-for-dates' uterus [68,69]

Approximately 15-25% of cases of advanced molar pregnancy are complicated by hyperemesis which is usually associated with uterine enlargement and markedly elevated hCG levels [69]. Pre-eclampsia can occur in up to 25% of advanced molar pregnancy, whilst it is extremely rare if the molar pregnancy is diagnosed prior to 10—12 weeks.

Clinical hyperthyroidism resulting from the cross-reaction between hCG and TSH, is also a feature of advanced molar pregnancy in a small number of patients. The presenting symptoms include thyroid enlargement, tachycardia, fever, tremor and very occasionally women can present with a thyroid storm [70].

Pulmonary insufficiency is associated with about 2% of cases of advanced molar pregnancy. In these cases, acute respiratory distress occurs after molar evacuation and is almost invariably associated with marked uterine enlargement. Other conditions associated with advanced molar pregnancy that can lead to respiratory distress include high-output congestive heart failure secondary to pre-eclampsia, anaemia or hyperthyroidism [71].

Abdominal and pelvic pain can result from enlarged theca lutein cysts of the ovary, which are commonly associated with advanced molar pregnancy and are assumed to be linked to the high hCG levels.

The majority of these findings were documented in American or European series prior to the routine use of ultrasound; however similar findings of heavy bleeding, anaemia and lung metastases are still recorded in areas where routine ultrasound is unavailable [72,73].

10.5.4 GTN Following a molar pregnancy

Following an evacuation approximately 15% of patients with a complete mole and 1% of women with partial mole will develop malignant disease [36,74]. Rates are probably higher in other countries than the UK, possibly because of differences in hCG criteria and overdiagnosis of neoplasia and a scarcity of whole-population demographics. A number of clinical factors have previously been suggested to help predict an increased risk for the need for additional treatment. Despite all of these studies, none of the approaches are currently routinely used to clarify which patients are actually destined to require treatment. At present, with no clinically effective method to accurately predict which women will require additional treatment, ideally all molar pregnancy patients should take part in a structured follow up programme.

The follow up programme will allow the patient to be closely monitored and called for treatment before any serious problems from the growing trophoblast tissue can occur. The routine indications for treatment as recommended by FIGO and a slightly wider group as used at Charing Cross Hospital are shown in Table 10.2.

Table 10.2

Indications for the treatment after a molar pregnancy
FIGO Indications
hCG plateau of 4 values +/- 10% over a 3 week period hCG increase of >10% of three values over a 2 week period Persistence of hCG for more than 6 months after molar evacuation
Charing Cross Hospital
Brain, liver, GI mets or lung mets >2cm on CXR Histological evidence of choriocarcinoma Heavy PV bleeding or GI/intraperitoneal bleeding Pulmonary, vulval or vaginal mets unless the hCG level is falling Rising hCG in two consecutive serum samples hCG >20,000 IU/L more than 4 weeks after evacuation hCG plateau in 3 consecutive serum samples Raised hCG level 6 months after evacuation (even if falling)* * no longer an absolute indication

An alternative approach that is considered when adequate follow-up resources are not available is to use adjuvant chemotherapy therapy for all women after their evacuation. Using either Methotrexate or Actinomycin D adjuvant therapy produces reduced but still significant relapse rates of 5-10%. In addition to these appreciable failure rates the use of adjuvant treatment has the additional disadvantage of delivering excess treatment for the majority of women who would have been cured by their evacuation alone [75,76] Unfortunately an approach of 'no adjuvant treatment' and 'no structured follow up' is still the case in many areas of the world and in these settings patients re-present with more advanced GTN with a variety of symptoms including severe haemorrhage, anaemia and lung metastases [72]. In this situation the diagnosis of GTN after the evacuation relies on the patient's presentation and investigation by their local medical teams. This management approach clearly leads to diagnosis with more advanced cases and potentially less favourable outcomes.

10.5.5 Choriocarcinoma

The presentation of choriocarcinoma can be extremely varied with symptoms and signs associated with the differing sites of metastatic disease occurring at a wide range of time after the causative pregnancy [3,12,77]. In Table 10.3 the most frequent presentations and sites of disease are listed.

Table 10.3

Choriocarcinoma: Disease Presentation and Sites of Metastases

Presentation	**Single site of**	**Multiple sites of**
Post partum bleed	Uterus 60%	Uterus 60%
Other PV bleeding	Vagina 6%	Vagina 7%
Cough/dyspnoea 14%	Lungs 10%	Lungs 93%
CNS symptoms 11%	Brain 13%	Brain 45%
Abdominal symptoms	Liver 3%	Liver 15%
Other 8%	Others 9%	Others 30%

Adapted from refs 8,9

The most frequent presentation is with vaginal bleeding which can be severe, either from a mass within the uterus or from vaginal metastases. Whilst in the immediate post partum period a degree of blood loss is not unusual, patients with choriocarcinoma often bleed heavily and have significantly elevated hCG levels. In comparison after a normal delivery the hCG level, which is normally in the region of 20,000 IU/L prior to delivery should fall to normal within 3 weeks. In the differential diagnosis of a uterine mass and an elevated hCG, the hCG level is generally only elevated to relatively low levels with retained products of conception.[78].

Characteristically gestational choriocarcinoma forms a rapidly growing malignancy with the ability to spread to any site in the body, with metastases reported in almost all conceivable sites. The most commonly involved are lung, vagina, central nervous system, liver, kidneys and gastrointestinal tract. The one organ that appears relatively rarely affected by choriocarcinoma is bone with spread here only very rarely reported.

Metastases to the lung are present in over 80% of women with choriocarcinoma and pulmonary involvement may cause cough, dyspnoea, hemoptysis and pleuritic chest pain due to pulmonary infarction or pleural space invasion. Fortunately respiratory failure is rare, as mechanical ventilation for these patients, with highly vascular

pulmonary lesions, can present difficult challenges and is associated with a high mortality [79].

Intra-abdominal metastases can produce intra-peritoneal bleeding, malaena and severe pain, whilst neurological manifestations may include headaches, seizures, loss of consciousness and hemiplegia. As a result of the broad range of presentations, clinicians should be alert to the possibility of choriocarcinoma in any a woman of child-bearing age with central nervous system symptoms, postpartum cerebrovascular accidents or evidence of a metastatic cancer of unknown origin.

In all of these cases, a simple laboratory serum hCG measurement may be life-saving, as even in advanced cases with cerebral metastases the expectation is cure with effective treatment.

10.5.6 PSTT

The majority of patients with PSTT present with either vaginal bleeding or amenorrhea [22–24]. Patients of all age groups are affected and there appears to be no significant association with gravidity or the type of prior pregnancy [80]. The interval from the antecedent gestation to diagnosis varies from one week to 25 years [22].

8.6 DIAGNOSING GTN

10.6.1 The value of hCG measurement

The constitutive production of hCG by all forms of GTN greatly aids the ease and accuracy of diagnosis of these rare illnesses. With a very few exceptions, the findings of an elevated hCG level in the absence of a pregnancy is highly suggestive of a malignancy, most commonly GTN.

As previously discussed the majority of GTN patients will have had a proceeding molar pregnancy and the post evacuation changes in the hCG levels are the main determinants in changing the diagnosis from that of the pre-malignant to that of malignant GTN requiring additional treatment. In these cases there is generally no requirement for an additional biopsy as it provides no clinically useful information and may precipitate heavy bleeding.

10.6.2 Diagnostic challenges in GTD

Whilst the majority of women with GTD will have a straightforward route to diagnosis, there are a number of clinically difficult situations where the use of modern technology can help in clarifying the diagnosis.

The most frequent situation is in clarifying the diagnosis between a partial or complete mole or non-molar pathology. With the widespread use of routine first trimester ultrasound the majority of molar pregnancies

are now evacuated before their classical histological changes become apparent. As a result the pathology review can present some challenges in achieving the correct diagnosis. A number of expert centres have published data demonstrating a high number of cases which have had their diagnosis altered on central review [81].

In addition to the histological analysis, a number of techniques have been shown to be useful in aiding accurate diagnosis. Molar ploidy analysis by flow cytometry is useful in distinguishing PHM from CHM [82], whilst testing for the expression of p57KIP2 (a maternally imprinted cdk inhibitor), is helpful in distinguishing the androgenetic complete moles where it is negative, from cases of partial mole or non-molar pregnancies which do express this antigen [83]. This distinction between the two types of molar pregnancy and non molar failed pregnancies can be helpful in determining the likelihood of the relative risk of developing persistent GTN and, when the diagnosis proves to be a non-molar failed pregnancy, stops unnecessary follow up and restrictions on the timing of future pregnancies.

10.7 DIFFERENTIAL DIAGNOSIS BETWEEN CHORIOCARCINOMA AND PSTT

The presence of relatively low hCG levels for the bulk of the disease, should raise suspicions for a PSTT [29]. Fortunately, the histopathology review usually establishes the diagnosis of PSTT from choriocarcinoma routinely. This distinction is important as the management of these two conditions differs significantly with regard to the sensitivity to chemotherapy and also importantly with the need for hysterectomy to complete the treatment of PSTT [22–24]

10.8 GESTATIONAL OR NON-GESTATIONAL CHORIOCARCINOMA

A number of non-gestational malignancies can mimic the clinical characteristics of gestational choriocarcinoma with production of hCG and with the histological appearance of trophoblastic differentiation. However whilst phenotypically appearing to be choriocarcinoma these tumours have one key difference from gestational tumours in that they are usually not curable with chemotherapy.

Genetic analysis examining the pattern of genetic polymorphisms from the patient and the partner allows the gestational or non-gestational genetic origin of the tumour to be determined [84]. This information can be used to optimise the approach to curative therapy in confirmed

gestational tumours and to avoid excessive toxic non-curative therapy in patients with non-gestational tumours that masquerade as GTN [85].

10.8.1 hCG elevations of uncertain origin

In the absence of pregnancy the finding of an elevated serum hCG level is generally taken as evidence of a malignancy, most usually GTN. However there are a number of rarer cases where there are non-malignant causes for positive assay results for hCG in patients' blood.

The presence of cross reacting or heterophilic antibodies in the blood of some patients can lead to false positive hCG results when tested in some assays. This phenomenon has been well documented in the medical literature but cases still occur where medical and surgical treatment is based on these misleading assays with unfortunate results [86]. Differing assays can still give divergent results and to aim to avoid these false positive it is prudent to check unusual results on more than on assay platform and also to test the urine for hCG as the cross reacting antibodies do not pass into the urine and so a positive result here is more likely to be a real finding.

In post menopausal women the pituitary gland can be a source of physiological hCG production in the absence of malignancy [87]. In these situations the levels tend to be low with results of 5-15 IU/L typical. Whilst these results can lead to diagnostic confusion, the lack of any radiological evidence of malignancy and the ability of oestrogen administration to produce normalisation of the hCG level should prevent the erroneous diagnosis of malignancy [88].

The rarest group of women with elevated hCG test results are those who have slightly raised levels, generally under 1000 IU/L, but without radiological evidence of disease. These patients form a challenging group to manage as investigations have suggested that approximately 25% of them will subsequently be shown to have GTN whilst the others appear to have innocent aetiologies. To help with these diagnostic difficulties a number of investigation/treatment protocols have been devised [89].

10.8.2 Unusual presentations of GTN

In the preceding sections we have outlined the most frequent features of GTN, in this section we will now review some rarer manifestations of GTN that can occur in the various organ systems. Patients with choriocarcinoma can present with a wide range of non-gynaecological complaints and clinicians of all disciplines should be aware of the potentially extremely wide range of symptoms and clinical findings.

10.8.3 Central Nervous System (CNS)

An intra-cranial haemorrhagic event can be the initial presentation of

GTN. The bleed can lead to sudden collapse and loss of consciousness or other neurological symptoms. Cerebral vasculature aneurysms can develop at sites of intra-cranial metastasis [90] leading to haemorrhage, and choriocarcinoma producing cerebral vascular occlusion leading to hemiplegia has also been recorded [91]. In addition to the cases presenting with either haemorrhage or vascular occlusion, CNS and ocular choriocarcinoma may also present with functional changes including the onset of epilepsy or visual field defects [92]. These neurological events may occur within days of a healthy delivery, shortly after the evacuation of a molar pregnancy or at times distant from these events [93].

10.8.4 Cardiovascular

Intravascular tumour thrombi from choriocarcinoma can present acutely with embolic complications causing acute dyspnoea and chest pain [94]. The more gradual development of symptoms from multiple emboli leading to pulmonary hypertension has also been documented and these cases have also been successfully treated [95]. Very rarely choriocarcinoma has also presented as an intracavitary tumor of the left atrium with the classic symptoms and findings of left atrial myxoma combined with an elevated hCG level [96].

10.8.5 Respiratory

Pulmonary metastases are relatively common in patients with GTN and are in most cases are asymptomatic. In contrast patients with large volume disease can present with respiratory failure whilst intrathoracic haemorrhage can lead to hemoptysis, dyspnoea, chest pain, bloody effusion and hypovolemia.

10.8.6 Gastrointestinal

A number of reports describe women suffering massive hemoperitoneum secondary to rupture of hepatic, splenic or pelvic foci of GTN [97]. Severe haemorrhage has also occurred following liver biopsy of nodules that were not suspected of being choriocarcinoma. The presentation of GTN may also mimic that of a ruptured ectopic pregnancy [98] and massive hemoperitoneum has been recorded from choriocarcinoma arising from an intra-abdominal pregnancy [99].

Gastrointestinal bleeding can also occur secondary to oesophageal, gastric and small bowel metastases leading to hematemesis and severe melaena. The range of gastro-intestinal presentations can also include intussusception, intestinal obstruction and colonic pseudo-obstruction.

10.8.7 Genito-urinary

Urological involvement with GTN is relatively rare but renal involvement may cause massive retroperitoneal haemorrhage. Renal metastases may cause abdominal pain, haematuria or oliguria, but are more usually found as incidental mass lesions during radiological staging. Direct pelvic spread to the bladder can occur in both choriocarcinoma and invasive mole, leading to haematuria.

10.8.8 Reproductive system

Several cases of choriocarcinoma presenting during a healthy pregnancy have been reported. Fetal compromise is often found in these cases but with early delivery and effective chemotherapy a positive outcome for mother and baby is possible [100]. The diagnosis of choriocarcinoma can also be made from detecting abnormalities within the placenta. Whilst macroscopically choriocarcinoma in a term placenta may be misinterpreted as a placental infarct, more detailed pathological examination of the placenta yields the diagnosis and approximately 50% of mothers will develop evidence of the disease later [101]. Very rarely choriocarcinoma may spread to the fetus which with early diagnosis and effective treatment usually gives a positive outcome [102].

10.8.9 Cutaneous

Cutaneous metastases are rare in GTN, but have been reported in a small number of cases as part of disseminated disease.

10.9 OTHER SITES OF DISEASE

Choriocarcinoma metastases can occur almost anywhere in the body. Unusual involvement, such as with spread to the bone or breast, can occur and effective treatment can result in cure. GTN has presented as pyrexia of unknown origin and once diagnosed responds well to treatment.

In addition to the cases mentioned above, there are many other unusual situations documented that provide diagnostic challenges. This wide range of seemingly unrelated presentations for GTN can lead to diagnostic challenges and resultant treatment delays. Incorporating a serum hCG assay in the investigation of women with these or other symptoms can result in achieving a lifesaving diagnosis.

A number of cases have reported establishing the diagnosis of choriocarcinoma by the use of simple pregnancy testing kits for hCG assay. However these kits are prone to false negatives, particularly in

patients with high hCG levels and should not be relied upon to exclude a trophoblastic tumour.

10.10 SUMMARY

Gestational trophoblast neoplasia forms a group of rare but almost uniformly curable malignancies. The introduction of routine first trimester ultrasound combined with effective follow up programmes has resulted in near 100% cure rates for patients with molar pregnancies which is generally achieved using treatments of low toxicity.

For the more challenging cases of choriocarcinoma and PSTT/ETT presenting with distant disease but without any gynaecological symptoms or a recent pregnancy, laboratory measurement of the serum hCG level can be life saving as it will allow the diagnosis to be made and effective treatment to be commenced.

The combination of the rarity of the diseases with the high cure rates makes GTN a low priority for medical research or new drug development. To produce the optimal outcome for these patients, optimising molar pregnancy follow up services and the education as to the potential diagnosis of GTN in women with cancer, for clinicians dealing with cancer, are the most important factors in ensuring effective patient care. Like a number of other trophoblast centres around the world, the unit at Charing Cross operates a 24hr a day emergency treatment and advice service and potential new cases or difficult diagnoses can usually be discussed at short notice by phone or email.

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