Chapter 23

Hydatidiform Moles

General Considerations

Understanding early trophoblastic development is essential to the discussion and categorization of trophoblastic lesions. Therefore, a brief review is presented here (see also Chap. 8). After fertilization, the blastocyst differentiates into embryonic and extraembryonic cells, the latter becoming **trophoblast**, and the forerunner of the placenta.

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The trophoblastic cells further differentiate into villous and nonvillous or extravillous trophoblast. **Villous trophoblast** consists of *villous cytotrophoblast and syncytiotrophoblast*. **Cytotrophoblast** is a term also used for the trophoblastic stem cells of the cell columns, the so-called stem trophoblast, but it is thought that once the cells form the inner layer of the chorionic villi they are then differentiated toward villous trophoblast. **Extravillous trophoblast** is composed of the trophoblast of the *chorionic plate, chorion laeve, cell islands, septa, implantation site*, and *basal plate*. Currently, the term "intermediate" trophoblast is commonly used to represent all types of extravillous trophoblast. Unfortunately, however, it has also been used to refer to a type of *villous* trophoblast that is transitional between cytotrophoblast and syncytiotrophoblast or between cytotrophoblast and villous cytotrophoblast. This is incorrect because nonvillous or extravillous trophoblast, or "intermediate trophoblast," by definition **cannot** be villous trophoblast. Therefore, the use of the term "intermediate trophoblast" should be abandoned. Simply stated, *villous and extravillous trophoblast are derived from different pathways of trophoblastic differentiation, and lesions arising from these cells have different morphological features, clinical attributes, and biologic behavior*.

Trophoblastic lesions comprise a complex and challenging group of lesions that are unique in pathology for the following reasons:

- They are composed, partly or exclusively, of genetic maternal derived from another individual (paternally derived genes).
- They are **gestational** and have **nongestational** counterparts that arise from gonadal germ cells rather than a conceptus.
- The nonneoplastic cells have features usually only associated with malignancy:
  - Destructive **stromal invasion** (in the implantation site)
  - Distant **deportation** of cells into the maternal circulation during pregnancy
  - **Cytologic features of malignancy**

Trophoblastic lesions are classified into several groups (Table 23.1). **Hydatidiform moles** are *nonneoplastic lesions derived from villous trophoblast*. They are divided into complete, partial, and invasive types. **Choriocarcinoma**, a malignant tumor of gestational trophoblastic origin, also *derives from villous trophoblast*. The remaining lesions, placental site trophoblastic tumor, exaggerated placental site, and placental site nodule derive from extravillous trophoblast.

Hydatidiform Moles

Pathogenesis

Hydatidiform moles are not neoplasms. They are, however, *associated with an increased risk for the development of* **persistent gestational trophoblastic disease**, specifically **choriocarcinoma**, a highly malignant tumor of trophoblastic origin (see Chap. 24). Traditionally, moles have been subdivided into complete and partial hydatidiform moles. **Complete hydatidiform moles** have a genetic complement that is *androgenetic, i.e., all the genetic material is paternally derived*. In most

instances, they result from *an ovum that has lost its nucleus, an "empty egg," which is then fertilized by a single sperm. Subsequent duplication of the haploid spermatozoal complement* leads to a diploid genotype (Fig. 23.1a). Thus, the majority of complete moles have a 46XX karyotype. A small number of complete moles have a 46XY karyotype. These, along with a minority of 46XX moles, arise from *dispermy, i.e., fertilization of an empty egg by two sperm with fusion of the two male pronuclei* (Fig. 23.1b). These

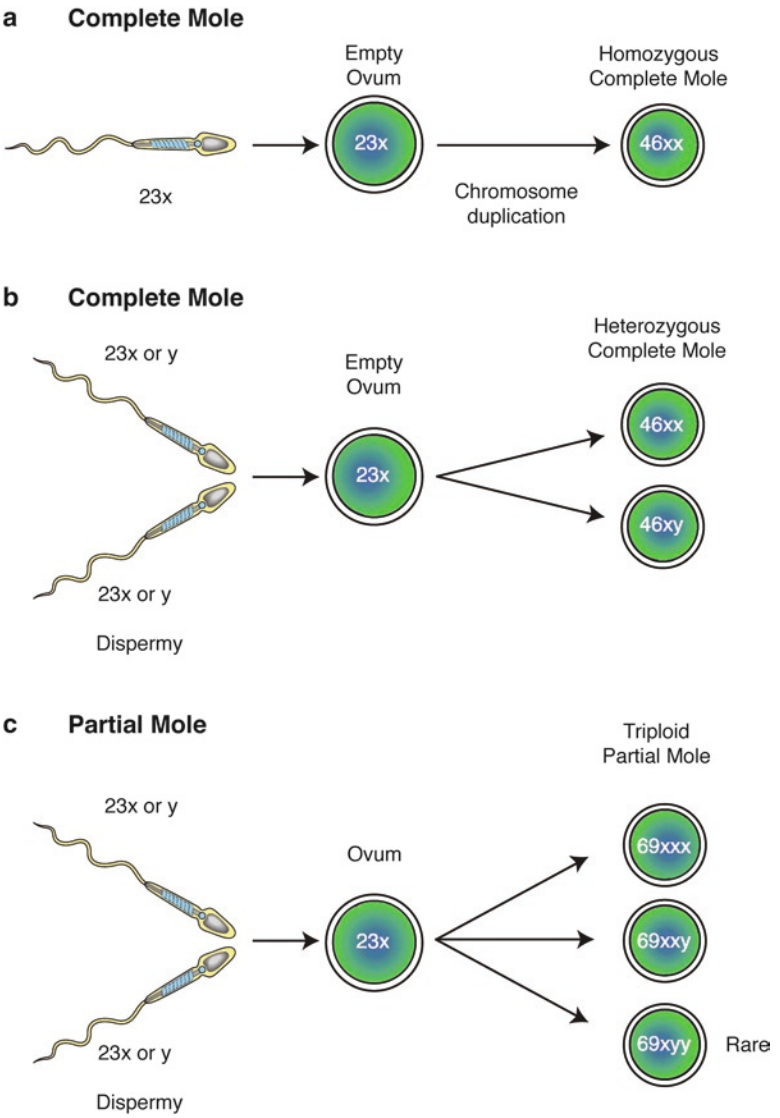

Figure 23.1. Origin of complete and partial hydatidiform moles. (**a**) Complete moles most commonly arise from fertilization of an empty ovum by a single sperm that then undergoes chromosomal duplication. (**b**) Less commonly complete moles arise from dispermy in which two sperm fertilize an empty ovum. (**c**) Partial moles arise from two sperm that fertilize a single ovum.

are sometime referred to as "heterozygous" complete moles. Moles with a 46YY karyotype are not found, and it is assumed that these conceptuses do not further develop. Dispermy represents about 15% of all complete moles. Triploid and tetraploid complete moles occur rarely; these are also derived solely from paternal DNA.

In comparison, **partial hydatidiform moles** are *usually triploid*. They develop from *fertilization of an ovum by two sperm, leading to a paternal to maternal chromosome ratio of 2:1* (Fig. 23.1c). Thus, partial moles generally have a 69XXX or 69 XXY karyotype. Rarely a 69XYY partial mole is identified. Tetraploid partial moles have also been described and have a paternal to maternal chromosome ratio of 3:1. The important differentiating feature between partial and complete moles is that complete moles are "completely" paternal DNA and partial moles have an altered maternal to paternal ratio, always with more paternal than maternal DNA.

Imprinting plays a pivotal role in the development of hydatidiform moles. Studies in mice have shown *that paternally derived genes are important for placental development, while maternal genes have more influence over fetal development*. Therefore, excess paternal genetic material leads to excessive growth of trophoblastic (placental) over fetal tissues, which is the sine qua non for the diagnosis of molar pregnancies. The fetus, if it can even be identified, is usually small, with stunted growth. Complete moles, having *only* paternal DNA, have more extreme trophoblastic proliferation than partial moles, which maintain some maternal DNA, albeit in the minority. On the other hand, *nonmolar triploid abortuses have a 2:1 maternal to paternal chromosome ratio* and derive from nondisjunction of maternal chromosomes. Since there is a maternal excess of genetic material, they do not show the trophoblastic proliferation seen in moles. Furthermore, in contrast to partial moles, the placenta is often quite small and stunted while the fetus is relatively normal in size, even though congenital anomalies are the rule. Maternal triploidy represents only about 10–15% of triploid conceptuses overall.

Since identification of an excess paternal contribution is *essential* in the diagnosis of molar pregnancies, various techniques have been developed to confirm paternal origin. These include **polymerase chain reaction, DNA fingerprinting, restriction fragment length polymorphism (RFLP) assessment,** and use of **short tandem repeat-derived DNA polymorphisms.** In addition, **flow cytometry** readily allows the diagnosis of triploidy although it cannot differentiate between paternal and maternal contributions.

Incidence and Epidemiologic Factors

The incidence of molar pregnancies in the United States is approximately 1 in 1,000 to 1 in 2,000 pregnancies. There are clear ethnic and geographic differences, with complete moles being particularly common in Hawaii, the Philippines, India, and Japan. The frequency is higher toward the beginning and the end of childbearing age, with the highest incidence in women over 45, but moles have been described in

women as young as 12 and as old as 60 years of age. Many other epidemiologic factors have been associated with an increased risk of molar pregnancy. These include race, ethnicity, ABO blood groups, diet, and previous treatment with certain drugs. However, no single, specific etiologic factor has been confirmed. There *is* an increased incidence of moles with a history of a previous molar pregnancy, which may be explained by a *genetic propensity for loss of chromosomal material from ova*. This is supported by reports of women with multiple recurrent moles from different fathers.

Complete Hydatidiform Moles

Pathologic Features

Macroscopically, complete moles have abundant tissue with *grossly identifiable translucent vesicles* that represent enlarged, hydropic villi. The vesicles are classically described as "grape-like" and may measure 2 cm in diameter or more (Figs. 23.2 and 23.3). Most or all of the villi show hydropic swelling, and often the uterine cavity is filled with molar tissue (Fig. 23.3). Procedural manipulation may, at times, result in collapse of some or all of the vesicles. These macroscopically identifiable villi are virtually never seen in hydropic abortuses.

On microscopic examination, the villi are *diffusely hydropic* due to massive fluid accumulation. This occurs primarily in the terminal villi. *Cisterns are present are consist of central acellular spaces within the hydropic villi* which form when the connective tissue of the villi dissociates (Fig. 23.4). *Trophoblastic hyperplasia is universally present and is*

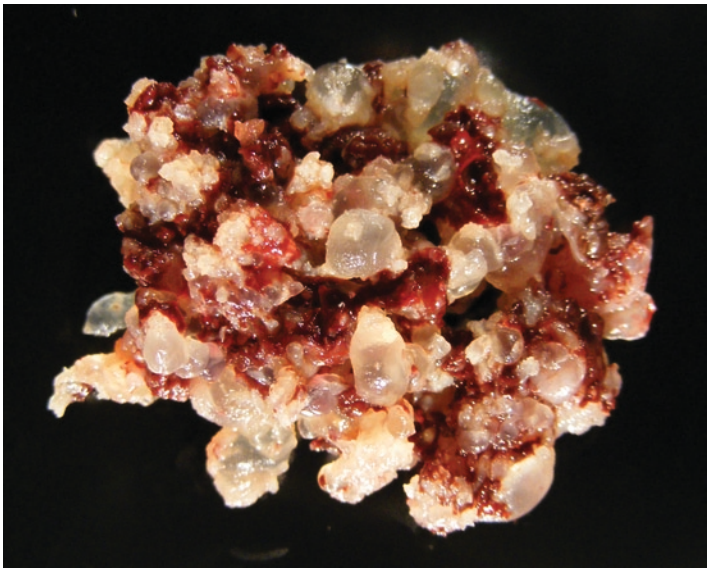

Figure 23.2. Complete hydatidiform mole. Note bulbous swelling of terminal villi.

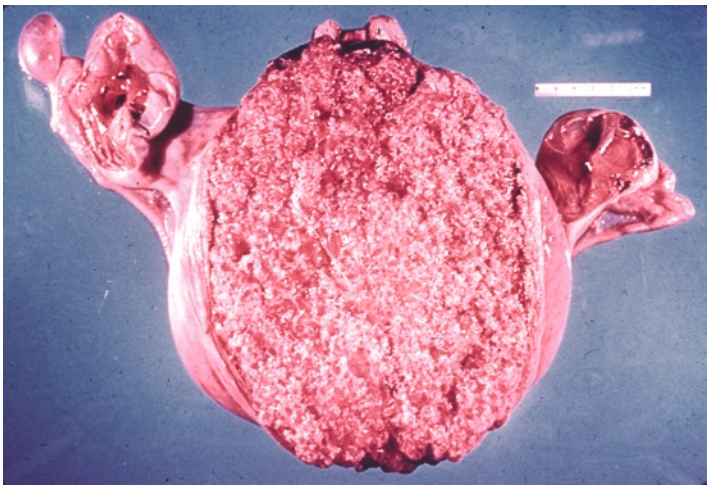

Figure 23.3. Hydatidiform mole in situ. Note the distention of the uterus and the bilateral theca lutein cysts of the ovaries. The vesicular nature of the molar villi is apparent grossly.

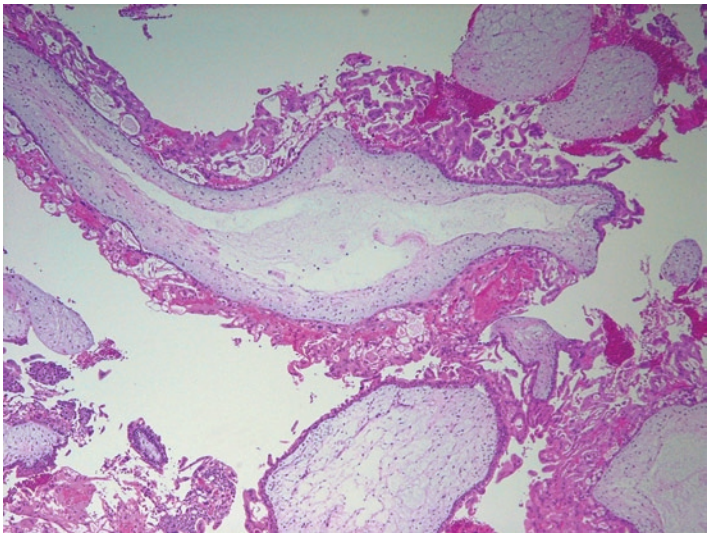

Figure 23.4. Complete mole demonstrating a large hydropic villus with cistern formation, an acellular region surrounded by loose stroma that is usually devoid of blood vessels. There is marked circumferential trophoblastic proliferation as well. H&E ×120.

a requirement for diagnosis. Proliferation varies from villus to villus, but is usually *circumferential around the entire villous perimeter and involves both cytotrophoblast and syncytiotrophoblast* (Fig. 23.5). This feature is key in the differential diagnosis with hydropic abortus (see below). *Trophoblastic atypia* is present, manifesting as nuclear pleomorphism and cytoplasmic vacuolization in syncytiotrophoblast. Mitotic figures

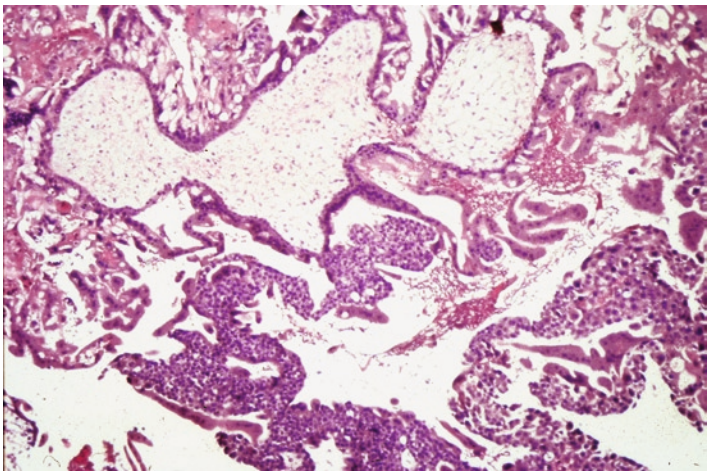

Figure 23.5. Marked circumferential trophoblastic proliferation in a complete mole. H&E ×100.

may be present, even in syncytiotrophoblast. Focally, degenerative change of the trophoblast may be present, the villous surface becoming enmeshed in fibrinoid. Many Hofbauer cells may be identified in the villous stroma. *Intervillous thrombi* are also common due to the aberrant intervillous circulation. The implantation site frequently shows an exuberant proliferation of implantation trophoblast. This exaggerated physiologic response, called an **exaggerated placental site** (see Chap. 25), is seen commonly enough in complete moles for its presence to be helpful in the differential diagnosis.

There have been many attempts at grading molar pregnancies in an effort to determine which moles are most likely to develop choriocarcinoma. Classifications based on trophoblastic atypia, proliferation, and so on have been proposed. However, grading has not been found to be of use so far in predicting behavior. The most important criterion in predicting prognosis is differentiation between partial and complete moles.

Embryonic and Fetal Tissue in Complete Hydatidiform Moles

Traditional teaching has been that complete moles are never associated with an embryo. Even though in the majority of cases embryos are absent, fetal blood vessels and fetal nucleated red blood cells may be encountered in many complete moles, and in rare cases an embryo may be present. This is logical since the stroma of the villi in complete moles, as with other conceptuses, is derived from **embryonic** mesenchyme. Thus, an embryo must have been present, at least initially. There are several reasons that embryos are rarely seen in complete moles. First, early embryonic death is common in complete moles. Since most moles are homozygous for all their genes, and most individuals carry several recessive lethal genes, it makes sense that some of these lethal genes would lead to early death. Second, small, stunted embryos may not be

identified the massive villous tissue and so they may be missed. Third, it is clear from studies of early abortion that the incidence of complete moles is much lower than would be expected. This is probably due to the subtlety of diagnostic features seen in early moles (see below). Therefore, early on when an embryo might still be visible, the diagnosis of a mole is less likely to be made. A documented case is shown in Fig. 23.6 in which a complete mole was identified with a tiny embryo, and the patient later developed disseminated choriocarcinoma. The conclusion is that although embryonic or fetal tissue is rare in complete moles, it is does occur. Therefore, the presence of these elements **does not rule out a complete mole**.

Clinical Features and Implications

Patients with complete moles usually present between the 11 and 25th week of pregnancy with a markedly elevated serum β-human chorionic gonadotropin (β-hCG). The levels are much higher than expected for the gestational age, in some cases reaching over 1,000,000 mI/mL. There may be associated *vaginal bleeding or an enlarged and distended uterus* ("size greater than dates"). Sonographically, there is *usually* no embryo or demonstrable heart activity and the presence of multiple echogenic signals described as a *speckled or snowstorm.* Sonographic examination used in conjunction with serum β-hCG levels gives a diagnostic accuracy reaching 90%. Complete moles, in comparison to partial moles, have higher levels of serum β-hCG, present more often in the first trimester and more often have increased uterine size for gestational age, and occur more commonly in women over the age of 40.

Complete moles have been associated with various clinical conditions in the mother, some of which are attributable to the elevated

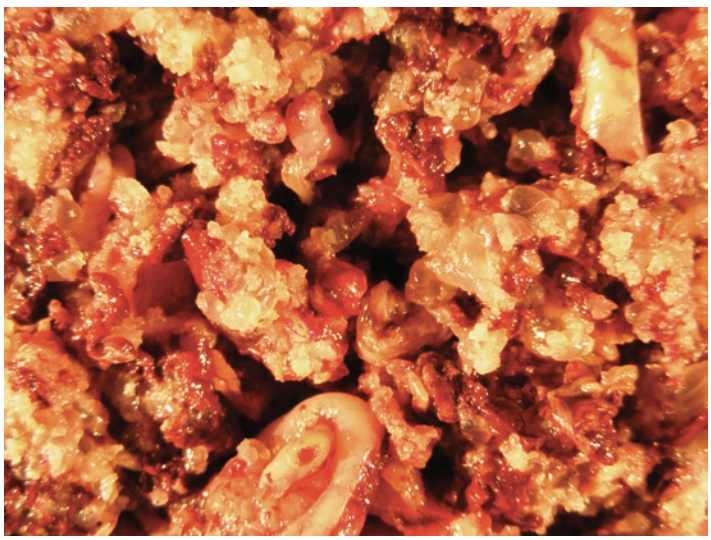

Figure 23.6. Photograph of a partial hydatidiform mole. Note the admixture of swollen, cystic villi with more normal appearing villous tissue.

hCG levels. **Multiple theca lutein cysts** or **hyperreactio luteinalis** in the ovary are present in 25–60% of patients with complete moles. These "functional" ovarian cysts may grow up to 35 cm in diameter, causing significant ovarian enlargement (Fig. 23.3). The cysts are usually multiple, with thin walls and filled with clear or hemorrhagic fluid. Microscopically, *multiple follicle cysts are lined by luteinized theca cells*. Granulosa cells may also show luteinization. The *ovarian stroma is usually edematous and contains scattered luteinized cells as well* (Fig. 23.7). The cysts regress spontaneously after termination of the pregnancy. Moles are also associated with *preeclampsia, eclampsia, pregnancy-induced hypertension, hyperemesis gravidarum, hyperthyroidism, and pulmonary edema* – conditions that spontaneously resolve after evacuation. At least some of these conditions are attributable to the elevated β-hCG levels.

Development of **persistent gestational trophoblastic disease** occurs in approximately 15–20% of women with a diagnosis of complete mole. Most develop persistent or invasive moles (see below), and 1–2% develop **choriocarcinoma**. Early and complete evacuation of the mole is the first line of therapy. Patients with a complete mole are usually followed with serial serum β-hCG levels and concurrent contraception for 6 months to a year or until they fall within the normal range. The reason for contraception is that rises in the titers caused by pregnancy may be confused with the development of persistent disease. If the β-hCG titers do not normalize of if they rise, persistent trophoblastic disease is usually diagnosed without the benefit of a tissue diagnosis and chemotherapy is given without pathologic confirmation.

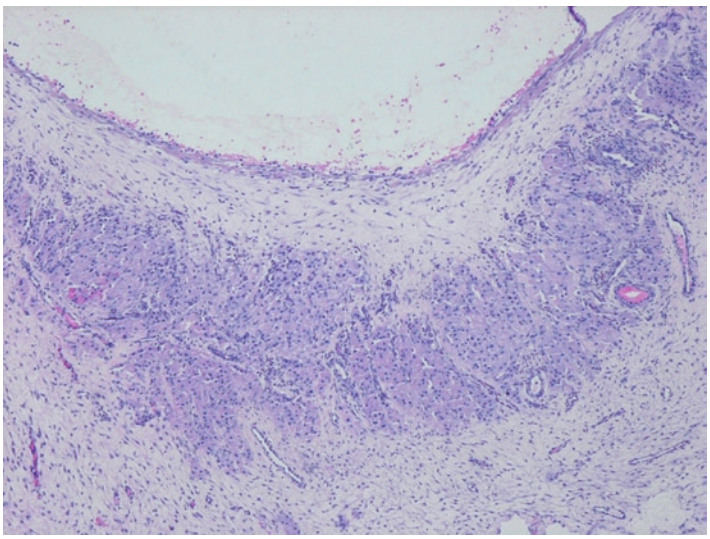

Figure 23.7. Hyperreactio luteinalis of the ovary in a patient with a complete mole. The ovaries were markedly enlarged by numerous luteinized follicle cysts and many luteinized cells in the stroma. A portion of a follicle cyst wall is seen here. H&E ×40.

Early Complete Hydatidiform Moles

With the advent of sonography and the early diagnosis and evacuation of moles, specimens at younger gestational ages are being sent for pathologic evaluation with increasing frequency. **Early complete hydatidiform moles** represent a greater challenge in diagnosis, as *the pathologic features are more subtle and less well developed*. They are thus more difficult to differentiate from partial moles and hydropic abortuses. It is likely that many of these have gone unrecognized in the past. Younger moles tend to *have smaller, less edematous villi, which are more bulbous, club shaped, or cauliflower shaped* than older moles (Fig. 23.8). The *villous stroma often shows a light blue discoloration or myxoid like change. Increased stromal debris and apoptosis has also been described. Cisterns are poorly formed, and trophoblastic proliferation is not as pronounced* as in the more "mature" mole. Capillary remnants and fetal blood vessels are also more easily found.

Biparental Complete Hydatidiform Moles

Recently, families have been described in which recurrent moles are common. Further study revealed that unlike the usual complete moles, which are completely androgenic, these were **biparental.** This phenomenon is due to an abnormal autosomal recessive gene affecting imprinting. Although the underlying mutation has not been fully described, linkage studies have shown that the gene, which lies on the long arm of chromosome 19, allows greater expression of paternal genes leading to, morphologically, a complete mole. Further study is ongoing.

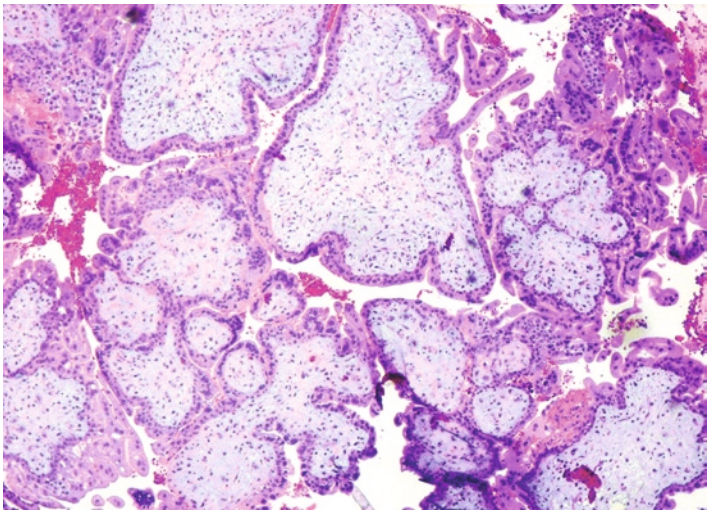

Figure 23.8. Early complete mole with club-like villi, moderate edema, and moderate trophoblastic proliferation. The stroma has a myxoid appearance. H&E ×100.

Ectopic Molar Pregnancy

Partial and complete moles may arise in the fallopian tube, ovary, or other ectopic sites. Moles arising in the fallopian tube are likely to result in *tubal rupture* if not treated promptly. The practice of administering methotrexate to patients with early ectopic pregnancies has interesting implications in the development and behavior of ectopic moles that have yet to be studied. *Overall, moles arising in ectopic locations have similar recurrence rates and risk of development of persistent gestational trophoblastic disease as their intrauterine counterparts.*

Partial Hydatidiform Mole

Pathologic Features

Partial hydatidiform moles are *most commonly triploid with two sets of paternal genes and one set of maternal genes*. The gross and microscopic features are *similar to those of the complete mole but the features are less striking*. The partial mole is less voluminous and is composed of *normal-appearing villous tissue intermixed with larger, distended villi or vesicles*. An associated embryo or fetal tissue is identified more commonly than in complete moles. Microscopically, partial moles have an *admixture of relatively normal immature villi and distended hydropic villi*. The villous outlines are scalloped and the villi are irregularly edematous. *Although cisterns are present, they tend to be scarce*. *Trophoblastic pseudoinclusions*, which are due to tangential sectioning of the irregular villous outlines, are easily identified (Fig. 23.9). *Focal villous fibrosis may be present*. As with complete moles, trophoblastic proliferation is required for diagnosis, but *the degree of trophoblastic proliferation and atypia is less* in partial moles (Fig. 23.10). The trophoblastic proliferation has been described as being more lace-like than that seen in complete

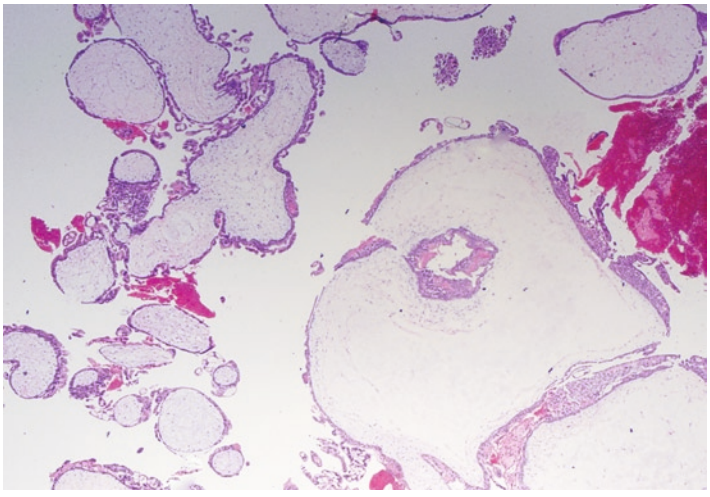

Figure 23.9. Partial hydatidiform mole showing trophoblastic "pseudoinclusions" and irregular invaginations of this villus. H&E ×200.

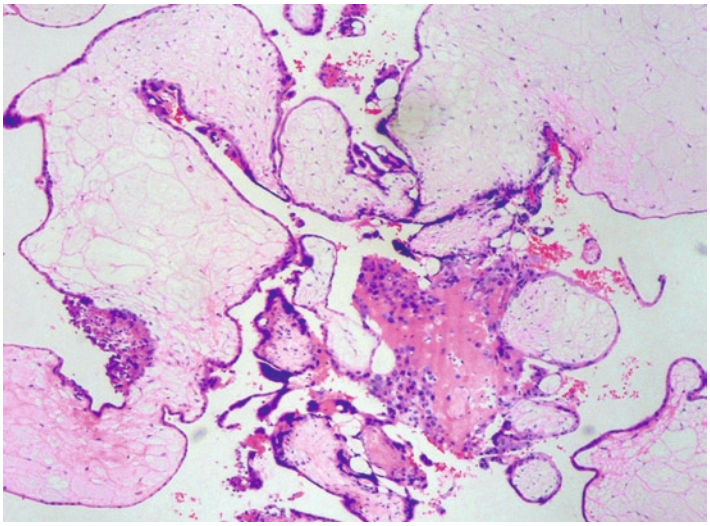

Figure 23.10. Partial mole demonstrating only modest trophoblastic proliferation. Two populations of villi, typical of partial moles, are seen here. H&E ×40.

moles. *Villous capillaries can usually be found*. Many features, such as trophoblastic pseudoinclusions, are occasionally seen in the chromosomally abnormal abortus.

Four major features have been suggested for partial moles, and if the following diagnostic criteria are not met, consideration should be given to ancillary studies:

- An admixture of two populations of villi (normal and hydropic)
- Enlarged villi with "cavitation" or cisterns
- Irregular villi with scalloped borders and trophoblastic pseudoinclusions
- Focal, mild trophoblastic hyperplasia

Clinical Features and Implications

Patients with partial moles usually present between the 18 and 20th week of gestation *with vaginal bleeding suggestive of a missed abortion*, "size less than dates," and *moderate elevations in serum β-hCG*. They also may show findings on sonographic examination similar to those seen for complete moles. Partial moles are associated with **persistent gestational trophoblastic disease** in less than 5% of cases, usually in the form of persistent molar tissue. These patients are generally treated with chemotherapy. There are only a few well-documented cases of patients with partial moles who subsequently developed malignant disease or choriocarcinoma. After a partial mole, patients are followed with serial β-hCG until it reaches normal levels.

Differential Diagnosis

There is much overlap in the histologic appearance of partial and complete moles, and even experienced pathologists may have difficulty

in differentiating between them. Problems usually occur between complete and partial moles, between partial moles and hydropic abortuses, and in diagnosing early moles. These differential diagnoses are discussed below and summarized in Table 23.2.

Hydropic Abortus Versus Partial Mole

Hydropic abortuses tend to have *less tissue than partial moles and do not show grossly identifiable vesicles*. The latter are not present in all partial moles, but are usually present admixed with more normal-appearing tissue. Microscopically, hydropic abortuses and partial moles both show moderate *hydropic change in a portion of chorionic villi*. The swollen villi of the abortus will be covered by thinned and *attenuated trophoblast* (Fig. 23.11) and this occurs when the villi swell after embryonic death and the trophoblast is literally stretched over the circumference of the villus. Proliferation of trophoblast may be seen in early abortuses but is clearly *polar*, growing from one aspect of the villus (Fig. 23.11). These are usually anchoring villi and represent an area of growth in the early placenta (see Chap. 8). In partial moles, there is *proliferation of trophoblast, which although focal, is circumferential* around the villous perimeter (Fig. 23.10). The abortus will show a spectrum of villi, from small normal villi all the way to large hydropic villi, while the *partial mole shows two distinct populations of villi*.

Partial Mole Versus Complete Mole

Complete moles tend to have more *voluminous tissue* than partial moles, with *easily identifiable vesicles* on gross examination (Fig. 23.2). Microscopically, the complete mole shows significantly *more trophoblastic proliferation that involves all the villous tissue* rather than *the focal proliferation* in partial moles. Complete moles have more *nuclear pleomorphism and anaplasia as well*. The proliferation in partial moles

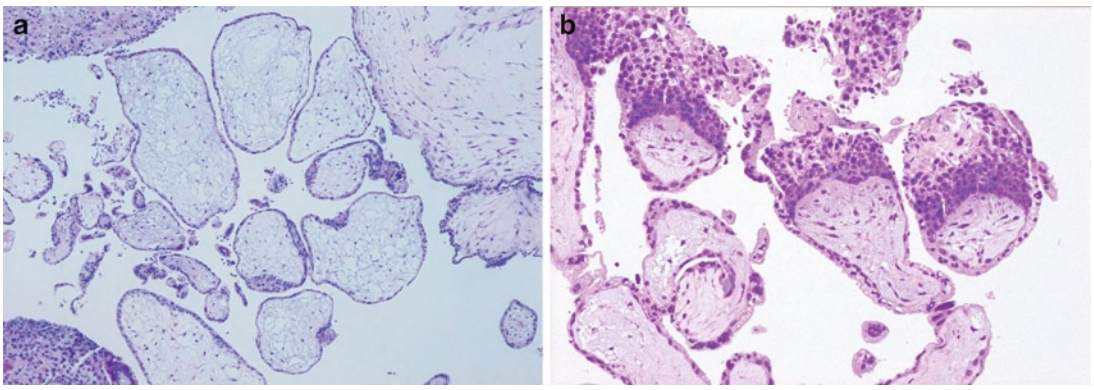

Figure 23.11. (**a**) Hydropic abortus with marked swelling of the villi. In contrast to a molar pregnancy, the trophoblastic cover is thin and attenuated. H&E ×40. (**b**) "Polar" proliferation of trophoblast, rather than circumferential proliferation may be present and is a feature that distinguishes hydropic abortuses from partial moles. H&E ×100.

is *clubbed or lacy* (Fig. 23.12) rather than the more solid proliferations seen in complete moles. Partial moles also have *two distinct populations of villi*: (1) a population of normal villi; and (2) villi with *edema, irregular villous contours, invaginations, and trophoblastic pseudoinclusions* (Fig. 23.9). The latter are not generally seen in complete moles. Finally, although embryonic or fetal tissue, blood vessels, and nucleated red blood cells may be seen in both complete and partial moles, they are much more common in partial moles.

Early Mole Versus Hydropic Abortus Versus Partial Mole

In early moles (particularly those less than 10 weeks), the histologic features are more subtle and therefore may be confused with hydropic abortuses or a partial mole. Hydropic abortuses have a complete range of villi, from large hydropic villi to small, normal villi. The hydropic villi may have *cisterns*, but these are covered by *thin, attenuated trophoblast*. On the other hand, early moles have a uniform population of villi with *bulbous, cauliflower-like or clubbed villi, myxoid-like stroma, and poorly formed cisterns*. They may often be smaller than those seen in partial moles. Blood vessels are more common, and the villous stroma is more cellular than in older moles and the villi have an appearance reminiscent of mesenchymal villi (see Chap. 7). The most important feature in differentiating an abortus from an early mole is that the latter shows *trophoblastic proliferation*, albeit less than an older mole.

Partial Mole Versus Twin Pregnancy with Complete Mole

Rarely, in twin pregnancy, one of the twins is a mole and the other normal. The distinction from a partial mole may be quite difficult, particularly if the tissue is disrupted. Both will have two populations of villi, some hydropic and some normal (Fig. 23.13), and both may

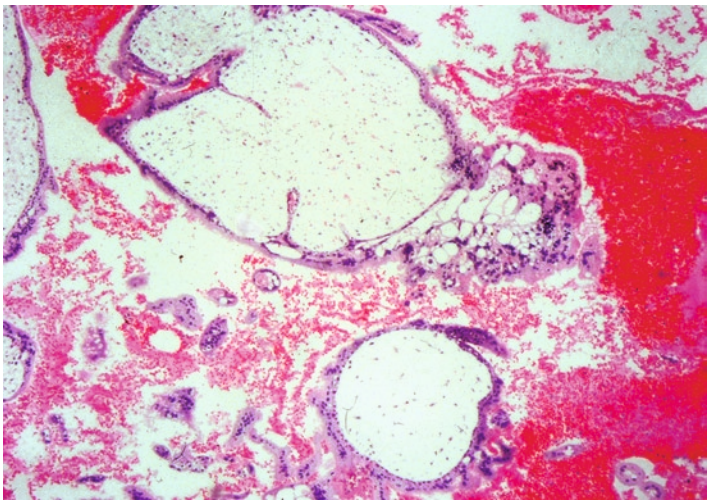

Figure 23.12. Partial mole showing irregular proliferation of trophoblast with lacy extensions. H&E ×40.

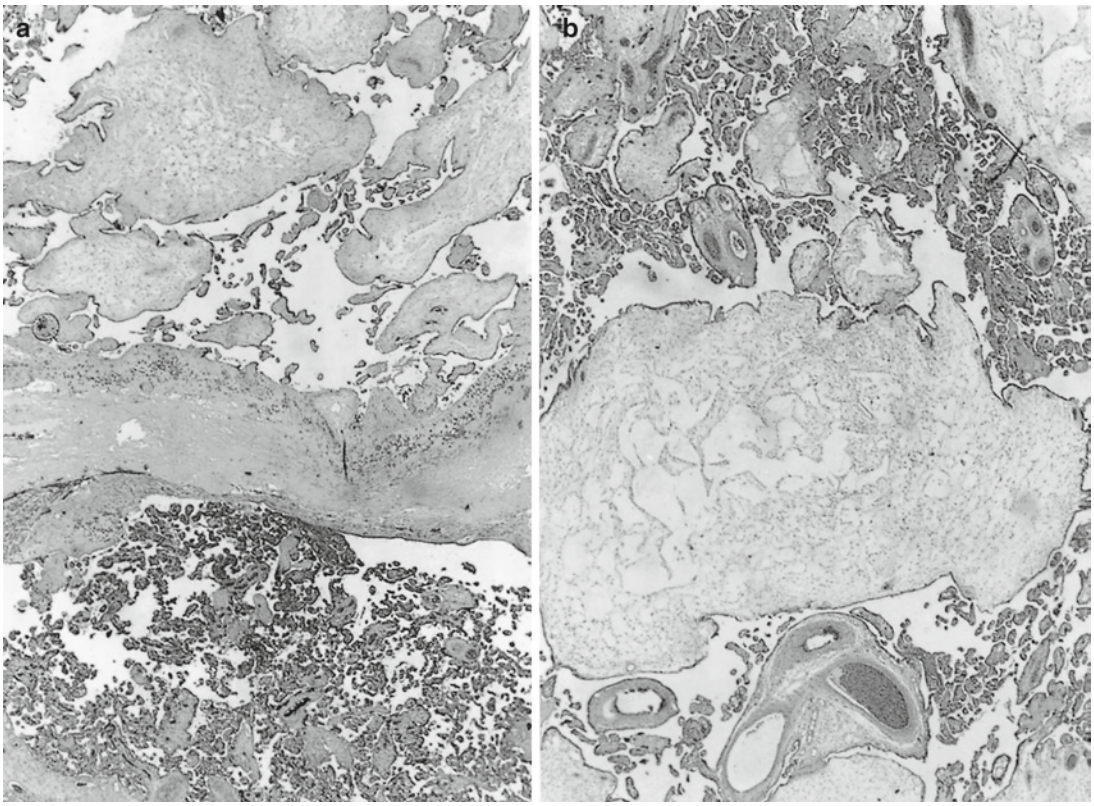

Figure 23.13. (**a**) Sharp division of molar villi (*top*) and normal villi (*bottom*) in twin gestation. H&E ×16. (**b**) Focal admixture of molar and normal villi. H&E ×16.

have fetal tissue. *The most important feature in differentiation is the presence of marked trophoblastic proliferation and atypia* in the complete mole. Of course, twin pregnancies occur in which a partial mole is combined with a normal pregnancy. Accurate diagnosis may be impossible unless the placentas may be grossly differentiated from each other.

Ancillary Testing

Since the histologic features are not completely reliable, in certain cases accurate categorization may be improved by performing ploidy analysis. Ploidy may be helpful in the following situations:

- Partial versus complete mole
  - Diploid → complete mole
  - Triploid → most likely a partial mole
- Partial mole versus hydropic abortus
  - Diploid → hydropic abortus
  - Triploid → most likely a partial mole

Caution is advised, as these rules are not strict. Particularly, *rare* complete moles are triploid or tetraploid. In addition, nonmolar triploidy may occur with a maternal excess of DNA, or **maternal triploidy.** These do not show the trophoblastic proliferation typical of moles and so are not usually confused histologically with moles.

Recently, *a maternally transcribed but paternally imprinted gene* has been described that is a cyclin-dependent kinase (CDK) inhibitor $p57^{KIP2}$ protein, referred to as **p57KIP2** or **p57.** This protein is strongly expressed in maternal tissues such as decidua and is expressed in cytotrophoblast and villous stromal cells if a maternal component is present, such as in partial moles and hydropic abortuses. However, it is **not** expressed in androgenetic complete moles, or in the rare biparental complete moles. Therefore, since this antibody is commercially available, immunohistochemistry for p57 may be helpful in the differential diagnosis of difficult cases. One must be careful, however, as rarely a biparental complete mole may occur. In addition, recently a case of a complete mole with retained maternal chromosomes resulting in positivity for p57 has been reported. A summary of the findings of flow cytometry and p57 is shown in Table 23.3. If flow cytometry or other methods are not available or the diagnosis is still unclear, a report reflecting uncertainty may be prudent and the patient may then be followed with β-hCG monitoring.

Suggestions for Examination and Report
(Hydatidiform moles)

Gross Examination: The presence of enlarged villi or vesicles should be noted and is most consistent with a molar pregnancy. If the clinical history suggests molar pregnancy (elevated hCG or typical sonography), and vesicles are not visible grossly, additional sections should be submitted. It is recommended that additional sections of moles be submitted in any cases so that there is sufficient tissue for histologic diagnosis. Identification of fetal or embryonic tissue should also be documented.

Comment: If the diagnosis is equivocal, additional sections can be submitted initially. If the issue is not then clarified, additional testing such as flow cytometry or p57 immunostaining should be employed. If the diagnosis is still in question or if ancillary testing is not available, and the differential is between complete and partial mole, the diagnosis of a **"hydatidiform mole"** can be made with a comment that differentiation between partial and complete is not possible. A suggestion should also be made for serial β-hCG testing, at least until the levels normalize. If the differential is between a hydropic abortus and a partial mole and cannot be resolved, a descriptive diagnosis should be rendered such as **"chorionic villi with hydropic change and trophoblastic proliferation, see comment."** The comment should then address the differential, again with the suggestion for serial β-hCG measurements.

Invasive Hydatidiform Mole

Pathogenesis

Invasive mole is a rare entity composed of *trophoblastic cells and molar villi, which invade the uterus and have the potential for invasion of adjacent structures*. Invasive moles usually develop subsequent to a molar pregnancy and are most often diagnosed by ultrasonography or other imaging technique. The patients may present with elevated serum β-hCG during follow-up after a molar pregnancy and often have vaginal bleeding. Since invasive moles are characterized by molar villi invading through the myometrium, they may be viewed as a *placenta accreta/increta of a molar pregnancy* (see Chap. 12). Their biologic behavior is very similar to choriocarcinoma.

Pathologic Features

Microscopically, *molar villi are admixed with proliferating cytotrophoblast and syncytiotrophoblast*. The villi invade the myometrium without intervening decidual tissue (Figs. 23.14 and 23.15). *Deep myometrial invasion is typical and uterine perforation is relatively common*. Invasive moles are often associated with abundant hemorrhage and necrosis, similar to that seen in choriocarcinoma. Differentiation between an invasive mole and choriocarcinoma is straightforward as, by definition, molar villi are present in invasive moles and not in choriocarcinoma.

Clinical Features and Implications

Invasive moles usually occur after a previously diagnosed molar pregnancy, and most commonly a rise in the serum β-hCG heralds the onset. Their behavior is similar to choriocarcinoma and usually requires similar therapy with chemotherapeutic agents, but hysterectomies are more commonly done with invasive moles. They may develop metastases, usually to the lungs, and late metastases have been reported. Prognosis is based on the nature of the mole and the efficacy of its initial removal. Rare cases of spontaneous regression have been described.

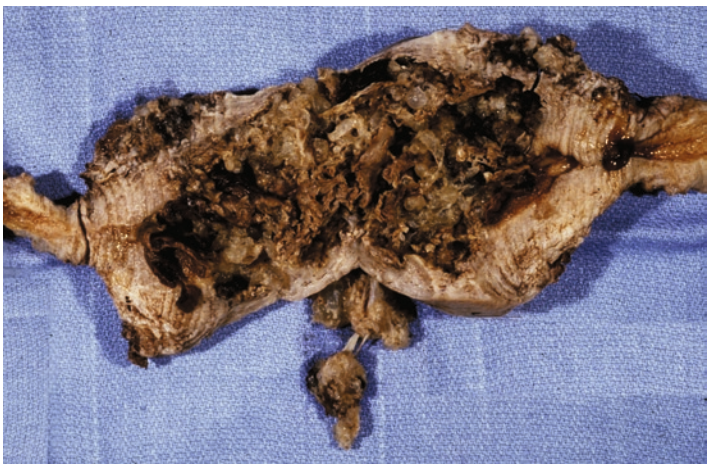

Figure 23.14. Hysterectomy specimen with a large, invasive, hemorrhagic lesion containing molar tissue.

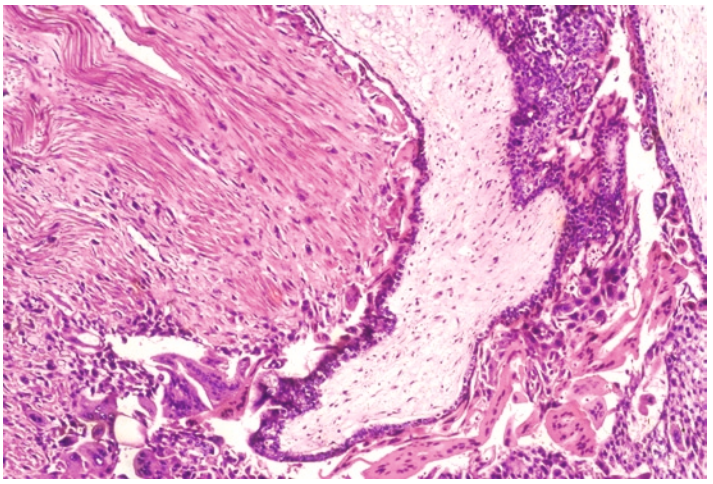

Figure 23.15. Invasive mole showing a molar villus invading the myometrium. Note the trophoblastic proliferation at the right. H&E ×200.

Suggestions for Examination and Report
(Invasive hydatidiform mole)

Gross Examination: When an invasive mole is suspected, generous sampling of the endomyometrium is advised as well as any grossly identifiable molar villi.

Comment: If an invasive mole is diagnosed, a comment on the extent of involvement is suggested.

Table 23.1. World Health Organization classification of gestational trophoblastic disease.

Hydatidiform mole
Complete mole
Partial mole
Invasive mole
Metastatic mole
Trophoblastic neoplasms
Choriocarcinoma
Placental site trophoblastic tumor
Epithelioid trophoblastic tumor
Nonneoplastic, nonmolar trophoblastic lesions
Placental site nodule and plaque
Exaggerated placental site

From Tavassoli FA, Devilee P. World Health Organization classification of tumours: Pathology and Genetics. Tumours of the Breast and Female Genital Organs. Lyon, France: IARC Press, 2003

Table 23.2. Differential diagnosis of complete and partial hydatidiform moles.

Characteristic	Hydropic abortus	Complete mole	Early complete mole	Partial mole
Ploidy[a]	Diploid	Diploid	Diploid	Triploid
Paternal/maternal chromosome ratio[a]	1:1	2:0	2:0	2:1
Embryo/fetus	May be present	Rarely present	Rarely present	May be present
Clinical presentation	Missed abortion	Size > dates	± Missed abortion	Size < dates
Serum β-hCG	Normal or low	Markedly elevated	Moderately to markedly elevated	Moderately elevated
Histology				
Villous enlargement	Moderate	Marked	Mild to moderate	Moderate with admixture of normal villi
Villous population	Range of villi from small to hydropic	Relatively uniform population of large hydropic villi	Relatively uniform population of mildly enlarged villi	Two populations of villi, one normal and one moderately hydropic
Villous shape	Round	Round	Clubbed or bulbous	Scalloped with trophoblastic pseudoinclusions
Cisterns	Usually absent	Common	Rare	Rare
Trophoblastic proliferation	None	Marked circumferential	Moderate circumferential	Mild to moderate and focal
Trophoblastic atypia	None	Common	Common	Minimal
Fetal blood vessels/nucleated red blood cells	Usually absent	Rare	May be present	Common
Persistent gestational trophoblastic disease	No	Up to 20% May develop choriocarcinoma	Up to 20% May develop choriocarcinoma	Less than 5%, usually not requiring chemotherapy

[a]Most common presentation, but variations may occur. See text for more information

Table 23.3. Differential diagnosis: ancillary testing.

	Ploidy[a]	p57
Hydropic abortus	Diploid	+
Partial mole	Triploid	+
Complete mole	Diploid	–

[a]Ploidy is indicated for the majority of cases as occasionally maternal triploidy or triploid complete moles may occur

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