Molar and Trophoblastic Disease

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9.1 Historical Overview

Gestational trophoblastic disease (GTD) has been known for over 2400 years and, in the last century, Dr. Ober was one of the first to compose a review of GTD history [1]. Hippocrates (460–370 AD) first described the hydatidiform mole as the "dropsy of the uterus." In 600 AD, Aetius of Armida (502–575 AD) described a uterus "filled with bladder-like objects," probably referring to a molar tissue. Velpeau and Boivin recognized hydatids as cystic dilations of chorionic villi in 1827. Marchand, in 1895, proved these tumors to be the sequelae of pregnancy, abortion, or hydatidiform mole and described the proliferation of the syncytium and cytotrophoblast [2]. Finally, Fels, Ernhart, Reossler, and Zondek proved the presence of high levels of gonadotropic hormone in the urine of patients with GTD [3].

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9.2 Definition and Synonyms of Gestational Trophoblastic Disease

GTD is a spectrum of tumors differently aggressive and a high potential for metastasis. Its pathogenesis is unique because the maternal tumor arises from the gestational tissue [4]. GTD refers to both the benign and malignant entities.

One of the most important features of the trophoblast is its capacity of invasion. Luckily, in a healthy trophoblast, the malignant-like behavior is strictly controlled. The trophoblast of the human placenta differentiates into the villous and extravillous type during early placentation. The extravillous trophoblast in early pregnancies starts invading the maternal uterus to regulate adequate blood flow and nutrient supply to the growing fetus. The villous trophoblast provides the epithelial cover of the placental villous trees that are in direct contact with maternal blood, while the extravillous trophoblast invades maternal uterine tissues, thus directly contacting maternal stromal and immune cells. A unique set of events includes the plugging and remodeling of the maternal vessels. Inadequate remodeling of the spiral arteries can seriously complicate a pregnancy, threatening the well-being of both the mother and the developing fetus. The trophoblast can be detected by PCR in maternal circulation [5]. However, when the regulatory mechanisms fail, it can lead to different, highly invasive, metastatic, and very vascular entities.

The term "GTD" comprises a range of pregnancy-related disorders and refers to the group of tumors differentiated by abnormal trophoblast proliferation.

These are complete or partial hydatidiform moles, which are noninvasive and invasive moles, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor, which are invasive and defined as gestational trophoblastic neoplasia (GTN).

The complete hydatidiform mole (CHM), partial hydatidiform mole (PHM), and invasive moles (IM) are characterized by the presence of villi and are known as hydatidiform moles (HM). HM is edematous immature

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_9

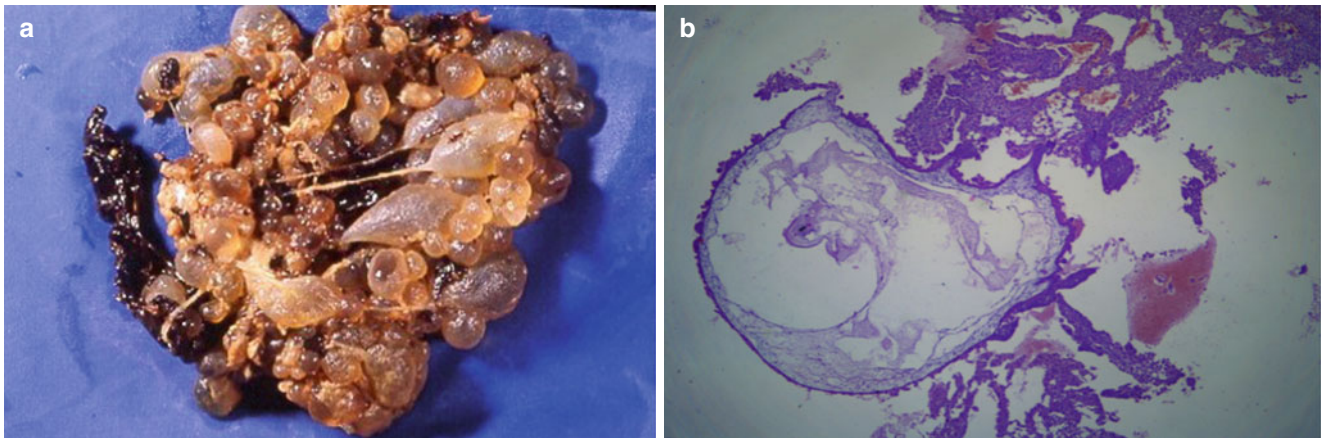

Fig. 9.1 (**a**) Macroscopic view of complete hydatidiform mole. The absence of an amnio-chorionic sac is evident. The villi are of giant size and show a form similar to a bunch of hydropic grapes. (**b**) Chorionic villi of complete moles exhibit hydropic swelling (Courtesy of Dr. Jasmina Atanackovic and Dr. Svetlana Milenkovic)

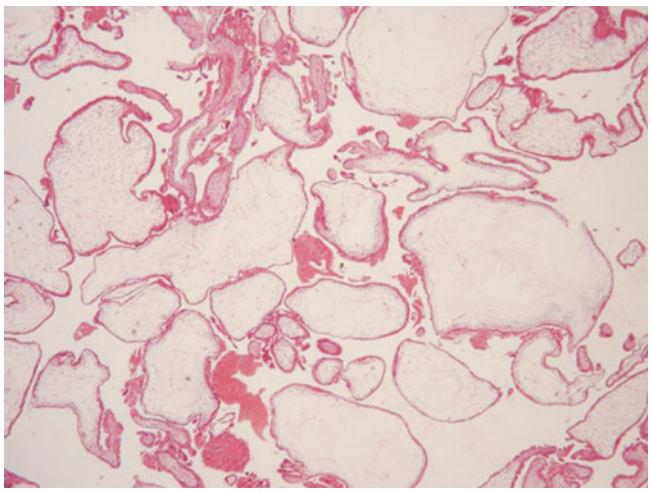

Fig. 9.2 General histological view of a complete hydatidiform mole. All villi are of large size. The stroma lacks vessels and contains a large amount of water

placenta [6]. By contrast, the lack of villi is a characteristic of choriocarcinoma (CC), placental site trophoblastic tumor (PSTT) (Figs. 9.1a, b and 9.2), and epithelioid trophoblastic tumor (ETT).

GTN develops for weeks or years following pregnancies or hydatidiform moles. Other terms used instead of GTN are persistent gestational trophoblastic disease and malignant gestational trophoblastic disease. The current WHO classification of GTD is as follows [7]:

1. Hydatidiform moles (HM)
   (a) Complete hydatidiform mole (CHM)
   (b) Partial hydatidiform mole (PHM)
2. Invasive hydatidiform mole
3. Gestational choriocarcinoma (CC)
4. Placental site trophoblastic tumor (PSTT)
5. Epithelioid trophoblastic tumor (ETT)
6. Tumor-like conditions
   (a) Exaggerated placental site reaction (EPS)
   (b) Placental site nodule (PSN)
7. Unclassified trophoblastic lesions

9.2.1 Epidemiology of Gestational Trophoblastic Disease

The rarity of GTD, inconsistencies in entity definitions, and lack of centralized databases are limited factors for accurate estimation of incidence. Still, it is clear that there is an ethnic predisposition to GTD. The highest incidence of the HM is among the African-Americans, American Indians, Eskimos, Hispanics and Asian populations [8]. The HM occurs with an incidence rate ranging from 2/1000 pregnancies in Japan and Southeast Asia [8] to 12/1000 pregnancies in Indonesia, India, and Turkey [9–11]. The incidence rates in Europe and America are approximately 0.57–1.1/1000 pregnancies [8]. CC affects 1 in 40,000 pregnancies in Europe and North America versus 9.2 in 40,000 pregnancies in Southeast Asia and Japan [3]. The incidence rate of CC is 1 in 50,000 deliveries in the UK in 2010, and PSTT accounted for about 0.2 % of the cases of GTD [3]. Worldwide, the incidence rates of both HM and CC have declined over the past decades [8].

There is substantial evidence showing an increased incidence of HM at the extremes of reproductive life. An increased risk of molar pregnancy is seen in the very young (<16 years), but is most associated with advanced maternal age (>45 years) [3].

In a study from Alaska [12], where the natives consume a high-protein diet consisting of fish, there is a higher incidence of HM compared to the Caucasian community. In another study from Mexico [13], the food histories of women

with HM and a control group of pregnant women were compared. No difference was detected in the intake of proteins, carbohydrates, and fats, excepting an inverse relationship between carotene and animal fat dietary intake [14, 15].

Women with a previous HM seem to be at a higher risk of having it again. The relative risk seems to be higher than that of the general population; however, it is even greater if a woman has had more than one mole [16]. The risk seems to decrease if there is one or more normal pregnancies following the HM. A recent study of subsequent pregnancies in 16,000 women confirms an increased recurrence risk of 1 % for a second molar pregnancy. This study has also revealed that this risk is associated with CHM rather than PHM [17].

In the last century, it has been recognized that among women with recurrent HM there is a number of women with familial recurrent hydatidiform mole (FRHM) – a rare autosomal recessive condition in which affected women have a predisposition to pregnancy losses, most of which are CM [18]. To date, mutations in two genes, NLRP7 (NLR family, pyrin domain containing seven) [19] and KHDC3L (KH domain containing 3-like, subcortical maternal complex member) [20], have been shown to be responsible for 75 and 5 % of the cases of FRHM, respectively. The data further indicate that the risk of a third HM is associated almost exclusively with CM, and this has led to the estimate that 1 in 640 women registered with a CM should have the FRHM [17].

There is little doubt that a previous HM is a predisposition for developing GTN. It is estimated that a malignant change will affect around 14 % CM and considerably higher than the 1 % for women with a PM [21]. The risk of GTN after HM has been estimated as 1000 times higher than after a term pregnancy [8]. However, a report from Japan has indicated that there has been a reduction in the incidence of HM from 4.9 to 1.9/1,000,000 of the population and of CC from 1.6 to 0.3/1,000,000 of the population [22]. The study by Eagles et al. [17] documented that there was no significant difference between the risk of developing GTN for typical sporadic CM and the diploid biparental CM associated with FRHM.

Women with blood type A or AB should have a higher risk of HM compared with women with a blood type B or O (with a relative risk of 0.9–4.8). The data also suggested a higher risk for persistent GTD and for CHM compared to PHM [23].

The use of oral contraceptives is generally associated with an increased risk of GTD and with relative risks ranging from 1.11 to 2.6 [23, 24]. There is insufficient information on other environmental and lifestyle factors or other possible etiological risk factors for GTD, such as smoking habits, alcohol consumption, socioeconomic status, and herbicide exposure [8, 9, 15, 23, 25].

9.2.2 Anatomo-Pathological Characteristics and Causes of GTD

The WHO classification of tumors of the female genital tract published in 2014 [26] has greatly modified the previous organization of gestational trophoblastic disease. Emphasis is given to lesions with aggressive behavior (choriocarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumor). These are followed by the nonneoplastic lesions (exaggerated placental site, placental site nodules, and plaques) and then by molar pregnancy or hydatidiform mole (complete, partial, and invasive), concluding with nonmolar abnormal villous lesions.

This classification, in its not truly academic peculiarity, mixes, without any discernible logical order, diseases with etiopathogenesis and evolutions which are too intricate to be able to easily distinguish and separate. It is difficult to see the link between malignant diseases and occasionally found nonneoplastic lesions, listing them before molar diseases which share a large part of their etiology with choriocarcinoma. Similarly, there is no doubt that an invasive mole belongs to the complete form, and it is not logical to insert the partial form between the two, especially as the partial form has a very different nosological meaning. No one felt the need to complicate the classification with the introduction of anomalous villous lesions which are nothing more than not yet completely absorbed villi. The desire to insert the old "trophoblastic diseases of undetermined significance," whose existence is not much believed in, is in fact a hindrance to the illumination of dubious lesions, which fortunately make up only a small amount of cases.

9.2.3 Complete Hydatidiform Mole

A CHM is a pathological condition wherein an anembryonic sac develops with the fertilization of an aneuploidic oocyte. This type of degenerative oocyte is frequent in women less than 15 years and more than 40 years, and it is fecundated by one or two sperms [27]. The embryo is precociously suppressed, and the extraembryonic portions (i.e., the villi with the trophoblastic epithelium) are present and proliferate. For these reasons the CHM have a diploid karyotype 46,XX. A rare condition of FRHM is composed by a biparental diploid tissue with karyotype 46,XY; the condition is due to a gene mutation (NLRP7) in the chromosomal region 19q13.4 [28].

Macroscopically (Fig. 9.1a), the chorionic plate is not recognizable as such, instead there being an unstructured mass of enlarged, edematous villi branching into cotyledon.

At histology (Figs. 9.1b and 9.2), the villi show very irregular branching, most being of an abnormal volume with circumferential hyperplasia and with variable degrees of trophoblastic proliferation. Particularly the syncytiotrophoblast

shows cytoplasm vacuoles and various degrees of nuclear atypia. The hyperplastic cytotrophoblast has a typically nuclear pleomorphism.

The stroma of the villi is edematous and hydropic with differing degrees of degenerative alteration, often displaying a central cavity known as a cistern. Vessels are absent.

Outside of the villi there is no sign of either the allantois or the yolk sac or of the embryo.

The trophoblast that lines the molar villi, the syncytiotrophoblast and the cytotrophoblast, is always negative for p57 (paternally imprinted maternally product of gene CDKN1C).

With respect to the early abortion, the differential diagnosis with the complete hydatidiform mole is based firstly on the presence of nonpolar trophoblastic proliferation in the neoplastic lesion (Fig. 9.3).

There is a general confusion in the definition of early CHM (first trimester). Typical signs are a basophilic stroma, immature vessels, and an irregular villous surface; however none of these is exclusive to early mole [29]. We are convinced that we can talk about a mole only when there is a documentable nonpolar trophoblast proliferation.

The extent of the trophoblastic hyperplasia and its atypical aspects are directly linked to the biological behavior of the lesion. The major risks consequent to the presence of a CM can be defined in three adverse events:

- Mole residues remain in the uterine cavity even after repeated scraping (*persistent mole*).
- Appearance of an invasive mole.
- Choriocarcinoma (more rarely).

The evolution to an invasive mole or a choriocarcinoma occurs in 8–30 % of complete mole cases.

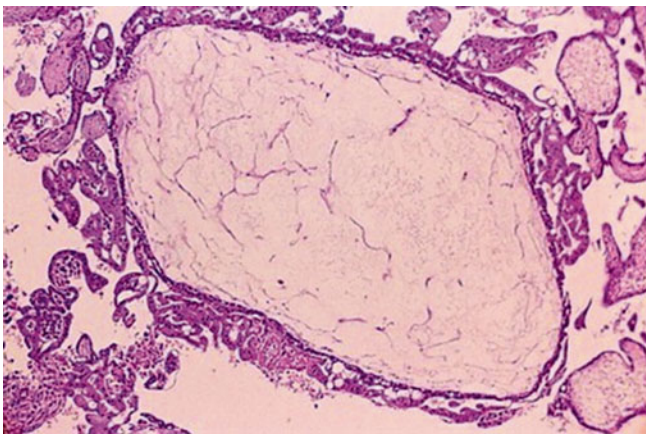

Fig. 9.3 Comparison between villi of a hydatidiform mole (**a**) and a spontaneous abortion (**b**). In molar villi the proliferative trophoblast involves a large part of (or the total) surface of the villus. In the normal placenta and in the spontaneous abortion, the trophoblastic proliferation is of polar type (the proliferation is functional to the creation of a mesenchymal villus from an immature intermediate villus), and it involves only one point of the surface

9.2.4 Partial Hydatidiform Mole

A PHM is a pathological condition wherein a gestational sac which can be anembryonic or embryonic can continue the pregnancy, with frequent development of the products of conception and of the amniochorial membrane. It was once thought that the incidence of PHM was less than that of CHM but they are comparable. In fact, the real incidence of PHM is more than likely underestimated because of the difficulty in diagnosing the digynic form [30].

The PHM is generally characterized by a triploid karyotype (more often 69,XXY; less frequently 69,XXX or 69,XYY). In the case of diandric triploidy, there is a greater proliferation of molar villi than in digynic triploidy where the villous anomalies are of a more modest extent and allow the survival of the fetus up to the 21st–22nd week of pregnancy.

Stereomicroscopic observation shows the presence of both normal and enlarged villi. This is a histological characteristic (Fig. 9.4), and the normal villi show a slight degree of stromal fibrosis, while the others are hydropic with a modest hyperplasia of the trophoblast which can be either circumferential or multipolar. Many of the villi have a large central cistern, while others are characterized by actual alterations of all the karyotype anomalies such as extreme and irregular scalloped contours and inclusions.

The cytotrophoblast that lines the molar villi is positive for p57. Staining with antibody anti-CD34 is useful to see the altered or collapsed vascular structures which are difficult to identify morphologically.

The evolution of the disease into an invasive form or in choriocarcinoma is very rare.

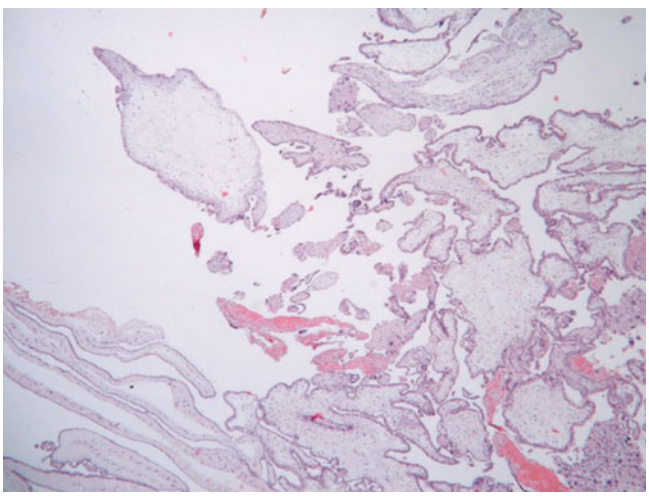

Fig. 9.4 Partial hydatidiform mole. The molar degeneration interests part of the villous tree. Part of the amnio-chorial membrane is evident in the *bottom left* of the picture

9.2.5 Invasive Mole

The invasive mole is characterized by the proliferation of molar villi with hyperplasia of the trophoblastic cells which not only penetrate the myometrium around the mole (Fig. 9.5) but can also (more rarely) invade the perimetrium and the hematic vessels, with distant diffusion in extrauterine sites (e.g., the lungs).

It can develop from a CHM, it rarely being of primitive form. It is the most common complication of GTD and occurs in about 16 % of all complete mole cases.

Lesions have a flaky appearance so hemorrhaging and drying the uterus wall and beyond, with clumps of enlarged edematous villi.

The histological diagnosis is based on finding molar villi and accompanying intermediate trophoblast outside of the endometrium.

Good practice usually determines a hysterectomy. Death, an exceptional occurrence, is generally linked to local phenomena such as perforation of the uterus. The progression of an invasive mole is to a choriocarcinoma, which however is an infrequent occurrence especially when there is a cytotoxic chemotherapy for the management of the lesion.

9.2.6 Choriocarcinoma

CC is a rare malignant neoplasia of a proliferation of cytotrophoblast and syncytiotrophoblast together, in the absence of chorial villi.

Any type of pregnancy can be affected by this disease, but in 50 % of cases it is preceded by a mole, in 25 % by an abortion, and in 22.5 % by a normal pregnancy. Onset in the third trimester of pregnancy of the intraplacental form is exceptional.

Macroscopically, a choriocarcinoma is an infiltrative lesion which destroys the myometrium and is flaky and hemorrhagic without defined borders. The surface can be polypoidal.

A histological examination shows the characteristic intimately related proliferation of atypical cytotrophoblast and syncytiotrophoblast. This proliferation has well-defined architectural characteristics (Fig. 9.6) of a central nucleus of cytotrophoblast nests surrounded by plurinucleate cells and maternal blood. Other characteristics are the lack of stroma or vessels and widespread but largely centralized hemorrhagic necrosis (Fig. 9.7).

All the neoplastic cells are intensely stained by immunohistochemical stain with antibody anti-keratin, in particular

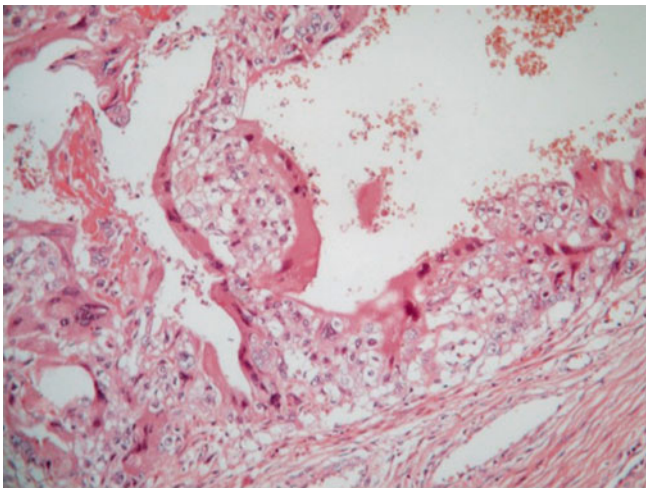

Fig. 9.6 Choriocarcinoma. Typical histological architecture of the tumor: the nucleus is composed of proliferative cytotrophoblast cells surrounded by syncytiotrophoblast. The maternal blood circulars in the neoplastic spaces

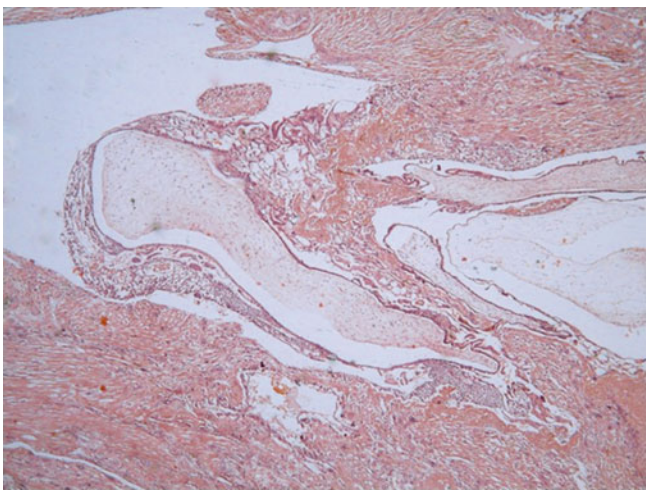

Fig. 9.5 Invasive mole. Some molar villi are present in the vascular spaces of the myometrium

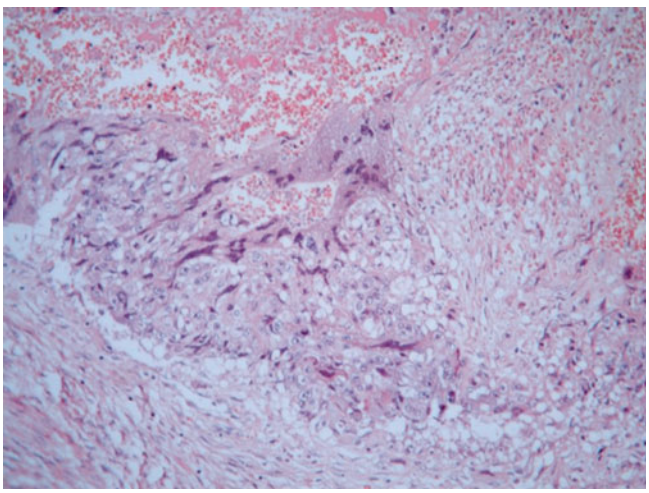

Fig. 9.7 Choriocarcinoma. Large foci of hemorrhage are constantly present in the tumor

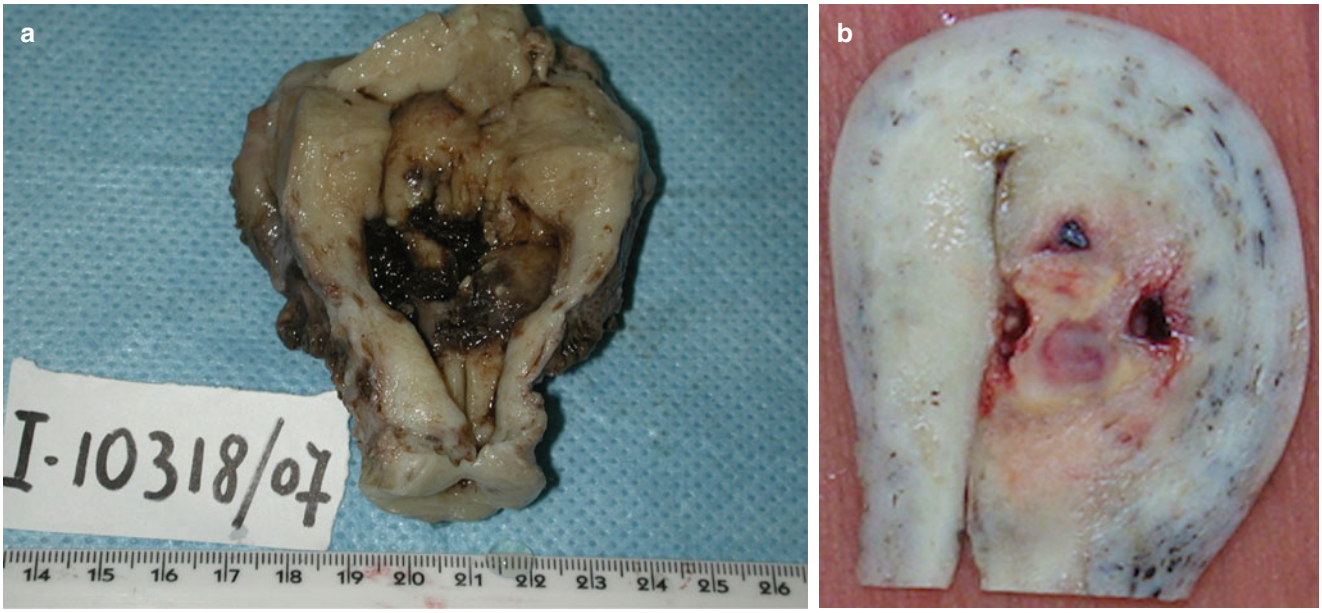

Fig. 9.8 (**a**) Placental site trophoblastic tumor. The macroscopic pattern of the lesion is characterized by a hemorrhagic mass infiltrating the uterine wall. This picture is not dissimilar of a choriocarcinoma. (**b**) Placental site trophoblastic tumor (Courtesy of Dr. Jasmina Atanackovic and Dr. Svetlana Milenkovic)

by Cam 5.2. The part composing atypical syncytiotrophoblast is intensely positive for inhibin alpha and β-hCG; it is weakly positive for human placental lactogen (hPL), while the atypical cytotrophoblast is always negative for all stains.

The symptoms range from metrorrhagia to those linked to metastasis (more frequent in the lungs, liver, and SNC). Some patients with choriocarcinoma metastasis do not have a uterine neoplasia, probably due to regression of the primitive neoplasia. Elevated serum levels of β-hCG are constant, and this hormone together with the production of other hormones causes an ovaric reaction leading to a polycystic transformation, which can simulate a primitive ovaric neoplasia (hyperreactio luteinalis).

The neoplasia invades the myometrial vessels as well as the myometrium so explaining the ease of metastasis. The most common causes of death are therefore:

- Hemorrhage, especially in cerebral metastasis
- Respiratory failure in lung metastasis
- Complications from the therapy (cytotoxic polychemotherapy)

9.2.7 Placental Site Trophoblastic Tumor (PSTT)

PSTT is a neoplasia of uniquely intermediate trophoblastic cells important for implantation of the placenta. A PSTT can be preceded by a molar pregnancy, but the frequency is much less than for a choriocarcinoma. At gross examination we observe a hemorrhagic neoplasm not different from a choriocarcinoma or another malignant tumor of the uterine wall (Figs. 9.8a, b).

PSTT examination shows a proliferation of elements from extravillous mononuclear trophoblast cells or multinucleated cells mimicking syncytiotrophoblast. The cells can vary in size and appearance of the nucleus, but they show evident atypical characteristics (though variable from medium to serious) (Figs. 9.8a, b). Limited mitosis and fibrinoid material are found among groups of neoplastic cells and substitute the vessel structure. Vessel infiltrative images are common (Fig. 9.10), with the tumor growing substituting the vessel walls, as what happens in normal extravillous trophoblast proliferation at the placenta implantation site.

All the neoplastic cells are intensely stained by immunohistochemical stain with antibody anti-keratin (Fig. 9.11), in particular by Cam 5.2; the atypical extravillous trophoblast is weakly positive for β-hCG, while it is strongly positive for hPL. All the neoplastic elements, which have a proliferation index (Ki 67) of 15 %, are intensely positive in immunohistochemistry for Mel-CAM, inhibin A, and HLA-G.

The tumor is generally benign, but susceptible to becoming aggressive, and can appear a long time after a pregnancy.

In general (90 % of cases), it is self-limiting in its growth with a low mitotic index (≤5 mitosis/10 HPF); the neoplasia infiltrates the myometrium dissecting the single muscle fibers and penetrates the blood vessel walls in a way analogous to its behavior in a normal pregnancy.

In the other 10 % of cases, however, it can lead to death due to the perforation of the uterus following a transformation into a malignant form, with lung, liver, and brain metastasis; in these

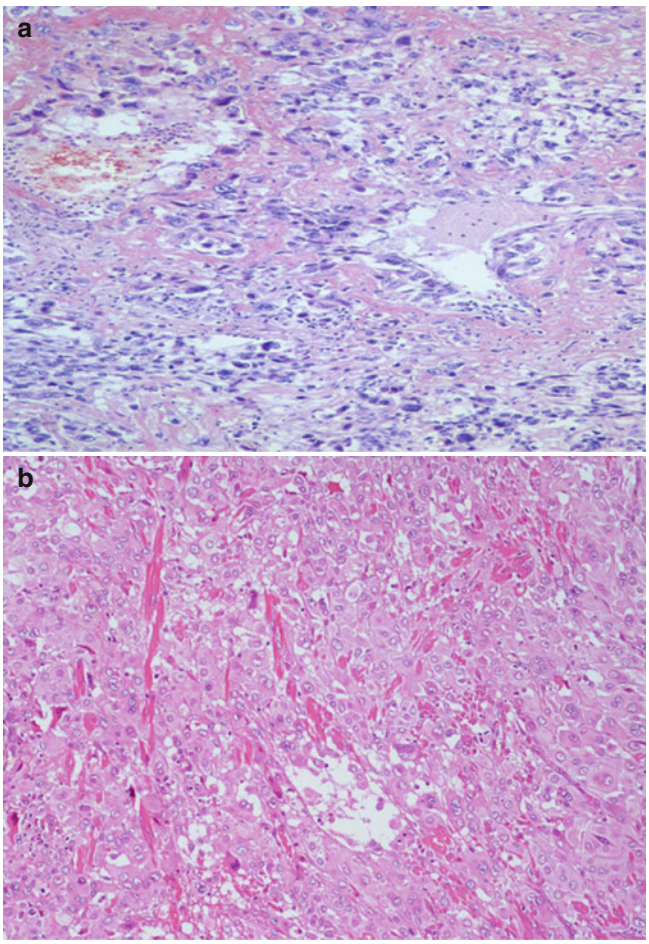

Fig. 9.9 (**a**) Histological microscopic images of placental site trophoblastic tumor (Courtesy of Dr. Jasmina Atanackovic and Dr. Svetlana Milenkovic). (**b**) Placental site trophoblastic tumor. Histological view of large cells with clear nuclei and abundant eosinophilia infiltrating the myometrium

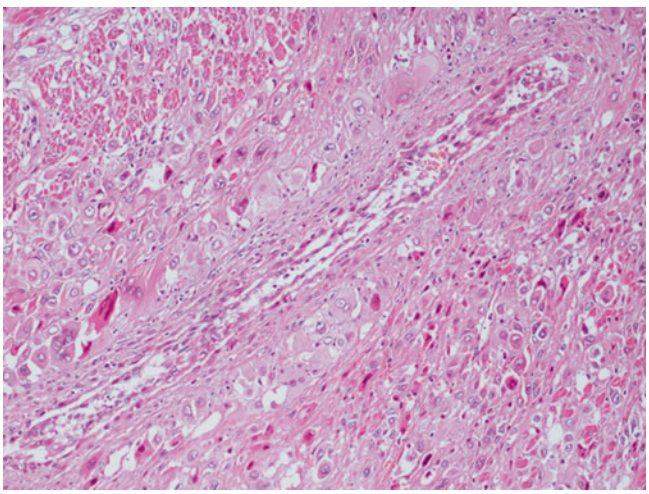

Fig. 9.10 Placental site trophoblastic tumor. Neoplastic cells are pleomorphic and some cells present numerous dark inactive nuclei. The maternal vessels are largely infiltrated by the neoplasia

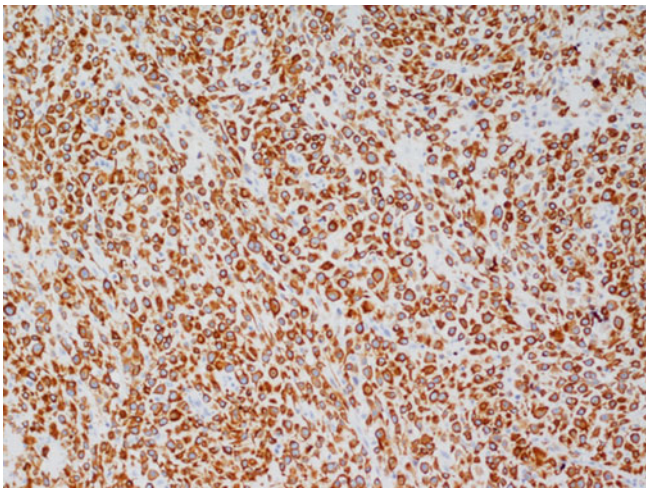

Fig. 9.11 Placental site trophoblastic tumor. The immunohistochemical reaction with antibodies against cytokeratins is strongly positive in the neoplastic cells. The reaction is very useful for the differential diagnosis with decidual cells or other uterine tumors

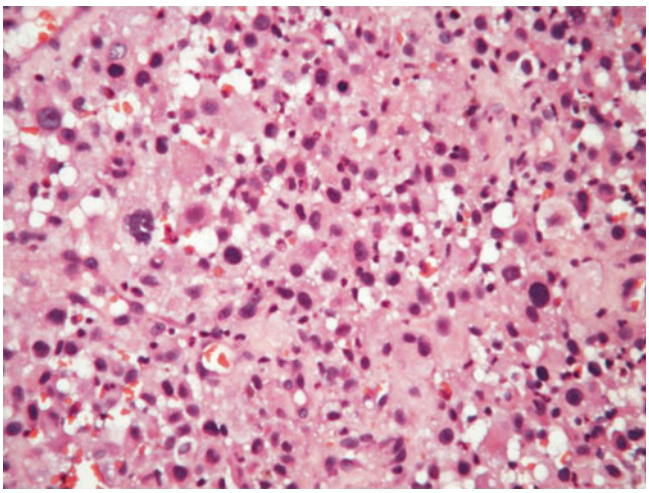

Fig. 9.12 Epithelioid trophoblastic tumor. With respect to the placental site trophoblastic tumor, the present tumor shows more monomorphic cells, necrosis, and diapedetic hemorrhages

cases the mitotic index is generally >5/10 HPF (1 HPF = 400 X). Serum levels of hCG are only moderately increased.

9.2.8 Epithelioid Trophoblastic Tumor

ETT is a neoplasia composed of a uniform population of intermediate trophoblastic cells similar to the trophoblastic cells in the chorion laeve, in consequence of the neoplastic transformation of villous intermediate trophoblastic cells (chorion membrane).

The lesion is ill defined and shows an increase in consistency due to a proliferation of epithelioid elements for the most part disassociated, of small size, monomorphic, and with rare mitosis (Fig. 9.12).

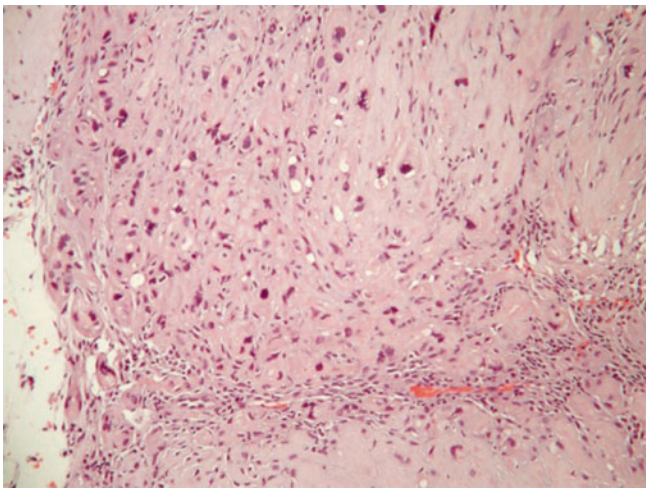

Fig. 9.13 Placental site nodule. The presence of pleomorphic cells in a contest of hyaline stroma in endometrium or endocervix may recall a residual sign of a previous pregnancy. The expression of cytokeratins is important to characterize the lesion

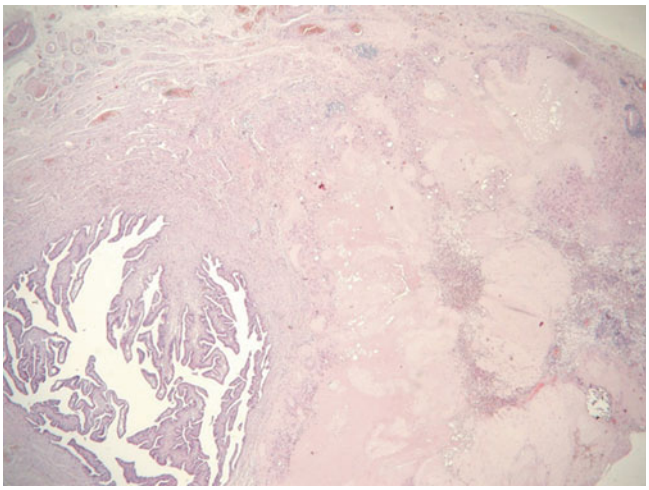

Fig. 9.14 This salpinx was removed in a menopausal woman with a diagnosis of tubal neoplasm. The histology reveals a large amount of hyaline stroma in the salpingeal wall

The behavior is of an expansive lesion, surrounded by lymphocytic infiltrate.

The cells of this neoplasia are strongly positive for placental alkaline phosphatase (PLAP) and for human placental lactogen (hPL), as they are for E-cadherin and for epidermal growth factor receptors (EGFR).

Being less aggressive than choriocarcinoma and more similar to PSTT, it can anyway relapse or metastasize, and it has a mortality of 10 % [31].

9.2.9 Exaggerated Placental Site Reaction

Exaggerated placental site reaction is a nonneoplastic lesion as an abnormal reaction of extravillous trophoblast following an inadequate or insufficient implantation, as frequent as in the implantation of chorial structures (chorion frondosum) with karyotype anomalies. It occurs in 2 % of normal pregnancies and early spontaneous abortions. There is a thickening of the decidua basalis with fibrinoid masses.

The lesion is characterized by an extensive infiltration of the implantation site (Fig. 9.13) by intermediate trophoblastic cells, sometimes also atypical, without significant replication activity.

Therapy is not required, and β-hCG administration is provided only in cases of a trophoblastic tumor not to be excluded in the implantation site.

9.2.10 Placental Site Nodule

A placental site nodule (PSN) is a remnant of the chorion from a previous pregnancy (from several months to years). Typically, it is found accidently in tissue obtained for other reasons, and therefore we cannot identify its rate of occurrence (Figs. 9.14 and 9.15). It is made up of cells similar to normal *chorion laeve* cells. No therapy is required.

In 2014, Kim [29] has proposed an interesting diagnosis path for uterine epithelioid lesions:

1. Uterine epithelioid smooth muscle neoplasm: SMA/desmin+
2. Squamous cell carcinoma: Ck 18−, p16/HPV+
3. Trophoblastic lesion: Ck 18+, p16/HPV−
   (a) Choriocarcinoma: dimorphic pattern/elevated serum β-hCG
   (b) Chorionic trophoblast proliferation: p63+; PLAP++; hPL±; CD 146−
      b.1 Placental site nodule: Ki67, 1–5 %
      b.2 Epithelioid trophoblastic tumor: Ki67 >10 %
   (c) Implantation site trophoblast proliferation: p63−; PLAP−; hPL+; CD 146+
      c.1 Exaggerated placental site: Ki67, 1–5 %
      c.2 Placental site trophoblastic tumor: Ki67 >10 %

9.2.11 Clinical Presentation of Gestational Trophoblastic Disease

Different types of GTD have different clinical presentation [31]. The clinical presentation of women with a molar pregnancy has changed notably over the past several decades [31–33]. The reasons for this are improvement of prenatal care and universally available sonography. As a result, most GTDs are detected when they are small, before any complications can develop [32, 33].

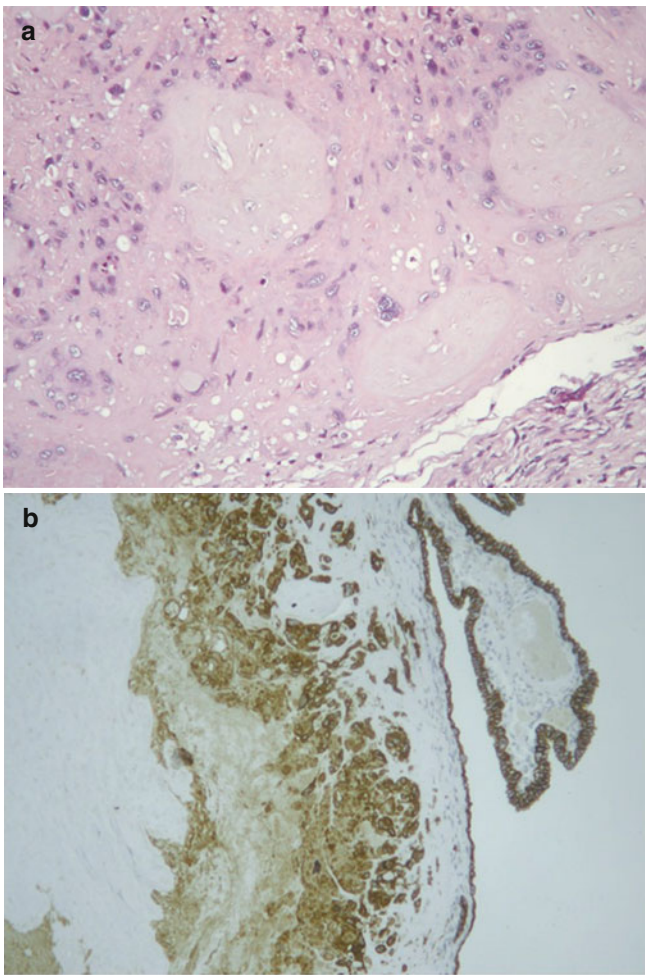

Fig. 9.15 Some case of the previous figure. At higher magnification (**a**) several cells with dark irregular nuclei are evident. These cells, in the tubal wall, were positive for the expression of cytokeratin (**b**). The present is an evident case of residuals of a previous unknown tubal pregnancy

9.2.12 Complete Hydatidiform Mole

The CHM is most commonly associated with vaginal bleeding, usually occurring at 6–16 weeks of gestation in 80–90 % of cases [8]. The other classic clinical signs and symptoms, such as uterine enlargement greater than expected for gestational dates, hyperemesis, and pregnancy-induced hypertension in the first or second trimester, occur less frequently in recent years due to earlier diagnosis and accurate hCG testing. Bilateral theca lutein cyst enlargement of the ovaries occurs in approximately 15 % of cases; hCG levels are often 100,000 mIU/mL, and fetal heart beats are absent [8, 31, 34].

9.2.13 Partial hydatiform mole

The PHM and complete mole are not characterized by the same features. More than 90 % of patients with PHM have symptoms of incomplete or missed abortion, and the diagnosis is usually given after a histological review of the curettage specimens. The main symptom is vaginal bleeding, which occurs in approximately 75 % of patients. Excessive uterine enlargement, hyperemesis, pregnancy-induced hypertension, hyperthyroidism, and theca lutein cysts rarely develop.

9.2.14 Gestational Trophoblastic Neoplasia

GTN has a varied presentation depending on the antecedent pregnancy event, the extent of the disease, and its histopathology. Postmolar GTN (invasive mole or choriocarcinoma) is usually associated with irregular bleeding after hydatidiform mole (HM) evacuation. Symptoms of postmolar GTN are an enlarged, irregular uterus and persistent bilateral ovarian enlargement. A metastatic vaginal lesion may occasionally be noted upon evacuation, which may cause uncontrolled bleeding. CC commonly preceded by non-molar gestation has no characteristic symptoms or signs and is mostly associated with tumor invasion of the uterus or with metastatic sites. The differential diagnostic code in patients with postpartum uterine bleeding and abnormal puerperal involution should consider GTN along with other possible causes, such as retained products of conception or endomyometritis, primary or metastatic tumors of other organ systems, or another pregnancy occurring shortly after the first. Bleeding resulting from uterine perforation or metastatic lesions may cause abdominal pain, hemoptysis, melena, symptoms of increased intracranial pressure from intracerebral hemorrhage or metastatic lesions [2, 35]. Patients may also have pulmonary symptoms, such as dyspnea, coughing, and chest pain, caused by extensive lung metastases. PSTTs and ETTs almost always cause irregular uterine bleeding, which usually occurs some time after a non-molar gestation; they rarely cause virilization or nephrotic syndrome as well. The uterus is usually symmetrically enlarged, and serum hCG levels are only slightly elevated [36, 37].

9.3 Diagnosis of Gestational Trophoblastic Disease

9.3.1 Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is a placental heterodimeric glycoprotein composed of two dissimilar subunits (alpha, α, and beta, β) joined non-covalently. The alpha subunit resembles the pituitary glycoprotein hormones and the beta subunit is unique to trophoblast production. Regular hCG, hyperglycosylated hCG, and hyperglycosylated hCG-free β are widespread in GTD. These three molecules plus ten

degradation products constitute the 13 forms of hCG β-subunit present in the serum or urine samples. Ideally, total hCG tests should detect all of these hCG-related molecules to optimally monitor pregnancy, gestational trophoblastic diseases, and cancer cases. The hCG molecules in GTD are more heterogeneous and degraded than those in a normal pregnancy. Prospective studies in large patient cohorts are needed to define the role of hyperglycosylated hCG and hCG-free β in the management of gestational cancers. Automated radiolabeled monoclonal antibody sandwich assays measure different mixtures of hCG-related molecules [38]. They can detect hCG accurately at much lower concentrations by using modern automated tests and significant knowledge about hCG structure and its degradation process [39].

Hydatidiform moles (HM) are commonly associated with notably elevated hCG levels, above those of a normal pregnancy. Approximately 50 % of patients with a CHM have pre-evacuation hCG levels of 100,000 mIU/mL [2, 40]. PHM, however, are commonly not characterized by such elevated hCG levels, 100,000 mIU/mL in 10 % of patients [2].

Following the evacuation of a hydatidiform mole, a clinical diagnosis of postmolar GTN is often made based on the rising or plateauing hCG levels. CC is usually diagnosed by the finding of an elevated hCG level, usually together with the discovery of metastases following other pregnancy events. PSTT and ETT are commonly associated with slightly raised hCG levels.

Quiescent gestational trophoblastic disease is a term applied to a presumed inactive form of GTN, characterized by persistent, unchanging low levels (200 mIU/mL) of "real" hCG for at least 3 months. These are patients with a history of a hydatidiform mole, gestational trophoblastic neoplasm (GTN) or choriocarcinoma, or spontaneously aborting pregnancy but without a clinically manifested disease. In all cases, no disease is detectable either clinically or by sophisticated imaging. The hCG levels do not change with chemotherapy or surgery [41–47]. Yet, in most of the studied cases, the patient has been treated with a single-agent chemotherapy, when the hCG fails to decrease with polychemotherapy and/or hysterectomy or other surgery. The studies indicate that these patients have residual syncytiotrophoblast cells with no or very few invasive cytotrophoblast cells and, therefore, have an active disease [42, 43]. In 10–25 % of these quiescent GTD cases, the persistent hCG concentration changes and starts to elevate rapidly 5 months to 10 years after the finding of the persistent elevated hCG. In most of these cases, a tumor is later identified, with its pathology indicating CC or other GTN. This might suggest that quiescent GTD is a premalignant syndrome with malignant transformation occurring in a number of cases [43–46]. According to the International Society for the Study of Trophoblastic Disease in 2001, false-positive hCG resulting from heterophile antibodies or LH interference should be excluded in managing this condition. The patients should be thoroughly examined for disease symptoms; immediate chemotherapy or surgery should be avoided. They should be monitored over a longer period with hCG testing at regular intervals while avoiding pregnancy. Treatment should be undertaken only when there is a clearly clinically manifested disease or a sustained rise in hCG level [47]. The risk of GTN after the normalization of hCG was 0.34 % following an HM, 0 % after a partial PHM, and 0.36 % after a CHM [48].

9.3.2 Ultrasonography

Ultrasonography plays a significant role in detecting both complete and partial moles, particularly the transvaginal scan with the Doppler flow and three-dimension power Doppler imaging [49, 50]. A characteristic vesicular ultrasonographic pattern, consisting of multiple echoes (holes) within the placental mass and without fetus, can be observed because the chorionic villi of complete moles exhibit diffuse hydropic swelling.

A clinician skilled in ultrasound examinations is able to detect most first trimester complete moles (Fig. 9.16) [49]. An elevated hCG measurement at the time of sonography may help to differentiate an early CHM from a missed abortion [2]. Ultrasonography may also facilitate the early diagnosis of a PHM by showing focal cystic spaces within the placenta together with an increase in the transverse diameter of the gestational sac [2]. Changes in the shape of the gestational sac may be part of the embryopathy of triploidy. When both findings are present, the positive predictive value for PHM approaches 90 %. The ultrasound may also show the presence of a growth-retarded fetus with multiple congenital anomalies (Fig. 9.17) associated with a focally hydropic placenta [51].

9.3.3 Surgical Evacuation

Uterine cavity suction and curettage (Fig. 9.18), regardless of uterine size, is the most commonly opted method of evacuation in patients suspected of having an HM and wanting to preserve fertility [52, 53]. Women who are nulliparous should not be given prostanoids (Fig. 9.19) to ripen the cervix, since these drugs can induce excessive uterine contractions and might increase the risk of pulmonary embolization by trophoblast [54]. Hysterectomy is rarely recommended, but it might be considered for women who do not want to have more children or who have life-threatening hemorrhage (Fig. 9.20) [55]. Patients must be informed that although hysterectomy prevents the risk of local invasion, it does not

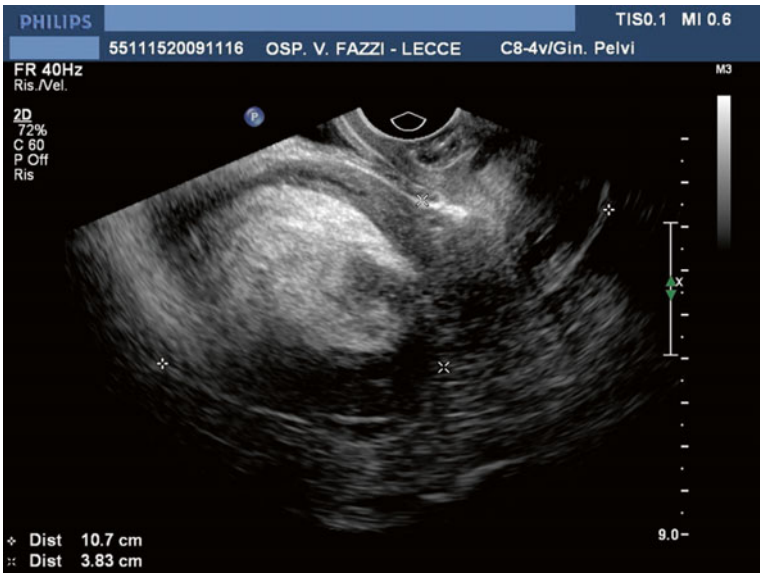

Fig. 9.16 A transvaginal uterine sagittal section of a pregnant uterus at 8 weeks with a completed mole, showed by a large hyperechoic area inside the uterus

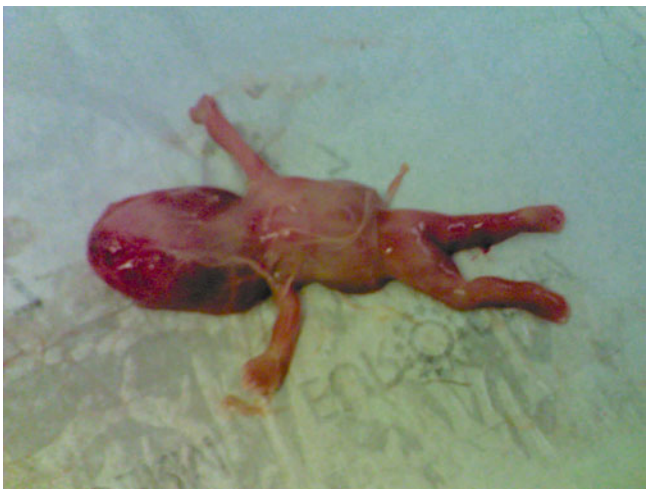

Fig. 9.17 A picture of a growth-retarded malformed fetus at 14 weeks in a pregnancy with a partial mole

eliminate potential need for chemotherapy and that the monitoring of hCG concentrations still needs to be done.

9.3.4 Gestational Trophoblastic Neoplasia Staging

Adequate staging and risk scoring systems are prerequisite for the proper treatment of patients with gestational trophoblastic neoplasia [56]. Staging and scoring systems are also important for comparing treatment results obtained from different centers, researching new chemotherapeutic drugs and treatment protocols, and assessing the prognosis, thus allowing multicenter comparisons and international trials. Such efforts would result in global improvement of both the survival rate and quality of life of the affected women.

9.3.5 Pretreatment Investigative Steps in Staging

Staging and scoring of a disease must be performed prior to GTN treatment [57]. This is essential for achieving optimal treatment results, as GTN is a highly curable disease even when widespread metastases are present [58, 59].

The basic checkup includes complete history and physical exam, pretreatment serum hCG testing, blood work including complete blood count and clotting function studies, and hepatic, renal, and thyroid function tests [57]. Pelvic examination is useful for identifying uterine enlargement and vaginal and pelvic metastases. Pelvic ultrasonography with a color Doppler can also be useful in identifying the site and size of the uterine tumor, the uterine wall involvement, and uterine volume. Furthermore, recent data suggest that Doppler measurements of the pulsatility index in the uterine arteries can predict the response to chemotherapy [7, 60]. Further investigation of metastasis includes a chest X-ray and abdominal ultrasonography [61].

Women who develop GTN following molar pregnancy are usually diagnosed early based on elevated hCG and do not require extensive investigation for staging [61]. In cases with elevated hCG following other types of pregnancy, a detailed investigation is required for staging purposes. Evaluation is performed by an abdominopelvic computerized tomography (CT) or magnetic resonance imaging (MRI) scans [61]. Approximately 40 % of patients with a negative chest X-ray have pulmonary micrometastases, which can be

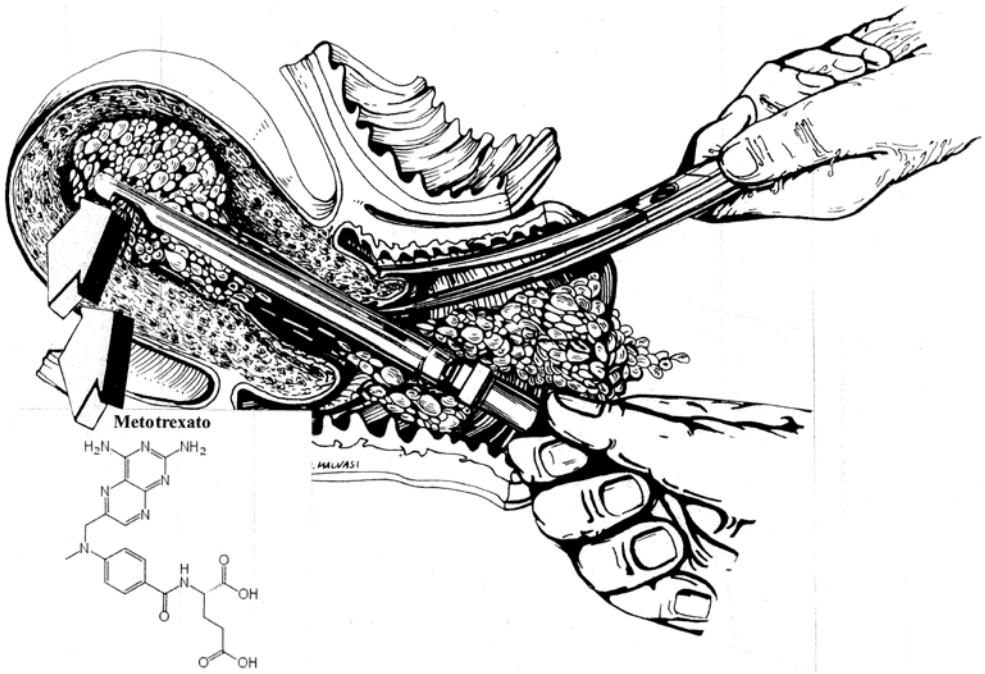

Fig. 9.18 The image represents a uterine cavity suction and its curettage, after MTX administration

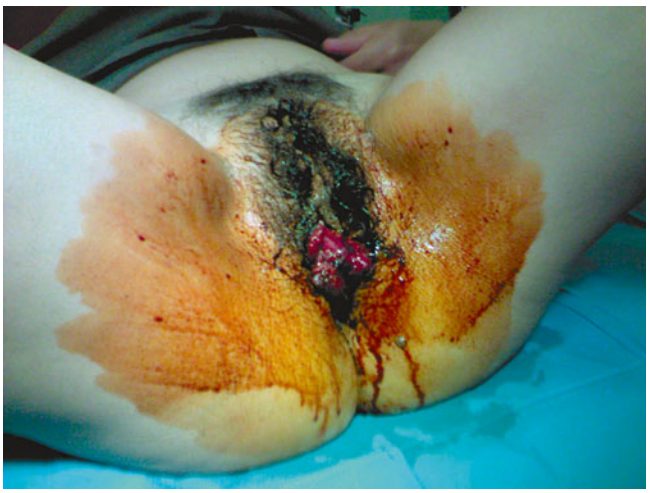

Fig. 9.19 A pregnant with two previous spontaneous deliveries who received prostanoids to stimulate spontaneous expulsion of a complete mole; she has been spontaneously ejecting the mole

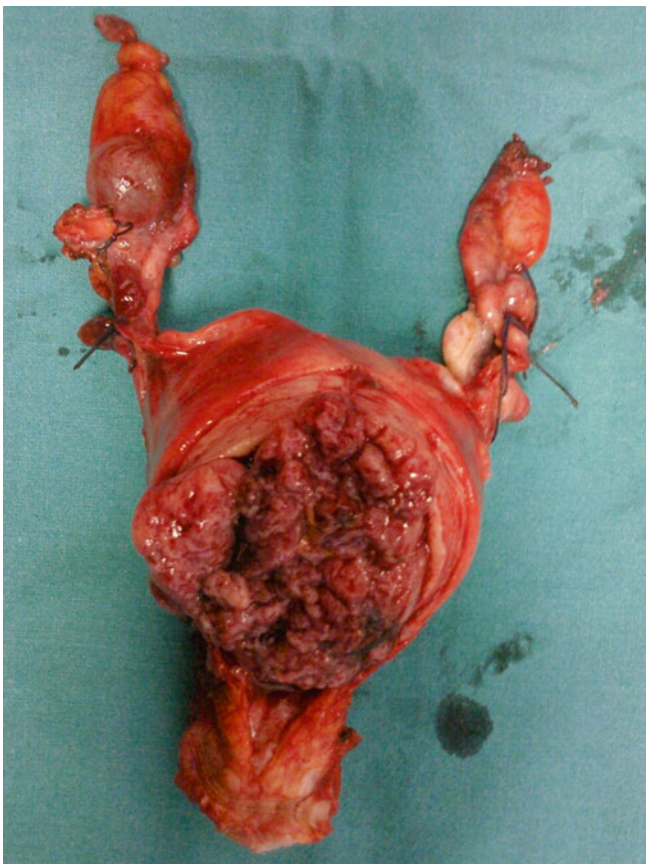

Fig. 9.20 A removed uterus with a complete mole at 9 weeks seen at longitudinal hysterotomy in a patient of 44 years with a familiar story of invasive cancers and personal history of ovarian borderline tumor

diagnosed with a chest CT scan, but its role in routine investigation is still debatable [3, 7]. When pulmonary and vaginal lesions and/or neurological symptoms are present, disseminated metastases can be expected, and this requires a brain MRI or a CT scan [7, 56]. Lumbar puncture and measuring hCG levels in the cerebrospinal fluid (CSF) can exclude cerebral metastases in patients with normal brain imaging, as the CSF/serum hCG ratio greater than 1:60 is indicative of a central nervous system (CNS) metastases [7]. The use of 18-fluorodeoxyglucose-positron emission

Table 9.1 The FIGO staging and risk factor scoring system for gestational trophoblastic neoplasia (GTN)

FIGO staging				
Stage I	Disease confined to the uterus			
Stage II	GTN extends outside the uterus but is limited to the genital structures (adnexa, vagina, broad ligament)			
Stage III	GTN extends to the lungs with or without genital organ involvement			
Stage IV	All other metastatic sites			
FIGO risk factor scoring				
FIGO risk factor scoring values	0	1	2	4
Age	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval from index pregnancy (months)	<4	4–<7	7–<13	≥13
Pretreatment serum HCG values (IU/L)	$<10^3$	10^3–$<10^4$	10^4–$<10^5$	$\geq 10^5$
Largest tumor size, including uterus (cm)	<3	3–<5	≥5	–
Site of metastases	Lung	Spleen Kidney	Gastrointestinal tract	Liver Brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	Two or more drugs

tomography (18 FDG-PET) enables the identification of the active disease sites in cases of unexplained high hCG levels and determines the potential for tumor resection [7, 56, 62]. Furthermore, it can determine the viability of the persistent disease foci [56]. FDG-PET may be a useful tool in investigating the response to treatment in patients with recurrent or resistant GTN [62, 63]. Except in highly selected cases, biopsies of GTN lesions should be avoided because of pronounced risk of severe hemorrhage [3, 56].

9.3.6 GTN Stages and Scores

Following the investigation, it is possible to define the extent of the disease and the presence of risk scoring factors. In 1983, the World Health Organization (WHO) recommended a prognostic scoring system based on risk factors for treatment failure. The risk factors determining the prognosis are defined by numerical values [2]. The sum of these is used to determine each case, either as a low risk or high risk one. In 1982, the International Federation of Gynecology and Obstetrics (FIGO) introduced an anatomic staging system for GTN, classifying patients into four stages [2].

In 2000, FIGO adopted a revised GTN staging system together with the modified WHO's risk scoring system. It was officially published in 2002 [64]. Each patient's diagnosis is assigned to the stage representing the anatomic localization of the disease and to a risk factor score representing the sum of all the risk factors. The FIGO staging and risk factor scoring system for GTN is presented in Table 9.1. Thus, a Roman numeral for stage and an Arabic numeral for score are assigned to each patient. This system does not include hydatidiform moles, and the patients are staged only in cases of persistent hCG and GTN. The FIGO staging and risk scoring systems cannot be fully applied to PSTT and ETT [65, 66].

Patients with a score of 0–6 represent a low-risk group, while a high-risk group has a score of seven or higher [64]. Patients with stage I disease generally have a low-risk disease, while those with stage IV have a high-risk disease. Stage II and III patients are those in whom both high-risk and low-risk score distinction is applied.

9.4 Treatment of Gestational Trophoblastic Disease

9.4.1 Basic Principles

During the early 1970s, in the UK, three registration centers were established for patients with gestational trophoblastic disease (GTD) [3, 63, 67], resulting in the largest database worldwide. Due to disease rarity, such national centralization in pathology review, treatment, and monitoring of patients with GTD is advisable [3, 63]. In this manner, patients can be provided with adequate level of expertise and the best available treatment. Available treatment options for GTN are presented in Table 9.2.

9.4.2 Management of Complete or Partial Molar Pregnancy

In patients wanting to preserve fertility, dilatation and suction curettage (D&C) (Fig. 9.21), with fast fresh histopathological

Table 9.2 Available treatments for gestational trophoblastic neoplasia

Treatment	Definition
None	No treatment
Chemotherapy	Performed either as a prophylactic treatment or as primary treatment following D&C with residual disease (uterine or extrauterine)
Surgery alone	Only hysterectomy (because of GTN), with normalization of serum β-hCG levels, performed on patients who did not undergo chemotherapy before and/or after hysterectomy
Chemotherapy + surgery	Chemotherapy plus surgery (abdominal and/or pelvic surgery, craniotomy, lobectomy of the lung, etc.) with the intention to treat GTN. Chemotherapy can be given before and/or after surgery

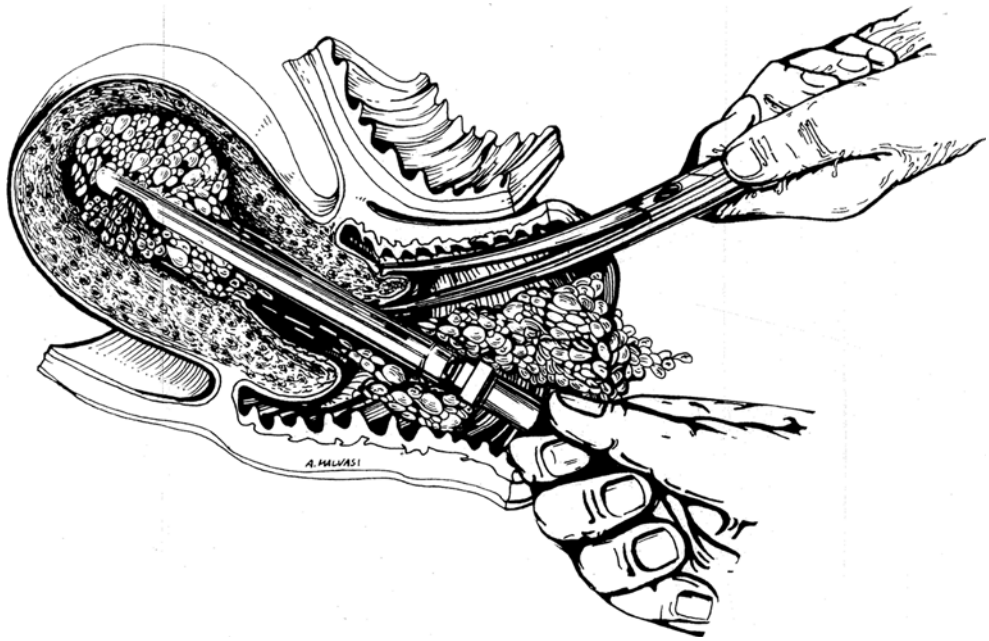

Fig. 9.21 A schematic representation of a dilatation and suction curettage (D&C) of a molar pregnancy by Karman cannula

examination of the specimens (Fig. 9.22), is the optimal method for evacuation [61]. The D&C preceded by the application of prostaglandins in the vagina (Fig. 9.23), better with ultrasound guidance, is the safest method of evacuating the uterine cavity, which minimizes the chances of uterine perforation [3]. Authors recommend more caution in this surgical procedure, as uterine perforation is always possible in every D&C procedure (Figs. 9.24 and 9.25). Sometimes, surgeons can remove directly molar pregnancy by using ring forceps and fingers (Figs. 9.26, 9.27 and 9.28). After D&C, the remaining residual trophoblastic tissue should be removed by gentle sharp curettage [8]. The use of oxytocin is advised in cases of severe bleeding [7]. Otherwise, its use is debatable, as oxytocin can raise intrauterine pressure, causing tumor embolism [61]. In Rh-negative women, Rh immune globulin should be administered at the time of suction [3]. Repeated D&C is not recommended due to risk of infection, hemorrhage, and uterine perforation [57, 63]; moreover, it will not eliminate the need for chemotherapy required because of myometrial invasion [3]. A second D&C may be needed only in selected cases when there is suspicion of a residual molar tissue after an ultrasound exam or due to vaginal bleeding. UK protocols recommend a second evacuation only in patients with a retained tissue when serum hCG is below 5000 mIU/mL [3, 7, 67]. Medical induction is optional in cases of a second trimester PHM, when surgical evacuation is technically not feasible. Otherwise, it is not recommended because of possible risks of trophoblastic tissue embolization, higher incidence of incomplete abortions, and increased likelihood for chemotherapy requirement [7, 68]. Hysterotomy is also not advisable, as it increases trophoblastic tissue dissemination and the development of postmolar GTN requiring chemotherapy, and it increases the cesarean section rate in subsequent pregnancies [8].

In women who do not wish to retain fertility, hysterectomy with the HM in situ is also an option, although it does not eliminate the need for chemotherapy [3]. Ovaries can be preserved following aspiration of the theca lutein cysts. In some cases, hysterectomy is required to control hemorrhage complications [68]. Women treated either way, including hysterectomy, need a serum hCG follow-up as the risk of postmolar GTN remains [8].

The issue of prophylactic chemotherapy with suction evacuation is debatable [8, 69, 70]. There are reports

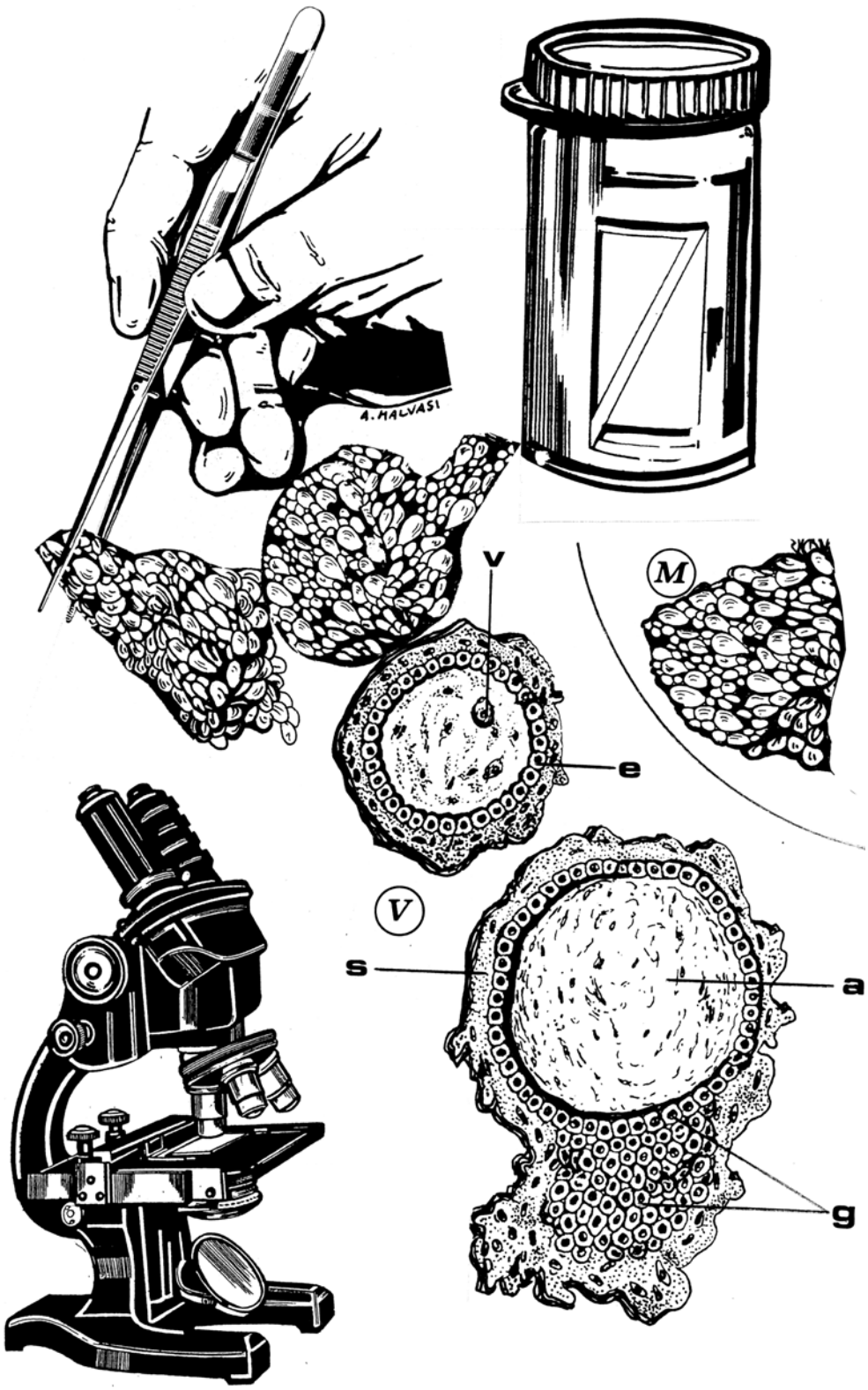

Fig. 9.22 A fresh histopathological examination of the specimens of a molar pregnancy, obtained by a D&C

indicating that chemoprophylaxis reduces the incidence of GTN from 3 to 8 % [8, 68]. However, Fu et al. [70] documented that patients who developed subsequent GTN are diagnosed later and require more chemotherapy cycles if they received prophylactic chemotherapy. Furthermore, such an approach would expose a large number of patients to cytotoxic chemotherapy, out of which a small number would develop GTN [61]. Hence, prophylactic chemotherapy is currently not recommended [70].

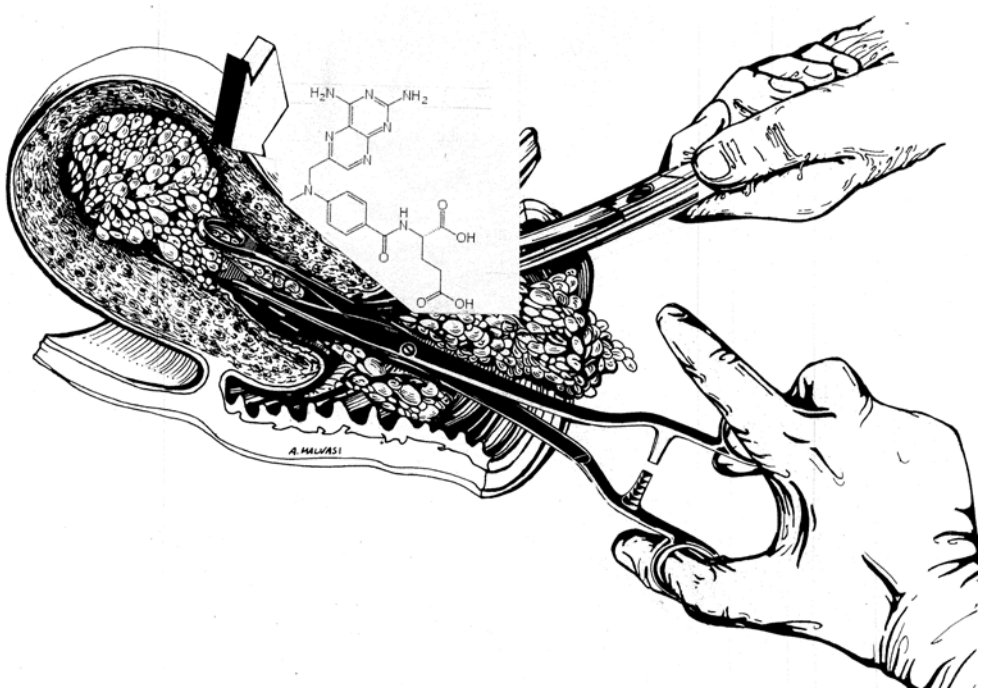

Fig. 9.23 A schematic representation of a molar pregnancy evacuated by Karman cannula introduced in the uterus after vaginal prostaglandin application

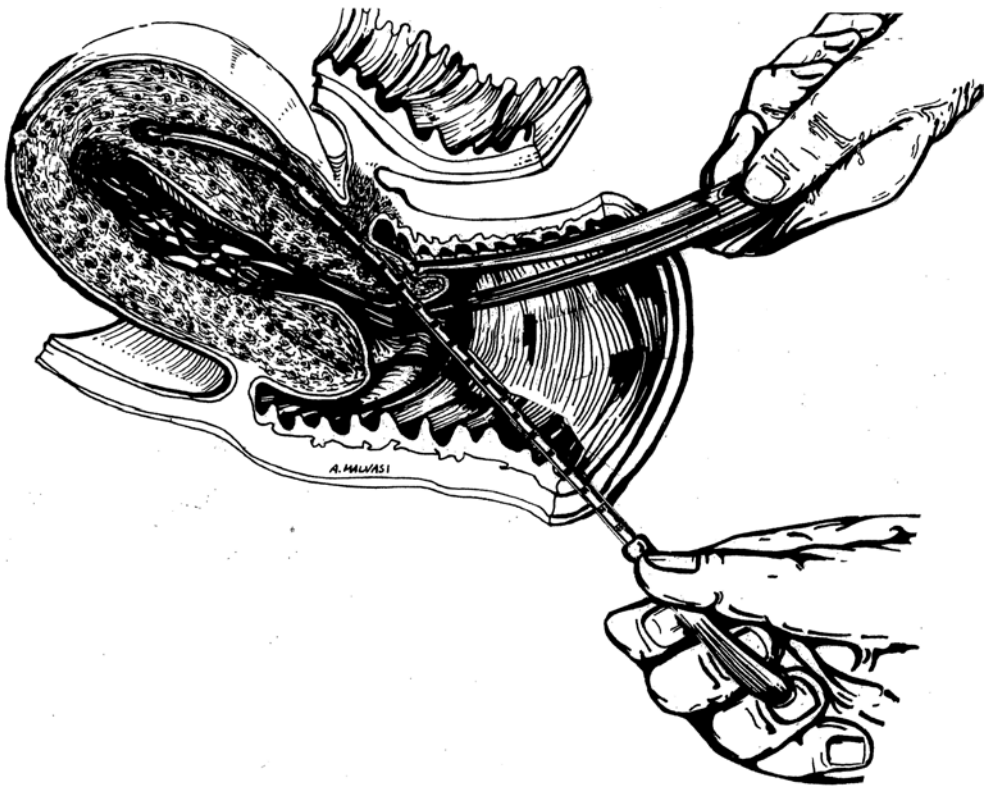

Fig. 9.24 A uterine perforation by hysterometer mistakenly introduced into the anterior uterine wall, in the myometrium, before a D&C

9.4.3 Management of Stage I GTN

The type of treatment in women with stage I GTN primarily depends on whether the patient desires future fertility. In patients who do not wish to retain fertility, hysterectomy with single-agent chemotherapy is a reasonable option, although it does not eliminate the need for chemotherapy [67]. Chemotherapy in such cases is useful for two reasons: the first being that it eliminates viable tumor cells that may have been disseminated during surgery and the other that it treats potentially present occult metastases. Literature data assert that chemotherapy is safe at the time of surgery and does not increase operative morbidity [56]. Fertility-sparing treatment implies local uterine resection with single-agent chemotherapy and can be applied in cases of well-circumscribed tumors.

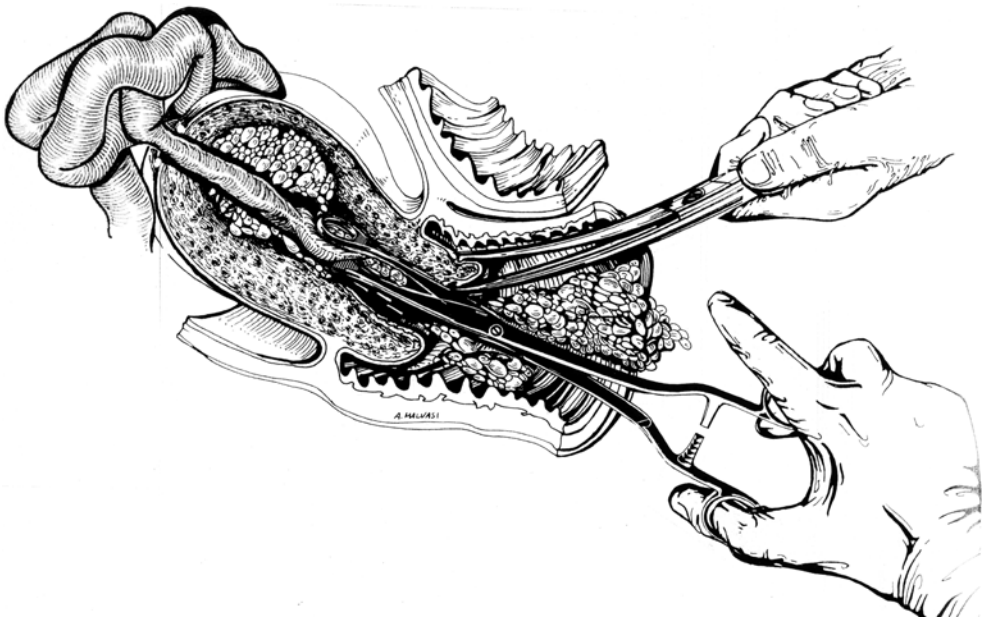

Fig. 9.25 Uterine perforation by ring forceps introduced in utero; the surgical forceps grasps the small bowel floating in the pelvis

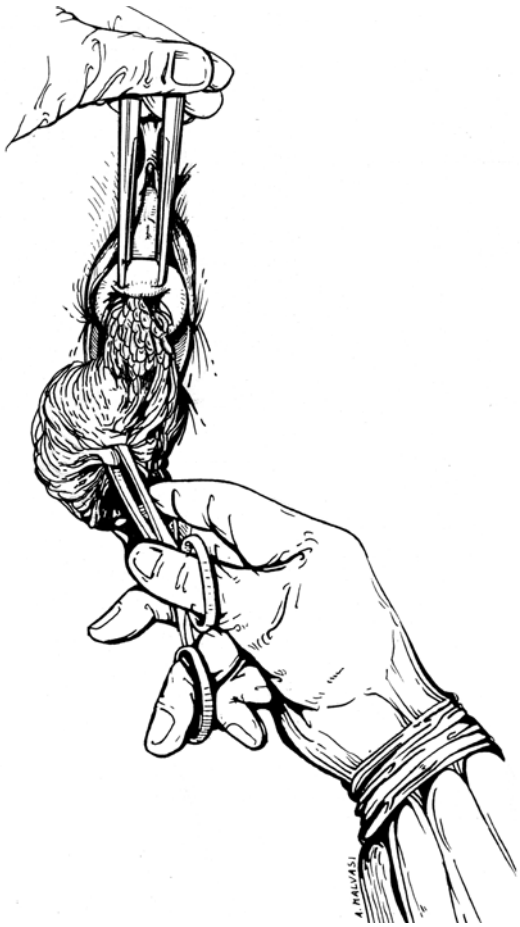

Fig. 9.26 The surgeon gently grabs, with the clamp ring, the molar pregnancy through the cervix, removing it by pulling it out of the uterus

9.4.4 Management of Stage II and III GTN

Depending of the risk scores, patients can be treated with single-agent chemotherapy in cases with low-risk scores or combination chemotherapy in cases with high-risk scores. Additional treatment options include hysterectomy, vaginal packing, arterial embolization, lung resection, and treatment of complications, mainly infection and hemorrhage [59, 61].

Hysterectomy is a reasonable option for reducing the uterine trophoblastic tumor load in patients with extensive uterine enlargement. Furthermore, it is necessary in patients with metastatic disease and complications, such as uterine perforation, hemorrhage, or infection [56]. Salpingo-oophorectomy is recommended in cases of theca lutein cyst complications [7]. Hysterectomy is also beneficial in patients with recurrent uterine disease. It also the treatment of chemoresistant tumors localized in the uterus, as well. In cases of a low-risk disease, hysterectomy can also contribute to the successful treatment with single-drug chemotherapy, as well as to fewer cycles and overall shorter duration of chemotherapy [56]. It proved to be safe both after and during the chemotherapy cycle, as it does not increase perioperative morbidity [56]. Furthermore, perioperative chemotherapy is useful for eradicating the possible dissemination of viable tumor cells during surgery [56].

In patients with vaginal metastases, profuse bleeding can be controlled by tamponade apposition [56]. When chemotherapy starts, lesions regress and bleeding is less likely. Hemostasis can be also achieved by angiographic embolization of the uterine or hypogastric arteries. This can only be performed in hemodynamically stable patients [7]. In settings where it is not possible, hysterectomy and arterial ligation are alternatives [61].

Lung resection is indicated in patients who are, overall, in good condition to sustain surgery, with single lung metastasis and no other metastatic sites and with controlled primary uterine malignancy and the hCG level below 1000 mIU/mL [56, 61, 71]. Such approach can improve remission rates. Thoracic surgery is also useful for curative resection of

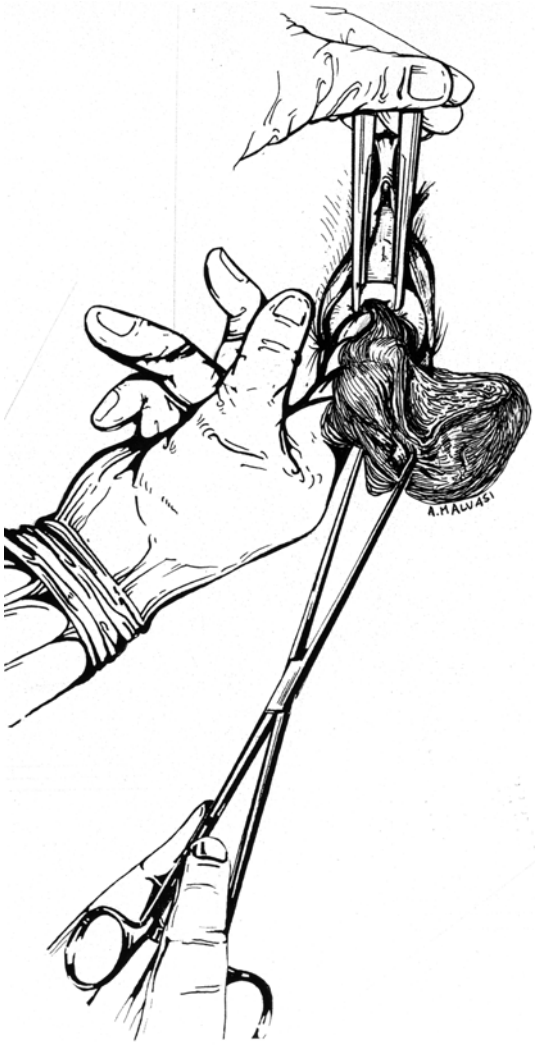

Fig. 9.27 The surgeon, keeping the molar pregnancy attached to the clamp ring, dilates the cervix by finger of the other hand, to facilitate the passage of molar pregnancy through the cervix

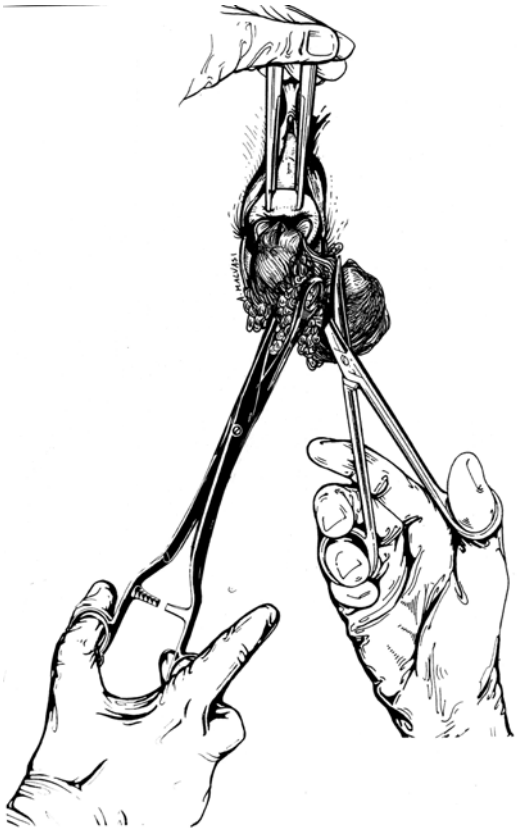

Fig. 9.28 During the removal of molar pregnancy through the cervix, the surgeon may also cut molar fragments as specimens for fresh histological analysis, by the pathologist

drug-resistant GTN foci [56, 67]. Nevertheless, the role of thoracotomy is limited, as most patients with lung metastases can be successfully treated with chemotherapy [56].

9.4.5 Management of the Stage IV GTN

These patients should be treated primarily with intensive polychemotherapy in combination with surgery and radiation therapy, if necessary. Unlike in cases with low-risk disease, hysterectomy does not improve the treatment outcome in patients with stage IV.

Optimal treatment for women with CNS involvement has yet to be established [35, 72]. Incidence of brain metastases ranges from 3 to 21.4 %, and these patients have low survival rates [72]. In cases with a disseminated disease, brain metastases are present in 90 % of patients [73]. CNS lesions can be treated by chemotherapy, either only by systemic chemotherapy or combined with intrathecal methotrexate (MTX) [72]. Apart from chemotherapy, brain metastases are treated with whole-brain irradiation or localized radiation, with metastasectomy and craniotomy to manage complications, such as hemorrhage and/or brain compression [7]. Irradiation has a dual role, both hemostatic and necrotic. In cases with multiple metastases, whole-brain irradiation is required, while solitary lesions can be treated locally. Metastasectomy is helpful in cases of superficial and solitary metastases and in cases resistant to chemotherapy [35]. Emergency craniotomy is necessary in cases with increased intracranial pressure caused by cerebral hemorrhage or edema [35, 72]. Cure rates reported in the literature for patients with cerebral metastases are 50–80 % [57]. Out of 101 patients treated in a single center over a 24-year period, 22 % had craniotomy which improved the prognosis [72]. The authors presented their experience in treating patients with brain metastases at Peking Union Medical College Hospital from 1990 to 2013. Patients with brain metastases were treated with polychemotherapy (fluorouracil/floxuridine, actinomycin D, etoposide, and vincristine). Their results assert that the disease can be cured and the patients have an overall 5-year survival rate of

Table 9.3 Indications for chemotherapy

Indications for chemotherapy	
hCG	Serum hCG levels above 20,000 IU/L more than 4 weeks after the evacuation
	Rising hCG levels
	hCG in body fluids >6 months after evacuation of molar tissue
Histology	Histological evidence of choriocarcinoma
Metastases	Evidence of brain, liver, or gastrointestinal tract metastases
	Radiological opacities >2 cm on chest X-ray
Hemorrhage	Long-lasting uterine hemorrhage following D&C
	Evidence of gastrointestinal or intraperitoneal hemorrhage

71.1 %, excluding early death cases. Prognosis is poor for those women with concomitant kidney metastasis and multiple site distant metastases and previous polychemotherapy failure history and who are over 40 years old with a FIGO score >12 [72].

Liver metastases are especially difficult to treat because of a pronounced risk of massive hemorrhage. In most cases, they can be successfully treated only by chemotherapy [56]. In highly selected cases, they are managed by hepatic resection and selective hepatic artery embolization [7, 56]. Seldom, liver metastases are simultaneously treated with radiotherapy and chemotherapy [7].

9.4.6 Principles of Chemotherapy

Chemotherapy is the first-line therapy for GTN [74]. Recommendations for its use are defined based on prognostic risk scores. According to the UK criteria, indications for chemotherapy are presented in Table 9.3 [67].

9.4.6.1 Low-Risk Disease

Low-risk GTN patients are those with stage I, II, and III cases with a FIGO score ≤6, and they usually respond well to single-agent chemotherapy [56]. Single-agent chemotherapy regimen applied in most GTN centers includes either methotrexate (MTX) or actinomycin D (ACTD) in various regimens [56, 57]. Most of the GTN treatment centers use MTX as the first line of therapy. In most patients with low-risk GTN, single-agent chemotherapy with MTX or ACTD is effective, well tolerated, and relatively safe and provides good results [63]. Literature data indicate that such an approach results in a remission rate of >90 % [57]. Those drugs are administered either at a fixed time interval or based on hCG regression curves [61]. Due to significantly higher toxicity, alternative drugs, such as etoposide and 5-fluorouracil, are rarely used as monochemotherapy in cases of low-risk GTN [7]. As ACTD is associated with much higher toxicity, most protocols include MTX with folinic acid (FA) rescue as the first line of therapy, with ACTD indicated only in patients who are not suitable for MTX, such as those with hepatic or renal dysfunction [56]. The most common side effects of MTX/FA include granulocytopenia, thrombocytopenia, rashes, stomatitis, and hepatotoxicity. According to the recent Cochrane review, ACTD treatment compared to MTX/FA has higher rates of primary cure and less treatment failure [75]. In patients with pleural effusions and large theca lutein cysts, it is also recommended to avoid MTX [57]. When patients become resistant to MTX/FA, they can be treated with ACTD, if hCG is less or equal to 100 mIU/mL, or with polychemotherapy if hCG is more than 100 mIU/mL [3]. In the UK, the cutoff level of hCG in such cases is 300 mIU/mL [3]. Polychemotherapy is advised for patients who develop a resistance to monochemotherapy. Approximately 20 % of low-risk patients will develop resistance to the initial chemotherapeutic drug [57]. Recent studies report that the uterine artery pulsatility index of ≤1 indicates an increased risk to MTX resistance in patients with low-risk GTN [60].

Patients with a recurrence of a low-risk disease, or MTX resistance, can be treated with ACTD or polychemotherapy, such as MAC (methotrexate, actinomycin D, and cyclophosphamide or chlorambucil) or EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine with folinic acid rescue) [7]. Etoposide is documented to increase the relative risk of later secondary malignancies [57]. Therefore, its use is reserved for cases with a high-risk metastatic disease, while in low-risk and nonmetastatic GTN patients, the MAC regimen is an acceptable option for polychemotherapy prior to regimens containing etoposide [61]. Approximately 10 % of low-risk patients will require polychemotherapy, with or without surgery, to achieve remission [57].

9.4.6.2 High-Risk Disease

Patients categorized as having high-risk GTN include those with stage II or III GTN and a FIGO prognostic score of ≥7 originally require treatment with polychemotherapy [56, 57]. There are various chemotherapy protocols used in treating a high-risk disease. However, accurate data on the efficacy and safety of these are still lacking [76]. In such patients, MAC protocol is insufficient, as cure rates are 63–71 % [56, 57]. In most centers, EMA-CO is the first-line regimen for the treatment of high-risk GTN due to its highest effectiveness-to-toxicity ratio [56, 63]. The documented side effects include mucositis, pleuritis, alopecia, liver damage, myelosuppression, and vincristine-associated peripheral neuropathy [7]. Still, 30–50 % of these patients develop resistance and require alternative treatments [61]. In such cases, it is crucial to recognize drug resistance, either by the plateauing or

rising hCG levels and/or by the appearance of new metastases. Other available protocols have also been recorded to be effective in GTN treatment [56]. Regardless of the chemotherapeutical agents used, it is essential to avoid treatment delays and dose reductions in order to reduce incidence of treatment failure and tumor resistance [56].

Both high-risk patients and those with resistant GTN requiring polychemotherapy must be treated with several cycles of chemotherapy to achieve remission. Response to chemotherapy is monitored by the serum levels of hCG [7]. Consolidation chemotherapy after hCG normalization is advisable in order to eradicate any residual disease foci [7]. It is advisable to administer two to four additional cycles of chemotherapy following three undetectable hCG levels [56]. Consolidation chemotherapy should be continued for 6 weeks after the normalization of hCG levels [3]. In patients with brain or liver metastases, therapy should be continued for 8 weeks [3].

Six weeks after the end of treatment, a detailed evaluation for persistent and recurrent GTN should be performed, and this should be repeated in 6 months [65]. Such evaluation includes a chest X-ray, a Doppler ultrasound of the pelvis, and either a CT or MRI imaging of all the disease sites. In cases of a recurrence in high-risk patients, aggressive polychemotherapy is recommended [58, 61].

Although the available agents have proven to be useful in GTN treatment, continuous scientific efforts are made in order to identify new drugs that would be active in cases when GTN becomes chemotherapy resistant.

9.4.7 Management of Placental Site Trophoblastic Tumor and Epithelioid Trophoblastic Tumor

PSTT is a rare, slow-growing variant of trophoblastic tumor which imposes significant diagnostic and management difficulties. It was first described in 1976 [7]. Given the rarity of PSTT and its variable biological behavior, there are limited data regarding its optimal management and prognosis [77]. Most of the reported data are either case reports or small case series [65]. PSTT can present following any type of pregnancy with a long interval after an antecedent pregnancy [7]. Those tumors grow slowly, metastasize later, and produce less hCG. Tumors are commonly limited to the uterus, infiltrating the myometrium and spreading in the pelvis via lymphatics before systemic dissemination [7].

These tumors are relatively chemoresistant; therefore, surgery represents the most feasible treatment [63]. Hysterectomy, with or without ovarian conservation and pelvic and retroperitoneal lymph node dissection, plays a major role in PSTT treatment [63, 65]. A patient's age, family, and reproductive history influence the decision on oophorectomy [65]. The ovaries in premenopausal women can be preserved for possible future surrogate pregnancies, except in cases with ovarian involvement or in women with a family history of ovarian cancer [63]. Fertility-sparing options include focal resection of the affected part of the uterus in cases with limited myometrial involvement [7, 77]. Leiserowitz and Webb [78] presented a case of term live neonate cesarean delivery in a patient treated by local tumor excision and uterine reconstruction for anterior fundal tumor. On the other hand, Pfeffer et al. [79] documented the foci of PSTT in a hysterectomy specimen of a patient previously treated with fertility-sparing partial hysterectomy. The multifocal disease in their patient was missed by imaging, such as Doppler ultrasound, MRI, CT, and PET scan. In cases of incomplete resection due to multifocal microscopic uterine disease, hysterectomy and adjuvant chemotherapy are further treatment options [79].

Surgery alone is often effective for the treatment of stage I patients with PSTT [56]. There is no definite evidence regarding the benefits of chemotherapy in stage I and stage II patients [65]. Nevertheless, this combined treatment approach is recommended in the UK for patients with stage II disease [65]. In addition, it is recommended in cases with stage I disease, where there is the presence of risk factors for recurrence, such as a long interval after an antecedent pregnancy, vascular invasion, deep myometrial invasion, serosal involvement, high mitotic index, or the combination of these factors [65]. Surgery, if feasible, is also advised for a residual and metastatic disease, as well as for a recurrent disease [63, 65].

In cases of metastatic disease and in patients with positive hCG levels after surgery, polychemotherapy is necessary, either alone or in combination with surgery [77, 79]. Polychemotherapy protocols include EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine), EP-EMA (etoposide, methotrexate, actinomycin D, cisplatin), and MAF (methotrexate, actinomycin D, etoposide) [65, 80]. It should be discontinued after 8 weeks of normal hCG [3, 63].

Patients diagnosed with PSTT should be exclusively managed in specialized centers with adequate level of expertise. Furthermore, such patients require a multidisciplinary treatment approach and teams of clinicians with expertise in managing GTN, consisting of gynecologists, medical oncologists, radiotherapists, and surgeons proficient in liver, brain, and thoracic surgery, as well as psychologists. The supportive care component must be included in the management of these women.

ETT was first described in 1998 [7]. It is the rarest type of GTN and reports are scarce [3, 56]. According to Davis et al. [81], the available data include a total of 108 reported cases, most of those being case reports. It is an extremely rare neoplasm derived from intermediate trophoblast and is frequently localized in the lower uterine segment or cervical canal [81, 82]. Its behavior is similar to PSTT [7]. Those

tumors are not chemosensitive and cornerstone treatment modality is surgery [7, 57, 82]. This is quite challenging, as those tumors are predominantly present in women of reproductive age [81]. Primary treatment modality for patients with intrauterine disease is hysterectomy [82]. If feasible, metastases are also treated surgically, by resection, i.e., lung resection and bowel resection [82].

9.4.8 Management of Chemoresistant and Recurrent GTN

Consolidation chemotherapy cycles are applied to avoid recurrence. Most recurrences happen in the first year of follow-up [63]. The risk of GTN recurrence is about 3 % in the first year after therapy completion, but later it is much lower [57]. Following initial chemotherapy, up to 25 % of GTN patients will develop resistance or recurrence, in which cases salvage chemotherapy, and in some instances, surgery is required [71, 83]. Reported recurrence rates range from 2.9 % for patients with stage I disease to 9.1 % for those with stage IV disease [56, 68]. Management of such patients requires a high level of expertise available in centers specialized for GTN treatment [57].

Risk factors for resistance and recurrence include advanced stage of the disease and high-risk score, an interval longer than 12 months between the antecedent pregnancy and the start of chemotherapy, high pretreatment hCG levels, histological diagnosis of choriocarcinoma, and undetectable serum β-hCG after seven cycles of chemotherapy and less than two cycles of consolidation chemotherapy [58, 71]. A significant risk factor for recurrence is also the patient's default from follow-up [58]. Recurrence after chemotherapy mostly occurs during the first 12 months of follow-up [67]. A great number of these patients can be cured with further chemotherapy [56].

Resistance to primary chemotherapy occurs in about 5 % of the patients with low-risk GTN without metastases and 10–15 % of those who have metastases [71]. For patients with a low risk of GTN, who become resistant to MTX, further treatment options include ACTD, followed by polychemotherapy with MAC or EMA-CO [71, 83]. ACTD is used in cases with low hCG levels (≤100 or ≤300 mIU/mL, depending of the institutional protocol), while in cases with higher levels polychemotherapy is used [71]. Due to increased risk of secondary malignancies in patients treated with etoposide, MAC is preferred over EMA-CO as the initial regimen [82].

Cases with high-risk GTN that develop resistance or recurrence are treated with various salvage polychemotherapy regimens, with or without surgery [71]. These chemotherapy protocols vary throughout the world [83]. These regimens mostly consist of etoposide or platinum in combination with bleomycin and isofosfamide [57, 58, 61]. In addition, surgery, when feasible, may also have an important role for these patients [2, 58, 61]. Both hysterectomy and focal uterine resection of the tumor mass are useful in cases of resistance [56]. Due to the heterogeneity of the cases, comparisons of these regimens in terms of efficacy and toxicity are difficult.

9.4.9 Psychological Counseling in Patients with Gestational Trophoblastic Disease

Women suffering from GTD are faced with significant psychological distress [56, 68]. However, data on health-related quality of life in those patients are limited [84]. The importance of psychological counseling is pronounced by high survival rates and overall excellent prognosis following chemotherapy. GTD jeopardizes both a woman's life and reproductive performance [85]. Forced delay in future pregnancies during the follow-up period potentially causes anxiety in these patients [85]. Marital and sexual problems could arise from the patient's perception of the nature of her disease inducing anger and guilt between patient and her partner. The negative impact of chemotherapy on these patients' sexual life is documented [84]. Furthermore, there is fear of possible side effects of chemotherapy, disease recurrence, infertility, and possible unfavorable outcome of a future pregnancy [84]. For all these reasons, approximately one-half of the affected women suffer from either physiological or sexual problems [68]. Hence, during therapy and follow-up, patients need emotional support from the medical staff and their family.

9.4.10 Follow-Up of Patients Treated for HM and GTN

Follow-up protocols vary depending on setting. Worldwide, different protocols for hCG surveillance are established with the same basic principles [63].

After the evacuation of molar pregnancy, remission is monitored with serial weekly hCG levels until non-detectable for 3 weeks. Further follow-up is performed with monthly investigation of hCG levels during a 6-month period [68]. During chemotherapy treatment, serum hCG concentrations are assessed twice a week, until hCG levels become normal [65]. Following normalization, hCG is measured once a week during consolidation chemotherapy cycles or at least once a week during 3 weeks [56, 74]. Further follow-up is conducted with monthly hCG assessment for 12 months, except in patients treated for stage IV disease, for whom this period is extended to 24 months [56]. In all stage patients, further checkups are advised every 6 months for the next 5 years [61]. Physical examinations are performed in

6–12-month intervals; other tests are rarely performed [57]. In the UK, follow-up with urine hCG assessments is continued for life [67].

After the normalization of hCG levels, women are advised not to get pregnant in order to allow efficient hCG follow-up. In cases of a molar pregnancy, this period is 6 months and in cases of GTD requires chemotherapy at least 12 months [65, 68]. During this period, reliable contraception including the use of low-dose oral contraceptives is strongly recommended [65]. The use of intrauterine devices is contraindicated, unless the hCG levels are normal [61]. Delayed conception allows the elimination of the mature ova that could have been damaged by exposure to chemotherapy [57]. In cases of pregnancies within 6 months after GTN treatment, the risk of miscarriage and stillbirths is increased [56].

The conception products of all future pregnancies should be histologically examined [61]. Following the completion of each future pregnancy, serum hCG level should be checked after 6 weeks and again after 10 weeks to exclude recurrence [63, 67].

9.4.11 Prognosis

In cases with CM, GTN may occur with a reported incidence ranging from 8 to 29 %, with an average of 15 % [58]. Following PM, 0.5–1 % of patients will develop GTN [3]. After D&C, hCG falls rapidly to normal levels in most patients with HM. In patients whose hCG levels become normal in up to 8 weeks following evacuation of the molar pregnancy, the occurrence of GTN is rare [8].

After a nonmetastatic and low-risk metastatic GTN treatment, the outcome is generally excellent. According to the FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer, the overall 5-year survival period of GTN patients is 97.3 % [64]. For stage IV disease, however, it is 62 % [64]. For the high-risk group of patients, the 5-year survival period is 79.5 %. It is important to underline that monitoring patients following a molar pregnancy would facilitate the diagnosis of GTN at an early stage, thus enabling prompt treatment and a survival rate of almost 100 % [64]. Stage IV disease is usually diagnosed in cases without a previous molar pregnancy, and it frequently is a choriocarcinoma. Therefore, choriocarcinoma should be considered in any women with symptoms of a metastatic disease of an unknown origin. This would facilitate a timely diagnosis in these patients.

The survival rate in patients with PSTT and ETT is approximately 100 % in women with nonmetastatic disease and 50–60 % in those with a metastatic disease [57]. Reliable data on optimum management, prognostic factors, and outcomes in women with PSTT are limited due to the rarity of the condition [65]. The overall prognosis is less favorable than in patients with other forms of GTN [65]. Patients with a recurrent disease have an unfavorable prognosis, with only 33 % achieving long-term remission [65].

Schmid et al. [65], in 2009, published the data on PSTT obtained in the UK. The study included 62 women treated over a 30-year period. Based on their findings, the overall 10-year survival period after the first treatment was 70 %, while recurrence-free survival was 73 %. Women with stage I disease had a 10-year overall survival rate of 90 %. The overall 10-year survival probability was 52 % for women with stage II disease and 49 % for stages III and IV. In cases with a recurrent or resistant disease, the prognosis was poor; approximately 22 % achieved a survival period beyond 60 months. The prognosis was worse for patients with a prolonged interval between the antecedent pregnancy and tumor development (over 48 months).

The data on survival and prognosis for patients diagnosed with ETT are mostly insufficient. The authors from the New England Trophoblastic Disease Center (NETDC) reviewed a case series of seven patients they treated for ETT [81]. They concluded that the most important factor for the poor prognosis is extrauterine disease. An interval greater than 4 years from an antecedent pregnancy is thought to be another possible marker for an unfavorable outcome. Conclusions on prognostic factors, treatment, follow-up protocols, survival rates, and incidence of recurrence are difficult to define due to insufficient data [81, 82].

The reported remission rates in women with chemoresistant and recurrent GTN are 52.6 % and 76.7 %, respectively [71]. The overall 5-year survival period for patients with GTN recurrence is 90 % [68]. In women with a recurrence of high-risk GTN, a 5-year survival rate is around 85 % [68].

Following treatment with etoposide-containing regimens, there is an increased risk of secondary malignancies, namely, acute myelogenous leukemia, colon cancer, melanoma, and breast cancer [57].

9.4.12 Fatal Outcomes

Although the overall survival of patients diagnosed with GTN is excellent, some of them die because of late presentation, complications, or drug resistance [3]. There are several risk factors associated with a fatal outcome of GTN. They include an antecedent non-molar pregnancy, high initial levels of hCG, choriocarcinoma, prolonged duration of the disease, multiple sites, and increased number of metastases and chemoresistance [66, 86, 87]. Causes of death described in the literature are hemorrhage, infection, multiorgan failure, or tumor lysis syndrome [66]. The incidence rate of early deaths, occurring within 4 weeks following the start of treatment, can be reduced with induction chemotherapy with a low dose of etoposide and cisplatin,

repeated weekly for one or two cycles in women with an extensive disease [66, 87].

Neubauer et al. [86] evaluated GTN with a fatal outcome at the Brewer Trophoblastic Disease Center in the USA. Out of a total of 443 women during the study period, 4 % with GTN died. Out of those, 95 % were treated for choriocarcinoma, while the remaining patients had PSTT. Non-molar index pregnancy was registered in 63 %. The causes of death included widespread chemoresistant disease, respiratory failure due to lung involvement, and fatal hemorrhage from the metastatic sites. The cited authors highlighted psychosocial factors as the contributing factors for unfavorable disease outcome, since 21 % of the women who died had delayed treatment due to psychosocial factors.

Lybol et al. [87] investigated 26 women who died from GTN over a period of four decades in the Netherlands. Early deaths occurred due to hemorrhage, sepsis, and pulmonary embolism. Patients who died after more than 4 weeks following the initiation of the treatment mostly died from metastases. Overall, 73.1 % of women died from metastatic disease. The most common cause of death was hemorrhage, either from the uterus or from metastases.

A recent analysis published by Bolze et al. [66] assessed the cases of fatal GTN from the French Center for Trophoblastic Diseases. The overall 5-year mortality rate after excluding PSTT and ETT cases in their series was 2 %. For PSTT and ETT, it was 7.6 %. A 5-year mortality rate in low-risk patients and high-risk patients was 0.3 % and 12 %, respectively. Women with a FIGO score of ≥13 represented 52 % of the fatal cases, and the 5-year mortality rate in those was 38.4 %. Therefore, they suggested a FIGO score of ≥13 as a criterion for defining the subgroup of GTN patients with increased risk of death. These patients should be managed in highly specialized centers capable of providing the necessary treatment and all the support measures, such as intensive care, interventional radiology, neurosurgery, and renal dialysis.

9.4.13 Persistent Gestational Trophoblastic Disease

Gestational trophoblastic tumors can develop after any type of antecedent pregnancy, most frequently after HM. Approximately 15 % of patients with complete HM and 0.5–1 % of patients with partial HM will exhibit persistent trophoblastic activity, which requires chemotherapy [61, 67]. This condition is defined as persistent gestational trophoblastic disease (PGTD) [67]. Most of these will have an invasive mole, while approximately 3 % will have choriocarcinoma or rarely PSTT or ETT [67]. The hCG regression curve serves as a reliable guide for chemotherapy administration, but can also be a means of identifying patients who are going to develop a persistent GTD [61].

Some patients develop PGTD after a non-molar pregnancy, i.e., non-molar abortions, ectopic pregnancies, or live births, and they account for approximately 17 % of the cases [58]. Differential diagnosis in these cases includes numerous primary non-gestational tumors with trophoblastic differentiation and hCG production, such as carcinomas of the bronchus, stomach, bladder, colon, etc. In these circumstances the genetic analysis of tumor origin is a valuable instrument for diagnosis, as the presence of paternal alleles reveal the gestational nature of the tumor [74, 88].

9.4.14 Management of Quiescent Gestational Trophoblastic Disease

Few GTD patients exhibit persistently low levels of hCG, without any clinical or imaging disease evidence [71]. They represent an entity called quiescent GTD [56, 71]. In these women, hCG levels are usually unchanged for at least 3 months, ranging from 50 to 100 mIU/mL [71]. Neither chemotherapy nor surgery leads to the normalization of hCG levels in such cases [71]. Patients with quiescent GTD can be identified by measuring hyperglycosylated hCG (hCG-H), which is present at very low levels or even undetectable [71]. Thus, it is a reliable tool for distinguishing GTN from quiescent GTD [71].

Patients with quiescent GTD and undetectable hCG-H should be monitored, and in most cases hCG levels will become normal within 6 months [71]. In 6–20 % of cases, over a period of several years, hCG levels will start rising, causing hCG-H to become detectable [56, 71]. When this occurs, chemotherapy will be required [71].

9.4.15 Twin Pregnancy with GTD

A healthy co-twin can develop alongside a complete or partial hydatidiform mole in 1 per 20,000–100,000 pregnancies [89]. In such cases, first a diagnosis by an ultrasound examination should be made. Amniocentesis is expected to aid the decision-making.

The complete hydatidiform mole with a coexisting fetus can be classified into three major types:

- Twin gestation, in which one twin is a normal diploid fetus with a normal placenta and the other twin is a complete hydatidiform mole without fetus
- Singleton gestation, consisting of a triploid fetus with partial hydatidiform mole placenta
- Twin gestation, in which one twin is a normal, diploid fetus with normal placenta and the other twin is a triploid fetus with partial hydatidiform mole placenta [90]

Categorization of the case is essential for proper management. The management of these pregnancies is difficult because they are usually associated with complications, such as fetal death, vaginal bleeding, preeclampsia, preterm delivery, and an increased risk of persistent GTD [91]. Some researchers recommended to terminate such pregnancies because of the low probability of a successful outcome and a high risk of developing a malignant disease [80, 91]. However, the results from a case series of 77 pregnancies suggest that about 40 % of women will deliver a healthy baby without an increased risk of malignant transformation of the complete hydatidiform mole [92].

Findings from a study of 2800 singleton molar pregnancies imply that late evacuation of complete hydatidiform mole is not associated with an increased rate of malignant disease [93].

Authors suggest that continuation of the pregnancy with complete hydatidiform mole and a coexisting fetus may be an acceptable option. Such pregnancies may continue until term if a normal anatomy is assured, and possible complications are under control. These patients require careful postpartum follow-up and any recurrent disease should be treated aggressively [94].

9.4.16 Risk of Repeat Gestational Trophoblastic Disease

Patients who had GTD are more at risk of having GTN after a subsequent normal pregnancy. Patients with previous GTD should undergo a detailed ultrasound exam in the first trimester of subsequent pregnancy to exclude a repeated molar pregnancy.

Eagles et al. [17] conducted a study of subsequent pregnancies in 16,000 women registered at Charring Cross Hospital in London during a 20-year period. Their results indicated that patients diagnosed with CM have a risk of repeated HM of 0.91 %, while those with PM have a lower risk of 0.28 %. In patients with CM, a second molar pregnancy was most likely to be the next one, while in those diagnosed with PM they found a history of live births and miscarriages before a second molar pregnancy. Out of 166 patients with a second HM, 22(13 %) had a third HM, most frequently CM. In this subgroup, FRHM was diagnosed in 11, which enabled the estimation that 1 in 640 of women diagnosed with CM has FRHM. FRHM is an autosomal recessive condition caused by mutation in either the NLRP7 or KHDC3L gene, predisposing women to molar pregnancies, although the absence of mutations in these genes does not exclude the diagnosis. Around 20 % of women affected with FRHM have possible mutations in some other genes that have yet to be identified [17]. These women, in order to achieve a normal pregnancy, should consider oocyte donation [17]. The presence of GTN requiring chemotherapy in this study was registered in 8.9 % of the patients following CM and 3.3 % of the patients diagnosed with PM.

9.4.17 Prognosis for Pregnancies After Molar Pregnancy and Gestational Trophoblast Neoplasia

It is generally accepted that patients with HM, either complete or partial, have later normal reproductive outcomes. Nevertheless, such patients are at increased risk of repeated molar pregnancy in future pregnancies [17]. After one molar pregnancy, the risk of developing HM in subsequent conception is 1–2 % [3, 67]. In patients who experienced two molar pregnancies, the risk is higher, and the reported incidence is 15–20 % [3, 67].

Most women affected with GTN are of reproductive age. Given the high overall current cure rate, fertility is an important issue for these women [57]. Approximately 7 % of the patients treated for GTN with chemotherapy will have secondary infertility [56]. In terms of subsequent pregnancies following GTN treatment, the prognosis is generally good, apart from the EMA-CO regimen bringing the menopause date forward by 3 years [3, 63]. Following chemotherapy, the overall pregnancy rate is more than 83 % [3], with term live birth rate over 70 % [68]. The incidence of congenital abnormalities is not higher [7]. There is no evidence showing the reactivation of the disease because of subsequent pregnancies [57].

Joneborg et al. [95] conducted a nationwide cohort study, including almost 3.7 million singleton births from the Swedish Medical Birth Register between 1973 and 2009. The authors investigated the risk of subsequent adverse maternal and neonatal outcome in women who had had HM. They did not find any association for pregnancy hypertension, placental abruption, and premature rupture of membrane (PROM). Surprisingly, women with a history of HM had a lower risk of preeclampsia. The same study found a minor but increased risk of low for gestational age (LGA) birth, preterm birth, and stillbirth.

Acknowledgment The authors thank Dr. Svetlana Milenkovic and Dr. Jasmina Atanackovic, histopathologists at the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade, Serbia, for their assistance in selecting photos.

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