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Surgery including fertility-sparing treatment of GTD

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A B S T R A C T

Gestational trophoblastic disease (GTD) consists of a spectrum of diseases, including hydatidiform moles, invasive mole, metastatic mole, choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). GTD is a relatively uncommon disease occurring in women of reproductive age, with high cure rates. Primary treatment of hydatidiform moles includes uterine evacuation, followed by close monitoring of serial hCG levels to detect for post-molar gestational trophoblastic neoplasia (GTN). In patients with GTN, the main therapy consists of chemotherapy, although some surgical procedures are important in selected patients to achieve curing. Hysterectomy is the mainstay treatment for PSTT or ETT and may be considered in selected patients for management of hydatidiform mole and malignant GTN especially in chemoresistant disease. Resection of metastatic lesions such as in the lung or brain can be considered in selected patients with isolated chemoresistant tumour. Surgical treatment of GTD will be discussed in this chapter.

Introduction

Gestational trophoblastic disease (GTD) consists of a spectrum of diseases, including hydatidiform moles (complete mole and partial mole), invasive mole, metastatic mole, choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). According to the

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International Federation of Gynecology and Obstetrics (FIGO), the term gestational trophoblastic neoplasia (GTN) was designated to a condition wherein there is a plateau comprising of at least four persistently elevated human chorionic gonadotrophin (hCG) values over a 3 week period (day 1, 7, 14, 21), or a sequential rise of hCG for two weeks (day 1, 7, 14) or longer, or histologic diagnosis of choriocarcinoma [1]. GTD is a relatively uncommon disease occurring in women of reproductive age, with high cure rates. Primary treatment of hydatidiform moles includes uterine evacuation, followed by close monitoring of serial hCG levels. In patients with GTN, the main therapy consists of chemotherapy, although some surgical procedures are important in selected patients in order to achieve curing. Surgical treatment of GTD will be discussed in this chapter.

Surgery for hydatidiform mole

Suction curettage

Surgical treatment plays an essential role in the management of molar pregnancies and can be attained by either suction curettage or hysterectomy. Generally, suction curettage is recommended for most women because it is effective, preserves fertility and has less morbidity. It involves mechanical dilatation of the cervix, electrical suction evacuation, and gentle sharp curettage. Mechanical dilatation of cervix is done gradually with Hegar dilators until a cannula diameter suitable for the uterine size can be inserted. Most surgeons use a diameter equal to the number of weeks of gestation of a similarly sized normal intrauterine pregnancy. The procedure is ideally performed under ultrasound guidance to reduce the risk of uterine perforation and help determine when the evacuation is complete.

Surgical uterine evacuation can also be done with manual vacuum aspiration (MVA), which can be carried out in the outpatient setting under local anaesthesia. It involves the use of a handheld syringe as a source of suction instead of an electric suction machine. It is an effective and safe alternative for surgical management of miscarriage and termination of pregnancy. Recently, a retrospective study that compared the use of MVA with electric vacuum aspiration for treatment of molar pregnancy reported similar outcomes in terms of incomplete evacuation, blood transfusion and development of post-molar GTN [2]. However, in this study the procedures were performed in the hospital operating theatre under general anaesthesia. There is no consensus in the literature regarding selection criteria and suitability of the women with molar pregnancy for MVA in the outpatient setting. Generally, MVA may be considered in an outpatient setting in women who can tolerate pelvic examination, are haemodynamically stable and have earlier gestation (<10 weeks) and no clinical signs of infection. MVA can be contemplated in areas with limited access to operating theatre, particularly in the current coronavirus disease 2019 (COVID-19) pandemic which has led to a steep decrease in elective surgery scheduling.

Cervical preparation immediately before surgical evacuation is safe. In a recent case-control study of 219 women, cervical ripening prior to uterine evacuation was not associated with increased risk of requiring chemotherapy [3]. However, the study found that a larger uterine size is associated with the subsequent need for chemotherapy. Prolonged cervical preparation should be avoided as far as possible to reduce the risk of trophoblastic cells embolisation. The use of osmotic dilators can be considered in some women, such as nulliparous patients or those with previous uterine scars. It is inserted on the day before the suction evacuation to facilitate cervical dilatation.

Oxytocin can be used to control haemorrhage, is preferably given after cervical dilatation and can be continued for several hours postoperatively to enhance uterine contraction. Administration of anti-D immunoglobulin is required in women with Rh-negative blood types after uterine evacuation because RhD factor is expressed on the trophoblast.

The rate of complication of suction curettage among patients with uterine size less than 16 week of gestation is very low. In a study of 310 women who underwent dilatation and suction curettage for molar pregnancy, the rate of uterine perforation was 0.6% [4]. In case of perforation, suction should be stopped immediately, and laparoscopy or laparotomy should be performed to assess the perforation site. Concurrently, the rate of oxytocin infusion should be increased. If haemostasis is satisfactory and there is no damage to the adjacent organs, evacuation can be safely completed under direct visualisation. However, repair of the perforation site or hysterectomy may be necessary to control bleeding, especially when the perforation site occurs at the area of deep myometrial invasion of the invasive mole.

Women who present with uterine size of more than 16 weeks' gestation have increased risk of complications during suction evacuation, particularly haemorrhage, uterine perforation and pulmonary compromise. As such, these patients should have large-bore intravenous cannulas and blood available for transfusion during the procedure. Central haemodynamic monitoring and immediate availability of laparoscopy or laparotomy should also be ensured. Ideally, an experienced surgeon should perform or supervise the procedure. Acute pulmonary complications were reported in 27% of patients with uterine enlargement of more than 16 weeks' size, which could occur during or promptly after uterine evacuation [5]. The pulmonary complications were mostly due to other medical complications of molar pregnancy, including pre-eclampsia, hyperthyroidism, anaemia and fluid overload. Another recognised cause of acute pulmonary compromise after molar evacuation is trophoblastic embolisation [6–8]; although this is rare [5]. Generally, pulmonary complications after a molar evacuation are managed with assisted ventilation and central monitoring, usually in the intensive care unit. However, late presentation of hydatidiform moles is less common nowadays with the availability of early pregnancy obstetric ultrasound [9–13].

At the end of the procedure, the evacuated tissues should be inspected and sent for histological examination. The Royal College of Obstetricians and Gynaecologists recommends that the product of conception (POC) of all failed pregnancies should be sent for histological assessment to exclude trophoblastic disease, owing to difficulty of making a diagnosis of molar pregnancy before evacuation [14]. Furthermore, POC obtained following all repeat evacuations, should also be examined histologically due to risk of persistent trophoblastic neoplasia after any pregnancy. However, POC from therapeutic termination of pregnancy does not require histological assessment, particularly when foetal parts have been seen on prior ultrasound scan. Partial mole can be differentiated from complete mole using immunohistochemistry staining for P57 and ploidy status [15].

Medical evacuation of uterus

Medical evacuation of uterus is not recommended for evacuation of molar pregnancy because these procedures increase maternal morbidity and risk of post-molar GTN. There is a theoretical concern that routine use of potent uterotonic agents could potentially embolise and disseminate trophoblastic tissue through the venous system [16]. Several studies have found higher risk of chemotherapy following medical evacuation compared with suction curettage [3,16]. Furthermore, many of these patients required suction curettage after medical evacuation to achieve complete removal. However, medical evacuation may be required for partial molar pregnancy of a greater gestation especially in the presence of foetal development, or coexisting molar and normal pregnancy, particularly when the size of foetal parts prevents the use of suction curettage. It can be performed using prostaglandins with or without combination of oxytocin.

Hysterotomy

Abdominal hysterotomy is rarely done nowadays for primary treatment of hydatidiform mole due to concerns of increased morbidity and post-molar GTN. Abdominal hysterotomy was performed historically when there was limited availability of suction curettage. It carries greater surgical risks compared to suction curettage including increased operative blood loss. The procedure involves vertical myometrial incision to evacuate the molar tissue, thus rendering the women requiring Caesarean delivery with any subsequent pregnancy to prevent uterine rupture. This is an important factor to consider as most women with molar pregnancies are in their reproductive years. Furthermore, the incidence of post-molar GTN was reported to be increased after hysterotomy compared to suction curettage. Curry et al. reported that only 64% (18 out of 24) of patients achieved spontaneous remission after hysterotomy, compared to 81% (243 out of 299) after suction evacuation [17]. More recently, the use of abdominal hysterotomy for evacuation has been confined to case reports of coexistent mole and a live twin foetus, due to obstetric indications such as placenta previa, prematurity and breech presentation or HELLP Syndrome [18–20].

Hysterectomy

Hysterectomy with salpingectomy may be considered as initial treatment for molar pregnancies in women who are older and do not wish to retain fertility [21]. It can be performed via laparotomy, laparoscopic or vaginal approach, depending on uterine size and the surgeon's expertise with the techniques. In addition to removing the molar pregnancy, hysterectomy allows permanent contraception and eliminates the possibility of local myometrial invasion as a source of persistent disease and hence reduces the need for subsequent chemotherapy. Previously, two studies in the USA of women aged 40–49 years [22] and ≥50 years [23] with complete mole found that none of the women receiving primary hysterectomy develop GTN. In contrast, for those women who had dilatation and curettage, GTN developed in 53% and 60% of women aged 40–49 years and ≥50 years, respectively [22,23]. Similarly, Zhao et al. found that the incidence of post-molar GTN in women aged >40 years was significantly lower in patients who had hysterectomy compared to patients who had dilatation and curettage (11% vs 37%, $P = 0.004$) for complete mole [24]. In contrast, Giorgione et al. reported that in women with hydatidiform mole aged >40 years, primary hysterectomy does not reduce the incidence of port-molar GTN when compared with dilatation and curettage (58% vs 30%, respectively, $P = 0.094$) [25]. Moreover, they also found that hysterectomy does not reduce the amount of chemotherapy required to treat GTN, although 42% (5 out of 12) of their patients who had primary hysterectomy achieved complete remission after surgery. Nonetheless, after hysterectomy for hydatidiform mole, serial monitoring of hCG is important for all patients because hysterectomy does not eliminate the possibility of post-molar GTN completely.

Ovaries can be conserved even if theca-lutein cysts are present because these cysts usually regress over few months after uterine evacuation as hCG levels decrease [26]. However, in the presence of large and symptomatic ovarian theca-lutein cysts, aspiration can be considered to reduce the volume and relief symptoms. Theca-lutein cyst may cause cyst complications such as torsion or rupture, which can usually be managed laparoscopically. In a majority of premenopausal women undergoing hysterectomy for GTD, ovaries can be conserved because GTN rarely metastasized to the ovaries, and these tumours are usually not influenced by hormones [27].

Postoperative monitoring

Following evacuation of molar pregnancy, monitoring of hCG levels postoperatively is mandatory to promptly identify and manage post-molar GTN regardless of whether fertility sparing surgery (e.g. suction curettage) or radical surgery (e.g. hysterectomy) is done. FIGO recommends hCG monitoring every 1–2 weeks until hCG normalised, and then monthly [1]. For partial mole, one additional confirmatory normal hCG measurement 1 month after first hCG normalisation is recommended. For complete mole, monthly hCG measurements are required for 6 months after hCG normalisation.

Surgery for malignant gestational trophoblastic neoplasia

Second suction curettage

Routine second suction curettage is not indicated for management of molar pregnancies. In a recent cohort study including 173 patients with molar pregnancy, routine second curettage performed around 7 days after first evacuation in patients with sonographic evidence of residual uterine tissue resulted in similar incidence of GTN compared to patients who did not have repeat curettage. However, the GTN risk score was found to be significantly lower in the group that had second curettage [28].

Women who develop post-molar GTN commonly present with vaginal bleeding and uterine enlargement. Second uterine evacuation has been utilised to remove residual trophoblastic tissue in the hope of allowing spontaneous regression and avoiding chemotherapy. Several retrospective series suggest that routine second uterine evacuation is unlikely to benefit the majority of patients with post-molar GTN [29–32]. One study found that second curettage performed for suspected post-molar GTN had either no impact or only resulted in a transient drop followed by a rise in hCG levels in a majority of patients, with only 20% of patients having a sustained drop in hCG levels and

spontaneous remission [31]. Similarly, other studies have reported that a second curettage led to change in management in only about 10% of patients, by either inducing remission or providing malignant GTN histology [29,30]. Furthermore, the reported incidence of uterine perforation during second curettage was up to 8% [31,33].

An observational study performed over a period of 10 years in the United Kingdom (UK) including 544 women who had second uterine curettage for persistent GTD, found that 68% had no more evidence of disease or required chemotherapy after repeat evacuation [34]. However, chemotherapy was needed more frequently for women with a histologic confirmation of persistent GTD and for urinary hCG levels of more than 1500 IU/L at time of repeat curettage. Another retrospective cohort study conducted in the Netherlands involving 2122 patients observed that only 9.4% of patients who underwent second curettage for low-risk GTN avoided chemotherapy compared to 0% in patients who did not have a repeat curettage [35]. Although the proportion of patients who avoided chemotherapy is not high, the study noted a debulking effect of second curettage leading to a reduction of the number of chemotherapy cycles required, on average by one cycle. The apparently conflicting results in these 2 large studies is probably due to the differences in definition of post-molar GTN. In the UK study, persistent GTN was defined as failure of serum hCG to normalise within 4–6 weeks or a rising hCG at any time during post-molar follow-up, while the Netherlands study used stricter criteria of 3 consecutive weeks of hCG plateau or rise with at least one measurement above the 95th percentile of normal regression based on a previously published uneventful hCG regression curve [36,37]. This fundamental difference suggests a lower-risk population in the UK study, leading to a much better treatment effect in the group of patients who underwent second curettage. More importantly, majority of these patients may not have met the FIGO diagnostic criteria of post-molar GTN initially and thus may not have required a second curettage or any treatment. Several groups have discussed the optimal criteria for repeat evacuation [37–39] and suggested that second evacuation may be considered in selected patients when the ultrasound confirms the presence of residual uterine tissue and hCG less than 5000 IU/L, after informing the patient of the surgical risks and relatively low chance of benefits [39].

Osborne et al. evaluated the efficacy of second curettage in a cooperative group multicentre prospective study including 64 patients with low-risk, non-metastatic GTN [40]. They reported that 47% of patients benefited from immediate second curettage and avoided chemotherapy, without significant morbidity. They suggested that second curettage could be considered as an alternative to immediate chemotherapy for these patients regardless of hCG level and the amount of intrauterine disease, although immediate chemotherapy is preferred for patients with WHO risk score of 5 or 6 and for patients at extremes of reproductive life, particularly <19 and >39 years of age. In a recent randomised trial investigating the role of second curettage, 89 patients with low-risk post molar GTN and hCG of <5000 IU/L were randomised to second curettage or no curettage before methotrexate treatment [41]. This study concluded that second curettage did not affect the number of chemotherapy cycles required and the relapse rate.

Generally, routine second curettage is not recommended for management of post-molar GTN. Instead, consultation or referral to the trophoblastic centre should be considered before second curettage. However, second curettage is an alternative to immediate chemotherapy for selected patients with nonmetastatic, low-risk GTN, particularly in patients with sonographic evidence of residual uterine tissue, significant vaginal bleeding and opting for this procedure with the aim of avoiding chemotherapy.

Hysterectomy

Hysterectomy may be necessary in the event of uncontrolled uterine bleeding [42]. However, with the availability of uterine artery embolisation nowadays, hysterectomy can often be avoided.

Low-risk GTN

Although chemotherapy is highly effective for treatment of GTN, hysterectomy has an important role in the management of some patients with malignant GTN, especially when the disease is localised or confined to the uterus. The first large series on 122 patients with choriocarcinoma treated with

hysterectomy was reported by Brewer et al., in 1963 [43]. This series included 70 patients (57.4%) with localised disease with 5-year survival of 41.5% compared to 19.2% in patients with metastatic disease. Of note, metastatic disease in this series could only be diagnosed by tissue biopsy or x-ray, indicating a higher proportion of patients with metastatic disease than reported. Due to earlier and better diagnosis, Hammond et al. reported, in 1980, an overall 100% sustained remission rate in 194 patients with low-risk disease [44]. Of these, 83.5% wished to retain fertility potential, and 89% were able to avoid hysterectomy. All 32 patients treated with primary hysterectomy followed by single-agent chemotherapy with methotrexate or dactinomycin achieved complete remission. These patients had a shorter duration and lower total dosage of chemotherapy that was equivalent to approximately one cycle of chemotherapy compared to similar patients with low-risk disease treated with chemotherapy alone. Similarly, Suzuka et al. found that in patients treated with etoposide for low-risk GTN, the total dosage of chemotherapy was lower in patients with localised disease treated with adjuvant hysterectomy, compared to those treated with chemotherapy alone, which was again equivalent to approximately one cycle of chemotherapy [45]. However, this effect was not seen among patients with low-risk metastatic disease, where similar dosages of etoposide were required for patients treated with adjuvant hysterectomy or chemotherapy alone.

In women who no longer wish to retain their fertility, first-line hysterectomy can be considered as an alternative to chemotherapy for treatment of low-risk non-metastatic GTN [46,47]. In 2018, Bolze et al. reported that 82.4% (61 out of 74) of patients who had first-line hysterectomy for low-risk non-metastatic GTN achieved normalisation of hCG without undergoing salvage chemotherapy [47]. In this study, a FIGO score of 5–6 and histology of choriocarcinoma were associated with higher risk of needing salvage chemotherapy. In primary treatment of low-risk GTN, hysterectomy was performed in about 25% of patients [48,49]. Thus, primary hysterectomy could be offered to women with localised disease or with minimal metastatic involvement if they have no wish to preserve fertility.

High-risk GTN

For patients with high-risk GTN, primary hysterectomy was not effective in reducing requirement for chemotherapy or improving cure rates [44]. Compared with patients with localised or low-risk metastatic disease, it is not surprising that hysterectomy would play a much less role in the reduction of tumour burden because these patients often present with disseminated disease. Instead, control of extrauterine disease with multiagent chemotherapy is critical to the success of treatment for these patients.

Chemoresistant GTN

Hysterectomy also has a role in the management of chemoresistant low-risk GTN. In patients with localised or low-risk metastatic GTN who failed to respond to primary chemotherapy, salvage hysterectomy can lead to complete remission in most patients, without needing multiagent chemotherapy [46,48,50,51]. For high-risk GTN, salvage hysterectomy may be considered in selected patients with small volume of extrauterine tumour. In a review of 25 patients with chemoresistant disease and relapse after treatment, who were referred to Charring Cross Hospital in UK for surgical treatment, the reported overall survival was 88% [52]. Three deaths happened in patients with significant extrauterine disease and rising hCG levels after hysterectomy. Similarly, another case series of 14 patients who underwent hysterectomy for recurrent GTN had sustained remission in 83% of cases [53]. Consequently, in the management of chemoresistant GTN, salvage hysterectomy may be necessary in selected patients to achieve cure.

PSTT/ETT

Hysterectomy is the cornerstone of treatment when there is histological diagnosis of intermediate trophoblastic tumour, namely placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT) [54,55]. Unlike other types of GTN, hCG levels are usually relatively lower, and these rare tumours respond poorly to conventional chemotherapy regimens. Therefore, hysterectomy is the recommended treatment for localised disease, and excision of isolated distant metastasis, especially in the lungs can be considered in selected patients. Around two-thirds of the patients with PSTT present with disease localised to uterus, with reported long-term survival rates ranging from 90% to 100% with

hysterectomy alone [54]. In a recent large series including 54 patients with ETT or mixed PSTT/ETT, two-thirds of the patients had FIGO stage I disease, of which all patients who underwent surgery only survived, compared to 71% of patients who underwent a combination of surgery and chemotherapy [56]. Four deaths in stage I disease occurred in patients with an interval of $\geq$48 months since the antecedent pregnancy (1 interval unknown) which is a poor prognostic factor of ETT. In PSTT and ETT, the incidence of pelvic lymph node metastasis is approximately 5%–15% in clinical stage I tumours [21,57]. Hence, pelvic lymph node biopsy should be considered during hysterectomy for localised PSTT and ETT, particularly with a large or deeply invasive tumour.

Myometrial resection

Myometrial resections can be considered in highly selected women with localised, non-metastatic GTN, who wish to preserve future fertility. A few case reports have described the use of local myometrial resection combined with uterine reconstruction for primary treatment of localised GTN and PSTT. In a report including 5 patients with PSTT treated with initial conservative myometrial resection, only 1 patient was treated successfully, while the remaining 4 required subsequent hysterectomy [58]. In another series of 22 patients with invasive hydatidiform moles, focal excision of myometrial lesion was utilised in patients with prolonged hCG regression and findings of myometrial lesions after evacuation of molar pregnancy [59]. All patients had lesions confined to the myometrium as delineated by pelvic angiography, ultrasonography and computerised tomography. Seven (32%) of these patients required postoperative chemotherapy due to failure of regression of hCG levels. This series also noted that the reproductive outcome of these patients was comparable to patients treated with chemotherapy only. Consequently, due to high cure rates with chemotherapy alone in patients with invasive mole, it is reasonable to contemplate myometrial resection as a salvage procedure in patients with chemoresistant disease.

Additionally, localised uterine wedge resection with reconstruction has been described for management of uterine perforation presenting with acute pain and shock, while receiving chemotherapy for persistent GTN [60,61]. Utilisation of uterine artery embolisation in order to minimise haemorrhage prior to surgical intervention has also been reported [61]. These patients subsequently had successful pregnancies. However, this technique should be used cautiously given the challenges of localising the lesion and the amount of resection needed to achieve remission. Preoperative imaging may not correlate with the tumour site, as in a case of PSTT, thus making the procedure ineffective [62]. Furthermore, patients planning for this procedure should be carefully assessed for distant metastasis, and the uterine lesion should be characterised using a combination of colour Doppler ultrasound, magnetic resonance imaging and hysteroscopy. Utilisation of intraoperative frozen section can be considered to evaluate surgical margins. Patients with low hCG values and lesions that are less than 2–3 cm are more likely to achieve complete resection [59].

Surgery for metastatic tumours

In the management of high-risk GTN, adjuvant surgical procedures may be required for chemoresistant disease, especially for isolated lesion in the lungs [63,64]. Furthermore, laparotomy may be required to control bleeding from other organs, such as liver, gastrointestinal tract, kidneys and spleen. In one case series, almost 50% of patients with high-risk disease required some surgical intervention for their treatment to achieve cure [65]. In general, resection of metastatic tumours is unlikely to offer benefits to patients with disseminated disease that is resistant to chemotherapy.

Pulmonary resection

Pulmonary wedge resection may be performed via video-assisted thoracoscopy surgery (VATS) or thoracotomy [64]. In terms of excision of extrauterine metastasis for GTN, this surgical procedure is the most frequently performed. Fortunately, the majority of patients do not require lung resection because most can be treated with chemotherapy alone. Notably, the radiographic evidence of tumour regression usually lags behind hCG levels response, with some patients having persistent pulmonary nodules

for months or years after completing chemotherapy [66,67]. The overall risk of recurrence in low-risk metastatic GTN is typically less than 5% [53]. Although patients with pulmonary lesions that persisted after normalisation of hCG levels may be at higher risk of recurrence [67]; these patients can be safely monitored using serial hCG without resorting to surgical resection [68].

Any women of reproductive age who presents with an overt metastatic malignancy of unknown origin, especially in the presence of lung, liver, brain or renal metastases should be screened for the possibility of GTN with a serum hCG. When pregnancy has been excluded in patients with high hCG values, excisional biopsy for histological confirmation of malignant GTN is not required. Nonetheless, in some series of patients with GTN treated with lung resection, the diagnosis of GTN was not suspected until after final pathology was available.

Resection of lung lesions may be considered in patients with chemoresistant GTN, especially when the lesion is solitary and unilateral, and the hCG levels are low [64]. Complete metastatic assessment to exclude the possibility of active disease elsewhere must be done before contemplating lung resection. Patients with disease in other sites or bilateral or multiple lung lesions are less likely to benefit from lung resection. Tomoda et al. reported that 14 out of 15 (93%) patients survived after pulmonary resection if they had solitary metastasis and low hCG values, compared to none of 4 patients with either metastatic disease elsewhere or urinary hCG levels of more than 1000 mIU/mL [69]. Rarely, more than one lung resection is required to achieve cure in some patients. Following lung resection, rapid drop of hCG values within 1–2 weeks postoperatively are usually associated with good outcome [64].

Craniotomy

The risk of central nervous system (CNS) metastasis in women with post-molar GTN is low, but up to 20% in patients with choriocarcinoma [70]. Thus, patients with post-molar GTN do not require routine CNS imaging in the absence of symptoms. However, patients with choriocarcinoma should have CNS imaging regardless of symptoms or locations of other site of metastases.

For patients with CNS metastasis, neurosurgery may be required to manage intracranial bleeding or raised intracranial pressure. Cerebral haemorrhage leading to acute neurological deterioration resulted in a significant proportion of early deaths before effective treatment could be started or very early after initiation of treatment [71,72]. The main aims of therapy involve prompt recognition of brain metastases, stabilisation of the patient's neurological condition and initiation of treatment. When GTN is clinically diagnosed based on raised hCG levels and metastatic disease, tissue biopsy for histological confirmation is not indicated as this can be dangerous and has little impact on clinical care.

Other treatment modalities, such as craniotomy with surgical excision, whole brain irradiation and stereotactic radiosurgery may be used along with systemic combination chemotherapy. The cure rates of brain metastases are reported to range between 50% and 80%, depending on the patient's symptoms and the number, size and location of brain lesions [70–75]. Savage at al reported on 27 GTN patients with brain metastases treated at the Charing Cross Hospital, UK, from 1991 to 2013 with overall cure rate of 85% [70]. All patients were treated with high-dose multiagent systemic and intrathecal chemotherapy, 5 patients required emergency craniotomy and 5 patients had stereotactic radiotherapy for residual lesions at the end of treatment. In their experience, whole brain radiotherapy is not part of their routine management. In contrast, Neubauer et al. recommended an approach using whole brain irradiation combined with systemic multiagent chemotherapy to treat patients with brain metastases. They reported overall survival of 51% and noted that presence of symptoms was associated with worse survival. These studies emphasise the varied strategies used in the treatment of brain metastases in GTN. Craniotomy is mostly reserved for management of isolated lesion especially in chemoresistant disease and for acute decompression due to intracranial haemorrhage.

Selective angiographic embolisation

Selective angiographic embolisation can be used to control haemorrhage due to GTN. For instance, uterine artery embolisation (UAE) has been used to manage bleeding from the uterus [76,77]; especially in patients who wish to retain their fertility potential. In a series including 8 patients,

angiographic embolisation was performed in GTN patients presenting with acute life-threatening haemorrhage and was successful in 86% of the patients [77]. Furthermore, bleeding from vaginal metastasis can often be controlled with UAE [78,79]; particularly when simple packing or suturing techniques failed to control haemorrhage.

Additionally, angiographic embolisation has been performed to treat intrauterine arteriovenous malformations (AVM) that can result after treatment of GTN [80–82]. It can cause recurrent vaginal bleeding or life-threatening haemorrhage, even after complete resolution of the GTN. In a systemic review by Touhami et al. describing 49 cases of uterine AVM following GTN, UAE was the most common procedure performed in 82% of patients and was successful in controlling bleeding in 85% of patients [82]. Although most patients (63%) had their bleeding controlled after a single UAE, some patients required repeated UAE or even hysterectomy to control bleeding. Successful term pregnancies have been reported after this intervention [82].

Summary

Suction curettage is recommended for treatment of hydatidiform moles, followed by monitoring of hCG levels to detect for post-molar GTN. Although routine second curettage is not recommended for management of post-molar GTN, it is an alternative to immediate chemotherapy for selected patients with nonmetastatic, low-risk GTN, particularly in patients with sonographic evidence of residual uterine tissue, significant vaginal bleeding and opting for this procedure with the aim of avoiding chemotherapy. Hysterectomy is the mainstay treatment for PSTT or ETT and may be considered in selected patients for management of hydatidiform mole and malignant GTN especially in chemoresistant disease. Resection of metastatic lesions such as in the lung or brain can be considered in selected patients with isolated chemoresistant tumour. Selective angiographic embolisation can be used to control haemorrhage or treat intrauterine arteriovenous malformations due to GTN.

Practice points

- Suction curettage is recommended for treatment of hydatidiform moles, followed by monitoring of hCG levels to detect for post-molar GTN
- Hysterectomy may be considered in selected patients for management of hydatidiform mole and malignant GTN especially in chemoresistant disease
- Hysterectomy is the mainstay treatment for PSTT or ETT
- Resection of metastatic lesions such as in the lung or brain can be considered in selected patients with isolated chemoresistant tumour
- Selective angiographic embolisation can be used to control haemorrhage or treat intrauterine arteriovenous malformations due to GTN

Research agenda

- Optimal criteria for second suction curettage in the management of post-molar GTN
- Efficacy of hysterectomy in reducing the risk of post-molar GTN

Declaration of competing interest

None.

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