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Gestational trophoblastic disease

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Most women with gestational trophoblastic disease are of reproductive age. Because the disease is readily treatable with favourable prognosis, fertility becomes an important issue. Hydatidiform mole is a relatively benign disease, and most women do not require chemotherapy after uterine evacuation. A single uterine evacuation has no significant effect on future fertility, and pregnancy outcomes in subsequent pregnancies are comparable to that of the general population, despite a slight increased risk of developing molar pregnancy again. If women develop persistent trophoblastic disease, single or combined chemotherapy will be needed. Although ovarian dysfunction after chemotherapy is a theoretical risk, a term live birth rate of higher than 70% has been reported without increased risk of fetal abnormalities. Successful pregnancies have also been reported after choriocarcinoma. Only a few case reports have been published on fertility-sparing treatment in placental-site trophoblastic tumour, and the successful rate is about 67%. Women are advised to refrain from pregnancy for at least 6 months after a molar pregnancy, and at least 12 months after a gestational trophoblastic neoplasia. Most of the contraceptive methods do not have an adverse effect on the return of fertility. Finally, at least one-half of these women suffer from some form of psychological or sexual problems. Careful counselling and involvement of a multi-disciplinary team are mandated.

Introduction

Gestational trophoblastic disease (GTD) is a pregnancy-related disorder, consisting of hydatidiform mole, invasive mole and metastatic mole, choriocarcinoma, placental-site trophoblastic

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tumour (PSTT) and epithelioid trophoblastic tumour. Gestational trophoblastic neoplasia (GTN) is diagnosed when a woman's human chorionic gonadotropin (hCG) level fails to return to normal after a pregnancy. In order to diagnose GTN, using the recommendation from the International Federation of Obstetrics and Gynecology (FIGO), hCG should either plateau, with at least four persistently elevated hCG values on days 1, 7, 14 and 21, or rise sequentially for 2 weeks on days 1, 7 and 14 or longer; lung metastases should be diagnosed by chest X-ray.[1] Gestational trophoblastic disease also includes invasive mole, choriocarcinoma and PSTT.[2] In FIGO's 26th report, most women with GTN are between 25 and 29 years of age, and 82.7% are younger than 40 years.[1] It is therefore important to preserve the fertility of this group of women. For this chapter, we conducted a literature search from PubMed, and reviewed references of articles on fertility and GTD. These will be discussed below.

Fertility after gestational trophoblastic disease

Hydatidiform mole

Hydatidiform mole includes partial mole and complete mole. Both conditions are regarded as benign, and most women do not require additional treatment after uterine evacuation. Several studies from different centres have investigated the pregnancy outcomes after a molar pregnancy; all showed no difference from the general population.[3–7] In particular, the rate of subsequent term live pregnancy was in the range of 68–83% for both partial and complete moles, whereas the rates of stillbirth rate, spontaneous miscarriage and congenital abnormalities were 0.3–1.3%, 9–20%, and 1.8–3.9%, respectively.

The treatment of choice for molar pregnancy is uterine evacuation, curettage, or both.[8–11] Although most women with hydatidiform mole can retain their fertility, it is essential to pay extra caution in carrying out uterine evacuation, as it may lead to torrential bleeding, necessitating hysterectomy. First, it is advised to avoid using misoprostol for cervical priming because of a small risk of uterine contraction, which may result in tumour embolism into the venous system.[8,9] Second, the procedure should be conducted by an experienced gynaecologist because the uterus tends to be bigger and more vascular and than the usual uteri. Third, it is usually not necessary to give an oxytocic agent. If heavy bleeding occurs, this can be given after the evacuation is completed.[8] In the USA, some centres advocate using intravenous oxytocin infusion starting at the onset of the uterine evacuation until several hours after the operation to increase uterine contractility.[10] Medical abortion is not recommended because of risks of bleeding, incomplete abortion, and tumour embolisation, which may, in turn, increase the need of subsequent chemotherapy.[11,12] Nevertheless, medical abortion may be considered in partial mole at second trimester because the fetal parts may obstruct the evacuation, and the risk of persistent trophoblastic disease is low.

Some investigators have evaluated the effectiveness and safety of prophylactic chemotherapy with either methotrexate or actinomycin-D for high-risk molar pregnancy. Prophylactic chemotherapy is considered on the basis of age, uterine size, presence of intra-uterine mass and ovarian cysts. A woman's history and presentation, during or shortly after uterine evacuation, is taken into account in order to decrease the chance of post-molar GTN and the potential side-effects of chemotherapy, which may affect the ovarian function.[13–18] Although most studies have shown a reduction in the incidence from 18–50% to 7–18%, with occasional tolerable side-effects, only two were randomised-controlled trials with about 30 women in each arm.[13,16] The criteria of high-risk molar pregnancy, however, differed in different centres. Currently, chemo-prophylaxis is usually considered in countries with limited resources for follow up, or in women with poor compliance to follow up.[11,16]

Hysterectomy is rarely carried out for women who have completed their families or with life-threatening haemorrhage. Hysterectomy can provide permanent sterilisation and prevent local myometrial invasion, but it cannot obviate the risk of metastasis and the need of chemotherapy.[9,11]

As there is a small risk of developing persistent trophoblastic neoplasia, women should be counselled to refrain from pregnancy for at least 6 months (see below). If women happen to conceive

before completing the 6-month follow-up period, the overall viable pregnancy rate increases to 75% (33 out of 44 women; 83% for partial mole and 65% for complete mole), with no detectable fetal abnormalities.[19]

After a molar pregnancy, the reported risk of repeated molar pregnancy is about 0.6–2%[5,6,20–24]; however, one study in Korea reported a rate up to 3.1% (two out of 65 women who became pregnant).[4] This is 10–20 times higher than the background risk of the general population, which is 0.1–0.2% depending on different regions. After two or more molar pregnancies, the risk increases to 5–28%.[6,20,25] It is, therefore, important to remind women to have their hCG measurement 6 and10 weeks after completing their pregnancies.[8,9]

Gestational trophoblastic neoplasia

About 0.5–1% of partial mole and 15–29% complete mole may progress to GTN requiring chemotherapy.[9,11,20,26,27] The variation in reported rates can be explained by the inconsistent definition of persistent trophoblastic neoplasia and criteria for chemotherapy used in different centres.[28] The role of repeating uterine evacuation is controversial. Pezeshki et al. reported their 10-year experience with second evacuation in 282 women with persistent GTD who had plateau or elevation of hCG level with or without symptoms or ultrasound abnormalities.[29] Among them, 171 (60%) women did not require subsequent chemotherapy, and chemotherapy was likely to be required when a histological diagnosis was made of persistent trophoblastic disease or when the hCG was greater than 1500 IU/L at the second evacuation. Despite the apparent benefit of repeating uterine evacuation reported in that study, another Dutch cohort study showed that only eight out of 85 women with persistent GTD (9.4%) were cured by second evacuation alone.[30] In addition, the procedure may potentially lead to uterine perforation, bleeding, uterine infection, Asherman's syndrome and cervical incompetence; four out of 85 (4.8%) women experienced uterine perforation and bleeding over 1000 ml in the Dutch cohort.[30] With the high effectiveness of chemotherapy, repeating evacuation is not widely practised in the USA, where vigilant follow up is readily available.[28,31]

The mainstay treatment for GTN is chemotherapy. As previously mentioned, different centres have different criteria for chemotherapy. One example used by the Charing Cross Hospital, London, UK, is shown in Table 1.[9] The staging system and regimens used also vary. The FIGO staging system with a risk score system from the World Health Organization is commonly used (Tables 2 and 3).[1] In general, low-risk GTN, usually with risk score less than 6, is treated by a single agent, such as methotrexate or actinomycin-D, whereas high-risk GTN, usually scoring 7 or above, is treated by multi-agent such as EMA-CO (etoposide, methotrexate, actinomycin-D, cyclophosphamide and vincristine with folinic acid rescue).[8–11]

The toxic effect of chemotherapy agents on ovarian function has raised concern. A recent review by Oktem and Urman[32] summarised the gonadotoxicity by different kinds of chemotherapy drugs and those commonly used to treat GTN (Table 4). In fact, a retrospective controlled survey attempted to compare the age of menopause between women treated with chemotherapy and those who were not. The former group (median 50, range 25–56 years) had menopause 3 years earlier than the latter

Table 1
Indications for chemotherapy for gestational trophoblastic neoplasia.

Brain, liver, gastrointestinal or lung metastases greater than 2 cm on chest X-ray.
Histological evidence of choriocarcinoma.
Heavy vaginal bleeding, gastrointestinal or intraperitoneal bleeding.
Pulmonary, vulval or vaginal metastases, unless the hCG level is falling.
Rising hCG in two consecutive serum samples of greater than 10% over at least 2 weeks.
hCG plateau in four consecutive serum samples over 3 weeks after evacuation.
Serum hCG greater than 20,000 IU/l more than 4 weeks after evacuation.
Raised hCG level 6 months after evacuation even if it is falling.

hCG, human chorionic gonadotropin.

Table 2
The staging system adopted by the International Federation of Obstetrics and Gynecology.

International Federation of Obstetrics and Gynecology staging and classification	
Stage I	Disease confined to the uterus.
Stage II	Gestational trophoblastic neoplasia extends outside of the uterus, but is limited to the genital structures (e.g. adnexal, vagina, broad ligament).
Stage III	Gestational trophoblastic neoplasia extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites.

group (median 53, range 40–57 years) (Log-rank χ^2 test = 12.6, $P = 0.0004$).[33] In addition, those who received combination chemotherapy (median 49, range 25–56 years) also had earlier menopause than those receiving single methotrexate (median 51, range 25–56 years) (Log-rank χ^2 test = 8.3, $P = 0.004$). The difference, however, was small and the investigators concluded that it was not of clinical significance.

Women can be further reassured that their pregnancy outcomes are comparable to those of the general population. In a recent review, data from 10 different international centres were summarised.[7] Women with persistent GTN, regardless of the risk scores and the chemotherapy regimens used, had favourable pregnancy outcomes. The live birth rate was 76.4% and the term delivery rate was 71.5%, whereas the rates of premature deliveries, stillbirth, miscarriage and congenital abnormalities were only 5.0%, 1.3%, 14.0% and 1.3%, respectively.[7] Khan et al.[34] focused their investigation on a low-risk group composed of 141 women who became pregnant. They found that 90.8% had live birth, 14.9% ended with miscarriage, and only two women (0.8%) developed repeated moles.[34] Using etoposide alone for the treatment of low-risk GTN, the investigators of a Japanese study showed that 92.3% (36 out of 39 women who wished to conceive) became pregnant and 91.7% had at least one live birth.[35] Out of the 56 pregnancies, 75% of women had a term live birth, 12.5% had first-trimester miscarriage, 1.8% had second-trimester miscarriage, none had fetal anomalies, and 3.6% had repeated moles. For women with high-risk GTN, a questionnaire survey involving 33 women treated with EMA-CO in the Netherlands showed a conception rate of 86%, term delivery rate of 76.2% (16 out of 21 pregnancies), miscarriage rate of 9.5%, and two (9.5%) fetal anomalies, which the authors thought were difficult to explain because of the small sample size.[36] In another report by Bower et al.,[37] 56% of the 272 women receiving EMA-CO conceived, resulting in 112 (73%) live births and three (2.0%) congenital abnormalities.[37] Although some investigators have found no relationship between the type of chemotherapy regimens and pregnancy outcomes,[38,39] Rustin et al.[40] showed that women receiving a combination of three or more drugs were less likely to conceive or have a live birth than those receiving methotrexate alone or in combination with

Table 3
Modified World Health Organization prognostic scoring system as adapted by the International Federation of Obstetrics and Gynecology.

Scores	0	1	2	4
Age (years)	<40	≥40	–	–[a]
Antecedent pregnancy	Mole	Abortion	Term	–
Interval from index pregnancy (months)	<4	4 to <7	7 to <13	≥13
Pre-treatment serum human chorionic gonadotropin (IU/l)	$<10^3$	10^3 to $<10^4$	10^4 to $<10^5$	$\geq 10^5$
Largest tumour size (including uterus)	–	3 to <5 cm	≥5 cm	–
Site of metastases	Lung	Spleen, kidney	Gastro- intestinal	Liver, brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	≥two drugs

[a] – Not applicable.

Table 4
Gonadotoxicity of different chemotherapy drugs used in gestational trophoblastic neoplasia.[32]

Groups	Drugs	Gonadotoxicity
Antimetabolites	Methotrexate	Mild toxicity; mainly on growing follicles
Alkylating agents	Cyclophosphamide, ifosfamide, cisplatin	High toxicity; mainly on primordial follicles
Spindle poison mitotic inhibitors	Vincristine	Moderate toxicity
Cytotoxic anti-tumour antibiotics	Actinomycin-D, bleomycin, hydroxyurea	Mild to moderate toxicity
Topoisomerase inhibitors	Etoposide	Unknown

one more drug ($P < 0.001$).[40] Those who received actinomycin D or vincristine were also less likely to have a live birth than those who did not ($P < 001$ and $P < 0005$, respectively). All these studies were retrospective and limited to a single institution. More prospective studies are needed to determine the influence of the type of chemotherapy regimen on the reproductive performances.

Women are advised not to become pregnant for at least 1 year after completing chemotherapy because it may be difficult to recognise a relapse if they happen to conceive. Also, the growth of primordial Graafian follicles is estimated to take more than 6 months.[41] By waiting for 1 year, this may allow damaged DNA to be repaired. Nonetheless, if women conceive during the mandated follow-up period, it is not necessary to terminate the pregnancy, as most studies have shown fair outcomes, with an overall 67.2% live birth rate and 2% fetal abnormality rate (Table 5)[38,42–44]; however, women conceiving within 6 months after chemotherapy might have a higher incidence of abnormal pregnancies, including miscarriage, stillbirth and repeated moles, than those who conceive more than 12 months later (37.5% *v* 10.5%; $P = 0.14$).[44]

The relapse rate is about 3% in low-risk GTN and 7–10% in high-risk GTN.[45] The New England Trophoblastic Disease Center has also observed that relapse after initial remission occurred in 2.9% of women with stage I disease, 8.3% of women with stage II disease, 4.2% of women with stage III disease, and 9.1% of women with stage IV disease.[46] In another review, Lurain[47] reported that about 20% of women with low-risk GTN and 30% of women with high-risk GTN would either relapse or become refractory to first-line chemotherapy. Multiple chemotherapy regimens, such as EP-EMA (etoposide, cisplatin, etoposide, methotrexate and actinomycin-D), MBE (methotrexate, bleomycin and etoposide), TP/TE (paclitaxel, cisplatin / paclitaxel, etoposide), BEP (bleomycin, etoposide and cisplatin), VIP or ICE (etoposide, ifosfamide and cisplatin or carboplatin), floxuridine, dactinomycin, etoposide, and vincristine (FAEV), have been reported, with response rates varying from 50– 85%.[48–51] The overall 5-year survival for women with relapsed GTN was more than 90%, which is nearly 100% for women with low-risk GTN and around 85% for women with high-risk GTN.[52] Hysterectomy is only rarely carried out for refractory diseases with single focus in the uterus.[53–55] Despite the relative favourable prognosis, pregnancy after remission of relapse is seldom described, which may be because of the rarity of the disease and the possible poor ovarian function and psycho-sexual problems after multiple courses of chemotherapy.

Choriocarcinoma

Owing to the chemosensitivity of the tumour, choriocarcinoma is now mainly managed with combined chemotherapy. In fact, several studies have shown that the recurrence rate and survival rate are similar between those who have had and those who have not had hysterectomy, with a trend favouring fertility-sparing treatment.[56,57] These studies have also reported a 77–79% term delivery rate and a 7–9% miscarriage rate.[56,57] Song et al.[56] reported two intrauterine deaths, three stillbirths, six neo-natal deaths and two infancy deaths among 355 total pregnancies. Goto et al.[57] also reported an 8.8% (three out of 34 term births) incidence rate of congenital heart abnormalities, which was higher than the background risk (0.7–1%) in the Japanese population. The total dosage of methotrexate received by these mothers was also significantly higher compared with the rest, whose children did not have cardiac abnormalities ($P < 0.02$). Another small study by Lan et al.,[58] included 22 women with choriocarcinoma and invasive moles who conceived within 1 year after completing chemotherapy. One

Table 5
Pregnancy outcomes for women with gestational trophoblastic neoplasia conceiving within 1 year after completing chemotherapy.

Reference	Years	Chemotherapy	Total pregnancies	Live births	Term deliveries	Preterm deliveries	Stillbirth	Miscarriage	Termination	Fetal anomalies	New moles	Relapse
Rustin et al.[38]	1984	Mixed	45	31	NA	NA	1	7	6	1	0	NA
Tuncer et al.[42]	1999	Mixed	39[a]	25	22	3	0	3	10	2	1	1
Blagden et al.[43]	2002	Single	153	NA	120	NA	2	12	17	1	2	3
Blagden et al.[43]	2002	Multiple	77	NA	44	NA	0	14	18	2	1	2
Matsui et al.[44]	2004	Mixed	38	26	NA	NA	1	7	4	1	0	NA
Total			352	82	186	3	4	43	55	7	5	6
				67.2% (82/122)	69.1% (186/269)	7.7% (3/39)	1.7% (4/236)	12.2% (43/352)	15.6% (61/352)	2.0% (7/352)	1.4% (5/352)	2.2% (6/269)

[a] Four women were lost to follow up, NA, not applicable.

suspected recurrence of GTN and another repeated hydatidiform mole were reported, and the fetal loss rate was 27.1% (6 out of 22). These included one repeated hydatidiform mole, one intrauterine death, one inevitable miscarriage and three threatened miscarriages, reiterating the need to wait for 1 year before contemplating the next pregnancy.[58]

Placental-site trophoblastic tumour and epithelioid trophoblastic tumour

Placental-site trophoblastic tumour arises from the implantation site intermediate trophoblast and constitutes only 1–2% of all GTN.[59] The cornerstone treatment modality is hysterectomy because it is less sensitive to chemotherapy compared with choriocarcinoma. Therefore, the desire of retaining fertility poses a great challenge to both doctors and patients. Only a few case reports have been published. Among the six women having fertility-sparing treatment, only four (66.7%) were successful, resulting in two patients having term pregnancies (Table 6).[60–64] It has been reported that poor survival is associated with age over 35 years, interval from preceding pregnancy over 24 months, deep myometrial invasion, advanced stage, maximum hCG level greater than 1000 IU/l, high mitotic rate, extensive coagulative necrosis and presence of clear cytoplasm.[65] Owing to the rarity of the cases, however, it is difficult to predict which women are suitable for fertility-sparing treatment. This approach can only be used when close monitoring is available and women are compliant to follow up.

Epithelioid trophoblastic tumour is derived from the chorionic-type intermediate trophoblast, and was first described in 1998.[66] Its behaviour is similar to that of PSTT, and hysterectomy is the mainstay treatment. No successful pregnancies after treatment have been reported.

Treatment of severe haemorrhage

Life-threatening haemorrhage can occur in women with GTN, as the uterus is usually enlarged with vascular and friable tumour inside. Traditionally, hysterectomy has been the main solution to this disastrous condition. With cutting-edge techniques in radiological intervention, selective angiography and transcatheter embolisation by gelfoam particles using modified Seldinger technique is now becoming more popular in intractable bleeding caused by uterine, vaginal, hepatic metastasis.[67–71] This technique is an attractive alternative to hysterectomy because it is minimally invasive, can be done under conscious sedation, and has a potential to preserve fertility. Successful term pregnancies have been reported after uterine artery embolisation in gestational trophoblastic tumour.[72–76] These small numbers of reported cases make it difficult to make definitive statements about obstetric outcomes. Experience of treating uterine fibroids shows an increased risk of miscarriage after uterine artery embolisation, along with some other adverse obstetric sequelae.[77] Complications can arise after embolisation, including post-embolisation syndrome (malaise, fever, pelvic pain and leucocytosis). If iliac vessels are embolised, severe complications, such as perineal skin sloughing, recto-vesico-vaginal fistulae and neurological deficits in the lower limbs can occur.[78,79]

Uterine resection, primary closure and balloon tamponade have also been reported for the control of bleeding in GTN.[80–82] These, however, are limited in selected cases only, and more reports are needed to establish their role.

Contraception

As mentioned previously, women should be advised to practice reliable contraception for at least 6 months after the hCG levels become normal in a molar pregnancy, and for at least 12 months in any GTN that requires chemotherapy. As these women already need to experience a delay in their fertility, it is important that the contraceptive method used does not have any adverse effect on the return of fertility upon discontinuation of use. It is also important that the chosen method is safe to be used in GTD. A summary of the United Kingdom Medical Eligibility of Contraceptive Use recommendations of the use of different contraceptive methods is presented in Table 7.[83] The most convenient method, though not the most reliable, is barrier method such as male or female condom or diaphragm. It is safe

Table 6
Characteristics and outcomes of women with placental-site trophoblastic tumour undergoing fertility-sparing surgery.

Reference	Years	Age	Gravidity, Parity	Pre-treatment hCG	Antecedent pregnancy	Pregnancy interval	Uterine tumour	Mitotic count	Treatment	Complications	Disease-free interval	Pregnancy outcomes
Leiserowitz and Webb[60]	1996	25	G1P1	21 IU/l	Term	15 months	2 × 1 × 1 cm	1/10 HPF	Laparotomy, hysterostomy, local excision and uterine reconstruction	None	At least 16 months	Two miscarriages and one term caesarean section at least 16 months later
Tsuji et al.[61]	2002	26	G2P1	0.95 ng/ml[a]	Miscarriage	4 months	3 cm	2/10 HPF	EMA-CO x 2 then hysterostomy, uterine resection and argon beam coagulation	None	9 months	NA
Machtinger et al.[62]	2005	26	G1P1	576 IU/l	Term	4 months	2.1 × 2 cm	17/10 HPF	Hysteroscopic resection then EMA-CO x 3	None	29 months	NA
Machtinger et al.[62]	2005	29	G4P2	60 IU/l	Miscarriage	3.5 months	2.9 cm	8/10 HPF	Laparotomy and segmental resection	Positive margin with vascular space invasion requiring hysterectomy	33 months	None
Numnum et al.[63]	2006	29	NA	130 IU/l	Miscarriage	NA	0 cm	NA	EMA-EP x 6	Grade 3/4 thrombocytopenia, ovarian dysfunction	2 years	Term vaginal delivery 2 years later
Pfeffer et al.[64]	2007	30	G1P0	11339 IU/l	Complete mole	2 months	2 cm on uterine resection, multifocal	5–7/10 HPF	MTX x 4, EMA-CO x 5, Gem/CP x 2, uterine resection	Progressive during adjuvant TE/TP (x 2) requiring hysterectomy	2.5 years	None

[a] Normal <0.2 ng/ml; EMA-CO, etoposide, methotrexate, dactinomycin, cyclophosphamide and vincristine; EMA-EP, etoposide, methotrexate, actinomycin-D, etoposide, cisplatin; Gem/CP, gemcitabine and carboplatin; hCG, human chorionic gonadotropin; HPF, high power field; MTX, methotrexate; NA, not available, TE/TP, paclitaxel and etoposide, paclitaxel and cisplatin.

Table 7
Recommendations from, United Kingdom Medical Eligibility of Contraceptive Use.[83]

	CHC	POP	DMPA/NET-EN	IMP	Cu-IUD	LNG-IUD	Barrier methods	Female sterilisation
Decreasing or undetectable β-hCG level	1	1	1	1	1	1	1	A
Persistently elevated β-hCG level or malignant disease	1	1	1	1	4	4	1	D

CHC, combined hormonal contraception; POP, progestogen-only pills; DMPA, depot medroxyprogesterone acetate; NET-EN, norethisterone enanthate; IMP, progestogen-only implant; Cu-IUD, copper-bearing intrauterine device; LNG-IUD, levonorgestrel-releasing IUD; hCG, human chorionic gonadotrophin; category 1, a condition for which there is no restriction for the use of the contraceptive method; category 2, a condition where the advantages of using the method generally outweigh the theoretical or proven risks; category 3, a condition where the theoretical or proven risks usually outweigh the advantages of using the method; category 4, a condition that represents an unacceptable health risk if the contraceptive health risk if the contraceptive method is used; category A, there is no medical reason to deny sterilisation to a person with this condition; category D, the procedure is delayed until the condition is evaluated, changes, or both. Alternative temporary methods of contraception should be provided.

to be used in GTN, provided that no vaginal metastasis exists. Women using the barrier method can resume their fertility immediately after cessation of use, and this method can also indirectly increase their fertility by reducing the incidence of sexually transmitted disease and pelvic inflammatory disease, which in turn lowers the chance of pelvic adhesion.[84]

One study[85] has shown that the use of oral contraceptives before the remission of hCG might increase the risk of GTN after molar pregnancy. Nevertheless, a randomised-controlled trial assigning 266 women to either oral contraceptives or barrier contraception after evacuation of a hydatidiform mole showed that the risk of post-molar GTN was 23% and 33% in the former and latter group, respectively.[86] The median time to spontaneous regression of hCG was also lower in the oral contraceptives group (9 weeks) then the barrier group (10 weeks), meaning that oral contraceptives can be used safely after evacuation for molar pregnancy. This result was further supported by other retrospective studies.[87–90] A systematic review, which included two randomised trials and seven observational studies, also showed that combined oral contraceptive pills did not increase the risk of post-molar trophoblastic disease.[91] On the other hand, a spontaneous return of menses and fertility occurs shortly after the cessation of the contraceptive pills.[84,92–94] This hormonal method also has beneficial effect on fertility, as its progestagen component thickens the cervical mucus, thereby reducing the risk of pelvic infection. It is also a reliable contraceptive method and can reduce the incidence of ectopic pregnancy.

Similarly, monthly combined injectables are safe in GTN. A study involving 70 women showed that 1.4% of women had return of fertility after the discontinuation of the injection at the end of the first month, and reached 82.9% at 1 year.[95] More than 50% were pregnant at 6 months. Longer time may be needed for return of fertility after the use of depot medroxyprogesterone (DMPA), which takes about 4–5 months for the return of ovulation and about 5–7 months for conception, although the ovulation suppression may rarely persist for as long as 18 months after the last injection.[84,96] A Thai study,[97] which included 796 women using DMPA, showed a median delay of 5.5 months before conception. As the effect of DMPA can last for 15 weeks, a median delay to conception of around 9 months after the last injection can be anticipated. A total of 21.8% of women failed to become pregnant in the first year, and dropped to 7.9% by the second year. As for subdermal implants, it was suggested that 6 weeks were needed for the return of ovulation.[98] Other studies showed that 76–100% women would conceive within 1 year upon removal of implantable contraceptives.[99,100]

Intrauterine contraceptive devices (IUCD) are not recommended when hCG is high because of risks of abnormal vaginal bleeding and uterine perforation. If it is used, it takes a median 4.5-month delay before conception[98]; however, the proportion of women who failed to conceive within 1 year was 21%, which dropped to 6.7% at the second year. It is also noteworthy that long-term use of IUCD may impair the fertility potential (linear trend $P = 0.005$), which the delivery rate was 46% for short-term users (less than 42 months) compared with 28% for long-term users (over 78 months).[101]

Psychosexual social studies

Psychosocial distress and sexual dysfunction have often been overlooked by clinicians. An Australian cross-sectional questionnaire analysis involving 176 women showed that 22 respondents (13%) required formal psychological intervention in response to the diagnosis of GTD.[102] A total of 36 (20.5%) of them were also receiving treatment for anxiety, depression, bipolar disorder, sleep disorder and eating disorder. In addition, up to 52% of the women experienced sexual dysfunction, and 26% thought that the diagnosis and treatment of GTD had a negative effect on their sexual life, especially among those who had received chemotherapy and those whose diagnoses were in the first pregnancies. Another survey including 47 patients receiving chemotherapy, surgery, or both, for GTN, showed that 70% experienced absent or low sexual desire, 42% complained of dyspareunia, 45% had lubrication problems, and 53% had changes in the relationship with their partners within the first year after remission.[103] Those women who have metastatic diseases and those who require chemotherapy also express mood disturbance, distress in relation to the disease, and poor quality of life.[104,105]

Part of the anxiety and mood disturbance might be attributed to the anxiety about disease recurrence and future pregnancy outcomes.[106] In fact, the Australian survey also tested the same cohort on their understanding about their condition.[107] About 80% of them perceived that bad luck was the cause of their disease, and 20–30% were not sure about the relationship between the disease and some habitual activities such as smoking, use of contraception, and exercises. Thirty per cent of women expressed reluctance to conceive again, and 57% expressed doubt about having a healthy baby. This illustrated that patients might not have sufficient knowledge about their disease, their prognosis and pregnancy outcomes. Thorough counselling, early detection of the distress of women, and involvement of a multi-disciplinary team may clarify some of the misunderstanding that some women have, and hence relieve their anxiety.

Use of assisted reproductive techniques

One review included 26 singleton molar pregnancies and 26 multiple molar pregnancies consisting of a hydatidiform mole and one or more co-existent fetus(es) after clomiphene, gonadotrophin, or both.[108] Fifteen per cent of the singleton pregnancies and 42% of the multiple pregnancies developed persistent trophoblastic neoplasia. It seemed that ovulation induction did not increase the risk of GTN compared with those who had not undergone the treatment. If multiple pregnancies result, however, the risk of GTN increases. On the other hand, another retrospective study examined 231 women receiving chemotherapy for persistent GTD. Three women (1.3%) received treatment for infertility before their molar pregnancies, compared with four out of 226 (1.8%) women not requiring treatment for persistent GTD.[109] No direct relationship between infertility treatment and need of chemotherapy was demonstrated.

Some investigators have suggested the use of intracytoplasmic sperm injection, preimplantation genetic diagnosis, and fluorescence in-situ hybridization to prevent recurrent molar pregnancy. Intracytoplasmic sperm injection may prevent complete mole arising from dispermic fertilisation and triploid partial mole arising from dispermic fertilisation. Preimplantation genetic diagnosis can help selection against the transferral of a 46, XX embryo, which may result from a haploid X-bearing sperm that duplicates inside an empty oocyte.[110] Fluorescence in-situ hybridisation can also identify a triploid partial mole, which may arise from other mechanisms. Such techniques, however, are not well proven and not readily available, and may potentially involve many social and ethical problems.

Conclusion

Most women with gestational trophoblastic disease can be readily treated by fertility-sparing therapies. Although there are numerous reports of successful pregnancies after these therapies, ovarian function may be affected if multiple chemotherapy agents are used. Besides, the psychological distress and sexual dysfunction have often been understated. It is important for physicians to provide accurate counselling regarding the nature of their disease, the safety of pregnancy, and the effects of chemotherapy drugs on fertility potential, so as to minimize the misunderstanding and anxiety of these women.

Practice points

- Women can be reassured that pregnancy outcomes after molar pregnancy and GTN are favourable, despite a 15–20-fold increased risk of having repeated molar pregnancies.
- There is no definite value of carrying out a second uterine evacuation or giving prophylactic chemotherapy in treating molar pregnancy.
- Women should be advised to practice contraception for at least 6 months after a molar pregnancy and at least 1 year after a GTN in order to avoid any misinterpretation of hCG results, and to possible harmful effects of the chemotherapy to the ovarian function and fetal outcomes.
- Chemosensitive nature of GTN where hysterectomy is rarely indicated except in drug resistance with sole focus in the uterus.
- In case of profound bleeding, other alternatives, such as uterine artery embolisation, can be considered.
- Women's psychological disturbance and sexual dysfunction should be taken into account in the treatment.

Research agenda

- To evaluate the role of prophylactic chemotherapy in preventing GTN in high-risk hydatidiform mole.
- To carry out prospective studies to determine the influence of the type of chemotherapy regimen on the reproductive performances.
- To examine the safety of fertility-sparing treatment in PSTT and epithelioid trophoblastic tumour.

Conflict of interest

None declared.

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