Fertility and pregnancy outcome in gestational trophoblastic disease

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ABSTRACT

The aim of this review is to provide an overview of existing literature and current knowledge on fertility rates and reproductive outcomes after gestational trophoblastic disease. A systematic literature search was performed to retrieve all available studies on fertility rates and reproductive outcomes after hydatidiform mole pregnancy, low-risk gestational trophoblastic neoplasia, high- and ultra-high-risk gestational trophoblastic neoplasia, and the rare placental site trophoblastic tumor and epithelioid trophoblastic tumor forms of gestational trophoblastic neoplasia. The effects of single-agent chemotherapy, multi-agent including high-dose chemotherapy, and immunotherapy on fertility, pregnancy wish, and pregnancy outcomes were evaluated and summarized. After treatment for gestational trophoblastic neoplasia, most, but not all, women want to achieve another pregnancy. Age and extent of therapy determine if there is a risk of loss of fertility. Single-agent treatment does not affect fertility and subsequent pregnancy outcome. Miscarriage occurs more often in women who conceive within 6 months of follow-up after chemotherapy. Multi-agent chemotherapy hastens the natural menopause by three years and commonly induces a temporary amenorrhea, but in young women rarely causes permanent ovarian failure or infertility. Subsequent pregnancies have a high chance of ending with live healthy babies. In contrast, high-dose chemotherapy typically induces permanent amenorrhea, and no pregnancies have been reported after high-dose chemotherapy for gestational trophoblastic neoplasia. Immunotherapy is promising and may give better outcomes than multiple schedules of chemotherapy or even high-dose chemotherapy. The first pregnancy after immunotherapy has recently been described. Data on fertility-sparing treatment in placental site trophoblastic tumor and epithelioid trophoblastic tumor are still scarce, and this option should be offered with caution. In general, patients with gestational trophoblastic neoplasia may be reassured about their future fertility and pregnancy outcome. Detailed registration of high-risk gestational trophoblastic neoplasia is still indispensable to obtain more complete data to better inform patients in the future.

INTRODUCTION

Gestational trophoblastic disease covers a range of pre-malignant and malignant pregnancy-related disorders associated with highly abnormal placental trophoblastic tissue. The pre-malignant forms consist of complete and partial hydatidiform moles, which are abnormal conceptions with a dominance of paternal genome, characterized by varying degrees of trophoblastic proliferation. The malignant forms are collectively termed gestational trophoblastic neoplasia and include invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor.[1] While a molar pregnancy can progress into any of the malignant forms of gestational trophoblastic neoplasia, choriocarcinoma, placental site, and epithelioid trophoblastic tumor can arise from any type of antecedent pregnancy.

The trophoblastic cells produce the pregnancy hormone, human chorionic gonadotropin. All forms of gestational trophoblastic disease. apart from placental site and epithelioid trophoblastic tumor, normally produce human chorionic gonadotropin at levels that correlate with the disease volume, making it a useful biomarker for disease progression, treatment response, and surveillance.[2] The progression of a previous molar pregnancy into gestational trophoblastic neoplasia is detected by plateaued or increasing human chorionic gonadotropin levels that occur in 15–20% of complete and 0.5–5% of partial hydatidiform moles.[3]

Post-molar gestational trophoblastic neoplasia and choriocarcinoma is typically treated with either single- or multi-agent chemotherapy. Patients are stratified to receive these treatments using the International Federation of Gynecology and Obstetrics (FIGO) prognostic scoring system.[4] Women scoring 0–6 have a low risk of developing resistance to single-agent therapy, whereas those scoring ≥7 are at high risk of developing resistance to single-agent therapy and therefore receive multi-agent chemotherapy from the outset. Patients with a FIGO score of >12 have an increased risk of early and late deaths so treatment modifications are needed to help reduce these risks. Fortunately, the overall cure rate approaches 100% in low-risk gestational trophoblastic neoplasia and is well above 90% in high-risk patients. The FIGO prognostic scoring system is not used for placental site tumor trophoblastic tumor and epithelioid trophoblastic tumor, as these disease forms behave both biologically and clinically in a distinct way, being less chemo-sensitive. Indeed, surgery is the preferred treatment in localized disease, whereas advanced disease is treated with multi-agent chemotherapy with or without additional immunotherapy, high-dose chemotherapy, and surgery.[5 6]

Since gestational trophoblastic disease affects young women of childbearing age and the prognosis is generally excellent, future reproductive outcomes are important. Potential concerns include side effects of chemotherapy, such as infertility, adverse obstetric outcomes, and early menopause as well as associated psychological sequelae. Women with a history of gestational trophoblastic disease often express anxiety related to the surveillance period, fear of disease relapse, and death, and outcome of subsequent pregnancies. These psychosocial sequelae may persist for years in both patients and their partners, and some women might even refrain from further pregnancies.[7 8] Reliable data on subsequent fertility and pregnancy outcomes are essential for proper counseling of women with a history of gestational trophoblastic disease and their partners, and emotional and social support should be part of treatment and follow-up.

In this review article, we discuss the available scientific data on fertility and reproductive outcomes after diagnosis and treatment of the different forms of gestational trophoblastic disease, as well as methods for fertility preservation, when applicable.

METHODS

A review of the existing literature on fertility and reproductive outcomes after gestational trophoblastic disease was performed by searching the databases of the Cochrane Library, PubMed, Embase, and Medline for studies involving hydatidiform mole, low-risk and high-risk gestational trophoblastic neoplasia. A study protocol and search were designed in collaboration with the Scientific Service Center of the Netherlands Cancer Institute. The search strategy and the medical subject headings terms are provided in the online supplemental appendix. Search results were screened for title and abstract independently by three reviewers, and if considered relevant, the full-text article was obtained and analyzed. Reference lists were checked to retrieve additional studies not found in the electronic search. Only studies written in the English language were included. Patients were included only if diagnosed with gestational trophoblastic disease or gestational trophoblastic neoplasia according to the FIGO criteria. Studies without clear description on treatment administration or procedures and studies without description of reproductive outcomes were excluded. Included articles were assessed for eligibility independently by four reviewers.

Data were extracted and interpreted in groups divided as follows: fertility and reproductive outcomes after hydatidiform mole, low-risk gestational trophoblastic neoplasia, (ultra) high-risk gestational trophoblastic neoplasia, placental site trophoblastic tumor or epithelioid trophoblastic tumor.

Fertility Rate after Gestational Trophoblastic Disease

A proper evaluation of fertility after treatment for gestational trophoblastic disease requires that affected women have attempted to become pregnant. Even though gestational trophoblastic disease evolves from a previous pregnancy, not all women are interested in a new pregnancy and some might avoid this due to treatment-related anxiety.[9] Several studies referred to in this review report fertility rates using all treated patients as the reference group, while others use women with a pregnancy desire as the denominator. This may explain potential differences between reports.

Chemotherapy and Fertility

The gonadotoxic effect of various chemotherapeutic agents is diverse, involving a variety of pathophysiologic mechanisms which are not unequivocally understood. Proliferating cells in tissues with high turnover (ie, growing ovarian follicles) are more vulnerable to the toxic effect of chemotherapy. The extent of ovarian failure and mutagenic effect depends on the type and accumulative dose of chemotherapy as well as the patient's age.[10] Often used agents in treatment of gestational trophoblastic neoplasia are methotrexate, actinomycin-D, etoposide, cyclophosphamide, vincristine, and platinum derivatives. The American Society of Clinical Oncology has reported on fertility preservation for patients with cancer, and included an evaluation of the risk of permanent amenorrhea by exposure to different chemotherapeutical agents, which is summarized for the most common agents used for treating gestational trophoblastic neoplasia.[11]

Methotrexate is a folinic acid antagonist and used as single agent, or as part of multi-agent, chemotherapy for gestational trophoblastic neoplasia. The American Society of Clinical Oncology guidelines classify methotrexate as very low (<20%) or no risk of inducing permanent amenorrhea in women.[11] Two systematic reviews of methotrexate for rheumatoid arthritis and ectopic pregnancies found no effect on ovarian reserve and similar reproductive outcomes as in healthy women.[12 13]

Actinomycin-D is an anti-tumor antibiotic used as single agent, or as part of multi-agent, chemotherapy. It is classified as no to very low risk (<20%) of amenorrhea.[11] To our knowledge, no studies have been published regarding the fertility rates or reproductive outcomes specifically after actinomycin-D treatment.

Etoposide is mainly used in combination with other agents in gestational trophoblastic neoplasia. The American Society of Clinical Oncology guidelines do not state anything about the risks of amenorrhea due to etoposide.[11] Only one retrospective study has described reproductive outcomes after etoposide as single-agent treatment. In that study 66 of 74 women with a pregnancy wish achieved one or more pregnancies, resulting in 78 live births.[14]

Cyclophosphamide is an alkylating agent used in multi-agent chemotherapy. The American Society of Clinical Oncology guidelines classify cyclophosphamide as high risk (>80%) of amenorrhea if six cycles are given to women aged >40 years in combination with methotrexate, fluorouracil, doxorubicin, or epirubicin, and as intermediate risk (20–80%) of amenorrhea in women aged 30–39 years.[11]

Vincristine is also used in multi-agent combinations and is classified as no to very low risk of amenorrhea.[11]

Cisplatin is classified as an intermediate risk (20–80%) of amenorrhea. Effects of cyclophosphamide and cisplatin on ovarian damage have been recently summarized in a review by Spears et al,[15] showing that cyclophosphamide induces premature ovarian insufficiency by up-regulated apoptosis in the follicles, and mouse/rat studies suggest loss of ovarian reserve and follicular atresia after exposure to cisplatin.

Hydatidiform Mole

Fertility and Reproductive Outcomes After Hydatidiform Mole

The incidence of hydatidiform mole varies widely, with rates of approximately one per 1000 pregnancies reported from Europe and North America and more than double that rate in Asia.[1]

Regardless of these differences and their causes, future fertility and the risk of further molar pregnancies are some of the major concerns among couples who have experienced a hydatidiform mole. Several studies have examined this issue, and while fertility and reproductive outcomes after a previous molar pregnancy have repeatedly been demonstrated to be similar to those of the general population (Table 1), the risk of a new hydatidiform mole has been reported to increase with successive molar pregnancies.[16–20] The largest study on recurrence rate of molar pregnancies by Eagles et al included 16 000 women with complete and partial hydatidiform mole, registered in a centralized referral center during a 20-year period. The authors demonstrated a risk of a new molar event for women with a previous complete hydatidiform mole of 1 in 100 and 1 in four after one and two consecutive complete hydatidiform moles, respectively, whereas women with partial hydatidiform moles had only a small increase in risk of a further mole. The risk of a third hydatidiform mole was almost exclusively associated with complete hydatidiform mole and may be related to a familial disposition.[21] This observation is supported by previous reports on the risk of recurrent molar pregnancies.[18 22]

Fertility and Reproductive Outcomes After Familial Recurrent Hydatidiform Mole

Recurrent molar pregnancies may be associated with a rare disorder called familial recurrent hydatidiform mole, in which affected women are predisposed to recurrent pregnancy loss, most of which are complete hydatidiform moles, and the chance of a normal pregnancy resulting in a live birth is very small.[23] Molecular studies by Helwani et al in 1999 first demonstrated the biparental contribution to the familial complete hydatidiform mole, as opposed to the sporadic androgenetic complete hydatidiform mole.[24] It is now recognized that familial recurrent hydatidiform mole is a rare autosomal recessive disorder in which mutations in two genes, NLRP7 and KHDC3L, are responsible for 75% and 5% of all cases, respectively.[25] The exact incidence is not known, and affected women are usually diagnosed after a number of recurrent complete molar pregnancies, when genotyping confirms a diploid biparental complete mole. Each molar pregnancy carries a risk of malignant transformation, and because there is no treatment for familial recurrent hydatidiform mole and outcomes of subsequent pregnancies are most likely recurrent complete hydatidiform mole, affected women should be counseled to avoid further pregnancies. Fisher et al have demonstrated that egg donation with a healthy oocyte from an unaffected donor can lead to a normal live birth, and this may be the only safe option for women with familial recurrent hydatidiform mole.[26]

Fertility and Reproductive Outcomes After Surgery for Hydatidiform Mole

For women who want to preserve their fertility, uterine evacuation by suction curettage is the preferred method for those with suspected hydatidiform mole.[1] Primary hysterectomy is an option for women who have completed their families. However, this procedure has not been demonstrated to decrease the subsequent need for chemotherapy.[27] Hysterectomy is also used in cases of life-threatening bleeding, but fertility can sometimes be preserved by embolization or by packing the uterus.[28]

Low-risk Gestational Trophoblastic Neoplasia

Approximately 95% of all women who are diagnosed with gestational trophoblastic neoplasia following a hydatidiform mole are in the low-risk group.[1] Post-molar gestational trophoblastic neoplasia is diagnosed according to specific criteria developed by FIGO, and mainly based on the dynamics of human chorionic gonadotropin. One of the following has to be present for a malignant diagnosis: sequential rise of three consecutive weekly human chorionic gonadotropin values for 2 weeks or longer, plateau of at least four persistently elevated human chorionic gonadotropin-values for 3 weeks or longer, or histological diagnosis of choriocarcinoma.[4] Women with low-risk disease (FIGO risk score 0–6) generally respond well to single-agent chemotherapy, although the risk of drug resistance rises with increasing risk score. The most commonly used first-line agents are methotrexate with folinic acid rescue and actinomycin-D, although other single-agent regimens have been used historically.[29] The updated Cochrane review published by Lawrie et al, 2016, concluded that actinomycin-D was more likely to achieve primary cure (risk ratio 0.65, 95% CI 0.57 to 0.75), whereas methotrexate was more likely to result in treatment failure (risk ratio 3.55, 95% CI 1.81 to 6.95). No difference in side effects was found between methotrexate and actinomycin-D, although there was a trend towards a greater risk of severe adverse events with actinomycin-D.[30] Despite this, many centers prefer methotrexate as first-line chemotherapy because of its mild toxicity profile with no hair loss and less nausea, vomiting, and myelosuppression. After completion of treatment, women are usually asked to refrain from a new pregnancy in the first 12 months of surveillance, to facilitate detection of recurrence and to avoid possible chemotherapy-related gonadotoxic and teratogenic effects.

Fertility and Reproductive Outcomes after Single-agent Chemotherapy

The prognosis of women treated for gestational trophoblastic neoplasia is generally excellent, and the potential adverse effects of chemotherapy on future fertility and reproductive outcomes therefore become important to explore. Several studies have investigated menstrual function after single-agent chemotherapy. Savage et al found no increased risk of premature or early menopause after methotrexate compared with the general population. Cioffi et al and Wong et al both reported a 97.5–100% rate menstrual recovery after methotrexate for low-risk gestational trophoblastic neoplasia.[31–33] Reports on ovarian function after single-agent actinomycin-D are more difficult to find. Most studies report on actinomycin-D in combination with other drugs or as second-line treatment after methotrexate failure. However, Yarandi et al compared the efficacy and toxicity of primary methotrexate and actinomycin-D in 81 and 50 women, respectively, and reported no ovarian failure in either group.[34]

Several studies have examined the impact of treatment for gestational trophoblastic neoplasia on fertility and subsequent reproductive outcomes and concluded that the chemotherapy protocols used have minimal effect on the subsequent childbearing potential. However, many of the studies describe chemotherapy treatment in general and do not separate single-agent and multi-agent chemotherapy. Few reports have focused on single-agent chemotherapy and fertility rates as well as obstetric outcomes (Table 2).[31 32 35–39] A meta-analysis by Tranoulis et al, evaluating reproductive and

Table 1 Overview of literature on fertility and reproductive outcomes after hydatidiform mole

		Women with pregnancy wish	Pregnant women	Total of pregnancies	Outcome of pregnancies							
					Miscarriage	TOP	Ectopic	Live birth	Preterm birth	Stillbirth	Cong abn	Repeat mole
Reference	HM	n	n	n	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Kim et al[16]	HM	ND	ND	77	8 (10.4)	ND	2 (2.6)	64 (83.1)	0 (0)	1 (1.3)	2 (2.6)	2 (2.6)
	CHM											
	PHM											
Matsui et al[17]	HM	891	ND	650	84 (12.9)	54 (8.3)	ND	489 (75.2)	11 (1.7)	3 (0.5)	7 (1.1)	9 (1.4)
	CHM			453	56 (12.4)	41 (9.1)	ND	344 (75.9)	4 (0.9)	2 (0.4)	ND	6 (1.3)
	PHM			197	28 (14.2)	13 (6.6)	ND	145 (73.6)	7 (3.6)	1 (0.5)	ND	3 (1.5)
Sebire et al[18]	HM	2578	ND	1417	240 (16.9)	64 (4.5)	5 (0.4)	1076 (75.9)	ND	5 (0.4)	ND	27 (1.9)
	CHM	2627	ND	1512	245 (16.2)	41 (2.7)	10 (0.7)	1185 (78.4)	ND	6 (0.4)	ND	25 (1.7)
	PHM											
Joneborg et al[19]	HM	ND	3709	ND	ND	ND	ND	5164	ND	22	204	20
	CHM											
	PHM											
Vargas et al[20]	CHM	ND	ND	1388	256 (18.4)	42 (3.0)	11 (0.8)	949 (68.4)	103 (7.4)	7 (0.5)	40 (2.9)	20 (1.4)
	PHM	ND	ND	357	64 (17.9)	12 (3.4)	2 (0.6)	260 (72.8)	8 (2.2)	1 (0.3)	4 (1.1)	10 (2.8)

Cong abn, congenital abnormalities; CHM, complete hydatidiform mole; HM, hydatidiform mole; ND, not described; PHM, partial hydatidiform mole; TOP, termination of pregnancy.

Table 2 Overview of literature on fertility and reproductive outcomes after gestational trophoblastic neoplasia treated with single-agent chemotherapy

Reference	Chemotherapy	Number of patients with pregnancy wish n	Number of pregnant women n	Number of pregnancies n	Outcome of pregnancies							
					Miscarriage n (%)	TOP n (%)	Ectopic n (%)	Live birth n (%)	Preterm birth n (%)	Stillbirth n (%)	Cong abn n (%)	Repeat mole n (%)
Woolas et al[35]	MTX	354	392	ND	38 (9.9)	ND	ND	ND	ND	ND	ND	ND
Blagden et al,[36]	MTX	ND	153	153	12 (8)	ND	ND	120 (78)	ND	2 (0.9)	1 (0.7)	2 (1.3)
Khan et al,[37]	MTX	ND	141	161	21 (13.0)	ND	ND	128 (79.5)	ND	0 (0)	ND	ND
Matsui et al[38]	MTX ACT-D ETO	ND	87	39 14 34	ND	6 (15.4) 0 0	ND	29 (74.4) 12 (85.7) 27 (79.4)	ND	ND	ND	ND
Goto et al[39]	MTX ACT-D	ND	209	446	57 (12.8)	33 (7.4)	6 (1.3)	339 (76)	9 (2)	0 (0)	3 (0.7)	5 (1.1)
Wong et al[32]	MTX	1	29	72	17 (23.6)	ND	ND	55 (76.4)	ND	0 (0)	1 (1.4)	0
Williams et al[56]	MTX ACT-D	ND	170	182	29 (15.9)	17 (9.3)	4 (2.2)	130 (71.4)	8 (4.4)	0 (0)	ND	2 (1.1)
Cioffi et al[31]	MTX, n=42 ACT-D, n=2 ETO, n=1	42	24	32	7 (21.9)	ND	0 (0)	25 (78.1)	ND	0 (0)	(0)	ND

Cong abn, congenital abnormalities; ACT-D, actinomycin D; EtO, etoposide; MTX, methotrexate; ND, not described; TOP, termination of pregnancy.

obstetric outcomes after chemotherapy for gestational trophoblastic neoplasia, found a fertility rate of 86.7% among women wishing to conceive after treatment. A sub-group analysis among all treated women demonstrated a statistically significant lower pregnancy rate after multi-agent chemotherapy than after single-agent chemotherapy (OR=0.54, 95% CI 0.38 to 0.77, p=0.001).[40] Blagden et al found higher conception rates in women in the single-agent group who conceived within a year after completion of treatment,[36] while no difference in pregnancy rate between single- or multi-agent chemotherapy was found in a recent MITO-9 analysis.[31] Studies comparing pregnancies in women who conceived within 6 months after completion of chemotherapy with those who conceived later, noted a higher rate of spontaneous abortions in early conceptions. However, these studies did not separate outcomes after single- and multi-agent chemotherapy. Braga et al demonstrated an 11-fold increase of miscarriage in women who conceived within 6 months compared with between six and 12 months of follow-up after chemotherapy, and a 23-fold increase compared with those conceiving after one year of follow-up.[41] The increased rate of miscarriage in women conceiving within 6 months of completion of chemotherapy was supported by Matsui et al.[42] Several studies have assessed obstetric outcomes after chemotherapy. Woolas et al assessed 728 women who tried to conceive after chemotherapy for gestational trophoblastic neoplasia, and found rates of miscarriages, terminations, live births, congenital anomalies, and repeat molar pregnancies similar to those of the general population, with no difference between women treated with single- or multi-agent chemotherapy.[35] This is supported by several other studies and illustrated in Table 2. Discrepancies between these studies is probably multifactorial, including differences between population- as opposed to hospital-based data that suffers from case ascertainment bias, variations in treatments used, timing of pregnancies, age, and racial backgrounds.

Fertility and Reproductive Outcomes after Surgery in Low-risk Gestational Trophoblastic Neoplasia

The role of a second dilatation and curettage to reduce the need for chemotherapy in women with low-risk disease confined to the uterus has been debated. Some authors report a benefit with a decreased incidence of post-molar gestational trophoblastic neoplasia in a limited number of women, as well as a reduction in the number of chemotherapy cycles.[43] The only prospective study on this matter found that 40% of women with low-risk non-metastatic disease did not need further chemotherapy after a second curettage if serum-human chorionic gonadotropin was <100 000 IU/L.[44] The potential risks with curettage, including bleeding, uterine perforation, infection, and intra-uterine adhesions (Asherman's syndrome) with an increased risk of secondary infertility, should be weighed against the cure rate of low toxicity single-agent chemotherapy. Although the correlation between the number of curettages and Asherman's syndrome is well known, it has not been reported as a complication of gestational trophoblastic disease treatment to our knowledge.

For women with low-risk gestational trophoblastic neoplasia confined to the uterus and who have completed their families, hysterectomy might be an alternative to chemotherapy, although it will not exclude the need for chemotherapy in all women.[45]

High-risk Gestational Trophoblastic Neoplasia

Gestational trophoblastic neoplasia usually occurs after evacuation of a hydatidiform mole but may follow any type of antecedent pregnancy, including non-molar abortion, ectopic pregnancy, and term pregnancy.[1] Patients with high-risk gestational trophoblastic neoplasia are treated with multi-agent chemotherapy. The most commonly used regimen is EMA-CO comprising etoposide, methotrexate and actinomycin-D alternating weekly with cyclophosphamide and vincristine.[46] Cumulative 5-year survival of patients treated with EMA-CO is between 75% and 94%.[47–51] Twenty per cent of high-risk patients develop resistance during or relapse after EMA-CO and need salvage chemotherapy with a platinum-containing schedule. When both further chemotherapy and salvage surgery fail, high-dose chemotherapy combined with peripheral blood stem cell support can be considered a method of last resort.[52] However, new therapies such as pembrolizumab, are promising and far less toxic.[53] Secondary hysterectomy or resection of metastatic disease may be performed in patients with gestational trophoblastic neoplasia in cases of chemotherapy resistance or to treat severe uterine hemorrhage.[54]

Fertility and Reproductive Outcomes after Multi-agent Chemotherapy

Current therapy for gestational trophoblastic neoplasia has resulted in high cure rates with preservation of fertility (Table 3), even in the setting of chemotherapy for widespread metastatic disease.[9 31 32 35 36 39 41 55 56] In a questionnaire study in the Netherlands, 78% of the fertile women treated with EMA-CO reported that they still had a desire for future pregnancy. In this study, 18 of the 27 (67%) patients experienced a regular menstrual cycle and three patients (11%) had amenorrhea.[9] The chance of premature ovarian failure was also low in other series, especially in women below the age of 40.[38 57] The incidence of secondary infertility is estimated to be around 4–5%.[38 58] Menopause has been reported to occur three years earlier than normal, so is unlikely to influence the chances of pregnancy.[59] Matsui et al studied the pituitary-ovarian function in 47 patients with low-risk gestational trophoblastic neoplasia treated with etoposide. Increased basal luteinizing hormone and follicle-stimulating hormone levels were found in half of the patients, especially those over 40 years old. Ovulation resumed within 121 days after cessation of chemotherapy in women under 39 years. However, five of nine patients aged over 40 remained anovulatory during the follow-up period. It is likely that the same results will be found in women with high-risk disease when etoposide is part of the treatment.[60] Even et al reported regular menses in 42 patients (71.2%), irregular menses in one (1.7%), transient amenorrhea lasting a median of 6 months in 14 (23.7%), and permanent amenorrhea in two patients aged 47 and 50 years (3.4%) of the 59 evaluable patients with high-risk gestational trophoblastic neoplasia treated with actinomycin-D, cisplatin, and etoposide.[61]

In many studies, the difference between treatment for low-risk and high-risk gestational trophoblastic neoplasia is not made (Table 4).[16 20 35 41 42 55 56 62–67] Because of the small number of included patients, it is mostly impossible to perform sub-group analyses based on age, type of chemotherapy, and number of administered chemotherapy cycles. Rustin et al reported in 1984 that 47 patients treated with multi-chemotherapy (three or more)

Table 3 Overview of literature on fertility and reproductive outcomes after gestational trophoblastic neoplasia treated with multi-agent chemotherapy

Reference	Chemotherapy	Number of patients with pregnancy wish n	Number of pregnant women n	Number of pregnancies n	Outcome of pregnancies							
					Miscarriage n (%)	TOP n (%)	Ectopic n (%)	Live birth n (%)	Preterm birth n (%)	Stillbirth n (%)	Cong abn n (%)	Repeat mole n (%)
Ross[55]	Multi agent	18	7	ND	ND	ND	ND	ND	ND	ND	ND	ND
Woolas et al[35]	Multi-agent	321	280	ND	35 (12.5)	ND	ND	ND	ND	ND	ND	ND
Blagden et al[36]	EMA/CO	ND	77	ND	14 (18)	18 (23)	0 (0)	44 (57)	ND	0 (0)	1 (1.3)	2 (2.6)
Lok et al[9]	EMA/CO	14	12	21	2 (9.5)	1 (4.8)	0 (0)	16 (76.2)	2 (9.5)	0 (0)	2 (9.5)	0 (0)
Goto *et al*[39]	Multi-agent	50	23	43	4 (9.3)	4 (9.3)	0 (0)	34 (79.1)	0 (0)	0 (0)	3 (7.0)	0 (0)
Braga et al[41]	EMA/CO, MAC, CHAMOCA, EP/EMA	ND	ND	54	23 (42.6)	ND	ND	31 (57.4)	2 (3.7)	0 (0)	ND	ND
Williams et al[56]	EMA/CO	ND	71	73	4 (5.8)	8 (11)	1 (1.4)	57 (78)	6 (8.2)	1 (1.4)	ND	2 (2.7)
Wong et al[32]	EMA/CO	5	8	19	4 (21)	1 (5)	0 (0)	14 (74)	ND	0 (0)	2 (11)	ND
Cioffi et al[31]	Multi-agent	18	12	18	3 (16.7)	0	0	15 (83.3)	1 (5.6)	0 (0)	0 (0)	0 (0)

Cong abn, congenital abnormalities; CHAMOCA, cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, doxorubicin, melphalan, vincristine; EMA/CO, etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine; EP/EMA, etoposide, cisplatin, etoposide methotrexate, actinomycin D; MAC, methotrexate, actinomycin D, chlorambucil; ND, not described; TOP, termination of pregnancy.

were less likely to have a live birth than those treated with methotrexate alone or in combination with only one other drug.[68] Also, Blagden et al showed more spontaneous miscarriages and terminations after multi-agent chemotherapy.[36] Some authors report a minor increase in stillbirths of 1.5% after chemotherapy for gestational trophoblastic neoplasia.[20 35] The possibility that this is due to chemotherapy-induced damage to the oocytes is not supported by the lack of any increase in congenital abnormalities.

In general, women are advised to postpone pregnancy 12 months after completion of multi-agent chemotherapy. A systematic review of 18 articles by Garcia et al in 2016 showed no evidence of decreased fertility after chemotherapy for gestational trophoblastic neoplasia, but a higher miscarriage rate was found in women who conceived within 6 months after chemotherapy compared with women who waited longer.[69] Also, older reports warn against pregnancy within a year after the end of multi-chemotherapy for gestational trophoblastic neoplasia because of a higher risk of recurrence of gestational trophoblastic disease (9.1%) and fetal wastage (27.3%).[70]

Fertility and Reproductive Outcomes After Surgery in High-risk Gestational Trophoblastic Neoplasia

Surgery can be an important part of the treatment of high-risk gestational trophoblastic neoplasia. In general, resection of metastases will not influence fertility. However, hysterectomy or partial hysterectomy could make future pregnancies impossible. Fertility-sparing partial hysterectomy in 34 patients with gestational trophoblastic neoplasia was described by Cheng et al; 25 patients achieved a pregnancy leading to 23 live births.[71] In selected patients, this might be an option to preserve fertility, although a combination with chemotherapy is still often necessary.

Fertility and Reproductive Outcomes after Ultra-high-risk Gestational Trophoblastic Neoplasia

Fertility and Reproductive Outcomes after High-dose Chemotherapy

Most women with gestational trophoblastic neoplasia are cured, but a small group become refractory to all standard chemotherapy regimens. For this small group, high-dose chemotherapy with peripheral blood stem cell support can be an option but recovery of ovarian function following this is rare. Indeed, no pregnancies have been described after high-dose chemotherapy for gestational trophoblastic neoplasia, although one patient has recovered regular menstrual cycles (personal communication). Other diseases requiring high-dose chemotherapy, such as high-risk neuroblastoma or germ cell tumors, also show that gonadal failure is common in long-term survivors. However, fertility was preserved in some survivors treated mostly before puberty.[72]

For hematological malignancies, a recent systematic review included 14 studies with 744 women with a median age of 26 years who underwent high-dose chemotherapy.[73] In women who achieved pregnancy, the interval between high-dose chemotherapy and pregnancy ranged from 2 to 156 months. A sub-group analysis of women after autologous high-dose chemotherapy showed an overall pregnancy rate of 25%. Of those women, 6.6% needed assisted reproductive technology to achieve a pregnancy, 80% of the pregnancies resulted in a live birth, 9% concerned a miscarriage, and 9% a termination of pregnancy. Clearly, the dose and

Table 4 Overview of literature on fertility and reproductive outcomes after gestational trophoblastic neoplasia treated with single agent or multi-agent chemotherapy

					Outcome of pregnancies							
Reference	Chemotherapy	Women with pregnancy wish n	Pregnant women n	Total pregnancies n	Miscarriage n (%)	TOP n (%)	Ectopic n (%)	Live birth n (%)	Preterm birth n (%)	Stillbirth n (%)	Cong abn n (%)	Repeat mole n (%)
Ross[55]	Single agent n=88 Multi-agent n=18	106	58 49 7	96	15 (15.6)	ND	ND	78 (81.3)	ND	3 (3.1)	3 (3.1)	ND
Hsieh et al[62]	MTX or ACT-D MTX/ACT-D/CP	ND	11	13	2 (15.4)	ND	ND	10 (76.9)	ND	ND	1 (7.7)	ND
Song et al[63]	Single agent (6-MP, 5-FU, KSM, MTX) n=91 Multi-agent n=107	ND	205	355	26 (7.3)	23 (6.5)	2 (0.6)	303 (85.4)	20 (5.6)	3 (0.8)	3 (0.8)	2 (0.6)
Ngan et al[64]	Etoposide MTX ACT-D Multi-agent	41	ND	41	6 (14.6)	2 (4.9)	0 (0)	32 (78)	1 (2.4)	0 (0)	ND	0 (0)
Kjer et al[65]	MTX/VC/ACT-D/CP MTX/ACT-D	30	29	62	6 (9.7)	ND	1 (1.6)	ND	ND	ND	ND	1 (1.6)
Ayhan et al[66]	CHM prophylaxis MTX n=43 MTX n=2 MX/ACT-D n=3 MTX/ACT-D/CP n=1	ND	49	65	8 (12.3)	7 (10.8)	ND	42 (64.6)	4 (6.2)	1 (1.5)	0 (0)	3 (4.6)
Kim et al[16]	ND	ND	38	50	9 (18)	ND	1 (2)	33 (66)	4 (8)	0 (0)	1 (2)	3 (6)
Woolas et al[35]	Single agent n=396 Multi-agent n=336	728	680	ND	ND	ND	ND	1000	ND	ND	ND	18 ()
Amr et al[67]	MTX EMA/CO MAC	55	42	120	7 (5.8)	ND	1 (0.8)	94 (78.3)	15 (12.5)	3 (2.5)	2 (1.7)	ND
Braga et al[41]	MTX or ACT-D n=167 EMA/CO, MAC, CHAMOCA, EP/EMA n=85	ND	ND	252	42 (16.7)	ND	ND	172 (68.3)	6 (2.4)	2 (0.8)	6 (2.4)	7 (2.8)
Vargas et al[20]	ND	ND	ND	667	123 (18.4)	28 (4.2)	7 (1)	446 (66.9)	44 (6.6)	10 (1.5)	12 (1.8)	9 (1.3)
Williams et al[56]	MTX or ACT-D n=745 EMA/CO n=459	ND	244	255	33 (12.9)	25 (9.8)	5 (2)	187 (73.3)	14 (5.5)	1 (0.4)	ND	4 (1.6)
Matsui et al[42]	MTX or ACT-D or ETO n=295 MEA or MAC n=83	133	129	243	27 (11.1)	35 (14.4)	ND	169 (69.5%)	2 (0.8)	5 (2.1)	ND	5 (2.1)

Cong abn, congenital abnormalities; ACT-D, actinomycin D; CHAMOCA, cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, doxorubicin, melphalan, vincristine ; CHM, complete hydatidiform mole; CP, cyclophosphamide; EMA/CO, etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine; EP/EMA, etoposide, cisplatin, etoposide methotrexate, actinomycin D; 5-FU, 5-fluorouracil; KSM, kasugamycin, strain of streptomycetes; MAC, methotrexate, actinomycin D, chlorambucil; MEA, methotrexate, etoposide, actinomycin D; 6-MP, 6-mercaptopurine; MTX, methotrexate; ND, not described; TOP, termination of pregnancy; VC, vincristine.

types of drugs used in high-dose chemotherapy vary between centers and malignancies and this might influence the chances of fertility preservation. Although theoretically, patients about to undergo high-dose chemotherapy might be considered for ovarian tissue storage or oocyte preservation, harvesting is usually not an option given the aggressive growth of these tumors, lack of time to harvest between cycles of ongoing chemotherapy, and amenorrhea following previous multi-agent chemotherapy.

Fertility and Reproductive Outcomes after Immunotherapy

Pembrolizumab is a humanized antibody blocking the T-cell inhibitory receptor PD-1, thereby inhibiting the binding of programmed cell death ligand 1 (PD-L1) that is widely expressed in some cancers, as well as in all normal and malignant trophoblasts. The interaction between PD-1 and PD-L1 prevents immune cell-mediated destruction of cancers, pregnancy, and gestational trophoblastic neoplasia. Consequently, preventing the interaction with pembrolizumab was recently used for the first time as salvage therapy in four heavily pre-treated patients with advanced choriocarcinoma or placental site and epithelioid trophoblastic tumor, and three achieved a complete remission.[53] It follows that the administration of pembrolizumab is not recommended during pregnancy, as it is likely to induce pregnancy loss, and the carcinogenic and genotoxic risks are currently unknown. To our knowledge, no case report has described pregnancy after pembrolizumab, despite its widespread use to treat melanoma and lung cancer. However, another immune checkpoint inhibitor, avelumab, that binds to PD-L1 to block the PD-1/PD-L1 pathway, has also been trialed in gestational trophoblastic neoplasia in the TROPHIMMUN study. Fifteen patients resistant to one single-agent chemotherapy were treated directly with avelumab. Eight women achieved remission and seven women needed to switch to actinomycin-D, multi-agent chemotherapy, or surgery in order to achieve human chorionic gonadotropin normalization.[74] Recently, Bolze et al reported the first woman to give birth to a healthy newborn after treatment with avelumab. She had methotrexate-resistant, low-risk, post-molar gestational trophoblastic neoplasia and was successfully treated with 11 cycles of avelumab and became pregnant 13 months after her last treatment cycle. Her pregnancy was uneventful and was delivered at a gestational age of 39 weeks.[75]

Placental Site Trophoblastic Tumor, Epithelioid Trophoblastic Tumor, and Atypical Placental Site Nodule

Placental site trophoblastic tumor and epithelioid trophoblastic tumor are the rarest forms of gestational trophoblastic disease and originate in the intermediate trophoblast. Atypical placental site nodule and exaggerated placental site are the pre-malignant counterparts of these lesions.[76 77] Placental site and epithelioid trophoblastic tumors are staged according to the FIGO staging system for gestational trophoblastic neoplasia, however, the prognostic risk scoring system is not used for these sub-types of gestational trophoblastic neoplasia.[4] FIGO stage and a prolonged interval between the antecedent pregnancy and start of treatment ≥48 months are the only two known prognostic factors for survival.[78 79] The recommended treatment for placental site and epithelioid trophoblastic tumor confined to the uterus is hysterectomy.[80] In advanced stages and/or a prolonged interval between antecedent pregnancy and start of treatment, chemotherapy in combination with surgery is advised.[78 79 81–83]

Fertility and Reproductive Outcomes after Placental Site Trophoblastic Tumor, Epithelioid Trophoblastic Tumor, and Atypical Placental Site Nodule

Little is known about fertility-sparing options in patients with placental site trophoblastic tumor. Only case reports or small case series are available. These were recently summarized in a systematic review by Chiofalo et al.[84] After a search including literature from 1996 to 2017, they found nine studies reporting on only 18 patients in total. All patients were assumed to be in FIGO stages 1 or 2, although not all studies reported the FIGO stage.[85–88] Eleven patients were treated with a laparotomic procedure, including seven local resections of the placental site trophoblastic tumor and four modified Strassman procedures (temporary ligation of the uterine artery), in which the presumed tumor is resected with a margin of one centimeter.[88] Three of the 11 patients received adjuvant systemic chemotherapy, but one relapsed after 3 months.[85 89] It should be noted that in five of 11 patients treated with an open procedure, a salvage hysterectomy still needed to be performed for suspected relapse and/or close or non-radical margins.[84] Six patients were treated with a minimally invasive approach (hysteroscopic tumor resection or dilatation and curettage). In this group, no salvage hysterectomies were reported and follow-up ranged between 8 and 104 months. In the patients treated with a minimally invasive technique, six were treated with systemic and/or intra-arterial chemotherapy.[85 87 90] One patient received multi-agent platinum-based chemotherapy only and delivered a healthy baby 24 months after treatment.[91] The authors conclude that a variety of treatment modalities have been used to preserve fertility in placental site trophoblastic tumor and that this treatment could be considered successful in 72% of cases.[84]

We performed a literature search which resulted in three extra studies published in the period during which Chiofalo et al performed their search,[79 92 93] and two reports published after 2017[94 95] resulting in reports on 28 extra cases. All studies are summarized in Table 5. Two reports where found on patients with placental site trophoblastic tumor in whom fertility-sparing surgery was intended but was not successful. Taylor et al reported on a patient in whom it was not possible to localize the tumor with hysteroscopy, MRI, and laparoscopy, precluding intended wedge resection. After three attempts, a hysterectomy was performed where a placental site trophoblastic tumor was found in the lower uterine segment.[93] Finally, Renaud et al reported on two patients with placental site trophoblastic tumor diagnosed on curettage, where no abnormalities were seen on MRI. The level of human chorionic gonadotropin was slightly elevated and after hysterectomy, residual placental site trophoblastic tumor was found in both cases.[96]

Reports on fertility-sparing treatment in epithelioid trophoblastic tumor are even more scarce and are incorporated in Table 5. One report mentions tumor resection by laparotomy for epithelioid trophoblastic tumor in a 25-year-old woman with stage 1 epithelioid trophoblastic tumor, who later delivered two babies.[97] Another report includes a 32-year-old woman in whom a tubal pregnancy was suspected after a previous hydatidiform mole. Resection of the ectopic mass in the fallopian tube was performed, and histology showed a mixed choriocarcinoma with epithelioid trophoblastic

Table 5 Overview of literature on fertility and reproductive outcomes after placental site and epithelioid trophoblastic tumor

Author	Method	Patients	Fertility-sparing treatment	Type of fertility-sparing procedure	Maternal outcomes	Fertility outcomes
Bonazzi et al[92]	Retrospective cohort	PSTT n=1	Hysteroscopic resection n=1		ND	ND
Zhang et al[83]	Literature review	PSTT n=2	Chemotherapy		ND	ND
Taylor et al[93]	Case report	PSTT n=1	Hysteroscopic resection		ND	Salvage hysterectomy
Imamura et al[98] 2015	Case report	ETT n=1	Laparotomic resection		Additional chemotherapy No recurrence	ND
Renaud et al[96] 2015	Case report	PSTT n=2	D&C		ND	Salvage hysterectomy
Tse et al[97]	Case report	ETT n=1	Laparotomic resection		ND	Live birth n=2
Zhao et al[79]		PSTT n=23	Chemotherapy n=20		Death n=1 Partial response n=1	Live birth n=7 (which group?)
			Laparotomic resection n=2		ND	ND
			D&C n=1		ND	ND
Chiofalo et al[84]	Systematic review nine studies	PSTT n=18	Open procedure n=11	Laparotomic resection n=7	Additional chemotherapy n=3	Salvage hysterectomy n=5
				Modified Strassman procedure n=4	ND	ND
			Minimally invasive approach n=6	D&C Hysteroscopic resection	ND	ND
			Chemotherapy only n=1		ND	Live birth n=1
Zhang et al[95]	Literature review and case report	PSTT n=42 ETT n=19 Mixed PSTT/ETT n=1	Local resection n=10		Additional chemotherapy n=10 No recurrence n=7 ND n=3	Live birth n=2
Alexander et al[94]	Case report	PSTT n=13	Hysteroscopic resection n=1		No recurrence	ND

PSTT, placental site trophoblastic tumor; ETT, epithelioid trophoblastic tumor; ND, not described; Min invasive approach, minimally invasive approach

tumor. There was a suspicion of multiple pulmonary metastases and the patient was treated with six courses of methotrexate, etoposide, and actinomycin-D and showed no signs of recurrence after 26 months.[98]

No reports were found on preservation of fertility in exaggerated placental site. Finally, Kaur et al have reported on 21 cases of atypical placental site nodule, in which three cases (14%) were associated with gestational trophoblastic neoplasia during follow-up or after expert review.[99] Women with atypical placental site nodule and a wish for children could consider a hysterectomy after completion of their family given this risk of developing malignant sequelae.

CONCLUSION

In this review, an overview is provided of the available literature on fertility and pregnancy outcome after limited and extensive therapy for gestational trophoblastic disease. The cure rate is high, and women have a high chance of regaining their menstrual function and achieving a pregnancy. The obstetric outcomes are like those of the general population. However, acute and permanent ovarian failure can occur, especially in older women. Because treatment should start as soon as possible after diagnosis of gestational trophoblastic neoplasia, there is often no time for fertility preservation procedures such as oocyte retrieval or in vitro fertilization with embryo cryopreservation.

Women treated with standard single-agent and multi-agent regimens for gestational trophoblastic neoplasia can be reassured about their future fertility and pregnancy outcomes. For women refractory to standard treatment, immunotherapy is evolving as an alternative to high-dose chemotherapy with peripheral blood stem cell support and could positively influence the risk of chemotherapy-induced ovarian failure. For women with placental site and epithelioid trophoblastic tumor, fertility-sparing surgery can be successful in selected cases, but diagnosis and treatment may be impeded because of poor visualization of target lesions to be resected. Detailed registration of (ultra) high-risk gestational trophoblastic neoplasia, placental site, and epithelioid trophoblastic tumor is still indispensable to obtain more complete data to inform patients in the future.

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