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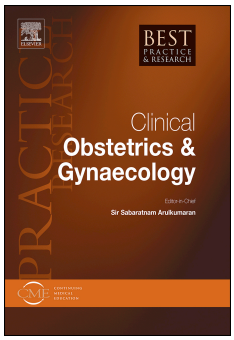

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Psychological aspects and fertility issues of GTD

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Abstract

Gestational Trophoblastic Disease (GTD) represents a spectrum of rare pregnancy-related disorders, including both premalignant and malignant entities. Although GTD's medical outcomes have been widely explored, limited data are available regarding the related psychological, sexual and fertility issues. The present chapter aims to enhance comprehension of the psychosocial impact of GTD by discussing the main quantitative and qualitative evidence available in this field.

Although patients globally report a good quality of life, clinically significant levels of anxiety and depression have been consistently found across studies. Similarly, despite the quality of couple relationships being generally satisfactory, they often complain of a lack of sexual desire. Moreover, pregnancy loss may raise significant and long-term fertility-related concerns.

Specific socio-demographic and clinical factors have been identified as predictors of psychosocial outcomes. On a clinical level, research suggests there is a need to provide multidisciplinary care to patients.

Keywords: Gestational Trophoblastic Disease; quality of life; fertility distress; sexual functioning; couple relationship.

GESTATIONAL TROPHOBLASTIC DISEASE: AN OVERVIEW

Gestational Trophoblastic Disease (GTD) represents a group of rare pregnancy-related disorders, characterized by abnormal trophoblastic proliferation. GTD encompasses both premalignant disorders, including complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM), and malignant entities, namely invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor [1-3]. The latter four, termed Gestational Trophoblastic Neoplasia (GTN), may develop after any gestation, but in most cases follow a molar pregnancy. Specifically, after CHM and PHM, malignant sequelae occur in 15% to 20% and 0.5% to 1% of patients, respectively [1].

Although previously considered a lethal disease, progressive improvements in the diagnostic process, clinical management and follow-up protocols, along with the development of effective treatments and centralization of care, have resulted in excellent cure rates (exceeding 98%), with fertility preservation also possible in malignant disease cases [1,4-6].

Standard treatment of hydatidiform mole requires surgery, which consists, in most cases, in the evacuation of the pathological tissue by suction and curettage. Hysterectomy may be considered in patients without metastases and in women who have completed their reproductive desire, particularly women of advanced maternal age [7]. However, prophylactic hysterectomy after 40 years does not seem to reduce the incidence of GTN and the amount of chemotherapy needed [8].

After the surgical evacuation of molar tissue, surveillance is mandatory to monitor the course of the disease and detect possible malignant sequelae in advance. Follow-up of hydatidiform mole requires serum beta-human chorionic gonadotropin (β-hCG) measurements for 6-12 months [1,3,7].

Post-molar GTN treatment requires a chemotherapy regimen, which should be determined on the basis of the prognostic factors identified by the FIGO scoring system. Women with a FIGO score < 7 are considered to have low-risk disease and can be treated with single-agent chemotherapy, whereas patients with high-risk diseases (FIGO score ≥ 7), require multi-agent regimens. In the case of resistant or relapsing disease, second-line chemotherapy should be implemented [9]. After chemotherapy completion, β-hCG surveillance for at least one year is needed to detect possible relapses, which mostly occur in the first 12 months after treatment. Therefore, patients should be advised to avoid pregnancy during this period, unless other factors, such as advancing age, motivate the desire for an earlier pregnancy [3].

Over the last decades, the development of specific surveillance protocols for hydatidiform mole and effective treatment regimens for GTN has significantly improved the prognosis of these conditions. Nowadays, women affected by malignant disease are expected, in most cases, to be long-term survivors and often express the desire to conceive after the completion of treatment [10]. Therefore, the susceptibility for recurrent molar pregnancy following a first diagnosis of CHM or PHM, as well as the risk of fertility damage after chemotherapy for GTN, represent aspects of major concern. Research suggests that more than 98% of women who become pregnant following a CHM or PHM will not develop another molar pregnancy and will not be more vulnerable to obstetrical complications [6]. Concerning GTN, although chemotherapy brings forward menopause onset by approximately three years [11], the majority of patients maintain or recover normal menstrual function and preserve their fertility potential [6,12,13]. Specifically, a recent meta-analysis showed that nearly nine out of ten women affected by GTN who have a desire for childbearing will achieve future pregnancies after chemotherapy, with favorable obstetrical outcomes even in cases of multi-agent regimens. Rates of neonatal malformation and adverse pregnancy outcomes are comparable to those of the general population, except for a small increase in stillbirth rate [10].

Despite the successful medical outcomes of these diseases, GTD affected women and their partners have to deal with significant emotional issues and radical changes in their psychological balance, which compels them to find new accommodation, both in their individual life and life as a couple. Indeed, illness forces them to face a sudden shift in their future perspectives, moving from experiencing joy and faithful wait, generally induced by pregnancy, to feelings of worry and anguish evoked by a potentially life-threatening diagnosis. The prolonged period of treatment and follow-up may become important sources of psychological distress. Concerns about disease recurrence and future pregnancy, potential fertility damage, and obstetrical complications could further enhance the emotional burden and significantly impair the global quality of life [14,15].

Nonetheless, while medical outcomes have been widely investigated, psychological research on GTD patients has been more limited and often undermined by significant methodological limitations and lack of specific measurement tools [14]. Therefore, most of the existing evidence does not allow us to comprehensively understand the complex nature of the psychosocial impact of these conditions. Despite being one of the primary causes of psychological distress, fertility concerns seem to have only been partially addressed by empirical research.

The present review aims to offer a global framework of the psychosocial condition of GTD affected women by reporting and discussing the main quantitative and qualitative evidence available in this field (see Table 1 for included studies). From a clinical point of view, this may enhance the awareness of health professionals regarding the numerous sequelae these conditions could produce on patients' global quality of life, as well as on couple emotional adjustment. This could, in turn, stimulate the development of multidisciplinary healthcare plans for GTD affected women, to ensure personalized and comprehensive support throughout the course of the disease.

QUALITY OF LIFE

Recently, the growing interest in patient subjective well-being [16-18] has prompted the assessment of the perceived effects of illness and treatment on physical, psychological and social dimensions [19], which have been well summarized by the concept of Health-Related Quality of Life (HRQoL) [13,14].

Although only a few studies have explored these issues in women with GTD, research consistently shows that patients tend to report a good perception of their quality of life [21-25]: it is globally comparable to that of the general population [26,27] and higher than other groups of cancer survivors [28-30]. The main quality of life domains investigated concern the physical, social, and emotional functioning, which are often assessed with heterogeneous tools. Studies reveal that GTD patients generally report low scores on the emotional dimension, thus underlining the need for healthcare workers to carefully address the psychological sequelae of GTD alongside physical and treatment issues [21,22,24,31]. The immediate post-diagnosis phase seems to have the strongest emotional impact, even though the psychological consequences of GTD may persist in the long term. Indeed, the process of adjustment to the disease compels women to face sudden emotional changes, including shock, uncertainty, sadness, and frustration [22]. The most frequently perceived emotion by GTD patients is fear, mainly related to possible relapse or second cancer [21].

Studies investigating the predictive factors of quality of life [21-25,32] found that several clinical, socio-demographic, and psychosocial variables may influence subjective well-being. From a medical viewpoint, the specific diagnosis (i.e., hydatidiform mole vs. gestational trophoblastic neoplasia), the stage of the disease, and the relative treatment regimen are significantly associated with quality of life outcomes [22,23,32]. Specifically, patients with

metastases treated with chemotherapy tend to report lower quality of life scores [22,31] and higher levels of psychological distress [21] compared to those who only undergo periodic β-hCG surveillance. Moreover, research has shown that the possibility of preserving reproductive function of the uterus and ovaries contributes significantly to maintaining a satisfactory quality of life [1,23,33-35].

Concerning socio-demographic variables, younger patients report better physical functioning than older ones, who tend to perceive greater limitations in their daily activities and therefore experience a lower quality of life [32]. The educational level [32] and the socio-economic status [21,24] are also positively associated with life satisfaction among GTD patients.

Furthermore, studies investigating the impact of children have shown that childless women tend to experience more intense emotions towards early pregnancy loss compared to those who have already had a child, probably due to greater concerns about their fertility and future reproductive goals [36]. However, a more recent study did not confirm the protective role of children [24], thus underlining the need for further research on this topic. Moreover, the literature consistently suggests that the desire and possibility to have a child in the future significantly contribute to maintaining a good quality of life [21,36], even in the long-term [22,23,25].

Considering the social and relational dimensions, studies suggest that the presence of support from partners, family, friends, and healthcare workers [21,22,25] is crucial in promoting quality of life. Concerning the couple relationship, sexual satisfaction emerges as another important predictor of quality of life [21,25]. Moreover, research shows that being part of a psychological support group may provide help and reassurance to patients, along with allowing a better understanding of the disease [22]. Finally, women who perceive a high level of social support tend to adopt more effective coping strategies in the acute phase of the

disease [22] and stop using these strategies over time, presumably because most GTD-specific stressors have been successfully managed previously [21].

ANXIETY AND DEPRESSION

Over half of women who receive a diagnosis of GTD are considered potentially at risk for developing symptoms indicative of a psychiatric disorder, especially anxiety and depression [14,15,21,22,24,37-41]. Unfortunately, these symptomatic manifestations are sometimes underdiagnosed and therefore do not receive adequate attention. They are often not addressed with prompt treatment. Indeed, clinicians and healthcare professionals often adopt a biomedical approach to managing the disease, neglecting its subjective meaning and psychological impact [22,42,43]. However, recently there has been growing awareness of the importance of combining standard medical therapy with psychological support for GTD patients [22].

Although a small number of studies have investigated the psychological effects of GTD, anxiety symptoms seems to have a higher incidence than depression [15,22,24,40], affecting up to 50% of patients [22,44,45].

Studies investigating the predictive factors of anxiety found that some clinical and socio-demographic variables may influence symptom onset [15,21,22,24,37,40]. Regarding clinical factors, anxiety seems to be positively associated with the severity of the disease and its related treatment [22,24,40,45,47]. Specifically, women with GTN are more likely to experience high levels of anxiety compared to those with hydatidiform mole. This may be due to the long-term physical and psychological consequences produced by chemotherapy, which is mandatory in cases of malignant disease [37,40]. Additionally, patients with metastatic cancer are considered particularly at risk of developing anxiety disorders [37]. In some cases,

anxiety symptoms are secondary to other emotional responses triggered by the diagnosis, which often elicit a sense of confusion, uncertainty, anger, and frustration. These feelings may persist over time and in certain circumstances may lead to a state of emotional exhaustion [22,24,37].

Anxiety is often related to fear and tends to occur at specific time-points, especially at the moment of diagnosis and during the periodic monitoring of β-hCG. Moreover, anxiety may be increased by the perception of physical symptoms, which are often misinterpreted as unequivocal signs of presistent disease [24,40,45].

From a socio-demographic point of view, younger and childless patients seem to be at greater risk for anxiety disorders [22,45,47]. Furthermore, these women are often troubled by the need to avoid conception during their follow-up and may show a persistent state of anxiety and worry associated with the perspective of future pregnancies, even after completion of treatment [22,24,45]. Patients who succeed in having a child after GTD show better global psychological functioning compared to women who do not, particularly with respect to anxiety symptoms [22]. However, some mothers report significant concerns about possible death and the consequent challenges for their children being taking care of [40].

Finally, the negative perception of GTD – specifically, the belief that the disease may have severe consequences – could promote the representation of the pathology as a serious threat, thus leading to higher levels of state anxiety [46].

Regarding depression and other mood disorders, a range of clinical manifestations may be observed in GTD patients, varying from occasional feelings of sadness and despondency to a defined psychiatric disorder [22]. Depressive symptoms have an incidence of about 15-20% among women with GTD; on average, patients report a mild level of depression or dysphoria and only a small percentage experience severe depression [15,21,22,24,38,39,41,42,46].

Depressive symptoms share most risk factors with anxiety [15,21,22,24,37,38,41,42]. The severity of the disease seems to have the most significant impact on patients' mood: women diagnosed with GTN tend to show higher depression scores than those diagnosed with hydatidiform mole [15,22]. In addition, depression occurs with higher frequency among patients with metastatic cancer [37]. The literature on cancer patients also documents that mood disorders are often associated with chemotherapy treatment [15,22,48,49] and its related sequelae on body image perception [22,24,25,50], as well as with fear of recurrence [41].

Undoubtedly, the sudden interruption of pregnancy determined by the treatment of the disease represents another important factor involved in the onset of depressive feelings, which in some cases persist even after the end of treatment and may recur during subsequent pregnancy [22,38].

SEXUAL FUNCTIONING AND RELATIONSHIP SATISFACTION

During the last thirty years, there has been a significant increase in research aimed at investigating the effects of gynecological cancer on sexual health, now widely recognized as an important component of quality of life [51].

However, studies concerning sexual functioning and relationship satisfaction of patients with GTD are still limited. Most research highlights the presence of sexual problems [22,37-41,49,52], regardless of disease type [37,39,49], time since diagnosis [22,49], and chemotherapy regimen [22,49].

Undoubtedly, multimodal treatment of GTN (i.e., chemotherapy and surgery) may damage physiological systems needed for a healthy sexual response, including hormonal, vascular, and neurological aspects of sexual function [52]. Fatigue may also cause sexual impairment in

patients who have reported being too tired for sexual intercourse [21]. However, the main dysfunction reported by GTD patients is the loss of sexual desire [38,40,41,52], which, in turn, often leads to difficulties in reaching orgasm. In most cases, these sequelae are related to psychological factors, rather than organic or functional problems [52].

Considering the etiology of GTD, it is not surprising that feelings of self-blame, partner blame, guilt, anger, fear of recurrence, and concerns related to fertility loss may be significantly implicated in sexual dysfunction [22]. As many studies have reported good relationship functioning [37,39,41,49], in particular in cases of metastatic disease [49], the most likely way for these feelings to manifest is through sexuality rather than openly directing resentment and frustration towards a supportive partner [49]. Therefore, qualitative analyses might be better able to assess the psychological aspects of sexual relationships as opposed to the physical measures of sexual performance. In fact, the former, rather than the latter, seems to be at risk [53].

Notwithstanding this, two studies show that most women do not attribute their current sexual problems to the disease [37], stating that their problems were also present before their diagnosis [52]. Although sexual dysfunction appears to be common among women before GTD, diagnosis and treatment may unmask or heighten previous difficulties [52].

Research investigating partners' psychological well-being [49,53] found that men often complain about illness-related sexual dysfunctions during active disease treatment; however, they do not recognize the persistency of these problems once the disease is in remission [49]. Moreover, partners report high levels of distress concerning women's well-being and future reproductive outcomes [49,53]. Nonetheless, they tend to assume the role of "supporters" rather than identifying them as "patients" [53]. In this regard, quantitative studies show that women seem to feel well supported by their partners [37,39], whereas qualitative studies highlight that this is not always easy or possible [38,40].

Finally, despite not directly affecting neither marital satisfaction nor patients' sexual functioning [22,37,49], the presence of children is a protective factor for patients' self-esteem [37] and partners' sexual functioning [53].

FERTILITY

GTD diagnosis compels women and their partners to face a sudden shift from feelings of hopefulness and happiness surrounding pregnancy to a painful state of loss and fear about their future health and fertility perspective [25,54]. The increase in β-hCG levels, generally considered as a positive outcome of a normal gestation, drastically changes its meaning, becoming a threatening disease marker for GTD. While facing a complex and rare disease, patients have to work through the pain of losing a pregnancy and deal with a sense of uncertainty and powerlessness related to their reproductive future. Although GTD treatment currently allows fertility preservation, and this also the case for malignant disease, women are compelled to postpone the next pregnancy, as they are advised not to conceive during follow-up [1,3]. Therefore, women may find themselves facing an ambiguous and conflicting situation, insofar with the desire for a future pregnancy against the fear of disease recurrence. These issues may compromise both short and long-term psychological balance and could profoundly affect their sense of identity, self-esteem, and femininity [43].

The literature has consistently documented how early pregnancy loss could produce long-term emotional sequelae, resulting in an increased rate of psychological and psychiatric morbidity [55]. In particular, studies reveal that between 18% and 32% of women show high anxiety levels four to six weeks after the loss; depressive symptoms appear to be above the clinical threshold in 8-20% women. For both conditions, the return to baseline rates seems complete

within one year [55]. Post-traumatic stress disorder is reported in 25-39% of women after early pregnancy loss, with an unclear resolution pattern [56–58].

Despite the etiology of GTD, research about the psychological impact of pregnancy loss and fertility concerns is still limited with conflicting results.

The first studies undertaken on these themes document that worries about a future pregnancy, along with fear of disease recurrence, could be considered of primary importance for this population of women [37]: feelings of lack of control over personal reproductive future, dissatisfaction with the current number of children, grief and anger about potential fertility impairment seem to persist in a considerable proportion of the sample, even 5-10 years after the first diagnosis [21]. Petersen et al. (2005) investigated these issues through a focus group, finding that women expressed significant concerns about limited future opportunities for having children [22]. The perspective of future conceptions seems to evoke persistent fears, anxiety, and panic due to unresolved molar disease concerns and intrusive memories associated with the loss of an anticipated baby. Moreover, women expressed feelings of disappointment and generalized hopelessness over the pregnancy loss, which was perceived in some cases as a personal failure [22].

However, subsequent studies have found that GTD patients did not seem overly worried about infertility and acknowledged that the risk of recurrence is minimal [45]. Moreover, these authors showed that, despite the persistence of some concerns about future pregnancies, a consistent proportion of women expressed intention of conceiving again [45,48]. Further, the most updated research on this topic [15,46] conducted with standardized and well-validated questionnaires highlights that, globally, women diagnosed with molar pregnancy and GTN did not report clinically significant levels of infertility-related stress.

The literature concerning fertility issues documents that GTD affected women tend to attribute greater value to childbearing after illness experience. In particular, Wenzel et al.

(1992) reported that 47% of women with molar pregnancy and 48% of those affected by persistent GTN gave more value to motherhood [37]. In line with these results, Stafford and Judd (2011) highlighted that for 46% of their sample conceiving became a more relevant goal after GTD diagnosis [48]. More recent studies seem to confirm this evidence, showing that the need for parenthood represents one of the main reported issues by GTD patients [15,46].

Research also revealed that some clinical and individual factors could impact on fertility concerns. In particular, one early study on this theme underlined that patients affected by metastatic GTN reported significantly higher concern about infertility and pregnancy than women with a non-metastatic disease [37]. Age seemed to also have a significant effect on fertility perception. In this regard, Di Mattei et al. (2015) observed that younger women (≤ 35 years) reported higher levels of infertility-related distress [15], confirming the results of previous research on cancer samples [59,60]. Moreover, younger patients seem to be more concerned about the importance of parenthood in their lives and are more worried about sharing fertility issues with their partners [15]. The presence of children turned out to be a protective factor with respect to fertility-related concerns in two studies [15,37]. Concerning psychological variables, Lok et al. (2011) found that women with high levels of anxiety scored higher for fear of infertility and fear of conceiving again [45]. However, a more recent study failed to replicate this result, finding no association between fertility issues and emotional distress [15]. Updated research has also documented that the specific perception of the mental illness may have a significant impact on infertility-related stress. In particular, individual beliefs about treatment efficacy predict a lower tendency to perceive discomfort and isolation from family that may arise from fertility-related problems [46].

Table 1. Summary of included studies

Authors, year, country	Participants	Time since diagnosis	Treatment	Type of Study	Measures

Carnelli et al., 2016 (ITALY) [46]	37 GTD patients (mean age=36.43, S.D.=9.37) - 25 (67.6%): HM - 12 (32.4%): GTN	0-25 months (mean=4.5 months)	- 25 (67.6%), all with HM: only β-hCG follow-up - 3 (25%), all with GTN: hysterectomy - 9 (75%), all with GTN: chemotherapy	Quantitative, cross sectional study	BDI-SF, STAI, FPI, PQ-R
Di Mattei et al., 2015 (ITALY) [15]	37 GTD patients (mean age=35.6 years; S.D.=2.81): - 20 (54%): HM - 17 (46%): GTN	1-36 months (mean=6.6 months)	- 20 (54%), all with HM: only β-hCG follow-up - 17 (46%), all with GTN: chemotherapy	Quantitative, cross sectional study	BDI-SF, STAI, FPI
Ferreira et al., 2009 (BRAZIL) [24]	54 patients with GTD (mean age=23.57) - 31 (57.4%): HM - 23 (42.6%): GTN	Not reported	All patients with GTN (N=23): chemotherapy (78.3% single-agent chemo; 21.7% multi-agent chemo)	Quantitative, cross-sectional study	WHOQOL-BREF, BDI, STAI
Flam et al., 1993 (SWEDEN) [38]	22 patients (age range: 21-53 years) with persistent GTD in complete remission	Not reported	All patients received chemotherapy (86.4% single-agent chemo; 13.6% multi-agent chemo)	Qualitative, cross-sectional study	Semi-structured interview with thematic analysis
Hengrasmee et al., 2004 (THAILAND) [42]	149 patients with gynecological cancer (mean age=46.6; S.D.=11.5) - 77 (51.7%): ovarian cancer - 34 (22.8%): cervical cancer - 20 (13.4%): corpus cancer - 18 (12.1%): GTN	< 3 - >12 months	- 33 (22.1%): chemotherapy alone - 12 (8.1%): radiation alone: - 9 (6%): surgery alone - 95 (63%): combined treatment	Quantitative, cross-sectional study	HRSR
Jewell et al., 2018 (USA) [41]	51 patients (mean age=41.6 years) with GTN in remission	3 months – 12 years (mean=4.5 years)	23 (45.1%): active ß-hCG surveillance with monthly ß-hCG level monitoring	Quantitative, cross-sectional study	Reproductive Concerns Scale (ad-hoc, non-validated measure), FSFI, DAS, CES-D, Menopausal Symptom Checklist, IES, ad-hoc questions assessing ß-hCG surveillance worries

Leenharattanarak & Lertkhachonsuk, 2014, (THAILAND) [23]	44 patients (mean age=31.6) with GTN in complete remission	Not reported	-31 (70.49%): chemotherapy alone (29.6% single-agent chemo; 40.95% multi-agent chemo) - 9 (20.5%): hysterectomy + chemotherapy - 4 (9.1%): hysterectomy + chemotherapy + radiation:	Quantitative study, cross-sectional study	FACT-G
Lok et al., 2011, (NETHERLANDS) [45]	76 patients (mean age=31.5 years, S.D.=4.8) with low-risk GTD (both CHM and PHM), with spontaneous normalization of β-hCG.	At the time of investigation, 80% of the sample have already completed the follow-up of 6 months.	All patients underwent uterine evacuation	Quantitative, retrospective study	Ad-hoc non-validated questionnaire concerning follow-up, anxiety and distress during surveillance period.
Petersen et al., 2005, (AUSTRALIA) [22]	74 women with GTD. The sample included both women who were receiving active follow-up and those who had received treatment in the previous 30 years.	- 30 (40,54%): < 18 months - 44 (59,46%): ≥ 18 months	25 (34%): chemotherapy	Mixed-methods; cross-sectional study	SWLS, HADS, SHF-12, focus group with 15 patients and relative partners
Quinlivan et al., 2012 (AUSTRALIA) [53]	41 male partners (mean age=39 years) of women with GTD recruited from Petersen's study sample (2005), who gave their consent for their partner to to participate in the study	See Petersen et al., 2005	- 45% of women were receiving treatment or were in the acute phase of follow-up - 55% of women had received treatment more than 18 months previously	Mixed-methods; cross-sectional.	HADS, SWLS, SHF-12, thematic analysis of written comments.

Singh et al., 2017 (UK) [40]	8 patients (mean age=41.63) with GTN in remission	1 – 11 years	- All patients received high-dose chemotherapy and stem cell transplantations - 6 (75%): hysterectomy - 3 (37.5%): thoracotomy - 1 (12.5%): pneumonectomy	Qualitative, exploratory study	Semi-structured interview with framework analysis
Stafford & Judd, 2011 (AUSTRALIA) [48]	See Stafford et al., 2011	See Stafford et al., 2011	See Stafford et al., 2011	Quantitative; cross-sectional study	Ad-hoc non-validated questionnaire measuring subjective perception of the impact of GTD on fertility and reproduction.
Stafford et al., 2011 (AUSTRALIA) [39]	176 GTD patients (mean age at diagnosis=32.1 years, S.D.=6.3) divided into 2 subgroups: - 149 (84.7%): GTD with spontaneous remission (62% with partial mole; 38% with complete mole) - 27 (15.3%): malignant GTN **(**85% with persistent molar disease; 2% with choriocarcinoma)	1.6-18.5 years (mean=4.7 years)	- 151 (86%): suction curettage - 18 (10%): dilation and curettage - 2 (7%): hysterectomy - 27 (15%): chemotherapy (16 single-agent chemo; 11 multiagent chemo)	Quantitative, cross-sectional study	FSFI, MSS, HADS, IES-R, ad hoc questions assessing the impact of GTD on the marital relationship

Wenzel et al., 1992 (UK) [37]	76 women (mean age=32 years, range: 30-52) with GTD: - 19 (25%): partial mole - 19 (25%): complete mole - 38 (50%): persistent GTD (15% had metastatic disease) 65 patients were in remission (normal or non-detectable hCG levels), 11 had active disease	< 1-5 years	Patients with HM: - 29 (76%): uterine evacuation alone - 9 (24%), all with complete mole: uterine evacuation + prophylactic chemotherapy Patients with persistent GTN: - 23 (61%): uterine evacuation + single-agent chemotherapy - 15 (39%): uterine evacuation + poly-chemotherapy	Mixed-methods, retrospective study	POMS, DAS, Cervical Cancer Study Questionnaire (selected items), WCS, Psychosocial Response to Illness Scale (ad-hoc, non-validated questionnaire), qualitative interview aimed at investigating the most stressful event experienced by women in the past year
Wenzel et al., 1994 (UK) [49]	Subgroup of 27 women with GTD and relative partners selected from the study sample recruited by Wenzel et al. (1992)	See Wenzel et al., 1992	See Wenzel et al., 1992	Quantitative; retrospective study	POMS, DAS, Cervical Cancer Study Questionnaire (selected items), Psychosocial Response to Illness Scale
Wenzel et al., 2002, (UK and USA) [21]	111 GTN survivors (mean age=37 years, range: 23-53)	5-10 years	- 71 (64%): dilation and curettage + chemotherapy - 40 (36%): chemotherapy only	Quantitative, retrospective study	MOS SF-3, QoL-CS, FACT-Sp, SAQ, COPE, ad-hoc questions assessing sexual functioning, Reproductive Concern Scale
Wenzel et al., 2004 (UK) [25]	See Wenzel et al., 2002	See Wenzel et al., 2004	See Wenzel et al., 2002	Quantitative, retrospective study	IES, SF-36, ISEL, MOS SF-36, QoL-CS, FACT-Sp, SAQ, COPE, Reproductive Concern Scale, ad-hoc questions assessing sexual functioning

Wilailak et al., 2011 (THAILAND) [28]	870 patients with gynecological cancer (mean age=53.4): - 22 (2.5%): GTN - 571 (65.6%): cervical cancer - 149 (17.1%): ovarian cancer - 108 (12.4%): endometrial cancer - 15 (1.7%): uterine sarcoma - 3 (0.3%): vulva cancer - 2 (0.2%): vaginal cancer	6 -173 months (median=61 months)	- 28.7%: surgery alone - 34.4%: radiation alone - 1.4%: chemotherapy alone - 35.5%: combination therapy	Quantitative, cross-sectional study	FACT-G
Zhao et al., 2003, (CHINA) [31]	191 patients (mean age=42.2) with gynecological cancer: - 105 (55%): ovarian cancer - 68 (35.6%): GTD - 18 (9.4%): other	< 6 months - >12 months: - 68 (35.6%): < 6 months; - 74 (38.7%): 6-12 months; - 49 (25.7): > 12 months	-141 (73.8%): chemotherapy alone - 50 (26.2%): chemotherapy + surgery	Quantitative, cross-sectional study	EORTC QLQ-C30

GTD=Gestational Trophoblastic Disease; HM=Hydatidiform Mole; GTN=Gestational trophoblastic Neoplasia; BDI-SF=Beck-Depression Inventory Short-Form; STAI=State-Trait Anxiety Inventory Form Y; FPI=Fertility Problem Inventory; IPQ-R=Illness Perception Questionnaire-Revised; WHOQOL-BREF=World Health Organization Quality of Life; HRSR= Health-Related Self-Report questionnaire; FSFI=Female Sexual Function Index; DAS=Dyadic Adjustment Scale; CES-D= Center for Epidemiologic Studies–Depression Scale; IES=Impact of Life Events Scale; FACT-G=The Functional Assessment of Cancer Therapy-General; SWLS= Satisfaction with Life Scale; HADS= Hospital Anxiety and Depression Scale; SHF-12= Sexual History Form-12; MSS= Marital Satisfaction Scale; IES-R=Impact of Event Scale-Revised; POMS= Profile of Mood States; WCS=Ways of Coping Scale; MOS SF-36= Medical Outcome Study Short Form-36; QoL-CS=Quality of Life – Cancer Survivorship; FACT-Sp=Functional Assessment of Cancer Therapy – Spirituality Scale; SAQ=Sexual Activity Questionnaire; COPE=Coping Orientations to Problems Experienced; SF-36=Short Form-36; ISEL= Interpersonal Support Evaluation List; EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.

CONCLUSIONS

This overview of the literature explores the numerous psychosocial sequelae of GTD, trying to offer a comprehensive picture of quantitative and qualitative evidence on this topic. Although women globally report a good HRQoL [21-25], research shows that these conditions may produce long-term effects on the emotional, social, and sexual functioning.

Clinically significant levels of psychopathological symptoms were consistently found in patients with GTD [15,21,22,24,38,39,41,42,44-46]. Despite the quality of couple relationships being highly satisfactory for most women [37,39,41,49], sexual dysfunctions – mainly related to a lack of desire – are often reported by patients and partners [38-41,49,52,53]. Moreover, early pregnancy loss due to GTD seems to induce intense and persistent fertility-related concerns in a substantial proportion of women [21,22,37].

These data should be interpreted in light of several limitations, which may undermine the generalizability of the results. Firstly, all studies are cross-sectional, thus providing only descriptive data at one-time point. Moreover, the long intervals since diagnosis, often reported by retrospective research, may introduce significant recall bias. It should also be noted that samples often consist of heterogeneous populations of patients, including different disease types, stage, treatment, and time since diagnosis. Furthermore, a significant proportion of studies uses ad-hoc, non-validated questionnaires.

Therefore, it is important to extend the research in this field to gain a better comprehension of the psychological issues related to GTD. Specifically, the implementation of longitudinal designs may allow the identification of possible changes in the psychological adjustment during the disease trajectory and, simultaneously, develop predictive models to detect which women would benefit from psychosocial interventions [43]. Moreover, research on well-defined samples, sharing the same medical condition, may significantly contribute to the comprehension of the unique pattern of psychological, social, sexual, and reproductive concerns relevant to different disease conditions. Finally, the integration of quantitative and qualitative evidence could help develop and validate specific measurement tools, aimed at assessing the most salient psychosocial domains for women with GTD. In particular, more systematic evaluations of fertility issues and couple relationships should be implemented, as these still represent a relatively neglected area of research.

Clinically, the collected evidence clearly highlights a need to develop multidisciplinary care plans for women with GTD, to address the relevant issues related to the disease. A minimum standard of care should include an initial psychosocial evaluation and educational interventions aimed at providing clear explanations about the etiology and the management of the disease, as well as the potential treatment side effects. Women should also be reassured about the favourable prognosis generally associated with GTD and the possibility of attaining future pregnancies after treatment. Educational interventions may significantly contribute to the comprehension of GTD, enhance adherence to treatments and surveillance protocols, contain fears and reproductive concerns, thus allowing for a better individual and couple psychological adjustment [43].

Particular attention and proactive care should be allocated to patients at risk for quality of life impairments, psychological distress, relational difficulties, and fertility concerns. Specifically, the literature suggests that women of younger age, affected by high-risk disease, undergoing chemotherapeutic treatment, with no children and poor social support may need more extensive interventions [15,21-25,31,32,36,37,40,46-49]. Mental health providers should offer assistance throughout the course of the disease, helping women reduce the magnitude of emotional reactions, develop adaptive coping skills for managing the disease, and enhance open communication with partners and family.

SUMMARY

Gestational Trophoblastic Disease (GTD) diagnosis, treatment and follow-up compel women and partners to come to terms with a range of psychological challenges. The unexpected pregnancy loss due to the disease and the prolonged period of treatment and follow-up represent significant sources of distress for many women.

Studies investigating GTD's psychosocial impact reveal that patients' HRQoL is globally comparable to that of the general population [26,27] and is higher than other cancer samples [28-30]. However, significant impairments in the emotional functioning have been consistently found [21,22,24,31].

The literature documents that anxiety symptoms occur in a substantial proportion of women, affecting up to 50% of patients [22,44,45], while severe depression is reported less frequently [15,21,22,24,38,39,41,42,46]. Moreover, although most women declare to be satisfied with the quality of their couple relationship [37,39,41,49], sexual dysfunctions due to lack of desire are often reported by both patients [38-41,52] and partners [49,53]. Although it has provided scarce and controversial results, research about fertility issues found that women tend to express intense concerns and fears about future pregnancies, which often persist in the long-term [21,22,37]. Nonetheless, patients tend to attribute a greater value to parenthood after recovering from the illness [15,37,46,48].

Women of younger age, affected by high-risk diseases, undergoing chemotherapy, with no children and poor social support seem to be more vulnerable to quality of life impairments, emotional distress and fertility concerns [15,21-25,31,32,36,37,40,46-49].

Multidisciplinary care plans, involving educational and psychosocial interventions, may help patients understand the specific nature of GTD and coping with disruptive emotional responses, thus fostering better adherence to treatment and psychological adjustment to the disease.

PRACTICE POINTS

- Healthcare workers should monitor the psychological sequelae of GTD alongside physical and treatment issues
- GTD should be addressed with multidisciplinary care plans, aimed at offering individualized and global assistance throughout the course of GTD
- Educational interventions should be provided as a minimum standard of care, in order to enable all women to adequately comprehend their condition and its related consequences
- Women who are more vulnerable to psychosocial morbidity should have access to more extensive and long-term interventions

RESEARCH AGENDA

- Implement longitudinal designs
- Develop validated disease-specific measures
- Extend the investigation on fertility issues and couple adjustment
- Evaluate the efficacy of ad-hoc psychosocial interventions

CONFLICT OF INTEREST STATEMENT

None.

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Highlights

- Gestational Trophoblastic Disease (GTD) may produce significant psychosocial consequences on both patients and partners.
- Although women globally report a good quality of life, significant distress symptoms have been consistently found across studies.
- Lack of sexual desire and persistent fertility concerns are complained by a substantial proportion of couples.
- Women of younger age, affected by high-risk diseases, undergoing chemotherapy, with no children and poor social support need particular attention.
- Multidisciplinary care plans should be developed to address all the relevant issues related to GTD.