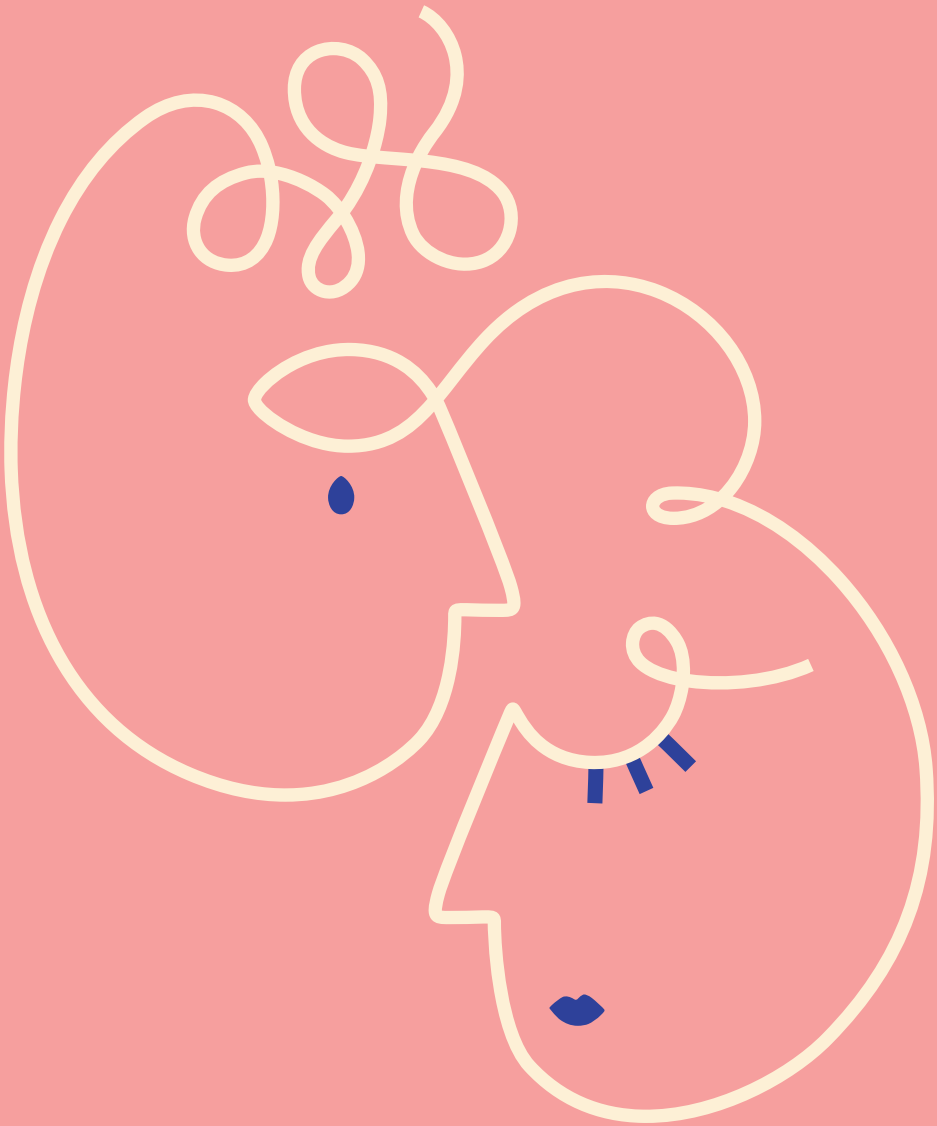


THE PSYCHOSOCIAL IMPACT OF GESTATIONAL TROPHOBLASTIC DISEASE

The person behind the patient



Laura Blok

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THE PERSON BEHIND THE PATIENT

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CONTENTS

CHAPTER 1	General introduction	7
CHAPTER 2	The psychological impact of gestational trophoblastic disease: a prospective observational multicentre cohort study	19
CHAPTER 3	Psychological impact over time of women with pregnancy loss due to gestational trophoblastic disease compared to miscarriage	33
CHAPTER 4	Evaluation of a web-based intervention for patients with gestational trophoblastic disease: a randomized controlled trial	49
CHAPTER 5	Evaluation of the psychosocial impact and received care in patients with gestational trophoblastic disease: a qualitative interview based study	67
CHAPTER 6	Identifying factors relevant to shared decision-making in chemotherapy for low-risk gestational trophoblastic neoplasia: an exploratory study	83
CHAPTER 7	General discussion	95
CHAPTER 8	Summary	107
CHAPTER 9	Samenvatting	113
APPENDIX	Research data management PhD Portfolio Bibliography Dankwoord Curriculum vitae	120



Chapter 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

In 1948, the World Health Organization defined the definition of health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (1). In 2011, Huber et al. proposed a new definition of health as “the ability to adapt and to self manage” (2). This perspective aligns with the growing understanding that health is not a static condition but rather a dynamic process influenced by the person’s ability to navigate challenges, both physical and psychological. This emphasizes the importance of mental and social well-being alongside physical health.

Physicians play a vital role in promoting and enhancing people’s health. They are responsible for not only diagnosing and treating diseases, but also addressing the broader aspects of an individual’s well-being. Although physical symptoms are often more readily recognized, the importance of psychological health is increasingly acknowledged. These psychological conditions may comprise various symptoms, including distress, depression and anxiety. Such manifestations can substantially impair daily functioning, interpersonal relationships and occupational productivity, thereby contributing to significant personal, societal and economic burdens (3). Psychological conditions can develop after a wide range of triggers, including traumatic experiences, chronic stress, illness or significant life changes. Consequently, it is not surprising that substantial evidence indicates a higher prevalence of psychological complaints in specific groups, such as patients with cancer (4-7).

This is particularly evident in patients facing both oncological diagnoses and pregnancy loss, two conditions independently associated with increased psychological burden (4-9). This thesis focusses on a group where both overlap: patients diagnosed with Gestational Trophoblastic Diseases (GTD). GTD encompasses a heterogeneous group of rare pregnancy-related conditions, including both premalignant and malignant forms. Although research is limited, existing studies indicate that patients with GTD are at risk for psychosocial symptoms (10-17). To fully comprehend the possible psychological consequences of GTD, it is essential to first consider the nature of the disease and its treatment regimen.

GESTATIONAL TROPHOBLASTIC DISEASE

GTD comprises of a diverse group of pregnancy-related disorders originating from abnormal proliferating trophoblastic cells. It consists of premalignant forms, including the complete and partial hydatidiform moles (CHM and PHM respectively) and of malignant forms such as the invasive mole, choriocarcinoma, placental site trophoblastic tumor and epithelioid trophoblastic tumor. The last four are collectively described as Gestational Trophoblastic Neoplasia (GTN) (18).

As mentioned, CHM and PHM are benign placental tumors with malignant potential. GTD is a rare condition, with varying incidence rates worldwide (19, 20). In the Netherlands, approximately 300 patients are newly diagnosed with GTD each year, corresponding to

an overall incidence rate of 1.66 per 1000 deliveries (21). Both CHM and PHM originate through abnormal fertilization, after which placental villi form small, hydatidiform structures (19, 20). CHM is the most common type and arises when an enucleated egg is fertilized by either one or two sperms, resulting in a diploid karyotype consisting of solely paternal genetic material. In this case, there is proliferation of trophoblastic tissue without fetal development. CHM can be recognized on an ultrasound as a grape-like cluster of swollen villi, without an embryo or identifiable fetal parts. In contrast, PHM originates after dispermic fertilization of a normal ovum, resulting in a triploid karyotype, possibly with fetal parts (19, 20). GTD patients may experience possible complaints such as vaginal bleeding and hyperemesis (20). Since the introduction of the first trimester ultrasonography and consequently an earlier diagnosis, the majority of patients however is still asymptomatic at time of diagnosis (19, 20, 22).

Trophoblast cells produce human chorionic gonadotropin (hCG). Since HM are characterized by abnormal proliferation of trophoblast cells, patients with HM show a marked increase in serum hCG concentrations. hCG is an important biomarker for disease progression, therapy response and post-treatment surveillance. It is important to monitor serum hCG levels with an hCG assay capable of detecting all forms of hCG, as GTD frequently produce aberrant hCG variants such as free beta-subunit (20). Therefore, in the Netherlands, all serum samples are typically sent to the central laboratory of the national registry for analyzation at the Radboud University Medical Center (Radboudumc) (23). In contrast to assays commonly used in general hospitals, the assay employed by this laboratory is designed to detect all native hCG forms, with emphasis on the free beta-subunit.

MANAGEMENT OF GESTATIONAL TROPHOBLASTIC DISEASE

Standard treatment for patients diagnosed with GTD is curettage, preferably under ultrasonic guidance, after which histological examination to confirm the diagnosis is performed (19, 24). After curettage, patients require weekly monitoring of serum hCG levels to detect potential progression of disease, since 15-20% of CHM and 0.5-5% of PHM will develop post-molar GTN (18, 25). During follow-up, patients are advised to postpone a future pregnancy, as a new pregnancy influences hCG levels and thereby compromises the ability to detect and monitor potential disease progression. Normalization of hCG levels occurs at a median of 7 weeks for CHM and 6 weeks for PHM after evacuation (26). For patients whose hCG levels normalize spontaneously following curettage, at least one additional confirmatory hCG measurement is recommended (27). Once this measurement confirms normalization, the likelihood of developing post-molar GTN is extremely low, and in the Netherlands, patients are typically discharged from follow-up (27-29). Internationally, patients with PHM generally require a single normal hCG measurement one month after normalization, whereas patients with CHM require monthly measurements for six months following normalization (20). After completing the recommended follow-up, patients are permitted to conceive again. The risk of recurrence in future pregnancies is 0.6-2% (30).

GESTATIONAL TROPHOBLASTIC NEOPLASIA

Post-molar GTN can occur after evacuation of a HM and is characterized by rising or plateauing blood hCG levels. Internationally, the Federation of Gynecology and Obstetrics (FIGO) criteria are used to diagnose post-molar GTN (31):

- a plateau of blood hCG levels ($\pm 10\%$) in 4 measurements over 3 weeks
- an increase in blood hCG levels ($>10\%$) in 3 measurements over 2 weeks
- histologic diagnosis of choriocarcinoma.

In the Netherlands, an additional requirement is applied: at least one hCG measurement must exceed the 95th percentile of the national hCG regression curve (23, 26). This hCG regression curve is based on a cohort of patients with uneventful hCG regression after evacuation of a HM. Because the hCG regression curve was developed and validated using data generated with the Radboudumc assay, which is specifically designed to detect all native hCG forms, it can only be reliably applied for hCG concentrations obtained by this method (26). The incorporation of this additional requirement prevents approximately 15% of patients from receiving unnecessary treatment, as these patients eventually achieve spontaneous normalization of hCG (23, 26).

MANAGEMENT OF GESTATIONAL TROPHOBLASTIC NEOPLASIA

Following GTN diagnosis, evaluation for metastases is needed (19, 20). Subsequently, GTN patients are classified to either low-risk or high-risk disease according to the FIGO-2000 classification system (31). Patients with a score of 0-6 are considered low-risk GTN, while patients with a score of 7 or higher are considered high-risk GTN. Treatment regimens are determined based on this risk classification, in which the high-risk category reflects an elevated risk of resistance to single-agent chemotherapy.

Low-risk GTN has an overall cure rate of 100% (32, 33). Internationally, treatment regimens vary (20, 33). Most frequently, regimens with methotrexate (MTX) or actinomycin D (actD) are used (33). In the Netherlands, patients with low-risk GTN are treated with MTX intramuscular 1 mg/kg on day 1, 3, 5 and 7, alternating with folinic acid (FA) orally 0.1 mg/kg on day 2, 4, 6 and 8 with an interval of seven days between every course (19). Nausea (15%), vomiting (5%), mucositis (25%) and conjunctivitis (25%) are reported as common side-effects of MTX treatment (34). After normalization of hCG, two additional consolidation courses are recommended (19). Thereafter, patients require monthly hCG measurements for one year to detect possible recurrence of disease (19). During this follow-up period, patients are advised to refrain from pregnancy.

ActD 1.25 mg/m² intravenously every 2 weeks is used as a suitable alternative for MTX, in case of resistance to MTX/FA chemotherapy, contraindications for MTX/FA or significant toxicity with MTX/FA (19). Side-effects of actD are mostly comparable to those of MTX/FA, although actD may additionally cause alopecia (33). After normalization, patients require two additional consolidation courses and hCG follow-up for one year while refraining from pregnancy.

High-risk GTN, which is relatively uncommon (6% of all cases), is treated with multiagent chemotherapy, usually EMA-CO (etoposide, methotrexate and dactinomycin alternating with cyclophosphamide and vincristine) (19, 35). The common side-effects of EMA-CO are alopecia, nausea, reversible neurotoxicity and myelosuppression (36). Survival rates of high-risk GTN are up to 95% (20). Patients with liver and/or brain metastasis have poorer outcomes (37, 38). Patients require hCG follow-up for 18 months while refraining from pregnancy.

PSYCHOLOGICAL IMPACT OF GTD

As indicated above, GTD patients must navigate through a range of challenges, including the loss of pregnancy, the rarity of the diagnosis, the surgical procedure for evacuation, frequent hCG monitoring with the potential need for chemotherapy and the recommendation to delay a future pregnancy. These challenges all have an impact on the psychological wellbeing of the patient. While it is acknowledged that GTD patients suffer from various psychological complaints such as anxiety, depression, distress and reproductive concerns, only limited and retrospective research has been conducted on this topic (10). This contrasts with the extensive body of research on patients who experienced a miscarriage, where pregnancy loss is widely acknowledged as a significant source of psychological distress. Studies on patients after miscarriage have reported psychological morbidity and highlighted the need for further research to improve patient care (8, 9, 39-44). Given that GTD patients face additional challenges beyond pregnancy loss, their psychological distress may be even more substantial.

When a miscarriage is diagnosed or when a molar pregnancy is suspected, patients are typically referred by their midwife to a local hospital for further evaluation, where the diagnosis of GTD usually becomes apparent. Because GTD is rare, gynecologists encounter these cases only sporadically, and although guidance is available through expert centers and national resources, the information patients receive may still vary across centers (21). Consequently, patients often seek supplementary information online (45, 46). However, while the availability of high-quality online medical information has increased, identifying reliable and comprehensive resources remains challenging. Patients with rare diseases frequently report that their information needs are not fully met (45, 47), even though access to accurate and trustworthy information contributes positively to the patient's experience (48). Therefore, there is opportunity to improve information provision for GTD patients.

Patients with GTD are also confronted with organizational challenges in their care trajectory. After diagnosis, they face a prolonged period of uncertainty related not only to the duration of intensive follow-up, but also to the emotional burden associated with each measurement, during which they are repeatedly confronted with the possibility of an unfavorable outcome. Most patients continue their trajectory of weekly hCG surveillance in their local hospital, where blood samples are taken and analyzed in the national laboratory of the Netherlands. While these hCG measurements enable the use of the validated hCG regression curve and has been shown to improve clinical

guidance for GTD patients (23, 26, 49–51), clinical care itself remains decentralized across local hospitals. Moreover, variability in referral practices to specialized expert centers means that patients receive different levels of specialist input and support. To support gynecologists in managing this rare condition, the Dutch Working Party on Trophoblastic Disease was founded in 1971. This multidisciplinary group of gynecologists, oncologists, pathologists and biochemists provides guidance through case-based consultation, maintains the national clinical guidelines and develops patient information resources. However, the decentralized structure poses challenges for optimal patient support and consistent care delivery.

Given the psychological challenges of GTD and the organizational complexities of decentralized care, there is a need to further evaluate the psychological impact of this condition. Understanding the impact can aid healthcare professionals in providing enhanced support and care for patients, while also equipping them with effective coping strategies. Moreover, research on the psychological impact of GTD can provide new insights that empower patients with crucial information and support the development of tailored interventions to address the specific challenges they face (8, 10).

APPROACH

To comprehensively explore the psychological impact of GTD, a mixed-methods approach was employed. Standardized questionnaires such as the Hospital Anxiety and Depression Scale (HADS) and the Impact of Event Scale (IES) were used to systematically assess anxiety, depression and post-traumatic stress symptoms. These validated instruments ensure consistent measurement and also enable comparison with other patient populations (52–54). Complementing this quantitative foundation, qualitative research provides deeper insight into patients' perspectives, capturing the context and nuances behind their thoughts, emotions and behaviors that questionnaires alone cannot fully reveal. Additionally, to explore opportunities for enhancing patient-centered care, we examined factors relevant to shared decision-making in GTN treatment choices. Shared decision-making is a collaborative process in which clinical evidence is integrated with patient values and preferences and has been increasingly recognized as a key component of person-centered care and associated with improved patient satisfaction and health outcomes (55–57).

OUTLINE OF THIS THESIS

This thesis focuses on the psychological problems and patient experiences of patients with GTD, providing insight into the psychological impact of the disease, ideally contributing to better care and support for these patients in the future.

Prospective data on the psychological impact of GTD on patients is scarce. For optimal care for these patients, more insight into the psychological impact is indispensable. In **CHAPTER 2**, the short-term psychological effects of patients with GTD are evaluated in a prospective observational multicenter study. An effort is made to identify patients at risk for developing psychological symptoms.

In **CHAPTER 3**, this psychological impact is further evaluated by following these patients over the course of one year. To better understand whether the psychological impact of GTD extends beyond pregnancy loss alone, patients with GTD were compared to patients who experienced a miscarriage. We also identified patients at risk for developing long term psychological complaints and who are therefore in need of extra supportive care.

As GTD is rare, obtaining comprehensive and reliable information for patients is challenging. In **CHAPTER 4**, we focused on improving online information for patients. We created an online tool designed to provide information about the diagnosis and treatment of GTD. Afterwards, we evaluated the impact of this web-based intervention on illness perception, knowledge, levels of distress and patient satisfaction.

In **CHAPTER 5**, we further explored the patients' perspectives by conducting semi structured interviews, aiming to better understand their experiences, challenges and needs with the aim of improving care based on their perspectives.

In **CHAPTER 6**, we explored which factors are relevant to shared decision-making in the choice of chemotherapy for patients with low-risk GTN, aiming to lay the groundwork for the future development of a decision aid tool.

The last chapter, **CHAPTER 7**, presents a general discussion, including recommendations for improving care and future research. This thesis concludes with a summary of the previously mentioned chapters.

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Chapter 2

THE PSYCHOLOGICAL IMPACT OF GESTATIONAL TROPHOBLASTIC DISEASE: A PROSPECTIVE OBSERVATIONAL MULTICENTRE COHORT STUDY

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ABSTRACT

Objective: To evaluate the short-term psychological consequences of Gestational Trophoblastic Disease (GTD).

Design: A prospective observational multicentre cohort study.

Setting: Nationwide in the Netherlands.

Population: GTD patients.

Methods: Online questionnaires directly after diagnosis.

Main Outcome Measures: Hospital Anxiety and Depression Scale (HADS), Distress Thermometer (DT), Impact of Event Scale (IES) and Reproductive Concerns Scale (RCS).

Results: 60 GTD patients were included between 2017 and 2020. Anxious feelings (47%) were more commonly expressed than depressive feelings (27%). Patients experienced moderate to severe adaptation problems in 88%. Patients who already had children were less concerned about their reproductivity than patients without children (mean score 10.4 versus 15.0, $p = 0.031$) and patients with children experienced lower distress (IES mean score 25.7 versus 34.7, $p = 0.020$). In addition, patients with previous pregnancy loss scored lower for distress than patients without pregnancy loss (IES mean score 21.1 versus 34.2, $p = 0.002$).

Discussion: We recommend physicians to monitor physical complaints and the course of psychological wellbeing over time in order to provide personalized supportive care in time for patients who have high levels of distress at baseline.

Conclusions: GTD patients experience increased levels of distress, anxiety and depression, suggesting the diagnosis has a substantial effect on the psychological wellbeing of patients. The impact of GTD diagnosis on intrusion and avoidance seems to be ameliorated in patients who have children or who have experienced previous pregnancy loss.

INTRODUCTION

Gestational Trophoblastic Disease (GTD) is a rare complication of pregnancy, occurring in 1.67 per 1000 deliveries in the Netherlands (1). It comprises a diverse group of disorders originating from abnormal proliferating placental tissue, including the premalignant complete (CHM) and partial (PHM) hydatidiform moles and the malignant counterpart Gestational Trophoblastic Neoplasia (GTN) (2). About 15-20% of the patients with CHM and 0.5-5% of the patients with PHM develop post-molar GTN (2-5), but even in widespread disease, outcomes are favourable (5-7). Every patient diagnosed with a molar pregnancy requires close monitoring of serum human chorionic gonadotropin (hCG) levels for weeks to months to detect potential progression or recurrence of disease (3, 4). In this period of follow-up, patients are advised not to become pregnant.

Even though prognosis is favourable, patients with GTD have to deal with loss of pregnancy, the surgical procedure for evacuation, frequent hCG measurements with possible need for chemotherapy and the advice to postpone a future pregnancy. It has previously been observed that these patients suffer from various psychological complaints (8). Earlier studies have established elevated levels in various psychological domains, such as anxiety, depression, distress and reproductive concerns. All these studies however (9-15), had a retrospective design since psychological complaints were evaluated several years after diagnosis and thereby possibly causing recall bias. In general, recall bias leads to less reliable results when more time has passed (16). In addition, recall bias is influenced by other factors, such as current psychosocial and physical wellbeing and life altering events (16, 17). Therefore, there is an urgent need to measure the psychological impact of GTD prospectively.

The objective of the present prospective observational multicentre study is to evaluate the short-term psychological impact of GTD diagnosis in order to optimise supportive care for GTD patients.

METHODS

Design

A prospective observational multicentre study using online questionnaires was performed. Patient representatives were not involved in the development of this research. Institutional ethics committee approval was obtained on 22 September 2015 by the Medical Ethical Committee of the Radboud University Medical Centre, Nijmegen, the Netherlands (2015-1816). Informed patient consent was obtained.

Participants and recruitment procedure

Patients with GTD were included between March 2017 and March 2020 if they were over 18 years old, were able to give informed consent, could speak Dutch sufficiently and had access to the internet. Our purpose was to evaluate a homogenous group of patients, so patients who already developed GTN at the time of first contact with

a centre participating in the study, were excluded. An effort was made to approach patients nationwide and 31 hospitals participated. 19 hospitals actually treated patients who were willing to participate. After suction curettage and histological confirmation of GTD, patients received information about the study and were asked permission by their gynaecologist to be contacted by the researcher within one week. After written informed consent, the researcher immediately mailed the link of the questionnaires to the patient. The time between the evacuation and the completion of the questionnaires was recorded. Patients who did not complete the questionnaires within two weeks after inclusion were reminded by telephone or email. Results were analysed only after completion of the study. Given the rarity of GTD, data of this database was collected in collaboration with and used by other institutes.

Demographic and clinical information

The patients' socio-demographics and clinical characteristics were collected via self-reported questionnaires which included age, marital status, number of children, level of education, employment status, previous pregnancy loss, previous psychological help and diagnosis (complete/partial mole, progressive disease, other).

Questionnaires

The following validated psychometric scales were used:

Hospital Anxiety and Depression Scale

Psychological distress was measured with the total score of the Hospital Anxiety and Depression Scale (HADS) (18). This questionnaire includes 14 items divided into two subscales (depression and anxiety), each with seven items. Subscale scores can range from 0 to 21. Higher scores indicate more anxiety or depressive symptoms and more psychological distress. A total score of 11 or higher indicates high distress. Subscale scores of ≥ 8 indicate existence of depressive/anxious feelings (18).

Distress Thermometer

The Distress Thermometer (DT) measures distress on a visual scale from 0 (no distress) to 10 (extreme distress) using a cut-off score of 4 to detect high distress (19-22).

Impact of Events Scale

The Impact of Events Scale (IES) was included to assess the frequency of intrusive and avoidant phenomena after or during a traumatic experience. Its 15 items (scoring 0, 1, 3, 5) are divided into two dimensions: Intrusion (7 items) and Avoidance (8 items). Total scores range from 0 to 75 with higher scores reflecting higher frequency of symptoms. A total score of 9-25 reflects moderate adaptation difficulties; a score higher than 26 indicates serious adaptation difficulties (23, 24).

Reproductive Concerns Scale

The Dutch version of the Reproductive Concerns Scale (RCS) was used to assess women’s reproductive concerns (25, 26). The instrument contains 14 5-point Likert scale (0-4) items resulting in scores ranging from 0-56. Higher scores indicate more reproductive concerns.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Version 25. Demographic and clinical characteristics were described as mean, median or numbers. The psychological outcomes for all questionnaires were described as mean scores. Psychological outcomes were also presented as number of patients scoring above a cut-off score (%). To identify possible influencing factors, patients were grouped based on having children, educational level, employment status, previous pregnancy loss and previous psychological help (t test, level of significance $p < 0.05$). In addition, Pearson correlation was performed to investigate potential correlation between patients using variables of age, time from diagnosis and outcomes for all questionnaires.

RESULTS

Seventy patients with GTD were identified and invited for the study. We were unable to get into contact with 8 patients and two patients declined participation, leaving 60 patients who consented to participate in the study. Reasons for declination were tiredness or fear for the questions to be too confronting. Baseline characteristics of the patients are shown in Table 1. The mean age was 32 years old (± 6.9). Fifty-seven percent of the patients had at least one child and 35% of the patients experienced a previous pregnancy loss. Median time between diagnosis and completion of the questionnaires was 39 days (IQR 25-50).

Table 1 Socio-demographic and clinical characteristics of patients with GTD.

	GTD patients N = 60
Age (years) mean $\pm$ SD	32 $\pm$ 6.9
Partner yes	98%
Cohabitating	88%
Having children	57%
Education level University or applied sciences	63%
Employed	92%
Previous pregnancy loss	35%
Previous psychological help	28%

GTD patients N = 60	
Diagnosis	
Complete mole	48%
Partial mole	32%
Mole unspecified	20%
Treatment	
Curettage	97%
Other surgery*	5%
Interval between diagnosis and questionnaires median (IQR) in days	39 (25-50)

*hysterectomy, hysterectomy + tubectomy and hysterectomy + ovariectomy, usually in addition to curettage.

Table 2 presents mean scores and the proportion of patients per subscale from all questionnaires. According to the HADS total score, 53% of the GTD patients experienced distress. Forty-seven percent and 27% of GTD patients scored ≥ 8 for anxiety and depression, respectively. In addition, 70% of the patients reported distress according to the DT. Furthermore, 25% and 63% of the patients experienced moderate and severe adaptation problems, respectively.

Table 2 Mean scores of the subscales from all questionnaires and proportion of patients scoring above the cut-off point for severe levels of psychological functioning.

GTD patients N = 60			
	Mean $\pm$ SD	Moderate	Severe
HADS total	12.9 $\pm$ 8.5		32 (53%)
HADS anxiety	7.7 $\pm$ 4.5		28 (47%)
HADS depression	5.2 $\pm$ 4.5		16 (27%)
DT	5.6 $\pm$ 2.9		42 (70%)
IES total	29.6 $\pm$ 15.7	15 (25%)	38 (63%)
RCS	12.4 $\pm$ 8.3		

HADS total: ≥ 11 distress, HADS-A/D ≥ 8 anxious/depressive feelings. DT: ≥ 4 increased distress. IES total: 9–25 moderate adaptation difficulties, ≥ 26 serious adaptation difficulties. RCS: higher scores represent more reproductive concerns.

Patients with children scored significantly lower for reproductive concerns than those without children (mean score 10.4 versus 15.0, $p = 0.031$). Patients with children scored also significantly lower for adaptation problems (IES total mean score 25.7 versus 34.7, $p = 0.020$, Table 3).

In addition, patients with previous pregnancy loss scored significantly lower for intrusion and avoidance than those without previous pregnancy loss (IES total mean score 21.1 versus 34.2, $p = 0.002$, Table 4). 17/21 patients with previous pregnancy loss already had children. There were no significant differences in anxiety, depression or distress between patients with or without previous pregnancy loss.

Table 3 Women with and without children compared: mean scores of the subscales from all questionnaires (t-test).

	With children N = 34	Without children N = 26	
	mean $\pm$ SD	mean $\pm$ SD	P
HADS total	11.7 $\pm$ 9.0	14.5 $\pm$ 7.6	0.214
HADS anxiety	7.1 $\pm$ 4.9	8.5 $\pm$ 4.0	0.223
HADS depression	4.6 $\pm$ 4.6	5.9 $\pm$ 4.4	0.270
DT	5.3 $\pm$ 3.2	6.0 $\pm$ 2.5	0.381
IES total	25.7 $\pm$ 17.4	34.7 $\pm$ 11.6	0.020*
RCS	10.4 $\pm$ 6.7	15.0 $\pm$ 9.2	0.031*

*Statistically significant.

Table 4 Women with and without previous pregnancy loss compared: mean scores of the subscales from all questionnaires (t-test).

	Previous pregnancy loss N = 21	No pregnancy loss N = 39	
	mean $\pm$ SD	mean $\pm$ SD	P
HADS total	12.3 $\pm$ 9.7	13.2 $\pm$ 7.8	0.707
HADS anxiety	6.8 $\pm$ 5.0	8.2 $\pm$ 4.3	0.285
HADS depression	5.5 $\pm$ 5.1	5.0 $\pm$ 4.2	0.715
DT	5.6 $\pm$ 3.3	5.6 $\pm$ 2.7	0.945
IES total	21.1 $\pm$ 18.8	34.2 $\pm$ 13.2	0.002*
RCS	12.4 $\pm$ 8.5	12.4 $\pm$ 8.2	0.993

*Statistically significant.

No other significant associations were found after grouping based on educational level and employment status.

There was correlation between the different tools that were used. The HADS total correlated significantly with the DT and the IES (Pearson correlation 0.710 and 0.624, respectively). There was no correlation with the RCS with any of the other questionnaires. There was also no correlation with time from diagnosis and age with any of the used questionnaires.

DISCUSSION

Main findings

This is the first prospective observational study describing the psychological effects of patients with GTD directly after diagnosis. The results show that a substantial part of patients with GTD experienced anxious feelings (47%), depressive complaints (27%) and distress (70%) shortly after diagnosis. Furthermore, 88% of the patients with GTD experienced moderate to severe intrusive thoughts and feelings and thoughts of avoidance suggesting that the diagnosis of GTD could be considered a traumatic event causing serious adaptation problems.

Strengths and limitations

Our study is the first study providing an understanding about the short-term psychological complaints in GTD patients. Even though GTD is rare, we managed to collect a sufficient patient sample through a nationwide approach and online data acquisition. As we included a homogenous population, the results are likely to be representative for all GTD patients. The use of validated psychometric scales made it possible to confirm the presence of psychological symptoms in our population and to compare our results with other study groups and the general population. However, the results of the comparative analysis, based on patients' characteristics, have a limited sample size and need to be confirmed in a larger cohort.

Interpretation

Previous retrospective studies focusing on GTD patients also reported psychological impact such as anxiety, depression, stress reactions and reproductive concerns (9-14, 27). One study analysing GTD patients used the HADS-A and reported lower anxiety rates than our study (10). This could be explained by the fact that the time between diagnosis and completing the questionnaires was nearly five years and anxiety is likely to diminish over time. Another study focusing on patients with GTD used the IES and reported lower mean scores for intrusion and avoidance (14), indicating low levels of stress reactions, whilst our study reported more severe levels of stress reactions. This could suggest that also feelings of intrusion and avoidance will decrease in time. However, in these studies, the severity of complaints could also be underestimated as an effect of recall bias. Also, reproductive concerns have been reported before (9, 14). In our study, GTD patients who already had children were less concerned about their reproductivity than patients without children, which is supported by other studies (9, 28). We reported that intrusion and avoidance was ameliorated in patients with children and in patients with previous pregnancy loss. Previous studies specifically for GTD patients used different measurements defining distress, and none of the performed studies used the IES. Since previous studies also applied different designs, comparing our data is not possible in a reliable way. Therefore, further research to evaluate the protective factors for distress in GTD patients is needed. However, we hypothesize that, since the majority of our patients with pregnancy loss already had children, this might contribute to the fact these patients suffered less from intrusion and avoidance. Parity is a protective factor possibly because reproductive capacity had already been proven, and therefore less distress in terms

of intrusion and avoidance is generated. To enable interpretation or comparison with other diseases or reference populations, we used extensively validated psychometric scales. Scores from normative data (i.e. data from a reference population) of women with similar age were lower than the scores reported in our study (anxiety 7% versus 47%, depression 5% versus 27% and distress 45% versus 88%, in the reference population and our sample, respectively (29, 30)), suggesting the diagnosis GTD has a substantial effect on the psychological wellbeing of women. In addition, scores on the HADS and IES from patients experiencing pregnancy loss were lower than the scores reported in our study (31, 32). It is conceivable that GTD patients scored higher since they not only experience the loss of pregnancy, but also face further treatment, postponement of a next pregnancy and the risk of developing a malignancy. Compared to other diseases, the diagnosis GTD seemed to have less impact than for example the diagnosis breast cancer, measured with the DT within one month after diagnosis (33). Nevertheless, patients characteristics such as age and parity which possibly influence the psychological wellbeing of patients, were not comparable in GTD patients and patients with breast cancer (33). Lastly, when we compared our results to women facing fertility problems, GTD patients reported less fertility concerns than women with concerns about fertility (26). However, GTD patients reported more concerns than healthy women (26).

CONCLUSION

The diagnosis GTD has a substantial effect on the wellbeing of patients shortly after diagnosis. GTD patients experience anxious feelings (47%), depressive complaints (27%) and distress (70%, DT). In addition, 88% of the patients with GTD experience moderate to severe adaptation problems. The impact of GTD diagnosis on intrusion and avoidance seems to be ameliorated in patients who have children or who have experienced previous pregnancy loss. Scores representing the impact of GTD diagnosis exceed those as reported in the general population and in patients experiencing miscarriage. Physicians aware of these psychological consequences should, in addition to monitoring physical complaints, also assess the course of psychological wellbeing over time in order to recommend personalized supportive care for patients who maintain high levels of distress. Furthermore, for a future study, a case control study is needed to further specify the additional effect of the diagnosis GTD upon pregnancy loss due to a miscarriage. In addition, it would be interesting to evaluate possible differences in psychological complaints in patients with GTD compared to GTN and follow them over time. This is important to evaluate patients at risk for developing more severe psychological complaints. Given the rare occurrence of GTD, follow-up of patients in specialized centres offering appropriate supportive care by experienced counsellors may be preferable.

DISCLOSURE OF INTERESTS

None.

CONTRIBUTION TO AUTHORSHIP

Laura Blok: data collection, data analysis, writing of the article.

Minke Frijstein: involved in development of the project, critical review of the article.

Yalck Eysbouts: involved in development of the project, support with writing the article.

Jose Custers: critical review of the article.

Fred Sweep: critical review of the article.

Christianne Lok: critical review of the article.

Nelleke Ottevanger: involved in development of the project, critical review of the article.

DETAILS OF ETHICS APPROVAL

Institutional ethics committee approval was obtained on 22 September 2015 by the Medical Ethics Committee (CMO) of Radboud University Medical Centre, Nijmegen, the Netherlands (2015-1816).

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Chapter 3

PSYCHOLOGICAL IMPACT OVER TIME OF WOMEN WITH PREGNANCY LOSS DUE TO GESTATIONAL TROPHOBLASTIC DISEASE COMPARED TO MISCARRIAGE

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ABSTRACT

Objectives: Pregnancy loss, either occurring after miscarriage or after gestational trophoblastic disease (GTD), has a psychological impact. Besides pregnancy loss, women diagnosed with GTD have to deal with a prolonged period of follow-up and potential advice to postpone a future pregnancy. We studied the severity and course of the psychological impact after GTD and miscarriage, to identify whether women with GTD need different psychological care.

Methods: A prospective multicentre study using online questionnaires was performed. Women diagnosed with GTD or miscarriage received the following questionnaires directly after diagnosis and after three, six and twelve months: a self-report questionnaire, the Hospital Anxiety and Depression Scale (HADS), the Impact of Event Scale (IES) and the Reproductive Concerns Scale (RCS).

Results: 74 women with GTD and 76 women with miscarriage were included. At baseline, the proportion of women scoring above cut-off level for HADS-A and IES was significantly higher for women with GTD than for women after miscarriage (43.2% versus 28.9%, ($p=0.02$) and 87.8% versus 78.9%, ($p=0.03$), respectively). During follow-up, the differences between both groups vanished and only the IES after twelve months remained significantly different between women with GTD and women after miscarriage (62.7% versus 37.3%, $p=0.005$). All outcomes, except the RCS, showed a significant decline. In women who scored above cut-off level on the HADS-total or IES at baseline and women with psychological or psychiatric history, significant higher scores, however, persisted.

Conclusion: Although women with GTD at baseline suffer more from anxiety and distress than women after miscarriage, no significant differences were seen using the HADS-total after twelve months. Conducting HADS or IES questionnaires directly after pregnancy loss is helpful to identify women at risk for remaining psychological symptoms to provide them extra psychological support.

INTRODUCTION

Pregnancy loss during the first trimester occurs frequently. Depending on maternal age, the likelihood of suffering from miscarriage ranges from 12 to 24% (1). Previous research demonstrated an association between miscarriage and psychological complaints, such as anxiety, depression, stress and reproductive concerns (2-6).

Gestational Trophoblastic Disease (GTD) has an incidence of 1.67 per 1000 pregnancies in the Netherlands (7). Women with GTD also have to deal with pregnancy loss. GTD originates from abnormal proliferating trophoblastic cells and consists of the pre-malignant complete (CHM) or partial (PHM) hydatidiform moles. Women with GTD require close monitoring of serum human chorionic gonadotropin (hCG) levels for weeks to months to detect potential progression of disease (8), as 15-20% of CHM and 0.5-5% of PHM will develop post-molar Gestational Trophoblastic Neoplasia (GTN) (8, 9). During this follow-up period, women are advised to refrain from pregnancy.

Consistent with women with miscarriage, women with GTD suffer from various psychological complaints (10-17). In women with miscarriage, it is known that such complaints diminish over time. It remains uncertain how these complaints evolve in women with GTD. As the duration and severity of psychological complaints determine the impact on women's emotional functioning, this has important implications for organizing supportive care for women with GTD.

The objective of this prospective observational multicentre study is to evaluate the course of psychological symptoms in women with GTD in comparison with women after miscarriage, to identify whether women with GTD need different supportive care.

METHODS

Design

A prospective multicentre follow-up study using online questionnaires was performed. The course of psychological complaints in women with GTD and women with a spontaneous miscarriage was compared at baseline (T0) and three (T3), six (T6) and twelve months (T12) after diagnosis or miscarriage. Institutional ethics committee approval was obtained by the Medical Ethical Committee of the Radboud University Medical Centre, Nijmegen, the Netherlands (registration number 2015-1816). Informed patient consent was obtained. In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centres if such is requested.

Participants and recruitment procedure

Both women with GTD and women with miscarriage were included if they were over 18 years of age, had access to the internet and were fluent in Dutch. Women with GTD were included nationwide between March 2017 and October 2021 and 20 hospitals enrolled

women. Women with miscarriage (any pregnancy spontaneously ending before 12 weeks of gestation) were identified from July 2018 till September 2021 in both the Radboud University Medical Centre in Nijmegen and the Maxima Medical Centre in Veldhoven. Women who already developed GTN at inclusion were not included. Participants received information about the study and after written informed consent, the researcher mailed the link of the questionnaires. The time between diagnosis and the completion of the first set of questionnaires was registered. Women who did not complete the questionnaires were reminded by telephone or email to prevent drop-out.

Questionnaires

The same set of validated psychological questionnaires was sent at T0, T3, T6 and T12 to women with GTD and women after miscarriage. To measure distress, the Hospital Anxiety and Depression Scale (HADS) and the Impact of Events Scale (IES) were used. The HADS contains two subscales (anxiety (HADS-A) and depression (HADS-D)) with each seven items (score 0-3). A total HADS score of ≥ 11 indicates high distress. Subscale scores of ≥ 8 indicate existence of anxious or depressive feelings (18).

The IES assesses the frequency of intrusive and avoidant phenomena after a traumatic experience. Its 15 items (scoring 0, 1, 3, 5) are divided into two dimensions: Intrusion (7 items) and Avoidance (8 items). Higher total scores reflect higher frequency of symptoms. A total score of 9–25 reflects moderate adaptation difficulties; a score higher than 26 indicates serious adaptation difficulties (19, 20).

Lastly, the Reproductive Concerns Scale (RCS) was used to assess women's reproductive concerns (21, 22). It contains 14 items (score 0-4) resulting in scores ranging from 0-56. A higher score indicates more reproductive concerns.

At baseline (T0), demographic and clinical data on age, marital status, cohabitating, number of children, education, employment, previous pregnancy loss, previous psychological help, diagnosis (for women with GTD) and treatment was collected. At T3, T6 and T12 women with miscarriage were asked whether they were pregnant again. All questionnaires were added as supplementary material.

The primary outcome was defined as the difference between the proportion of women with GTD or after miscarriage that scored above cut-off level (≥ 11) for the HADS at twelve months. Secondary outcomes were defined as the proportion of women with GTD or after miscarriage that scored above cut-off level for the HADS, the IES and the outcomes of the RCS at any time during follow-up.

Sample size

58 women in each group were required to have a 80% chance of detecting a difference in the proportion of women with a HADS total score of ≥ 11 (50% versus 25%) at the 5% level of significance (23). Correcting for a potential drop-out rate of 20%, 70 women were needed for each group.

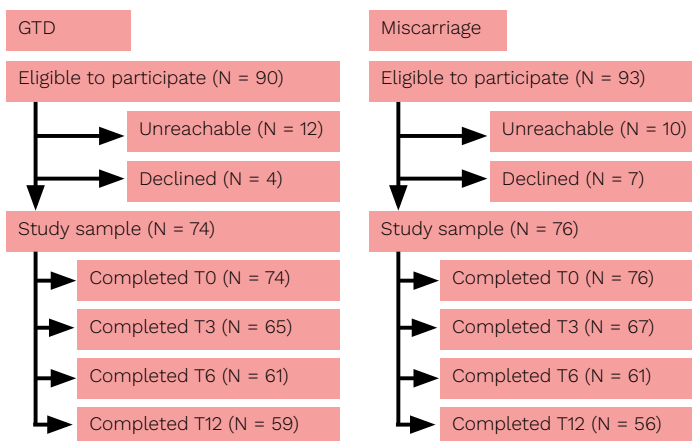
Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Statistics Version 25. Demographic and clinical characteristics were described as mean, median or numbers and compared using Chi-square tests and independent *t*-tests. The Shapiro Wilk test for normality was used. The outcomes for all questionnaires were described as median scores with interquartile ranges (IQR) and compared using Mann-Whitney U tests. Outcomes of the HADS and IES were also presented as number of women scoring above the cut-off score (%). Women were grouped based on whether they scored under or above cut-off score for HADS-total or IES at baseline, whether they have children, their educational level and employment status, previous pregnancy loss and previous psychological help to identify possible contributing factors. Repeated measures ANOVA was used to compare the outcomes of the questionnaires during the follow-up period. A two-sided P value of <0.05 was considered statistically significant.

RESULTS

The Flowchart in Figure 1 shows a summary of the recruitment and response rates for women recently diagnosed with GTD and women with a recent miscarriage. 18 women who were already diagnosed with GTN at baseline were excluded. After twelve months, 59 of the 74 (79.7%) women with GTD and 56 of the 76 (73.7%) women with miscarriage completed all the questionnaires. The reason for loss to follow-up was generally unknown. There were no significant differences in baseline median scores between women who dropped out and women who did not.

Figure 1 Flow-chart showing the number of women for both groups.



Baseline characteristics are shown in Table 1. There was a significant difference in educational level between both groups. Also, the median time that elapsed from diagnosis to completion of the first questionnaires was significantly longer in women with GTD (36 versus 26 days ($p=0.02$)).

Table 1 Socio-demographic and clinical characteristics of women.

	Women with GTD	Women with miscarriage	
	N = 74	N = 76	P
Age (years) <i>mean $\pm$ SD</i>	33.2 $\pm$ 7.2	32.9 $\pm$ 4.2	$p = 0.81$
Partner yes	98.6% (73)	94.8% (72)	$p = 0.18$
Cohabiting	90.5% (67)	92.2% (70)	$p = 0.35$
Having children	58.1% (43)	52.7% (40)	$p = 0.50$
Number of children <i>median (IQR)</i>	1 (0-1)	1 (0-1)	-
Education level			
High school or secondary school	9.5% (7)	2.6% (2)	$p = 0.08$
Vocational education	25.7% (19)	11.8% (9)	$p = 0.03^*$
Applied sciences or university	64.8% (48)	85.6% (65)	$p < 0.01^*$
Employed	93.2% (69)	98.7% (75)	$p = 0.09$
Previous pregnancy loss	29.7% (22)	31.6% (24)	$p = 0.81$
Previous psychological help	33.8% (25)	39.5% (30)	$p = 0.47$
Interval between diagnosis and first questionnaires <i>median (IQR) in days</i>	36 (23)	26 (13-38)	$p = 0.02^*$
Diagnosis^a			
Complete mole	31.1% (23)	-	n.a.
Partial mole	35.1% (26)	-	n.a.
Unknown by patient	33.8% (25)	-	n.a.
Treatment			
Spontaneous	-	5.3% (4)	n.a.
Medication	-	84.1% (64)	n.a.
Curettage	94.6% (70)	5.3% (4)	n.a.
Medication and curettage	-	5.3% (4)	n.a.
Surgery ^b	5.4% (4)	-	n.a.

*Statistically significant. ^aSelf reported information by the patient. ^bTypes of surgery: hysterectomy ($n=1$), hysterectomy + bilateral salpingo-oophorectomy ($n=2$) or tubectomy ($n=1$, extra-uterine molar pregnancy). N.a. not applicable.

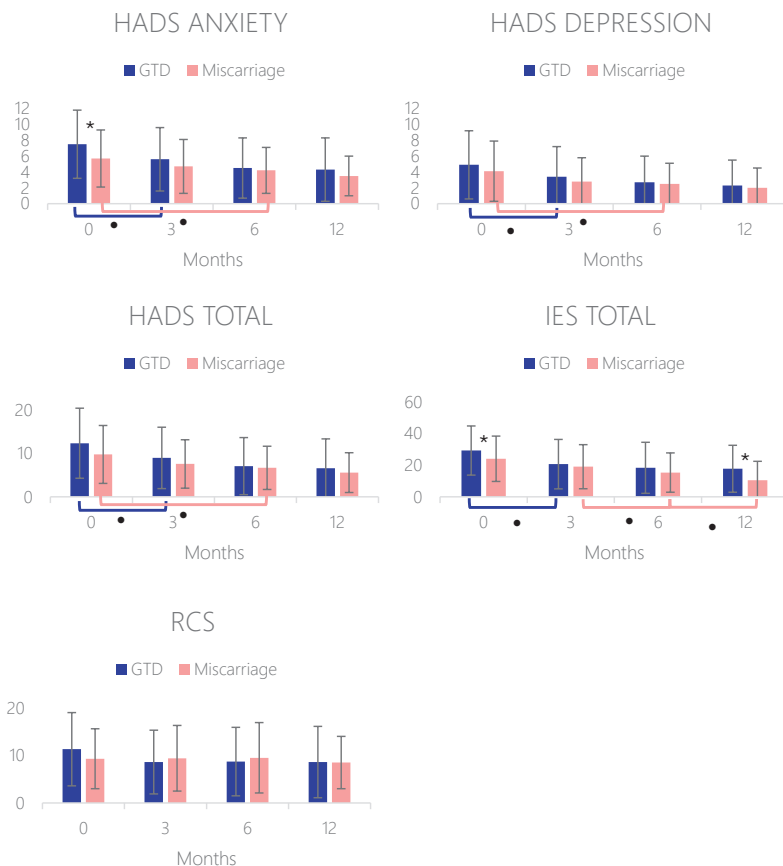
Table 2 and Figure 2 show the course of median scores from all questionnaires for women with GTD and with miscarriage. At T0, women with GTD scored significantly higher than women with miscarriage for HADS-A (7.0 versus 5.0, respectively, $p=0.02$).

Additionally, women with GTD scored significantly higher than women with miscarriage for IES-total at T0 (31.0 versus 22.5, respectively, $p=0.03$) and at T12 (15.0 versus 4.5, respectively, $p=0.005$).

Table 2 Median scores (IQR) and the proportion of women per subscale from all questionnaires for each group.

		Women with GTD		Women with miscarriage		
	T	median (IQR)	severe N (%)	median (IQR)	severe N (%)	P
HADS-A	0	7.0 (7.0)	32/74 (43.2%)	5.0 (5.0)	22/76 (28.9%)	0.02*
	3	5.0 (5.0)	21/65 (32.3%)	4.0 (5.0)	13/67 (19.4%)	0.17
	6	4.0 (4.5)	9/61 (14.8%)	4.0 (3.5)	8/61 (13.1%)	0.90
	12	3.0 (6.0)	12/59 (20.3%)	3.0 (3.0)	5/56 (8.9%)	0.74
HADS-D	0	3.0 (5.5)	18/74 (24.3%)	3.0 (5.0)	14/76 (18.4%)	0.25
	3	2.0 (6.0)	10/65 (15.2%)	1.0 (5.0)	8/67 (11.9%)	0.65
	6	1.0 (5.0)	6/61 (9.8%)	1.0 (4.0)	3/61 (4.9%)	0.67
	12	1.0 (3.0)	6/59 (10.2%)	1.0 (3.0)	3/56 (5.3%)	0.53
HADS-total	0	10.0 (10.3)	36/74 (48.6%)	9.0 (10.7)	32/76 (42.1%)	0.06
	3	7.0 (7.0)	23/65 (35.4%)	6.0 (9.0)	20/67 (29.9%)	0.31
	6	5.0 (9.0)	16/61 (26.2%)	6.0 (6.0)	12/61 (19.7%)	0.67
	12	4.0 (8.0)	14/59 (23.7%)	4.5 (4.0)	8/56 (14.3%)	0.89
IES-total	0	31.0 (27.5)	65/74 (87.8%)	22.5 (21.5)	60/76 (78.9%)	0.03*
	3	18.0 (26.5)	47/65 (72.3%)	18.0 (22.0)	46/67 (68.7%)	0.65
	6	12.0 (23.0)	38/61 (62.3%)	13.0 (16.0)	40/61 (65.6%)	0.51
	12	15.0 (23.0)	37/59 (62.7%)	4.5 (17.3)	22/56 (37.3%)	0.005*
RCS	0	9.5 (8.0)	-	8.0 (9.0)	-	0.10
	3	8.0 (8.0)	-	8.5 (7.3)	-	0.62
	6	7.0 (6.5)	-	7.0 (10.0)	-	0.67
	12	7.0 (10.0)	-	8.0 (7.0)	-	0.66

HADS-total ≥ 11 indicates high distress, *HADS-A/D* ≥ 8 anxious/depressive feelings (Hospital Anxiety And Depression Scale). *IES-total*: 9–25 moderate adaptation difficulties, ≥ 26 serious adaptation difficulties (Impact of Events Scale). *RCS*: higher scores represent more reproductive concerns (Reproductive Concerns Scale). *Statistically significant

Figure 2 Overview of the median scores and IQR from the questionnaires of both groups compared.

*Statistically significant difference between the groups

•Statistically significant reduction

The repeated measures analyses reported a significant reduction in all outcomes across twelve months in both groups (HADS-A $p < 0.01$ for both, HADS-D $p < 0.01$ for both, HADS-total $p < 0.01$ for both and IES $p < 0.01$ for both), except the RCS ($p = 0.05$ for GTD and $p = 0.46$ for miscarriage). In the GTD group, a significant reduction of outcomes was seen during the first three months (HADS-A (2.0 (95% CI 0.5-3.5) $p < 0.01$), HADS-D (1.9 (95% CI 0.5-3.2) $p < 0.01$), HADS-total (3.8 (95% CI 1.2-6.5) $p < 0.01$) and IES (8.7 (95% CI 3.6-13.7) $p < 0.01$), see Figure 2 and Table 2). After the first three months, no further significant reduction was seen in this group.

In women after miscarriage, a significant reduction was seen in the first six months (HADS-A (1.5 (95% CI 0.3-2.8) $p < 0.01$), HADS-D (1.4 (95% CI 0.3-2.4) $p < 0.01$), HADS-total (2.9 (95% CI 0.9-4.8) $p < 0.01$), IES (7.7 (95% CI 3.3-12.0) $p < 0.01$)). The reduction for the IES

was also significant at three to six months (4.7 (95% CI 0.6-8.7) $p=0.02$) and six to twelve months (4.7 (95% CI 0.1-9.3) $p=0.04$). No further significant reduction was seen in women after miscarriage.

In Table 3, women were grouped based on whether they scored above or under the cut-off level score of the HADS-total at baseline. Both women with GTD and women after miscarriage who scored above the HADS-total cut-off score at baseline, scored significantly higher at all the subsequent time points (three, six and twelve months) for HADS-A, HADS-D, HADS-total and IES. Women in both groups who scored above cut-off score on the HADS-total at baseline, did not differ in baseline characteristics with women with lower HADS-total scores at baseline.

Table 3 Median scores (IQR) for women with GTD and women after miscarriage depending on HADS-total score at baseline (T0).

	T	Women with GTD					Women with miscarriage				
		HADS-total ≥ 11 (T0)	N	HADS-total < 11 (T0)	N	P	HADS-total ≥ 11 (T0)	N	HADS-total < 11 (T0)	N	P
HADS-A	3	5.5 (6.0)	33	4.0 (5.5)	32	$<0.01^*$	7.0 (6.0)	28	3.0 (2.0)	39	$<0.01^*$
	6	5.0 (4.0)	29	3.0 (5.0)	32	0.04^*	4.0 (3.5)	25	3.0 (4.0)	36	$<0.01^*$
	12	5.0 (6.8)	28	2.5 (5.0)	31	0.05^*	4.0 (4.5)	22	3.0 (3.0)	34	$<0.01^*$
HADS-D	3	3.0 (7.0)	33	1.0 (3.3)	32	0.02^*	5.0 (5.0)	28	1.0 (1.0)	39	$<0.01^*$
	6	3.0 (6.5)	29	0.0 (2.3)	32	0.01^*	3.0 (3.0)	25	1.0 (2.0)	36	$<0.01^*$
	12	2.0 (5.0)	28	0.5 (2.0)	31	0.04^*	2.0 (3.5)	22	1.0 (2.0)	34	$<0.01^*$
HADS-total	3	9.0 (11.8)	33	5.0 (8.0)	32	$<0.01^*$	12.0 (9.0)	28	4.0 (4.0)	39	$<0.01^*$
	6	7.0 (10.0)	29	3.5 (5.0)	32	0.01^*	7.0 (7.0)	25	4.0 (4.0)	36	$<0.01^*$
	12	6.0 (10.5)	28	3.5 (6.3)	31	0.03^*	6.0 (7.0)	22	4.0 (4.0)	34	$<0.01^*$
IES-total	3	24.0 (26.8)	33	13.0 (26.3)	32	0.01^*	28.0 (24)	28	16 (20.0)	39	$<0.01^*$
	6	23.0 (32.8)	29	10.0 (15.8)	32	0.02^*	21.0 (20.5)	25	9 (15.0)	36	$<0.01^*$
	12	20.0 (18.3)	28	8.0 (21.8)	31	0.12	12.0 (22.5)	22	3.0 (10.0)	34	0.04^*
RCS	3	7.5 (7.8)	33	9.0 (8.0)	32	0.61	9.0 (15.5)	28	9.0 (7.0)	39	0.98
	6	6.5 (7.8)	29	8.0 (7.0)	32	0.12	9.0 (12.5)	25	6.0 (6.0)	36	0.39
	12	4.5 (8.0)	28	9.0 (8.0)	31	0.15	9.0 (8.0)	22	8.0 (7.0)	34	0.19

Values are median (IQR) unless indicated otherwise. HADS-total ≥ 11 indicates high distress, HADS-A/D ≥ 8 anxious/depressive feelings (Hospital Anxiety And Depression Scale). IES-total: 9–25 moderate adaptation difficulties, ≥ 26 serious adaptation difficulties (Impact of Events Scale). RCS: higher scores represent more reproductive concerns (Reproductive Concerns Scale). *Statistically significant

Grouping women based on whether they scored above or under the cut-off score of the IES-total at baseline showed comparable results to those after grouping based on HADS-total cut-off scores.

Women with GTD who consulted a psychiatrist, psychologist or other healthcare worker, scored significantly higher on the HADS-A (9.0 (6.5) versus 6.0 (5.8), $p=0.04$), HADS-D (5.0 (8.5) versus 3.0 (4.0), $p=0.03$) and HADS-total (14.0 (14.0) versus 9.0 (8.8), $p=0.02$) at baseline than women with GTD who had never consulted one prior to diagnosis of GTD. Women after miscarriage who consulted a psychiatrist, psychologist or other healthcare worker, scored significantly higher on the HADS-A (7.0 (6.3) versus 4.5 (4.3), $p<0.01$), HADS-D (4.5 (6.8) versus 2.5 (4.0), $p=0.02$), HADS-total (14.0 (11.0) versus 6.5 (8.3), $p<0.01$) and IES-total (28.0 (20.0) versus 21.0 (22.3), $p<0.01$) at baseline than women after miscarriage who had never consulted one before the miscarriage.

Women with GTD who already had children scored significantly lower than women with GTD without children on the HADS-D (3.0 (4.3) versus 4.0 (7.0), respectively, $p=0.02$), IES-total (24.5 (30.3) versus 36.0 (18.0), respectively, $p=0.03$) and the RCS (8.0 (8.0) versus 13.0 (8.0), respectively, $p=0.01$) at baseline.

Women with GTD with previous pregnancy loss scored significantly lower on the IES-total than those without previous pregnancy loss (14.5 (31.5) versus 33.0 (21.0), $p<0.01$) at baseline.

After one year, 46 of the 54 women in the miscarriage group had become pregnant again (2 missing data). These women scored statistically significantly lower on the IES-total at twelve months (3.0 (13.8) versus 23.0 (24.8), $p<0.01$) than women who were not pregnant.

DISCUSSION

Summary of main results

Psychological complaints were seen after pregnancy loss, especially in women with GTD. After twelve months the proportion of women scoring above cut-off level for the HADS-total was not different between women with GTD and after miscarriage. Directly after diagnosis however, the proportion of women who scored above cut-off for HADS-A and IES was significantly higher for women with GTD than women after miscarriage (43.2% versus 28.9%, ($p=0.02$) and 87.8% versus 78.9%, ($p=0.03$), respectively). These differences diminished during the year after diagnosis. Nevertheless, women with GTD scored significantly higher on the IES after twelve months than women after miscarriage (15.0 versus 4.5 respectively, $p=0.005$), indicating women with GTD still suffered moderate to severe adaptation problems. In women with psychological history and who scored above cut-off level at baseline, higher scores persisted. The RCS did not show any differences between both groups.

Results in the context of published literature

Prospective data on the psychological impact of women with GTD is scarce. Previous retrospective studies reported anxious and depressive symptoms, stress reactions and reproductive concerns in women with GTD (10-17). We found only one study, focusing on early pregnancy loss, which reported prospective data on psychological consequences

in women with GTD as well (4). Sample size was limited ($n=14$), but their outcomes were broadly similar. For women after miscarriage, extensive research on the course of the psychological impact has been performed (2-4, 6, 24, 25). In several studies the same validated psychometric scales were used as in our study. Both HADS-A and HADS-D scores for women with miscarriage at baseline in our study were comparable with other studies (3, 4, 6). In line with our findings, these HADS-D scores were within normal ranges (3, 6, 26, 27). Our results for the IES at baseline were also comparable to other studies in women with miscarriage (6). It is notable that at baseline, women with GTD scored significantly higher for anxiety (HADS-A) and distress (IES) than women after miscarriage. This difference can be explained by the fact that women with GTD not only deal with the loss of pregnancy, but also underwent surgical evacuation, face potential further treatment, postponement of a next pregnancy and the risk of developing a malignancy. Additionally, for women with GTD, the reduction of all outcomes was steeper than for women after miscarriage, probably as their scores were initially more elevated than those of women after miscarriage. Furthermore, although in both groups outcomes for the IES reduced over time, they still remained elevated after one year, consistent with other studies (4, 5). However, the IES scores of women with GTD one year after diagnosis remained significantly higher than of women after miscarriage. This suggests that losing a pregnancy by itself is a traumatic event causing prolonged distress reactions, and the diagnosis GTD on top of that is even more traumatic, even one year after diagnosis. The HADS-A rates in both of our study populations normalized over time, which is also reported in other studies (2, 3, 25, 27). After miscarriage, 46 of 54 women became pregnant during follow-up. Although the number of non-pregnant women was relatively small ($n=8$), pregnant women scored significantly lower on the IES than non-pregnant women. This effect could have possibly positively influenced IES rates in the miscarriage group. The number of pregnancies in the GTD group during follow-up is unknown.

Strengths and weaknesses

To our knowledge, this is the first prospective study evaluating the psychological impact in women with GTD during the year after diagnosis. For a better understanding of these psychological consequences, women with GTD were compared to women with a recent miscarriage. Validated psychometric scales were used to compare our results to other study and reference populations. Due to the nationwide design of our study, the online data acquisition and the frequent reminders, an adequate sample size was collected with adequate response rates. Nevertheless, the drop-out rate needs to be considered as a limitation, as this leads to the possibility of participation bias. Reassuringly, full respondents and women who dropped out had comparable characteristics and outcomes at baseline. In addition, due to the drop-out rate in the group for women after miscarriage of 27% at T12, the calculated sample size at T12 was not achieved and thus the found statistical significance must be interpreted with caution. Baseline characteristics showed that both women with GTD and miscarriage were relatively highly educated, especially women after miscarriage. In addition, data on ethnicity is unknown and it all included Dutch speaking patients. Therefore, our data might be of moderate generalizability. It is important to acknowledge that women with GTD completed the first set of questionnaires significantly later than women with miscarriage (median difference of 10 days) and this might have influenced our results. Women with a CHM face different

perspectives than women with a PHM and a small proportion of women with GTD will have developed GTN during the period of follow-up. However, the major difference in psychological outcomes was at baseline, at the moment all women had GTD, as women with GTN at baseline were excluded. Also, the guideline in the Netherlands does not make a distinction in follow-up after normalization with hCG in women with CHM or PHM. In addition, four GTD patients underwent a surgery different than curettage (hysterectomy or tubectomy), which may have affected the psychological outcomes, although also in these women uncertainty can remain as hCG follow-up is still necessary and GTN can develop. Lastly, information about psychological support received during follow-up is unknown. In general, outcomes of the questionnaires could be biased by other situations in the women's lives.

Implications for practice and future research

Physicians could conduct HADS or IES questionnaires directly after diagnosis to identify those women and provide them supportive care, to prevent long term psychological complaints. Establishing patient-reported outcome measures (PROM) for women with GTD could contribute to a better understanding of the variety of psychological consequences these women experience. Therefore, future research should focus on developing a GTD specific PROM including important questionnaires at specific timepoints based on the current study. This will determine the most effective ways to support these women, to improve their psychological wellbeing.

CONCLUSION

Psychological complaints, measured by the HADS and IES, were seen in women with GTD and after miscarriage directly after pregnancy loss, but decreased during the following year. Women with GTD however suffered more from anxiety and distress at baseline, and their IES scores remained elevated after one year in comparison to women after miscarriage. Women with psychological history and who scored above cut-off level for IES or HADS at baseline, maintained higher scores during follow-up.

DETAILS OF ETHICS APPROVAL

Institutional ethics committee approval was obtained on 22 September 2015 by the Medical Ethics Committee (CMO) of Radboud University Medical Centre, Nijmegen, the Netherlands (2015-1816).

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Chapter 4

EVALUATION OF A WEB-BASED INTERVENTION FOR PATIENTS WITH GESTATIONAL TROPHOBLASTIC DISEASE: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Objective: Gestational trophoblastic diseases (GTD) comprise a group of rare diseases originating from the trophoblast affecting women of childbearing age. Providing optimal information to patients with a rare disease is challenging because of the small number of patients and limited clinical expertise of many healthcare professionals. Both knowledge and lack of knowledge in patients may influence illness perception. We investigated whether a web-based interactive intervention influences illness perception and knowledge in women with GTD.

Design: This was a multicenter randomized control trial conducted at general and academic hospitals in the Netherlands, including newly diagnosed GTD patients between 2017 and 2019.

Methods: Sixty-nine patients were randomized between direct access or postponed access to an online tool on GTD and received online questionnaires about illness perception, knowledge, and anxiety. The main outcome measures were illness perception (primary outcome measure) and knowledge (secondary outcome measure).

Results: Patients using the online tool were satisfied with the information from the tool (92%). Although they had a higher level of knowledge compared to the control group ($p = 0.006$), illness perception did not change. Also, no differences in levels of anxiety, depression, or distress were observed between the groups.

Limitations: Participants had access to other information sources and many searched other websites. It is unknown what kind of websites were visited and when. It is unknown if the increased knowledge levels and low levels of distress will sustain over time as no long term follow-up took place. Healthcare professionals were not interviewed on how they experienced the consultation before and after using the tool by the patients.

Conclusions: The online tool did not change illness perception but was shown to be valuable for newly diagnosed GTD patients to gain knowledge. The improvement in knowledge after digital education indicates that this tool can be used as an effective method of supporting GTD patients' informational needs without causing extra distress.

INTRODUCTION

Gestational trophoblastic diseases (GTD) develop from abnormally proliferating trophoblastic tissue. GTD includes the pre-malignant complete and partial hydatidiform moles as well as the malignant entities: invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. The malignant forms are collectively known as gestational trophoblastic neoplasia (1, 2). Although worldwide incidence of GTD varies, the disease is rare in all countries (3, 4). In the Netherlands, GTD has an incidence of 1.67 per 1,000 deliveries (3). Given the rarity of GTD, high-level evidence is limited, and treatment protocols vary between and within countries (5). Healthcare professionals are often unfamiliar with the management of GTD, especially in countries with limited access to specialized care. Centralized management of GTD is associated with decreased mortality and is beneficial for patients with a rare disease like GTD (6-8). Although many GTD experts acknowledge the necessity to set up GTD centers, centralization of care is a difficult process and has been implemented in only a few countries (5-7). As a consequence, GTD information to patients is not optimal or up-to-date, and patients have to search for additional information themselves. A recent study shows that many patients with rare diseases feel that their needs for information have not been met completely (9, 10).

Patients with GTD have a good prognosis even in widespread disease (2), but they often have to deal with loss of pregnancy, surgical procedures for evacuation or removal of metastases, frequent hCG measurements, sometimes chemotherapy, and delaying another pregnancy. Therefore, psychological morbidity among GTD patients is common (11-13), and this emphasizes the importance of adequate patient information.

Internet has become an established source for health information, and the number of individuals using the internet to search for health information continues to grow (10, 14). Several studies describe the positive effects of online information (15-18). Cancer patients using online information cope better with their illness, experience less uncertainty and anxiety, know better what to expect, and have increased ability to manage their situation (15-17). However, online health information must be reliable, complete, and consistent. Patients primarily trust information provided by health authority specialists and organizations (15, 16).

Unfortunately, online information about GTD is scarce. Therefore, a web-based intervention developed by GTD experts would be an adequate and reliable tool for patients to supplement gaps in knowledge and to recall information given to them by their healthcare provider. This might stimulate shared decision-making and patient empowerment. In this randomized controlled trial, we aim to determine whether patients' illness perception and knowledge changed after using a web-based intervention without experiencing higher levels of distress.

METHODS

Design

A multicenter randomized control two-armed trial was performed between March 2017 and September 2019. Twentythree Dutch hospitals participated in this nationwide study (see online suppl. material S2; for all online suppl. material, see www.karger.com/doi/10.1159/000529239).

Participants and procedure

Patients recently diagnosed with GTD were informed about the study by their gynecologist. Subsequently, the gynecologist asked permission for establishing contact with the researcher within 1 week. Patients with a language barrier, no access to internet, poor vision, or under 18 years old were excluded.

Patients were randomized (1:1) into two groups using the online randomization system Castor EDC®. No stratification was applied. The intervention group received direct access to the online tool. The control group received delayed access to this tool after the completion of the second questionnaire (end of study). All participants were asked to fill out questionnaires at baseline (T0) and after 2 weeks (T1). Participants in the intervention group received a login code for the online tool after they completed the baseline questionnaire. This delayed access protocol was chosen because it was considered not beneficial for participants in the control group by not giving them access to the information source. They were offered a login code to the online tool not earlier than after completion of the T1 questionnaire. Participants were reminded to complete the questionnaires by e-mail or telephone if necessary.

Online intervention

In 2016, an interactive web-based intervention (www.voorhetgesprek.nl) was developed by a multidisciplinary team of Dutch specialists. Patient information on GTD was written in collaboration with the National Working Party on Trophoblastic Tumors. Three former GTD patients contributed to the development of the content and tested the online tool. The tool provides information about symptoms, diagnosis, and treatment of GTD and encourages patients to prepare questions for their next doctor's visit. The six main subjects are (1) general information on GTD, (2) molar pregnancy, (3) the pregnancy hormone hCG, (4) post-molar gestational trophoblastic neoplasia, (5) rare types of GTD, and (6) peer support and research. Patients can place check marks, leave comments, formulate questions, and test acquired knowledge by answering questions in the online tool.

Materials

Questionnaires were used to obtain sociodemographic data and to measure illness perception, knowledge about GTD, levels of distress, and patients' satisfaction. Illness perception reflects thoughts and emotions of patients about their symptoms and influences physical functioning. Knowing the illness perception of patients is important for treatment and educational programs. It can be measured with the validated Brief Illness Perception Questionnaire (B-IPQ) (19). The B-IPQ questionnaire contains nine items: consequences, timeline, personal control, treatment control, identity, concern, understanding, emotional response, and narrative cause of disease. The first eight items are scored based on a Likert scale of 1–10, and responses are reported individually for each question based on the patient's interpretation of her illness perception. Higher scores indicate a more threatening view of patients' illness, except for items 3, 4, and 7. These items are reversed, and higher scores are supposed to be beneficial. In addition, the B-IPQ included an open question aimed to assess patients' opinions toward the three main causes of the disease in ranking order. According to the original description of the B-IPQ, summary scores are calculated by adding all of the BIPQ individual items to reflect the overall positivity or negativity of an individual's illness perception. The smallest detectable change in items was set at 2 points (19). The B-IPQ has been validated for use in the Netherlands (20).

General knowledge about GTD was measured by agreement of the patient with 15 statements (correct, false, do not know; see online suppl. material S3). The total score reflected the number of correct answers (range 0–15).

Personality characteristics were evaluated with the Dutch General Self-Efficacy Scale (DGSES) which is the validated Dutch translation of the General Self-Efficacy (GSE) questionnaire (21). GSE correlates with depression and anxiety (22). Scores range between 10 and 40, with higher scores indicating higher levels of self-efficacy.

Levels of distress were measured by the Hospital Anxiety and Depression Scale (HADS) and the Distress Thermometer (DT) (23, 24). The HADS is composed of two scales – anxiety (7 items) and depression (7 items). Items are rated on a 4-point Likert scale and range from 0 to 3, with higher scores indicating greater anxiety and depression, respectively (24). The two scores can be calculated separately with three cut-offs: normal (0–7), borderline (8–10), or disturbance (>11). The HADS has been validated for use in the Netherlands (25). The Distress Thermometer is a single item visual analog scale ranging from 0 to 10, with 0 representing “no distress” and 10 “severe distress” (23). In this study, we used the original DT without the additional problem list.

Patients' satisfaction was assessed by self-developed questions. Questions concerned satisfaction with the patient information in general (5-point Likert scale, ranging from 1 “not at all” to 5 “very much” and grading from 0 to 10) and what sources patients used to search for information about GTD (open question). To assess patients' satisfaction with the online tool, we used questions concerning whether patients had a clearer understanding of GTD (yes, no, partially), level of distress after using the tool (less distress, same level of distress, or more distress) and regret about using the tool (yes, no, sometimes). The

participant was asked whether they would recommend the tool to other GTD patients or family members (yes, no, don't know) and if they were satisfied with the tool (5-point Likert scale, ranging from 1 “not at all” to 5 “very much” and grading from 0 to 10) and what contributed to their grading score (open question).

All questionnaires were filled out at T0 and T1 in both groups except for the questionnaires on DGSES (T0, both groups) and satisfaction (T1, both groups). Evaluation of the online tool was measured at T1 in the intervention group only.

Statistics

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25.0. Descriptive statistics were generated to characterize the study sample in terms of sociodemographic background and to describe the experiences with the online tool.

Data were processed using the χ^2 test or Fisher's exact test for categorical variables and Student's *t* test for parametric continuous variables. Nonparametric data were compared using the Mann-Whitney U test. All statistical tests were two-sided, with an alpha of 0.05 denoting statistical significance. Student's *t* test was used to compare mean scores of illness perception, levels of distress, and knowledge between groups. Subsequently, to account for individual differences in illness perception, levels of distress, and knowledge at baseline, analysis of covariance (ANCOVA) was used to assess between-group differences, where the T1 score was the dependent variable and the baseline score (T0) of the same variable was the covariate.

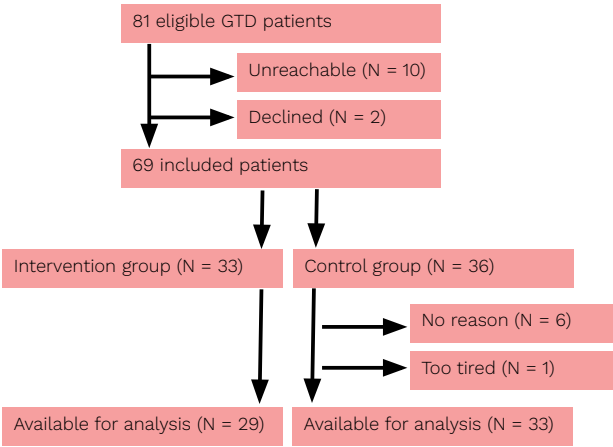
We chose illness perception as the primary outcome measure, as validated questionnaires are available for this in contrast to knowledge. Secondary outcome measures were knowledge, levels of distress, and satisfaction. Twenty-five patients in each group were required for the Wilcoxon signed rank test to calculate a 92% power of detecting a difference of 2 points in the mean overall score of illness perception (B-IPQ) (SD = 2) at T1 between both groups at a 2-sided α of 0.05 [19]. We anticipated a dropout rate of 10% and aimed to include 60 patients.

RESULTS

Response and dropouts

Eighty-one patients diagnosed with GTD were contacted by the researcher. In total, 69 patients were enrolled in the randomized controlled trial. Data from 62 patients ($n = 29$ intervention group, $n = 33$ control group) from 23 different hospitals were available for analyses. Figure 1 illustrates the patient selection. The dropout rate was 10% (7/69). All patients in the intervention group visited the online tool before they filled out the last questionnaire.

Figure 1 Flow chart illustrating the patient's selection procedure.



Patient characteristics

As shown in Table 1, both groups were similar with regard to background characteristics except for history of pregnancy loss ($p = 0.048$). The majority of the GTD patients were in their thirties and highly educated. Three patients had very rare GTD (i.e., complete hydatidiform mole and coexistent fetus ($n = 2$) and placental site trophoblastic tumor. One patient did not know the type of her GTD. The control group had significantly higher total DGSES scores compared to the intervention group ($p = 0.001$), indicating higher levels of selfefficacy.

Table 1 Patient characteristics.

	Intervention group (<i>n</i> = 29)	Control group (<i>n</i> = 33)	P
Age, mean (SD)	30.4 (5.2)	34.7 (7.1)	0.076
Partner, <i>n</i> (%)	28 (97)	32 (97)	0.926
Children, <i>n</i> (%)	17 (59)	19 (58)	0.934
Number of children, median (IQR)	1 (1–1.5)	1 (1–2)	0.178
Educational attainment, <i>n</i> (%)			0.804
Low	2 (7)	2 (6)	
Medium	10 (34)	9 (27)	
High	17 (59)	22 (67)	
Pregnancy loss in history, <i>n</i> (%)	7 (24)	16 (49)	0.048

	Intervention group (n = 29)	Control group (n = 33)	P
Diagnosis^a, n (%)			
Complete mole	8 (28)	12 (36)	0.330
Partial mole	7 (24)	10 (30)	
Mole unspecified	12 (41)	8 (24)	
Choriocarcinoma	1 (3)	0 (0)	
PSTT	0 (0)	1 (3)	
CHMCF	0 (0)	2 (6)	
Unknown	1 (3)	0 (0)	
Post-molar GTN	5/27 (19)	4/30 (13)	0.568
Received treatment, n (%)			
Curettage	23 (80)	24 (73)	0.425
Curettage + chemo	3 (10)	4 (12)	
Curettage + other surgery	1 (3)	3 (9)	
Other surgery	0 (0)	2 (6)	
Chemotherapy alone	1 (3)	0 (0)	
Second curettage + chemo	1 (3)	0 (0)	
Interval between start treatment – first questionnaire in weeks, median (IQR)	4 (3–7)	5 (3–7)	0.966
DGSES total score, mean (SD)	26.3 (4.9)	30.7 (4.5)	0.001

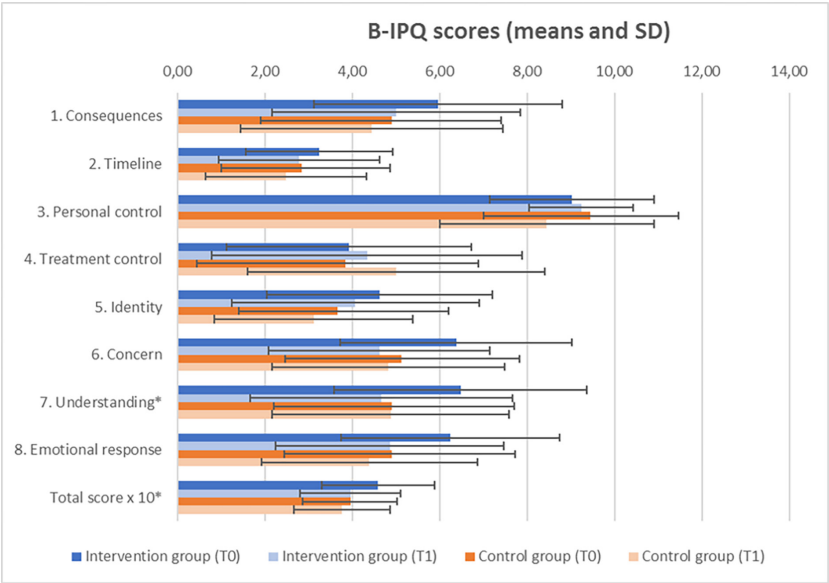
CHMCF, complete hydatidiform mole and coexistent fetus; DGSES, Dutch General Self-Efficacy Scale; GTN, gestational trophoblastic neoplasia; PSTT, placental site trophoblastic tumor. ^a Anamnestic data, not pathological.

Illness perception

No differences in illness perception after use of the tool were observed between the groups. Figure 2 presents the means and SD of B-IPQ scores at T0 and T1. The total B-IPQ score was significantly higher in the intervention group compared to the control group at baseline ($p = 0.041$), but was not significantly different after 2 weeks ($p = 0.489$). After correcting for the baseline scores, there was also no significant difference in overall B-IPQ scores at T1 between groups ($p = 0.677$).

For most items, both groups had higher but not significantly different B-IPQ scores at baseline compared to T1. The intervention group had higher scores, suggesting that this group had a slightly more threatening view of their illness compared to the control group at baseline, but in both patient groups, the threatening view of GTD decreased over time.

Figure 2 Brief Illness Perception Questionnaire (B-IPQ). Answer scales on items 3, 4, and 7 are converted because of reversed answer scales.



* $p < 0.05$ between groups at T0.

Levels of anxiety, depression and distress

At baseline and after 2 weeks, there were no significant differences in mean distress scores between both groups (Table 2). In addition, there was no significant difference between groups in mean distress scores at T1 after correcting for the baseline scores ($p = 0.289$ (HADS-A), $p = 0.152$ (HADS-D), $p = 0.991$ (total HADS), and $p = 0.356$ (DT)). The anxiety and depression rates were mainly in the normal range (0–7) in both groups at T0 and T1, except for the HADS-A score at T0 the means and SD of B-IPQ scores at T0 and T1. The total B-IPQ score was significantly higher in in the intervention group which was in the borderline range (8–10).

Table 2 Mean anxiety, depression, and distress scores in GTD patients.

	Intervention group (n = 29) mean (SD)	Control group (n = 33) mean (SD)	P
At baseline (T0)			
HADS-A	8.6 (4.2)	6.7 (4.4)	0.086
HADS-D	5.9 (4.3)	4.7 (4.6)	0.303
Total HADS score	14.5 (7.7)	11.4 (8.5)	0.139
DT score	5.9 (2.5)	4.9 (2.8)	0.137
After 2 weeks (T1)			
HADS-A	6.0 (4.0)	5.8 (4.1)	0.816
HADS-D	5.0 (4.9)	3.2 (3.3)	0.085
Total HADS score	11.0 (8.4)	8.9 (6.8)	0.283
DT score	5.3 (2.9)	4.2 (2.8)	0.144

^aHADS-A, Hospital Anxiety and Depression Scale – anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale – depression subscale; DT, Distress Thermometer.

Knowledge

General knowledge about GTD was measured with 15 statements (see online suppl. material S3). Mean score at baseline was not significantly different between the intervention and control groups (9.0 ± 2.9 vs. 9.7 ± 2.5 ; $p = 0.313$). The mean total score after 2 weeks was 11.2 ± 2.7 in the intervention group and 10.0 ± 2.7 in the control group ($p = 0.079$). There was a significant difference between groups in mean score at T1 after controlling for the baseline scores ($p = 0.006$). This indicates that the online tool increased knowledge at the individual level.

Patient information and satisfaction

Most patients received information about GTD before or shortly after the curettage (Table 3). The majority of patients (79%) searched online for information. In the intervention group, 86% used additional information sources besides the online tool to gain information about GTD (Table 3).

Only half (51%) of all 62 GTD patients were satisfied with other patient information sources on GTD. This outcome was also reflected in the mean total score: 6.7 ± 1.4 . There was no significant difference ($p = 0.405$) between the intervention group (mean 6.9 ± 1.3) and control group (mean 6.6 ± 1.5).

The majority of the intervention group ($n = 26$) was satisfied (92%) with the online tool, including 31% who were extremely satisfied. One patient (4%) was neutral, and only one was dissatisfied with the tool. The mean total score was 7.8 ± 1.2 .

All patients explained what contributed to their score: patients found all the information they needed ($n = 10$), and the online tool provided clear information ($n = 8$), had a clear structure ($n = 3$), contained trustworthy information ($n = 3$), added value for a better understanding of the disease ($n = 2$), was user friendly ($n = 1$), was valuable ($n = 1$), and provided a choice of what to read and what to skip ($n = 1$).

Fifty-four percent of the patients experienced no difference in the level of distress after visiting the online tool, 38% experienced less distress, and 8% experienced more distress. A majority of patients (88%) had a clearer understanding of GTD after visiting the online tool. Most patients would recommend the online tool to other GTD patients (89%) or to family and friends (77%), and 11–15% would consider it. The dissatisfied patient also had regret ($n = 1$) of visiting the online tool. Due to an online programming failure, 3 patients did not receive the part of the questionnaire about online tool evaluation and were missing.

Table 3 Patient information.

	Intervention group ($n = 29$)	Control group ($n = 33$)	P
Patients received first GTD-related information from physician, n (%)			
Before curettage	10 (35)	19 (58)	0.293
On the day of curettage	2 (7)	2 (6)	
1–2 weeks after curettage	13 (45)	6 (18)	
3–4 weeks after curettage	2 (7)	2 (7)	
>5 weeks after curettage	1 (3)	1 (3)	
Other ^a	1 (3)	3 (9)	
Information sources, n (%)			
Online tool ± other information sources	29 (100)		-
Online websites	20 (69)	29 (88)	0.116
Doctors	16 (55)	26 (79)	0.060
Leaflets	10 (35)	7 (21)	0.269
Nurses or midwives	9 (31)	7 (21)	0.401
Books	2 (7)	0 (0)	0.215
Friends or relatives	1 (3)	2 (6)	1,000
Local or national GTD protocol	1 (3)	0 (0)	0.468
Online tool only	4 (14)	-	-

^aAfter further diagnostic investigation ($n = 2$), before start chemotherapy ($n = 1$), and after TAH+BSO ($n = 1$).

DISCUSSION

Our online intervention does not change illness perception but is beneficial for patient education about GTD without causing higher levels of anxiety and distress or feeling more threatened by the illness. Ninety-two percent of the patients in the intervention group were satisfied or extremely satisfied with the online tool, suggesting that this tool supports GTD patients' informational needs. Patients also obtained information from other sources, such as the internet and the consultation with the practitioner, but only half were satisfied with these sources of information. The number of cancer patients using the internet for information is increasing (26), and as GTD patients are generally young, most of them will search for information online. Offering GTD patients high-quality information allows the supplementation of gaps in knowledge immediately after diagnosis and helps to prepare for consultation with a specialist in a GTD center, resulting in stimulation of shared decision making and patient empowerment (26, 27). It is known that internet usage is associated with age (26, 28, 29) but also with higher education levels, higher incomes, and higher levels of self-efficacy (30, 31).

Given the rarity of GTD and the variety of protocols worldwide (5), there is a plausible risk that the information that patients read online is not always up-to-date, correct, or in line with (inter)national protocols. In our study, nearly half of the patients (49%) were not satisfied with the current patient information sources on GTD in general. This emphasizes the need for trustworthy online information tools, developed and kept up-to-date by GTD experts. Stafford and Judd explored GTD health literacy in a cross-sectional study (32). Their findings suggest that additional web-based interventions can be helpful, but with complex subjects such as GTD, it remains important for the patient to have a personal discussion with an experienced healthcare professional who is able to answer these questions. This is particularly important for patients without access to internet, less educated patients, and patients with very rare forms of GTD.

However, healthcare professionals, especially in countries with limited access to specialized care, are often unfamiliar with the management of GTD themselves and may have difficulty answering all the questions of the patient. This emphasizes the requirement for adequate education about GTD for healthcare professionals as well, for which a tool such as the currently described one can help.

Our results are consistent with previous studies which have shown the promising potential of web-based information tools for patients with cancer (17, 27, 29, 33, 34). Higher knowledge levels after visiting the tools were reported (27, 29, 33, 34), with stable (27, 33) or reduced symptoms of anxiety or depression (17, 27), while the tools often had a positive effect on patient satisfaction (17, 33). There is only one other study investigating illness perception in GTD patients (35). This Italian study used the IPQ-revised (IPQ-R) questionnaire (36), which has different subscales compared to the test we used which makes direct comparison impossible. However, the majority of patients in this study perceived their illness as chance/bad luck which is consistent with our and previous studies (32, 37).

Higher overall scores of illness perception were found in our intervention group. Therefore, the intervention group seemed to be more vulnerable compared to the control group. This is confirmed by their significantly lower levels of self-efficacy. Low self-efficacy levels are associated with anxiety and depression (38). Nguyen et al. (29) found that the use of tailored information in preparation of a visit to a physician increases self-efficacy in cancer patients. Furthermore, viewing tailored online information before a hospital visit was shown to decrease patients' anxiety, as they were better informed about and prepared for the next steps in their treatment (29). In line with previous studies, GTD patients seem to suffer more from anxiety symptoms than from depression (12, 39). Anxiety could be related to the fear of recurrence, infertility, and conceiving again (13). Parts of these concerns could be taken away by the increased knowledge gained after using the tool.

The main limitation of this study is that participants had access to other information sources (see Table 3). Despite half of the patients in our study having access to the online tool, most of them had searched other websites. It is unknown what kinds of websites were visited and when (before or after use of the intervention tool). So, the use of multiple information sources probably caused bias, and therefore the results should be interpreted with caution. It does, however, reflect the real-life situation where patients will not be limited to one website. Moreover, patients benefited from the tool because the availability of other online GTD information is scarce; patients gained knowledge by using the tool, were satisfied with the tool, and recommended the tool to other GTD patients, family, and friends. In this study, we have no longitudinal follow-up after more than 2 weeks. It is unknown if the increased knowledge levels and low levels of distress will sustain over time. Our aim was to investigate illness perception and knowledge during diagnosis. Therefore, no long term follow-up took place. It is unknown why 7 patients dropped out of this study. If they were, for example, too overwhelmed by the impact of the (online) information or questionnaires, this could have underestimated the extent of experienced distress. In both groups, the number of patients with a low level of education was small. It is possible that patients with low health literacy may have refused participation in the trial which makes generalization of our results to this group with possible low health literacy impossible. Data on socio-economic status was not collected. Although this may correlate with educational level, we cannot be sure that the tool is applicable in all sociocultural and socio-economic contexts. The abovementioned factors should be taken into account in a future multicenter international trial with stratification for education level and rare forms of GTD.

Notwithstanding these limitations, this is the first randomized controlled study that evaluated the impact of an online tool for GTD patients. Although GTD is a rare disease, we included a relatively large group of patients, and these data are important for increasing our understanding of patients' experience of GTD and their needs. Since patients were satisfied and gained knowledge about their disease without experiencing higher levels of distress, the online tool seems valuable to support GTD patients' informational needs. Especially for healthcare professionals in countries without GTD centers, referring patients to websites developed and supported by GTD experts may be beneficial. Given

the low burden associated with implementing or adapting (such as translation) this online tool and strong positive reviews by GTD patients, these findings could have relevance for improving GTD care quality worldwide.

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STATEMENT OF ETHICS

The study was exempted from judgment according to the Medical Research Involving Human Subjects Act by the Medical Ethical Committee of the Netherlands Cancer Institute – Antoni van Leeuwenhoek (NKI-AvL) (METC16.1614). All participants provided written informed consent before randomization.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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AUTHOR CONTRIBUTIONS

Minke Frijstein, Marianne ten Kate Booij, Yalck Eysbouts, Nelleke Ottevanger, and Christianne Lok: study concept and design. Minke Frijstein, Laura Blok, and Yalck Eysbouts: data acquisition. Minke Frijstein and Christianne Lok: data analysis and interpretation. Minke Frijstein, Marianne ten Kate-Booij, and Christianne Lok: manuscript preparation. Laura Blok, Marianne ten Kate-Booij, Yalck Eysbouts, Nienke van Trommel, Fred Sweep, Leon Massuger, Dennis van Hamont, Henk Schreuder, Marieke Smink, Jan Molkenboer, Peggy Vencken, Nelleke Ottevanger, and Christianne Lok: manuscript editing and review.

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Chapter 5

EVALUATION OF THE PSYCHOSOCIAL IMPACT AND RECEIVED CARE IN PATIENTS WITH GESTATIONAL TROPHOBLASTIC DISEASE: A QUALITATIVE INTERVIEW BASED STUDY

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ABSTRACT

The diagnosis gestational trophoblastic disease (GTD) is known to have a significant psychological impact on women. Our objective was to provide insight in the psychological and physical consequences of women with GTD, while also reflecting on their coping strategies and their experiences of received care. A qualitative study was carried out using semi-structured interviews among women recently diagnosed with GTD. Interviews were audio-recorded, transcribed verbatim and analysed using a thematic network approach. Eight interviews were analysed. The abruptness of the diagnosis resulted in women feeling sad, uncertain and powerless. Coping strategies included seeking emotional support, accurate information, peer connections and distraction. Women were generally satisfied with care, emphasizing personalization, empathy, medical expertise and feeling heard as important aspects. They appreciated offered psychological support from specialized nurses. Nevertheless, aspects such as provided information, communication and logistical issues need improvement. The results of this study emphasize the importance of comprehensive patient information, the need for personalized psychological support and more frequent consultations at reference centres, while treatment is conducted locally.

INTRODUCTION

Gestational trophoblastic disease (GTD) refers to a group of rare pregnancy-related conditions that arise from abnormal growth of trophoblast cells. GTD encompasses a spectrum of conditions, including the premalignant complete (CHM) and partial hydatidiform moles (PHM), and malignant entities collectively described as Gestational Trophoblastic Neoplasia (GTN), such as the invasive mole, choriocarcinoma, placental site trophoblastic tumour and epithelioid trophoblastic tumour (1). Women diagnosed with GTD generally undergo curettage followed by weekly monitoring of human chorionic gonadotropin (hCG) levels in blood to detect potential progression of disease. For patients whose hCG levels spontaneously normalize, one additional confirmatory hCG measurement is necessary after which patients are discharged from follow-up. Patients with rising or plateauing hCG levels progress to GTN and require further treatment with chemotherapy followed by a period of follow-up for one year or more, without getting pregnant (2, 3).

Previous research has demonstrated that GTD patients endure psychological distress, with several psychological consequences such as anxiety and grief, persisting over a longer period of time (4–7). These consequences arise from the various challenges patients face, like pregnancy loss, the experience of illness with its implications and the lack of knowledge about the diagnosis (8). Even though quantitative research is proficient in identifying potential psychological concerns, it falls short in providing a comprehensive understanding of the patient's experience and in uncovering what truly matters to the patient (9). To address this gap, an interview-based qualitative study was conducted to explore the psychological and physical consequences of women with GTD, while also reflecting on their coping strategies and experiences of received care, which is the best approach for understanding how to improve the quality of health care (9). By exploring these experiences, this study aims to provide valuable recommendations that contribute to the development of patient-centred care strategies, ultimately enhancing the support provided to future patients.

METHODS

Design

To gain insight in the feelings and experiences of received care in women with GTD, a qualitative study using semi structured interviews was conducted. The Consolidated criteria for Reporting Qualitative studies (COREQ) were followed (10). Institutional ethics committee approval (2015-1816) and informed patient consent were obtained.

Participants and recruitment procedure

Women with a recent diagnosis of GTD or GTN were interviewed between December 2022 and December 2023. Inclusion criteria were: women over 18 years old, able to give informed consent and proficient in Dutch. Women were asked permission by their gynaecologist to be contacted by the researcher and received further information about the study, including topics that will be discussed during the interview. After informed consent, an interview was scheduled. The elapsed time between diagnosis and the interview was documented, as well as the current stage of the patient's trajectory. Participants were aware of the voluntary participation and the possibility to withdraw. Participants were recruited until data saturation was obtained. Subsequently, two additional interviews were conducted to confirm this.

Data collection

Interviews were semi-structured, using a topic list (Appendix 1). The topic list was developed by the first author, reviewed by the research team and iteratively evolved based on the findings of the interviews. The interviews were held by telephone and lasted between 40 and 75 minutes. They were recorded digitally and transcribed verbatim. The first author interviewed all the participants. She is a PhD candidate and a resident in Obstetrics and Gynaecology (MD) and all participants were unknown to her. The first three interviews were carried out by both the first and last author. The first author transcribed all the interviews. Transcripts were not returned to participants for correction.

Data analysis

Data analysis was carried out concurrently with data collection, to be able to reflect on the data and change the topic list if needed. Inductive thematic analysis was conducted independently by the first and third author, using Atlas.ti 23.2.1 for Mac (11). At first, open coding was used after which these codes were clustered into themes. This led to a coding tree. To guarantee inter-coder reliability, discrepancies were discussed until consensus was reached. During this process, themes were defined, refined and supported with illustrative quotes. Data saturation was confirmed when no new codes emerged during the analysis.

RESULTS

All women were treated in our reference centre for GTD. Eight of ten contacted patients gave consent and participated. The women who refused to participate did not feel comfortable sharing their experiences. The characteristics of the participants are shown in Table 1. All participants were Caucasian, among three had children. Two women were diagnosed with CHM, while six women had GTN, with two cases of choriocarcinoma. The timing of the interviews varied: five women were undergoing chemotherapy, while three completed their treatment. Eight themes providing insight into the experience were identified (see Figure 1).

Table 1 Characteristics of participants.

ID	Age	Ethnic back- ground	Children	Previous pregnancy loss	Employed	Diagnosis	Treatment	Timing interview
1	29	Caucasian	no	no	yes	GTN (CHM)	Curettage + MTX/ dactinomycin	During follow- up (2 months after chemo)
2	31	Caucasian	no	no	yes	CHM	Curettage	1 month after normalization
3	32	Caucasian	1	no	yes	GTN (PHM)	Curettage (2x) + MTX	During chemo
4	31	Caucasian	no	no	yes	GTN (CHM)	Curettage + MTX	During chemo
5	28	Caucasian	1	no	yes	CHM	Curettage	10 days after normalization
6	31	Caucasian	2	yes	yes	GTN (chorio- carcinoma)	EMA-CO	During chemo
7	33	Caucasian	no	yes	yes	GTN (chorio- carcinoma)	Curettage + MTX	During chemo
8	40	Caucasian	no	no	yes	GTN (PHM)	Curettage + MTX/ Act-D	During chemo

Abbreviations: Gestational trophoblastic neoplasia (GTN), complete (CHM) and partial hydatidiform mole (PHM), methotrexate (MTX), etoposide, methotrexate and dactinomycin alternating with cyclophosphamide and vincristine (EMA-CO) and actinomycin D (actD)

Psychological complaints

Women did experience a complex array of emotions when dealing with GTD. Shortly after diagnosis, women had feelings of shock, sadness and stress. The diagnosis came very unexpected and women described this period as a rollercoaster ("I went from cloud nine to a really dark place.", ID 3). Many women were afraid of the curettage. Furthermore, women described a period of uncertainties and stress, especially with the weekly hCG measurements and possible (side-)effects of chemotherapy. They found it was tough to go to the hospital that often. Women felt powerless and lived from week to week, dealing with the frustration and loss of control over their situation. Also, women grappled with feelings of guilt and concerns related to work and personal relationships and lost trust in their bodies. Some were afraid that it would return, but others had faith in recovery. Some women felt lonely, as no one understood their diagnosis and one woman found it very confronting to look like a 'cancer patient' after she lost her hair, while she did not feel sick. Overall, the period after the diagnosis was emotionally challenging.

Physical complaints

Women experienced several physical symptoms, including nausea, vaginal bleeding, fatigue (resulting in reduced energy and/or decreased physical fitness) and dizziness. Several women claimed to feel worse before starting chemotherapy, blaming the amount of pregnancy hormones in their bodies. Furthermore, women described various side effects of chemotherapy, with fatigue being the most reported, alongside nausea and amnesia. Additionally, they mentioned mouth sores ("I could hardly swallow due to the blisters in my mouth.", ID 1), dry eyes and hair loss.

Coping

Women faced the challenge of dealing with their diagnosis in various ways, with support from their partners and social circle being one of the common denominators. They actively initiated conversation with them and this served as a therapeutic outlet. Some women initially chose not to involve too many people and only shared their story after the situation improved ("Initially, I hesitated to share it with too many people because discussing it felt emotionally draining and it was difficult to talk about.", ID 5). Others, claiming to be a more open person, felt free to share it immediately.

Furthermore, most women expressed that finding accurate information was a challenge. The desired amount of information however, varied. While some preferred having precise information, others chose not to dwell on negative possibilities. This was also seen in experiences with peers: some found comfort in connecting with women who had been through similar situations ("No matter how challenging it was at times, I saw it as mental preparation, knowing what was possibly going to happen.", ID 2), while others didn't share that need ("... it made me feel more pessimistic about what could happen.", ID 4). Requesting referrals to a specialized centre was another common thread, as they perceived that their treating gynaecologist did not always possess adequate expertise.

Also, coping strategies included seeking distractions, such as meeting with family or friends, while trying to stay positive ("The good prognosis is helpful for maintaining a positive outlook.", ID 4) and accepting the situation. Most women received support from a specialized nurse and although not everyone initially felt the need for it, it offered valuable resources for coping. Through all the ups and downs, women with children found strength in the presence of their healthy children. Recognizing the significance of their role as mothers, they took solace in that aspect of their lives.

Relationship

Partners played crucial roles in providing support by attending medical appointments, positioning themselves as sounding board and offering emotional care. The partners, although feeling somewhat powerless, were consistently there. For all couples, the experience brought them closer together and made their relationship stronger.

Support

Their social network played an important role, with women finding comfort in sharing their experiences. Initially, people in their environment were expressing shock and not knowing how to react, but they consistently showed sympathy and concern. Some individuals from their network had experienced pregnancy loss as well and offered a sense of understanding, whereas often it came as a surprise that people who also experienced pregnancy loss hadn't shared it with them ("It saddens me that other people are carrying such heartache without talking about it.", ID 2). Moreover, one woman observed that her relatives were hesitant to share joyous news. Lastly, although the women felt support, the absence of knowledge about GTD made it difficult for them to explain the situation to others ("At some point, I switched terms because GTD is something nobody knew.", ID 2), leaving some feeling isolated.

Pregnancy loss

Women dealt differently with pregnancy loss. For some women, it didn't feel like they lost a pregnancy ("I feel more like I've been ill than actually having lost a baby.", ID 5 and "It never developed into an embryo, so there never really was an embryo.", ID 8). Another woman described her experience as a lost dream rather than losing a baby. Then there were women with an early ultrasound already revealing the pregnancy's nature and therefore being prepared for the pregnancy loss ("I didn't mind it in that sense because I hadn't really embraced it yet.", ID 4). Women also tried to put the pregnancy loss into perspective and learned that many women have to deal with pregnancy loss. Lastly, there were women who were devastated after the pregnancy loss, especially after finding out they were dealing with GTD.

Postponing a future pregnancy

Not all women were advised to postpone a future pregnancy. For those who had to, some felt that the one-year waiting period was manageable as they believed it is important to first recover physically and emotionally. However, for some, the ticking biological clock and the frustration of delaying family plans weighed on their minds. While one woman expressed contentment with her existing family, others were eager to see how this waiting period would affect their lives, with one woman opting to focus on other endeavours like raising a puppy.

Most women did not experience fear for a future pregnancy. Only two women expressed their concerns and fears about the potential impact of their diagnosis on their future fertility. One shared her worries about whether she will still be able to conceive after the challenges she faced. The second woman contemplated the chances of recurrence and potential implications for her childbearing with the increased chance of a preterm delivery after two curettages.

Experience of received care

Overall, women were satisfied with the received care. Important positive aspects were personalization, empathy, medical knowledge and the feeling of being taken seriously. Healthcare providers knowing the patients by name, taking an interest in their personal lives and making them feel at ease during treatment created a sense of trust and reassurance. Another positive contribution was medical staff providing ample explanations and practical advice ("I went home with all my questions answered.", ID 4). Women were positive about the nurses ("The nursing staff is truly excellent, which makes undergoing the treatments more comfortable.", ID 7) and appreciated the ambiance of the hospital ward. It was also very much respected that one gynaecologist spontaneously called to inform how she was doing and that women felt welcome to call with questions or requests. Lastly, all women agreed that patients should be offered psychological support, as those who received support were all content with it ("I can tell it (*the support*) was a good thing, even if I hadn't considered it myself.", ID 3-4-6).

There were also aspects that could be improved, mainly regarding information, logistics and communication. Almost all women in local hospitals experienced lack of knowledge about their condition and encountered challenges in finding appropriate information online. Sometimes women received inconsistent information or they had to wait until their case was reviewed by a reference hospital (“The local hospital can feel somewhat redundant in this case”, ID 4). In contrast, their experiences with the reference centre were characterized by clear and comprehensive information. Therefore, although centralization of care also comes with disadvantages such as longer travel distance, most women would advise patients to directly be referred to a reference centre. Regarding logistics, multiple women described the treatment as very time-consuming. Especially the women who had to travel more than one hour to the hospital, asked themselves if treatment at their local hospitals was not possible. However, they also stated that “your own health is the most important (ID 4)” and therefore were willing to travel. Lastly, there were some minor thoughts of improvement. Some had to deal with different gynaecologists, causing confusion and unclear communication. One woman emphasized the importance of discussing personal expectations, ensuring that individual patient perspectives and needs are considered. Additionally, preparing for various scenarios could help women better understand the potential outcomes and make informed decisions. While all women opted for centralization of care, multiple women declared receiving chemotherapy and/or taking blood tests in local hospitals may offer more convenience.

Figure 1 Structured overview of eight key themes associated with the impact and experiences of patients dealing with Gestational Trophoblastic Disease (GTD).

IMPACT AND EXPERIENCE OF PATIENTS WITH GTD	Psychological complaints	<ul style="list-style-type: none">• Shock, sadness, stress and uncertainties• "Rollercoaster"• Feelings of guilt
	Physical complaints	<ul style="list-style-type: none">• Nausea• Fatigue• Side-effects of chemotherapy
	Coping	<ul style="list-style-type: none">• Seeking emotional support and accurate information• Getting in touch with peers• Looking for distractions
	Relationship	<ul style="list-style-type: none">• Partner crucial role
	Support	<ul style="list-style-type: none">• Social network• Absence of general knowledge
	Pregnancy loss	<ul style="list-style-type: none">• "Lost dream"• "More like being ill"• Sad and devastated
	Postponing future pregnancy	<ul style="list-style-type: none">• Manageable• First recover physically• Frustrating
	Experience of received care	<div><div><ul style="list-style-type: none">+ Personalization+ Empathy+ Medical expertise</div><div><ul style="list-style-type: none">- Lack of knowledge and information- Logistics- No consultation at reference hospital</div></div>

DISCUSSION

This qualitative study was performed to provide new insights in the psychological and physical consequences of women with GTD, while also reflecting on their coping strategy and experience of received care. The results showed that women experienced shock, sadness and a loss of control (“I went from cloud nine to a really dark place”), accompanied by various physical complaints. Women adopted diverse coping strategies, such as seeking emotional support and accurate information, getting in touch with peers, looking for distractions and receiving psychological support. They expressed overall satisfaction with healthcare, citing personalization, empathy and medical expertise as positive aspects. Nevertheless, providing comprehensible information and the option for consultations at reference centres were important aspects for improvement.

Previous research has highlighted the psychological impact of GTD, but its consequences have not been studied qualitatively (4, 5, 12). Conducting interviews offers a deeper exploration of women’s thoughts, feelings and experiences. Therefore, this study represents a significant source of new information. The women in this study highlighted the importance of psychological support (8, 13). Additionally, many women expressed a lack of access to comprehensive information, leading to confusion, anxiety and stress. They also noticed a deficiency in knowledge among healthcare professionals and specifically gynaecologists, who were not always acquainted with recent guidelines and were sometimes unable to provide them with accurate information. This was also reflected by a recent survey among Irish GTD patients, in which 26.5% of the participating patients reported having to explain to healthcare professionals why they needed hCG monitoring (8).

Additionally, our study reveals new insights into coping strategies of GTD patients. These include seeking emotional support in their social circles and peers, a practice consistent with community and support-seeking behaviours (14, 15). The importance of partners as a significant source of support is also seen in studies about women after pregnancy loss (15, 16). Nevertheless, women in our study experienced moments of feeling lost and observed that, despite efforts by their social circles to be supportive, discussing the topic remained challenging (“It saddens me that other people are carrying such heartache without talking about it”). Not only did they face the challenge of explaining the rare nature of GTD, the pregnancy loss itself remains a taboo subject as well. Even though there are growing initiatives to raise awareness and break the silence surrounding pregnancy loss, there is still work to be done to create a supportive and understanding culture. Furthermore, women in our study reflected differently on pregnancy loss compared to those observed in studies focusing on miscarriages, as they reported women being devastated after pregnancy loss (15, 17). In our study however, some women did not perceive the experience as losing a pregnancy, but rather as falling ill, as they considered there to be a defect in fertilization and no living foetus ever existed.

The main strength of our study is the use of semi-structured interviews, allowing for an in-depth exploration of women's experiences after the diagnosis of GTD at different moments in the patients' trajectory. However, this indicates the study relied solely on self-reported data and participants' accounts might be influenced by social desirability. The interviews were held shortly after diagnosis to minimize recall bias. Nevertheless, it became apparent that women might need time to process and reflect on their emotions, as they were sometimes struggling to effectively assess their current feelings. Lastly, obtaining generalizable data was not an aim of this study and therefore, experiences of the women were personal and to ascertain broader applicability to the wider population, larger-scale research is needed.

In conclusion, multiple aspects of care for GTD patients can be improved based on the outcomes of this study. First of all, the provision of information for patients needs to be enhanced, with particular emphasis on increasing awareness for GTD in general. Strategies such as clear communication during consultations and online resources tailored to patient needs should be implemented. Secondly, it should be feasible for patients to have direct access to a GTD specialist, ensuring they receive the appropriate treatment and advice, including psychological support. This could be accomplished by centralizing the care for GTD patients. However, evidence of significant effects on the psychological outcome is lacking (18) and centralizing care might lead to more complicated logistic issues. Therefore, it is important for further research to focus on exploring interventions to address logistical challenges, such as centralized versus decentralized models. Additionally, future studies should explore the preferred method of provision of information and effective ways of supporting GTD patients.

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DISCLOSURE

The authors report there are no competing interests to declare.

DETAILS OF ETHICS APPROVAL

Institutional ethics committee approval was obtained on 22 September 2015 by the Medical Ethics Committee (CMO) of Radboud University Medical Centre, Nijmegen, the Netherlands (2015-1816).

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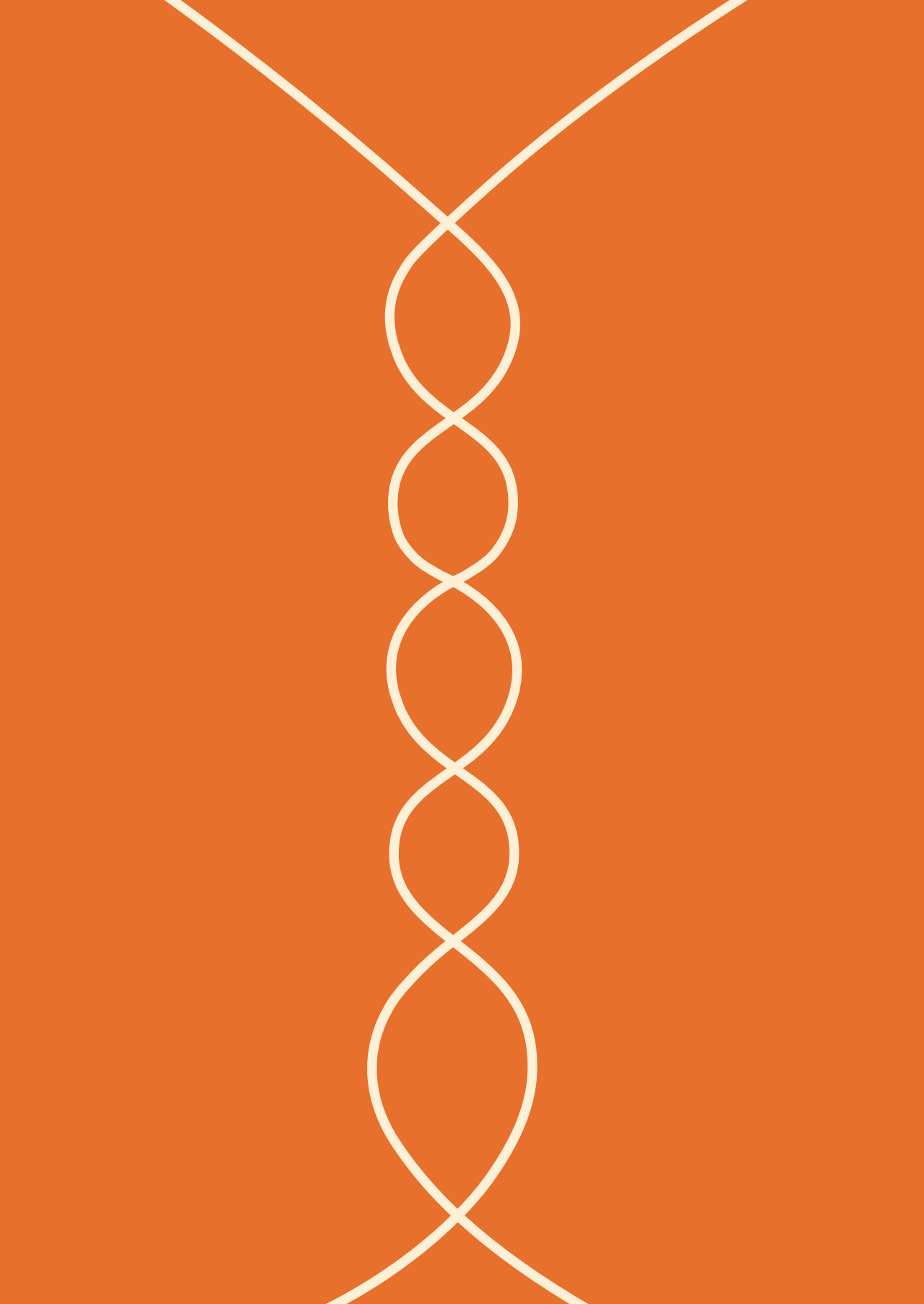
None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Chapter 6

IDENTIFYING FACTORS RELEVANT TO SHARED DECISION-MAKING IN CHEMOTHERAPY FOR LOW-RISK GESTATIONAL TROPHOBLASTIC NEOPLASIA: AN EXPLORATORY STUDY

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UNPUBLISHED DATA

ABSTRACT

Introduction: Shared decision-making (SDM) has not yet been explored in the context of gestational trophoblastic neoplasia (GTN). For low-risk GTN, two single-agent chemotherapy options exist, methotrexate (MTX) and actinomycin D (ActD), that differ in administration, side effects and potential quality-of-life impact. This study aimed to identify factors relevant to chemotherapy decision-making in low-risk GTN from both patient and healthcare provider perspectives.

Methods: A descriptive questionnaire-based study was conducted among patients treated for low-risk GTN in the Netherlands and healthcare providers. Participants rated 20 predefined factors on a 5-point Likert scale and identified their three most important factors, analyzed using Borda count ranking.

Results: Eleven patients and 22 healthcare providers completed the questionnaires. Side effects were the highest-ranked factor for both groups, followed by fertility considerations (among patients) and treatment effectiveness (among healthcare providers).

Discussion: This study provides the first insight into SDM-relevant factors in low-risk GTN care. The findings highlight meaningful differences between patient and provider perspectives and offer a foundation for developing a GTN-specific decision-aid tool.

INTRODUCTION

In recent years, there has been a growing emphasis on person-centred care and shared decision-making (SDM) within healthcare systems (1-4). SDM is a collaborative process in which healthcare professionals and patients work together to make informed decisions about treatment and care (5). This approach integrates the best available clinical evidence with the patient's values, preferences and individual circumstances. SDM represents a shift from a traditionally physician-led model of care toward one that emphasises patient autonomy, engagement and partnership. It is increasingly recognised as a key component of person-centred care and has been associated with improved patient satisfaction, treatment adherence and health outcomes (6-8).

While SDM has been widely promoted across various areas of healthcare, its application in rare and complex conditions, such as Gestational Trophoblastic Disease (GTD), has, to the best of our knowledge, not yet been explored. GTD encompasses a spectrum of pregnancy-related disorders, including Gestational Trophoblastic Neoplasia (GTN), for which first-line treatment in low-risk cases involves single-agent chemotherapy (9-11). The two most commonly used agents are methotrexate (MTX) and actinomycin D (ActD), which differ in administration routes, treatment regimens, side effects and potential impact on quality of life (9, 12). MTX, the standard first-line treatment in the Netherlands, is administered intramuscularly and requires concurrent folinic acid supplementation, typically given in an eight-day alternating regimen every two weeks. ActD, used more frequently as primary treatment in countries such as the United States, is administered intravenously, either through a five-day or pulsed biweekly schedule. Although both treatments are considered clinically equally effective, they vary in burden of administration and toxicity. MTX is associated with gastrointestinal symptoms, mucositis and liver toxicity, while ActD is, in addition to these symptoms, also more linked to systemic side effects, such as anaemia, fatigue and alopecia (12, 13). These differences may influence patients' preferences, making this clinical context particularly relevant for SDM.

Despite this potential for SDM in this setting, little is known about the factors that influence the chemotherapy decision-making process for patients with low-risk GTN. Existing literature on SDM on therapy options in women with cancer has focused on the more common female cancers and often centres on the patient's perspective, with limited attention to the views of healthcare providers (14-16). This knowledge gap presents a barrier to effective implementation of SDM in clinical practice for GTN care. Therefore, the aim of this study is to gain insight into patient and healthcare provider reported factors that are relevant to chemotherapy choice between MTX and ActD in low-risk GTN, as a first step toward the development of a SDM tool. By examining the perspectives of GTN patients as well as healthcare professionals through structured questionnaires, this study seeks to contribute to an understanding of the decision-making process in GTN care and to support the future integration of SDM into clinical practice.

MATERIALS AND METHODS

Design

To gain insight into the factors influencing the decision-making process when choosing between MTX and ActD chemotherapy in patients with low-risk GTN, a descriptive questionnaire-based study was conducted. Relevant decision-making factors were identified through a literature review and a prior (unpublished) qualitative study. The literature review identified factors reported to influence treatment decision-making in oncological care (14–25). Subsequently, a qualitative study using semi-structured interviews among patients treated for low-risk GTN was conducted to assess the relevance of these factors in this specific context. Findings from both the literature review and the qualitative interviews informed the final selection of 20 factors for inclusion in the questionnaires.

The questionnaires were pilot-tested prior to distribution, and minor revisions were made based on the feedback received. The final questionnaires were distributed to patients with low-risk GTN in the Netherlands and to healthcare providers involved in the treatment of low-risk GTN worldwide. Institutional ethics committee approval was obtained, and all participants provided informed consent.

Participants and recruitment procedure

Patients who had been treated with chemotherapy for low-risk GTN were approached by their medical oncologist and received written and verbal information about the study. After providing informed consent, patients received access to the online questionnaire. Given the rarity of low-risk GTN, patients who were treated with chemotherapy the preceding year were eligible for inclusion. Healthcare providers involved in the treatment of low-risk GTN were also eligible for participation and were recruited at the bi-annual XXII World Congress on Gestational Trophoblastic Diseases, held in Lyon, France, in 2024.

Questionnaires

Two questionnaires were constructed to collect data concerning the factors influencing the decision-making process: one from the patients' perspective and one from the healthcare providers' perspective. The questionnaires were available in both Dutch and English.

Patient socio-demographic and clinical characteristics included age, marital and parental status, level of education, employment status, primary treatment and, if applicable, secondary treatment. Baseline characteristics of healthcare providers included age, gender, years of clinical experience, medical specialization, type of hospital affiliation, country of origin and training, the annual number of low-risk GTN patients treated and primary chemotherapy regimen prescribed routinely.

Patients were asked to rate the importance of each of the 20 factors in relation to their potential choice between treatment with MTX or ActD using a standard 5-point Likert-type scale ranging from not important/not applicable (1 point) to very important (5 points). Healthcare providers rated the importance of the same factors using the identical scale. Finally, both patients and healthcare providers were asked to list their three most important factors, both before and after completing the questionnaire.

Data collection and statistical analysis

Patients completed the questionnaires online, using the Castor EDC platform. Healthcare providers completed the questionnaires during the congress, after which the responses were digitized. Statistical analysis was performed using IBM SPSS Statistics Version 27. Demographic and clinical characteristics were described as mean, median or numbers. The list of factors predicted to influence the decision-making process was analysed and visualised using median scores. Additionally, a Borda count ranking method was applied to the top three factors selected by participants, assigning 3 points to first-ranked, 2 points to second-ranked and 1 point to third-ranked factors, to identify the most influential factors in the decision-making process. Responses were categorised into predefined thematic clusters.

RESULTS

Fifteen patients provided informed consent of whom eleven completed the questionnaires. Twenty-six healthcare providers agreed to participate in the study and twenty-two of them completed the questionnaires. Baseline characteristics of both patients and healthcare providers are shown in Table 1 and 2, respectively. The healthcare providers were working in a variety of countries (n), including Myanmar (4), the Netherlands (4), Canada (2), Denmark (2), the United States of America (2), Egypt (1), France (1), Ireland (1), Israel (1), Italy (1), Japan (1), the United Kingdom (1) and Venezuela (1). The majority of the patients received MTX as chemotherapy. In Table 3, the median Likert scores per factor for both healthcare providers and patients are presented. Patients rated several factors higher than healthcare providers, with the largest differences observed for fertility, recommendation of the treating physician, avoidance of second-line treatment, and cancer recurrence. Healthcare providers assigned a median score of 3 to 18 out of 20 factors and a median score of 4 to the remaining two, whereas patient median scores ranged from 2 to 5.

Table 1 Baseline characteristics of patients.

	Patients N = 11
Age (years) <i>mean ± SD</i>	31 ± 2.0
Partner	10 (90.9%)
Having children	3 (27.3%)
Country of birth the Netherlands Niger Thailand Belarus	8 (72.7%) 1 (9.1%) 1 (9.1%) 1 (9.1%)
Education level university or applied sciences	8 (72.7%)
Employed	5 (45.5%)
Received chemotherapy MTX actD other	10 (90.9%) 0 (0%) 1 (9.1%)
Received second line chemotherapy actD other	5 (45.5%) 2 (18.2%) 3 (27.3%)

Table 2 Baseline characteristics of healthcare providers.

	Healthcare providers N = 22
Age (years) <i>mean ± SD</i>	52 ± 9.6
Gender <i>female</i>	12 (54.5%)
Working experience (years) <i>mean ± SD</i>	18.7 ± 11.4
Specialization gynaecologist oncologist gynaecological oncologist	12 (54.5%) 4 (18.2%) 6 (27.3%)
Type of hospital affiliation local general hospital regional teaching hospital supra-regional hospital (specialized) university hospital	1 (4.6%) 3 (13.6%) 3 (13.6%) 15 (68.2%)
Low-risk GTN cases treated yearly 0-1 2-5 6-10 >10	3 (13.6%) 6 (27.3%) 9 (40.9%) 4 (18.2%)
Chemotherapy used as primary treatment MTX ActD	21 (95.5%) 1 (4.5%)

Table 3 Median Likert scores per factor for both healthcare providers and patients.

Factors	Patients N = 11	Healthcare providers N = 22
Side effects	4	4
Alopecia	4	3
Nausea and vomiting	3	3
Mucositis	3	3
Concentration problems	4	3
Stimulus processing problems	4	4
Fatigue	4	3
Fertility	5	3
Duration treatment	3	3
Number of hospital visits	3	3
Travel time and distance	3	3
Recommendation treating physician	5	3
Avoidance second treatment	5	3
Cancer recurrence	5	3
Opinion of others	2	3
Familial concerns	3	3
Financial situation	3	3
Age of patient	3	3
Influence on return to work	4	3
Influence on return to social life	4	3

Range: not important (1 point), slightly important (2 points), moderately important (3 points), important (4 points) and very important (5 points).

Borda count

Among patients, prior to completing the questionnaire, the most frequently prioritized factors were side effects (28 points), fertility (10 points) and treatment duration (8 points). After completing the questionnaire, side effects remained the most important factor (31 points), followed by fertility (11 points) and treatment effectiveness (8 points).

For healthcare providers, before completing the questionnaire, side effects were also the most frequently prioritized factor (33 points), followed by treatment effectiveness (15 points) and route or frequency of administration (15 points). Following completion of the questionnaire, side effects remained the top priority (39 points), with effectiveness (18 points) and administration (10 points) again ranking among the most commonly cited factors.

DISCUSSION

This study explored the factors influencing the treatment decision-making process in patients with low-risk GTN, incorporating perspectives from both patients and healthcare providers. To our knowledge, this is the first study to examine this topic specifically in the context of low-risk GTN. Our findings demonstrate that for both patients and healthcare providers, side effects consistently emerged as the most influential factor in SDM, followed by fertility considerations (among patients) and treatment effectiveness (among healthcare providers).

The prioritization of side effects by both patients and healthcare providers underscores the importance of quality-of-life concerns in this clinical context. Although side effects are a common concern in cancer therapy, their particular relevance in this setting may reflect the favourable prognosis of low-risk GTN and the relatively young age of patients (9, 12). In this context, minimizing treatment burden becomes a key consideration in the absence of major differences in survival outcomes. A notable discrepancy emerged between patients and healthcare providers in how they weighted individual factors. Patients assigned higher scores across nearly all factors, with the largest differences observed for fertility, recommendation of the treating physician, avoidance of second-line treatment, and cancer recurrence (all median 5 vs. 3). Healthcare providers rated the majority of factors with a median of 3, which may reflect a more evenly distributed weighting across factors or a tendency towards central scoring. This pattern suggests that healthcare providers may underestimate the weight patients assign to factors with direct personal consequences. Conversely, opinion of others was the only factor rated lower by patients than by healthcare providers (median 2 vs. 3), suggesting that social influence may play a smaller role in patients' decision-making than healthcare providers assume. Furthermore, fertility emerged as a consistently important consideration for patients. This aligns with previous findings in gynaecologic oncology, where reproductive potential significantly influences treatment preferences (26). Although both MTX and ActD are considered safe with respect to fertility preservation (27), the prominence of this theme indicates the need for adequate counselling. These results suggest that, if

SDM were to be implemented in the care of patients with low-risk GTN, fertility-related concerns and broader quality-of-life considerations, including occupational and social functioning, should receive explicit attention during consultations.

A notable strength of this study is its dual-perspective design, which incorporates both patient and healthcare provider viewpoints. To effectively implement SDM, it is essential that both patients and professionals are engaged in the decision-making process. Understanding healthcare providers' perspectives is therefore necessary for guiding the development of tools that facilitate SDM in low-risk GTN care. Nevertheless, several limitations should be acknowledged. First, the patient sample size was relatively small, reflecting the rarity of the disease. In addition, all patients had received MTX and the patient cohort was recruited from a single country, although with various cultural backgrounds. These factors may limit the generalizability of our findings. Second, healthcare providers were recruited during a specialist congress and most reported MTX as their standard treatment, potentially introducing selection bias in favour of participants with a strong interest or expertise in this field.

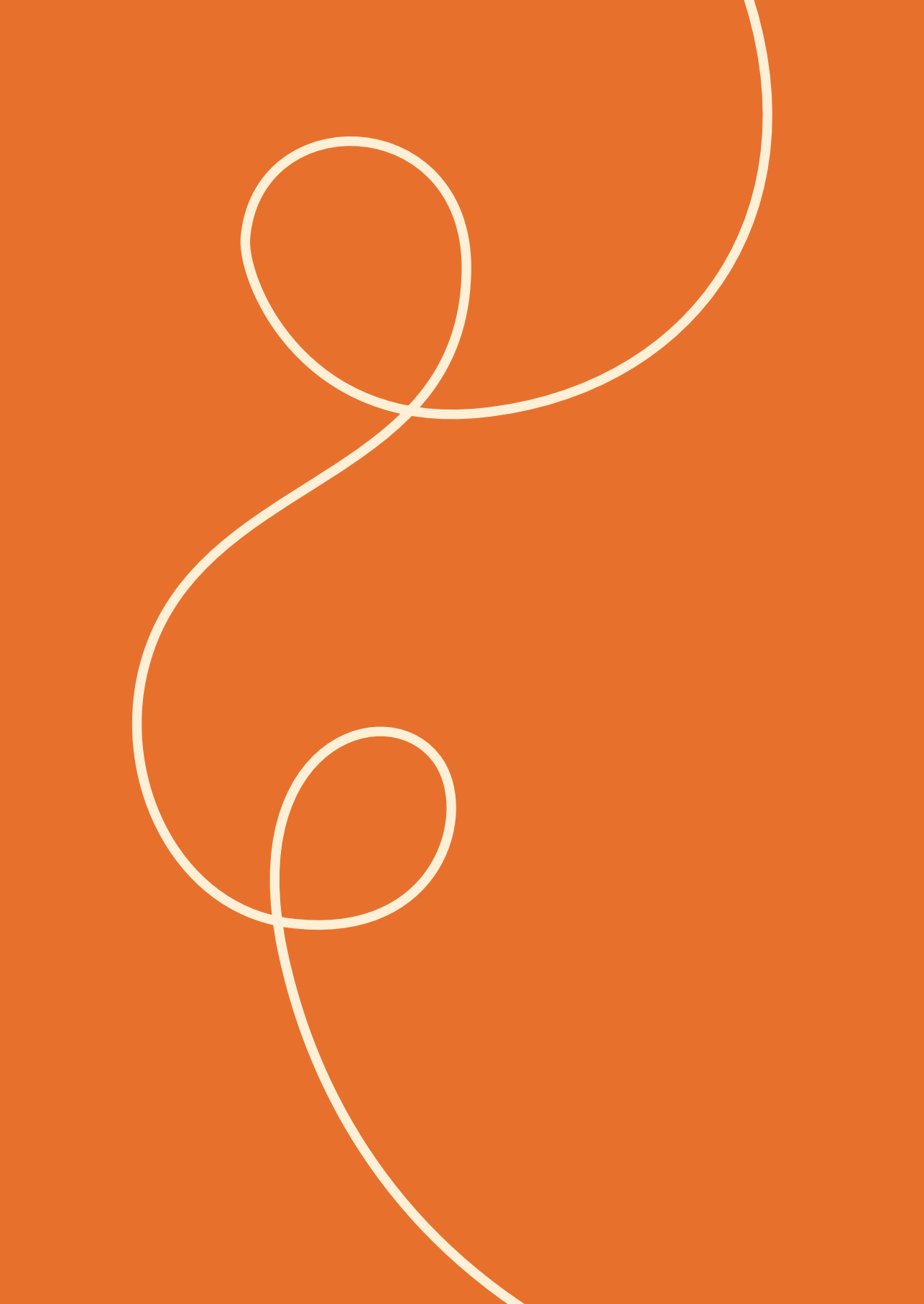
Future research should aim to translate these findings into practical applications, including the development of a decision-aid tool tailored to the GTN context. Such a tool should incorporate the prioritized factors identified in this study and be co-designed with patients and healthcare providers to ensure usability and relevance. Furthermore, qualitative research may offer deeper insights into the decision-making experiences of patients, including how they interpret and weigh medical information and how they perceive their role in the process.

In conclusion, this study identifies key factors influencing chemotherapy choice in low-risk GTN from both patient and healthcare provider perspectives. These findings offer a foundation for the development of a decision aid tool and the future implementation of SDM in GTN care.

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Chapter 7

GENERAL DISCUSSION

GENERAL DISCUSSION

Despite the favorable prognosis of GTD, patients face psychological challenges related to pregnancy loss, disease uncertainty and treatment. This thesis explores the psychological impact and experiences of GTD patients. Through five studies using both quantitative and qualitative methods, short- and long-term psychological symptoms are reported, qualitative insights from patient interviews are provided and in addition, opportunities to improve care through a web-based intervention and shared decision-making are evaluated. This chapter summarizes the main findings, discusses their implications for clinical practice and proposes opportunities to optimize care with suggestions for future research.

MAIN FINDINGS

In **CHAPTER 2**, we demonstrated that GTD has a substantial short-term psychological impact, with 47% of patients experiencing anxiety, 27% depression and 88% moderate to severe adaptation problems. Parity and previous pregnancy loss were identified as protective factors.

In **CHAPTER 3**, we followed GTD patients for one year and compared them with patients after miscarriage. Although general psychological symptoms declined over time in both groups, GTD patients experienced significantly more anxiety and distress at baseline and in addition, trauma-related symptoms (intrusion and avoidance) remained elevated even after 12 months. Patients with high baseline scores or a psychiatric history were at risk of persistent symptoms, underscoring the need for early screening.

In **CHAPTER 4**, we evaluated a web-based information tool through a randomized controlled trial. The tool significantly improved patient knowledge without increasing stress levels. However, it did not change illness perception, suggesting that while accessible information is valuable, it may not fully address patients' emotional needs.

In **CHAPTER 5**, qualitative interviews revealed that patients felt sad, uncertain and powerless after diagnosis. They valued personalized care, empathy and medical expertise, but identified gaps in information provision, communication and logistics. Patients expressed a preference for centralization of care to ensure consistent access to specialized support.

In **CHAPTER 6**, we identified factors relevant to shared decision-making in chemotherapy choices for low-risk GTN. Side effects were the most important factor for both patients and healthcare providers, while patients additionally prioritized fertility whereas healthcare providers emphasized treatment effectiveness. These findings provide a foundation for developing a decision aid tool.

INTERPRETATION OF MAIN FINDINGS

This part of the discussion focuses on the psychosocial findings (**CHAPTERS 2, 3 and 5**), whereas intervention studies (**CHAPTERS 4 and 6**) are discussed under opportunities for improving care.

Psychological impact

Health encompasses physical, mental and social well-being rather than merely the absence of disease (1, 2). For patients diagnosed with GTD, this broader definition is particularly relevant, as many experience psychological symptoms, including anxiety, insecurity, sadness and distress, alongside their physical symptoms (3). These psychological symptoms can impact daily functioning, interpersonal relationships and occupational productivity (4). Despite these burdens, research on the psychosocial impact of GTD remains limited (3). Therefore, the first chapters of this thesis focused on the psychosocial impact of GTD.

We confirmed that the diagnosis of GTD is psychologically impactful. **CHAPTER 2** revealed that 47% of patients reported anxiety, 27% had depressive symptoms and 70% experienced distress shortly after diagnosis. Additionally, 88% suffered from moderate to severe intrusive thoughts and feelings and thoughts of avoidance, suggesting the diagnosis of GTD could be considered as a potentially traumatic event requiring adaptation. In **CHAPTER 3**, we followed these patients for one year and demonstrated that while general psychological symptoms (anxiety, depression and distress) gradually diminished, symptoms associated with trauma, manifested as intrusive thoughts and avoidance, remained elevated even one year post-diagnosis. Most studies on psychological problems in cancer patients indicate that psychological symptoms are most pronounced around the time of diagnosis and tend to diminish over time, particularly symptoms of anxiety, whereas depressive symptoms show a less consistent pattern of improvement (5, 6). Some studies even suggest that psychological symptoms may fluctuate over time, with persistence or recurrence even several years after diagnosis (7). In line with these observations, the data presented in **CHAPTER 3** showed that although the difference did not reach statistical significance, a notable trend was observed: the prevalence of depressive symptoms 12 months after GTD diagnosis was more than twice as high as that observed in patients following miscarriage (20.3% versus 8.9%). Nevertheless, both groups scored substantially higher than age-matched female normative populations (5%) (8, 9). These findings align with earlier observations in cancer patients, suggesting that depressive symptoms may persist over time and that the psychological impact of GTD can be long-lasting for a subset of patients (5, 6, 10).

Moreover, we compared GTD patients with patients who had experienced miscarriage, as both groups had gone through the significant life event of pregnancy loss. In **CHAPTER 3** we demonstrated that, directly after diagnosis, GTD patients scored significantly higher on anxiety and trauma-related symptoms than patients following miscarriage, and that differences in trauma symptoms persisted even after one year, suggesting ongoing difficulties in adaptation. Consistent with earlier research, the psychological symptoms

were common among all patients following pregnancy loss and generally declined over time, indicating that patients with GTD require psychosocial support (11). Importantly, the comparison with patients after miscarriage demonstrated that the psychological impact of GTD extends beyond pregnancy loss alone. The additional burden of disease uncertainty, treatment requirements and reproductive restrictions may contribute to a more pronounced and prolonged traumatic response, emphasizing the need for GTD-specific psychosocial support rather than relying solely on miscarriage counseling frameworks.

This comparison also revealed important protective factors. In **CHAPTERS 2 and 5**, we found that the presence of children or a history of pregnancy loss, reduced adaptation problems and reproductive concerns in GTD patients, which is consistent with other studies in this population (12, 13). Parity might act as a protective factor due to previous reproductive success. Building on these findings, **CHAPTER 3** demonstrated that not all patients follow the same psychological course. Patients with a psychological or psychiatric history or those presenting with high baseline symptom scores were at risk of experiencing persistent long-term psychological symptoms. These findings underline the importance of adopting early screening to identify patients at elevated risk of persistent psychological distress.

Patients' experiences

In **CHAPTER 5**, qualitative insights revealed that the diagnosis often left patients feeling sad, uncertain and powerless. Pregnancy loss was experienced differently: for some it was deeply distressing, whereas others perceived it as part of managing a medical condition rather than grieving for a baby. Furthermore, sharing their stories fostered openness within social circles and also peer support helped patients to cope and prepare for future challenges. Additionally, their partners fulfilled a crucial role in helping patients cope with their diagnosis. Partners provided emotional support and accompanied patients to appointments, underscoring the importance of both involving partners in the care trajectory and considering couple-based support interventions. Also, patients frequently reported a lack of tailored information. Logistical challenges, such as delays in care coordination and hCG results, contributed to frustration and suggested that further centralization of GTD care could improve patient satisfaction.

OPPORTUNITIES FOR IMPROVING CARE

The findings presented in the preceding chapters underscore the substantial and enduring psychological impact experienced by patients diagnosed with GTD. Alongside these psychosocial findings, our studies identified specific gaps in information provision (**CHAPTERS 4 and 5**), standard care (**CHAPTER 5**) and decision-making processes (**CHAPTER 6**). This highlights several opportunities to improve care by enhancing information provision, psychological support, centralizing care and implementing shared decision making.

Accessible and reliable information

In **CHAPTER 5**, patients reported a lack of tailored and comprehensive information about GTD, noting the absence of condition-specific leaflets and the sometimes limited up-to-date knowledge among gynecologists. Consequently, patients often turned to the internet, where identifying reliable sources proved challenging, leaving their informational needs only partially met (14-16). This highlights a broader issue faced by patients with rare conditions, as they frequently encounter difficulties accessing adequate information, yet providing accurate and accessible information can enhance understanding and foster a sense of control (17-19). Furthermore, in **CHAPTER 4**, we reported that nearly half (49%) of the patients expressed dissatisfaction regarding the currently available sources of information about GTD. To address this, we developed an interactive online information tool, which significantly improved patient knowledge without increasing psychological distress. However, the tool did not change illness perception, indicating that while improving knowledge is essential, it is insufficient to meet patients' emotional needs. Our findings suggest that informational interventions should be complemented by personal discussions with experienced healthcare professionals and integrated psychosocial support, as will be further discussed in the following sections.

To address the ongoing gaps in information, a coordinated approach is needed. At the national level, GTD expert centers should develop standardized, evidence-based patient information materials, including condition-specific leaflets and digital resources. These can be distributed to all treating hospitals to ensure consistency in counseling. A centrally maintained website, overseen by the Dutch Working Party on Trophoblastic Disease in collaboration with patient organizations, should provide accessible and regularly updated information reflecting current guidelines. Additionally, at the local level, gynecologists and oncologists should ensure timely referral to specialized centers where patients can receive expert guidance and personalized counseling, thereby bridging the gap between general information and individual support.

Psychological support

The findings presented in this thesis raise the question of how healthcare providers could best support GTD patients, particularly those at risk of prolonged psychological distress. Although GTD is not malignant in all cases, its psychosocial consequences mimic those of oncological populations (6, 20-23). It is recommended in the Dutch national oncology guideline "Detecting the need for psychosocial care" to use validated systematic screening tools, such as the DT or the HADS, to identify patients who may benefit from early psychosocial support (24-27). The findings from this thesis provide strong evidence supporting the adoption of such screening tools for GTD patients as well (**CHAPTER 3**). Specifically for patients who initially score above the cut-off on HADS-total or the IES, as well as those with a psychological or psychiatric history, are likely to experience persistent elevated scores.

However, evidence on how to best support GTD patients with psychological complaints remains limited. Research in related populations, such as patients experiencing miscarriage, indicates that supportive care and counseling, whether provided by

specialized nurses or through structured bereavement interventions, can significantly improve emotional coping and psychosocial well-being (28-30). In oncology settings, a wide range of supportive interventions, including psycho-education, mobile app-based coaching and stress reduction programs, have shown to reduce anxiety and depression and enhance quality of life (31, 32). In addition, evidence demonstrates that cognitive behavioral therapy is effective for managing depressive symptoms and anxiety in cancer patients, while mindfulness-based stress reduction programs show moderate but consistent benefits in reducing anxiety and perceived stress (33, 34). Given the psychological parallels between GTD patients, cancer patients and patients experiencing early pregnancy loss, it is possible that similar interventions could benefit GTD patients.

To translate these insights into clinical practice, we propose a risk-stratified approach based on findings from this thesis. All GTD patients should complete HADS and IES questionnaires shortly after diagnosis to identify those at elevated risk. Patients with low baseline scores should be offered psycho-educational materials regarding depression and anxiety, along with routine clinical monitoring and psychological support when needed (31, 33). Patients with more severe psychological symptoms require more intensive support. They should be offered assignment of a specialized nurse (as valued by patients in **CHAPTER 5**) and a referral to evidence-based interventions such as cognitive behavioral therapy or mindfulness-based stress reduction (33). Support can be delivered at specialized GTD centers or through video consultations when travel is not feasible. Nevertheless, no research has directly evaluated such structured intervention programs for GTD patients and further studies are needed to confirm their effectiveness and optimize its implementation.

Centralization of care

The delivery of specialized psychological support, as outlined above, relies on the availability of experienced healthcare providers and expertise. This highlights a broader organizational need: the centralization of GTD care.

As discussed in **CHAPTER 5**, patients expressed a preference for centralizing care, driven by the desire for access to specialized medical expertise, dedicated GTD nurses and comprehensive, up-to-date information. Currently, most GTD patients in the Netherlands are treated locally, often without direct interaction with specialized reference centers. In case of GTN, referral to a specialized center is inconsistent, with some patients receiving referrals while others continue to be managed at the local hospital. Although clinical consultations between local gynecologists and GTD experts do occur, these often take place without the patient's involvement and might result in delay while patients wait for feedback. This contributes to the perception reported in **CHAPTER 5** that the role of the local hospital can feel redundant. Moreover, existing research demonstrates that centralized care for GTD is associated with reduced mortality rates and facilitates optimal management of this rare disease (35-38). Similar benefits have been observed for other rare cancers. For medullary thyroid cancer, centralization to academic hospitals in the Netherlands improved overall survival and for soft tissue sarcomas, centralized care

resulted in increased resection rates and improved five-year survival (39, 40). Thus, centralization offers clinical advantages and aligns with patients' preferences, potentially enhancing their overall satisfaction with their care.

We therefore recommend that all patients diagnosed with GTD will be referred to a specialized GTD center for initial consultation and treatment planning, ideally within two weeks of diagnosis. While the Netherlands' compact geography makes travel to expert centers feasible and patients interviewed in our study (**CHAPTER 5**) indicated willingness to travel for optimal care, it is still important to balance centralized expertise with practical accessibility. A hybrid model may best meet these needs: patients receive consultations from specialized GTD centers, while certain elements of diagnosis, treatment and follow-up, such as chemotherapy administration and blood withdrawal, may be delivered locally when clinically appropriate. In such cases, continuous specialist involvement can be maintained through structured video or telephone consultations. Centralization would also enable consistent access to specialized GTD nurses, standardized and up-to-date informational resources and integrated psychological interventions as discussed earlier. While the web-based tool developed in **CHAPTER 4** provides valuable baseline information, ongoing maintenance is required to ensure the content reflects evolving clinical guidelines, newly published evidence and patient needs. These resources are best sustained through coordinated efforts at specialized centers. Therefore, it is crucial that patients have the opportunity to engage directly with an expert who can provide personalized guidance and address individual questions. Moreover, appointing a case manager and implementing a secure messaging system for rapid communication of hCG results could enhance continuity of care and reduce anxiety during surveillance. These interventions may significantly improve patient experience and emotional well-being.

Shared decision making

In recent years, shared decision making has emerged as a cornerstone of person-centered care, promoting a collaborative approach in which clinical expertise is integrated with the patient's values, preferences and circumstances (41-43). In **CHAPTER 6**, we explored which factors influence treatment decision-making in patients with low-risk GTN. Both patients and healthcare providers identified side effects as the most important consideration, while patients additionally prioritized fertility whereas healthcare providers emphasized treatment effectiveness and mode of administration. By identifying key factors that influence chemotherapy choices in low-risk GTN, the findings presented in **CHAPTER 6** lay the groundwork for the development of a decision aid tool and represent a first step toward implementing shared decision making in GTN care.

To translate these findings into clinical practice, a decision aid tool should be developed that integrates the factors identified in **CHAPTER 6**. Such a tool would present information on treatment effectiveness, side effects, fertility implications and practical considerations, such as mode of administration and treatment duration. The tool should be co-designed with patients and healthcare providers to ensure usability and relevance. Shared decision making conversations should be integrated into the care pathway,

ideally during consultation at a specialized GTD center where oncologists have expertise in both treatment options. Future research should evaluate the tool's impact on patient-reported outcomes, such as quality of life.

METHODOLOGICAL CONSIDERATIONS

One of the major strengths of this thesis is the use of both quantitative (**CHAPTERS 2, 3 and 4**) and qualitative (**CHAPTER 5**) research methods. Quantitative methods were used for prospectively assessing the psychological impact of GTD over time, providing evidence on the prevalence and course of psychological symptoms (**CHAPTERS 2 and 3**). A randomized controlled trial further assessed the effectiveness of a web-based information tool (**CHAPTER 4**) and qualitative methods explored patients' experiences and needs in depth (**CHAPTER 5**). Furthermore, these studies are the first to prospectively examine the psychological consequences of GTD, addressing a significant gap in the existing literature. Additionally, the nationwide multicenter design enabled inclusion of a relatively large cohort of GTD patients despite the rarity of the condition. The use of validated psychometric scales (HADS, IES, DT and RCS) allowed comparison with other populations and normative data.

Several limitations should be acknowledged. The studies in this thesis included relatively small sample sizes, which is inherent to the rarity of GTD but limits statistical power and generalizability of findings. Additionally, all participants were Dutch-speaking and relatively highly educated, limiting generalizability to other populations. Furthermore, selection bias may have been introduced through the dropout rate in the longitudinal studies. Patients who remained in the study may have responded differently from those who withdrew. Additionally, we did not assess if and what type of psychological support patients received during follow-up, which may also have influenced outcomes. Follow-up in most studies was limited to 12 months and therefore longer-term psychological trajectories remain unknown. Finally, all psychological data were self-reported, which may introduce response bias.

FUTURE PERSPECTIVES

This thesis provides the first prospective evidence of the substantial and enduring psychological impact of GTD and identifies opportunities for improvement of care. Based on its findings, a number of recommendations for future research can be given.

Our findings demonstrate that psychological symptoms decline over time in most GTD patients, yet a subset experiences persistent distress beyond 12 months. However, elevated scores on psychological questionnaires do not necessarily indicate a need for professional support, as they may reflect a normal, time-limited response to a distressing diagnosis. Further research is therefore needed to better distinguish between transient reactions and maladaptive responses that substantially interfere with daily functioning and social or occupational life. In addition to the protective and risk factors identified

in this thesis, further research could explore whether additional factors contribute to risk stratification. Additionally, no evidence exists on which psychological interventions are effective for GTD patients specifically. Randomized controlled trials comparing structured interventions such as cognitive behavioral therapy, mindfulness-based stress reduction and nurse-led counseling versus usual care are needed, with patient-reported outcomes including anxiety, depression, post-traumatic stress symptoms and quality of life measured over at least one year.

The web-based tool developed in this thesis improved patient knowledge but did not change illness perception (**CHAPTER 4**). Comparative effectiveness trials evaluating web-based tools alone versus tools combined with structured nurse consultations are needed. Furthermore, building on key factors identified in **CHAPTER 6**, a shared decision-making tool should be co-designed with patients and healthcare providers, followed by pilot trials measuring impact on patient-reported outcomes. Additionally, qualitative studies (such as focus groups or interviews) could offer valuable insights into how patients interpret medical information, how they perceive their role in the decision-making process and what support they need to participate.

The present research supports centralizing care for GTD in the Netherlands, as patients expressed preference for specialized expertise, dedicated nurses and comprehensive information. While local treatment remains feasible, it should be accompanied by structural (video or telephone) consultations with GTD specialists to ensure high-quality, personalized care. Furthermore, the recommendations from this thesis, including systematic screening, psychological support, centralization and shared decision-making, require coordinated national implementation. Future research should therefore evaluate the impact of integrated centralized care models incorporating these recommendations on patient outcomes.

CONCLUSION

Returning to the definition of health, it is essential for healthcare providers to recognize that health not only involves the treatment of physical symptoms and disease, but should also consider of mental, emotional and social well-being. The research presented in this thesis illustrates this principle, providing the first prospective evidence of long-term psychological consequences in GTD patients, demonstrating the need for systematic screening and establishing a foundation for shared decision-making in GTN treatment. Greater recognition of psychological distress and patient-reported experiences by healthcare providers and policy makers should guide future policies and support the integration of psychosocial support into standard GTD care pathways. Healthcare providers can empower patients to actively engage in their care and regain a sense of control, by providing clear information, psychological support and opportunities for shared decision-making. Ultimately, physicians play a key role in helping patients to achieve a balanced and fulfilling life, where health is defined by more than the mere absence of illness.

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Chapter 8

SUMMARY

SUMMARY

Health is not merely the absence of disease but encompasses physical, mental and social well-being. Psychological symptoms such as distress, anxiety and depression can substantially affect daily functioning and quality of life. This thesis focuses on psychological impact in patients diagnosed with Gestational Trophoblastic Disease (GTD). GTD comprises of a diverse group of pregnancy-related disorders originating from abnormal proliferating trophoblastic cells. It consists of premalignant forms, including the complete and partial hydatidiform moles and of malignant forms such as the invasive mole, choriocarcinoma, placental site trophoblastic tumor and epithelioid trophoblastic tumor. The last four are collectively described as Gestational Trophoblastic Neoplasia (GTN).

CHAPTER 1 presents the general introduction of this thesis. First, general information about epidemiology, pathophysiology and management of GTD is reported, followed by the outline of this thesis.

CHAPTER 2 describes the short-term psychological consequences of the diagnosis GTD for patients in a prospective observational multicentre study. The following validated psychometric scales were used to determine psychological distress and reproductive concerns of these patients: the Hospital Anxiety and Depression Scale (HADS), the Distress Thermometer (DT), the Impact of Events Scale (IES) and the Reproductive Concerns Scale (RCS). Between March 2017 and March 2020, sixty patients diagnosed with GTD agreed to participate. They were asked to complete the previous mentioned questionnaires online. The majority of patients were in their early thirties, had a partner, were employed and had at least one child. 35% had experienced a previous pregnancy loss and 28% of the patients had some sort of psychological support in the past. The median time between diagnosis and completion of the questionnaires was 39 days. The results showed that the diagnosis GTD had a substantial effect on the wellbeing of patients shortly after diagnosis, with 47% of the patients experiencing anxiety, 27% reporting depressive complaints and 70% reporting distress. Furthermore, 88% of the patients experienced moderate to severe intrusive and avoidance symptoms, suggesting that the diagnosis could be considered as a traumatic event causing serious adaptation problems. Levels of distress and reproductive concerns were lower in patients who already had children. In addition, previous pregnancy loss also resulted in lower levels of distress. Given this substantial psychological impact associated with a GTD diagnosis, we recommended physicians to assess the psychological wellbeing of their patients, for example with the HADS or DT, and provide supportive care for those who showed high levels of distress.

Whereas chapter 2 reflects on the psychological consequences shortly after diagnosis, **CHAPTER 3** evaluates the course of these psychological consequences in this group of patients during the following year. To put these consequences into perspective, patients with GTD were compared to patients experiencing pregnancy loss due to a miscarriage. We performed a prospective observational multicentre study using the same questionnaires as described in chapter 2, repeatedly sent at baseline (T0) and at three

(T3), six (T6) and twelve months (T12) after diagnosis to both patients diagnosed with GTD and miscarriage. Patients with GTD were included nationwide from March 2017 to October 2021 and patients with miscarriage were included in two Dutch hospitals from July 2018 to September 2021. We aimed to enrol 58 patients in each group and by taking a possible drop-out into account, 74 patients with GTD and 76 patients with miscarriage were included. In both groups patients were in their early thirties, mostly living together with their partners and employed. Half of the patients had at least one child and a third experienced previous pregnancy loss. At baseline, the groups differed significantly only in terms of educational level, which was higher among patients after miscarriage, and the median time from diagnosis to completion of the first questionnaires, which was longer in patients with GTD. Psychological symptoms were seen in both patients with GTD and miscarriage at T0. These symptoms decreased during the subsequent year in both groups. Patients with GTD however suffered significantly more from anxiety (HADS-A) and distress (IES) at baseline (43.2% versus 28.9%, $p=0.02$ and 87.8% versus 78.9%, $p=0.03$, respectively) and their IES scores remained elevated after one year in comparison to patients after miscarriage (62.7% versus 37.3%, $p=0.005$). This indicated that patients with GTD still suffered moderate to severe levels of intrusive and avoidance symptoms one year after diagnosis. In patients who initially scored above the cut-off level on HADS-total or IES, as well as those with a psychological or psychiatric history, higher scores persisted. Therefore, conducting HADS or IES questionnaires directly after pregnancy loss is helpful for the identification and guidance of patients at risk for prolonged psychological distress.

CHAPTER 4 examines whether access to reliable and up-to-date information is effective in supporting patients with GTD. Obtaining comprehensive information for patients with a rare condition is challenging, partly due to the limited availability of (online) resources and the often limited clinical expertise of healthcare professionals with this uncommon disease. Today, many young patients seek information about their condition online, making availability of high-quality online patient information important. It remains unclear whether online tools can effectively provide sufficient knowledge without inducing additional stress in patients with GTD. Therefore, a multicentre randomized controlled trial was conducted to evaluate whether an interactive online tool influences patients' knowledge, illness perceptions and stress levels. Between March 2017 and September 2019, 62 recently diagnosed GTD patients were randomized to either immediate access to the interactive online tool (intervention group, $n=29$) or delayed access (control group, $n=33$). At baseline (T0), participants in both groups completed the Brief Illness Perception Questionnaire (IPQ-K), the Dutch General Self-Efficacy Scale (DGSES), the HADS, the DT and questions on general knowledge of GTD. After two weeks (T1), all participants completed the same set of questionnaires, with the exception of the DGSES, which was only administered at baseline. The intervention group also completed an evaluation of the online tool. After completion of all the questionnaires, patients in the delayed access group received the online tool as well. The majority of participants were in their thirties, highly educated, had a partner and had one child. Baseline characteristics were comparable between groups, with the exception of previous pregnancy loss and DGSES scores, which were higher in the control group. A significant difference was observed in mean knowledge scores at T1 ($p=0.006$), whereas no significant differences were found in mean stress scores (HADS and DT) or illness perception (IPQ-K). These findings indicate

that the online tool enhances patients' knowledge without affecting levels of stress. Most participants in the intervention group reported satisfaction with the tool (92%) and the majority would recommend it to other GTD patients (89%). Although the tool did not alter illness perception, the high level of satisfaction suggests that it successfully addresses the informational needs of GTD patients.

CHAPTER 5 explores the psychological and physical consequences experienced by patients diagnosed with GTD through a qualitative approach. Semi-structured interviews were conducted with eight recently diagnosed patients and thematic network analysis was applied to identify key insights. The abrupt diagnosis often left patients feeling sad, uncertain and powerless. Coping strategies included seeking emotional support, accurate information, connections with peers and using distraction techniques. Most patients were satisfied with care, emphasizing personalization, empathy, medical expertise and feeling heard as important aspects. Psychological support from specialized nurses was especially appreciated. However, gaps were noted in the quality of provided information, communication and logistical arrangements. The findings underscore the need for better patient information, tailored psychological support and more regular consultations at reference centres during locally administered treatments.

CHAPTER 6 describes an exploratory study aimed at identifying factors relevant to shared decision making in the choice of chemotherapy for patients with low-risk GTN. Although methotrexate (MTX) and actinomycin D (actD) are considered equally effective treatment options, they differ in route of administration, side effects and impact on quality of life, making this clinical context suitable for shared decision making. However, little is known about which factors are considered relevant by patients and healthcare providers when making this treatment choice. Therefore, a descriptive questionnaire-based study was conducted among patients treated with chemotherapy for low-risk GTN in the Netherlands and healthcare providers involved in the treatment of low-risk GTN worldwide. Based on a literature review and a prior qualitative study, twenty factors potentially relevant to chemotherapy choice were identified and included in the questionnaires. Participants rated the importance of these factors using a 5-point Likert scale and were additionally asked to rank their three most important factors before and after completing the questionnaire. In total, ten patients and twenty-two healthcare providers completed the questionnaires. Overall, patients tended to rate nearly all factors as more important than healthcare providers. Side effects were prioritised as the most important factor by both patients and healthcare providers. Fertility considerations were particularly important for patients, whereas healthcare providers more often prioritised treatment effectiveness and route of administration. This study provides first insights into factors relevant to shared decision making in low-risk GTN care. By identifying key considerations from both patient and healthcare provider perspectives, these results form a basis for the development of a decision aid and support the future implementation of shared decision-making in the treatment of low-risk GTN.

CHAPTER 7 provides a general discussion of the thesis, in which the main findings of the studies are summarized and discussed. Furthermore, implications for clinical practice and suggestions for future research are proposed.



Chapter 9

SAMENVATTING

SAMENVATTING

Gezondheid is meer dan de afwezigheid van ziekte en omvat ook het fysieke, mentale en sociale welzijn. Psychologische klachten zoals stress, angst en depressie kunnen het dagelijks functioneren en de kwaliteit van leven aanzienlijk beïnvloeden. In dit proefschrift evalueren we de psychologische klachten bij patiënten met een trofoblastziekte (Gestational Trophoblastic Disease, GTD). GTD is een groep zwangerschap-gerelateerde aandoeningen die ontstaan uit abnormaal delende trofoblastcellen. Er zijn premaligne vormen, zoals de complete en partiële mola hydatidosa, en maligne vormen zoals de invasieve mola, choriocarcinoom, Placental Site Trofoblastic Tumor en Epitheloïde Trofoblast Tumor. De laatste vier worden gezamenlijk Gestational Trophoblastic Neoplasia (GTN) genoemd.

In **HOOFDSTUK 1** wordt algemene informatie gegeven over de epidemiologie, pathofysiologie en behandeling van patiënten met GTD, gevolgd door een overzicht van de inhoud van dit proefschrift.

In **HOOFDSTUK 2** worden de psychologische korte termijneffecten bij patiënten met GTD beschreven in een prospectieve, observationele, multicenter studie. Diverse gevalideerde psychometrische vragenlijsten werden gebruikt om psychologische klachten en reproductieve zorgen te meten: de angst en depressie schaal (HADS), de Last Meter (LM), de Schok VerwerkingsLijst (SVL) en de Voortplanting Bezorgdheid Schaal (VBS). Tussen maart 2017 en maart 2020 gaven zestig patiënten met de diagnose GTD toestemming om deel te nemen aan het onderzoek. Zij werden gevraagd om de bovengenoemde vragenlijsten online in te vullen. De meerderheid van de patiënten was begin 30, had een partner, een baan en ten minste één kind. 35% had eerder een miskraam doorgemaakt en 28% van de patiënten had eerder een vorm van professionele psychologische ondersteuning gehad. De mediane tijd tussen de diagnose en het invullen van de vragenlijsten was 39 dagen. De resultaten lieten zien dat de diagnose GTD een aanzienlijke impact had op het welzijn van de patiënten kort na het horen van de diagnose, waarbij 47% van de patiënten angst ervaarde, 27% depressieve klachten meldde en 70% stress rapporteerde. Bovendien had 88% van de patiënten last van het herbeleven en/of het vermijden van onaangename gevoelens of herinneringen. Dit suggereert dat de diagnose als een traumatische gebeurtenis kan worden beschouwd die ernstige aanpassingsproblemen veroorzaakt. Het niveau van stress en zorgen over de vruchtbaarheid was minder bij patiënten met kinderen. Daarnaast bleek dat een eerder verlies van een zwangerschap ook voor lagere niveaus van stress zorgde. Gezien de substantiële psychologische impact van de diagnose GTD, is het belangrijk dat artsen het psychologische welzijn van hun patiënten evalueren en eventueel aanvullende ondersteunende zorg bieden aan patiënten met vastgestelde hoge niveaus van stress.

Waar we in hoofdstuk 2 de psychologische gevolgen kort na de diagnose beschrijven, evalueren we in **HOOFDSTUK 3** het verloop van deze psychologische gevolgen in dezelfde groep patiënten gedurende het daaropvolgende jaar. Om deze gevolgen in perspectief te plaatsen, werden patiënten met GTD vergeleken met patiënten die een zwangerschap hadden verloren door een miskraam. We voerden een prospectieve observationele

multicenterstudie uit met dezelfde vragenlijsten zoals beschreven in hoofdstuk 2, maar nu herhaaldelijk verstuurd bij de beginmeting (T0) en na drie (T3), zes (T6) en twaalf maanden (T12) aan zowel patiënten gediagnostiseerd met GTD als patiënten met een miskraam. Patiënten met GTD werden landelijk geïnccludeerd tussen maart 2017 en oktober 2021 en patiënten met een miskraam werden van juli 2018 tot september 2021 geïnccludeerd in twee Nederlandse ziekenhuizen. Het doel was om in beide groepen met 58 patiënten de statistische analyses te verrichten. In verband met mogelijke uitval werden hiertoe 74 patiënten met GTD en 76 patiënten met een miskraam geïnccludeerd. In beide groepen waren de patiënten begin dertig, woonden samen met hun partner en hadden een baan. De helft van de patiënten had ten minste één kind en een derde had eerder een miskraam meegemaakt. Er waren geen significante verschillen tussen de twee groepen bij de beginmeting, behalve het opleidingsniveau (hoger voor patiënten met een miskraam) en de mediane tijd tussen de diagnose en het invullen van de eerste vragenlijsten (die was langer bij patiënten met GTD). Psychologische klachten werden gezien bij zowel patiënten met GTD als bij patiënten na een miskraam op T0. Deze klachten namen in beide groepen af gedurende het daaropvolgende jaar. Patiënten met GTD hadden echter significant meer last van angst (HADS-A) en stress (SVL) op T0 (43,2% versus 28,9%, $p=0,02$ en 87,8% versus 78,9%, $p=0,03$, respectievelijk) en hun SVL-scores bleven na een jaar significant hoger in vergelijking met patiënten na een miskraam (62,7% versus 37,3%, $p=0,005$). Dit geeft aan dat patiënten met GTD ook een jaar na diagnose nog klinisch relevante psychologische klachten ervaren die samenhangen met de diagnose. Bij patiënten die aanvankelijk boven de afkapwaarde scoorden op HADS-totaal of op de SVL, evenals bij patiënten met een psychologische of psychiatrische voorgeschiedenis, bleven de hogere scores gedurende het daaropvolgende jaar aanwezig. De HADS- of SVL-vragenlijsten afgenomen direct na het verlies van een zwangerschap zijn hiermee relevant gebleken voor het identificeren van patiënten met een verhoogd risico op aanhoudende psychologische symptomen. Deze patiënten kan extra psychologische ondersteuning aangeboden worden.

In **HOOFDSTUK 4** wordt onderzocht of toegang tot betrouwbare en actuele informatie effectief is in het ondersteunen van patiënten met GTD. Het verstrekken van adequate informatie aan patiënten met een zeldzame aandoening is een uitdaging, deels vanwege de beperkte hoeveelheid beschikbare (online) informatie en de vaak beperkte klinische ervaring van zorgprofessionals met deze zeldzame aandoening. Tegenwoordig zoeken veel patiënten online naar informatie over hun ziekte, waardoor goede online patiëntinformatie van groot belang is. Het is van GTD niet bekend of online tools effectief zijn in het verstrekken van voldoende kennis zonder extra angst of stress te veroorzaken bij patiënten met GTD. Daarom onderzochten we in een multicenter gerandomiseerd gecontroleerde studie of een online interactief hulpmiddel invloed heeft op kennis, ziekteperceptie en het niveau van stress bij dergelijke patiënten. Tussen maart 2017 en september 2019 werden 62 recent gediagnosticeerde GTD-patiënten gerandomiseerd tussen directe toegang tot een online interactieve tool (interventiegroep, $n=29$) of uitgestelde toegang (controlegroep, $n=33$). Patiënten in beide groepen vulden bij de beginmeting (T0) de korte ziekte perceptie vragenlijst (IPQ-K), de Nederlandse General Self-Efficacy Scale (DGSES), de HADS, de LM en vragen over algemene kennis van GTD in. Na twee weken (T1) ontvingen alle patiënten dezelfde set vragenlijsten, met uitzondering van de DGSES, welke alleen bij de beginmeting werd ingevuld. Daarnaast ontving de interventiegroep een evaluatie van het

online hulpmiddel. Nadat alle vragenlijsten waren ingevuld, ontving de controlegroep ook de toegang tot het online hulpmiddel. De meerderheid van de patiënten was in de dertig, hoogopgeleid, had een partner en één kind. De basiskarakteristieken in beide groepen waren statistisch vergelijkbaar, met uitzondering van de voorgeschiedenis van een eerder verloren zwangerschap en de DGSES-scores (beide hoger in de controlegroep). Er werd een significant verschil gevonden in de gemiddelde kennis-scores bij T1 ($p=0,006$), terwijl er geen significante verschillen waren in gemiddelde stress-scores (HADS en LM) of in ziekteperceptie (IPQ-K). Dit wijst erop dat het online hulpmiddel de kennis van patiënten effectief vergrootte zonder extra angst of stress te veroorzaken. De meerderheid van de patiënten in de interventiegroep was tevreden met het hulpmiddel (92%) en de meeste patiënten zouden het aanbevelen aan andere GTD-patiënten (89%). Hoewel de tool de ziekteperceptie niet veranderde, suggereert de hoge tevredenheid dat het online hulpmiddel de informatiebehoefte van GTD-patiënten ondersteunt.

In **HOOFDSTUK 5** gebruiken we een kwalitatieve benadering om te onderzoeken welke psychologische en fysieke gevolgen patiënten met GTD ervaren. Semigestructureerde interviews werden afgenomen bij acht recent gediagnosticeerde patiënten, waarna thematische netwerkanalyse werd toegepast om belangrijke inzichten te identificeren. De onverwachte diagnose leidde vaak tot gevoelens van verdriet, onzekerheid en machteloosheid. Om hiermee om te gaan, zochten de patiënten emotionele steun, probeerden ze accurate informatie te verkrijgen, hadden ze contact met lotgenoten en zochten ze afleiding. De meeste patiënten waren tevreden over de zorg en benoemden de persoonlijke benadering, empathie, medische expertise en het gevoel gehoord te worden als cruciale aspecten. Patiënten die psychologische ondersteuning kregen door gespecialiseerde verpleegkundigen waardeerden dit in het bijzonder. Toch waren er punten van kritiek zoals de kwaliteit van de verstrekte informatie, de communicatie en de logistieke organisatie. Deze punten kunnen verbeterd worden door het verstrekken van betere informatie aan patiënten, op maat gemaakte psychologische ondersteuning en regelmatigere consultaties in expertise centra terwijl de behandeling van laag-risico GTD bij voorkeur wel lokaal plaatsvindt.

In **HOOFDSTUK 6** wordt een exploratieve studie beschreven waarin factoren worden onderzocht die relevant zijn voor samen beslissen bij de keuze voor chemotherapie bij patiënten met een laag-risico GTN. Hoewel methotrexaat (MTX) en actinomycine D (actD) als even effectief worden beschouwd, verschillen zij in toedieningswijze, bijwerkingen en invloed op kwaliteit van leven. Dit maakt deze behandelkeuze geschikt voor samen beslissen. Tot op heden was echter weinig bekend over welke factoren patiënten en zorgverleners hierbij relevant achten. Daarom werd er een vragenlijststudie uitgevoerd onder patiënten die in Nederland zijn behandeld met chemotherapie voor laag-risico GTN en onder zorgverleners die betrokken zijn bij de behandeling van GTN wereldwijd. Op basis van een literatuurstudie en een eerder kwalitatief onderzoek werden twintig potentieel relevante factoren opgenomen in de vragenlijsten. De deelnemers beoordeelden het belang van deze factoren op een 5-punts Likertschaal en rangschikten daarnaast hun drie belangrijkste factoren vóór en na het invullen van de vragenlijst. In totaal vulden tien patiënten en tweeëntwintig zorgverleners de vragenlijsten volledig in. Bijwerkingen werden door zowel patiënten als zorgverleners consequent als de belangrijkste factor genoemd. Vruchtbaarheid speelde met name voor patiënten een belangrijke rol, terwijl

zorgverleners vaker de effectiviteit van de behandeling en de wijze van toediening prioriteerden. Deze studie biedt eerste inzichten in factoren die relevant zijn voor samen beslissen bij de behandeling van laag-risico GTN. De resultaten vormen een belangrijke basis voor de ontwikkeling van een keuzehulp en ondersteunen de toekomstige implementatie van samen beslissen in de zorg voor patiënten met laag-risico GTN.

In **HOOFDSTUK 7** worden de belangrijkste bevindingen van de studies samengevat en bediscussieerd. Daarnaast worden er implicaties voor de klinische praktijk en suggesties voor toekomstig onderzoek voorgesteld.



Appendix

RESEARCH DATA MANAGEMENT

PHD PORTFOLIO

BIBLIOGRAPHY

CURRICULUM VITAE

DANKWOORD

RESEARCH DATA MANAGEMENT

Ethics and privacy

This thesis is based on the results of research involving human participants, conducted in accordance with relevant national legislation and regulations, guidelines, codes of conduct and Radboudumc policy. A statement that the study was not subject to the Dutch Medical Research Involving Human Subjects Act (WMO) was obtained from the recognized Medical Ethics Review Committee ‘METC Oost-Nederland’ (2015-1816). Informed consent was obtained from participants to collect and process their data for chapters 2, 3, 4, 5 and 6. Consent was not obtained for sharing and reuse of the (pseudonymized) data for future research. The privacy of the participants was warranted by pseudonymization; the pseudonymization key was stored separately from the research data on a secured network drive accessible only to project members.

Data collection and storage

Data for chapters 2, 3 and 4 were collected using Castor EDC for secured online questionnaires and subsequently exported to SPSS (SPSS Inc., Chicago, Illinois, USA). All research data presented in this thesis were stored at the Department of Gynecology of the Radboud University Medical Center and in Castor EDC, accessible only to project members working at the Radboudumc, and will be retained for 15 years after termination of the studies.

Data sharing according to the FAIR principles

Chapters 2, 3, 4 and 5 are published, of which chapters 2, 3 and 5 with open access. Chapter 6 is not published. The data underlying chapter 2-5 are not suitable for reuse and will be archived with closed access for 10 years in DACs of the Radboud Data Repository (see table below).The data used in the unpublished chapter 6 are archived at the department server. Upon publication of the chapter the data will be archived via the Radboud Data Repository with closed access as well.

The table below details where the data and research documentation for each chapter can be found on the Radboud Data Repository (RDR). All data archived remain available for at least 10 years after termination of the studies.

Chapter	RDR - DAC
2	DOI 10.34973/ca3x-2597
3	DOI 10.34973/ca3x-2597
4	DOI 10.34973/ca3x-2597
5	DOI 10.34973/ca3x-2597

DAC = Data Acquisition Collection

PHD PORTFOLIO

PhD candidate: **Laura Blok**
Department: **Laboratory medicine**
PhD period: **01-05-2019 – 01-06-2026**
PhD Supervisor: **Prof. dr. C.G.J. Sweep**
PhD Co-supervisors: **Dr. P.B. Ottevanger and dr. Y.K. Eysbouts**

Training activities	Hours
Courses	
Radboudumc - Course qualitative research (2022)	84
Radboudumc - Scientific integrity (2024)	20
Conferences	
International Society for the Study of Trophoblastic Diseases (ISSTD) Toronto 2019 – oral presentation	30
International Society for the Study of Trophoblastic Diseases (ISSTD) Sydney 2022 – oral presentation	30
Total	164

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Oral presentations

International Society for the Study of Trophoblastic Diseases (ISSTD) - The psychosocial impact of Gestational Trophoblastic Disease, Toronto (Canada), 10-2019

International Society for the Study of Trophoblastic Diseases (ISSTD) - The psychosocial impact of pregnancy loss: comparison of patients with gestational trophoblastic disease to patients with a miscarriage - a prospective one year follow-up study, Sydney (Australia), 10-2022

CURRICULUM VITAE

Laura Jannet Blok werd op 6 augustus 1994 geboren in het toenmalige Sint Josephziekenhuis in Veldhoven. In 2012 behaalde zij haar Gymnasium diploma aan het Were Di in Valkenswaard en begon zij in datzelfde jaar met de studie Geneeskunde aan de Radboud Universiteit in Nijmegen. Zij sloot haar Bachelor in 2015 af met een klinische stage in zowel het S. Orsola-Malpighi Ospedale in Bologna (Italië) als in het Regional Hospital of Buea in Buea (Kameroen) om vervolgens met haar master te beginnen. Tijdens deze fase van haar opleiding werd de interesse in de Gynaecologie en Obstetrie gewekt. Het laatste jaar van haar master stond dan ook in het teken van dit specialisme waarbij ze haar senior-coschap binnen de Gynaecologie en Obstetrie van het Jeroen Bosch Ziekenhuis doorbracht, voor een keuze coschap opnieuw naar Afrika vertrok om 3 maanden in het Sengerema Designated District Hospital in Sengerema (Tanzania) te werken en tijdens haar wetenschappelijke stage bij de afdelingen Gynaecologie & Medische Oncologie de basis van dit proefschrift legde onder begeleiding van dr. Nelleke Ottevanger en dr. Yalck Eysbouts. Na het afronden van haar studie Geneeskunde in 2019 ging Laura aan het werk als arts-assistent Obstetrie en Gynaecologie in het Maxima Medisch Centrum in Veldhoven en vervolgde haar carrière in het VieCuri in Venlo, waar ze in januari 2022 is gestart met de opleiding tot gynaecoloog. Naast haar opleiding tot gynaecoloog rondde zij dit proefschrift af. Laura woont samen in Eindhoven met Christiaan Rosendaal en hun dochter Ella.

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