

# The psychological impact of gestational trophoblastic disease: a prospective observational multicentre cohort study

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**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** Sixty 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 were patients without children (mean score 10.4 versus 15.0,  $P = 0.031$ ), and patients with children experienced lower distress levels (IES mean score 25.7 versus 34.7,  $P = 0.020$ ). In addition, patients with previous pregnancy loss scored lower for distress compared with

patients without pregnancy loss (IES mean score 21.1 versus 34.2,  $P = 0.002$ ).

**Discussion** We recommend that physicians monitor physical complaints and the course of psychological wellbeing over time in order to provide personalised 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.

**Keywords** Anxiety, depression, distress, gestational trophoblastic disease, pregnancy loss, reproductive concerns, stress.

**Tweetable abstract** Patients with gestational trophoblastic disease (GTD) experience short-term psychological consequences such as distress, anxiety and depression, suggesting that the diagnosis GTD has a substantial effect on the psychological wellbeing of patients. Various patient characteristics affect the impact of GTD diagnosis.

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## Introduction

Gestational trophoblastic disease (GTD) is a rare complication of pregnancy, occurring in 1.67 per 1000 deliveries in the Netherlands.<sup>1</sup> 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).<sup>2</sup> About 15–20% of patients with CHM and 0.5–5% of patients with PHM develop post-molar GTN,<sup>2–5</sup> but even in widespread disease, outcomes are favourable.<sup>5–7</sup> 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.<sup>3,4</sup> 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.<sup>8</sup> Earlier studies have established elevated levels in various psychological domains, such as anxiety, depression, distress and reproductive concerns. All these studies, however,<sup>9–15</sup> had a retrospective design, as psychological complaints were evaluated several years after diagnosis, possibly causing recall bias. In general, recall bias leads to less reliable results when more time has passed.<sup>16</sup> In addition, recall bias is influenced by other factors, such as current psychosocial and physical wellbeing and life-altering events.<sup>16,17</sup> 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. 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 homogeneous group of patients, so patients who had 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. Nineteen 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 by their gynaecologist for permission to be contacted by the researcher within 1 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 2 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 were collected in collaboration with and used by other institutes.

### Demographic and clinical information

The patients' socio-demographic 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 (HADS)*

Psychological distress was measured with the total score of the HADS.<sup>18</sup> 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  $\geq 8$  indicate existence of depressive/anxious feelings.<sup>18</sup>

#### *Distress thermometer (DT)*

The 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.<sup>19–22</sup>

#### *Impact of Events Scale (IES)*

The 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.<sup>23,24</sup>

#### *Reproductive Concerns Scale (RCS)*

The Dutch version of the RCS was used to assess women's reproductive concerns.<sup>25,26</sup> The instrument contains 14 items on the 5-point Likert scale (0–4) resulting in scores ranging from 0 to 56. Higher scores indicate more reproductive concerns.

### Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Version 25 (IBM Corp, Armonk, NY, USA). Demographic and clinical characteristics were described as mean, median or number. 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 contact eight patients and two patients declined participation, leaving 60 patients who consented to participate in the study. Reasons for declining to participate were tiredness or fear that the questions would be too confrontational. Baseline characteristics of the patients are shown in Table 1. The mean age was 32 years ( $\pm 6.9$  SD). Of the patients, 57% had at least one child and 35% had experienced a previous pregnancy loss. Median time between diagnosis and completion of the questionnaires was 39 days (interquartile range [IQR] 25–50).

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

	GTD patients <i>n</i> = 60
Age (years) mean $\pm$ SD	32 $\pm$ 6.9
Partner	98%
Yes	
Co-habiting	88%
Having children	57%
Education level	
University or applied sciences	63%
Employed	92%
Previous pregnancy loss	35%
Previous psychological help	28%
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.** 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 <i>N</i> = 60		
	Mean $\pm$ SD	Moderate N (%)	Severe N (%)
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:  $\geq 11$  distress, HADS-A/D  $\geq 8$  anxious/depressive feelings. DT:  $\geq 4$  increased distress. IES total: 9–25 moderate adaptation difficulties,  $\geq 26$  serious adaptation difficulties. RCS: higher scores represent more reproductive concerns.

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; 47% and 27% of GTD patients scored  $\geq 8$  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.

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). Seventeen of 21 patients

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

	With children, <i>n</i> = 34 mean $\pm$ SD	Without children, <i>n</i> = 26 mean $\pm$ SD	<i>P</i>
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 mean ± SD	No pregnancy loss, n = 39 mean ± SD	P
HADS total	12.3 ± 9.7	13.2 ± 7.8	0.707
HADS anxiety	6.8 ± 5.0	8.2 ± 4.3	0.285
HADS depression	5.5 ± 5.1	5.0 ± 4.2	0.715
DT	5.6 ± 3.3	5.6 ± 2.7	0.945
IES total	21.1 ± 18.8	34.2 ± 13.2	0.002*
RCS	12.4 ± 8.5	12.4 ± 8.2	0.993

\*Statistically significant.

with previous pregnancy loss already had children. There were no significant differences in anxiety, depression or distress between patients with and those without previous pregnancy loss.

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 immediately 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 GTD could be considered a traumatic event causing serious adaptation problems.

### Strengths and limitations

Our study is the first study that provides an understanding of 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 homogeneous population, the results are likely to be representative

of 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.<sup>9–14,27</sup> One study analysing GTD patients used the HADS-A and reported lower anxiety rates than our study.<sup>10</sup> This could be explained by the fact that the time between diagnosis and completing the questionnaires was nearly 5 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,<sup>14</sup> indicating low levels of stress reactions, whereas our study reported more severe levels of stress reactions. This could suggest that feelings of intrusion and avoidance will also decrease in time. However, in those studies, the severity of complaints could also have been underestimated as an effect of recall bias. Reproductive concerns have also been reported before.<sup>9,14</sup> In our study, GTD patients who already had children were less concerned about their reproductivity than were patients without children, which is supported by other studies.<sup>9,28</sup> 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. As 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 hypothesise that, as 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, therefore less distress in terms of intrusion and avoidance was 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 of 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<sup>29,30</sup>), 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.<sup>31,32</sup> It is conceivable that GTD patients scored higher because 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 with other diseases, the diagnosis GTD seemed to have less impact than, for example, the diagnosis of breast cancer, measured with the DT within 1 month after diagnosis.<sup>33</sup> Nevertheless, patient characteristics such as age and parity which may influence the psychological wellbeing of patients, were not comparable in GTD patients and patients with breast cancer.<sup>33</sup> Lastly, when we compared our results with women facing fertility problems, GTD patients reported less fertility concern than women with concerns about fertility.<sup>26</sup> However, GTD patients reported more concerns than healthy women did.<sup>26</sup>

## 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 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 personalised supportive care for patients who maintain high levels of distress. Furthermore, for a future study, a case control study is needed further to 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 with GTN and follow them over time. This is important to evaluate patients at risk of developing more severe psychological complaints. Given the rare occurrence of GTD, follow-up of patients in specialised centres offering appropriate supportive care by experienced counsellors may be preferable.

## Disclosures of interests

None declared. Completed disclosure of interest forms are available to view online as supporting information.

## Contribution to authorship

LJB: data collection, data analysis, writing of the article. MMF, PBO: involved in development of the project, critical review of the article. YKE: involved in development of the

project, support with writing the article. JAEC, FCGJS, CARL: 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 (2015-1819).

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## Data availability

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

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