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Effect of hCG follow-up on anxiety, depression, and quality of life in women with gestational trophoblastic disease

Vliv sledování hCG na úzkost, depresi a kvalitu života u žen s gestační trofoblastickou chorobou

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Summary: Objective: To assess the effect of normalization of the hormone, human chorionic gonadotropin, on anxiety, symptoms of depression, and quality of life in patients with gestational trophoblastic disease, and to identify risk factors associated with these outcomes. **Methods:** This longitudinal study included 51 women under postmolar follow-up or during treatment for gestational trophoblastic neoplasia between 2017 and 2019 in two Brazilian trophoblastic disease centers. **Results:** The normalization of human chorionic gonadotropin led to a significant reduction in the depression scores and increased physical health domain scores in both study groups, namely the hydatidiform mole and gestational trophoblastic neoplasia groups. Having children and the desire for children were associated with lower scores for depression and anxiety, and higher scores for the psychological health domain of quality of life. Perceiving health as "very poor" was associated with higher scores for depression and anxiety, and lower scores for quality of life with respect to physical health, psychological health, and social relationship domains. **Conclusion:** Disease remission was associated with reduced depression symptoms and better quality of life in the physical health domain. While having a negative perception of health was associated with higher anxiety and depression scores and poor quality of life, having children and the desire for children improved anxiety and depression symptoms and quality of life in the psychological health domain.

Key words: gestational trophoblastic disease – anxiety – depression – quality life

Souhrn: Cíl: Posoudit vliv normalizace hormonu lidského choriového gonadotropinu na úzkost, symptomy deprese a kvalitu života u pacientek s gestační trofoblastickou chorobou a identifikovat rizikové faktory spojené s těmito výsledky. **Metody:** Tato longitudinální studie zahrnovala 51 žen, které byly v období postmolárního sledování nebo během léčby gestační trofoblastické neoplazie v letech 2017–2019 ve dvou brazilských centrech pro trofoblastickou chorobu. **Výsledky:** Normalizace hladiny lidského choriového gonadotropinu vedla k významnému snížení skóre deprese a zvýšení skóre v oblasti fyzického zdraví v obou studijních skupinách, konkrétně ve skupině s hydatiformní molou a gestační trofoblastickou neoplazií. Mít děti a touha po dětech byly spojeny s nižším skóre deprese a úzkosti a vyšším skóre v oblasti psychického zdraví, která se týká kvality života. Vnímání zdraví jako „velmi špatného" bylo spojeno s vyšším skóre deprese a úzkosti a nižším skóre v oblasti kvality života, pokud jde o fyzické zdraví, psychické zdraví a sociální vztahy. **Závěr:** Remise onemocnění je spojena se snížením symptomů deprese a lepší kvalitou života v oblasti fyzického zdraví. Zatímco negativní vnímání zdraví bylo spojeno s vyšším skóre úzkosti a deprese a špatnou kvalitou života, mít děti a touha po dětech zlepšily symptomy úzkosti a deprese a kvalitu života v oblasti psychického zdraví.

Klíčová slova: gestační trofoblastická choroba – úzkost – deprese – kvalita života

Introduction

Gestational trophoblastic disease (GTD) is derived from the abnormal proliferation of trophoblastic tissue and may be benign or malignant. The benign form, namely molar pregnancy or hydatidiform mole (HM), is classified as either a partial hydatidiform mole (PHM), when a nonviable fetus is present, or as a complete hydatidiform mole (CHM), when no fetus but only placental tissue is present. The malignant form of GTD,

called gestational trophoblastic neoplasia (GTN), comprises four subtypes of disease: invasive mole (IM), choriocarcinoma (CC), placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT), which display different histological, clinical, and therapeutic features. Although GTN most commonly follows a HM, it can arise after any form of pregnancy [1–4].

Despite wide regional variations, HM incidence in most parts of the world is 1 per 1,000 pregnancies, with prior HM, abortion and extremes of reproductive age (< 15 and > 45 years) being the main risk factors [5–7]. In Brazil, HM occurrence is estimated as 1 per 200–400 pregnancies [1,8]. Because it may follow any type of pregnancy, the incidence of GTN is not well known. However, according to some reports, progression into GTN occurs in 20% of CHM and 0.5–5% of PHM cases [1,3,9,10].

A GTN diagnosis is established based on the level of the hormone human chorionic gonadotropin (hCG) measured weekly after molar evacuation. The normalization of hCG (≤ 5 mUI/mL) indicates HM remission, whereas its plateau or rise indicates the development of GTN [1,3,9,10]. The appropriate treatment for GTN, most commonly chemotherapy, results in a cure rate of over 90%, even with metastasis [11]. The GTN treatment response is also determined by the hCG level with hCG normalization indicating the cure [9,10,12]. The loss of a pregnancy and the possibility of developing postmolar GTN impose a double loss, which includes the loss of the dream of motherhood and subsequently the loss of the health of the woman herself. A sudden shift from experiencing a possible pregnancy to a potentially life-threatening diagnosis, surgical treatment and/or chemotherapy, and the delay in future pregnancy can cause great physical and psychological suffering [9,13–17].

The monitoring of hCG levels, as viewed by the patients, is a source of stress and anxiety, as it is a constant reminder of the disease [18,19]. Lok et al. [20] demonstrated that over 50% of the patients under postmolar surveillance reported tension, insecurity and anxiety before weekly hCG measurements. Jewell et al. [18] observed that 20% of the women with GTN had a mood score suggestive of depression, which was more evident in women under active hCG surveillance than in formerly treated patients, indicating that the higher level of concern surrounding ß-hCG surveillance was associated with depression.

The grief that follows the loss of a pregnancy may not be socially accepted, especially over the first weeks as in a case with HM. The lack of validation of such feeling and space for its psychological elaboration may adversely influence the quality of life of the woman and her partner, and contribute to the development of anxiety and/or depression symptoms [14,18,21–23]. In addition to the grief elaboration process, women experience anxiety and reproductive concerns. Fears of infertility, disease recurrence in a future pregnancy, or even of another type of cancer, as in the case of GTN, frequently occur [18,23–25].

Over the last decades, GTD medical management has been widely researched. However, studies on GTD psychosocial aspects and their short- and long-term impact on women's health and life are scarce [18,26]. Thus, the objective of this study was to analyze the effect of hCG normalization on anxiety and depression symptomatology, as well as on the quality of life in women with GTD, and to identify the potentially associated factors.

Materials and methods

This collaborative longitudinal study was approved by the Ethics Committee of Federal University of São Paulo (CAAE: 73944417.4.0000.5505). Additionally, written informed consent was obtained from all participants. Patients with GTD attending the two Gestational Trophoblastic Disease Centers, between March 1st 2017 and May 31st 2019, were invited to participate in the study. These two specialized referral centers cover two large health districts in São Paulo state, Brazil, and provide GTD care to the female population aged between 15 and 59 years of 7,719,954 as estimated in 2021 [27]. Moreover, since all Brazilian centers specialized in the treatment of GTD are affiliated with a public university and belong to the Brazilian Public Health System, the population of our study can be considered as representative of the Brazilian population of women with GTD. The only inclusion criterion was a positive hCG test result either during the postmolar follow-up or during GTN treatment. Women not proficient in Brazilian Portuguese were excluded.

The sample size was calculated based on a pilot study on anxiety, depression and quality of life before and after hCG normalization, which included 21 women with GTD. This pilot study showed significant differences between pre- and post-hCG normalization quantitative measures of state anxiety ($P = 0.001$, parametric paired Student T-test) and depression ($P = 0.002$, nonparametric paired test of Wilcoxon), while the quality of life remained unchanged ($P = 0.726$, parametric paired Student T-test). Thus, to detect differences between pre- and post-hCG normalization quantitative measures of state anxiety and depression, with a statistical power of 80% and significance level at 5%, the sample size was estimated in 9 and 18 patients, resp. With regard to the quality of life, the sample size was estimated as 51 patients to demonstrate that similarity at both time points with a power of 80% and significance level of 5%. An effect size of 0.52 was considered.

The study participants were asked to answer three translated validated questionnaires, State-Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI),

and World Health Organization Quality of Life – WHOQOL-bref at two time points:

1. when hCG test result was positive;
2. when hCG normalization (≤ 5 mUI/mL) was achieved.

In addition, an individual 20minute interview was conducted at when hCG test result was positive to obtain demographic and clinical information on age, education level (completion/incompletion of elementary school (1st–9th grade), completion/incompletion of high school (10th–12th grade), completion/incompletion of college/university, and graduate school), marital status (single, married, divorced), subjective health status (very poor, poor, neither poor or good, good, very good), diagnosis of HM or GTN, having children prior to diagnosis (yes/no), desire for children (yes/no), employment status (yes/no), whether or not chemotherapy was required, type of chemotherapy agent used, and loss of partner after illness (yes/no).

The state-trait anxiety inventory (STAI) consists of two scales one related to state anxiety (STAI-S) and the other to trait anxiety (STAI-T). Whereas the state of anxiety reflects a transient reaction directly related to a situation of adversity that presents itself at a given moment, anxiety trait refers to a more stable aspect related to an individual's propensity to deal with more or less anxiety throughout life. Each scale consists of 20 items scored on a 4-point Likert scale with a range from 1 (almost never) to 4 (almost always) on STAI-T, and 1 (not at all) to 4 (very much so) on STAI-S. For both anxiety categories, "state" and "trait" 0–29 scores indicate low anxiety; 30–39 scores indicate moderate anxiety; 40–49 indicate moderate-to-severe anxiety; and 50–80 indicate severe anxiety [28,29].

The Beck Depression Inventory (BDI) is a 21-item self-rating instrument that measures the following signs and symptoms of depression: mood, pessimism, sense of failure, dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, indecisiveness, distortion body image, work difficulty, sleep disorder, fatigability, loss of appetite, weight loss, somatic preoccupation and loss of libido. Each item is rated from 0 to 3 based on the severity of the symptom. The cutoff points adopted for a population with no previous diagnosis of depression are as follows: scores of 0–15 absence of depression; 16–20, dysphoria; and > 20, compatible with depressive symptoms [30,31]. The World Health Organization Quality of Life – WHOQOL-bref is an abbreviated version of the WHOQOL-100 quality of life assessment instrument consisting of 26 questions. It requires less time to be completed; however, it has satisfactory psychometric characteristics, which are comparable to the version with 100 questions. Two of the 26 questions correspond to the general quality of life issues, whereas the remainders address one item from each of the 24 facets contained in the original instrument. The WHOQOL-bref assesses four domains: physical health (activities of daily living, dependence on medicinal substances and medical aid, energy and fatigue, mobility, pain and discomfort, sleep and rest and work capacity), psychological health (bodily image and appearance, negative feelings, positive feelings, self-esteem, spirituality/religion/personal beliefs, thinking, learning, memory and concentration), social relationships (personal relationships, social support and sexual activity) and environment (financial resources, freedom, physical safety and security, health and social care: accessibility and quality, home environment, opportunities for recreation/leisure activities, physical environment (pollution/noise/traffic/climate) and transport). The WHOQOL-bref contains 5-point Likert response scales concerned with intensity (none to extremely), capacity (none to complete), frequency (never to always), and evaluation (very poor to very good and very dissatisfied to very satisfied). Higher mean scores (range 0–100) denote better patient conditions [32].

Statistical analyses were performed using IBM SPSS 20.0 (Armonk, NY, USA) and Stata 12 software (College Station, TX, USA). The significance level was set at 5% ($P \leq 0.05$). Categorical variables are described as absolute frequencies, and numerical variables as summary measures. The associations were assessed using the Chi-square and Fisher's exact test. Analysis of variance (ANOVA) was used to compare anxiety, depression and quality of life between the HM and GTN patients. When the data were not normally distributed, the non-parametric Kruskal-Wallis test was used to compare mean values. Mixed linear regression models were used to assess the effect of demographic and clinical variables (GTN vs. HM, normal hCG vs. positive hCG, age, education level, marital status, subjective health status, having children prior to diagnosis, desire for children, being employed, loss of partner) on all four quality of life domains, depression and anxiety.

The internal consistency, as assessed using Cronbach's alpha coefficients, was very good for the questionnaires STAI-S, STAI-T and BDI ($\alpha = 0.90$). Regarding the WHOQOL questionnaire, internal consistency was reasonable for the physical health and psychological health domains ($\alpha = 0.75$ and 0.78, resp.), weak for the environment domain ($\alpha = 0.67$) and poor for the social relationships' domain ($\alpha = 0.54$).

Results

A total of 68 patients agreed to participate in the study. Of these, 51 (26 with HM and 25 with GTN) completed the two-stage data collection process and were included in the analysis. Tab. 1 shows the sociodemographic and clinical characteristics of the studied population. Fig. 1 shows that all 25 cases of GTN were classified as low-risk. In this group, only one patient received surgical

Tab. 1. Sociodemographic and clinical characteristics (N = 51).
Tab. 1. Sociodemografické a klinické charakteristiky (n = 51).

	HM (N = 26)	GTN (N = 25)	Total (N = 51)
Age (years) – mean ± SD	28.6 (9.6)	31.6 (7.1)	30 (8.5)
Educational level N (%)			
incomplete elementary school	3 (11.5)	2 (8)	5 (9.8)
complete elementary school	1 (3.8)	2 (8)	3 (5.9)
incomplete high school	5 (19.2)	5 (20)	10 (19.6)
complete high school	10 (38.5)	8 (32)	18 (35.3)
incomplete college	3 (11.5)	2 (8)	5 (9.8)
complete college	3 (11.5)	4 (16)	7 (13.7)
post-graduation	1 (3.8)	2 (8)	3 (5.9)
Marital status N (%)			
single	7 (26.9)	4 (16)	11 (21.6)
married/living as married	18 (69.3)	19 (76)	37 (72.5)
divorced	1 (3.8)	2 (8)	3 (5.9)
Employment status N (%)			
unemployed	10 (38.5)	12 (48)	22 (43.1)
employed	16 (61.5)	13 (52)	29 (56.9)
Having children N (%)			
no	13 (50)	11 (44)	24 (47.1)
yes	13 (50)	14 (56)	27 (52.9)
Desire to have children N (%)			
no	5 (19.2)	9 (36)	14 (27.5)
yes	21 (80.8)	16 (64)	37 (72.5)
Subjective perception of health status N (%)			
very bad or weak	2 (7.7)	3 (12)	5 (9.8)
neither bad nor good	8 (30.8)	9 (36)	17 (33.3)
good or very good	16 (61.5)	13 (52)	29 (56.9)

GTN – gestational trophoblastic disease/gestační trofoblastické onemocnění, HM – hydatidiform mole/hydatiformní mola, N – number/počet, SD – standard deviation/směrodatná odchylka

treatment (TAH – total abdominal hysterectomy). The other 24 patients were treated with monochemotherapy. Six of these women developed resistance to first-line treatment; however, all of them achieved remission with second-line mono chemotherapy.

Among the study participants, the mean age was 30 years (SD ± 8.5) and over half (53%) of them already had children. Nonetheless, 72.5% of the women expressed the desire to have children. At the beginning of the study (T1 – positive hCG) 10% of the participants rated their health as "very poor" or "poor" and 57% considered it as "good" or "very good" (Tab. 1). The mean time from uterine evacuation to spontaneous remission of the HM was 73 days, and the mean time from diagnosis of GTN to remission was 104 days. The mean (± SD) absolute values of hCG at T1 were 5,689.9 mUI/mL (± 14,194.8) for HM and 1,878.8 mUI/mL (± 2,164.4) for GTN, respectively. No difference in the mean hCG level (P = 0.961) was observed between the groups with HM and GTN. The time elapsed between T1 and T2 in the MH and GTN groups was 91.0 days (± 70.3) and 146.3 days (± 123.8), resp., and also did not significantly differ (P = 0.984) between the groups.

As shown in Tab. 2, no interactions were observed for STAI-S (P = 0.126) and STAI-T (P = 0.534), BDI (P = 0.513) and WHOQOL-bref (physical domains: P = 0.815; psychological: P = 0.423; social: P = 0.450; environment: P = 0.647). There were no differences in means between the HM and GTN groups at either assessment point (T1 and T2).

When hCG test result was positive, both groups, HM and GTN, rated the state anxiety (45.7 and 46.9, resp.) and trait anxiety (43.2 and 44.4, resp.) as "moderate to severe" (40–50 score). The normalization of hCG significantly reduced both state anxiety (41.2 and 37.5; P < 0.001) and trait anxiety (40.7 and 40.0; P = 0.027) irrespective of the group. However, only the ratings of state anxiety switched from "moderate-to-severe" to "moderate" in the GTN group, whereas the others remained "moderate-to-severe" (Tab. 2).

Despite reducing anxiety scores, hCG normalization showed no association with state anxiety (P = 0.064) and trait anxiety (P = 0.277) on multivariate analysis. Tab. 3 shows that women with incomplete elementary school and those with incomplete high school had significantly lower scores for state anxiety (–8.5, P = 0.019; –7.9, P = 0.004; resp.) and trait anxiety (–10.7, P = 0.002; –10.6, P = 0.020; resp.) anxiety. The trait anxiety scores were also lower in post-graduate women compared to those who completed high school (–10.6, P = 0.020).

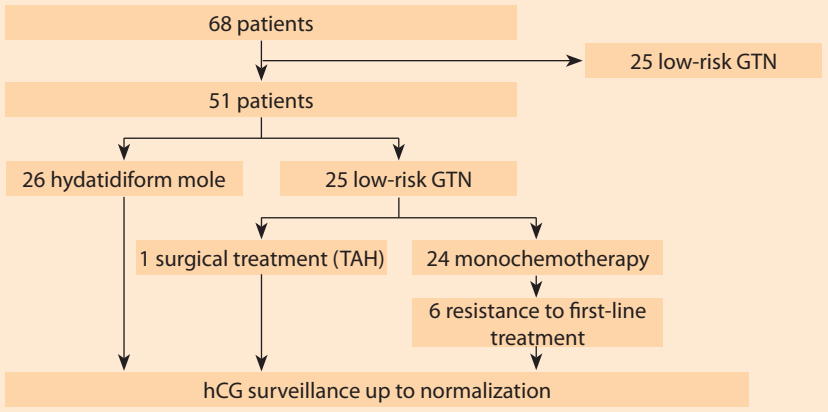
The other variables that significantly reduced anxiety scores were having children (–5.5, P = 0.049 state anxiety; –9.1, P = 0.001 trait anxiety) and desire for children (–6.6, P = 0.005 state anxiety). However, among women who perceived their health as "very poor", state anxiety (13.5, P = 0.008) and trait anxiety (15.3, P = 0.002) significantly increased compared to patients who considered it "good".

During hCG level surveillance, before remission (positive hCG), the mean BDI

scores in both HM and GTN groups were compatible with the absence of depression symptoms (13.6 and 11.0, resp., both < 16). The normalization of hCG levels, regardless of the group studied (P = 0.513), had a significant improvement effect (P < 0.001) reducing depression scores by 4.2 and 3.0 points in the HM and GTN groups, resp. (Tab. 2).

Irrespective of whether the patient had HM or GTN (P = 0.815), normalization of hCG had an effect of increasing scores in the physical domain of quality of life (WHOQOL-bref physical domain – P = 0.004).

The effect of hCG normalization on the reduction of depression symptoms



GTN – gestational trophoblastic disease/gestační trofoblastické onemocnění, hCG – human chorionic gonadotropin/lidský choriogonadropin, TAH – total abdominal hysterectomy/totální abdominální hysterektomie

Fig. 1. Flowchart of the included patients.
Obr. 1. Vývojový diagram zahrnutých pacientů.

Tab. 2. Summary measures of WHOQOL-4 domain, BDI, STAI-S and STAI-T scores.
Tab. 2. Souhrnné ukazatele skóre WHOQOL-4, BDI, STAI-S a STAI-T.

	Time of evaluation			P value		
	T1	T2	T2–T1	Group (HM vs. GTN)	T2 vs. T1	Group vs. hCG normalization (GTN vs. T2)
WHOQOL – physical aspect				0.892	0.004	0.815
HM	61.5 ± 18.8	68.5 ± 15.8	7.0 ± 13.7			
GTN	62.6 ± 13.8	68.6 ± 14.3	6.0 ± 16.7			
WHOQOL – psychological aspect				0.891	0.595	0.423
HM	66.2 ± 18.3	65.5 ± 16.3	–0.6 ± 13.8			
GTN	64.8 ± 15.2	68.0 ± 16.1	3.2 ± 19.5			
WHOQOL – social aspect				0.374	0.117	0.450
HM	72.1 ± 19.1	74.4 ± 15.1	2.2 ± 18.2			
GTN	66.3 ± 19.8	72.7 ± 16.4	6.3 ± 20.2			
WHOQOL – environment aspect				0.381	0.262	0.647
HM	61.9 ± 13.6	63.2 ± 11.4	1.3 ± 13.9			
GTN	63.5 ± 13.7	66.6 ± 10.0	3.1 ± 14.1			
BDI				0.374	< 0.001	0.513
HM	13.6 ± 10.4	9.4 ± 9.0	–4.2 ± 6.5			
GTN	11.0 ± 7.1	8.0 ± 6.1	–3.0 ± 6.4			
STAI-S				0.610	< 0.001	0.126
HM	45.7 ± 11.0	41.2 ± 10.9	–4.5 ± 12.0			
GTN	46.9 ± 11.0	37.5 ± 9.2	–9.4 ± 10.5			
STAI-T				0.892	0.027	0.534
HM	43.2 ± 9.7	40.7 ± 10.6	–2.5 ± 6.9			
GTN	44.4 ± 11.2	40.0 ± 9.8	–4.4 ± 13.8			

P – repeated measures ANOVA
GTN – gestational trophoblastic disease/gestační trofoblastické onemocnění, HM – hydatidiform mole/hydatiformní mola, N – number/počet
WHOQOL – World Health Organization Quality of Life (higher mean scores, range 0–100, denote better patient condition), BDI – Beck Depression Inventory (0–15 scores, absence of depression; 16–20, dysphoria; and over 20, compatible with depressive symptoms), STAI-S – State Anxiety Inventory, STAI-T – Trait Anxiety Inventory (scores 0–29 low anxiety; 30–39 medium-low anxiety; 40 medium anxiety; 41–50 medium-high; 51–80 severe anxiety), T1 – time 1 (when hCG was positive), T2 – time 2 (when hCG normalization was achieved)

Tab. 3. Linear model estimated for the four WHOQOL domains, BDI, STAI-S and STAI-T.
Tab. 3. Lineární model odhadnutý pro čtyři domény WHOQOL, BDI, STAI-S a STAI-T.

	WHOQOL								BDI		STAI-S		STAI-T	
	Physical health		Psychological health		Social relationships		Environment							
	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P
Groups (GTN vs. HM*)	−3.9 (−15.2 to 7.4)	0.503	−7.2 (−19.4 to 5.0)	0.246	−16.5 (−30 to −3.0)	0.017	−5.4 (−14.5 to 3.6)	0.239	−5.0 (−11.9 to 1.9)	0.157	5.2 (−2.8 to 13.2)	0.203	3.2 (−4.4 to 10.9)	0.405
hCG normalization (T2 vs. T1*)	7.0 (0.3 to 13.7)	0.039	−0.6 (−7.8 to 6.5)	0.861	2.2 (−5.7 to 10.2)	0.582	1.3 (−4.0 to 6.7)	0.627	−4.2 (−6.6 to −1.8)	0.001	−4.5 (−9.2 to 0.3)	0.064	−2.5 (−7.0 to 2.0)	0.277
Group vs. hCG normalization	−1.0 (−10.5 to 8.5)	0.836	3.8 (−6.4 to 14.1)	0.467	4.1 (−7.3 to 15.5)	0.482	1.8 (−5.8 to 9.4)	0.643	1.2 (−2.3 to 4.7)	0.501	−4.9 (−11.7 to 1.8)	0.150	−1.9 (−8.3 to 4.5)	0.563
Educational level (complete high school*)		0.012		0.001		0.05		0.003		0.083		0.009		0.002
elementary school – incomplete	14.4 (4.4 to 24.4)	0.005	19.9 (9.1 to 30.7)	< 0.001	11.8 (−0.2 to 23.8)	0.054	2.5 (−5.5 to 10.5)	0.541	−6.7 (−13.2 to −0.1)	0.045	−8.5 (−15.6 to −1.4)	0.019	−10.7 (−17.5 to −3.9)	0.002
elementary school – complete	−4.4 (−16.0 to 7.2)	0.460	−9.6 (−22.1 to 2.9)	0.130	−11.7 (−25.6 to 2.2)	0.098	−3.2 (−12.4 to 6.1)	0.506	5.9 (−1.7 to 13.5)	0.125	4.7 (−3.5 to 12.9)	0.261	0.6 (−7.2 to 8.5)	0.880
high school – incomplete	10.9 (3.4 to 18.5)	0.005	5.2 (−2.9 to 13.3)	0.211	−2.2 (−11.2 to 6.9)	0.634	4.9 (−1.1 to 11.0)	0.111	−2.9 (−7.9 to 2.0)	0.241	−7.9 (−13.3 to −2.6)	0.004	−9.2 (−14.3 to −4.1)	<0.001
college – incomplete	2.1 (−7.6 to 11.8)	0.668	7.4 (−3.0 to 17.8)	0.164	1.8 (−9.8 to 13.4)	0.765	−6.9 (−14.7 to 0.8)	0.080	−3.7 (−10.0 to 2.6)	0.252	−2.4 (−9.2 to 4.5)	0.500	−6.2 (−12.7 to 0.4)	0.065
college – complete	−0.2 (−8.7 to 8.4)	0.971	0.1 (−9.2 to 9.3)	0.986	−8.9 (−19.2 to 1.4)	0.089	7.2 (0.3 to 14.1)	0.04	1.6 (−4.0 to 7.2)	0.578	1.5 (−4.6 to 7.5)	0.635	−5.2 (−11.1 to 0.6)	0.077
post-graduation	6.1 (−7.2 to 19.3)	0.369	18.2 (3.9 to 32.5)	0.012	0.8 (−15.1 to 16.7)	0.918	15.2 (4.6 to 25.8)	0.005	−4.6 (−13.2 to 4.1)	0.302	−3.9 (−13.2 to 5.5)	0.421	−10.6 (−19.6 to −1.7)	0.020

B – estimated regression model coefficient, 95% CI – 95% confidence interval
Cronbach's alpha coefficients was 0.90 to STAI-S, STAI-T and BDI, 0.75 and 0.78 to WHOQOL physical health and psychological health domains, resp., 0.67 to the environment domain and 0.54 to the social relationship's domain
GTN – gestational trophoblastic disease/gestační trofoblastické onemocnění, HM – hydatidiform mole/hydatiformní mola, N – number/počet
WHOQOL – World Health Organization Quality of Life, BDI – Beck Depression Inventory, STAI-S – State Anxiety Inventory, STAI-T – Trait Anxiety Inventory, T1 – time 1 (when hCG test result was positive), T2 – time 2 (when hCG normalization was achieved)
*reference categories

remained significant (P = 0.001) in both groups, on multivariate analysis. Moreover, there was a significant association of having children (P = 0.009), desire for children (P = 0.010) and being employed (P = 0.007) with lower mean BDI scores (6.8, 5.9 and 5.1, resp.) compared to not having children, no desire for children, or unemployment. In contrast, the perception of health as "very poor" (13.5, P = 0.004) or "neither poor or good" (4.2, P = 0.045) was associated with increased depression scores.

Regarding the quality of life, hCG normalization led to increased physical health domain scores (P = 0.004) regardless of the group studied (P = 0.815) (Tab. 2). On multivariate analysis, hCG normalization remained significantly associated with higher physical health scores (P = 0.039). Higher physical scores also showed associations with incomplete elementary school and incomplete high school education (14.4, P = 0.005; 10.9, P = 0.005, resp.). Conversely, perceiving health as "very poor" (−14.9, P = 0.040), "poor" (−23.8, P < 0.001) and "neither poor or good" (−10.1, P = 0.002) reduced the scores on the physical health domain. Having children or the

Tab. 3 – continuing. Linear model estimated for the four WHOQOL domains, BDI, STAI-S and STAI-T.
Tab. 3 – pokračování. Lineární model odhadnutý pro čtyři domény WHOQOL, BDI, STAI-S a STAI-T.

	WHOQOL								BDI		STAI-S		STAI-T	
	Physical health		Psychological health		Social relationships		Environment							
	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P
How is your health (good*)		< 0.001		0.001		< 0.001		0.001		0.022		0.054		0.025
very poor	–14.9 (–29.1 to –0.7)	0.040	–23.6 (–38.9 to –8.3)	0.002	–25.6 (–42.6 to –8.5)	0.003	–9.6 (–21 to 1.7)	0.096	13.5 (4.2 to 22.8)	0.004	13.5 (3.5 to 23.6)	0.008	15.3 (5.7 to 24.9)	0.002
poor	–23.8 (–36.1 to –11.5)	< 0.001	–21.8 (–35.1 to -8.6)	0.001	–27.0 (–41.8 to –12.3)	< 0.001	–17.8 (–27.6 to –8)	< 0.001	7.0 (–1.0 to 15.0)	0.087	4.4 (–4.3 to 13.1)	0.322	2.8 (–5.5 to 11.2)	0.504
neither poor nor good	–10.1 (–16.4 to –3.7)	0.002	–5.8 (–12.6 to 1.1)	0.099	–6.0 (–13.6 to 1.6)	0.120	–10.6 (–15.7 to –5.5)	< 0.001	4.2 (0.1 to 8.4)	0.045	3.3 (–1.2 to 7.7)	0.156	3.5 (–0.8 to 7.8)	0.115
very good	3.6 (–7.0 to 14.2)	0.508	–9.0 (–20.5 to 2.4)	0.121	–9.9 (–22.6 to 2.8)	0.126	–5.9 (–14.3 to 2.6)	0.176	3.9 (–3 to 10.9)	0.264	–2.4 (–9.9 to 5.1)	0.531	5.2 (–2,0 to 12.3)	0.158
Having children (yes vs. no*)	1.0 (–6.8 to 8.9)	0.793	11.7 (3.3 to 20.2)	0.006	6.3 (–3.1 to 15.6)	0.19	1.9 (–4.3 to 8.2)	0.545	–6.8 (–11.9 to –1.7)	0.009	–5.5 (–11.1 to 0.0)	0.049	–9.1 (–14.4 to –3.8)	0.001
Desire for children (yes vs. no*)	3.7 (–3.2 to 10.6)	0.294	8.7 (1.2 to 16.2)	0.022	3.5 (–4.8 to 11.8)	0.404	–3.6 (–9.1 to 2.0)	0.205	–5.9 (–10.5 to –1.4)	0.010	–4.8 (–9.7 to 0.1)	0.056	–6.6 (–11.3 to –2.0)	0.005
Employed (yes vs. no*)	2.9 (–2.8 to 8.6)	0.311	5.4 (–0.7 to 11.5)	0.084	0.9 (–6.0 to 7.7)	0.803	0.5 (–4.0 to 5.1)	0.821	–5.1 (–8.8 to –1.4)	0.007	1.3 (–2.7 to 5.3)	0.531	–3.4 (–7.2 to 0,5)	0.085
Loss of partner (yes vs. no*)	3.6 (–6.1 to 13.4)	0.466	5.6 (–4.9 to 16.1)	0.295	8.8 (–2.9 to 20.4)	0.142	4.9 (–2.9 to 12.7)	0.221	–1.3 (–7.7 to 5.0)	0.683	–0.8 (–7.7 to 6.1)	0.824	4.7 (–1.9 to 11.3)	0.162

B – estimated regression model coefficient, 95% CI – 95% confidence interval
Cronbach's alpha coefficients was 0.90 to STAI-S, STAI-T and BDI, 0.75 and 0.78 to WHOQOL physical health and psychological health domains, resp., 0.67 to the environment domain and 0.54 to the social relationship's domain
GTN – gestational trophoblastic disease/gestační trofoblastické onemocnění, HM – hydatidiform mole/hydatiformní mola, N – number/počet
WHOQOL – World Health Organization Quality of Life, BDI – Beck Depression Inventory, STAI-S – State Anxiety Inventory, STAI-T – Trait Anxiety Inventory, T1 – time 1 (when hCG test result was positive), T2 – time 2 (when hCG normalization was achieved)
*reference categories

desire for children had no influence on the physical health, but significantly increased the psychological health scores (11.7, P = 0.006; 8.7, P = 0.022, resp.).

Incomplete elementary education also had a positive effect on the psychological health (19.9, P < 0.001) and social relationships (11.8, P = 0.054). However, women with complete college/university and post-graduation education showed higher environment domain scores (15.2, P = 0.005; 7.2, P = 0.040) than participants with complete high school education.

The social relationships scores were lower in the GTN group than in the HM group (–16.5, P = 0.017). Health perception as "very poor" and "poor" reduced not only the scores related to physical health but also those on psychological health (–23.6, P = 0.002; –21.8, P = 0.001), social relationships (–25.6, P = 0.003; –27, P < 0.001) and environment (–17.8, P < 0.001). Having children (11.7, P = 0.006) and desire for children (8.7, P = 0.022) influenced only the psychological health (Tab. 3).

Discussion

Our results showed that depressive symptoms and quality of life in the physical health domain improved after disease remission among the study participants. A negative health perception was associated with a higher risk of depression and anxiety and poor quality of life in all domains, except the environmental domain. Having children or desire to have children were protective factors against depression and anxiety, and improved quality of life in the psychological domain.

Because most studies differ in terms of the design (quantitative or qualitative), type of disease (benign or malignant), and timing of questionnaire administration (active or remitted disease, mean interval between diagnosis and questionnaire administration), among other aspects, the literature findings on the emotional aspects and the quality of life in GTD should be cautiously compared [33]. To our knowledge, no longitudinal study similar to ours is available in the literature for comparison.

Among our patients, in both the HM and GTN groups, the mean initial BDI scores indicated the absence of depression (< 16). After hCG normalization, these scores were further significantly decreased. Since we also observed that the scores of depression were increased in patients who had a negative perception of health when hCG test result was positive, these findings suggest that hCG normalization might bring about a more positive perception of health and lead to a consequent reduction in the depression scores.

Among our patients, having children had a protective role against depressive symptoms probably because, as it proves a woman's ability to bear a child, it can reduce the negative psychological impact caused by a diagnosis with GTD [17]. However, Di Mattei et al. [33] found no association between the presence of children and depression. In line with other reports [23,34], desiring children and being employed were also found to play a protective role among our patients. In a Brazilian qualitative study, symptoms of depression were observed in 9.1% of the study participants, aged > 40 years, GTN treated with polychemotherapy or hysterectomy as the associated factors [35]. In this study, the anxiety scores were consistent with moderate-to-severe anxiety when hCG test result was positive and moderate to moderate-to-severe after hCG normalization. However, a multivariate analysis showed that hCG normalization did not significantly decrease anxiety. This is an unexpected finding as it goes against the apprehension and anxiety displayed by our patients while awaiting hCG normalization, an indication of disease remission. The questionnaires were administered for the second time at 47 days on average after of hCG normalization. This interval might have been too short to produce a significant difference. Nonetheless, Stafford et al. [25] demonstrated that the anxiety levels in GTD patients remained high even after five years disease remission. Our findings corroborate others in the literature, which report more anxiety symptoms than depressive symptoms among patients with GTD [17,26,33]. Notably, Di Mattei, et al. [33] have reported an important correlation between anxiety and depression, supporting that patients with high scores for anxiety should receive support to not develop depression.

Among our patients, the desire for children was associated with increased scores in the psychological domain of quality of life as observed by Ferreira et al. [36]. In a study conducted five years after GTD remission, Stafford et al. [25] found that the levels of intrusion, avoidance and GTD-specific traumatic stress were higher in the women had not a subsequent pregnancy compared with those who had a subsequent pregnancy. Therefore, we can assume that desiring children, which in the short-term can be a protective factor, may affect the patient's mental health as it is not fulfilled. Fertility perception seems to be negatively affected by GTD diagnosis, especially in young and in childless women [28]. Hence, the patients desiring to conceive should receive psychological support after postmolar follow-up or GTN treatment.

With regard to schooling, Stafford et al. [25] found that anxiety and depression were associated with lower education levels, whereas Blok et al. [17] reported no association. In our study, compared with completion of high school, both the highest (post-graduation) and lowest (elementary school) education levels were associated with lower anxiety scores and higher scores for psychological quality of life. We were unable to find an explanation for these conflicting results. Perhaps, using a subjective approach, such as patient-reported outcome measures, as suggested by Ireson et al. [37], can be helpful to better understand the emotional aspects of patients with GTD.

We expected that, in comparison with women with HM, patients with GTN would show some emotional impairment. However, only the scores for the social relationships domain of quality of life tended to be lower in patients with GTN. This may be explained by the fact that all our patients had GTN of the low-risk type and did not experience alopecia as they received monochemotherapy with drugs of low-toxicity (methotrexate or actinomycin-D), even in cases of treatment resistance [38]. Ferreira et al. [36] also did not observe worsening of quality of life or symptoms of depression and anxiety in patients treated with chemotherapy where 78.3% of them used monochemotherapy. However, our results disagree with those reported by Di Mattei et al. [33], who reported higher depression scores in a group of patients with GTN whose risk score and stage were not described, but included cases of CC and PSTT that commonly require more aggressive treatment. Furthermore, these authors point out that, because their univariate analysis might have been biased by a confounding effect, this point should be re-examined in the future in a larger sample.

The limitations of this study include the lack of qualitative data, which could clarify some points, such as the relationship of the education level with the quality of life, depression, and anxiety. By longitudinally investigating mental health and quality of life in women with HM and GTN, before and after hCG normalization, the present study contributes

with novel findings relevant for patients with GTD. Future longitudinal studies including a qualitative approach may broaden our understanding of the effects of disease remission on the mental health of GTD patients.

Conclusion

In summary, our results demonstrated an association of hCG normalization (remission of the disease) with lower depression scores and higher physical quality of life scores in women with GTD. Whereas having a negative perception of health was associated with higher anxiety and depression scores and poor quality of life. Having children and the desire for children improved anxiety and depression symptoms and quality of life in the psychological domain. In view of these findings, it is recommended that the patient be given free access to the facility, both remotely (via WhatsApp and/or Apps) and in person (even on unscheduled appointments), and that accessible and empathetic language be used to strengthen her bond with the multiprofessional team and provide space for her psychoemotional and physical needs.

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