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Persistent low-level real human chorionic gonadotropin after gestational trophoblastic disease: Natural history and predictors of subsequent gestational trophoblastic neoplasia

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HIGHLIGHTS

- Persistent low-level real hCG occurred in only 1.1% of patients with GTD.
- More than 75% of patients achieved spontaneous hCG normalization without treatment.
- Delayed low-level hCG onset predicted postmolar GTN and GTN relapse.
- High preevacuation hCG levels were associated with subsequent GTN.
- Surveillance until FIGO criteria avoided overtreatment without compromising outcomes.

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ABSTRACT

Objective. To characterize the natural history of persistent low-level real human chorionic gonadotropin (hCG) after gestational trophoblastic disease (GTD) and identify predictors of subsequent gestational trophoblastic neoplasia (GTN).

Methods. Retrospective cohort study included patients with persistent low-level real hCG (≤100 IU/L for ≥3 months) during postmolar surveillance or after GTN remission at specialized GTD referral centers in Rio de Janeiro, Brazil, between 2000 and 2022. Clinical characteristics, hCG patterns, and oncologic outcomes were analyzed. Risk differences (RD) and 95% confidence intervals (CI) were calculated to identify factors associated with subsequent GTN.

Results. Among 7304 patients with GTD managed during the study period, 72 (0.9%) developed persistent low-level real hCG. Spontaneous hCG normalization occurred in 88.4% (38/43) of patients during postmolar surveillance and 75.9% (22/29) after GTN remission. During postmolar surveillance, vaginal hemorrhage (RD:35.7%, 95%CI:10.6–60.8), preevacuation hCG ≥100,000 IU/L (RD:22.7%, 95%CI:5.2–40.2), and delayed onset of persistent low-level real hCG ≥7 weeks (RD:16.6%, 95%CI:3.3–30.0) were associated with an increased risk of postmolar GTN. Among patients monitored after GTN remission, age ≥ 34 years (RD:19.1%, 95%CI:11.0–49.1), preevacuation hCG ≥100,000 IU/L (RD:30.4%, 95%CI:11.6–49.2), and delayed onset of persistent low-level real hCG ≥14 weeks (RD:43.8%, 95%CI:19.4–68.1) were associated with relapsed GTN.

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Conclusions. Persistent low-level real hCG after GTD frequently resolves spontaneously and does not necessarily represent active malignancy. Careful surveillance until fulfillment of FIGO criteria appears to be the most appropriate management strategy, minimizing unnecessary interventions.

1. Introduction

Gestational trophoblastic disease (GTD) comprises a spectrum of placental trophoblastic disorders, including hydatidiform mole (HM) and gestational trophoblastic neoplasia (GTN), the latter of which encompasses invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) [1,2]. Although HM affects only approximately 1 in 1000 pregnancies worldwide, it is the most common form of GTD and the principal precursor lesion for GTN [3,4]. Despite cure rates exceeding 90% with modern chemotherapy, GTN remains an important and potentially preventable cause of morbidity and mortality when diagnosis or referral is delayed [5,6].

A unique characteristic of GTD is the availability of an exceptionally sensitive biological marker, human chorionic gonadotropin (hCG), which plays a central role throughout the disease continuum [7,8]. Beyond its role in the evaluation of HM and diagnosis of GTN, serial hCG monitoring serves distinct purposes across the GTD spectrum. Following molar evacuation, postmolar hCG surveillance is used to document spontaneous regression and detect the development of postmolar GTN. In patients treated for GTN, post-treatment hCG monitoring is used to assess response to chemotherapy, confirm complete remission, and detect disease relapse. Consequently, serial hCG measurement remains the cornerstone of follow-up throughout the entire continuum of GTD [1,2].

During serial hCG surveillance, clinicians occasionally encounter patients with persistently low-level serum hCG [9–18]. According to the International Federation of Gynecology and Obstetrics (FIGO), this condition is generally characterized by hCG ≤100 IU/L that persists in the absence of clinical, radiological, or biochemical evidence of pregnancy or active disease [19,20]. While false-positive hCG results ultimately explain some of these cases [21–23], others represent genuine hCG production by residual trophoblastic cells, a phenomenon historically referred to as quiescent GTD [24], a term whose accuracy remains controversial [25,26]. In the postmolar setting, persistent low-level real hCG may reflect residual trophoblastic activity that has not fulfilled the FIGO diagnostic criteria for GTN [24]. Conversely, after successful treatment of GTN, renewed low-level real hCG raises concern for disease relapse but may also represent persistent trophoblastic activity in the absence of clinically active malignancy. Distinguishing these scenarios remains challenging because their biological basis is incompletely understood and reliable markers of active disease are lacking.

The clinical implications of persistent low-level hCG are substantial. In routine practice, patients with previous HM may undergo unnecessary chemotherapy because persistent hCG is interpreted as postmolar GTN, whereas patients previously treated for GTN may be subjected to retreatment under the assumption of relapsed GTN [27–31]. Similarly, hysterectomy is not infrequently considered because of concern for PSTT or ETT, neoplasms that may present with a relatively low-level of hCG [17]. Historical series have demonstrated that many women under this condition have received ineffective chemotherapy and even unnecessary surgical procedures before the benign nature of their condition was recognized [27–31].

Even when a conservative strategy of observation is adopted, important uncertainties remain. The natural history of this condition is heterogeneous, ranging from spontaneous normalization of hCG levels to prolonged biochemical persistence and, in a minority of patients, progression to GTN. Consequently, clinicians currently lack reliable prognostic markers capable of identifying which patients are at higher risk of unfavorable outcomes and therefore require closer surveillance. Improving risk stratification in this setting could reduce overtreatment, prevent avoidable morbidity, and enhance the safety of follow-up protocols.

This study aimed to evaluate the natural history and identify prognostic factors of persistent low-level real hCG after remission of GTD, either following spontaneous remission after HM or complete remission after chemotherapy for GTN. By improving our understanding of the natural history of this condition, this study may help clinicians balance the risks of overtreatment and delayed diagnosis, thereby minimizing unnecessary interventions while maximizing the safety of follow-up.

2. Methods

2.1. Study design and setting

This retrospective cohort study included patients with GTD who developed persistent low-level real hCG during follow-up. Patients were identified from the database of the Rio de Janeiro Trophoblastic Disease Center, located at the Maternity School of the Federal University of Rio de Janeiro (ME-UFRJ), Brazil, and from the private practice of one of the authors (A.B.).

The study period extended from January 1, 2000, to December 31, 2022. During this interval, all patients with GTD were managed according to contemporary international guidelines, including FIGO recommendations, and underwent serial hCG monitoring as part of routine clinical follow-up [1,2,32,33].

2.2. Population

Eligible patients were those with a previous diagnosis of HM or GTN who had achieved remission, either spontaneous remission following molar evacuation or complete remission after chemotherapy for GTN, and subsequently developed persistent low-level real hCG, defined as serum hCG ≤100 IU/L persisting for at least 3 consecutive months, in the absence of clinical, radiological, or biochemical evidence of pregnancy or active disease [2,19].

For analytical purposes, patients were stratified into two distinct clinical groups according to the context in which persistent low-level real hCG was identified: (1) patients under postmolar surveillance following evacuation of a hydatidiform mole (HM), according to the follow-up recommendations in effect during the study period (historically 6 months after complete HM and 3 months after partial HM, subsequently reduced to 3 and 1 month, respectively, following the 2020 FIGO update [20]); and (2) patients under surveillance after achieving complete remission of GTN, defined as normalization of serum hCG to <5 IU/L following completion of chemotherapy according to contemporary FIGO recommendations, who underwent at least 12 months of post-remission surveillance [20]. Only patients who subsequently developed persistent low-level real hCG while under surveillance were included. During the follow-up, hCG could fluctuate over time, with intermittent rises, plateaus, and subsequent declines while remaining ≤100 IU/L.

Given the rarity of persistent low-level real hCG after GTD, no formal a priori sample size calculation was performed. All consecutive eligible patients identified during the study period were included, and the

sample size was therefore determined by the total number of cases meeting the predefined eligibility criteria.

Exclusion criteria were: ectopic HM, twin HM, prior hysterectomy performed either during molar evacuation or as primary treatment of GTN, incomplete medical records, loss to follow-up, pregnancy during surveillance, and false-positive hCG results confirmed after clinical evaluation.

The study was designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology recommendations for cross-sectional studies.

2.3. Management

Patients with persistent low-level real hCG were counseled regarding the uncertain clinical significance of this condition and the rationale for conservative management. After providing informed consent, they underwent weekly serum hCG monitoring and were managed expectantly until either spontaneous hCG normalization occurred or FIGO diagnostic criteria for GTN were fulfilled [2]. In patients who developed persistent low-level real hCG after achieving remission of GTN, a complete FIGO-based assessment for uterine and metastatic disease was performed [2]. Patients without evidence of active disease were managed expectantly with serial hCG monitoring, performed weekly in cases of rising hCG levels and biweekly in cases of plateau values. Treatment was initiated only when hCG evolution fulfilled FIGO criteria for GTN or when hCG levels exceeded 100 IU/L. Throughout follow-up, strict hormonal contraception was recommended to avoid pregnancy, preserve the interpretability of serial hCG measurements [34,35], and minimize potential interference from pituitary gonadotropin production.

Patients with persistent low-level real hCG who remained clinically stable were counseled that conception could be attempted after 12 months of surveillance. Those who did not conceive remained under serial hCG monitoring and were followed for a minimum of 24 months after remission, regardless of whether they were managed expectantly or received chemotherapy. This surveillance period was considered adequate for detecting delayed disease progression and late GTN relapse.

Serum hCG measurements were performed throughout the study period using automated chemiluminescent immunoassays. Until 2018, hCG was measured using the Immulite platform manufactured by Diagnostic Products Corporation (DPC), whereas following laboratory standardization, all subsequent measurements were performed using the Immulite platform from Siemens Healthcare Diagnostics. Given the continuity of the assay platform, hCG results were considered comparable throughout the study period.

The FIGO criteria for diagnosis, staging, and prognostic classification of GTN are summarized in Supplementary Table 1 [2,32,33]. Supplementary Table 2 details the investigations used for metastatic evaluation and disease staging, whereas treatment protocols are presented in Supplementary Table 3.

2.4. Clinical variables

Demographic, clinical, laboratory, treatment, and follow-up data were extracted from medical records.

The following variables were collected from medical records: age at diagnosis (years); number of pregnancies; parity; gestational age at HM evacuation (weeks); occurrence of clinical symptoms at diagnosis [vaginal bleeding, hyperemesis gravidarum, enlarged uterus for gestational age, preeclampsia, theca lutein cysts, hyperthyroidism, and acute respiratory distress syndrome – Supplemental Table 4 presents the definition of each of these conditions]; preevacuation hCG level (international units per liter - IU/L); and time to disease remission (weeks).

Variables related to persistent low-level real hCG included the time from remission to the onset of persistent low-level real hCG (weeks) and the time from detection of persistent low-level real hCG to hCG elevation >100 IU/L, when applicable.

2.5. Outcomes

Outcomes definitions used in the present study are summarized in Supplemental Table 5.

2.6. Statistical analysis

Categorical variables were expressed as absolute and relative frequencies. In contrast, continuous variables were summarized as median, interquartile range (IQR), minimum, and maximum values due to the small sample size and non-normal distribution of the data.

Comparisons between independent groups were performed using Chi-Square or Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables.

Additionally, risk differences (RD) with corresponding 95% confidence intervals (95%CI) were calculated for selected dichotomized variables to estimate the absolute difference in the occurrence of postmolar GTN and relapsed GTN between exposure groups. Variables were categorized according to clinically relevant cutoff values. Positive RD values indicated a higher absolute risk of the outcome in the exposed group compared with the reference group. RD whose 95%CI did not include zero were considered statistically significant. Considering the small sample size and the low frequency of events in some cells, an approach based on absolute risk measures was adopted instead of traditional parametric regression models, which showed numerical instability and high variability in the estimates.

The results were interpreted with emphasis on effect magnitude and confidence intervals rather than solely on statistical significance based on *p*-values. This approach was justified by the fact that, in small samples, hypothesis tests have limited statistical power, whereas confidence intervals provide a more informative measure of the precision of the estimates [36].

Logistic regression models were initially considered for multivariable analysis; however, their application proved inadequate because of the instability associated with the small sample size and the occurrence of cells with low or zero frequencies. Under these conditions, maximum likelihood-based methods may produce biased estimates or excessively wide confidence intervals, even when correction techniques such as penalized logistic regression (Firth method) are applied [37].

Therefore, the findings should be interpreted as exploratory and hypothesis-generating, being suitable for identifying trends of association but insufficient for definitive causal inference or precise effect estimation.

A significance level of 5% was adopted; however, the primary interpretation was based on the consistency between effect magnitude, direction of association, and confidence interval precision.

Statistical analyses were performed using SAS OnDemand for Academics (SAS Institute Inc., Cary, NC, USA).

2.7. Ethical considerations

The research protocol was approved by the Institutional Review Board of the ME-UFRJ (77,833,124.2.0000.5275).

3. Results

During the study period, 7304 patients with GTD were managed at the participating centers. Among them, 168 developed persistent low-level hCG during follow-up. After systematic evaluation, 96 patients were excluded according to the predefined criteria detailed in Supplementary Table 6, leaving 72 patients available for outcome analysis (Fig. 1). Based on the cases available for analysis, the prevalence of

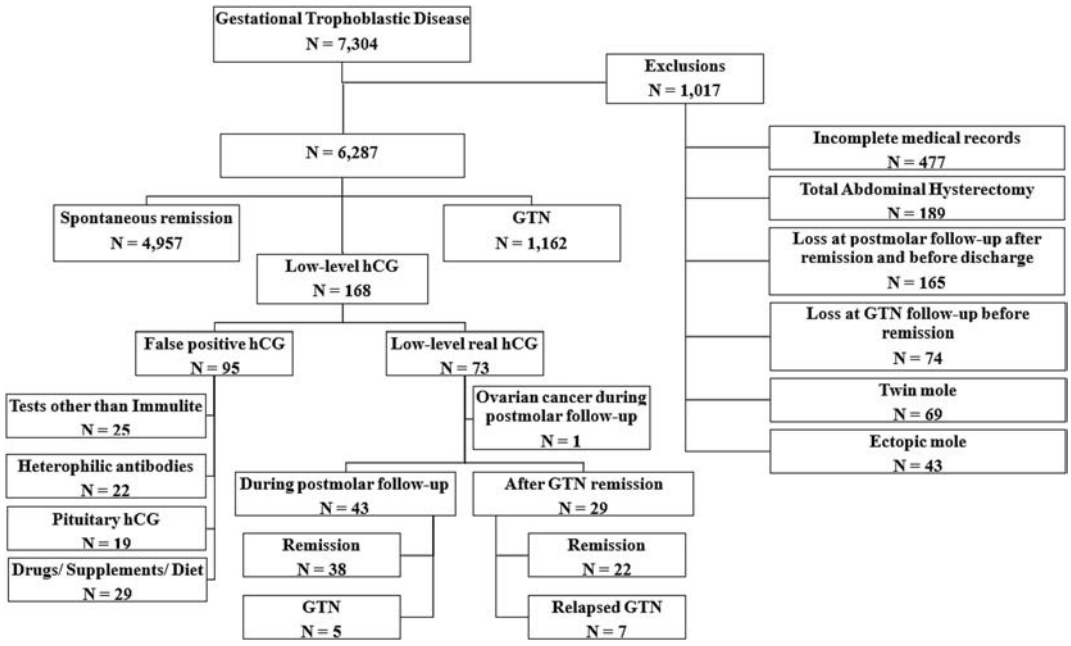

Fig. 1. Study flowchart and clinical outcomes of patients with persistent low-level real human chorionic gonadotropin (hCG) after gestational trophoblastic disease.
GTN. Gestational trophoblastic neoplasia.

persistent low-level real hCG was 0.9% (72/7304) among all patients with GTD managed during the study period.

Among the 72 patients included, spontaneous hCG normalization occurred in 88.4% (38/43) of those identified during postmolar surveillance and 75.9% (22/29) of those identified after GTN remission, whereas 11.6% (5/43) and 24.1% (7/29), respectively, subsequently developed GTN (Fig. 1).

Table 1 summarizes the clinical characteristics of patients who developed persistent low-level real hCG during postmolar surveillance according to their subsequent clinical outcome. Patients who subsequently developed postmolar GTN differed from those who achieved spontaneous remission by presenting more frequently with vaginal hemorrhage at diagnosis (100.0% vs. 23.7%, $p = 0.002$), higher preevacuation hCG levels (135,000 vs. 97,000 IU/L, $p = 0.009$), and a

Table 1
Clinical characteristics and outcomes of patients with persistent low-level real human chorionic gonadotropin (hCG) during postmolar surveillance.

Characteristics	$N = 43$	Remission $N = 38$	Postmolar GTN $N = 5$	p-value*
Age (years)	28 (25–29) [20–42]	28 (25–29) [20 – 40]	33 (29–35) [25–42]	0.0830
Gravidity				0.9161
1	18 (41.86)	16 (42.11)	2 (40.00)	
2	19 (44.19)	17 (44.74)	2 (40.00)	
3	6 (13.95)	5 (13.16)	1 (20.00)	
Parity				0.8023
0	25 (58.14)	22 (57.89)	3 (60.00)	
1	15 (34.88)	13 (34.21)	2 (40.00)	
2	3 (6.98)	3 (7.89)	0 (0.00)	
Gestational age at diagnosis (weeks)	9 (9–10) [7 - 12]	9 (9–10) [7 – 12]	9 (9–9) [8 – 10]	0.7628
Hemorrhage	14 (32.56)	9 (23.68)	5 (100.00)	0.0021
Enlarged uterus for gestational age	10 (23.26)	8 (21.05)	2 (40.00)	0.5749
Theca lutein cysts larger than 6 cm	8 (18.60)	6 (16.79)	2 (40.00)	0.2276
Preeclampsia	2 (4.65)	2 (5.26)	0 (0.00)	0.9999
Hyperemesis	4 (9.30)	3 (7.89)	1 (20.00)	0.4019
Preevacuation hCG level (IU/L)[1]	100,000 (88,000 - 120,000) [59,000–200,000]	97,000 (65,000 - 110,000) [59,000–180,000]	135,000 (120,000 - 150,000) [110,000−200,000]	0.0093
Time to remission (weeks)	9 (8–10) [7 – 14]	9 (8–10) [7 – 12]	10 (10−12) [10 – 14]	0.0084
Time to achieve persistant real low hCG levels (weeks)	8 (6–8) [5 - 24]	7 (6–8) [5 – 8]	19 (16–22) [12 – 24]	0.0002
Time to achieve hCG >100 IU/L[1] (months)	0 (0–0) [0–19]	0 (0–0) [0–0]	14 (11–17) [9 – 19]	< 0.0001

1. IU/L. International units per liter.
Continuous variables are presented as median (IQR) [min–max], and categorical variables as n (%). The Mann–Whitney *U* test was used for continuous variables, and the chi-square or Fisher's exact test for categorical variables, as appropriate.

longer time to remission (10 vs. 9 weeks, $p = 0.008$). Patients who subsequently developed postmolar GTN developed persistent low-level real hCG later during follow-up (19 vs. 7 weeks, $p < 0.001$), with hCG levels exceeding 100 IU/L after a median of 14 months (IQR: 11–17 months). No significant differences were observed between groups in gravidity, parity, gestational age at diagnosis, uterine enlargement, theca lutein cysts, preeclampsia, or hyperemesis, although patients who progressed to GTN tended to be older than those who achieved spontaneous remission.

Supplemental Table 7 summarizes the characteristics of the five patients who developed postmolar GTN following persistent low-level real hCG. Four patients achieved remission with first-line treatment, whereas one developed chemoresistant disease. Owing to the small number of events, meaningful comparisons between groups were limited. The patient who developed chemoresistance presented with hyperemesis at diagnosis, higher pre-evacuation hCG levels, and a longer time to remission than patients who responded to first-line therapy. No patient developed metastatic disease, required multiagent chemotherapy, or died during follow-up.

Table 2 summarizes the characteristics of patients who developed persistent low-level real hCG after achieving remission of GTN. Compared with those who subsequently re-achieved hCG remission, patients who developed relapsed GTN were older (39 vs. 32.5 years, $p = 0.020$) and had higher preevacuation hCG levels at the time of their antecedent HM (160,000 vs. 125,000 IU/L, $p = 0.025$). The most striking difference between groups was the timing of persistent low-level real hCG development. Patients who experienced GTN relapse developed persistent low-level real hCG substantially later after remission than those who remained disease-free (32 vs. 12.5 weeks, $p < 0.001$). Furthermore, among patients who relapsed, hCG levels exceeded 100 IU/L after a median of 6 months (IQR, 5–7 months), whereas no patient in the non-relapse group reached this threshold ($p < 0.001$). No significant differences were observed regarding gravidity, parity, gestational age at diagnosis, clinical presentation, pretreatment hCG level, metastatic disease, histology of choriocarcinoma, type of chemotherapy, time to remission, number of chemotherapy cycles required to achieve remission, or consolidation treatment.

Supplemental Table 8 compares patients with relapsed GTN who achieved remission with single-agent chemotherapy and those who required multiagent chemotherapy. Patients treated with polychemotherapy were older (43 vs. 35.5 years, $p = 0.034$) and presented with higher preevacuation hCG levels during the antecedent HM (270,000 vs. 150,000 IU/L, $p = 0.034$). They also had higher pretreatment hCG levels at GTN diagnosis (75,000 vs. 10,250 IU/L, $p = 0.034$) and a longer interval between HM evacuation and initiation of chemotherapy (5 vs. 3 months, $p = 0.022$). Patients requiring

Table 2
Clinical characteristics of patients with persistent low-level real human chorionic gonadotropin (hCG) after remission of gestational trophoblastic neoplasia according to the subsequent development of relapsed gestational trophoblastic neoplasia.

Characteristics	$N = 29$	No relapsed GTN $N = 22$	Relapsed GTN $N = 7$	p-value
Age (years)	34 (30–39) [25–44]	32.50 (28–37) [25–42]	39 (33–43) [32–44]	0.0203
Gravidity				0.1825
1	11 (37.93)	9 (40.91)	2 (28.57)	
2	13 (44.83)	11 (50.00)	2 (28.57)	
3	4 (13.79)	2 (9.09)	2 (28.57)	
4	1 (3.45)	0 (0.00)	1 (14.29)	
Parity				0.2913
0	14 (48.28)	11 (50.00)	3 (42.86)	
1	12 (41.38)	10 (45.45)	2 (28.57)	
2	3 (10.34)	1 (4.55)	2 (28.57)	
Gestational age at diagnosis (weeks)	9 (9–10) [8 – 11]	9 (9–10) [8 – 10]	9 (9–10) [8 – 11]	0.3498
Hemorrhage	20 (68.97)	16 (72.73)	4 (57.14)	0.6424
Enlarged uterus for gestational age	11 (37.93)	7 (31.82)	4 (57.14)	0.3746
Theca lutein cysts larger than 6 cm	6 (20.69)	4 (18.18)	2 (28.57)	0.6119
Preeclampsia	4 (13.79)	2 (9.09)	2 (28.57)	0.2381
Hyperemesis	5 (17.24)	3 (13.64)	2 (28.57)	0.5688
Preevacuation hCG level (IU/L)[1]	140,000 (100,000 - 170,000) [79,000–300,000]	125,000 (90,000 - 150,000) [79,000–250,000]	160,000 (145,000 - 270,000) [110,000−300,000]	0.0247
Time to beginning of chemotherapy (months)	4 (4–4) [3 – 5]	4 (4–4) [3 – 5]	4 (3–5) [3 – 5]	0.9998
Pretreatment hCG level (IU/L)[1]	35,000 (11,000 - 72,000) [2500–120,000]	32,000 (11,000 - 72,000) [2500–120,000]	35,000 (9500–75,000) [7500–90,000]	0.8784
Metastatic disease at GTN presentation	7 (24.14)	5 (22.73)	2 (28.57)	0.9998
Histology of CCA	5 (17.24)	3 (13.64)	2 (28.57)	0.5688
Type of chemotherapy				0.1315
Single	23 (79.31)	19 (86.36)	4 (57.14)	
Multiagent	6 (20.69)	3 (13.64)	3 (42.86)	
Time to remission (weeks)	14 (12–17) [8 – 18]	15 (12–17) [8 – 18]	13 (12–14) [11 – 17]	0.4546
Number of chemotherapy cycles until remission	6 (6–8) [4 – 9]	6 (5–9) [4 – 9]	6 (6–7) [5 – 8]	0.7136
Number of chemotherapy consolidation cycles	3 (1–3) [0–3]	3 (2–3) [0−3]	1 (0–3) [0–3]	0.0799
Time to achieve persistant real low hCG levels (weeks)	14 (11–19) [9–48]	12.50 (10–15) [9 – 19]	32 (27–44) [23–48]	< 0.001
Time to achieve hCG >100 UI/L[1] (months)	0 (0–0) [0–8]	0 (0–0) [0–0]	6 (5–7) [4 – 8]	< 0.001

1. IU/L. International units per liter.
Continuous variables are presented as median (IQR) [min–max], and categorical variables as n (%). The Mann–Whitney U test was used for continuous variables, and the chi-square or Fisher's exact test for categorical variables, as appropriate.

multiagent chemotherapy developed persistent low-level real hCG earlier after remission (27 vs. 40 weeks, p = 0.034) and reached hCG levels >100 IU/L sooner than those successfully treated with a single-agent regimen (5 vs. 7 months, $p = 0.031$). Metastatic disease occurred exclusively among patients treated with polychemotherapy (100.0% vs. 0.0%, $p = 0.029$). No deaths were observed during follow-up.

Fig. 2 presents the absolute RD for the occurrence of postmolar GTN among patients with persistent low-level real hCG during postmolar follow-up, according to selected clinical variables. Age ≥ 27 years was associated with an absolute increase of 11.4 percentage points (p.p.) in the risk of postmolar GTN compared with younger patients; however, this association did not reach statistical significance (RD:11.4%, 95% CI:6.6–29.4). In contrast, vaginal hemorrhage at diagnosis was associated with a significantly higher risk of postmolar GTN, corresponding to an absolute increase of 35.7 p.p. (95%CI;10.6–60.8). Similarly, pre-evacuation hCG levels ≥100,000 IU/L were associated with an absolute increase of 22.7 p.p. in the risk of postmolar GTN (95%CI:5.2–40.2). Patients who required ≥7 weeks to develop persistent low-level real hCG also demonstrated a significantly increased risk of postmolar GTN, with an absolute RD of 16.6 p.p. (95%CI:3.3–30.0). Variables whose 95%CI did not cross the null value were considered significantly associated with the occurrence of postmolar GTN. Detailed calculations and contingency tables used to derive these RD are provided in Supplementary Table 9.

Fig. 3 presents the absolute RD for relapsed GTN among patients with persistent low-level real hCG after remission, according to selected clinical variables. Age ≥ 34 years was associated with an absolute increase of 19.1 p.p. in the risk of relapse (95%CI:11.0–49.1). Similarly, pre-evacuation hCG levels ≥100,000 IU/L were associated with a 30.4 percentage-point increase in the risk of relapsed GTN (95% CI:11.6–49.2). The strongest association was observed for patients who required ≥14 weeks to develop persistent low-level real hCG, corresponding to an absolute increase of 43.8 p.p. in the risk of relapse (95%CI:19.4–68.1). In contrast, hemorrhage at diagnosis, pretreatment hCG levels ≥35,000 IU/L, and metastatic disease were not significantly associated with relapsed GTN, as their confidence intervals included the null value. Detailed data underlying these RD estimates are presented in Supplementary Table 10.

4. Discussion

This study provides important insights into the clinical significance of low-level real hCG after GTD, a rare but clinically challenging condition that affects fewer than 1% of patients with GTD, and often creates uncertainty regarding the need for intervention [27–31]. Because persistent detectable hCG is frequently interpreted as evidence of active disease, affected patients may be exposed to unnecessary treatments, including chemotherapy and even hysterectomy [27–31]. Most patients experienced spontaneous hCG normalization, both during postmolar surveillance (88.4%) and after GTN remission (75.9%). Importantly, delaying treatment until fulfillment of FIGO criteria did not appear to compromise outcomes, even in patients with persistently detectable hCG for more than three months, as subsequent GTN remained highly curable with low rates of chemoresistance and no disease-related deaths.

A possible explanation for these findings is that persistently low-level hCG may reflect only limited trophoblastic activity. In such a biological state, the amount of actively proliferating trophoblastic tissue may be insufficient to produce a meaningful response to chemotherapy, which could explain the poor efficacy of treatment reported in historical series of patients in this setting [12,13]. Conversely, deferring treatment until hCG levels demonstrate sustained growth or fulfill FIGO criteria for active GTN may allow therapy to be administered at a stage when trophoblastic proliferation is more clearly established and therefore more susceptible to cytotoxic agents. Although this hypothesis remains speculative, it provides a biologically plausible explanation for why expectant management did not appear to adversely affect oncologic outcomes in the present study.

These findings also extend previous observations from our group regarding patients with HM who presented with persistently detectable hCG levels that remained continuously declining beyond an expected surveillance period of 6 months [38]. In this scenario, we demonstrated that most patients achieved spontaneous remission without chemotherapy and that delaying treatment until objective evidence of GTN emerged did not adversely affect oncologic outcomes [38]. These findings ultimately contributed to the removal of persistent elevated hCG beyond 6 months as a FIGO diagnostic criterion for GTN [33].

The current study addresses an even more challenging clinical scenario. Unlike patients with continuously declining hCG levels, the patients included in the present cohort exhibited persistent low-level real hCG that frequently fluctuated, occasionally increased, or remained stable over time. However, despite these variations, hCG values remained ≤100 IU/L and did not fulfill FIGO diagnostic criteria for active GTN [2,20,21]. These findings suggest that small populations of residual trophoblastic cells may remain biologically active and continue producing low amounts of hCG for prolonged periods without necessarily representing malignant disease. Although the biological mechanisms underlying this phenomenon remain incompletely understood, our

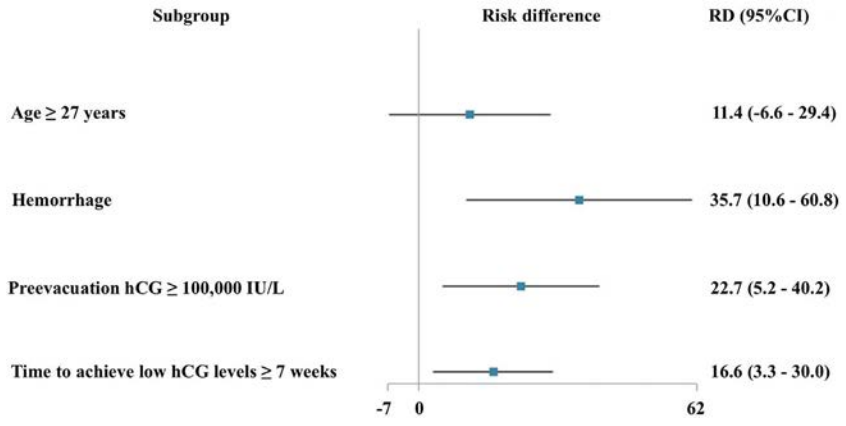

Fig. 2. Absolute risk differences (RD) for the development of postmolar gestational trophoblastic neoplasia among patients with persistent low-level real human chorionic gonadotropin (hCG) during postmolar surveillance.
CI. Confidence interval.
IU/L. International units per liter.

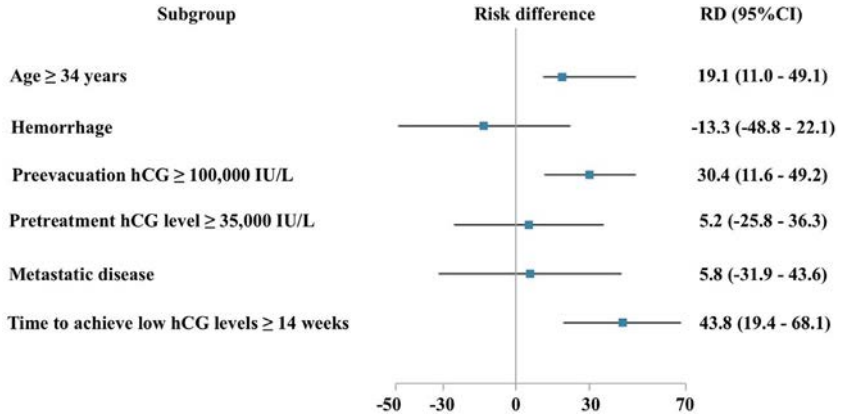

Fig. 3. Absolute risk differences (RD) for relapsed gestational trophoblastic neoplasia among patients with persistent low-level real human chorionic gonadotropin (hCG) after remission of gestational trophoblastic neoplasia.
CI. Confidence interval.
IU/L. International units per liter.

data indicate that careful surveillance remains the most appropriate management strategy in the absence of objective evidence of GTN. Such an approach minimizes the risk of overtreatment and avoids exposing patients to the potential morbidity of unnecessary chemotherapy or surgery while maintaining oncologic safety [27–31].

The greatest diagnostic uncertainty occurred among patients who had previously achieved remission after chemotherapy for GTN and subsequently presented with renewed elevations in hCG above the normal range (5 IU/L). In these cases, relapsed GTN represented the principal diagnostic concern. However, the behavior of hCG was inconsistent with active disease. Instead of the sustained increase typically observed in relapsed GTN, hCG values fluctuated over time, with intermittent rises, plateaus, and subsequent declines while remaining ≤100 IU/L. This erratic biological behavior created uncertainty regarding whether the observed elevations reflected true disease reactivation or persistent low-level hCG production by residual trophoblastic cells.

An important finding of the present study was the identification of clinical characteristics associated with a higher likelihood of subsequent GTN among patients presenting with persistent low-level real hCG. Although most patients experienced spontaneous normalization of hCG levels, those with higher preevacuation hCG concentrations and a longer interval between remission and the onset of persistent low-level real hCG were consistently more likely to develop active disease. Notably, delayed emergence of low-level real hCG was identified as a risk marker in both clinical scenarios evaluated, suggesting that the timing of its appearance may provide clinically meaningful prognostic information and help identify patients requiring closer surveillance. These findings indicate that persistent low-level real hCG should not be viewed as a homogeneous condition and raise the possibility that late-onset low-level hCG reflects residual trophoblastic populations with greater malignant potential. Whether this phenomenon represents trophoblastic dormancy, persistence of biologically active trophoblastic clones, or simply a surrogate marker of the original disease burden remains unknown and warrants further investigation [17].

Previous studies describing patients with persistent low-level real hCG have reported that a proportion of these cases may eventually develop active malignancy and have recommended prolonged surveillance, including serial measurements of hyperglycosylated hCG (hCG—H) when available [7,8,11–14]. Produced predominantly by invasive cytotrophoblasts, hCG-H has been proposed as a marker of active trophoblastic proliferation and disease reactivation [39,40]. Hyperglycosylated hCG testing was not available for routine clinical use at our institution during the study period. Moreover, the clinical utility of this biomarker remains limited by issues related to assay availability, standardization, and inconsistent performance across studies [25,26]. Consequently, after detailed counseling and informed consent, patients were managed with careful surveillance based on serial hCG measurements and clinical assessment alone. This strategy appeared to be safe in our cohort, as treatment could be deferred until objective FIGO criteria for GTN were fulfilled without apparent compromise of oncologic outcomes.

The present study has several important strengths. To our knowledge, this represents the largest reported cohort of patients with persistent low-level real hCG after GTD, a condition for which the available literature remains limited to small retrospective series and isolated case reports. In addition, all patients were managed within specialized GTD reference centers by the same clinical team, according to standardized follow-up protocols and using a consistent hCG monitoring strategy throughout the study period. These characteristics reduced variability in clinical management and strengthened the internal validity of the findings. Nevertheless, some limitations should be acknowledged. The rarity of the condition resulted in a limited number of outcome events, precluding robust multivariable analyses and preventing the development of a validated prediction model. Furthermore, although this is the largest cohort reported to date, all patients were managed within the same specialized referral group and may therefore represent only one clinical phenotype of persistent low-level real hCG. Additional multicenter studies including larger and more diverse populations are needed to confirm our findings, refine risk stratification, and further elucidate the biological mechanisms underlying this intriguing condition.

In conclusion, persistent low-level real hCG after GTD resolves spontaneously in more than 75% of patients. Even when GTN subsequently develops, treatment initiated only after fulfillment of FIGO criteria does not appear to compromise outcomes. Careful surveillance, therefore, represents the most appropriate management strategy, minimizing unnecessary interventions while maintaining oncologic safety.

CRediT authorship contribution statement

Raphael Alevato: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Antônio Braga:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gabriela Paiva:** Writing – review & editing, Visualization. **Edward Araujo Júnior:** Writing – review & editing, Visualization. **Sue Yazaki Sun:** Writing – review & editing, Visualization. **Luana Giongo Pedrotti:** Writing – review & editing, Methodology,

Formal analysis. **Marina Bessel:** Writing – review & editing, Methodology, Formal analysis. **Solange Artimos de Oliveira:** Writing – review & editing, Visualization. **Joffre Amim-Junior:** Writing – review & editing, Visualization. **Jorge Rezende-Filho:** Writing – review & editing, Visualization. **Ross Berkowitz:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Neil Horowitz:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2026.08.008.

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