Frequency and factors associated with gestational trophoblastic neoplasia in patients treated at a referral center in western Brazil

https://doi.org/10.56238/sevened2024.007-001

Raphael Lopes Ferraz[1], Camilla Soares Gomes[2], Milena Cecília Barroso Fernandes[3], Letícia Soares da Silva[4], Monica Maria Bandeira de Melo[5], Marcio Antônio Couto Ferreira[6], Bruno Monção Paolino[7] and Izildinha Maestá[8]

[1] Resident Physician of Gynecology and Obstetrics at the Federal University of Amazonas (UFAM)/ Getúlio Vargas University Hospital (HUGV)
-Graduated in medicine from Nilton Lins University (UNL), resident in gynecology and obstetrics HUGV / UFAM
E-mail: raphalopesferraz@gmail.com
[2] Undergraduate student at the University of the State of Amazonas (UEA) School of Health Sciences – ESA/UEA
- Medical student at UEA
E-mail: csg.med18@uea.edu.br
[3] Undergraduate student at the University of the State of Amazonas (UEA) School of Health Sciences – ESA/UEA
- Medical student at UEA
E-mail: mcbf.med19@uea.edu.br
[4] Undergraduate student at the University of the State of Amazonas (UEA) School of Health Sciences – ESA/UEA
- Medical student at UEA
E-mail: lsds.med21@uea.edu.br
[5] Gynecologist at the Oncology Control Center Foundation of the State of Amazonas (FCECON)
- Graduated in Human Medicine from the Federal University of Amazonas (UFAM - 1982), Title of specialist in gynecology and obstetrics (FEBRASGO) Title of specialist in Colposcopy (ABPTGIC -1986)
E-mail: monicabandeira@ymail.com
[6] Professor at the Faculty of Social Studies (FES) of the Federal University of Amazonas (UFAM)
Degree in Statistics, a postgraduate degree in Industrial Statistics, a Master's degree in Production Engineering and a PhD in Environmental Sciences and Sustainability in the Amazon from the Federal University of Amazonas (UFAM).
E-mail: macouto@ufam.edu.br
[7] Doctor from the São Paulo State University (Unesp-Botucatu)/ Professor of women's health at the University of the State of Amazonas (UEA) School of Health Sciences – ESA/UEA
Degree in Medicine from the University of Rio de Janeiro (UNIRIO, 2005). Medical Residency in Gynecology and Obstetrics at the Fernandes Figueira Institute/Oswaldo Cruz Foundation (IFF-FIOCRUZ 2009). Title of Specialist in Gynecology and Obstetrics by the Brazilian Federation of Gynecology and Obstetrics (TEGO:0063/09). Medical Residency in Mastology from the Oncology Control Center Foundation of the State of Amazonas (FCECON 2016). Full Member of the Brazilian Society of Mastology (TEMA: 2017). Assistant Professor of the Discipline of Women's Health at the University of the State of Amazonas (UEA). Master's degree in surgery from the Graduate Program in Surgery (PPGRACI) of the Federal University of Amazonas (UFAM) in 2018. PhD in the Graduate Program in Obstetrics and Gynecology at São Paulo State University (Unesp - Botucatu), in 2023.
E-mail: bpaolino@uea.edu.br
[8] Doctor Professor and associate professor at the São Paulo State University (Unesp-Botucatu) / Hospital da Clínicas da Faculdade de Medicina de Botucatu
Bachelor's degree in Human Medicine from São Paulo State University (1987), Master's degree in Surgery [Botucatu] from São Paulo State University (1996) and PhD in Gynecology and Obstetrics [Botucatu] from São Paulo State University (1999). Postdoctoral Fellow at the New England Trophoblastic Disease Center, Harvard Medical School, in the position of Associate Researcher (2011, 2013, 2015, 2017, 2019), producing scientific articles together with professors/researchers from Harvard Medical School and projects related to gestational trophoblastic disease. National scientific exchange with the Brazilian Network for Research in Trophoblastic Diseases. He is currently an Adjunct Professor III in a Regime of Full Dedication to Teaching and Research (RDIDP) at the São Paulo State University and Member of the international advisory committee ISSTD - International Society for the Study of the Trophoblastic Diseases Officer for South America. Leader of the CNPq research group Center for Studies in Trophoblastic Diseases, certified on 12/09/2014. CNPq Research Productivity Scholarship - Level 2. Specialization in Gynecology and Obstetrics, working in extension, teaching and research.
E-mail: i.maesta@unesp.br

ABSTRACT

Introduction:Gestational Trophoblastic Disease (GTD) is a rare complication in pregnancy that is divided into two groups: the benign form Hydatidiform Mole (MH) and the malignant form Gestational Trophoblastic Neoplasia (GTN). GTN is divided into four types of histopathological disorders, namely: invasive mole (MI), choriocarcinoma, placental site tumor (PTTT) and epithelioid trophoblastic tumor (TTE) Objectives: To identify the frequency of GTN in patients treated at the referral center of the Oncology Control Center Foundation of the State of Amazonas (FCECON) from 2011 to 2018, specifying their sociodemographic data, clinical data and disease characteristics and mortality. Methodology: This is a retrospective observational study that included patients diagnosed and treated with GTN at FCECON from 2011 to 2018. Data were obtained from medical records, then tabulated and descriptive statistics were performed. Results: The frequency of GTN was 11 patients, aged 29.8 years, most of them brown (72.7%), the most frequent clinical picture was vaginal bleeding (45.4%), IM was the most common form of GTN (54.5%), the low-risk classification was the most frequent (63.6%), the lung was the main site of metastases (54.5%) and mortality was 27.3% of the cases. Conclusion: Despite the advances in diagnosis and treatment described in recent decades, GTN in Amazonas still has a high mortality rate.

Keywords: Full mole, Partial mole, Choriocarcinoma .

INTRODUCTION

Gestational Trophoblastic Disease (GTD) is a complication of pregnancy that occurs in the West in a ratio of one case to 1,000 to 2,000 pregnancies (DE ANDRADE, 2009). Most molar pregnancies have the classic appearance on ultrasound from the first trimester, represented by the absence of an embryo and multiple cysts of different sizes (RAMOS et al., 2021). Gestational trophoblastic disease is divided into two groups: hydatidiform mole (MH) and gestational trophoblastic neoplasia (GTN). MH is the benign form of the disease and presents in two different clinical forms, with distinct morphological, genetic, and clinical characteristics: complete hydatidiform mole (CHM) and partial hydatidiform mole (MHP) (SECKL et al., 2013, CARDOSO et al., 2020).

Gestational trophoblastic neoplasia (GTN) is divided into four histopathological types, namely: invasive mole (MI), choriocarcinoma, placental site tumor (SPTT), and epithelioid trophoblastic tumor (TTE) (SECKL et al., 2013) IM and choriocarcinoma are highly responsive to chemotherapy, whereas SPTT and TTE require surgical intervention requiring chemotherapy in selected patients (NGAN et al., 2018). Approximately 50% of all cases of GTN occur after molar pregnancies, the remaining 50% originate from non-molar pregnancies (25% after miscarriages or ectopic pregnancies and 25% after childbirth) (GOLDSTEIN; BERKOWITZ, 2012).

Postmolar GTN is diagnosed according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO), which establishes the curve as plateau or ascent. The plateau is defined by four or more hCG values for at least three consecutive weeks (1st, 7th, 14th, and 21st days), while an increase in the hCG value by 10% or more for at least two consecutive weeks (1st, 7th, and 14th days) indicates an upward curve. Additionally, any increase in hCG detectable for six months after molar dissection; or result of histopathological examination of choriocarcinoma, TTSP) and TTE will be considered for diagnosis NTG (NGAN et al., 2015)

The staging of GTN is established by FIGO (*FIGO ONCOLOGY COMMITTEE,* 2002) in conjunction with the modified prognostic scoring system of the World Health Organization (*WHO,* 1983). Stages FIGO I–III with a score of 0-6 identify low-risk NTG, whereas stage FIGO IV, or any stage accompanied by a score of ≥7, indicate a high risk of single-agent chemotherapy resistance (QT) and risk of relapse. In such cases, initial treatment with combination chemotherapy is recommended in order to optimize outcomes (LITKOUHI; AL KHAN, 2017; NGAN et al., 2015). Single-agent chemotherapy, methotrexate or actinomycin D, is used in patients with low-risk GTN, while multi-agent chemotherapy regimens such as EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine) or EP-EMA (etoposide, methotrexate, actinomycin-D, cisplatin) are indicated in those with high-risk NTG (LITKOUHI; AL KHAN, 2017; NGAN et al., 2015).

OBJECTIVE(S)

The general objective of the research was to find out the frequency of NTG in patients treated at the Oncology Control Center Foundation of the State of Amazonas (FCECON) from 2011 to 2018. Specifically, to describe sociodemographic data of patients diagnosed with GTN treated at the follow-up outpatient clinic at FCECON from 2011 to 2018 (age and race) and clinical data (gestational age (GA), clinical picture and surgical treatment), Describe the types of GTN; Classify NTGs into high and low risk according to FIGO criteria; Describe forms of treatment, Describe main sites of metastases and Calculate mortality.

METHODOLOGY

This is an observational, retrospective, descriptive, and analytical study that included patients diagnosed with GTN who underwent treatment at the FCECON referral center from 2011 to 2018. Patients who had a diagnosis of GTN and underwent treatment at FCECON from January 2011 to December 2018 were included, and patients with incomplete data in their medical records were excluded.

The research sample was estimated at 11 patients, based on the search for ICD in the institution's medical records. The study was carried out at FCECON, a state tertiary hospital that is a reference in cancer treatment in the northern region of Brazil. In this reference center, all care is integrated into the Unified Health System (SUS). Data were obtained from secondary data sources, such as physical and electronic medical records. The information was included in an EXCEL spreadsheet database and later transferred to the Epi-Info 7 program for tabulation and descriptive statistical analysis. The work was approved by the CEP of FCECON, CAAE 32779020.3.0000.0004.

RESULTS AND DISCUSSION

Table - 1 Epidemiological characteristics of patients in the Manaus RC from 2011 to 2018

Variables	**Study Population N = 11 (100%)**
Middle Ages	29.8 (23 - 39) years
Race	White 0 (0%) Indigenous 2 (18.2%) Black 1 (9.1%) Parda 8 (72,7%)
Median Distance to RC	80 (3,5 – 703) Km
Parity	2.4 (1 - 7) pregnancies

Source: Survey data

The frequency of GTN was 11 cases. The mean age of the patients in the study was 29.8 years (23 – 39 years), contrasting with the literature that reports an increased risk of the disease from 35 years of age (BRAGA et al., 2018). They were usually multiparous, with an average of 2.4

deliveries.

Although there is no report in the literature of the relationship between GTN and race, a higher number of patients declared themselves to be brown (72.7%), followed by indigenous patients (18.2%) was observed. The median distance between the patients' residence and the FCECON was 80 km, which is relevant since it is documented in the literature that distances greater than 80 km between the residence and the treatment center are a risk factor for the treatment and follow-up of these patients with reports of unfavorable outcomes. (CLARK et al., 2016). This data becomes very significant because Amazonas is the largest Brazilian state and has a small terrestrial communication network between its municipalities.

Table - 2 - Clinical and therapeutic characteristics of NTGs in the Manaus RC from 2011 to 2018

Variables	**Study Population N= 11(100%)**
Clinical presentation	Vaginal bleeding 5 (45.4%) No symptoms 4 (36.4%) Hemoperitoneum 1 (9.1%) AKI 1 (9.1%)
Gestational Age at Diagnosis	Known (13 weeks) 1 (9.1%) Unknown 10 (90.1%)
Surgical treatment	1Curettage 4 (36.4%) 2 or more curettages 2 (18.2%) Histerectomia 4 (36.4%) Not performed 1 (9%)

Source: Survey data

Table 2 shows that gestational age (GA) was identified in only one patient, and in 91% of the cases this basic and vitally important information was not available at the beginning of their treatment. Vaginal bleeding was the most common clinical condition in 5 patients (45.4%), which is consistent with the literature (DE ANDRADE, 2009). An important reflection on this topic is made with the differential diagnosis of first trimester hemorrhages, and the histopathological investigation of curettages of miscarriages is essential so that there is no underdiagnosis of GTD.

Regarding surgical treatment, it was observed that 36.4% of the patients underwent only one curettage, and 36.4% of them underwent hysterectomy. The discussion about the high number of hysterectomies is important to reflect on this procedure in the reproductive life of patients, as well as the standardization of treatment according to the recommendations of FIGO.

Table 3 shows that the origin of GTN was mainly IM in six cases (54.5%), followed by Choriocarcinoma with two cases (18.2%), which confirms the literature that cites that up to 50% of all cases of GTN occur after molar pregnancies (GOLDSTEIN; BERKOWITZ, 2012).

The most common histological subtype that originated the 6 cases of IM was MHC with four (66.6%) cases, followed by undefined mole in two (33.4%) cases, which is also consistent with the literature (GOLDSTEIN; BERKOWITZ, 2012)

Table - 3 - Clinical and therapeutic characteristics of NTGs in the Manaus RC from 2011 to 2018

Variables	**Study Population N= 11 (100%)**	
Evolution from spring to NTG	Grinding Wheel Invader 6 (54.5%) Choriocarcinoma 2 (18.2%) Metastatic GTN 3 (27.3%)	
Classification of tumors by the FIGO Score	High risk 4 (36.4%) Low Risk 7 (63.6%)	
Metastasis	Pulmonary Mesoxalpinge Nor metástase	6 (54,5%) 1 (9,1%) 4 (36,4%)
Mean hCG levels pre-chemotherapeutic (QT)		12656 (6,9 – 457.000) native/ml
Number of QT cycles		5,4 (1-10)
Types of QT	Single Agent Multi Agent	6 (54,5%) 5 (45,5%)
Evolution	Healing Death	8 (72,7%) 3(27,3%)

Source: Survey data

A total of 63.6% of tumors were classified as low risk by the FIGO score and 36.4% as high risk. Single-agent chemotherapy treatment was performed in 54.5% of patients, while 45.5% underwent multi-agent chemotherapy. The mean pre-chemotherapy hCG level was 12656 mUL/ml and the mean QT was 5.4 cycles.

The main site of metastasis was the lung in 54.5% of the cases, in agreement with data found in the literature. (FREITAS et al., 2020)

The mortality found was 27.3% of the patients, considered very high compared to the Brazilian average of 4% (FREITAS et al., 2020) and of the private centers in the city of Manaus where no deaths were observed (CABRAL et al., 2022). Despite the decrease in the morbidity and mortality of GTN in Brazil in recent decades, mainly due to advances in diagnosis, treatment and the organization and standardization of conducts in referral centers, the same did not occur in users of the public health system in Amazonas. It is noteworthy that, although uncommon, mortality from this highly curable disease is a sentinel marker of the quality of obstetric care provided by the health system.

CONCLUSION

The frequency of GTN in FCECON in the period from 2011 to 2018 was 11 cases and despite the decrease in mortality from this disease in Brazil in recent decades, in Amazonas, this reduction was not observed in the public health service. This is one of the first studies on the subject in patients using SUS in the state of Amazonas, where this disease is still little known. Further prospective studies are suggested for better evaluation and standardization of patient care conducts according to FIGO guidelines.

REFERENCES

1. Braga, A., et al. (2018). Doença trofoblástica gestacional. *Rev. Femina*, (4).

2. Cabral, A. F., et al. (2022). Perfil das pacientes com doença Trofoblástica Gestacional atendidas em centros de saúde suplementar da Amazônia. *Brazilian Journal of Health Review*, *5*(4), 14515–14522.

3. Cardoso, J. L. R., et al. (2020). Principais condutas acerca da gestação normal com doença trofoblástica: uma revisão integrativa de literatura. *Revista Eletrônica Acervo Saúde*, *12*(3), e3087. [Link](https://doi.org/10.25248/reas.e3087.2020)

4. Clark, L. H., et al. (2016). The effect of distance traveled on disease outcomes in gestational trophoblastic neoplasia. *American Journal of Obstetrics and Gynecology*.

5. De Andrade, J. M. (2009). Mola hidatiforme e doença trofoblástica gestacional. Hydatidiform mole and gestational trophoblastic disease. *Rev Bras Ginecol Obstet*, *31*, 94–101.

6. FIGO Oncology Committee. (2002). FIGO staging for gestational trophoblastic neoplasia 2000. *International Journal of Gynecology and Obstetrics*, *77*(3), 285–287.

7. Freitas, F., et al. (2020). Gestational trophoblastic neoplasia lethality among Brazilian women: A retrospective national cohort study. *Gynecologic Oncology*.

8. Goldstein, D. P., & Berkowitz, R. S. (2012). Current management of gestational trophoblastic neoplasia. *Hematology/Oncology Clinics of North America*, *26*(1), 111–131.

9. Litkouhi, B., & Al-Khan, A. (2017). Gestational trophoblastic disease. *Operative Obstetrics*, *376*(9742), 523–533.

10. Ngan, H. Y. S., et al. (2015). FIGO Cancer Report 2015: Update on the diagnosis and management of gestational trophoblastic disease. *International Journal of Gynecology & Obstetrics*, *131*, S123–S126.

11. Ngan, H. Y. S., et al. (2018). Update on the diagnosis and management of gestational trophoblastic disease. *International Journal of Gynecology and Obstetrics*, *143*, 79–85.

12. Ramos, B. V., et al. (2021). Mola hidatiforme: manifestações clínicas e critérios diagnósticos por imagem. *Brazilian Journal of Health Review*, *4*(1), 3607–3616.

13. Seckl, M. J., et al. (2013). Gestational trophoblastic disease: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, *24*(SUPPL.6).

14. WHO Scientific Group on Gestational Trophoblastic Diseases. (1983). Gestational trophoblastic diseases: report of a WHO scientific group. *WHO bulletin. WHO Technical report series, 692*. World Health Organization. [Link](http://www.who.int/iris/handle/10665/39169)