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Original Article

TRATAMENTOS NA DOENÇA TROFOBLÁSTICA GESTACIONAL: UMA REVISÃO INTEGRATIVA

TREATMENTS FOR GESTATIONAL TROPHOBLASTIC DISEASE: AN INTEGRATIVE REVIEW

TRATAMIENTOS EN LA ENFERMEDAD TROFOBLÁSTICA GESTACIONAL: UNA REVISIÓN INTEGRADORA

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RESUMO

Objetivo: Compilar os dados da literatura sobre o tratamento da Doença Trofoblástica Gestacional e o seguimento pós-molar. **Método**: revisão integrativa a partir da Biblioteca Virtual em Saúde, por intermédio das bases de dados MEDLINE, LILACS, BDENF e Coleciona SUS utilizando os descritores controlados “doença trofoblástica gestacional”, “mola hidatiforme” e “coriocarcinoma”; e o descritor Coleciona não controlado “tratamento”, “neoplasia trofoblástica gestacional” e “seguimento pós-molar”. **Resultados:** foram selecionados 15 artigos. Diante dos diagnósticos relatados nesses manuscritos, três não informavam o tipo de doença trofoblástica gestacional; dois relataram mola hidatiforme completa, dois mola hidatiforme parcial, dois mola hidatiforme, dois coriocarcinoma, um neoplasia trofoblástica gestacional e um relatou mola hidatiforme completa em gestação gemelar. Em relação às evoluções da doença trofoblástica gestacional, cinco artigos citaram a neoplasia trofoblástica gestacional, sendo que em três desses houve registro de metástase pulmonar. Para tratamentos instituídos, 73,3% citaram o esvaziamento da cavidade uterina por vácuo-aspiração como método de escolha inicial. No tratamento monoterápico, 71,4% citaram tratamento quimioterápico com metotrexate e poliquimioterápico, e 50% relataram o uso de etoposida, metotrexato, actinomicina-D, ciclofosfamida e oncovin. **Conclusão:** sugere-se a necessidade de profissionais capacitados quanto a essa patologia, de modo a garantir a saúde da população feminina e assim garantir qualidade de vida.
Descritores: Doença trofoblástica gestacional; Enfermagem obstétrica; Terapêutica.

ABSTRACT

Objective: To compile the literature data on the treatment of gestational trophoblastic disease and post-molar follow-up. **Method:** integrative review from the Virtual Health Library, through the MEDLINE, LILACS, BDENF and Coleciona SUS databases using the controlled descriptors "Gestational Trophoblastic Disease", "Hydatidiform mole" and "Choriocarcinoma"; and the uncontrolled descriptor "Treatment", "Gestational Trophoblastic Neoplasia" and "Post-Molar Follow-up". **Results:** Fifteen articles were selected. In view of the diagnoses reported in these manuscripts: three did not report the gestational trophoblastic disease type; two reported complete hydatidiform mole; two partial hydatidiform mole; two hydatidiform mole; two choriocarcinoma; one gestational trophoblastic neoplasia; and one reported complete hydatidiform mole in twin gestation. In relation to the evolution of the gestational trophoblastic disease, five articles mentioned gestational trophoblastic neoplasia, and in three of these, there was a record of pulmonary metastasis. For instituted treatments, 73.3% cited emptying of the uterine cavity by vacuum aspiration as the initial chosen method. In the monotherapy treatment, 71.4% cited chemotherapy with methotrexate and polichemotherapeutic, and 50% reported the use of etoposide, methotrexate, actinomycin-D, cyclophosphamide and oncovin. **Conclusion:** it is suggested the need for professionals trained in this pathology, in order to guarantee the female population health and thus ensure quality of life.
Keywords: Gestational trophoblastic disease; Obstetric nursing; Therapy.

RESUMEN

Objetivo: Compilar los datos de la literatura sobre el tratamiento de la enfermedad trofoblástica gestacional y el seguimiento post molar. **Método**: revisión integradora de la Biblioteca Virtual en Salud, a través de las bases de datos MEDLINE, LILACS, BDENF y Colecciona SUS, utilizándose descriptores controlados "Enfermedad Trofoblástica Gestacional", "Mola hidatiforme", "Coriocarcinoma”; y el descriptor no controlado "Tratamiento", "Neoplasia Trofoblástica Gestacional" y "Seguimiento Post Molar". **Resultados**: se seleccionaron 15 artículos. De los diagnósticos relatados en estos manuscritos, tres no informaron el tipo de enfermedad trofoblástica gestacional; dos informaron mola hidatiforme completa, dos mola hidatiforme parcial, dos mola hidatiforme, dos coriocarcinoma, uno neoplasia trofoblástica e uno mola hidatiforme completa en embarazo gemelar. En relación con la evolución de la enfermedad trofoblástica gestacional, cinco artículos citaron neoplasia trofoblástica, ocurriendo registro de la metástasis pulmonar en tres de ellos. Con los tratamientos establecidos, 73,3% citaron el vaciado de la cavidad uterina mediante aspiración al vacío como método de elección inicial. En el tratamiento en monoterapia, 71,4% citaron quimioterapia con metotrexato y múltiples fármacos, y 50% reportaron uso de etopósido, metotrexato, actinomicina-D, ciclofosfamida y oncovin. **Conclusión**: hay necesidad de profesionales cualificados sobre esta enfermedad con el fin de garantizar la salud de la población femenina y la calidad de vida.
Descriptores: Enfermedad trofoblástica gestacional; Enfermería obstétrica; Terapéutica.

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INTRODUCTION

Gestational Trophoblastic Disease (GTD) comprises a set of conditions that, although relatively infrequent, can progress to life-threatening and severe forms[1]. By definition, GTD comprises a group of tumors that proliferate from the placental trophoblastic epithelium and present different degrees of reversion, invasion and malignant transformation[2]. Besides the risk of malignancy, GTD is a source of psychological distress because the implied gestational loss, fear of chemotherapy and uncertainties about future pregnancies[3].

In cases of diagnosis of GTD, treatment may occur through uterine evacuation by electric or manual vacuum aspiration (MVA), associated with medications in specific situations[4]. After the initial procedure, patients should perform post-molar follow-up, which is fundamental for the early diagnosis of progression to malignant forms of GTD. This follow-up is based on the proper interpretation of the Beta human chorionic gonadotrophin (Beta-hCG) regression curve and immediate care in case of anomalous decrease in Beta-hCG levels[5-6]. Despite its importance, however, there is no consensus among specialists on the mode of post-molar follow-up[5], what hinders the standardization of conducts.

Another challenge in the assistance to GTD patients is the referral to reference centers[5]. This is because, although referral is highly recommended in the literature[6], the number of reference centers for GTD in Brazil is smaller than the number of states, posing a major problem, for this is country of continental dimensions[5].

In view of the above, the following guiding questions emerged: What are the main complications following the diagnosis of GTD? What are the most commonly used forms of treatment used after diagnosis of GTD? How should post-molar follow-up be conducted?

Despite its complexity, GTD is still little addressed in both undergraduate nursing courses and postgraduate courses in the area, and there is no consensus between specialized services on the adequate conduct.

These aspects justify the relevance of a systematized review of the literature on GD in order to eliminate the knowledge gap in the training of health professionals and to provide subsidies for the structuring of behavioral protocols and new referral centers. Thus, the present integrative review aimed to compile literature data on the treatment of GTD and post-molar follow-up.

METHOD

The present study is an integrative review with the purpose of "meeting a standard of excellence regarding methodological rigor, so that its product may bring contributions to science and to clinical practice" [7:340]. It is a method that allows the synthesis of knowledge acquired during the course of the research, organizing it so as to apply its results in the practice[8].

The steps adopted for the realization of this integrative review include the formulation of the problem to be investigated; location and critical assessment of studies included in the sample; data collection, analysis, presentation, and interpretation; and, finally, refinement of the review[7].

Literature was searched in the Virtual Health Library (VHL), through the *Medical Literature Analysis and Retrieval System Online* (MEDLINE), Latin American and Caribbean Literature in Health Sciences (LILACS), Nursing Database (BDENF) and National Collection of Information Sources of SUS (Colecciona SUS) databases.

The inclusion criteria were: articles available and published in full length, in Portuguese and without temporal limitation. On the other hand, the exclusion criteria were: articles out of the scope under study or focusing on animal research, dissertations, theses, letters to reader, opinion articles, review articles and opinions.

The controlled descriptors "gestational trophoblastic disease", "hydatidiform mole" and "choriocarcinoma", and the uncontrolled descriptors "treatment", "gestational trophoblastic neoplasia" and "post-molar follow-up" were used in the search. Descriptors were crossed as follows: "gestational trophoblastic disease" AND "treatment"; "Hydatidiform mole" AND "treatment"; "gestational trophoblastic neoplasia" AND "treatment"; "choriocarcinoma" AND "treatment"; and "post-molar follow-up" AND "treatment".

Thirty-five manuscripts were found after crossing the descriptors and applying the inclusion criteria. When applying the exclusion criteria, two articles showed not to address the

object under study, 12 were repeated in the results of the descriptors used, four were duplicated in the databases, and two did not present the established forms of treatment for GTD. Finally, 15 articles composed the study sample.

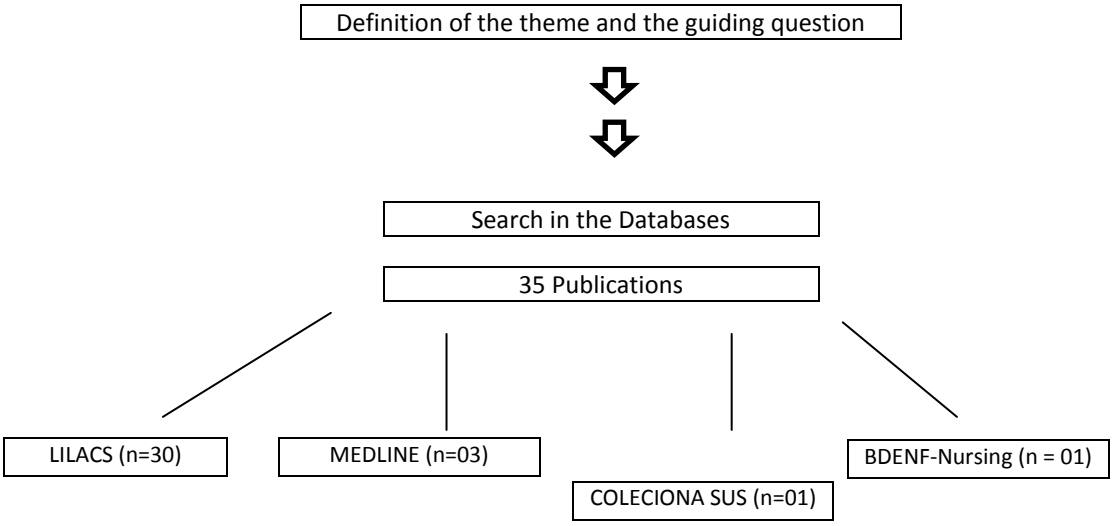
Data was collected from the findings of the case reports and the results obtained in the articles selected for the study, gathering information about the diagnoses found, the treatments employed and the progression of the GTD in the analyzed cases. To this end, an instrument was specifically prepared for this study, gathering information on: journal, year, title, diagnosis, treatment and progression.

After reading all the articles in full length, the data from each case were recorded and presented in boxes and tables. The analysis was based on relevant literature.

RESULTS AND DISCUSSION

The selected descriptors resulted in the following numbers: 13 articles when crossing the descriptors "gestational trophoblastic disease" AND "treatment"; seven articles when crossing "hydatidiform mole" AND "treatment"; three articles when crossing "gestational trophoblastic neoplasia" AND "treatment"; seven articles when crossing "choriocarcinoma" AND "treatment"; and five articles with the descriptor "post-molar follow-up".

Figure 1 – Selection of the study sample.



Source: Direct search/2016.

After checking the inclusion and exclusion criteria, only 15 out of the 35 articles composed the study sample, as shown in the Figure.

Figure 2 shows the journals where the articles selected to compose the sample were published, as well as their titles and the forms of treatments reported.

Figure 2 - Publications that composed the study sample - Fortaleza-CE, Brazil, 2016.

Journal/year	Title	Treatment
Brazilian Journal of Gynecology and Obstetrics/1998	Complete Mole in Twin Pregnancy: Case Report.	Vacuum aspiration and chemotherapeutic treatment.
Brazilian Journal of Gynecology and Obstetrics/1999	Persistence of metastatic pulmonary imaging after treatment of gestational trophoblastic disease.	Uterine curettage and chemotherapeutic treatment.
Brazilian Journal of Gynecology and Obstetrics/2000	Characteristics of Chorionic Gonadotropin Regression Curves After Complete Hydatidiform Mole.	Vacuum aspiration and chemotherapy.
Brazilian Journal of Gynecology and Obstetrics/2003	Complete hydatidiform mole and eclampsia: case report.	Uterine vacuum aspiration and chemotherapeutic treatment.

Brazilian Journal of Gynecology and Obstetrics/2004	Gestational trophoblastic disease complicated by hemorrhage.	Dilatation and curettage (D&C), vacuum aspiration and chemotherapeutic treatment.
Brazilian Journal of Gynecology and Obstetrics/2006	Uterine arteriovenous malformation after gestational trophoblastic disease.	Vacuum aspiration, dilatation and curettage (D&C) and chemotherapy.
Brazilian Journal of Gynecology and Obstetrics/2009	Hydatidiform mole and gestational trophoblastic disease.	Vacuum aspiration, hysterectomy and chemotherapy treatment.
Brazilian Journal of Cancerology, 2009	Primary ovarian choriocarcinoma: report of a case in a 10-year-old patient.	Total abdominal hysterectomy.
Brazilian Journal of Nursing/2010	Choriocarcinoma: a case study.	Vacuum curettage, total abdominal hysterectomy and chemotherapeutic treatment.
Medical Journal of Minas Gerais/2010	Gestational trophoblastic disease: lessons from a paradigmatic case	Vacuum aspiration for patients wishing to preserve fertility and hysterectomy for those at risk of neoplasia.
Brazilian Journal of Gynecology and Obstetrics/2012	Challenges of the treatment of patients with gestational trophoblastic disease.	Vacuum aspiration and chemotherapeutic treatment
Femina, 2014	Clinical complications of molar pregnancy.	Vacuum-aspiration.
Santa Catarina Archives of Medicine/2014	Pulmonary metastasis due to choriocarcinoma: case report.	Uterine curettage and chemotherapeutic treatment for metastatic choriocarcinoma.
Brazilian Journal of Gynecology and Obstetrics/2015	Gestational trophoblastic neoplasia after spontaneous normalization of human chorionic gonadotrophin in a patient with partial hydatidiform mole.	Unspecified uterine evacuation and chemotherapeutic treatment.
Brazilian Journal of Medicine/2015	Update on the diagnosis and treatment of molar pregnancy.	Manual vacuum aspiration (MVA) and chemotherapeutic treatment in the presence of GTN.

Source: Direct search/2016.

As for the diagnoses reported in the articles, three did not inform the type of gestacioal trophoblastic disease (GTD)[1,9-10], two reported complete hydatidiform mole (CHM)[11-12], two reported partial hydatidiform mole (PHM)[13-14], two only mentioned hydatidiform mole (HM)[2,5], two mentioned choriocarcinoma[15-16], one article only mentioned gestational trophoblastic neoplasia (GTN)[17] and another reported complete hydatidiform mole in twin gestation[18], as shown in Table 1.

Table 1- Diagnostics of GTD forms - Fortaleza-CE, Brazil, 2016.

Diagnoses
Unspecified GTD[1,9-10]
CHM[11-12]
PHM[13-14]
HM[2,5]
Choriocarcinoma[15-16]
GTN[17]
CHM in twin pregnancy[18]

Source: Direct search/2016.

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Two of the other articles reported cases of three women who had diagnoses of GTN associated to and HM[19], and the other manuscript evaluated 2,764 patients who presented CHM and PHM diagnoses[20].

As for the progression of GTD, five articles cited GTN, three reported pulmonary metastasis, two reported unspecified metastasis, two reported gestational trophoblastic tumors (GTT), one manuscript reported vaginal metastasis, another mentioned sepsis, one with a history of choriocarcinoma, one with death after treatment, and the other with permanent HM, without further specification, as shown in Table 2.

Table 2 - Progression after treatment for GTD - Fortaleza-CE, Brazil, 2016.

Progression
GTN[5,9,13,18,20]
Pulmonary metastasis[16-17,19]
Unspecified metastasis[2,5]
Gestational Trophoblastic Tumor (GTT)[11-12]
Vaginal metastasis[19]
Sepsis[19]
Choriocarcinoma[14]
Death[16]
Permanent HM[14]

Source: Direct search/2016.

Other authors cited uterine perforation as a consequence of uterine curettage, requiring laparotomy[19-20].

Three articles did not cite or refer to complications of GTD in their results, discussion and conclusion. Regarding the forms of treatment used, 73.3% of the articles cited evacuation of the uterine cavity by vacuum aspiration as the initial method of choice for the treatment of GTD. Regarding dilatation and curettage (D&C), 26.7% of the articles reported that this is also a procedure that can be performed as initial measure against GTD. However, another 20% reported that total hysterectomy is an alternative initial method of choice, especially for women with established offspring[1,10].

Evacuation of the uterine cavity by vacuum aspiration may be seen as a secondary measure to previous treatment of GTD, as in previous curettage[19].

After aggravation or malignization of GTD, more severe forms of treatment are implemented, such as total abdominal hysterectomy (13.3%), monochimotherapy treatment for low-risk GTN (46.7%) and polychemotherapy for high-risk GTN (53.3%).

In the case of monochimotherapy, 71.4% of the articles cited methotrexate (MTX) as chemotherapeutic agent, 42.9% cited a history of chemotherapy with actinomycin-D (Act-D), and 14.3% did not specify the chemotherapeutic agent used in the treatment.

As for polychemotherapy, 50% of the articles mentioned treatment with the etoposide, methotrexate, actinomycin-D, cyclophosphamide and oncovin (EMA/CO), and 50% of the articles reported methotrexate with folinic acid (MTX/FC), 6.7% reported the use of bleomycin, etoposide and cisplatin (BEP) and another 6.7% reported etoposide, methotrexate, actinomycin-D and cisplatin (EP/EMA).

However, two articles[5,11] did not specify the drugs used. All forms of treatment found during the research are shown in Table 3.

Table 3 - Treatments used in women with GTD - Fortaleza-CE, Brazil, 2016.

Treatment forms	Treatments used
Initial	Evacuation of the uterine cavity by vacuum aspiration[1,2,5,9-10,12-14,18-20] Dilatation and curettage (D&C) [16-17, 19-20] Total hysterectomy [1,10,15]
After aggravation or malignization	Total abdominal hysterectomy[14,19] Monochemotherapy[2,5,13-14,17,18-20] Polychemotherapy[2,5,12-14,16,19-20]
Monochemotherapeutic agents (drugs)	Methotrexate (MTX)[2,13,17,14,18] Actinomycin-D (Act-D)[2,12,20] Not specified[5] EMA/CO[2,14,19-20]
Polychemotherapeutic agents (drugs)	MTX/FC[12-13,16,20] BEP[20] EP/EMA[2]

Source: Direct search/2016.

Thus, it was observed that 73.3% of the study sample used uterine evacuation by vacuum-aspiration as the initial and preferred choice for treatment of GTD and that, in the event of metastasis or GTN, polychemotherapy is the treatment of choice, depending on severity and diagnosis.

Among the classification of GTD, HM is the most common form, affecting about 1:200-400 pregnancies in Brazil[19]. However, this form can progress to GTN. Regarding these subdivisions, studies have indicated that CHM is more frequent than PHM[21]. This statistic was confirmed in the present study, since eight of the articles analyzed reported an initial diagnosis of HM. And regarding the HM forms, CHM was also reported more frequently: four articles reported the presence of CHM and three, PHM.

Twin pregnancy occurring with live fetuses is a rare episode, with a incidence ranging from 1 per 22,000 to 100,000 deliveries. In these cases, one of the placentas has a normal fetus and the other presents molar degeneration[22]. This was also observed in the present research, as in the only case involving twin pregnancy, there were two placentas, one containing a fetus and the other containing a CHM.

Choriocarcinoma, classified as form of GTN, is also a rare condition and affects one in 40,000 pregnant women[23]. During the data collection, two diagnoses of this pathology were observed, that is, 13.3% had an initial diagnosis of choriocarcinoma. Other types of GTD or GTN, such as invasive mole and PSTT (Placental Site Trophoblastic Tumor), were not identified as initial diagnoses in the studies surveyed.

After diagnosis of GTD, affected women must be referred to specialized centers for clinical follow-up and uterine evacuation, where the most indicated method is vacuum aspiration, because uterine curettage presents risks of perforation due to cervical softening and increase. After emptying the uterine cavity, post-molar follow-up should be performed by monitoring hCG levels, so as to allow early detection of progress to GTN[19].

This preference for vacuum aspiration was observed in the articles studied; 73% of the articles reported this procedure as the method of choice for uterine evacuation.

Two articles cited uterine perforation as a result of curettage, and laparotomy was required to correct this complication, thus endorsing that vacuum aspiration is less risky than uterine curettage.

It is estimated that, after uterine evacuation, 80% of women diagnosed with CHM and 95% of the diagnosed with PHM progressed to cure without requiring further treatment. However, when women progress otherwise, and the abnormal placental tissue continues to grow, this is called GTN[24].

Still, according to the aforementioned author, the treatment of HM requires a previous classification into low risk or high risk complete mole. Low risk happens when uterine size is equal to or less than estimated gestational age (GA), hCG levels are compatible with a normal

gestation and maternal age is less than 40 years. On the other hand, high risk happens in the opposite characteristics, besides the presences of enlarged ovaries and cysts.

The appropriate treatment for low risk patients is preferably uterine evacuation by vacuum aspiration. However, abdominal hysterectomy is performed in certain situations, but only in the case of women who wish surgical sterilization. This observation was confirmed in the studies: 20% of the authors cited total abdominal hysterectomy as an alternative initial method for treatment of GTD in women who are satisfied with offspring[24]. This procedure is also performed after aggravation or malignization of the GTD[14,19].

Vacuum aspiration can be secondarily performed, after uterine curettage without satisfactory effect. However, this was not seen in the comparative studies.

In the case of high-risk patients, a combination of vacuum aspiration or abdominal hysterectomy and a single chemotherapy cycle should be performed in order to retard the progression to GTN. In the suspicion of progression to GTN, metastases should also be searched[24].

GTD is considered a type of gynecological cancer where both benign and malignant forms may progress to severe complications and aggravations, sometimes requiring chemotherapy in both cases[25]. In the sample of studies analyzed, all patients diagnosed with GTN and/or metastasis were submitted to chemotherapy, with drug choice depending on the severity of the diagnosis.

The chemotherapeutic treatment for GTN is most often performed with methotrexate and folinic acid. Methotrexate can cure about 90% of patients with low-risk GTN. Besides, this drug does not have side effects on the ovaries or on future pregnancies. However, when patients have resistance or toxicity to Methotrexate, the drug should be replaced by Actinomycin-D[24].

In cases of high-risk or persistent GTN, combined chemotherapy is the best choice, which consists in the use of various drugs to seek healing. In these cases, the scheme of choice is the EMA/CO, which includes etoposide, methotrexate, actinomycin-D, cyclophosphamide and oncovin[24].

In the study samples, it was observed that 46.7% of the reports used monochemotherapeutic treatment, in which 71.4% used methotrexate and 28.6% actinomycin-D, proving that the first drug is the preferred choice for low-risk GTN. In turn, 53.3% of the sample reported a history of treatment with multidrug therapy, where 50% reported the use of EMA/CO and another 50% cited MTX/FC. However, as percentages are equal, we cannot state that there is a preference for EMA/CO in the treatment of GTN or high-risk metastasis.

CONCLUSION

The study sought to know the forms of treatment used in women with GTD. Thus, it was observed that, after diagnosis of GTD, the most commonly used method for uterine evacuation is vacuum aspiration, as this method reduces the risks of uterine perforation during the procedure.

GHM was observed to occur more frequently than PHM, either isolated or in twin pregnancy. Furthermore, six articles cited metastasis as a complication and progression of GTD, showing the degree of malignancy of this disease.

It was also observed that polychemotherapy, using EMA/CO or MTX/FC, was more frequently chosen in the patients who needed to undergo chemotherapeutic treatments, whether due to progress to GTN or to metastasis.

These data show how relevant the knowledge and classification, aggravations, progression and treatment of this pathology is in order to reduce the risks of neoplasia and metastasis, so as to enable early diagnosis and appropriate treatment.

Therefore, we suggest the need to inform and specialize professionals regarding this pathology, in order to guarantee the health of the female population, as well as to make them aware of the importance of preventive and recuperative measures to ensure their quality of life.

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