13
PRESENTATION AND MANAGEMENT OF MOLAR PREGNANCY AND GESTATIONAL TROPHOBLASTIC NEOPLASIA IN LATIN AMERICA

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13.1 INTRODUCTION

Gestational Trophoblastic Disease (GTD) in Latin America (LA) has a wide range of presentation and management, depending on socioeconomic, political and geographic variables [1,2,3]. Thus, while some referral centers have sophisticated methods for an early and accurate diagnosis and treatment, still there are a high number of patients admitted with a late Hydatidiform Mole (HM) or advanced Gestational Trophoblastic Neoplasia (GTN). In most Latin-American countries, GTD is not included in public health policies.

In this chapter, the experience of the GTD referral unit of the Department of Obstetrics and Gynecology of Hospital Universitario de Caracas (HUC), Universidad Central de Venezuela (UCV), will be described along with the experience of other specialized centers in LA.

13.2 EPIDEMIOLOGY

The majority of Latin-American literature about epidemiological information is related to HM. However, there could be over or under estimation of certain statistical parameters determined by several factors. Among them: the data is provided by referral centers; not all the patients are treated in Obstetrics and Gynecology departments, and different denominators are used for statistical analysis, like number of deliveries, live births or pregnancies.

In the HUC, from 2000 to 2012, 141 patients with HM were diagnosed with a prevalence of 2.2 per 1000 pregnancies; 73% of these cases were partial mole [4]. In all cases with histopathological diagnosis, complementary immunohistochemical study with p57 KIP 2 was performed to differentiate CM from PM [5]. Other centers in Venezuela report prevalence between 1:626 to 1:1,147 deliveries [6]. Table 13.1 shows a comparison among different centers in LA [1,3,7-17].

Table 13.1

Table 1
Rate of molar pregancy in Latinamerican Centers

Country	Author et al.	Centre	Rate per 1000 Deliveries	Pregnancies	live birth
Argentina	Giuliano - Bianconi (1)	Hospital de Clinicas José de San Martin		0,5	
Colombia	Acosta-Bendeck (7)	Hospital General de Barranquilla	4,04		
Chile	Aitken S (8)	Hospital Felix Bulnes Cerda	1		
Cuba	Quiñonez A (9)	Hospital Provincial Ob/gyn Cienfuegos		1,4	
Brasil	Belfort P (10)	Researches in Rio Janeiro* and Gioãna**	8**		18 *
Brasil	Maestá I (11)	Hospital das Clinicas Universidad Botucatu			6,6
Mexico	Lara F (12)	Insituto Nacional de Cancerología		2,4	
Mexico	Lira J (13)	Instituto Nacional de Perinatología			2,4
Paraguay	Rondón and Lopez (14)	Unselected Hospital Admissions		0,2	
Perú	Albinagorta (15)	Hospital Nacional Cayetano Heredia		2,33	
Ecuador	Andrade P	Maternidad Isidro Ayora	2,67		
Costa Rica	Zamora L (16)	Hospital General		1,5	
Venezuela	Paiva S (17)	Maternidad Concepcion Palacios		1,63	
Venezuela	Cortés-Charry R (4)	Hospital Universitario de Caracas		2,2	

Note: Some of this parameters were calculated using the original data from the cited articles

PRESENTATION AND MANAGEMENT OF MOLAR PREGNANCY AND GESTATIONAL TROPHOBLASTIC NEOPLASIA IN LATIN AMERICA. Prof Rafael Cortés Charry

Multicenter LA retrospective study was performed between 2000 to 2011, 5771 medical records with Gestational Trophoblastic Disease were revised and 1333 (23.1%) patients of this group were diagnosed with GTN [4]. Epidemiological reports of GTN are scant. In the HUC from 1997 to 2004 data was reported indicating a prevalence of 0.7:1000 deliveries [18] and between 2000 to 2012, 64816 pregnancies were admitted, and 54 patients were diagnosed with GTN, with a prevalence of 0.9:1000 deliveries. Another referral center in Caracas, Maternidad Concepción Palacios (MCP), reported a prevalence of choriocarcinoma (CC) of 0.07:1000 live births in a period of ten years [19]. In Brazil, some geographic regions report a high incidence of GTN, for example in Botucatú 2.5:1000 [11], Gioania 1: 925 deliveries [2] and Salvador Bahia 2.0: 1000 deliveries [20].In Peru, data from Inami - Hospital Maternidad de Lima, shows a prevalence of 0,07:1000 deliveries. In México, extrapolated data from a research in the National Institute of Perinatology, the prevalence was 0.028:1000 live births [13]. Several reports about CC, either case series or isolated cases, are cited in the Latin American and Caribbean Health Sciences (LILACS)[21,22,23]. A high percentage originates from molar pregnancy, in the Durand Hospital in Argentina 34% of molar pregnancies progress toward GTN [24].

Socioeconomic and nutritional factors have been implicated as risk factors for the disease [25], but it is necessary to perform more research. As reported by the international experience, women in reproductive age are the group with the highest incidence of HM in LA, while contrary to other regions; young patients represent an important percentage of the GTN high risk group [1-3, 12, 18, 19]. A recent multicenter study with 955 patients showed that complete mole was more frequent in adolescents but this fact was not a statistically significant risk to develop GTN [26]. Some factors have been related to the evolution of HM to GTN like Rh negative factor [27], hCG serum levels pre-evacuation higher than 100,000 IU/mL, and some types of hCG regression curves and its usefulness in the early diagnosis of GTN; patients with GTN showed deviation

from the normal hCG curve at 3.84 ± 2.57 weeks and reached plateau or rise 8.40 ± 2.94 weeks [28].

13.3 CLINICAL PRESENTATION AND MANAGEMENT IN HYDATIDIFORM MOLE

In the HUC, during the periods of time aforementioned in this article, the main complaint of patients with HM was vaginal bleeding, which is consistent with the majority of the investigations [8]. In that decade, there was an increase in the diagnosis of HM in asymptomatic patients, due to the routine use of transvaginal ultrasound during the first trimester of pregnancy. Other typical symptoms and signs found in patients with molar pregnancies were: uterine length higher than the expected for amenorrhea, pelvic pain, and other symptoms produced by hormonal effect like nausea and vomiting. Clinical and subclinical hyperthyroidism was found in 30.5% in a selected population with HM. Symptoms related to toxemia were less frequently found in HUC patients and in several studies [29].

Some isolated cases of molar pregnancy with live fetus have been reported, and this rare presentation was diagnosed by ultrasound examination [30-33]. The clinical presentation in cases of partial mole (PM) is nonspecific; it can mimic an incomplete abortion, with the possibility of under diagnosis. Another important limitation in the diagnosis of PM is the fact that not all centers perform histopathological examination of all abortion material. Zapata et al in Venezuela, Gutierrez et al in Mexico and Biscaro et al in Brasil, reported a percentage of unsuspected diagnosis of molar pregnancy in abortion material oscillating between 1.16 to 12 %. [34-36].

Finally, most hospitals do not have other essential resources to make an accurate diagnosis like immunohistochemical studies [1,2,3].

When a patient with HM is admitted to the HUC, a rigorous clinical history and examination is performed. Some basic tests are required for the admission: hCG serum levels, transvaginal US, chest X-ray, complete blood count, SGOT, SGPT, urea, creatinine, uric acid, blood type, VDRL, VIH and thyroid hormones. The objective of these basic steps is to have a better diagnostic approximation, to determine the general condition of the patient, to prepare the patient for vacuum aspiration, and, to select patients for other imaging studies if some of the previous examinations suggest the possibility of GTN.

In Latin America, the most frequent method of treatment for HM is electric vacuum evacuation [1-3, 11] although manual vacuum aspiration (MVA) is used like an alternative method too; some centers in Mexico use this procedure and researchers promote it as a simple, safe, inexpensive and efficient ambulatory method [37,38].

A multicenter study in HUC Venezuela (unpublished data, presented in XIV ISSTD congress in Fukuoka), involved 21 patients and MVA was performed to evacuate HM. The high efficacy of MVA was probed using post-evacuation clinical and hysteroscopic findings. It was observed that there is equal operatory time, bleeding and need of second curettage than with traditional Electric Vacuum aspiration. With the objective to decrease operatory time, we recommended to use two or three manual vacuum systems simultaneously.

When vacuum aspiration is not available, the curettage is performed with sharp curettes [15] although it is a dangerous practice. In most cases, an oxytocin infusion is used during the evacuation, although some researchers use prostaglandin analogues prior to the aspiration [39]. In patients over forty who completed childbearing, a hysterectomy may be performed, ideally after obtaining histopathological diagnosis.

The follow up protocol consists of weekly clinical evaluation and hCG determination until three serial negative values are obtained; then monthly samples are taken for 6 to 12 months depending on the center, then annual for life, until the patient decides to get pregnant again. In a patient with a pregnancy after a hydatidiform mole, we perform a serum quantitative hCG 4 weeks after completion of this gestation. If it is positive, monitoring of hCG values should be performed until negative. Some of the most aggressive cases we've had in the HUC were patients with choriocarcinoma after a normal pregnancy that had a prior molar pregnancy.

The use of prophylactic chemotherapy (p-Chem) is controversial, although some referral centers in Latin America use it on patients with high risk to be lost for follow-up. Methotrexate (MTX) is the most frequently used medication, although a study in Brazil used Actinomycin D in high risk young population, with an important reduction (48%) in the risk of developing post molar GTN [40,41]. P-Chem may reduce the risk of progression to GTN in women with CMs who are at a high risk of malignant transformation; however, current evidence in favor of P-Chem is limited by the poor methodological quality and small size of the included studies. As P-Chem may increase drug resistance, delay treatment of GTN and expose women unnecessarily to toxic side effects, this practice cannot currently be recommended [42].

Unfortunately the percentage of patients lost for follow-up is 12% in specialized centers in LA [4]. To decrease these rates, the patient needs to be adequately informed, and the management should be multidisciplinary, including psychologists and social workers [43,44]. A recent Latin American multicenter study also demonstrated that once the diagnosis of molar pregnancy is made, patients should be referred to specialized centers in the treatment of GTD. This would have a positive impact on the survival and response rates to treatment [4]

13.4 CLINICAL PRESENTATION AND MANAGEMENT OF GESTATIONAL TROPHOBLASTIC NEOPLASIA

A study including 25 patients with GTN between 1997 and 2004 in the HUC, showed that the most frequent presentation was the alteration of the follow up curve of hCG post evacuation of molar pregnancies (56%); most patients were asymptomatic. Score and staging system have been accepted by ISSTD, WHO, FIGO, and ASGO [45], and this classification is used in the majority of LA centers. The main complaint was vaginal bleeding. Several researchers have demonstrated that pulmonary metastases are the most frequent extra pelvic metastases, with a frequency of 53% to 80%. However, not all patients with pulmonary metastases have associated symptoms like cough, hemoptysis, and dyspnea. Two cases in the HUC series were admitted with acute respiratory insufficiency [18].

In the HUC report, other pelvic metastases were vaginal. In some cases, an exhaustive medical history revealed a previous misdiagnosed GTD; most of these cases were referred from another non-specialized center, where histopathological studies were not possible. As reported in some LA publications, some patients are referred with the diagnosis of post-partum or post curettage vaginal hematoma, post-partum endometrioma, and vaginal extension of cervical carcinoma, among others [46-47]. In some cases, primary or metastatic GTN could resemble a ruptured ectopic pregnancy [48,49].

Brain and gastrointestinal metastases were less frequent than others in the majority of LA studies, but when they were present, they represented a sign of alarm due to the possibility of acute decompensation or death. Symptoms related with central nervous system involvement are headache, seizures and others depending on the compromised area of the brain. When there is hepatic involvement, sometimes jaundice is present, but in most cases an acute intra-abdominal haemorrhage is the first clinical presentation. Unfortunately, still in some cases the diagnosis is made during the autopsy of the patient. Cruz et al in Mexico, reviewed the clinical records of 40 autopsies performed in 10 years, in which the conclusion of the evaluation was metastatic choriocarcinoma; in 55% of the cases the diagnosis was first made at the time of the autopsy [24]

Most of LA centers use for diagnostic imaging transvaginal B-D and Doppler ultrasound, chest X-ray or CT and brain, abdominal and pelvic computed tomography (CT). It is important to remember that CT detects 40% of pulmonary lesions not detected in the chest x ray, but these are not to be considered in the FIGO score because it does not change the ultimate prognosis of patients [50]. Sometimes, the abdominal CT is substituted by magnetic resonance imaging (MRI). In the HUC only in highly selected cases, a CT-positron emission tomography is employed [51].

Monochemotherapy with MTX is the most widely used treatment

for low risk GTN in LA. Several protocols of administration are proposed; the most frequently used is MTX 1 mg/kg days 1,3,5,7 and rescue with Folinic Acid (FA) 0.1 mg/kg or 15 mg 24 to 30 hours after administration of MTX, days 2,4,6,8. In case of drug resistance, alternative monochemotherapy with Actinomycin D (ActD) is administered in a five days protocol or single dose of 1,25 mg/m2 every two weeks. Relatively low toxicity has been associated with these chemotherapy protocols: vomiting, stomatitis, alopecia, photo sensibility and low platelet count. Severe soft tissue damage may occur with extravasation of ActD, so it should be administered through a secure intravenous with close monitoring during infusion. Etoposide, Capecitabine and EMA/CO are used as a third line in low risk GTN. When remission is reached, we suggest one cycle of consolidation. In South America complete remission was reported in 99.6% of patients with LRGTN [4].

When a high risk GTN is diagnosed, the first line of treatment is EMA-CO regimen; if resistance to this therapy is demonstrated, EMA-EP regimen is selected. If signs of toxicity are present, specific drugs are administered: Granulocyte Colony Stimulating Factor (G-CSF), or platelet transfusion. In isolated cases, a third or fourth line chemotherapy is necessary

In recent publications from Argentina, the high risk group with scores 7 to 13 was treated with EMA / CO and in patients with more than a 13 score EMA/EP was used. On second lines or further, for relapse or resistance the following drugs were used: EMA/EP, paclitaxel, VEIP, EP, Carboplatin-Gemcitabine, Capecitabine, and TP/TE. Complete response occurred in 98.2% and 100 % were compliant. Three patients died and in all 3 cases the outcome was related to inadequate initial treatment [24,52,53].

In cases of GTN relapsed to treatment, restaging is recommended. We share the opinion of Charing Cross that in patients with extensive disease, initial therapy with low doses of Etoposide and Cisplatin is appropriated to avoid tumoral lysis syndrome and hemorrhage at the beginning of treatment reducing the risk of early death in selected patients [54]. Others regimens are suggested in selected cases: one day EMA-EP [55], Paclitaxel-Etoposide and Paclitaxel-Cisplatin (TE-TP) [56], Bleomycin-Etoposide-Cisplatin (BEP) [57], Fluorouracil-Actinomycin D (FA) [58,59], FAEV [60], 5-fluorouracil, methotrexate and etoposide (FEM)[61], and Methotrexate, Bleomycin, and Etoposide (MEB) [62].

In case of treatment with EMA-EP, it is helpful to have a good intravenous infusion before and after the therapy of anti-emetic drugs like antagonist of 5-HT serotonin receptor, corticosteroids, and G-CSF, 48 hours after finishing the cycle until 48 hours before the following one, to decrease toxicity [63,64,65]. In Argentina, similar regimens are used. In the Province of Santa Fé, the Oncology Group of Litoral, in a study with 386 cases, 10.7% had GTN of high risk, and the treatment with MAC produced remission in 82% of them [1]. In Hospital Durand of Buenos Aires, of 358 cases 36,5% were GTN. In HRGTN the first line of therapy is

EMA/CO [52]. An interesting case report with the use of Capecitabine in a patient with multiple drug resistant was published, and an excellent response was achieved [52,53,66]. Unpublished data of Bianconi in Argentina reports that in high risk patients after several treatments with multiples lines, capecitabine reached rates of cure of 50%.

In the National Institute of Oncology in Mexico, 71 cases were diagnosed with GTN; 15 of those with low risk disease received single agent chemotherapy (11 MTX and 4 Etoposide), seven received Etoposide and Actinomycin D, and one received Etoposide- MTX. The response to this first line of chemotherapy was 88%. In 3 cases, a second line therapy with Etoposide /CDDP in 1 patient, and Etoposide Actinomycin D in two, were used, and the global survival was 100%. Forty one patients with high risk GTN who received single and multiple agent chemotherapy (EMA-CO and CHAMOCA), had a global survival of 94% [12]. A recent multicenter study reported that cure was achieved in 89,4% of patients with HRGTN in the intent to treat group [4].

Usually, hysterectomy is performed in patients over 40 years old with nonmetastatic disease and who no longer want to preserve fertility, although in several cases in the HUC series, it was performed due to profuse vaginal bleeding. Some LA centers are performing uterine artery selective embolization in cases with profuse bleeding. In the HUC, between 1970 -1978, Professor Bartollome Celli proposed that hysterectomy decreased the number of cycles of chemotherapy to achieve remission.

Selective criteria are employed to perform surgery in metastatic GTN, like in cases of isolated uterine, pulmonary, gastrointestinal or brain persistent nodule [67].

Radiotherapy is used in isolated brain or gastrointestinal nodules resistant to chemotherapy. Recently cranial irradiation was used in HUC in one case of solitary and haemorrhagic brain nodule (Figure 1-2) in a symptomatic patient (seizures); external radiotherapy with 300 cGy/day, for a total dose of 3000 cGy, with good response.

During chemotherapy treatment it is important to perform clinical and laboratory testing to evaluate response to the treatment, resistance and toxicity and imaging examinations with the objective of detecting resistance. The cornerstones to evaluate treatment response is the quantitative hCG, but only specialized public centers, and some private hospitals in LA have the DPC inmulite Siemens ®.

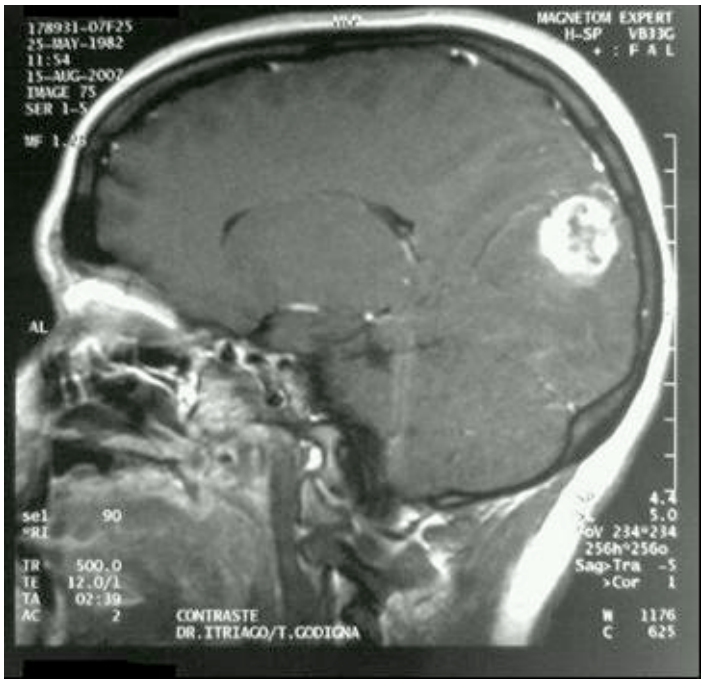
Although mortality rates documented by LA series are low, this fact may not reflect the reality of the disease in the region, because not all the deaths produced by GTD are recognized as a consequence of it, especially those occurring in non-specialized centers, in rural areas or in places without professionals trained to diagnose the disease. [22]. Another important problem is that there are not enough numbers of codes assigned to the wide variety of entities included in GTD in the book of International Statistic Classification of Diseases and Related Problems (CIE-10) [68].

13.5 HISTOPATHOLOGICAL DIAGNOSIS

A special mention is deserved regarding the progress in histopathological diagnosis in GTD. Numerous centers in LA are familiar with the histological criteria used to diagnose early molar pregnancies [49], and they are employed in the routine evaluation of abortion material when this examination is possible. In the HUC immunohistochemistry with p57 is performed in all cases of molar pregnancies [5], and some researchers are trying to find a clinical-immunohistochemical correlation. It is still necessary that there is a wider diffusion of information among pathologists, with the objective of unifying diagnostic criteria.

13.6 FUTURE

A recent study was performed at the HUC with the main objective of determining the time of regression of hCG post completion of non-molar pregnancies. The results suggest that this time lasts up to three weeks, in term gestation mainly [70]. Based on this result a multicenter LA research is being promoted with the objective of determining if hCG could be used as a screening method to detect GTN after any gestation in high risk populations; this would be very useful in centers where histopathological study is not available.



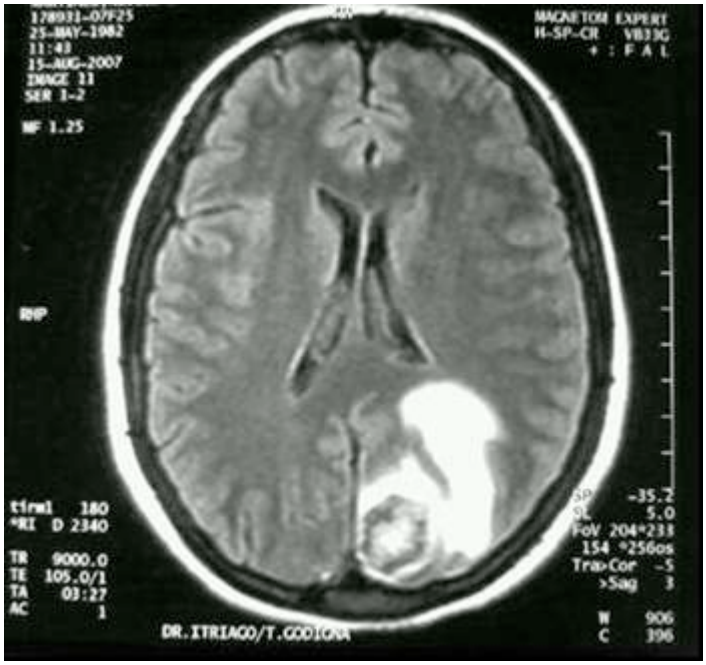


Figure 13.1 and 13.2. MRI using contrast with Gadolinium shows:
Metastasis of choriocarcinoma in left parietal posterior region, oedema produces a mass effect in the left occipital horn.

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