CLINICAL PARTICULARITIES AND DIAGNOSTIC METHODS IN THE HYDATIDIFORM MOLE

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Key words: hydatidiform mole, pregnancy, hyperthyroidism

Abstract. Aim of this study was to establish a significant way to the prognosis improvement in trophoblastic pathology in patients with hydatidiform mole. **Objective.** A mole is a particularity of embryonic development where a pregnancy occurs paradoxically without an embryo (the mole pregnancy) and develops only its placental tissue. It is important to demonstrate that the clinical diagnostic should always be completed by a histo-pathological diagnostic and also by the description of the natural history of the disease until the time of diagnostic. **Material and method.** The cases included in the study (n=45) were hospitalized in ”Elena Doamna” Clinical Hospital Iaşi, in the period of time between 2008 and 2013, and diagnosed with hydatidiform mole. The study was a retrospective one, case-control type. Starting from the already diagnosed illness and following the clinical and paraclinical parameters outlined in literature, the objective of the study was to establish the main risk factors that trigger the molar pregnancy. **Results.** The epidemiological characteristics show the following main risk factors for a molar pregnancy: age over 30, urban area, tobacco and alcohol consumption. The mean values of βHCG decreased significantly after the hydatidiform mole was removed, from 26,624 to 9,859 mUI/ml ($p<0.05$).**Conclusions.** Every woman with a history of hydatidiform mole has an increased risk of developing carcinoma. After the complete or partial removal of the hydatidiform mole, it is necessary to monitor the values of βHCG twice a month until they stabilize.

INTRODUCTION

The benign and malignant proliferative lesions appeared during pregnancy in the trophoblastic layer of the veloz villi were generically grouped under the name of “gestational trophoblastic disease (GTD)’’, based on the concept that claims that the benign hydatidiform mole, the invasive mole and the chorio-carcinoma are successive phases of a dynamic and continuous proliferative process that interests the fetal chorion (3, 5, 9, 10, 12).

According to this concept, which was taken over by the entire modern literature regarding chorio-carcinoma, a histologically benign hydatidiform mole can be just a phase in the evolution of the disease, having the potential of persisting or relapsing as a malignant tumour (5, 8, 9).

The reality of this lineage is imposed by the fact that the hydatidiform mole invariably precedes the invasive mole and 50% of the chorio-carcinomas have a gestational origin (2, 4, 7, 8).

The fact that the concept of GTD was assimilated, contributed in a significant way to the prognosis improvement in trophoblastic pathology through a careful monitoring of the patients with “benign moles”, following the same criteria as in the cases with a more aggressive histopathology in order to get an early detection of the proliferative trophoblastic sequelae (1, 13, 14).

A scientific group belonging to the World Health Organization (WHO) analysed the terminology that is sometimes confusing when referring to gestational trophoblastic diseases on the one hand, and the clinical terms, on the other hand, fighting the tendency of equating a histo-pathological term with its clinical name. WHO considers that it is useful for the invasive mole and the chorio-carcinoma to be grouped under a common clinical term, because they require a similar therapeutic conduct, even though there are important biological and prognostic differences between them (7).

AIM

The placenta is a transitory organ for gestation, and it also has an endocrine function, first of all because it produces human chorionic gonadotropin (HCG), which is a proteolipid hormone, secreted by the trophoblast. The trophoblast is the first embryo tissue which differentiates, becoming extra-embryo and taking an essential part in placenta formation.

The attempts to correlate the histologic grade of the mole with its malignant potential and thus identifying the patients who need cytostatic treatment were not satisfactory

The aim of this study was to establish a significant way to the prognosis improvement in trophoblastic pathology in patients with hydatidiform mole.

OBJECTIVE

A mole is a particularity of embryonic development where a pregnancy occurs paradoxically without an embryo (the mole pregnancy) and develops only its placental tissue. It is important to demonstrate that the clinical diagnostic should always be completed by a histo-pathological diagnostic and also by the description of the natural history of the disease until the time of diagnostic.

MATERIAL AND METHODS

The cases selected and included in the personal study (n=45) were hospitalized in "Elena Doamna" Clinical Hospital Iaşi, in the period of time between 2008 and 2013,and were diagnosed with hydatidiform mole. The average for the period was about 8 cases a year, with a decreasing tendency for the following period (y= 15.8 – 2.37 x).

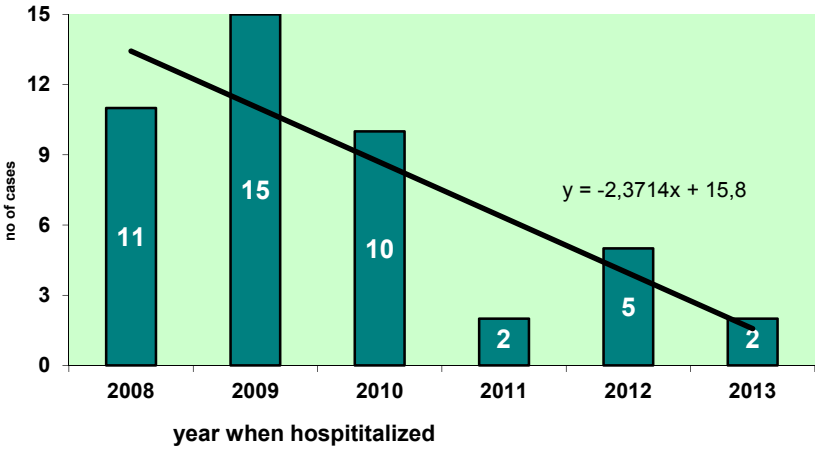


Fig. 1. The distribution of the cases with hydatidiform mole between 2008 and 2013 period

The determination of tumor markers and serum enzymes is relevant for diagnosing and monitoring the evolution of metastatic tumours.
The concentration and/or changes of the tumour markers in blood and in other fluids in the body is influenced by multiple factors: the total number of cells that produce markers, the synthesis rate and the rate of release for tumour markers, the expression of the tumour markers, the type of tumour "non-secretor", tumour blood perfusion rate, the extension of the necrosis for the tumour tissue, the presence of antibodies.
Malignancy of a hydatidiform mole is expressed by persistently increased values (in plateau) or by an increase in the titer values of βHCG during the monitoring period. In these circumstances, the best attitude is to send the patient to an oncologist immediately for a proper evaluation and treatment.
The factors associated with an increased risk of developing post-molar GTD are: age > 40 years old, uterine dimensions that are bigger than the normal pregnancy age, lutein ovarian cysts > 6 cm in diameter, values of βHCG > 100,000 mUI/ml, medical complications during pregnancy (2, 4, 6).

RESULTS AND DISCUSSIONS

The evaluation of the risk factors, through the frequency distribution and confirmatory tests of significance, shows the following profile of the patient with a molar pregnancy:

- average age of about 30 years old;
- living in the urban area is a slightly higher relative risk for the elderly patients (RR=1.43);

- the socio-occupational status did not show significant differences between the age groups, even if the frequency of unemployed people below 30 years old was about 50% (p=0.301);
- high educational level, high school studies, post high school and college was noticed mainly for the age group over 30 years old (65.2%), but statistically speaking the frequency distribution was not significantly higher when compared with the same level of instruction for the age group under 30 years old, where 54.5% of the patients had a high educational level (p=0.670);
- for older age 56.5% of the patients smoke, so the relative risk is over 4 times higher, which favours the appearing of the hydatidiform mole (RR=4.14);
- for the patients over 30 years old, the relative risk of getting a molar pregnancy while regularly consuming alcohol is about 3 times higher (RR=2.87).

Table 1. Epidemiological characteristics on age groups for the patients with hydatidiform mole

Profile	Age group ≥30 years old (n=23)		Age group <30 years old (n=22)		Significance		RR	IC95%
	n	%	n	%	X^2	p		
Urban area	15	65.2	10	45.5	1.07	0.301	1.43	0.83-2.48
Unemployed	7	30.4	11	50.0	1.07	0.301	0.61	0.29-1.28
High educational level	15	65.2	12	54.5	0.18	0.670	1.20	0.74-1.94
Smoker	13	56.5	3	13.6	7.25	**0.007**	4.14	1.36-9.59
Alcohol consumption	3	13.0	1	4.5	0.23	0.633	2.87	0.32-5.55

Diagnostic methods

The diagnostic of molar pregnancy suspicion before removing chorionic villi is given when there is a form of eclampsia manifested by nausea and excessive vomiting, a bigger uterine volume than expected for the pregnancy age, blood loss. The absence of the fetal heart beats and the impossibility to identify the fetal body parts through trans-abdominal palpation, ultrasound scan, amniography and, even pelvic angiography, offers presumptive elements of diagnostic (11).

The volume of the uterus can be variable, depending on blood accumulation and evacuation, its soft consistency, bundling is not perceptible (the fetus absence). Abdominal and pelvic pain is variable in intensity and also intermittent.

Generally, the symptoms are more obvious in the case of a complete mole and they are: amenorrhea, nausea, vomiting, bleeding, anemia, disproportional size of the uterus, early preeclampsia (normally, pregnancy induced hypertension occurs over 24 weeks), hyperthyroidism, luteal ovarian cysts.

Hyperthyroidism can be diagnosed in 25% of the moles, but it only manifests in 2-7% of the cases. Here are the signs of hyperthyroidism: weight body loss, tiredness, tachycardia, arrhythmia, heat intolerance, excessive sweating, and irritability. Hyperthyroidism appears because of the excessive stimulation of TSH secretion.

Signs of lung impairment are rare, only when the disease extends to the lungs, producing an acute lung failure. Sometimes, after the molar pregnancy has been removed, there can be a migration of mole fragments in the lungs, causing dyspnea, tachycardia, hypotension.

Together with hyperthyroidism and acute pulmonary failure, there have also been some other complications like cardiomyopathy and nephropathy.

Etiologic diagnosis

The first period: appeared most frequently at the age of 14 in 51.1% of the patients, followed by the age of 12 (22.2%) and 13 (17.8%). There are very few patients who had their first period at the age of 15 (2.2%) and 16 years (2.2%) and a percentage of 4.4% of the patients claim that the age of their first period was 11 years old.

46.7% of the patients had abortions, one abortion being the most frequent number (20%), but we have to mention the fact that 8.9% of the patients have more than 5 abortions in their obstetrical history, one patient declaring 14 requested abortions.

The obstetrical history of the patients showed deliveries for 31.1% of the women, 15.6% of the patients in the investigated lot having only one delivery.

17% of the patients were recorded with irregular menses, with a moderate flow in 33% of the cases.

The main ***signs and symptoms*** that were identified at admission were (based on the cases studied): moderate hemorrhage (51.1%); reduced hemorrhage (28.9%); hypogastric pain (42.2%) and abdominal-pelvic pain (15.6%); leucorrhea (11.1%); nausea and vomiting (11.1%).

The paraclinical diagnostic

The haemoglobin (Hb) varied from 9 to 12.5 mg/dl, the average of the lot being 11.57 ± 1.03 mg/dl.

The haematocrit (Ht) varied in the interval 21-47%, recording an average value of 39.61% ± 5.74.

The individual values of leukocytes varied from 3,800 to 16,200 / mm^3.

Thrombocytes varied in the interval 135,000-314,000 /mm^3, with a recorded mean value of 230,364/mm^3 on the cases studied, being within normal limits.

The first evaluation found the mean values of βHCG to vary from 1.5 mUI/ml to 91,300 mUI/ml, having an average value of 26,624 mUI/ml for the lot. After the removal of the hydatidiform mole, the individual values of βHCG decreased significantly, varying in the interval (142.4 - 59,100 mUI/ml), and the lot average being 9,859 mUI/ml ($p<0.05$).

Histological examination

The hydatidiform mole (molar pregnancy) is a disease of the trophoblast that is characterized by the hydropic thickening of the chorionic villi (accumulation of liquid) and trophoblast proliferation, without myometrial and vascular invasion; chorionic villi are disintegrated and have lost blood vessels (3).

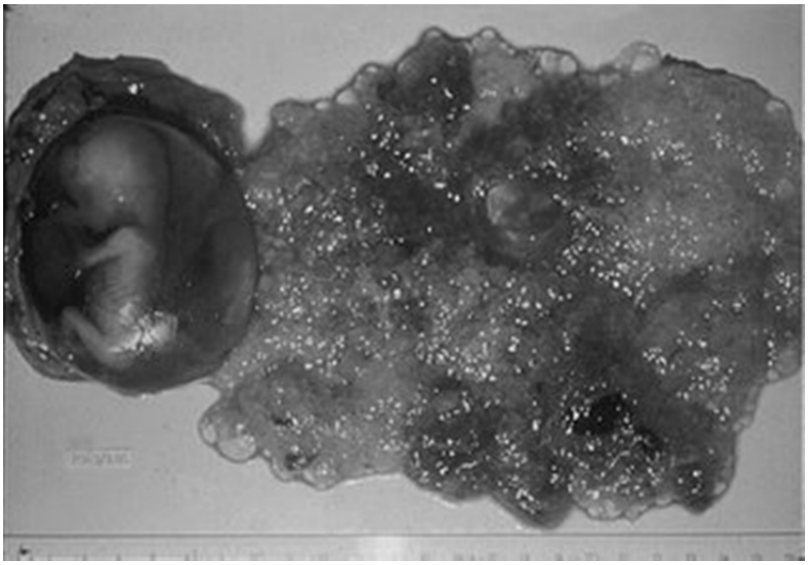


Fig. 2. The hydatidiform mole
(http://enfermagemnossavida.blogspot.ro/2010/04/mola-hidatiforme.html)

The invasive mole (*chorioadenoma destruens*) is a disease that has a local evolution, is rarely metastatic, and is characterized at microscopic level by the trophoblastic invasion of the myometrium, with identifiable villous structures. Microscopically it is characterized by cyto-trophoblast hyperplasia, syncytial elements and the persistence of the vilo structures (2, 8).

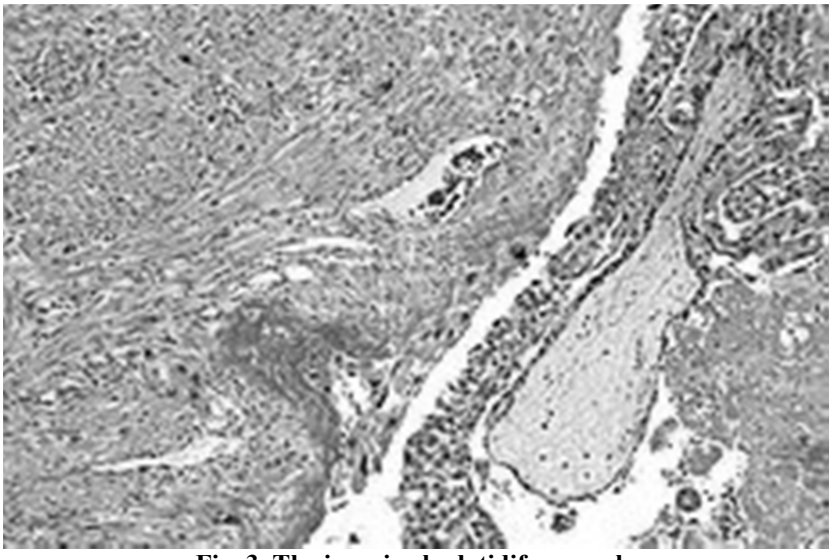
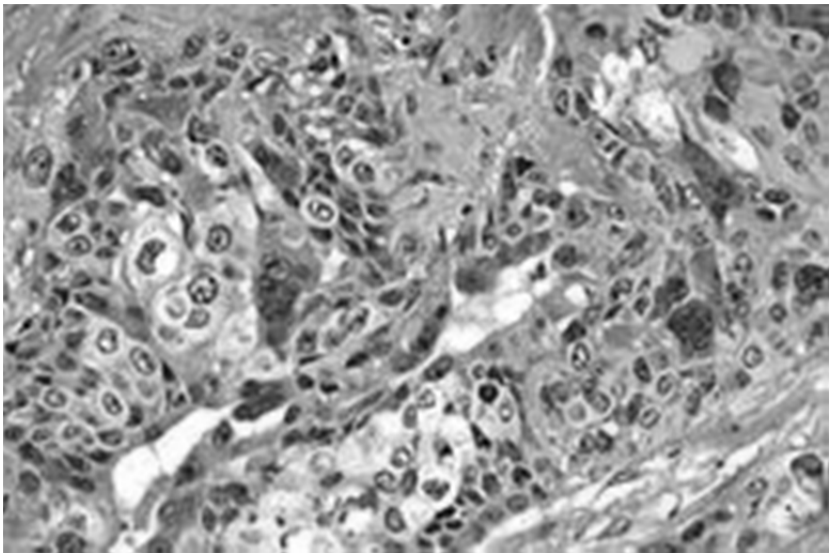


Fig. 3. The invasive hydatidiform mole
(http://en.wikipedia.org/wiki/Invasive_hydatidiform_mole)

The chorio-carcinoma is the malignant tumour of the trophoblastic epithelium. The uterine muscle and the blood vessels are invaded by areas of hemorrhage and necrosis. The groups of trophoblastic cells invade the normal tissue and disseminate in the distance in lungs, brain, liver, pelvis, vagina, spleen, intestines and kidneys (3).



Picture 4. Choriocarcinoma
(http://en.wikipedia.org/wiki/Choriocarcinoma)

Tumours located in the placenta are extremely rare and they come from the placental implantation premises, being derived from the cells of the intermediary trophoblast (that secretes larger quantities of human placental lactogen (HPL) than βHCG); clinically they appear as nodules in myometrium and endometrium after the removal of the mole. HPL is present in all the tumour cells, while its immuno-peroxidase is positive for βHCG only in certain cells, and the seric levels of βHCG are low. Usually these tumours appear after a non-molar abortion or a term pregnancy and only occasionally after a hydatidiform mole (8).

After the complete or partial removal of the hydatidiform mole it is necessary to monitor the values of βHCG every two weeks until they normalize (values below 5 mUI/ml), and this is proven by two consecutive measurements. After that it is recommended to have a monthly evaluation for six months, and then every 3 months up to a year. The patients will be encouraged to use contraception during this period of time (12, 15).
Every woman with a medical history of hydatidiform mole has an increased risk of developing chorio-carcinoma. That is why every subsequent pregnancy requires a histological examination of the maternal face of the placenta and the monitoring of the βHCG values for 6-8 weeks postpartum.

CONCLUSIONS

Being over 30 years old represents, through the frequency of the indicators with which this age is associated, an increased risk of having a molar pregnancy. For the older patients coming from the urban area the relative risk of having a molar pregnancy was 1.43 times higher.
Smoking, associated with age, induces a relative risk of getting a hydatidiform mole 4 times bigger. Alcohol consumption represents a risk factor about 3 times higher for the patients over 30 years old.
The obstetrical history shows mainly that: first menses appeared at the age of 14 (51.1%), 46.7% of the patients experienced abortion and only 31.1% of the women gave birth, generally to one child (15.6%). Irregular menses appear in 17% of the patients and 33% of them have a moderate flow.
The main symptoms found on admission were hemorrhage (51.1%) and hypogastric pain (42.2%).
Hematological parameters showed a slight anemia in patients with hydatidiform mole, the mean value of hemoglobin being 11.57 mg/dl, and the mean value of hematocrit being 39,61%. With few exceptions, the mean values of thrombocytes and leucocytes are kept within normal limits.
The mean values of βHCG decreased significantly after hydatidiform mole removal, from 26,624 to 9,859 mUI/ml ($p<0.05$).
After the complete or partial removal of the hydatidiform mole, it is necessary to monitor the values of βHCG twice a month until they stabilize. The patients will be encouraged to use contraceptive methods.

REFERENCES

1. Bagshawe KD. Risk and prognostic factors in trophoblastic neoplasia. *Cancer* 1976; 38(3):1373-1385.
2. Baker VV. Gestational trophoblastic disease. În: Abeloff MD, Armitage AO, eds. *Clinical oncology*. 2nd ed. Philadelphia: Churchill Livingstone, 2000: 2041-2050.
3. Brăila MG, Bădulescu F, Bădulescu A. Boli trofoblastice gestationale. În: Berceanu S, Bădulescu A, Braila MG, Bădulescu F, eds. *Patologia tumorală genito-mamară*. Bucureşti: Editura Didactică şi Pedagogică R.A., 2000: 324-354.
4. Cohn DE, Herzog TJ. Gestational trophoblastic diseases: new standards for therapy. *Curr Opin Oncol* 2000;12:492-496.
5. DePaolo S, Mangili B. Tumori del trofoblasto. În: Bonadonna G, ed. *Medicina oncologica*. 7ma ed. Milano: Masson, 2003:1135-1142.
6. Granai CO, Walter H, Robert D. Gynecologic cancer. În: Skeel RT, ed. *Handbook of cancer chemotherapy*. 6th ed. Philadelphia: Lipincott, Williams & Wilkins, 2003: 294-326.
7. Kavanagh JJ, Gershenson DM. Gestational trophoblastic disease: hydatidiform mole, nonmetastatic and metastatic gestational trophoblastic tumor: diagnosis and management. In: Katz VL, Lentz GM, Lobo RA, Gershenson DM, eds. *Comprehensive Gynecology*. 6th ed. Philadelphia, PA: Elsevier Mosby; 2012:chap 35.
8. Kudella AP, Freedman RS, Kavanagh JJ. Gestational trophoblastic tumors. În: Pazdur R, ed. *Cancer management: a multidisciplinary approach*. 8th ed. New York: CMP Oncology, 2004: 499-508.
9. Lurain JR. Gestational trophoblastic neoplasia. În Chang AE, eds. Oncology - *an evidence-based approach*. New York: Springer, 2006:892-902.
10. Lurain JR. Gestational trophoblastic tumors. *Semin Surg Oncol* 1990; 6(6):347-353.
11. Medeiros F et al. Germ cell tumors of the ovary. In: *Diagnostic Gynecologic and Obstetric Pathology*, 2006, 920–921 (eds Crum CP and Lee KR) Philadelphia: Elsevier Saunders.
12. Ministerul Sănătăţii. Curriculum de pregătire în specialitatea obstetrică-ginecologie. *CNPDS*. 2007.
13. Miron L. Boala trofoblastică. In: Miron L, Miron I, eds. *Chimioterapia cancerului - principii şi practică*. Iaşi: Kolos, 2005:402-424.

14. Muggia FM, Burke TW, Small W Jr. Gestational trophoblastic disease. În: DeVita VT Jr., Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology*. 7th ed. Philadelphia: Lippincott, Williams & Wilkins, 2005:1360-1363.
15. Newlands ES, Bower M, Holden L, Coll E. Management of resistent gestational trophoblastic tumors. *J Reprod Med* 1998;43:53-59.

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