

Prevalence of gestational trophoblastic disease in ectopic pregnancy

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Summary

Objective. To describe the prevalence of gestational trophoblastic disease in ectopic pregnancy. **Study design.** Medical records of 105 patients from January 2007 to October 2009. We excluded of the study 5 cases (one case where the answer of the biopsy was not clear; 4 others with diagnosis of adnexial mass where the pregnancy test had resulted positive but the answer of biopsy have been resulted ruptured ovary cyst and pyosalpingitis). So definitely the size of the sample was 100 patients. **Results.** 79 patients with EP underwent surgery due to a (diagnosis of EP with hem peritoneum and enraptured ectopic pregnancy) and in 18 of them the answer of the biopsy was GTD. 4 of 75 cases admitted in our hospital with diagnosis of EP, (pregnancy test was used instead of estimation of the level of β -hCG because our hospital couldn't offer estimation of the level of β -hCG during 24 hours) have been not confirmed diagnosis of EP by biopsy, but ruptured ovary cyst with hem peritoneum, pyosalpingitis. 31 cases with EP (enraptured EP) underwent medical treatment with methotroxate. In 10 cases last management was failed and surgical intervention was institutionalized and histological analysis revealed GTD in 6 of them (partial mole). β -hCG level was detected in 31 cases with enraptured fallopian pregnancy; in all cases where treatment with methotroxate has been failed and GTD was confirmed, the level of β -hCG was > 10.234 mIU/ml. 21 cases with enraptured fallopian pregnancy were successfully treated, and at this point we never learned the answer of biopsy. We registered one case with cervical pregnancy and one cornual (interstitial portion) pregnancy. **Conclusion.** we found 18 cases of

GTD in EP /11.500 deliveries (1,56 per 1,000 deliveries), prevalence of the GTD in EP was about 18%.

Key words: EP (ectopic pregnancy), GTD (gestational trophoblastic disease), β hCG (beta subunit of human gonadotropin chorionic choriocarcinoma).

Introduction

Gestational trophoblastic disease (GTD) includes a variety of entities ranging from hydatidiforme mole to choriocarcinoma (CC). Partial mole refers to a molar pregnancy with some normal and some swollen villi plus fetus, cord, and/or amniotic membrane elements (5). The prevalence of this entity varies from one country to another: in southeast Asia the rates are double for Eurasians people as compared to those of Chinese, Malaysian, or Indian origin. A decreased rate has also been reported among blacks in the United States in comparison to whites, and rates are higher among those of Latin American origin. Mexicans and Filipinos appear to have elevated rates in comparison to Japanese and Chinese. In the United States the rate is estimated to be approximately 0,75-1 per 1000 (2,3). The rates from Southeast Asia are 1,5- 2,5 times higher with much larger variations, and rates up to 8 per 1000 have been reported (4,9).

Due to the gestational character of this entity, GTD can originate in any of the following events: abortion and normal, ectopic or molar pregnancy. The development of GTD in an ectopic pregnancy is very rare, about 1,5 / 100 000 deliveries. There is wide variation in the reported incidence of hydatidiform mole. In the USA the rate is estimated to be approximately 0,75 to 1 per 1000 pregnancies. The rates from Southeast Asia are 1,5 to 2.5 times higher with much larger variations, and rates up to 8 per 1000 have been reported (1). Hospital Universitario de Caracas(HUC), as a reference center for GTD in Venezuela, reports an incidence of 1,54 per 1000 pregnancies (4,11). Choriocarcinomas have developed after normal pregnancy (1 per 40.000 term pregnancies) (2,7). The disease also follows incomplete abortion and ectopic pregnancy. The development GTD in an ectopic pregnancy is very rare event: 1,5 per 1,000.000 deliveries. but only a few cases are documented in the literature (6,9).

Strict histological criteria for GTD should be applied when evaluating an ectopic molar pregnancy due to the possibility of over diagnosis. At the same time we must be applied very strict criteria for GTD when evaluating an ectopic molar pregnancy due to the possibility of over diagnosis (3,12).

The terms complete and incomplete (partial) mole have been used to describe the variations of molar pregnancy. In complete mole only paternal chromosomes are

believed to be present; there are 46 chromosomes and nearly always 46,XX although a few moles with 46,XY karyotype have been reported. Incomplete, or partial, moles are usually triploid and have 69 chromosomes of both maternal and paternal origin. Bagshave reported that neoplasia that required chemotherapy occurs in approximately 1 in 200 cases of partial mole, compared with 1 in 12 with complete mole (1).

None of this criterion alone is sufficient to confirm the presence of a hydatidiform mole (usually detected by ultrasound examination of the pelvis).

Instead of, diagnosis depends upon the correlation of clinical and pathological features including a persistently elevated beta- human chorionic gonadotrophin (β hCG) level in serum or urine, an assessment of histological features, and DNA flow cytometric analysis to determine the ploidy.

The complete mole and partial mole can usually be differentiated by determining the ploidy status of the lesion with DNA cytometri (it must be emphasized that DNA flow cytometri is only of value in distinguishing a diploid from a triploid mole once the diagnosis of molar pregnancy has been made histologically) (1,13).

Materials and methods

A medical record review of 105 patients with diagnosis of ectopic pregnancy, suspect of ectopic pregnancy and adnexial mass) admitted to the emergency room of the obstetrics and gynecology university hospital from January 2007 to October 2009. Epidemiologic, clinical, biochemical and histopathologically data were analysis. We excluded of the study 5 cases (one case where the answer of the biopsy was not clear; 4 others with diagnosis of adnexial mass where the prenosticon test had resulted positive but the answer of biopsy have been resulted ruptured ovary cyst and pyosalpingitis. So definitely the size of the sample was 100 patients. All patients are undergone the ultrasound examination (80% of them transvaginal ultrasound examination and the rest of them transabdominal examination), vaginal examination and β -hCG estimation or prenosticon test as well.

Only 20 patients didn't have the chance to get neither β -hCG estimation nor prenosticon test evaluation. All patients with enraptured Ectopic pregnancy have been undergone medical treatment (Methotrexate 1 mg/kg weight). Because of the absence of the folic acid we could never applied the maximal dosage of the

Methotroxate (1,2 mg/kg weight). The hisyopathological examination was done in citpathological laboratory of Obstetric Gynecologic University Hospital, Tirana, Albania. We registered in one special paper all clinical datas and values of β -hCG of the patients with ectopic pregnancy, whom biopsy confirmed presence of the GTD.

Results

We incorporated in the study 100 patients with ectopic pregnancy: one of them was cervical pregnancy and the other one corneal pregnancy. The biopsy was taken in 79 patients, meanwhile 21 of 31 are successfully treated with methotroxate.

The answers of the biopsy of 79 cases resulted: 60 cases with ectopic pregnancy; 1 case Missed abort (cervical pregnancy) and 18 cases with GTD. Only five of 100 included in the study have shown in their gynecological history an previous ectopic pregnancy treated by surgery; only in 3 of 100 cases the ectopic pregnancy had come after in vitro fertilization procedure: one case was treated with methotroxate, meanwhile 2 other cases were treated by surgery. At 2 later cases the biopsy of one case was ectopic pregnancy and the biopsy of the other one was partial mole. The methotroxate therapy failed in ten patients, and surgery was called immediately.

The answer of the biopsy of these cases was ; in four cases (ectopic pregnancy); in 6 cases (GTD). Only one case of the later group resulted enraptured ectopic pregnancy after the methotroxate treatment and underwent laparoscopically surgery.

The value of the β -hCG was done negative from 20 – 35 days after surgical intervention. The value of the β -hCG before treatment with methotroxate fluctuated from 3.925 mUI/ml – 13.456 mUI/ml; and after the treatment the value of β -hCG varied from 3.450 mUI/ml – 11.456 mUI/ml (Table I); the other side the value of the β -hCG in first four cases with enraptured ectopic pregnancy before treatment with methotroxate fluctuated from 1900 mUI/ml – 4.800 mUI/ml; after the treatment this value varied from 456 mUI/ml – 3.200 mUI/ml. the time of negativisation varied from 14-21 days after surgical intervention.

Only 79 patients with ectopic pregnancy underwent the surgical intervention and the histological analysis, the others underwent medical treatment. From January 2007 to October 2009, there were 11500 deliveries. The prevalence of GTD in ectopic pregnancy was 1,5 per 1,000 deliveries. The mean patient age was 23 years

Table I - Clinical, laboratories, dosage, in 6 patients with GTD ine ectopic pregnancy, who failed Methotroxate therapy.

Icase	B-hCG level before treatment (mUI/ml)	Dosage of methotroxate	B-hCG level after treatment (mUI/ml)	Intervention	Biopsy	Time negativization
1	10320	1 mg/kg	10720	Tubectomy	MP	45 d
2	9000	1 mg/kg	8790	t/ect	MP	27 d
3	13456	1 mg/kg	11456	t/ect	MV	40 d
4	9270	1 mg/kg	10720	t/ect	MP	36 d
5	8375	1 mg/kg	9850	t/ect	MP	33 d
6	8150	1 mg/kg	8900	t/ect	MV	29 d

(range from 18 – 32). From 18 cases with GTD; 9 of them have no had pregnancy before, the others had more than 2 abortions, more than two deliveries, 5 patient had 6 pregnancy G6P2 S/C A3. In related to the mode of the treatment: 31 cases with Ectopic Pregnancy underwent medical treatment (methotroxate 1 mg/kg weight: one dose applied by i/m route), 3 of women were undergone ART therapy, and the final result, was ectopic pregnancy.

Ten patients failed in this way management, so in the next step they underwent the surgical treatment. The total number who got the surgical intervention was 79; one of them got laparoscopically rout, the others laparotomy one; one D&C. Salpingoectomy was performed on 77 patients; only in one case was performed adnexectomi. The histopathological analysis revealed 18 women with GTD; one missed abort; the rest of women (no. 60) with nonmolar ectopic pregnancy. The mean gestational age at which rupture of the fallopian tube occurred was 7 weeks in ectopic pregnancy complicated with GTD this is earlier than the mean gestational age in non molar ectopic pregnancy , which was 8,5 weeks. The level of β -hCG was detected before medical or surgical treatment of ectopic pregnancy in 75 cases and pregnancy test is estimated in 4 cases only (later cases are excluded of the study); so evaluation of β h CG and test of pregnancy was done in more than 80 % of the patient incorporating in the study; only in 25 cases had never chance to perform neither β -hCG nor pregnancy test because objective and subjective reasons (heavy hemo peritoneum or our hospital couldn't offer estimation of the β -hCG level during 24 hours). The level of β -hCG varied in patients with partial mole from 6.642 – 15.678 mUI/ml; complete mole 7.920 – 24.733 mUI/ml, and 1.256 – 13.439 mUI/ml in nonmolar ectopic pregnancy.

Would we believe the pregnosticon test?

The pregnosticon test resulted false positive in 4 patients (pyosalpinx); one patient with ruptured ovary cyst with hem peritoneum. From 100 women with ectopic pregnancy, 59 have had at least 2 abortions; 41 patients didn't refer any history related to pregnancy; from 31 women with EP, who took the methotroxate therapy 14 have had more than 2 abortions only; The negative value of the beta – hCG in women with ectopic pregnancy complicated of GTD was achieved for 9 cases on fourth week after surgical intervention; for 3 cases on the fifth week; two cases on the second week and 6 cases lost to follow up.

Discussion

The occurrence of moles in the fallopian tube has been described and it includes tubal rupture since 1964 by Westerhout; indeed the occurrence of placental site nodules has been reported in the fallopian tube by Muto in 11991 and Nayer in 1996. Now it is not a big surprise finding out a combination of ectopic pregnancy with intrauterine molar pregnancy. This has been described for the first time by Sze in 1998. In our study we have been identified 11 cases with partial mole and 7 cases with

complete mole, but at this point, today exist a big debate in related to standard histological criteria, which are very necessary in getting the right diagnosis.

The differential diagnosis between the three categories – hydropic abortus, partial hydatidiform mole, complete hydatidiform mole is very difficult on histological ground alone. This has been demonstrated by Gschwendtner et al. (8). They studied, retrospectively, their “molar” specimens with ploidy analysis. This was done after the strict criteria proposed by Paradinás (1994) had been applied (1). This aspect has also been studied by Genest (2001). Agreement was found in histology and ploidy with complete hydatidiforme mole, and in 79% of partial hydatidiforme mole and triploidy. However, that completely reliable histologic features do not exist tha allo accurate categorization; ploidy study is required, especially in gestational young specimens. The prevalence of the ectopic GTD in this case series was higher than reported in most studies. Probability that this higher incidence could be done occasionally or had been related with non strict histologic criteria.

The mean gestational age at which rupture of the fallopian tube occurred was 7 weeks in ectopic pregnancy complicated with GTD this is earlier than the mean gestational age in non mole ectopic pregnancy, which is 8,5 weeks. This fact may result from the higher ability for invasion and penetration of trophoblastic tissue in GTD as compared to the trophoblast in a normal pregnancy.

The time of negativization of the level of β -hCG in women with molar ectopic pregnancy is longer than in women with non molar ectopic pregnancy. In abnormal pregnancy, ectopic pregnancy and Missed abortion the level of β -hCG do not double every 48 hours like as in normal pregnancy. If the level of β -hCG during 48 hours increased < 66%. The risk of presence of abnormal pregnancy was extremely high when the level of β -hCG increased < 66 % during 48 hours (**Kadar et al. comprihensiv**).

As in other cases of ectopic pregnancy, transvaginal ultrasound was e helpful diagnostic tool, with a frequent finding of an adnexal mass and hemopertoneum. However, it does not differentiate an ectopic Gestation from GTD in an ectopic pregnancy.

No single diagnostic criterion can be applied to confirm the presence of a hydatidiform mole (usually detected by ultrasound examination of the pelvis). Instead of, diagnosis depends upon the correlation of clinical and pathological features including a persistently elevated beta-human chorionic gonadotrophin (β -hCG) level in serum or urine, an assessment of histological features, and DNA flow cytometric analysis to detect the ploidy.

The complete mole and partial mole could usually been differentiated by determining the ploidy status of the lesion with DNA cytometri (it must be emphasized that DNA flow cytometri in distinguishing a diploid from a triploid mole once the diagnosis of molar pregnancy has been made histologically).

The incidence of ectopic pregnancy in women who have been undergone the the artificial reproductive technology (ART) is about 1% (5). In our study we have been incorporated three cases with ectopic pregnancy; and one of then have been resulted with GTD. this was not a surprise. Abnormal ova and sperm as well as fertilization products were identified in this relatively young couple.

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