Can Laboratory and Clinical Signs Predict Persistence in Gestational Trophoblastic Disease?

Gestasyonel Trofoblastik Hastalıklarda Sürerlik Laboratuvar ve Klinik Bulgularla Tahmin Edilebilir mi?

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Abstract
Purpose: Laboratory and clinical signs of gestational trophoblastic disease (GTD) and their importance in the prediction of persistence of this disease were evaluated.
Material and Methods: Ninety-two patients with GTD were evaluated prospectively. Patients were divided into four groups as complete mole, partial mole, invasive mole and choriocarcinoma. All patients were evaluated for persistence by clinical, ultrasound and laboratory findings. Methotrexate+folinic acid were administered to the patients with persistent disease. Combined chemotherapy protocols were applied to patients with no mor minimum response. Hysterectomy was performed on older patients who had no desire for a child.
Results: Molar pregnancy and gestational choriocarcinoma rates were 4.8/1000 and 2/10,000 respectively. Mean age and mean beta-hCG levels were higher in the invasive mole group. Theca–lutein cysts and excessive uterine enlargement were detected in a higher proportion of patients with complete or invasive mole. These findings were seen more frequently in cases with persistence.
Conclusion: Persistent GTD can be predicted by clinical and biochemical markers. Risk of the development of persistence is lower in patients under the age of 35, in the absence of theca-lutein cysts and hCG level below 100,000 IU. In addition, negative predictive value of hCG level shows low risk of persistence to the same extent as negative predictive value of combination of parameters. With early detection and effective treatment, prognosis is excellent.

Keywords: **Chorionic Gonadotropin, beta Subunit; Human; Gestational Trophoblastic Neoplasms; Theca lutein cell.**

Özet
Amaç: Gestasyonel trofoblastik hastalıkların (GTH) laboratuvar ve klinik bulguları ve bunların GTH sürerliliğinin tahmin edilmesinde kullanımı araştırıldı.
Gereç ve Yöntem: GTH tanısı alan 92 hasta prospektif olarak incelendi. Hastalar komplet mol, parsiyel mol, invaziv mol ve koryokarsinom olarak 4 gruba ayrıldı. Hastalar klinik, ultrason ve laboratuar tetkikleri ile sürerliğin gelişimi olasılığı açısından değerlendirildi. Sürerlilik hastalığı olanlara metotreksat-folinic asit tedavisi; yeterli cevap alınamayanlarda kombine kemoterapi; çocuk isteği olmayan uygun yaştaki hastalara histerektomi uygulandı.
Bulgular: Molar gebelik ve koryokarsinom oranı sırasıyla 4,8/1000 ve 2/10.000 olarak bulundu. İnvaziv mol grubunda ortalama yaş ve tedavi öncesi beta-hCG seviyesi daha yüksekti. Komplet ve invaziv mol grubunda Teka-lutein kistleri ve aşırı uterin büyüme daha fazla görüldü. Bu bulguların görüldüğü hastalarda sürerlilik gelişiminin daha fazla olduğu bulundu.
Sonuç: Persistan GTH'da sürerlilik, klinik ve biyokimyasal belirteçlerle tahmin edilebilir. Bu risk 35 yaşın altındakilerde, teka-lutein kistlerinin yokluğunda ve beta-hCG'nin 100.000 IU'nin altında olduğunda düşüktür. HCG seviyesinin negatif prediktif değeri tek başına, diğer parametrelerle kombine edilmeden düşük sürerlilik riskini aynı oranda göstermektedir. Erken tanı ve etkin tedavi ile sürerlilik gösteren hastalıkların prognozu oldukça iyidir.

Anahtar Kelimeler: **Gestasyonel Trofoblastik Neoplazmlar; Koryonik Gonadotropin; beta alt birimi, insan; Teka lutein hücreleri.**

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Introduction

Trophoblasts are main cells forming placenta. Tumors originating from these cells are called gestational trophoblastic diseases (GTD) (1). GTD is generally divided into four groups by histopathologic examination: complete-partial mole, invazive mole, placental site trophoblastic tumor and choriocarcinoma (2). Mole hydatidiform has low malignant potential. Fifteen percent of the patients with molar pregnancy develop locally invasive trophoblastic tumor and 4% metastatic tumor (3). Invasive mole is usually located in the uterus but can form metastase in 40% of cases. It can also turn to choriocarcinoma in 15% of the cases if not treated properly (1,2,3).

It is very important to diagnose the disease before development of invasive mole or choriocarcinoma. A uterine size greater than that expected and bilateral ovarian enlargement (> 8 cm) on presentation are found to be weakly predictive of developing persistent disease (4). Histopathologic characterization of the molar gestation is not consistently shown to be benefical in predicting persistent disease (5). Although the ratio of free ß-hCG to hCG is higher in molar pregnancies than in normal pregnancies, the ratio is not helpful in distinguishing persistent disease from nonpersistent disease (6). Consequently, none has been sufficiently accurate to guide treatmen management.

In the present study, laboratory and clinical signs of gestational trophoblastic disease and their importance in the prediction of persistence were evaluated. Incidence of disease, sensitivity, specificity, negative and positive predictive value of laboratory and clinical signs for prediction of persistence were calculated.

Materials and Methods

Ninety-two patients diagnosed with gestational trophoblastic disease (GTD) were evaluated in Selçuk University Faculty of Medicine, Department of Obstetrics and Gynecology between 01.1998-31.12.2001 prospectively. Systemic and pelvic examinations were carried out on all patients. The obstetric history of all patients was obtained. The age of the patients and their partners, cause of admission, gestational age, gravida, parity, previous molar pregnancy or previous treatments for GTD, and duration between previous and last pregnancy, type of gestation (normal, abortion, molar or ectopic gestation) and outcome of the last pregnancy were evaluated. Serum beta-hCG levels were measured, anteroposterior chest X-ray was taken, heamotologic tests, and liver, renal, thyroid function tests and blood type of patients were determined. Abdominal-pelvic ultrasonography were applied all patients. Cases with choriocarcinoma or persistent disease were evaluated by brain, lung and abdominal computed tomography. Written informed consent was obtained from all patients.

Suction curettage was applied to all patients and curettage material was sent for histopathologic examination. Patients were divided into four groups according to the classification of WHO as complete mole, partial mole, invasive mole and choriocarcinoma. All patients were followed postcurattively by beta-hCG levels weekly. During hormonal follow-up, if beta-hCG level did not fall to the normal level after 8 weeks or rising or plateau forming levels of hCG values were accepted as persistent disease.

Clinical staging system was used during the treatment of patients (Table I). Hysterectomy was applied to older patients above 40 years of age without child desire The older patients who has not planned to become pregnant in future were operated with hysterectomy. Single agent chemotherapy (Methotrexate+folinic acid, MTX-FA) was applied to patients with persistent disease or nonmetastatic choriocarcinoma. A minimum 1 log fall in hCG levels was accepted as sufficient response to chemotherapy. If there was not an adequate response after two treatments of MTX-FA, combined chemotherapy regimens were applied.

Table I. Clinical staging system used during the evaluation of patients with gestational trophoblastic disease (7).

Nonmetastatic gestational trophoblastic disease
Good-prognosis metastatic gestational trophoblastic disease Last pregnancy less than 4 months ago. hCG (<100,000 IU (24 hour urine) or <40,000 mIU/mL b No liver or brain metastases. No prior chemotherapy
Poor-prognosis metastatic gestational trophoblastic disease Last pregnancy more than 4 months ago. HCG titer high (>100,000 IU (24 hour urine) or >40,000 mIU/mL blood). Liver or brain metastases. Prior chemotherapy. Occurrence after a full-term pregnancy.

Methotrexate + Actinomycin D + Chlorambucil (MAC) and Etoposide + Methotrexate +Actinomycin D – Cyclophosphamide + Vincristine (EMA-CO) protocols were used for combined chemotherapy. MAC protocol was applied to patients who did not respond to single agent chemotherapy or low risk metastatic disease. For patients with high risk metastatic choriocarcinoma, EMA-CO protocol was preferred. In order to decrease the risk of relapse, combined chemotherapy was applied until hCG level return to normal for three times consecutively.

Patients with persistent disease, metastatic disease or choriocarcinoma were examined with ultrasonography and pelvic examination and on monthly. Chest X-ray or CT of these patients was performed every 6-12 months.

Oral contraceptives were administered to patients during hormonal follow up by beta hCG. Patients who became pregnant during follow up were followed up antenatal. In hormonal following period, patients who didn't use oral contraceptives and became pregnant were antenatally followed up.

Data were summarised as mean ± SD in parametric conditions, median (min-max) in nonparametric conditions and as percentages. In order to calculate incidence, cases of GTD during study period were divided labors occured during the same period. Sensitivity, specificity, negative (NPV) and positive predictive value (PPV) of laboratory and clinical signs in prediction of persistance were calculated. Using SPSS package program, for the cases where parametric conditions were satisfied, analysis of variance (ANOVA) was used for the comparison of groups; and Kruskal Wallis test was used where those conditions were not satisfied. For comparisons of categorical data, ki-square test were used. Level of significance was taken as $p<0.05$.

Results

A total of 92 patients with GTD were admitted to our clinic during a 4-year period. Complete mole was detected in 58 (63.0%) patients, partial mole in 12 (13.0%), invasive mole 19 (20.7%) and choriocarcinoma in 3 (3.3%) patients. Incidence of GTD was 0.6%. The molar pregnancy and gestational choriocarcinoma incidence were 0.48% and 0.02%, respectively.

The mean age of patients was 28.8 9.34 (17-53). Eighty nine percent of the cases in the complete mole group, 66.0% of cases in partial mole group and all patients in choricarcinoma group were under the age of 35. However 74.0% of patients in invasive mole group were above 35 years. Mean age of the patients was significantly higher in the invasive mole group than the other groups ($p<0.05$, Table II). There was no statistically significant difference between complete, partial mole and choriocarcinoma groups in terms of age. The mean age of the partner was 31.6 9.3 years (19-56). It was significantly higher in the invasive mole group than the other groups ($p<0.05$, Table II).

Median parity of patients was 1 (0-11). Invasive mole was detected more frequently in multiparous patients; 89.5% of patients in the invasive mole group were multiparous ($p<0.05$, Table II). One case in the choriocarcinoma group was multiparous. Blood type of patients was 55.8% type A (32 in complet mole, 8 in parsiel mole, 10 in invasive mole and 1 in coriocarcinoma) , 26.7% type O (16 in complet mole, 2 in parsiel mole, 5 in invasive mole and 2 in coriocarcinoma), 11.7% B (7 in complet mole, 2 in parsiel mole, 2 in invasive mole and none in coriocarcinoma) and 5.8% AB (3 in complet mole, none in parsiel mole, 2 in invasive mole and none in coriocarcinoma). When groups compared in terms of blood type of patients and their partners, no statistically significant difference was found between them ($p>0.05$).

None of the patients had previous molar pregnancy. Of all patients, 26.2% had 1, 11.8% had 2 and 11.3% had 3 or more (3-5) previous abortuses. There was no statistically significant difference between groups in terms of previous abortuses ($p>0.05$). Molar pregnancy was the first pregnancy in 21.7% of patients. The previous pregnancy

Table II. Clinical and laboratory findings in gestational trophoblastic diseases (GTD).

Type of GTD	Partner age (year)	Age (year)	Case number (%)	Multiparity (%)	hCG over 100.000 IU/ml (%)	Theca-lutein cysts (%)	Excessive uterine enlargement (%)
Complete	27.7 ± 6.4	25.6 ± 6.3	63.0	31.0	48.2	13.8	43.1*
Partial	33.3 ± 9.0	29.8 ± 10.5	13.0	33.3	0.0	0.0	0 .0
Invasive	42.1 ± 9.1*	39.6 ± 9.1*	20.7	89.5*	78.9*	57.9*	36.8*
Choriocarcinoma	31.6 ± 2.8	30.0 ± 1.7	3.3	33.3	100.0*	33.3*	33.3
Total GTD	31.6 ± 9.3	28.8 ± 9.0	100	43.4	50.0	21.7	35.8

*p < 0.05 :statistically significant difference from the other groups.

had been terminated by term birth in 45.6% of cases and abortus in 32.7%. The mean time between the last pregnancy and diagnosis of GTD was 24 months. No relation was found between these two parameters due to the fact that very long time had passed since last pregnancy. Two choriocarcinoma developed after complete molar pregnancy and 1 after term delivery. Mean gestational age was 10.5 3.3 (4-20) weeks. Gestational age was below 12 weeks in 75.2% of all patients. Seventy-four percent of patients in the complete mole group, all patinets in the partial mole and 78.9% in the invasive mole group were below 12 weeks at the time of diagnosis. There was no difference between groups in terms of gestational age at the time of diagnosis.

Excessive uterine enlargement was detected in 43.1% of complete moles, 36.8% of invasive moles (Table II). Uterus was smaller than normal in 50.0% of partial moles and 20.6% of complete moles. Excessive uterine enlargement was detected in a higher proportion of the patients diagnosed with complete or invasive mole ($p<0.05$).

Pretreatment hCG level was below 100,000 mIU/ml in all patients with partial mole. hCG level was above 100,000 mIU/ml in 48.2% of patients with complete mole, 78.9% of cases with invasive mole and all patients with choriocarcinoma (Table II). Pretreatment hCG level was above 500,000 mIU/ml in 36.8% of cases with invasive mole but only in 10.2% of cases with complete mole. When the groups were compared, hCG levels were found to be significantly lower in the complete and partial mole groups than in the invasive mole group ($p<0.05$). No significant difference was found between the complete, partial mole and choriocarcinoma groups in terms of pretreatment hCG levels.

Theca-lutein cysts were reported in 20 (21.7%) cases. hCG levels were found to be above 100,000 mIU/ml in 90.0% of these cases. 40.0% of theca-lutein cysts were found in the complete mole group, 55.0% in the invasive mole goup and 5.0% in choriocarcinoma group. Theca-lutein cysts were seen in 13.8% of complete mole cases, 57.9% of invasive mole cases and 33.3% of choriocarcinoma cases. Cysts were not seen in the partial mole group (Table II). There was a significant difference between all groups ($p<0.05$).

In the present study age, beta hCG levels and presence of theca-lutein cysts were found to be significantly higher in the invasive mole group than in the others. Sensitivity, specificity, positive predictive value and negative predictive value of these 3 parameters are shown in Table III.

The most frequent symptom of GTD was vaginal bleeding (81.5%). Abdominal pain (8.6%), vesicles dropping out of vagina (2.2%), hyperemesis gravidarum (14.1%), signs of preeclampsia (7.6%) and hyperthyroidism (5.4%) were also observed. 11.9% of cases had no symptoms and were detected during antenatal follow-up. The majority of thr hyperemesis gravidarum, preeclampsia and hyperthyroidism were seen in the invasive and complete mole groups. Metastasis to lung (2 cases) and vagina (one case) were observed in choriocarcinoma patients.

Suction curettage was applied to all patients. After currettage hCG levels returned to normal in 6 weeks in 76.0% of patients. During hormonal follow-up weekly,

Table III. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of parameters showing persistence in GTD.

Parameters	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)
Age (>35 years)	63.6	85.7	58.3	88.2
Theca-lutein cyst	54.5	88.5	60.0	86.1
hCG(>100.000 IU/ml)	81.8	57.1	37.5	90.9
Combination of parameters	75.0	83.3	60.0	90.9

if beta-hCG levels did not fall or rising-plateau forming values levels of beta-hCG were accepted as persistent disease (19 cases). Single agent chemoteraphy was applied to 9 (47.3%) patients with persistence. Hysterectomy was applied to 8 (42.1%) patients over the age of 40 years without child desire. Both hysterectomy and chemotherapy were applied to 2 patients. Two patients in the invasive mole group who did not enter remission with single agent chemoteraphy and one patient with choriocarcinoma were treated with MAC regimen. EMA-CO regimen was given to 2 patients with choriocarcinoma and an other choriocarcinoma patient who did not enter remission with MAC regimen. Hormonal levels returned to normal in 9 weeks (4-13) after chemotherapy. All cases in the invasive mole group entered remission in 10 weeks. Cases with choriocarcinoma entered remission in 12-13 weeks. Patients were followed up at least 2 years after treatment, and nine (9.7%) patients became pregnant in spite of oral contraceptive terapy during this period. Six of them terminated with term birth, 3 with abortus.

Discussion

In literature, it has been reported that the incidence of molar pregnancy is varied from 0.6 to 2/1000 pregnancy in terms of regional differences (8). In the present study, the incidences of GTD, molar pregnancy and gestational choriocarcinoma were 6/1000, 4.8/1000 and 2/10,000, respectively. When compared with literature, GTD incidence is found to be higher than data those had been reported. This is probably due to that our hospital is a reference center in Konya, Turkey

GTD is mostly seen in cases below 20 years of age and after 35 years. Invasive mole incidence is higher after 35 years (9). In the present study we observed that eleven percent of patients in the complete mole group and 74% of patients in invasive mole group were above 35 years of age. Twenty percent of patients were over 40 years in the present study. Partial mole was seen in similiar rates in all age groups in the reproductive period. Maternal age over 35 was accepted as a risk factor for invasive mole development. There is no relation between paternal age and risk of GTD development. La Vecchia et al. reported that paternal age over 45 increases risk of GTD (10). However Matsuura and Messerli reported no increase in incidence with paternal age (11, 12). In this study paternal age was significantly higher in the invasive mole group. But paternal age is usually paralel to maternal age. So it was accepted that it does not affect GTD incidence.

The most frequent symptom of GTD is vaginal bleeding. Also signs of preeclampsia, hyperemesis gravidarum and hyperthyroidism can be seen. Sometimes a patient is admitted due to abdominal pain and vesicles dropping out of the vagina (13). Vaginal bleeding was the most frequent symptom in our study (81.5%). 14.1% of patients had hyperemesis gravidarum, 7.6% had signs of preeclampsia and 5.4% had hyperthyroidism. Most cases of hyperemesis gravidarum, preeclampsia and hyperthyroidism were seen in the invasive and complete mole groups. Also hCG levels were higher than 100,000 mIU/ml in all groups.

Parity plays no role in the development of GTD (14). In our study, parity was found higher in the invasive mole group. This was related to the higher age of the patients in this group and the increase of parity with age. The higher rate of parity in invesive mole group may be attributed to older subjects in this group.

Bagshave and coworkers examined the effect of blood types on molar pregnancy and they did not find any difference between patients and their partners, and the control group (15). In our study 55.8% of the patients had blood type A. The second most frequent type was O. Blood types of patients and partners did not affect the prognosis of GTD.

The most important risk factor in the development of GTD is previous molar pregnancy. The risk of molar pregnancy increases 10 times in patients with previous molar pregnancy (16). None of the patients in our study had a previous molar pregnancy. Previous abortuses increase molar pregnancy risk (17). However only 11% of patients had 3 or more previous abortuses in our study. Choriocarcinoma may develop after any type of pregnancy. Seventy percent if it develops after complete mole, 20% after abortus or tubal pregnancy and 10% after term

pregnancy (18). In our study, there were 3 choriocarcinoma cases: 2 developed after complete mole and 1 after term pregnancy.

GTD is diagnosed and treated in the early stages 6-10 weeks (19). In our study 75% of cases were under 12 weeks at the time of diagnosis. Mean gestational age was 10.5 weeks. Delay in diagnosis was due to the low sociocultural status of patients and insufficient antenatal follow up. Hyperemesis gravidarum, preeclampsia and hyperthyroidism were found more frequently in cases with advanced gestational age, although there was no significant difference in terms of persistancy between early and late gestational weeks.

Beta hCG is the most important marker in the diagnosis and follow up of GTD (20). In the present study, excessive uterine enlargement was detected in 43.1% of complete moles, 36.8% of invasive moles and none of the partial mole. Excessive uterine enlargement has been reported to be 50% in complete moles and 3-4% in partial moles (2). Beta hCG levels were reported to be higher than 100,000 mIU/ml in complete mole with excessive uterine enlargement (21). In our study, the hCG levels were found to be above 100,000 mIU/ml in all complete mole cases with excessive uterine enlargement (43.1% of complete mole cases). All of the choriocarcinoma cases and 78.9% of invasive moles had hCG levels of above 100,000 mIU/ml. There was a significant relation between hCG levels over 100,000 mIU/ml and persistence of disease. We also found that persistence had developed in 24.0% of complete moles with excessive uterine enlargement and in 27.2% of complete moles with normal or smaller uteruses. Thus we suggest that the patients with high hCG levels must be followed up carefully for persistence.

Theca-lutein cysts are seen mostly in complete mole cases because of high hCG levels (21). It was reported that theca-lutein cysts were observed in 37.0% of cases with GTD (22). In our study, theca-lutein cysts were detected in 21.7% of cases and hCG level above 100,000 mIU/ml in 90% of these cases. These cysts were seen in 13.8% of complete moles, 57.9% of invasive moles and 33.3% of choriocarcinoma cases. Cysts were not detected in partial mole group. There was a significant relation between persistence of disease and theca-lutein cysts.

Early metastasis to vagina, lung and late metastasis to the liver and brain are seen in metastatic GTD (1,2,3). In the present study, metastasis was only seen in choriocarcinoma cases: lung metastasis in 2 cases and vaginal metastasis in one.

Today, suction curretage is the treatment of choice in young patients who desires preservation of fertility (1,2). After curretage, if the beta hCG level does not fall or rising-plateau forming values of beta hCG are accepted as persistent disease and chemotherapy is started. Hysterectomy is another treatment choice in older patients without child desire (2).

The first treatment in persistent GTD is single agent (methotrexate-folinic acid) chemotherapy (23). The cure rate is 80-90% with this regimen (24). Also hysterectomy can performed on cases above 40 years of age without child desire. In our study, hysterectomy was applied in 10 cases with invasive mole (52.6%), and complete cure was seen in 8 cases after hysterectomy. Eleven cases together with 2 patients whose hCG levels did not fall after hysterectomy were given MTX-FA. Complete cure was seen with one chemotherapy cure in 9 patients. The cure rate was 81.8%.

For the cases that not respond to single agent chemotherapy or those with high risk metastatic disease, combined chemotherapy was applied. The most frequently used combined regimens are MAC and EMA-CO (25, 26). Remission rate with MAC is 49% (27,28) and is not sufficient for primary treatment of high risk patients. EMA-CO has a 76-94% complete remission rate. Hence it is used as a primary treatment in high risk patients (29).

In our study, 2 patients with persistent disease whose hCG level was not reduced after MTX-FA, MAC regimen was applied. These patients entered remission with one chemotherapy cure. hCG levels returned to normal in an average of 10 weeks in the invasive mole group.

MAC regimen was given as the first treatment to one choriocarcinoma case. When no response was observed EMA-CO regimen was applied. For the other two choriocarcinoma cases, EMA-CO regimen was given directly. Patients entered remission in an average of 12-

13 weeks. The mean number of chemotherapy applied was 9. Lung metastasis was seen in 2 cases and vaginal metstasis in one case. Metastasis diminished completely during chemotherapy.

In a study of Lan et al., 22 patients who became pregnant within a year of chemotherapy were examined. They found 9.1% GTD, 27.1% fetal loss, and 40.9% term healthy pregnancies (30). In the present study, patients were followed up for a minimum of two years. In 9 (9.7%) patients pregnancy was seen. 6 (66.6%) of these pregancies ended with term labour and 3 (33.3%) with abortuses.

As a result, persistent GTD can be predicted by clinical and biochemical markers. Age, pre-treatment beta hCG levels and the presence of theca-lutein cysts are important parameters in predicting persistence. The risk of the development of persistence is lower in patients under the age of 35, in the absence of theca-lutein cysts and hCG level below 100,000 mIU/ml. Patients with a risk of persistence must be followed carefully. With early detection and effective treatment their prognosis is very good. The evaluation of the clinical and biochemical markers may assist in defining a subset of patients at high risk for persistent disease, who require closer follow-up and administration of prophylactic chemotherapy.

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