

Epidemiologic Characteristics and Management of Subjects Who Were Diagnosed with Trophoblastic Disease

Gestasyonel Trofoblastik Hastalık Tanısı Almış Olguların Epidemiyolojik Özellikleri ve Tedavi Yönetimleri

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ORIGINAL
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ÖZGÜN
ARAŞTIRMA

ABSTRACT
ÖZET

Objective: To evaluate retrospectively the patients diagnosed and treated with gestational trophoblastic disease (GTD) in our clinic.

Material and Methods: Sixty-nine women diagnosed with GTD between January 1996 to December 2010 were included into the study. Age, gravida, parity, abortus, curettages, job and education, consanguinous marriage, gestational age, blood groups, menarche age, type of GTD, hyperthyroidism, serum β -HCG levels before and after a week following the treatment were recorded.

Results: Eleven thousand five hundred twenty-two deliveries occurred and 69 cases were diagnosed with GTD. One patient, diagnosed with invasive mole, was excluded from the study because she did not follow the recommended chemotherapy. Out of 68 patients; 37 (54.43%) patients were incomplete mole, 29 (42.63%) were complete mole, (1.47%) were invasive mole and 1 (1.47%) patient was choriocarcinoma. The treatment of 65 (95.6%) patients were curettage under general anesthesia, 2 (2.9%) were hysterectomy and 1 (1.5%) was chemotherapy. Patients were followed with β -HCG and a minimum of six months contraception was recommended.

Conclusion: The incidence of GTD was 5.9 per 1000 deliveries. Our patients had poor educational status, high parity and gravida. These factors seem to be etiologic reasons. Educating the patients and lowering the high birth rate can decrease the incidence of GTD. Gestational trophoblastic neoplasias are a group with high chemosensitivity. Early diagnosis and treatment may enable high remission rates even in malignant forms. It was concluded that this could be achieved by generalizing public health services and antenatal follow-ups especially in developing communities.

Key words: Gestational trophoblastic disease, incidence, mole, hydatidiform

Amaç: Kliniğimizde gestasyonel trofoblastik hastalık (GTH) tanısıyla takip edilen ve tedavileri yapılan hastaların retrospektif olarak değerlendirilmesi.

Gereç ve Yöntemler: Çalışmaya Ocak 1996-Aralık 2010 arasında İstanbul Taksim Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'nde GTH tanısı konulan 69 hasta alındı. Hastaların yaş, gravida, parite, abortus ve küretaj sayıları, meslek, eğitim durumları, akraba evliliği, gebelik haftaları, kan grupları, menarş yaşları, GTH'nin histolojik tipi, hipertiroidi varlığı, tedavi öncesi ve sonrası serum β -HCG düzeyleri ve uygulanan tedaviler kaydedildi.

Bulgular: Kliniğimizde 1996-2010 yılları arasında 11522 doğum gerçekleşti ve 69 olguya GTH tanısı konuldu. Bir vaka invaziv mol tanısı ile kemoterapi tedavisine yönlendirildi fakat hasta takip ve tedavilere devam etmediğinden çalışma dışı bırakıldı. Kalan 68 hastanın; 37'si (%54,43) inkomplet mol, 29'u komplet mol (%42,63), biri invaziv mol (%1,47) ve biri koryokarsinom olarak tespit edildi. Tedavi olarak 65 hastaya (%95,6) genel anestezi altında vakum küretaj, 2 hastaya (%2,9) histerektomi ve 1 hastaya (%1,5) kemoterapi uygulandı. Tüm hastalar β -HCG takibine alındı ve en az 6 ay kontrasepsiyon önerildi.

Sonuç: Kliniğimizin gestasyonel trofoblastik hastalık insidansı 1000 doğumda 5,9 olarak bulundu. Hastalarımızın düşük eğitim seviyeli oluşları, yüksek gravida ve parite sayılı olmaları etyolojik nedenler arasındadır. Hastaların eğitilmesinin, gravida ve parite sayılarının azaltılmasının insidansın azaltılmasına katkısı olabileceği düşünüldü. Gestasyonel trofoblastik neoplaziler ise neoplazmlar içinde kemosenitivitesi yüksek bir gruptur. Erken tanı ve tedavi ile malign formlarında bile çok yüksek oranlarda remisyon sağlanabilmektedir. Bunun da özellikle gelişmekte olan toplumlarda toplum sağlığı hizmetlerinin ve antenatal takiplerin yaygınlaştırılması ile sağlanabileceği kanaatine varıldı.

Anahtar kelimeler: Gestasyonel trofoblastik hastalık, insidans, mol hidatiform

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Introduction

Today, gestational trophoblastic disease (GTD) is a disease that may be diagnosed early and treated effectively (1). GTD including hydatiform mole, invasive mole and chorio-carcinoma is a tumor group that has the chance for treatment even in the presence of metastasis (2, 3). Although its pathogenesis is not clear, abnormal gametogenesis, fertilization and malignant transformation of trophoblastic tissue are the main pathologic changes in GTD (4, 5). Socioeconomic status, blood type, age of menarche, maternal age, parity, history of molar pregnancy, genetic factors, malnutrition, parasites and infections are among the risk factors (6). Incidence may vary according to geographic areas. Incidences has been reported as 0.75 in 1000 pregnancies from the USA, 1.6 from Mexico, 2 from Japan, 1.54 from England and 0.3-16 from Turkey (2, 5, 7). This study was aimed to retrospectively evaluate the patients who were diagnosed as GTD and treated in the Department of Gynecology and Obstetrics, Taksim Research and Training Hospital, Istanbul, Turkey between 1 January 1996 and 31 December 2010 and to compare with other clinical results.

Material and Method

In our study, records of 69 patients who were diagnosed as GTD in the Department of Gynecology and Obstetrics, Taksim Research and Training Hospital, Istanbul, Turkey between 1 January 1996 and 31 December 2010 were analyzed retrospectively. Age, gravida, parity, number of abortions and curettages, educational and occupational status, presence of consanguinity, gestational week, blood type, age of menarche, histologic type of GTD, presence of hyperthyroidism, serum β -HCG levels before and after treatment and therapies applied to the patients were recorded. Hemogram, renal, hepatic and thyroid function test results of all patients were obtained. Cerebral, whole abdomen and thorax tomographies were performed with the aim of screening for metastasis and patients who had findings of metastasis were recorded. Vacuum curettage was performed for definite diagnosis and treatment to the most of the patients and appropriate patients underwent hysterectomy by taking age, parity and patient's demand into consideration. Results of pathology materials were also recorded. Pre and post-treatment β -HCG values (mIU/mL) were statistically assessed using student's t-test. Patients diagnosed as hydatiform mole were divided into subgroups as complete and incomplete mole and in-group statistical analysis were performed in terms of age, gestational week, β -HCG levels. Patients with diagnosis of chorio-carcinoma and invasive mole could not be grouped due to the small number of patients. The obtained data were analysed with SPSS 15.0 programme. Descriptive statistics, one-sample chi-square test, t test and Mann-Whitney Test were performed to compare parameters.

Results

A total of 11522 women gave birth at the Department of Gynecology and Obstetrics, Taksim Research and Training Hospital, Istanbul, Turkey between January 1996 and December 2010 and the incidence of GTD was estimated as 5.9/1000 live births. One out of 69 patients was guided for chemotherapy with a diagnosis of invasive mole. However, this patient was excluded as she did not comply with follow-ups and treatment.

The distribution of demographic data of the patients with GTD are given in Table 1. The mean age of patients in the study group was 29.56 ± 7.58 (min: 17-max: 45). 80.9% (n=55) of the patients were housewives, 45.6% (n=31) were illiterate, 30.9% (n=21) had consanguineous marriages.

Distributions of ages according to pathological type in GTD patients was calculated with a histogram and the t test was performed in independent samples. There was consanguinity in a total of 21 (30.8%) patients. A non statistically significant difference was found between GTD patients with complete (30.41 ± 7.2) and incomplete (28.68 ± 7.5) mole in terms of age. ($t=0.947$, $df=64$, $p=0.991$). 80.9% of patients (n=55) were housewives, 10.3% (n=7) were workers, 8.8% (n=6) were officers. The difference between employment groups in GTD was found statistically significant ($X^2=69.206$, $df=2$, $p<0.001$). When the education levels of the patients were investigated, it was found that 45.6% (n=31) were illiterate, 33.8% (n=23) were primary school graduates, 16.2% (n=11) were high school graduates, 4.4% (n=3) were university graduates.

According to the results given in Table 1 of a single sample chi-square test, GTD was higher between the ages of 25-29 (27.9%). The difference between age groups in GTD was found statistically significant ($\chi^2=21.147$, $df=6$, $p=0.002$). GTD was most seen in illiterate (45.6%) patients. The difference between the level of education in GTD was found statistically significant ($\chi^2=27.294$, $df=3$, $p>0.001$). Age of menarche varied between 9 and 15 and the mean age was calculated as 11.42 ± 1.79 . Mean gestation week at the time of diagnosis was 9.5 ± 3.45 . A non significant difference was found between GTD patients with complete (9.86 ± 3.62) and incomplete (9.21 ± 3.31) mole in terms of gestation week. Distributions of gestation weeks according to pathological type in GTD patients was calculated with a histogram and Mann-Whitney U Test was performed ($U=479.5$; $p=0.458$).

Distribution of clinic data of the patients with GTD are given in Table 2. Thirty-seven of 68 GTD patients (54.43%) were classified as incomplete mole, 29 (42.63%) complete mole, 1 (1.47%) invasive mole and 1 (1.47%) chorio-carcinoma. According to the one sample χ^2 test results given in Table 2, the difference observed

Table 1. Distribution of demographic data of the patients with gestational trophoblastic disease according to age, employment and education

	n	%	X^2	p
Age (year)			21.147	0.002
15-19 years	5	7.4		
20-24 years	14	20.6		
25-29 years	19	27.9		
30-34 years	12	17.6		
35-39 years	6	8.8		
40-44 years	10	14.7		
45-49 years	2	2.9		
Total	68	100.0		
Employment			69.206	<0.001
Housewife	55	80.9		
Worker	7	10.3		
Officer	6	8.8		
Total	68	100.0		
Education Level			27.294	<0.001
None	31	45.6		
Primary	23	33.8		
High	11	16.2		
University	3	4.4		
Total	68	100.0		
Consanguinity			9.941	0.002
Yes	21	30.9		
No	47	69.1		
Total	68	100.0		

Table 2. Distribution of clinical data of patients with gestational trophoblastic disease according to type, complaints, gravida, abortus and curettage

	n	%	χ^2	p
Pathological Type			62.118	<0.001
Incomplete mole	37	54.4		
Complete mole	29	42.6		
Invasive mole	1	1.5		
Chorio-carcinoma	1	1.5		
Total	68	100.0		
Complaint for admission			114.471	<0.001
Vaginal bleeding	54	79.4		
Delay of menstruation	8	11.8		
Passage of vesicle	3	4.4		
Emesis and vomiting	2	3.0		
Inguinal pain	1	1.0		
Total	68	100.0		
Gravida			76.706	>0.001
1	21	30.8		
2	15	22.0		
3	5	7.4		
4	8	11.8		
5-9	13	19.1		
10 and above	6	8.9		
Total	68	100		
Abortus			63.529	<0.001
None	45	66.1		
1	11	16.2		
2	9	13.3		
3	3	4.4		
Total	68	100		
Curettage			202.353	<0.001
None	55	80.9		
1	3	4.4		
2	4	5.9		
3	3	4.4		
4	1	1.5		
5	2	2.9		
Total	68	100.0		

between the GTD pathological types was statistically significant ($\chi^2=62.118$, $df=3$, $p<0.001$). Although the most frequent complaint on admission was vaginal bleeding (81.3%), delay of menstruation (12.4%), passage of vesicle (3%), emesis and vomiting (2.3%), inguinal pain (1%) were also noted. According to the one sample χ^2

test results given in Table 2, the difference observed between the complaints on admission was statistically significant ($\chi^2=114.471$, $df=3$, $p<0.001$). 21 (30.8%) patients were primigravidas, the number of patients with 5 or more gravidas was found as 19 (27.9%). The difference observed between the gravidas was statistically significant. ($\chi^2=76.706$, $df=11$, $p<0.001$). Distributions of gravida according to pathological type in GTD patients was calculated with a histogram and Mann-Whitney Test was performed. A non significant difference was found in GTD patients between complete and incomplete mole in terms of gravida ($U=461.5$, $p=0.321$).

Twenty-seven (39.7%) patients were nulliparous. There was no history of spontaneous abortion in 45 (66.1%) patients, 11 (16.2%) patients had one abortion. The difference observed between the abortions was statistically significant ($\chi^2=63.529$, $df=3$, $p<0.001$). Distributions of abortions according to pathological type in GTD patients was calculated with a histogram and Mann-Whitney U Test was performed. A non significant difference was found in GTD patients between complete and incomplete mole in terms of abortion. While 55 (80.9%) of the patients had never undergone curettages, 2 (2.9%) had 5 curettages. The difference observed between the number of curettages was statistically significant ($\chi^2=202.353$, $df=5$, $p<0.001$). Distributions of the number of curettages according to pathological type in GTD patients was calculated with a histogram and Mann-Whitney U Test was performed. A non significant difference was found in GTD patients between complete and incomplete mole in terms of curettages ($U=530.00$, $p=0.897$).

Vacuum curettage was performed in 65 (95.6%) patients under general anesthesia. 2 (2.9%) patients underwent hysterectomy and 1 (1.5%) patient was administered chemotherapy. One patient who had a complete mole and 1 patient who had an invasive mole underwent hysterectomy.

Distribution according to blood type was as follows: 39 (57.3%) group A, 18 (26.5%) group O, 6 (8.8%) group B and 5 (7.4%) group AB (Table 3). Distributions of blood groups according to pathologic type in GTD patients was calculated with a histogram and Mann-Whitney Test was performed. A non significant difference was found in GTD patients between complete and incomplete mole in terms of blood groups ($U=528.5$, $p=0.910$).

Hyperthyroidism was detected in a total of 4 patients and of them, 2 had incomplete hydatiform mole, 1 had invasive mole and 1 had chorio-carcinoma. Mean β -HCG values of the patients before and after curettage were estimated as 131.2 ± 2765 mIU/mL and 35.2 ± 8.752 mIU/mL, respectively. Reduction in β -HCG values following curettage was found statistically significant (t test, $p<0.001$). A non significant difference was found between GTD patients with complete (132.63 ± 2.534 mIU/mL) and incomplete mole (129.15 ± 3.216 mIU/mL) in terms of β -HCG levels (t test, $p=0.99$). Lung metastasis was detected in one patient. All patients were followed-up once a week until β -HCG levels became normal, once in three weeks after β -HCG levels had become normal and thereafter monthly for one year. Remission occurred at approximately the 36th day in the incomplete mole group and the 38th day in the complete mole group. Patients were recommended contraception for at least 6 months.

Table 3. Distrubituon of blood groups

	n	%	X ²	p
Blood group			102.676	<0.001
A Rh+	37	54.4		
A Rh-	2	2.9		
B Rh+	5	7.4		
B Rh-	1	1.5		
AB Rh+	5	7.4		
AB Rh-	0	0		
O Rh+	15	22.1		
O Rh-	3	4.4		
Total	68	100		

Discussion

Gestational trophoblastic diseases (GTD) are a group of diseases including benign and malignant diseases and the incidence varies widely between geographic regions (6). Incidence of molar pregnancy has been found 2-3 times greater in South-Eastern Asia than America and Europe (8). While the incidence of molar pregnancy is 11.5/1000 in Indonesia, it is less than 1/1000 in America (6). It has been reported as 1.9 in Japan and 2.8 in Thailand (9). From Turkey, it has been reported as 12.9/1000 by Gul et al., 6.6/1000 by Cetin et al., 0.83/1000 by Yalcin et al., 8.1/1000 by Kurdoglu et al. in 1997; 24.5/1000 by Gul et al. and 1.78/1000 by Oguz et al. in 2000 (10-14). In our study the GTD incidence was found as 5.9/1000 births. According to pathological distribution, 54.3% were incomplete, 42.3% were complete, 1.47% were invasive mole and 1.47% were chorio-carcinoma.

The most common causes of admission in molar pregnancies are vaginal bleeding, passage of vesicle, hyperemesis and hyperthyroidism symptoms (15). In our study, the most common complaint on admission was vaginal bleeding (81.3%) followed by delay of menstruation (12.4%), passage of vesicle (3%), emesis and vomiting (2.3%) and inguinal pain (1%).

The number of patients was highest in the 25-29 age group (27.9%) with a mean age of 29.6±7.39 years. Mole incidence has been reported to rise in early and late fertile pregnancies in the literature (8, 10). It has been shown that molar pregnancy incidence has risen 5 times in mothers 35 years and above and 1.5 folds in 20 years and below (16). Additionally treatment gets more aggressive as age increases in gestational trophoblastic neoplasias.

The relationship between socioeconomic status and molar pregnancy is not clear. Although molar pregnancy incidence tended to increase in communities with low socioeconomic status due to inadequate protein intake in the studies of Marquez- Monter and Hsu (17, 18), this view was disapproved in many studies (19). In our study, 55 (80.9%) patients were found to be housewives and 31 of them were illiterate. Twenty three (33.9%) of the patients were elementary school graduates. The incidence of molar pregnancy was detected to increase with poor socioeconomic status in our study, similar to those of Marquez- Monter (18) and Hsu (17).

Previous studies indicate that an increase in the number of pregnancies does not change the incidence of molar pregnancy (20, 21). In our study, the number of patients with 5 and more gravidas was found as 19 (27.9%). It was concluded that investigating only the effect of number of pregnancies on molar pregnancy incidence without taking the effects of other factors like socioeconomic conditions, maternal age and educational level into consideration would not be appropriate.

In the literature, molar pregnancy has been reported to be seen more frequently in women with blood type A (13). Thirty nine (57.2%) of the patients were detected to have blood type A in our study also.

Hyperthyroidism is reported in the ratio of 7% in the literature (2-7). Secretion of thyroid hormone from trophoblasts or structural similarity of human chorionic gonadotropin to thyroid stimulating hormone explains hyperthyroidism development. Four (5.9%) patients had hyperthyroidism in our study. Of them, 2 had incomplete hydatiform mole, 1 had invasive mole and 1 had chorio-carcinoma.

The first choice of treatment is vacuum curettage in the diagnosis and treatment of molar pregnancy. Hysterectomy is an alternative treatment for patients who do not want a pregnancy. The main treatment is chemotherapy in gestational trophoblastic neoplasias (15). In our study, 65 (95.6%) patients had vacuum curettage under general anesthesia, 2 (2.9%) patients underwent hysterectomy. Sufficient outcomes were obtained with vacuum curettage. Uterine perforation developed in 2 (3%) patients. No findings of the disease were observed during follow-ups of the patients who only had vacuum curettage or who underwent hysterectomy, 100% recovery was achieved.

In our study the patients were treated with methotrexate only, however chemotherapy was changed to etoposide, methotrexate, actinomycine-D, cyclophosphamide, vincristine (EMA-CO) protocol due to responsiveness to methotrexate treatment. Three more cures of chemotherapy were applied after β -HCG levels became normal. In recent years, EMA-CO protocol which is more effective and has less toxicity is preferred, and remission rates have been reported as 76-94% (22). Complete remission could be achieved with EMA-CO protocol in our case also.

All patients were followed up once a week until β -HCG levels become normal, once in three weeks after β -HCG levels had become normal and thereafter monthly during one year. When the time to normal β -HCG levels is compared with the literature, duration was reported to be longer in malignant cases. In the study of Oguz et al. (14) remission was found to occur in approximately 40 days in the hydatiform group, 87 days in persistent mole cases and 113 days in malignant GTD cases. In our study, remission occurred at approximately the 36th day in the incomplete mole group and the 38th day in the complete mole group. Patients were recommended contraception for at least 6 months.

The most common sites for metastasis in GTD are lungs (80%), vagina (30%), pelvis (20%), liver (10%) and brain (10%) (2). Lung metastasis was detected in one patient in our study. Lung metastasis that is classified as grade 3 is highly sensitive to chemotherapy and remission can be usually achieved. Also in our patient, we

observed that lung metastasis regressed after the EMA-CO protocol applied following methotrexate therapy.

Conclusion

It is obvious that molecular and genetic studies are needed in order to explain the etiopathogenesis of GTD, which is a group of diseases with obscure pathogenesis. However, when it is considered that the only prevention option is establishing a well-organized family planning system and improving educational level, the necessity for a community-wide healthcare system and regular antenatal follow-up is clearly seen. Additionally, early diagnosis and treatment are of importance due to high chemosensitivity of gestational neoplasms and possibility of remission even in malignant forms.

Conflict of interest

No conflicts of interest were declared by the authors.

Authors' contributions: Conceived and designed the experiments or case: AEY, BDÇ, BÖ, AB. Performed the experiments or case: AEY, BDÇ, BÖ, AB. Analyzed the data: AEY, BDÇ, BÖ, AB. Wrote the paper: AEY, BDÇ, BÖ, AB. All authors read and approved the final manuscript.

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