

Gestational trophoblastic disease in Sanliurfa, Southeast Anatolia, Turkey

M. Harma, M.D., Assist. Prof.; M. Harma, M.D., Assist. Prof.; S. Yurtseven, M.D., Resident
N. Gungen, M.D., Resident

Department of Gynecology and Obstetrics, University of Harran, Faculty of Medicine, Sanliurfa (Turkey)

Summary

Purpose of investigation: This study was carried out to determine if the extremely high rate of gestational trophoblastic disease (GTD) previously reported from a center in Southeast Anatolia also applied in our area.

Methods: Records of GTD and deliveries in all hospitals in Sanliurfa during the period July 1998 to October 2003 were retrospectively studied.

Results: During the period, there were 6,016 deliveries and 73 cases of GTD identified, giving an incidence of GTD of 12.1 per 1,000 deliveries. Of these cases, 66 (90.4 %) were diagnosed as having hydatidiform mole (64 complete and 2 partial), two (2.7%) invasive mole and five (6.9%) choriocarcinoma. Vaginal bleeding was the most common symptom. No clear correlations were found with gravidity or age.

Conclusion: We confirmed that the incidence of GTD in Southeastern Anatolia is much higher than the national average and one of the highest in the world. Thus we explored possible reasons for this and suggest areas for further study.

Key words: Gestational trophoblastic disease; Hydatidiform mole; Invasive mole; Choriocarcinoma.

Introduction

Gestational trophoblastic disease (GTD) consists of a group of neoplastic disorders arising from placental trophoblastic tissue after normal and abnormal fertilization. According to the WHO classification, they include hydatidiform mole (complete and partial), choriocarcinoma, placental site trophoblastic tumor, and miscellaneous and unclassified trophoblastic lesions [1]. Hydatidiform mole (HM) is by far the most commonly observed variant.

The incidence of GTD varies considerably in different countries, with Turkey being somewhere in the middle ranks. Ozalp *et al.* [2] conducted a literature search of 929,323 pregnancies in Turkey between 1932 and 2000 and reported an incidence of hydatidiform mole of 1.87 per 1,000 deliveries. In sharp contrast to this, Gul *et al.* [3] found an incidence of GTD of 12.9/1,000 deliveries and of HM of 11.8/1,000 deliveries in Diyarbakir in Southeastern Anatolia.

Our primary aim was to see if this extremely high incidence also applied to Sanliurfa, another center in the region.

Material and Methods

Figures for total hospital deliveries were obtained from all hospitals in the city. All cases of GTD were diagnosed at our hospital from patients attending directly or referred because of a suspicious history, such as vaginal bleeding following a miscarriage or delivery or with a uterine size discordant with gestational age. Beta subunit human chorionic gonadotrophin (beta-HCG) serum levels, chest X-rays and ultrasonography

were performed on all these patients and the diagnosis was established by histopathological examination after dilatation and curettage.

Data on age, number of pregnancies, obstetric and other medical history were all extracted from the files.

Results

For the period July 1998 to October 2003, we identified 73 cases of GTD among 6,016 deliveries – a rate of 12.1/1,000 deliveries. Of these, 66 (90.4%; a rate of 11.0/1,000 deliveries) were HM (64 complete and 2 partial), five (6.9%) were choriocarcinoma and two (2.7%) were invasive moles.

The major presenting symptoms are listed in Table 1. Vaginal bleeding was the most common. Bilateral theca-lutein cysts were found in 46 cases (63%) and abdominal ascites in one.

In patients with HM, uterine size was larger than expected from gestational dates in 51 patients (72.2%), normal in eight (12.2%) and smaller in seven (10.6%).

Table 2 classifies patients by type of GTD and gravidity. In the HM group, 18 (27.3%) cases were primigravidas while 24 (36.3%) were in their fifth or greater pregnancy. Two (40%) of the choriocarcinoma cases were primigravidas and three (60%) had five or more pregnancies.

The age distribution of the patients ranged from 16 to 53 years, with a mean age of 30.48 ± 9.54 in HM cases, 38.25 ± 12.7 in invasive mole cases and 37.85 ± 14.2 in choriocarcinoma cases (Table 3).

Four patients with choriocarcinoma had metastatic infiltration, three had lung metastases, two had liver metastases and one had lung, liver, kidney, spleen and bone metastases.

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Table 1. — *Presenting Symptoms.*

Symptom	Hydatidiform mole		Choriocarcinoma		Invasive mole	
	(n)	(%)	(n)	(%)	n	(%)
Vaginal bleeding	31	46.9	4	80	2	100
Vaginal bleeding with expulsion of vesicles	18	27.2	—	—	—	—
Hyperemesis gravidarum	1	1.5	1	20	—	—
Absence of fetal movements	13	19.6	—	—	—	—
Abdominal distension with pain and cramps	3	4.5	—	—	—	—
Total	66	100	5	100	2	100

Table 2. — *Gravidity distribution.*

Number of pregnancies	Hydatidiform mole		Choriocarcinoma		Invasive mole	
	(n)	(%)	(n)	(%)	n	(%)
1	18	27.3	2	40	—	—
2	9	13.6	—	—	—	—
3	6	9.1	—	—	—	—
4	9	13.6	—	—	—	—
5 or more	24	36.3	3	60	2	100
Total	66	100	5	100	2	100

Table 3. — *Age distribution of patients.*

Age (years)	Hydatidiform mole		Choriocarcinoma		Invasive mole	
	(n)	(%)	(n)	(%)	n	(%)
15-20	7	10.6	1	20	—	—
21-25	16	24.2	1	20	—	—
26-30	19	28.7	—	—	1	50
31-35	3	4.5	—	—	—	—
36-40	8	12.1	—	—	—	—
41-53	13	19.6	3	60	1	50
Total	66	100	5	100	2	100

The preferred treatment for HM mole was suction curettage with oxytocin infusion or misoprostol induction performed under general anesthesia, but hysterectomy was performed on nine older women. The only complication was one case of pulmonary embolus after the suction curettage procedure.

All cases underwent monthly beta-HCG tests to check for recurrence. Treatment of choriocarcinoma was by multi-agent chemotherapy in three cases and by surgery in two cases with severe vaginal bleeding.

Discussion

The reported incidence of GTD varies widely throughout the world. For example, rates for HM vary from 1.2/1,000 deliveries in Singapore [4] to 17.5/1,000 deliveries in Indonesia [5]. Ozalp *et al.* conducted a literature search of 929,323 pregnancies in Turkey between 1932 and 2000 and reported an incidence of HM of 1.87/1,000 deliveries. This is roughly in line with Mungan *et al.*'s finding from their hospital in Ankara, the capital city of Turkey, of a rate of 2.48/1,000 deliveries [6]. In sharp contrast to these results, Gul *et al.* [2] found an incidence

of GTD of 12.9/1,000 deliveries and of HM of 11.8/1,000 deliveries in Diyarbakir in Southeastern Anatolia. This is very close to the rate we found of 11.0/1,000 deliveries.

The reasons for this dramatic difference between the regions are obscure. Gul *et al.* state that 'trophoblastic diseases occur more frequently in women of high fertility with high parity, from low socio-economic class'.

According to UN Population Fund data [7], the total fertility rate in Eastern Turkey in 1996 was 4.4 and that in Western Turkey was 2.0. Like Gul *et al.*, we found a concentration of cases in primigravidas and those in their fifth or greater pregnancy – both of which would, of course, happen more frequently with a higher fertility rate. On the other hand, a review by Alieri *et al.* [8] did not find a consistent relationship between the incidence of GTD and gravidity.

The best established risk factor for hydatidiform mole is maternal age [9-14]. Our findings were broadly similar to those in these studies for choriocarcinoma, with a predominance in those under 25 or over 40. However, unlike the results of these studies but similar to Gul *et al.*, we found the greatest preponderance of HM in the 21-30 year age group. The reason for this difference between our region and others is obscure and raises the possibility that factors causing excess occurrence of GTD in this age group may be responsible for at least some of the overall excess incidence in our region. This warrants further investigation.

Given that Southeastern Anatolia is one of the poorer regions in Turkey, socioeconomic factors would seem to be likely determinants of the difference in incidence of GTD in the region. However, studies validating a relationship between socioeconomic conditions and incidence of GTD are impossible to find and the few studies that looked at this question [15, 16] have reached negative conclusions and have in fact concluded that, taken together, environmental conditions and/or socioeconomic conditions do not seem to have a more profound effect than racial and ethnic disposition.

It should also be remembered that, as in many other countries, fertility rates show a linear increase from the richest quintile to the poorest, so confounding is inevitable.

Broad variations in the distribution of GTD exist worldwide, with higher frequencies in some parts of Asia, the Middle East and Africa [8], but the extent to which this can be attributed to genetic factors is unclear. The limited genotyping that has been done of populations in Southeast Anatolia [17-19] has also not shed much light on the matter but this is another possible factor that needs to be explored.

Diet is another factor that could be investigated. Our group earlier reported that lower serum folate and higher serum vitamin B12 levels were found in patients with complete HM than in controls [20]. The significance of this finding to the high incidence of GTD in our region is dubious but it may at least indicate the possibility of diet being a factor.

A factor that could account for half or more of the

observed increase in incidence of GTD in our area is that, like the great majority of studies, our study was based on hospital deliveries. However, while nationally some 90% of births are in hospitals, in the Eastern Region of Turkey the figure is only 41% [21]. While precise figures are not available for our area, they are probably not greatly different from the latter.

In common with other studies [3, 22, 23], vaginal bleeding was the most common presenting symptom. However, absence of fetal movements was more common (19.6% vs 12.8%) in our study than in that of Gul *et al.* and was not reported at all in the other studies.

Following on from a previous study by our group [24], which showed equivalent falls in beta-HCG serum levels after treatment with vacuum evacuation, induction with misoprostol, or hysterectomy, treatment of HM was by vacuum induction or induction with misoprostol, with hysterectomy reserved for treatment of older women. All patients were followed with monthly beta-HCG serum assays to look for recurrences.

Choriocarcinoma was treated with multi-agent chemotherapy in three cases and surgically in two cases with severe vaginal bleeding. All cases continue to be monitored and, to date, have all responded satisfactorily to treatment.

Conclusion

The incidence of GTD in Sanliurfa, Turkey was found to be 1 per 82.6 deliveries. No single risk factor stands out but nutrition, age, parity, ethnic and genetic factors can be considered as possible etiologic factors. Genetic factors may turn out to be the most important but efforts to change risk factors by improving nutrition and decreasing the high gravidity may help to decrease the incidence of GTD in our area. The high incidence of HM in the 21-30 year old group deserves further study.

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Address reprint requests to:
M. HARMA, M.D.
6. Sokak, 2/9, Bahcelievler
06500 Ankara (Turkey)