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The Effects of Chemotherapy on the Levels of Serum Anti-Müllerian Hormone in Patients with Gestational Trophoblastic Neoplasia

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Abstract

Background: Gestational trophoblastic neoplasia (GTN) is a group of tumors highly responsive to chemotherapy. It has been suggested that cancer therapies have detrimental effects on female fertility. Anti-Müllerian hormone (AMH) is considered fertility potential and ovarian reserves in women. The aim of this study was to compare serum AMH levels between the patients with GTN treated with chemotherapy and the patients with hydatidiform mole who underwent suction curettage without receiving any chemotherapy.

Methods: In 35 patients with GTN, serum AMH levels were measured before suction curettage and after the administration of chemotherapy and compared with serum AMH levels measured in 35 patients with hydatidiform mole, who did not receive any chemotherapy as a control. In controls, serum levels of AMH were measured before suction curettage and at the time when beta human chorionic gonadotrophin (ß-hCG) levels approached zero concentration.

Results: The mean serum AMH levels in the GTN group were significantly lower than those measured in the control group after chemotherapy. In addition, serum AMH levels measured after intervention in each group significantly decreased compared to the basal levels (p=0.034). Serum AMH levels showed significant differences between the patients who received chemotherapy regimens with methotrexate (MTX) alone, actinomycin-D (Act-D) alone, or the combination of MTX and Act-D (p=0.001).

Conclusion: Our study showed that fertility preservation is of great importance in patients with GTN treated with chemotherapy. Furthermore, both MTX and Act-D could have potential adverse effects on ovarian reserve.

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Introduction

Gestational trophoblastic neoplasia (GTN) is a group of tumors that arise from abnormal proliferation of placental trophoblast cells (1). It is divided into four tumor subtypes, including invasive mole, choriocarcinoma, placental-site trophoblastic tumor, and epithelioid trophoblastic-tumor (2, 3). Although the incidence of GTN varies in different regions of the world, it is seen in averagely 1-2 per 2000 pregnancies (4).

The treatment modalities available for GTN in-

clude single agent chemotherapy, combination chemotherapy, surgery such as hysterectomy, and radiation (5). GTN is highly responsive to chemotherapy even with distant metastasis (6). With improvements in the ability to diagnose and treatment of any cancer type, the mortality rate from malignancies has decreased. Expected long-term survival rate of cancers has been reported approximately 80% for affected children and adolescents (7). With increased survival rates from a large number of malignancies, reproductive health after cancer therapy is becoming a major quality of life issue for many young girls and women (8). Many cancer therapies have detrimental effects on female fertility, most importantly due to the damage to ovaries. These consist of chemotherapy drugs and radiotherapy with the degree of injury being dependent on the type of treatment, the dose of drugs, and the age of the patient (9).

Anti-Müllerian hormone (AMH) is a member of the transforming growth factor-beta (TGF-β) superfamily of growth and differentiation factors expressed in the granulosa cells of primary, preantral, and small antral follicles (10). The key role of AMH is to suppress the recruitment of primordial follicles, and so preventing premature ovarian insufficiency (POI). In addition, AMH appears to have an important role in the selection of the dominant follicle by inhibiting the sensitivity of larger antral follicles to follicle-stimulating hormone (FSH) (9).

The measurement of the levels of AMH is considered to be the best marker for the prediction of ovarian reserve, which reflect reproductive function. Low levels of AMH represent a low ovarian reserve (11). AMH can also be used to monitor the effects of chemotherapy on fertility (12). However, reproductive function following chemotherapy in gynecological cancers has not been widely discussed. The purpose of this study was to compare the serum AMH levels between the patients with GTN treated with chemotherapy and those with hydatidiform mole who underwent suction curettage without receiving any chemotherapy.

Methods

Study population: A total of 70 patients with suspected molar pregnancy were consecutively enrolled in our study. The participants aged between 18 and 45 years who had a positive history of amenorrhea or irregular menstruation with an abnormally high beta human chorionic gonadotropin (ß-hCG) levels and transvaginal sonography (TVS) findings, including cystic changes, irregularity, or increased echogenicity in the decidua, chorionic villi or myometrium suggestive of molar pregnancy were included (13). Exclusion criteria were the presence of any endocrine disorder, such as hyperprolactinemia, Cushing's syndrome, hypothyroidism, and hyperthyroidism or a history of previous surgery on ovaries.

This study was approved by Research Committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1395.565) and registered in Iranian Registry of Clinical Trials (IRCT2011041 65810N2). Moreover, the procedures in this study were conducted based on the Declaration of Helsinki principles. Informed consents were obtained from the subjects prior to their participation in the study.

Intervention: All the patients underwent uterine suction curettage. The definite diagnosis of molar pregnancy was confirmed by pathology findings. Following suction curettage, serum ß-hCG levels of patients were measured weekly.

Allocation to case and control group was done on the basis of decreasing trend of serum ß-hCG levels. The control group consisted of 35 women whose serum levels of ß-hCG reached zero levels without any intervention other than suction curettage. The case group comprised 35 women with diagnosis of GTN. According to the International Federation of Gynecology and Obstetrics (FIGO), criteria for the diagnosis of post molar GTN are as follows:

1) plateaued ß-hCG levels last for four measurements over a period of three weeks or longer [day 1, 7, 14, and 21], 2) a rise in ß-hCG level for three consecutive weekly measurements over at least a period of two weeks or more, 3) elevated ß-hCG level remained for six months or more, and 4) a histological diagnosis of choriocarcinoma (14). All the patients with diagnosis of GTN underwent chemotherapy regimens that consisted of methotrexate (MTX) alone, actinomycin-D (Act-D) dose of drug alone, or the combination of MTX and Act-D (MTX + Act-D).

Hormonal measurements: Blood assays for ß-hCG were routinely performed every week. Furthermore, blood samples for AMH were obtained twice from the patients, one sample before suction curettage and the other one at the time when serum ß-hCG reached zero levels after suction curettage and chemotherapy in control and case

groups, respectively. The serum was separated from the whole blood, placed in sterile tubes, and stored at -80°*C* until analysis. Serum levels of AMH were measured using Enzyme Linked Fluorescent Assay (ELFA-VIDAS ® kit, Biomérieux, France) (11).

Statistical analysis: Statistical tests, including the paired t-test, independent sample t-test, chi square test, and ANOVA were done using SPSS version 24 (IBM Corp., USA).

Results

Thirty-five women with diagnosis of GTN and 35 controls were recruited for our study. The mean age of participants in the control and case group was 27.7±5.5 and 27.8±4.9 years, respectively, which showed no significant difference between the two groups (p=0.964). In terms of gravidity, the majority of the cases (57.1%) and controls (54.2%) were primigravida. The mean parity of the cases was 0.22±0.42 and that of the controls was 0.34±0.59 with no significant differences between groups (p=0.357) (Table 1).

The average time interval between two measurements of AMH levels was significantly longer in the cases compared to the controls (65.71± 19.33 *vs*. 52.11±13.43 days; p=0.001). Before suction curettage, the mean serum levels of AMH did not show significant differences between the case and control groups (p=0.084). At the time when serum ß-hCG reached zero levels after suction curettage in controls and chemotherapy in cases, measurement of serum AMH showed significantly lower levels in the cases in comparison to the controls (p=0.017). Before suction curettage, the mean serum levels of AMH was 3.04± 1.75 nanogram/milliliter (*ng/ml*) in the control group. When ß-hCG levels reached zero, the mean serum AMH levels of controls decreased to 2.95± 1.75 *ng/ml*. The difference between the two measurements was statistically significant (p=0.011). In the case group, the mean serum levels of AMH was 2.36±1.47 *ng/ml* prior to suction curettage and 2.06±1.23 *ng/ml* after chemotherapy, which was significantly lower than those before intervention (p=0.034) (Table 2).

Table 1. Gravidity and parity status in case and control groups (n %)

Variables	Case	Control	p-value
Gravidity			
1	20 (57.1%)	19 (54.2%)	0.841
2	11 (31.4%)	10 (28.5%)	
3	3 (8.5%)	4 (11.4%)	
4	1 (2.8%)	2 (5.7%)	
Parity			
0	27 (77.1%)	25 (71.4%)	0.375
1	8 (22.8%)	8 (22.8%)	
2	-	2 (5.7%)	

Table 2. A) serum anti-Müllerian hormone levels before and after intervention in case and control groups

Groups	Serum AMH levels (*ng/ml*)		p-value
Control			
	Before suction curettage	3.04±1.75	0.011
	After serum ß-hCG level reaches zero	2.95±1.75	
Case			
	Before suction curettage	2.36±1.47	0.034
	After chemotherapy	2.06±1.23	

AMH=Anti-Müllerian Hormone; ng=Nanogram; ml=Milliliter; ß-hCG=beta Human Chorionic Gonadotropin

B) Serum anti-Müllerian hormone levels before suction curettage and after chemotherapy with different regimens [mean (minimum-maximum)]

Type of chemotherapy	Serum AMH levels (*ng/ml*)		p-value
	Before suction curettage	After chemotherapy	
MTX	2.27 (0.65-4.8)	2.11 (0.52-4.5)	0.001
Act-D	2.45 (1.20-5.02)	2.28 (1.05-4.7)	
MTX + Act-D	2.62 (0.92-6.9)	2.42 (0.76-6.5)	

MTX=Methotrexate; Act-D=Actinomycin-D; ng=Nanogram; ml=Milliliter; AMH=Anti-Müllerian Hormone

Table 3. Frequency of the patients receiving methotrexate or actinomycin-D in case group (n %)

No. doses	MTX	Act-D
1	14 (60.7%)	-
2	8 (32.1%)	9 (75%)
3	1 (7.1%)	2 (16.7%)
4	-	1 (8.3%)

MTX=Methotrexate; Act-D=Actinomycin-D

Chemotherapy with MTX or Act-D alone was administered to 23 (65.7%) and 7 (20%) patients in the case group, respectively. In addition, 5 (14.3%) patients received chemotherapy regimen with MTX+Act-D. Before suction curettage, the mean serum levels of AMH was 2.27 *ng/ml* in MTX, 2.45 *ng/ml* in Act-D, and 2.6 *ng/ml* in MTX+Act-D group. After chemotherapy, the mean serum AMH levels decreased to 2.11 *ng/ml* in MTX, 2.28 *ng/ml* in Act-D, and 2.42 *ng/ml* in MTX+Act-D group. Regarding the serum levels of AMH before and after intervention, there was significant differences between the groups (p= 0.001) (Table 3).

Discussion

The adverse effects of chemotherapy on ovarian function have long been recognized (15). Chemotherapy can induce symptoms of sex hormone deficiency, amenorrhea, and impaired fertility among women (16). AMH, a dimeric glycoprotein produced by granulosa cells of preantral and small antral follicles, may be a very useful marker to monitor chemotherapy-induced gonadal damage (17).

There are several types of cancer known to be associated with decreased ovarian reserve. Fong et al. evaluated serum AMH levels in patients with hematological malignancies. Their study showed that the patients treated with multi-drug chemotherapy had significantly lower levels of serum AMH (18, 19). Fréour et al. reported that AMH levels rapidly decreased to undetectable levels in most women with breast cancer during chemotherapy and persisted at very low levels after the treatment. In addition, they concluded that serum AMH is a relevant tool for ovarian reserve assessment and follow-up during treatment in premenopausal women with breast cancer (20).

Although the status of ovarian function in a variety of cancers following chemotherapy has been studied, fertility preservation of women with gynecological cancers receiving chemotherapy has not been widely discussed. In this study, an attempt was made to compare the levels of serum AMH between the patients with GTN who received chemotherapy as case group and the patients who underwent suction curettage for treatment of molar pregnancy as controls. Our results showed that after intervention, serum AMH levels were significantly lower in the cases in comparison to the controls. In addition, both case and control groups had significantly lower levels of AMH after chemotherapy and suction curettage, respectively.

Iwase et al. investigated serum AMH concentrations in patients with GTN previously treated with chemotherapy and the ones who solely underwent suction curettage to treat hydatidiform mole. Their results suggested that serum AMH levels measured in the GTN group after chemotherapy significantly decreased in comparison to those measured in the control group. Furthermore, they observed that serum AMH levels were significantly lower in the patients who had received a regimen including etoposide than in the patients who had not received treatment with etoposide (21). Bi et al. evaluated serum AMH levels before and after chemotherapy in 34 patients with GTN. After three chemotherapy cycles, they observed a significant reduction in AMH levels compared to the basal levels. Serum AMH levels showed a further decline at two weeks after chemotherapy completion (12).

Our data are consistent with previous reports that post-chemotherapy serum AMH concentrations are lower in the patients with GTN compared to the women who did not receive any chemotherapy. Therefore, serum AMH level would be a useful marker in order to predict the effects of GTN treatment on fertility. These findings also highlighted the importance of fertility preservation in GTN patients prior to chemotherapy. It is suggested that gynecologists should inform the patients with GTN about the potential negative effects of chemotherapy on fertility before initiation of the planned treatment and refer the patients to fertility specialist to discuss the risk of ovarian damage and currently available fertility preservation options.

Ovarian toxicity is also influenced by the type of chemotherapy agent, cumulative dose, and duration of treatment (22). MTX is a folic acid analogue that disturbs DNA repair and cell division by inhibiting the dihydrofolate reductase enzyme.

It has been shown that rapidly proliferating cells in the bone marrow, gastrointestinal cells, and primordial follicles in the ovarium might be affected by the MTX treatment (23). Act-D is another chemotherapeutic drug used in the treatment of various tumors, such as Wilms tumor, melanoma, and trophoblastic neoplasia (24).

Our study demonstrated that patients who were treated with chemotherapy regimens, including MTX, Act-D, or MTX+Act-D had significantly lower serum levels of AMH compared to the controls. Iwase et al. reported that patients receiving regimens with MTX and/or Act-D had lower AMH levels than control patients with hydatidiform mole who did not receive chemotherapy (21). Bi et al. also suggested that after three cycles of chemotherapy, both the patients who received only Act-D and those who underwent combination chemotherapy regimens with FAV (5-fluorouracil, Act-D, vincristine), FAEV (floxuridine, Act-D, etoposide, vincristine), and EMA/CO (etoposide, MTX, dactinomycin, cyclophosphamide, vincristine) presented with significantly lower levels of AMH (12). Our results are in concordance with these findings. However, Oriol et al. concluded that a single-dose MTX treatment for ectopic pregnancy does not compromise ovarian reserve in terms of serum AMH levels (25).

Our results showed that monotherapy with MTX or Act-D could impose negative effects on ovarian reserve. It has been suggested that inhibition of the pituitary gonadal axis by gonadotropin-releasing hormone (GnRH) agonists would reduce the rate of folliculogenesis and render the germinal epithelium less susceptible to the gonadotoxic effects of chemotherapy (26). Therefore, the use of GnRH agonists is strongly recommended in GTN patients receiving monotherapy regimens with MTX or Act-D.

Conclusion

This study showed that serum AMH levels in patients with GTN who received chemotherapy were significantly lower in comparison to the patients with hydatidiform mole who just underwent suction curettage. The patients who were solely treated with suction curettage also presented with significantly lower serum levels of AMH than those before intervention. These findings highlighted the importance of fertility preservation especially for the patients with GTN receiving chemotherapy. Furthermore, our study demonstrated that both MTX and Act-D could negatively affect ovarian reserve. Therefore, the use of GnRH agonists might be effective to reduce the gonadotoxic effects of these drugs in GTN patients.

Conflict of Interest

Authors have no conflict of interests to declare.

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