Original Article

The Effect of Vitamin A on Decreased β-hCG Production in Molar Pregnancy

Mahdiss Mohamadianamiri[1], Nooshin Eshraghi[1], Samaneh Rokhgireh[2], Fahimeh Karimi[1], Maryam Ebrahimi[1*]

1- Akbarabadi Hospital, Iran University of Medical Science, Tehran, Iran.
2- Endometriosis Research Center, Iran University Medical of Science, Tehran, Iran.

Received: 15 July 2019, Accepted: 1 November 2019

Abstract

Background and Aim: Gestational trophoblastic disease (GTD) is defined as a group of disorders; they are characterized by uncontrolled trophoblastic cell proliferation and overproduction of β-HCG. It seems that an inappropriate diet is one of the major risk factors of GTD. Regardless of the size of the uterus; mole depletion by curettage suction is usually the preferred treatment. This study aimed to evaluate the effect of vitamin A and curettage suction on the faster reduction of β-hCG level, and faster recovery of disease, consequently. **Materials and Methods:** In this study case (n=26) and control (n=26) groups received 50,000 IU of vitamin A intramuscularly, before and after curettage. β-hCG was measured weekly and after reaching zero every month for six months. RIA was used for measurement. **Results:** Vitamin A reduced the level of β-hCG to zero in the patient compared to the control, one week earlier; this effect was statistically significant (P-Value <0.05). One of the members of the control group during follow-up progressed to gestational trophoblastic disease (GTN). There was no significant relationship between ABO blood groups among the two groups (P-Value: 0.9). There was no significant relationship between gravity, parity and hematology parameters between the two groups (P-Value >0.05). **Conclusion:** Finally, it can be said that vitamin A intake in patients with GTD, along with other therapies, can improve the speed of recovery; it can prevent the disease progression. However, it does not prevent progression to GTN, completely. Therefore, further studies are needed in future studies.

Keywords: Vitamin A, Gestational Trophoblastic Disease, β-HCG, Hydatidiform Moles.

[*]**Corresponding Author:** Maryam Ebrahimi; Email: Drmkhoddami@yahoo.com
Please cite this article as: Mohamadianamiri M, Eshraghi N, Rokhgireh S, Karimi F, Ebrahimi M. The Effect of Vitamin A on Decreased β-hCG Production in Molar Pregnancy. Arch Med Lab Sci. 2019;5(3):1-6. https://doi.org/10.22037/amls.v5i4.29185

Introduction

Gestational trophoblastic disease (GTD) is a group of disorders that comprises a range of tumors with different biological characteristics ranging from benign to malignant (1). GTD includes several groups such as hydatidiform mole, invasive mole, and choriocarcinoma; it is caused by the uncontrolled proliferation of trophoblast cells and impaired apoptosis (2). so far, many effective factors have been introduced which are involved in the pathogenesis of the gestational trophoblastic disease (GTN); however, the main factor has not been identified (3). Some of these risk factors are gestational age, previous mole history, β-hCG levels, and platelet count (4). patients diet has been introduced as an important factor in GTD development, recently. Therefore, people with a diet that lacks essential vitamins such as folate, E, and A, are more susceptible to GTD (5, 6). Among these, Vitamin A appears to play an important role in preventing cell proliferation and inducing apoptosis. Vitamin A induces apoptosis in cells by stimulating p53 activation; recent studies suggest that vitamin A intake can reduce the proliferation of malignant cells by inducing apoptosis, in some cancers (7). Thus, they declared that concomitant use of chemotherapy with vitamin A is associated with increased remission, in patients with high-risk GTD (8). In the

present study, we investigated the vitamin A effect on β-hCG reduction in patients with molar pregnancy after curettage.

Methods

Patients and control selection

This study was performed on 52 patients with a history of molar pregnancy who referred to Firoozgar Hospital of Iran University of Medical Sciences during 2018-2019. The inclusion criteria were as following: gestational age below 12 weeks, no history of the Underlying disease, β-hCG <100,000 IU, and complete mole; The exclusion criteria included β-hCG > 100,000IU and incomplete mole. Evaluated variables included gravity, parity, patients age, hematological parameters, the β-hCG level before and after treatment, and blood group. The studied patients were divided into two groups of A (n=26) and B(n=26). Group A members received 50000IU before and after curettage intramuscularly; Group B members did not receive any vitamin A, they just underwent curettage suction (figure.1).

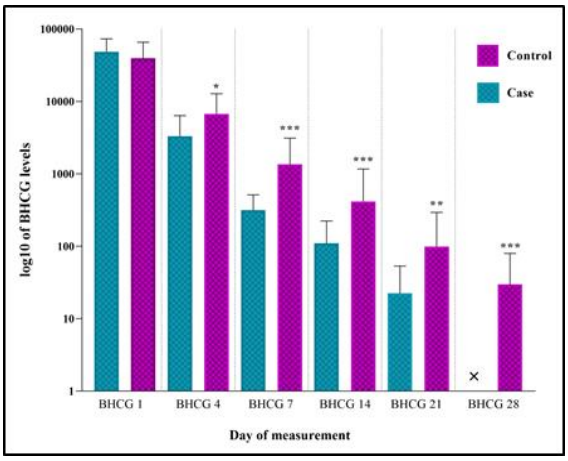

Figure.2. Evaluation of decreased β-hCG level in patient and control subjects

The serum β-hCG level was measured by the radioimmune assay (RIA) method. Serum β-hCG levels were measured before the curettage suction and in the 4th, 7th, 14th, and 28th days after treatment. measuring process continued, until the weekly level of β-hCG achieve to zero; this β-hCG was compared with the levels before the treatment. After reaching zero, it was measured monthly for up to 6 months in both groups.

Statistical analysis: Chi-square statistical method was used to measure nominal data; dependent and independent sample t-tests were done to measure quantitative data. Data were analyzed by SPSS software (version 23). $P < 0.05$ was considered statistically significant.

Results

The mean age was 30.00±6.22 in group A (case group), and 33.12±4.85 in group B (control group); age differences were not statistically significant between the two groups (P-Value: 0.25).

Evaluation of hematological parameters in two groups

After evaluating hematological parameters, higher levels of MCHC, PLCR, MPV, PDW, platelet, MCH, and hemoglobin were observed in the patients; whereas RDW, MCV, white and red blood cells were significantly higher in the control group. None of the findings were statistically significant (Table 1).

The Relationship between β-hCG Levels in two groups

The mean level of β-hCG was 48392/08±24900.77 mIU/ml, before treatment and vitamin A intake, in the intervention group. It was 26266/93±39394/31 mIU/ml in the control group, no significant relationships were observed between them (P-Value: 0.899).

The mean β-hCG levels were measured in the intervention group in the 4th and 7th days after treatment, which were 3307.92±3052.12 mIU/ml and 303.00±203.16 mIU/ml, respectively; these values were 6082.08±6714.46 mIU/ml and 1753.52±1356.69 mIU/ml in the control group, respectively. These differences were statistically significant (P-Value: 0.02 for day 4 and P-Value: 0.000 for day 7). The mean β-hCG level was 109.50±113.47 mIU/ml, 22.46±30.79 mIU/ml and 0.00±0.00 mIU/ml in the 4th week after treatment in the intervention group respectively; these amounts were 748.79±415.73 mIU/ml, 194.37±98.96 mIU/ml and 49.85±29.73 mIU/ml in the control group, respectively. These differences were statistically significant (Table 2).

Table 1. Associated hematological parameters between patient and control subjects

Variable	Patients	Control	P-value
MCHC	35.49± 2.01	34.88± 1.72	0.105
PLCR	32.08± 7.29	27.92± 9.37	0.09
MPV	10.67± 0.96	10.20± 1.14	0.231
PDW	14.04± 1.80	13.44± 2.28	0.059
RDW	13.21± 0.90	13.63± 1.02	0.112
PLT	235.38± 73.18	235.31± 66.71	0.581
MCH	31.34± 1.59	30.49± 1.74	0.668
MCV	85.80± 3.52	87.00± 3.11	0.475
HCT	35.25± 2.68	35.77± 3.37	0.162
Hb	12.64± 0.95	12.62± 1.20	0.07
RBC	4.00± 0.45	4.09± 0.46	0.937
WBC	7.83± 2.35	7.94± 2.91	0.985
Pariteh (Median, (Range))	0 (0-3)	0 (0-2)	0.899
Gravid (Median, (Range))	1 (1-5)	1 (1-3)	0.902

Data are expressed as mean ± SD (n=26 for patients and n=26 for control). P-value calculated by independent t test.
Abbreviation: MCHC: mean corpuscular hemoglobin concentration; PLCR: Platelet larger cell ratio; MPV: mean platelet volume; PDW: Platelet distribution width; RDW: Red blood cell distribution width; PLT: Platelet; MCH: *mean cell hemoglobin;* MCV: Mean corpuscular volume; HCT: hematocrit; Hb: Hemoglobin ; RBC: Red blood cell; WBC: White blood cell.

Table 2. Associated hematological parameters between patient and control personals

Variable	Patients(mIU/ml)	Control (mIU/mL)	P-value
β-hCG 1	48392.08± 24900.77	26266.93± 39394.31	0.899*
β-hCG 4	3307.92± 3052.12	6082.08± 6714.46	0.02*
β-hCG 7	303.00± 203.16	1753.52± 1356.69	0.000*
β-hCG 14	109.50± 113.47	748.79± 415.73	0.001*
β-hCG 21	22.46± 30.79	194.37± 98.96	0.015*
β-hCG 28	0.00± 0.00	49.85± 29.73	0.000*
A	8 (30.8%)	6 (24%)	0.90**
B	2 (7.7%)	6 (24%)	
AB	1 (3.8%)	3 (12%)	
O	15 (57.7%)	10 (40%)	
Rh:			
Positive	26 (100%)	25 (96.2%)	
Negative	0.0	1 (3.8%)	

Data are expressed as mean ± SD (n=26 for patients and n=26 for control) for BHCG. For ABO and RH blood group expressed as number (%). *calculated by Mann-Whitney. ** calculated by chi-square.

As shown, the intervention group had a faster rate of β-hCG reduction in comparison to the control group. The level of β-hCG was reduced to zero in the intervention group during the fourth week after treatment; it was 49.85±29.73 mIU/ml in the control group too. This finding emphasizes the effect of vitamin A on the accelerated reduction of the β-hCG level.

Evaluation of blood groups in two groups

Results showed that all patients were Rh-positive, while in the control group, 96.2% had positive Rh-, and about 3.8% were negative. The frequency of groups A and O were higher in the patient's group, while the B and AB blood groups were more frequent in the controls; this difference was not statistically significant (P-Value: 0.23) (Table 2).

Discussion

Molar pregnancy is a disease characterized by overproduction of β-hCG by placental cells (9, 10); inherited and acquired factors affect the disease. Mutations in the apoptosis controller genes are one of the heredity factors and acquired including gestational age, previous molar, gravity, parity, and many others (11, 12). Recently, vitamin A is introduced as an effective factor in cell apoptosis; its use combined with chemotherapy drugs can prevent malignant cell proliferation (13, 14). Vitamin A is involved in many physiological processes such as differentiation, proliferation, and normal cell growth (15). In pathogenic conditions, it inhibits the proliferation of tumor cells by inducing apoptosis; it prevents metastasize to other parts of the body by inhibiting angiogenesis (16). Vitamin A inhibits cancer cell proliferation by regulating the function of transcription factors (17). This organic matter active the signaling pathways that inhibit the cell cycle and the cancer cells growth (7, 18).

A study by Andri et al. was conducted to evaluate the role of vitamin A in preventing malignancy of molar pregnancy; the disease progression rate and malignancy were lower in vitamin A receiver in comparison with those who did not receive any vitamins. Also, this study evaluated some of the risk factors and their association with disease progression. The results showed that there were no significant relationships between the age of patients and the molar pregnancy incidence. Also, no significant relationships were observed between parity and the progression of disease and malignancy in both groups (7). In the study by Kolusari and associates the levels of vitamins A, E, and D were evaluated in patients with molar pregnancy; the results showed higher levels of vitamins in control individuals. They play the antioxidant role in the body and protect against the production of reactive oxygen species. No significant relationships were detected between gestational age, gravidity, and parity in patients and controls (6). The present study revealed no significant relationships between the ages of the patients treated with vitamin A and the control group (P-Value: 0.25). Also, it was found that there were no significant relationships between gravity and parity of both groups (P-Value: 0.90 for gravity and P-Value: 0.89 for parity). Research by Shamshiri Milani et al. which investigated molar pregnancy risk factors revealed that the percentage of blood group A was higher in the control group compared to the patients (41.5% vs. 59.5%). Other ABO blood groups were more frequent in the control group too; however, the frequency of A blood group was statistically significant (P-value: 0.00) (19). In the present study, the frequency of different blood groups was not statistically significant (Table 2).

A study by Bakhtyari et al. which evaluated the role of risk factors in the pathogenesis of molar pregnancy revealed that the level of β-hCG was higher in high-risk molar patients. β-hCG reduces after treatment; it achieves to the control level. They concluded that β-hCG levels could be used as a risk factor in the patient's follow-up; it is applicable after treatment, as well as before treatment to identify high-risk patients (20). In the present study, the level of β-hCG in the patient group reached zero faster; it prevented the progression of the disease. Also, statistical analysis showed that there was a significant difference between the two groups after vitamin A intake .

The findings of research by Fatama et al. in 2015, state platelets count was higher in patients with molar pregnancy compared to controls. In contrast, the differences in WBC, PDW, and MPV were higher in the control group compared to patients; But this difference was only significant for platelets (P-Value: 0.00) (21). In the present study, after evaluating clinical parameters between patients with molar pregnancy and controls, it was shown that there was no significant relationship between these parameters in the two groups.

Conclusion

Finally, according to the data obtained from this study, unlike other researches there was no significant

relationship between hematological parameters in two groups of individuals under study; our analysis revealed that hematological parameters cannot be considered as suitable prognostic factors. But the most important point observed in this study was the effect of vitamin A on preventing disease progression and accelerating the recovery of patients. vitamin A intake is suggested in the early stages of the disease and even as a prophylactic for those who are at the risk of molar pregnancy; it can prevent the progression into malignancy by reducing the production of β-hCG.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgement

This article is the result of a research plan conducted in Gynecology and Obstetrics adopted by the Iran University of Medical Sciences and Health Services. The IRI's Committee on Ethics ratified this research plan under the following code: IR.IUMS.FMD.REC 1398.9311290001380.

Funding/Support

We wish thanks from the Iran University of Medical Sciences for financial support.

References

1. Shaaban AM, Rezvani M, Haroun RR, Kennedy AM, Elsayes KM, Olpin JD, et al. Gestational trophoblastic disease: clinical and imaging features. Radiographics. 2017;37(2):681-700. https://doi.org/10.1148/rg.2017160140

2. Ngan HY, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan P, et al. Update on the diagnosis and management of gestational trophoblastic disease. International Journal of Gynecology & Obstetrics. 2015;131:S123-S6. https://doi.org/10.1016/j.ijgo.2015.06.008

3. Usui H, Qu J, Sato A, Pan Z, Mitsuhashi A, Matsui H, et al. Gestational Trophoblastic Neoplasia From Genetically Confirmed Hydatidiform Moles: Prospective Observational Cohort Study. International Journal of Gynecologic Cancer. 2018;28(9):1772-80. http://dx.doi.org/10.1097/IGC.0000000000001374

4. Verit FF. May platelet count be a predictor of low-risk persistent gestational trophoblastic disease? Archives of gynecology and obstetrics. 2011;283(4):695-9. https://doi.org/10.1007/s00404-010-1408-2

5. Lertkhachonsuk A, Hanvoravongchai P. Comparison of Cost-Effectiveness Between Actinomycin D Versus Methotrexate-Folinic Acid in the Treatment of Low-Risk Gestational Trophoblastic Neoplasia. The Journal of reproductive medicine. 2016;61(5-6):230-4. https://europepmc.org/article/med/27424364

6. Kolusari A, Adali E, Kurdoglu M, Yildizhan R, Cebi A, Edirne T, et al. Catalase activity, serum trace element and heavy metal concentrations, vitamin A, vitamin D and vitamin E levels in hydatidiform mole-Serum levels of catalase, Zn, Co, and vitamin A, D, and E were significantly lower in patients with hydatiform mole compared with healthy pregnant women and non pregnant controls. Clinical & Experimental Obstetrics & Gynecology. 2009;36(2):102. https://doi.org/10.1177/147323000803600622

7. Andrijono A, Muhilal M. Prevention of post-mole malignant trophoblastic disease with vitamin A. Asian Pac J Cancer Prev. 2010;11(2):567-70. https://www.ncbi.nlm.nih.gov/pubmed/?term=Prevention+of+Post-

8. Sutanto EH, Winarno GN, Firmansah A. Effect of Methotrexate Combination with Vitamin A on Serum Levels of beta hCG in Low Risk of Gestational Trophoblastic Tumors Treatment. Indonesian Journal of Obstetrics and Gynecology. 2012;35(2):84-6. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Sutanto

9. Cunnigham F. leveno KJ, Bloom SL, Hauth JC, Gilstrap LC, Wenstrom KD. Williams Obstetrics. NewYork: McGraw Hill; 2005. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q

10. Rajaei E, Shahbazian N, Rezaeeyan H, Mohammadi AK, Hesam S, Zayeri ZD. The effect of lupus disease on the pregnant women and embryos: a retrospective study from 2010 to 2014. Clinical rheumatology. 2019;38(11):3211-5. https://doi.org/10.1007/s10067-019-04682-3

11. Lawler S, Pickthall V, Fisher R, Povey S, Evans MW, Szulman A. Genetic studies of complete and partial hydatidiform moles. The Lancet. 1979;314(8142):580. DOI:10.1016/s0140-6736(79)91632-5

12. Feizollahi N, Zayeri ZD, Moradi N, Zargar M, Rezaeeyan H. The effect of coagulation factors polymorphisms on abortion. Frontiers in Biology. 2018;13(3):190-6. https://doi.org/10.1007/s11515-018-1500-8

13. Mazul AL, Weinberg CR, Engel SM, Siega-Riz AM, Zou F, Carrier KS, et al. Neuroblastoma in relation to joint effects of vitamin A and maternal and offspring variants in vitamin A-related genes: A report of the Children's Oncology Group. Cancer epidemiology. 2019;61:165-71. https://doi.org/10.1016/j.canep.2019.06.009

14. Haybar H, Shahrabi S, Rezaeeyan H, Jodat H, Saki N. Strategies to inhibit arsenic trioxide-induced cardiotoxicity in acute promyelocytic leukemia. Journal of cellular physiology. 2019;234(9):14500-6. https://doi.org/10.1002/jcp.28292

15. Oliveira S, Costa J, Faria I, Guerreiro SG, Fernandes R. Vitamin A Enhances Macrophages Activity Against B16-F10 Malignant Melanocytes: A New Player for Cancer Immunotherapy? medicina. 2019;55(9):604. https://doi.org/10.3390/medicina55090604

16. Tang X-H, Gudas LJ. Retinoids, retinoic acid receptors, and cancer. Annual Review of Pathology: Mechanisms of Disease. 2011;6:345-64. DOI:10.1146/annurev-pathol-011110-130303

17. Russo I, Caroppo F, Alaibac M. Vitamins and melanoma. Cancers. 2015;7(3):1371-87. https://doi.org/10.3390/cancers7030841

18. Kim J, Park MK, Li W-Q, Qureshi AA, Cho E. Association of Vitamin A Intake With Cutaneous Squamous Cell Carcinoma Risk in the United States. JAMA dermatology. 2019;155(11):1260-8. doi:10.1001/jamadermatol.2019.1937

19. Milani HS, Abdollahi M, Torbati S, Asbaghi T, Azargashb E. Risk Factors for Hydatidiform Mole: Is Husband's Job a Major Risk Factor? Asian Pacific journal of cancer prevention: APJCP. 2017;18(10):2657. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5747385/

20. Bakhtiyari M, Mirzamoradi M, Kimyaiee P, Aghaie A, Mansournia MA, Ashrafi-vand S, et al. Postmolar gestational trophoblastic neoplasia: beyond the traditional risk factors. Fertility and sterility. 2015;104(3):649-54. https://doi.org/10.1016/j.fertnstert.2015.06.001

21. Eskicioglu[1] F, Ulkumen BA, Calik E. Complete blood count parameters may have a role in diagnosis of gestational trophoblastic disease. Pakistan journal of medical sciences. 2015;31(3):667. doi: http://dx.doi.org/10.12669/pjms.313.7109