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Serum amyloid A may be associated with hydatidiform mole

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Abstract

Hydatidiform mole (HM) is a gestational trophoblastic disease. Potential risk factors are advanced maternal age, reproductive factors, oral contraceptive use, history of gestational trophoblastic disease, oxidative stress, and other environmental factors. Serum amyloid A (SAA) protein has an important role in acute phase response but is also associated with pathologic fibril formation in chronic inflammation. The aim of the current study is to determine the relationship between maternal SAA levels in patients with both complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM), and to examine its potential role in the disease in pathogenesis. Fifty healthy pregnant women in the first trimester of pregnancy with completely normal pregnancy follow-up, and 50 patients who were diagnosed with HM, who were also in the first trimester of pregnancy included in the study. There was no difference between patients and the control group according to body mass index (BMI), gravidity, parity, number of living children, number of miscarriages, level of blood TSH, and hemoglobin level between the two groups. SAA levels in patients with HM were significantly higher than those in healthy controls. This may be an important underexplored pathway mediating the relationship between oxidative stress and abnormal placental proliferation

Keywords: hydatidiform mole, molar pregnancy, serum amyloid A (SAA)

1. Introduction

Hydatidiform mole (HM) (also known as molar pregnancy or mole) is a part of gestational trophoblastic disease, which originates in the placenta. HM is a premalignant disease with two genetically different forms, as complete HM (CHM) and partial HM (PHM), and can progress to a malignant condition known as gestational trophoblastic neoplasia (GTN). CHM and PHM differ in the gross morphology, chromosomal pattern and clinical outcome. CHMs are diploid and both copies are paternally derived (1). PHMs are triploid, usually resulting from fertilization of a normal ovum with two spermatozoa (2). The prevalance of CHM and PHM ranges from 1 to 3 per 1000 pregnancies depending on geographic differences (3).

Potential risk factors are prior molar pregnancy, advanced maternal age, oral contraceptive use, dietary factors and other environmental factors (4,5). But the etiology of HM is not yet completely understood. However, oxidative stress (OS) may be related in to pathogenesis. Enhanced maternal oxidative stress with inflammation and genotypic abnormalities leads to defective placentation and grape-like degeneration of the placenta (6,7).

Serum amyloid A (SAA) protein has an important role in acute phase response but is also associated with pathologic fibril formation in chronic inflammation. Mainly synthesized in the liver (8). SAA stimulates recruitment of immune cells to inflammatory sites and induction of enzymes that degrade extracellular matrix (9,10). Studies have demonstrated that maternal SAA is closely associated with complicated pregnancies that such as preeclampsia and early pregnancy loss (11-13). But, maternal SAA levels have not been studied before in molar pregnancies. The aim of our study is to determine the relationship between maternal SAA levels in patients with HM, and to examine a possible role in the disease in pathogenesis.

2. Materials and Methods

This is a prospective case control study that was conducted at the gynecologic oncology and early pregnancy departments of a tertiary research and education hospital, between September 2017 and September 2020. Fifty healthy pregnant women in the first trimester of pregnancy with completely normal pregnancy follow-up, and 50 patients who were diagnosed with

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HM, who were also in the first trimester of pregnancy. Approval was obtained from the ethics and the education issues coordinating committee of the hospital and all the participants signed an informed consent prior to their enrolment.

Patients with HM underwent evacuation of the uterus by suction curettage. Patients with PHM and CHM were included in the study group. The evacuated material was sent for pathology analysis. The control group included first-trimester pregnancies with normal biochemistry and complete blood results without medical problems. Patients with multiple pregnancies, systemic disease, presence of maternal or fetal infection, smoking, and using any chronic drug or antioxidant excluded from the study. Gestational ages were estimated according to the last menstrual period or crown-rump length of the embryo, if an embryo was present. Biometric measurements were performed using an ultrasound device with an endovaginal transducer. Sociodemographic, reproductive, medical and laboratory data, fetal ultrasonographic information, and patient follow-up forms were collected from both groups. Blood samples were obtained just before the suction curettage in the operating room in patients with HM, and blood samples of the controls were taken during the first trimester of antenatal visits. HM was confirmed through histopathologic diagnosis in all patients in the study group. Levels of SAA were assayed and determined by the nefelometric method with an enzyme-linked immunosorbent assay kit (BioSource Europe, Nivelles, Belgium), according to the manufacturer's protocol.

The data were analyzed using SPSS version 21.0 (IBM, Armonk, NY, USA). Normally distributed data were presented as the mean±standard deviation; between-group differences were assessed using the Student t test. Skewed numerical data were presented as the median and interquartile range (IQR); between-group differences were com- pared non-parametrically using the Mann–Whitney U test. The $\chi 2$ or Fisher exact tests were used to compare the two groups. P values were less than 0.05 considered statistically significant.

3. Results

We included 50 patients with hydatidiform mole and 50 healthy pregnant women in our study. The mean age of the patients with hydatidiform mole was 28.49± 3.78 years and 28.49± 3.78 years in the control group. In the univariate analysis, there was no difference between patients and the control group according to BMI, gravidity, parity, number of living children, number of miscarriage and smoking status (Table 1). Also, there was no difference between the two groups according to level of blood TSH and hemoglobin level (Table 2). Serum amyloid A levels were higher in patients with hydatidiform mole (152.57± 60.47 vs 135.75±34.58 p=0.03) (Table 2 and Fig. I). Demographic and clinical characteristics between the patients with hydatidiform mole and the control group are presented in Table 1 and Table 2.

Table 1. Basal characteristics of whole study population

Variable	Patient (n:50)	Control (n:50)	p
Age (year, ±STD)	28.8±7.54	28.49± 3.78	N/S
BMI (kg/m^2, ±STD)	25.72±2.73	26.1±2.85	N/S
Gravidity (n, median)	2 (1-6)	2 (1-4)	N/S
Parity (n, median)	1 (0-5)	1 (0-3)	N/S
Live children (n, median)	1 (0-3)	1 (0-5)	N/S
Miscarriage (n, median)	1 (0-3)	1 (0-5)	N/S
Smokers (n, %)	6 (%12)	5 (%10)	N/S
Gestational age (weeks, median)	8 (7-11)	9 (7-11)	N/S

BMI: body mass index

Table 2. Laboratory findings of the patients and control group

Variable	Patient (n:50	Control (n:50)	p
TSH	1.49±1.05	1.30±0.99	N/S
Hemoglobin	12.75±2.32	12.6±2,27	N/S
SAA (mg/L)	152.57± 60.47	135.75±34.58	0.03
CRP (mg/L, ±STD)	6.7±2.2	7.2±1.9	N/S
AST (U/L, ±STD)	24.4±12.6	27.6±8.9	N/S
ALT (U/L, ±STD)	35.3±10.3	37±7.4	N/S
GGT (U/L, ±STD)	24±7.7	23±9.3	N/S
TSH (mIU/L, ±STD)	3.78±1.2	3.56±1.1	N/S
Blood Glucose (mg/dL, ±STD)	96±4.4	93±4.9	N/S

SAA: Serum amyloid A TSH: Thyroid Stimulating Hormone, Crp: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine transaminase, GGT: gamma-glutamyl transferase, TSH: thyroid stimulating hormone

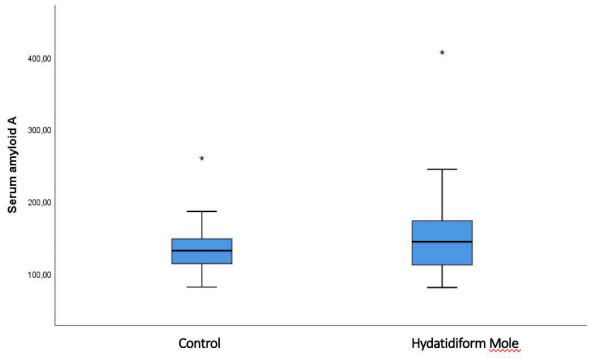

Fig. 1. Serum amyloid A levels of the study population

When we examined the patients in HM patients, there were no significant differences between the CHM and PHM groups in terms of SAA levels (p>0.05) (Table 3).

Table 3. Laboratory findings for the partial and complete hydatidiform mole groups

Variable	Partial mole (n:28)	Complete mole (n:22)	p
TSH	1.47±0.43	1.53±0.47	N/S
Hemoglobin	12.25±1.33	12.85±1.89	N/S
SAA (mg/L)	153.2±29.6	149.9± 30.4	N/S

4. Discussion

Oxidative stress plays an important role in the pathogenesis of molar pregnancy (7,14,15). And the aim of this study was to assess the relationship between serum amyloid A levels as an OS marker and hydatidiform mole.

Oxidative stress is related to the deterioration of the prooxidant and antioxidant balance and present in most organs exposed to high oxygen metabolism such as the placenta (16). Good placental oxygenation is essential during pregnancy for

cell replication, proliferation and maturation, embryo development, and pregnancy maintenance. Abnormal placental proliferation leads to uneven blood perfusion, hypoxia and oxidative stress (6,7,17). Also, increased ROS production can lead to uncontrolled trophoblastic hyperplasia by enhancing apoptotic activity (18). There is an emerging confluence of opinions that suggests that oxidative stress is one of the main underlying mechanisms in the pathogenesis of a continuum of disease processes in molar pregnancy (7,1,15,19,20).

Maternal SAA is a member of apolipoproteins associated with high-density lipoproteins in plasma. It is also associated with inflammatory response highly similar to erythrocyte sedimentation rate and C reactive protein (CRP) (21). Other known functions of SAA include immunomodulation, cell proliferation, cell differentiation, cell migration, and invasion (11,22,23). Although SAA is predominantly synthesized in the liver, hepatic sources, including first-trimester trophoblasts, have been described (22). CRP has already been reported as a potential prognostic marker in molar pregnancy (24). Both proteins, CRP and SAA, are synthesized by the liver following pro-inflammatory stimuli, and have been reported to be comparably upregulated in serum of renal cell cancer patients after treatment with interleukin (IL)-2 (25). Despite these similarities, the sensitivity of SAA to detect inflammatory changes has been reported to be higher than CRP (26). Relatively trivial inflammatory stimuli can lead to SAA responses. It has been suggested that SAA levels correlate better with disease activity in early inflammatory joint disease than do ESR and CRP.

Although numerous studies have examined the relationship between SAA and early pregnancy loss, preeclampsia, preterm birth and hemolysis, elevated liver enzymes, low platelet count (HELLP), to the best of our knowledge, this is the first study to date of maternal SAA levels in HM (11-13,21).

In our study, SAA levels were higher in patients with HM compared with the healthy pregnant group. In subgroup analyses, there were no differences between complete HM and partial HM.

Several potential limitations of our study should be noted. First, this is a preliminary study with a small sample from one single center, and all the patients are Turkish. Therefore, these results can not be generalized to all populations. The generalizability of our findings can be increased by including women from other centers. Second, SAA concentrations were tested only one time at the baseline, so we were unable to assess the association between SAA changes of in normal and molar pregnancy. These issues should be addressed in future well-controlled multicenter studies with a large sample.

In conclusion, SAA levels in patients with HM were significantly higher than those in healthy controls. This may be an important underexplored pathway mediating the relationship between oxidative stress and abnormal placental proliferation. Since the pathophysiology of HM is multifactorial and not fully understood yet, it has been difficult to develop preventive strategies. Future studies are now needed to investigate the mechanism of OS in patients with HM.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: N.T.Ö., M.K.P., A.K., Ö.E., G.Ö., M.M.M., Design: N.T.Ö., M.K.P., A.K., Ö.E., G.Ö., M.M.M., Data Collection or Processing: N.T.Ö., M.K.P., A.K., Ö.E., Analysis or Interpretation: N.T.Ö., M.K.P., A.K., Ö.E., Literature Search: A.T., N.T.Ö., İ.Y., Writing: A.T., N.T.Ö., İ.Y.

Ethical Statement

Approval was obtained from Health Science University Zekai Tahir Burak Women's Health Practice and Reserch Center Medical Specialty Education Committee, the study started. The committee decision date is 12/02/2018 and the number of committee decisions is 31.

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