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ASSOCIATION BETWEEN SERUM AMYLOID A AND HYDATIDIFORM MOLE

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ABSTRACT

Background: Early detection of hydatidiform moles is crucial as it allows for timely intervention and management. If left untreated, molar pregnancies can lead to complications such as gestational trophoblastic neoplasia, which may impose significant mortality risk and require more intensive treatment. Therefore, it would be helpful to identify new diagnostic markers to aid in the early detection of molar pregnancy. **Aim of study:** To evaluate the association between serum amyloid A and hydatidiform mole. **Patients and methods:** The study has been conducted at Baghdad Teaching Hospital/ Medical City, Baghdad. The data was collected from the 1st of January 2024 to the 1st of September 2024. A total number of 120 pregnant women in the first trimester were enrolled in the study; which included 30 patients with complete molar pregnancy (group I), 30 patients with partial molar pregnancy (group II), and 60 healthy pregnant women as controls (group III). **Results:** Statistical comparison of mean serum amyloid-A values revealed the following: Serum amyloid A levels were significantly lower in controls than the study cases. Whereas no significant difference was detected between patients with partial and molar pregnancy. It was revealed that serum amyloid-A was a significant predictor of molar pregnancy. The optimum cut-off point with the highest (sensitivity + specificity) was determined to be 0.55 ng/ml; as it had a sensitivity of 86.6%, specificity of 76.6%, PPV of 78.78%, NPV of 85.18%. **Conclusion:** Based on the findings of the current study, serum amyloid A is significantly elevated in patients with hydatidiform mole. Moreover, it was shown to be a significant predictor in the diagnosis of H mole. However, it could not differentiate between partial and complete molar pregnancy.

INTRODUCTION

Serum Amyloid A (SAA) is a group of apolipoproteins predominantly associated with high-density lipoprotein (HDL) in plasma. As an acute-phase protein, SAA's concentration can increase up to 1,000-fold in response to inflammation, infection, or trauma.[1] SAA is synthesized primarily in the liver, under the regulation of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). Its functions extend beyond acting as a marker of inflammation; SAA plays a role in lipid metabolism, immune response modulation, and tissue repair.[2]

Hydatidiform mole (HM) is a type of gestational trophoblastic disease characterized by abnormal trophoblastic proliferation. It is classified into two types: complete mole (CM) and partial mole (PM). A complete mole occurs when an egg with no genetic material is fertilized by a sperm, leading to the growth of abnormal tissue without an embryo.[3] In contrast, a partial mole occurs when an egg is fertilized by two sperms, resulting in abnormal tissue and an embryo with severe defects. Clinically, HM presents with symptoms such as vaginal bleeding, excessive nausea and vomiting, and abnormally high levels of human chorionic gonadotropin (hCG).[4]

The study of the association between SAA and HM is crucial for several reasons. Identifying reliable biomarkers for early detection and monitoring of HM can significantly improve patient outcomes. As an inflammatory marker, SAA might reflect underlying pathological processes in HM, such as abnormal trophoblastic invasion and immune response.[5] Understanding this association could lead to better diagnostic tools, enabling clinicians to differentiate

between benign and malignant forms of gestational trophoblastic disease more effectively.[6]

This study aims to evaluate the association between serum amyloid A and hydatidiform mole.

PATIENTS AND METHODS

Study place and time

The study has been conducted at Baghdad Teaching Hospital/ Medical City, Baghdad. The data was collected from the 1st of January 2024 to the 1st of September 2024.

Study design

An analytic case control design has been chosen for this study.

Research population

A total number of 120 pregnant women in the first trimester were enrolled in the study; which included 30 patients with complete molar pregnancy (group I), 30 patients with partial molar pregnancy (group II), and 60 healthy pregnant women as controls (group III).

Inclusion criteria

Inclusion criteria involved first trimester pregnant women diagnosed with complete or partial molar pregnancy (as diagnosed in section 2.6.4) along with gestational age-matched controls.

Exclusion criteria

Pregnant women with the following conditions were excluded:

1. Patients with multiple pregnancies.
2. Obese women.
3. Women with previous molar pregnancies.
4. Women with any underlying medical conditions that could significantly affect serum amyloid A levels (infections, liver or kidney disease, rheumatoid arthritis).
5. Presence of maternal or fetal infection.
6. Smoker and alcoholic women.
7. Participants taking medications that could influence serum amyloid A levels (e.g., corticosteroids, nonsteroidal anti-inflammatory drugs) were excluded.

Participants consent

All participants were assured that their personal information and any data collected will be used solely for research purposes. Participants were informed that their names and any other identifying information will be kept confidential and will not be associated with their research data in any published study. Verbal consent was obtained from all participants prior to data collection.

Approval and official permission

An official letter of approval has been obtained from the scientific committee of the scientific council of Obstetrics and Gynecology – Iraqi Board for Medical Specializations and Baghdad Teaching Hospital.

Data collection and clinical assessment

A total number of 120 participants were included. Detailed history was taken and information about demographic and clinical characteristic using semi-structured questionnaire which includes presenting complaint, age, parity, last menstrual period, age of marriage, smoking, obstetrical history, past medical history and past surgical history. All patients underwent full general, abdominal, and pelvic examination.

Ultrasonographic assessment

All study participants underwent transvaginal ultrasound in lithotomy position with high frequency inducer device.

For complete molar pregnancy, key ultrasonographic findings were the following.[7]

1. Snowstorm appearance: defined as a mixed echogenic pattern in the uterus, indicating hydropic villi and intrauterine hemorrhage.
2. The absence of fetal structures: No identifiable embryo or amniotic fluid.
3. The identification of a thick cystic placenta, which may fill the uterus.
4. The presence of theca-lutein cysts in the ovaries, which may appear as multiple large cysts.

For partial molar pregnancy, key ultrasonographic findings were the following.[8]

1. The presence of a smaller-than-expected fetus, which may show signs of growth restriction or developmental abnormalities.
2. The presence of low amniotic fluid levels and an unusual appearance of the placenta with scattered cystic spaces.

Laboratory investigations

1. Quantitative beta-hCG levels: hCG levels greater than 100,000 mIU/mL were considered highly suspicious for molar pregnancy.[8]
2. Complete blood count.
3. Coagulation studies: PT, PTT.
4. Liver function test (ALT, AST, ALP).
5. Renal function test (B.urea , S.creatinie).
6. Blood type.
7. Thyroid function tests.
8. Serum amyloid A.
9. beta hCG.

Evacuation procedure

Patients underwent evacuation of pregnancy in case of diagnosis of molar pregnancy. The evacuation procedure was conducted under general anesthesia. The patient was prepared for cervical ripening using vaginal misoprostol suppositories 25µg. Cervical dilatation was conducted in case of closed os or insufficient cervical dilatation in order to insert a sponge in order to remove the molar

tissue. A suction device may be used to remove any remaining tissue or debris from the uterine cavity. The procedure was conducted under abdominal ultrasonographic guidance in order to confirm the total removal of the molar tissue and to identify any potential abnormalities. After completion of procedure, the evacuated tissue was sent for histopathological study.

Serum amyloid A sample collection

Before the process of uterine evacuation, five milliliters of venous blood were collected from each woman placed in sterile tubes which were labeled with the patient's name allow samples to clot for two hours at room temperature and centrifuged for 20 Minutes at 1000 rounds per minutes. Serum was collected carefully and immediately stored at -20°C – -80°C. Avoid repeated freeze-thaw cycle.

Data entry and analysis

Data entry was done using Microsoft Excel 2019. Data was recorded into different quantitative and qualitative variables for the purpose of analysis. Analysis was done using statistical package for social sciences (SPSS version 26). Data was summarized using measures of frequency (mean), dispersion (standard deviation), tables and graphs. Independent sample t-test was used to test for statistical significance between continuous variables. Fischer's exact test was used for categorical variables. A two-tailed p value of less than or equal to 0.05 was assigned as a criterion for declaring statistical significance.

Statistical ROC analysis was conducted in order to evaluate the role of serum amyloid A as a biomarker for molar pregnancy.

RESULTS

The study sample

A total number of 120 pregnant women were included in the study sample: 60 cases (30 with complete mole and 30 with partial mole) and 60 controls.

Demographic characteristics of the study groups

No significant difference between the three study groups was detected regarding maternal age, BMI, and family history of molar pregnancy; whereas a statistically significant difference was detected regarding parity and history of molar pregnancy as shown in **Table (1)**.

Table (1): Basic characteristics of the studied sample.

Basic characteristics	Group			P value
	Complete mole (n=30)	Partial mole (n=30)	Controls (n=60)	
Age				
<30 years	18	17	42	0.846
	60.0%	56.7%	70.0%	
30-45 years	12	13	18	
	40.0%	43.3%	30.0%	
Mean ± SD	27.6 ± 7.2	28.1 ± 6.4	26.1 ± 7.0	
BMI				
Normal weight	16	15	34	0.964
	53.3%	50.0%	56.7%	
Overweight	14	14	26	
	46.7%	46.7%	43.3%	
Obese	0	1	0	
	0.0%	3.3%	0.0%	
Parity				
Nulliparous	6	7	30	**0.023**
	20.0%	23.3%	50.0%	
Parous	24	23	30	
	80.0%	76.7%	50.0%	
Gestational age at diagnosis				
Mean ± SD	10.6 ± 3.1	9.8 ± 2.4	9.3 ± 1.8	0.472
History of molar pregnancy				
Yes	11	9	1	**0.003**
	36.7%	30.0%	3.3%	
No	19	21	29	
	63.3%	70.0%	96.7%	
Family history of molar pregnancy				
Yes	3	4	0	0.154
	10.0%	13.3%	0.0%	
No	27	26	30	
	90.0%	86.7%	100.0%	

Laboratory investigations of the study groups

No statistically significant difference was detected between the three study groups regarding Hb, liver function tests (AST, ALT, ALP) and CRP. Whereas cases with complete and partial molar pregnancy had significantly lower TSH, and higher T3 and T4 levels than controls; as shown in **Table (2).**

Table (2): Laboratory investigations of the studied sample.

Variable (Mean ± SD)	Group			P value
	Complete mole (n=30)	Partial mole (n=30)	Controls (n=60)	
Hb (g/dl)	11.7 ± 2.6	11.4 ± 2.2	11.5 ± 2.6	0.635
TSH (mIU/L)	1.73 ± 0.6	1.63 ± 0.4	2.1 ± 0.7	**0.027**
FT3 (pmol/L)	4.27 ± 0.83	4.02 ± 0.67	3.62 ± 1.13	**<0.001**
FT4 (pmol/L)	12.13 ± 1.89	12.24 ± 2.01	10.37 ± 1.82	**<0.001**
AST (U/L)	23.5 ± 15.3	20.6 ± 11.7	18.7 ± 5.8	0.537
ALT (U/L)	35.9 ± 13.0	36.1 ± 14.8	33.6 ± 12.1	0.368
ALP (U/L)	104 ± 23.6	99.3 ± 31.6	102.5 ± 19.5	0.463
CRP (mg/dl)	0.6 ± 0.2	0.5 ± 0.3	0.5 ± 0.2	0.262

Comparison of mean serum amyloid-A values

Statistical comparison of mean serum amyloid-A values revealed the following: Serum amyloid A levels were significantly lower in controls than cases. Whereas no significant difference was detected between patients with partial and molar pregnancy; as shown in table (3).

Table (3): Comparison of mean serum amyloid-A values between cases of complete molar pregnancy, partial molar pregnancy, and controls.

Serum amyloid-A	Cases		Controls	P value		
	Complete mole	Partial mole		P1	P2	P3
Mean ± SD	1.04 ± 0.58	1.09 ± 0.58	0.49 ± 0.17	0.900	**<0.001**	**<0.001**
P1: Complete mole vs. partial mole; P2: Complete mole vs. control; Partial mole vs. control						

3.6 Efficiency of serum amyloid-A for the diagnosis of molar pregnancy

The ROC analysis revealed that serum amyloid-A was a significant predictor of molar pregnancy (AUC = 0.897, P value <0.001); as shown in **Figure (1).** The optimum cut-off point with the highest (sensitivity + specificity) was determined to be 0.55 ng/ml; as it had a sensitivity of 86.6%, specificity of 76.6%, PPV of 78.78%, NPV of 85.18%; as shown in **Table (4).**

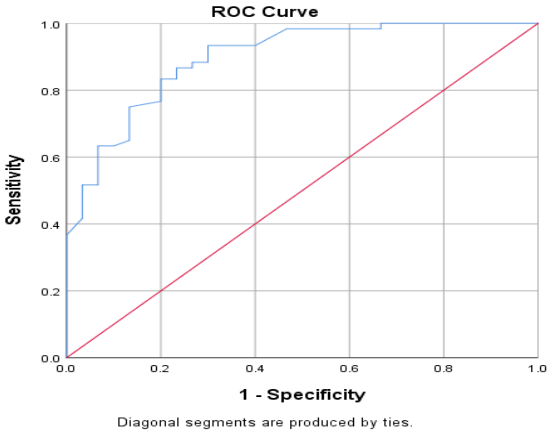

Figure (1): ROC analysis diagnostic indices of serum amyloid-A for prediction of molar pregnancy.

Table (4): Accuracy of 0.55 ng/ml as a cut-off point of amyloid-A in the differentiation between cases of molar pregnancy and controls.

Amyloid-A	Diagnosis		Total
	Cases	Controls	
≥0.55 ng/ml	52	14	66
<0.55 ng/ml	8	46	54
Total	60	**60**	120

DISCUSSION

The incidence of hydatidiform mole varies worldwide with rates of 1-2 per 1000 pregnancies in Europe and North America. Higher rates were reported in developing countries such as India and Indonesia (10 per 1000 pregnancies).[9] In Erbil City/ Iraq, a study conducted at the Maternity Teaching Hospital tertiary center reported a rate of 13.1% among incomplete miscarriage cases.[10] Early detection of hydatidiform moles is crucial as it allows for timely intervention and management. If left untreated, molar pregnancies can lead to complications such as gestational trophoblastic neoplasia, which may impose significant mortality risk and require more intensive treatment.[11] Therefore, it would be helpful to identify new diagnostic markers to aid in the early detection of molar pregnancy. The present study was conducted aiming to identify the role of serum amyloid A for the diagnosis of hydatidiform molar pregnancy.

The present study found that women with molar pregnancy were significantly more likely to be

multiparous than controls. This finding is in concordance with the study by Niloufar et al. who reported that there was a significant relationship between hydatidiform mole (HM) and multiparity, with an odds ratio of 1.85 indicating that multiparous women had a higher incidence of molar pregnancy than primiparous women.[12] However, the study by **Shamshiri et al.** reported no significant association between parity and the risk of molar pregnancy.[13]

Additionally, the current study revealed that cases with complete molar pregnancies exhibited significantly lower TSH levels compared to those with partial molar pregnancies. Both groups demonstrated significantly lower TSH levels than the control group. This can be attributed to the reason that the β-subunit of hCG shares structural similarity with TSH, allowing it to bind to TSH receptors on thyroid cells. This binding stimulates the thyroid gland to produce more thyroid hormones (T3 and T4), leading to a state of hyperthyroidism.[14]

This finding is in concordance with a study by Düğeroğlu et al. involving 50 women diagnosed with hydatidiform mole. The study reported that pateints with complete moles exhibited significantly lower TSH levels compared to those with partial moles. The mean TSH level in patients with complete moles was notably lower (0.28 uIU/ml) than partial mole (0.91 uIU/ml), while free thyroxine (fT4) levels were significantly higher among patients with complete molar pregnancy.[15]

Amir et al. reported that among 47 patients with molar pregnancy, one case was clinically hyperthyroid, but 10 exhibited serum total thyroxine (T4) values exceeding normal pregnancy levels (8 to 17 µg/dL).[16]

The study by Samimagham et al. found that among 65 patients with hydatidiform mole; 12.3% of the patients had subclinical hyperthyroidism, 41.5% had clinical hyperthyroidism, and 46.2% were healthy. The study also reported that a significant inverse relationship was found between the serum level of β-HCG and thyroid function in patients with clinical and subclinical hyperthyroidism.[17]

Regarding serum amyloid A, the present study found that it was significantly elevated in the cases group. Moreover, a serum value of 0.55 ng/ml had 86.6% sensitivity and 76.6% specificity to diagnose molar pregnancy. However, it could not differentiate between partial and complete mole.

This finding is in concordance with the study by Ozkan et al. who included 50 healthy pregnant women in the first trimester of pregnancy with completely normal pregnancy, and 50 patients who were diagnosed with HM (28 with partial mole and 22 with complete mole). Their study reported that serum amyloid A levels were higher in patients with HM compared with the healthy pregnant group. They also reported there were no differences between complete HM and partial HM. Unfortunately, their study did not evaluate its diagnostic accuracy. A specific cutoff point for the diagnostic tool was also not provided.[18]

The proposed mechanisms for elevated serum amyloid A in molar pregnancy is that SAA is associated with inflammatory response highly similar to erythrocyte sedimentation rate and C reactive protein. It is primarily produced by the liver in response to inflammation, infection, and tissue injury. It acts as an acute phase protein, meaning its levels increase significantly during inflammatory states. In the context of molar pregnancies, which are characterized by abnormal trophoblastic proliferation and potential tissue damage, elevated SAA levels can be a reflection of the body's inflammatory response to these pathological changes.[19]

CONCLUSION

Based on the findings of the current study, serum amyloid A is significantly elevated in patients with hydatidiform mole. Moreover, it was shown to be a significant predictor in the diagnosis of H mole, as a cutoff value of 0.55 ng/ml had a sensitivity of 86.6% and specificity of 76.6%. However, it could not differentiate between partial and complete molar pregnancy.

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