Original Article

Toxoplasmosis and Antiphospholipid Autoantibodies Associated with Preeclampsia

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Abstract

Background: *Toxoplasma gondii is* a single-celled, low-specificity parasite that obligatorily settles inside host cells, infects many different hosts, and is associated with many diseases. **Objective:** The purpose of the current study is to look into the relationship between toxoplasmosis and preeclampsia (PE). **Materials and Methods:** 60 healthy women and 80 women with PE diseases participated in a case–control study to test anti-*T. gondii* and antiphospholipid IgM and IgG antibodies by Enzyme Linked Immunosorbent Assay. A formalized questionnaire was designed to collect participant demographic data and PE risk factors during sampling. **Results:** The seroprevalence antibodies were 35% and 10% for both *Toxoplasma*-IgG and -IgM, respectively, in women exposed to Preeclampsia, compared to 0% and 6.66% for healthy pregnant women, respectively, and significant difference ($P < 0.0001$) between the two groups was recorded for IgG antibody only. Anti-phospholipid IgM and IgG antibodies were statistically significant differences between the two groups and had a larger in pre-eclampsia patients than the control group ($P < 0.05$) and ($P < 0.01$), respectively. Anti-phospholipid IgM antibodies were greater ($P < 0.001$) in PE patients group with latent toxoplasmosis (28.57%) than other group, anti-phospholipid IgG antibodies were greater ($P < 0.001$) in PE patients without *Toxoplasma* infection than both PE patients with *Toxoplasma* and healthy pregnant women groups. The results showed that there is a significant relationship between abortions and PE, as well as between the stage or period of pregnancy and the disease, and significant relationship was recorded between the number of pregnancies and PE. **Conclusion:** The study concludes that toxoplasmosis and prevalence of antiphospholipid antibodies are risk factors for PE in women.

Keywords: Antiphospholipids antibodies, pre-eclampsia, toxoplasmosis

Introduction

Preeclampsia (PE) is a foremost cause of maternal and fetal morbidity and mortality, affecting 2%–8% of pregnancies.[1] In Iraq PE was more common than in other nearby developing nations.[2] It is defined as recently developed hypertension after 20 weeks of pregnancy lacking a history of hypertension with at least one of the subsequent general signs: proteinuria, thrombocytopenia, renal failure, liver dysfunction, lung edema, headache, and visual impairments.[3] The precise etiology of PE is unknown. Nonetheless, there is a growing amount of evidence linking maternal infections to PE. According to Rustveld *et al*.,[4] women with bacterial or viral illnesses had a twofold increased chance of developing PE. PE is associated with an increase maternally circulating cytokines, including interferon-γ, interleukin-6, interleukin-10, and tumor necrosis factor-α.

There is growing evidence that a variety of infectious characteristics, such as periodontal disease, urogenital infection, and parasitic infection, are involved in the etiology of the disease.[5] It was previously discovered that infected women with placental malaria were 2.3 times more likely to develop pre-eclampsia.[6] In the other trial, women who tested positive for Herpes Simplex Virus-2 and rubella IgG were 5.5 and 4.9 times, respectively, more possible to develop pre-eclampsia.[7] COVID-19 infection in pregnant women is a factor that increases the likelihood of PE later in the future.[8] A 342,090 women in a British

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cohort study done between 2020 and 2021 during the coronavirus outbreak found that women infected with the virus had greater rates of stillbirths, premature births, pre-eclampsia and forced caesarean sections than women who were not infected, the same study indicated that women infected with SARS-CoV-2 experienced PE at a rate of 3.9%, compared to 2.5% in those who were not.[9] Al-Shareef *et al*.[10] found a significant relationship between the presence of IgG antibodies to the parasite *Toxoplasma gondii* and infection with PE among Sudanese women.

There are anti-angiogenesis factors, which are dissolved in the blood of the pregnant woman and are known as toxins. When these factors increase, a condition of PE is generated, so the condition is referred to as toxemia of pregnancy.[11] Antiangiogenic factor, soluble fms-like tyrosine kinase 1 (sFlt-1), was enhanced in the placenta of PE patients.[12]

The most important risk factors involved in the development of pre-eclampsia are a history of pre-eclampsia, persistent high blood pressure, and pre-pregnancy diabetes mellitus, antiphospholipid syndrome, and fatness.[13] Antiphospholipid syndrome has been linked to pre-eclampsia during gestation, which may create health challenges for the mother and her fetus.[14]

The current study aimed to prove the possible relationship between *T. gondii* infection and exposure to Preeclampsia in women in Babylon province and study other possible risk factors.

Materials and Methods

Samples collection

In the months of October 2022 to January 2023, 140 venous blood samples were gathered from expectant mothers (the samples included 60 pregnant women in good health and 80 pregnant women with pre-eclampsia) under sterilization conditions using single-use medical syringes and medical gloves from Al-Mahaweel General Hospital and private laboratories in Hilla city belong to Babylon Governorate, their ages were between 15 and 42 years. The cases of PE was diagnosed by a professional physician who performed medical examinations on them. Also, by asking questions to the patient and taking precautionary measures such as measuring blood pressure, albumin is tested by dipping the Urinalysis Reagent Strip manufactured by HIGHTOP, China into a urine sample to ensure the high percentage of protein in the urine.

A questionnaire was created and given to women, and the following data were gathered: name, address, previously known as the abortion number, total number of children, age, date on which the sample was collected, gestational age, and other related diseases. 5 mL of blood was taken from each pregnant lady, and the serum was separated and stored in sterile lab tubes at –20ºC until use.

Enzyme Linked Immunosorbent Assay detection of *Toxoplasma gondii* IgG and IgM antibodies

The Enzyme Linked Immunosorbent Assay (ELISA) technique was used to test serum samples with a TOXO IgG and IgM kit (Aeskulisa Kit, AESKU.DIAGNOSTICS GmbH & Co., Germany) according to the manufacturer's instructions.

Enzyme Linked Immunosorbent Assay detection of anti-phospholipids IgG and IgM antibodies

According to the manufacturer's recommendations, serum samples were tested using the Enzyme Linked Immunosorbent Assay method with an anti-phospholipids IgG and IgM antibodies kit (Aeskulisa Kit).

Statistical analysis

The statistics were examined by MedCalc® Statistical Software version 22.009 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023). Chi-square test was used to compare the independent variables between groups. If P value was 0.05 or below, it was declared statistically significant.

Ethical approval

The ethics outlined in the Helsinki Declaration were followed in the conduct of the study. The patient's verbal and written agreement was obtained before any samples were taken. The study methodology, subject information, and permission form were reviewed and approved by a local ethics commission to acquire this approval, according to the document numbered 4348 dated in September 4, 2022.

Results

One hundred and forty blood samples were collected from participants residing in separate areas and villages in Babylon Governorate, 80 samples from pregnant women with pre-eclampsia and 60 samples from healthy pregnant women as a control group who attended Al-Mahaweel General Hospital and some private laboratories in same Governorate, their ages were between 15 and 42 years.

All samples were analyzed by ELISA technique to determine the prevalence of anti-*Toxoplasma* IgG and IgM. According to Table 1, which details the prevalence of *T. gondii* specific IgM and IgG antibodies in both patients and control groups. Anti-*T. gondii* IgM antibodies were found in eight (10%) of the patients and four (6.66%) of the controls, without statistical differences between the two groups ($P > 0.05$). Anti-*Toxo.* IgG antibodies were 28 (35%) in the cases group and 0 (0%) of the controls. The patient group had a greater seroprevalence IgG of *T. gondii* than the control group based on statistical analysis ($P < 0.0001$). For the presence of both antibodies together (mixed IgG and IgM), there were no significant differences between the two groups ($P > 0.05$).

Table 1: Seroprevalence anti-*T. gondii* antibodies in preeclampsia patients and healthy women (pregnant)

Toxoplasma antibodies	Preeclampsia patients, $N = 80$		Healthy pregnant women, $N = 60$		P value by χ^2
	N (+)	%	N (+)	%	
IgM	8	10	4	6.66	$P = 0.4872$
IgG	28	35	0	0	$P < 0.0001$
Mixed	4	5	0	0	$P = 0.0799$

Table 2: Seroprevalence anti-phospholipid antibodies in preeclampsia patients and healthy pregnant women

Anti-phospholipid antibodies	Preeclampsia patients, $N = 80$		Healthy pregnant women, $N = 60$		P value by χ^2
	N (+)	%	N (+)	%	
IgM	8	10	0	0	$P = 0.0120$
IgG	12	15	0	0	$P = 0.0018$

Table 3: Seroprevalence anti-phospholipid antibodies in study groups (preeclampsia with and without latent toxoplasmosis patients and healthy pregnant women)

Anti-phospholipid antibodies	Preeclampsia patients with Toxo., $N = 28$		Preeclampsia patients without Toxo., $N = 52$		Healthy pregnant women, $N = 60$		P value by χ^2
	N (+)	%	N (+)	%	N (+)	%	
IgM	8	28.57	0	0	0	0	$P < 0.0001$
IgG	0	0	12	23.08	0	0	$P < 0.0001$

Table 4: Relationship of abortion with preeclampsia

Status of abortion	Patients (preeclampsia)		Control		P value by χ^2
	n	%	n	%	
Abortion	28	35	8	13.3	$P = 0.0038$
No abortion	52	65	52	86.7	
Total	80	100	60	100	

The occurrence of anti-phospholipid IgM and IgG antibodies in both the patient and control groups is shown in Table 2. There were significant differences between the two groups when anti-phospholipid IgM antibodies were detected in 8 (10%) of the patients and 0 (0%) of the controls. Anti-phospholipid IgG antibodies were discovered in 12 (15%) of the case group and 0 (0%) of the control group. According to statistical analysis, the patient group IgG antibodies had a larger than the control group ($P < 0.01$).

Anti-phospholipid IgM antibodies were substantially greater ($P < 0.0001$) in the group of PE patients with latent toxoplasmosis (28.57%) than in the other group, where they were 0% in the group of PE patients without *Toxoplasma* and healthy pregnant women. Anti-phospholipid IgG antibodies were present in 23.08% of PE patients without *Toxoplasma* infection, which was considerably greater ($P < 0.0001$) than PE patients with *Toxoplasma* (0%) and healthy pregnant women (0%) as in Table 3.

Table 4 shows the relationship between the numbers of previous abortions that women experienced and pre-eclampsia. 35% of patients with Preeclampsia had previous abortions compared to 13.3% in the control group ($P < 0.01$).

A 55% of the patients had Preeclampsia in the third trimester, compared to 10% and 35% for the first and second trimesters, respectively, supported by statistical analysis ($P < 0.0001$) [Table 5].

Significant differences were recorded ($P < 0.001$) between the number of pregnancies and the incidence of pre-eclampsia among the participants in the current study [Table 6].

Discussion

The idea of generating physiological diseases through exposure to disease factors is an existing clue and has become a reality for many diseases such as ulcers, cancer, and heart diseases as a result of bacteria and viruses infections.[15]

Table 5: Relationship between pregnancy stages and pre-eclampsia

Trimesters of pregnancy	First trimester	Second trimester	Third trimester	Total
n	8	28	44	80
%	10	35	55	100
***P* value by χ^2**		$P < 0.0001$		

Table 6: Relationship between numbers of pregnancy and pre-eclampsia

Number of pregnancy	*n*	%	*P* value by χ^2
First	0	0	$P = 0.0006$
Second	16	20	
Third	12	15	
Fourth	12	15	
Fifth	16	20	
Sixth	4	5	
Seventh	12	15	
Eighth	8	10	
Total	80	100	

The current study recorded a positive significant ($P < 0.0001$) relationship between the presence of IgG antibodies to *T. gondii* in pregnant women with PE compared to healthy pregnant women. This result is not consistent with study of Trogstad *et al*.,[15] which did not find a significant relationship between the presence of IgG antibodies for *T. gondii* and PE, whereas women who had positive antibodies to some viruses were less likely to develop PE, explaining the reason that these women are more likely to acquire primary disease infections and thus be at risk PE more.

On the other hand, our findings agree with the result of Alshareef *et al.*[10] that women who have IgG antibodies to *Toxoplasma* parasite are more susceptible to pre-eclampsia, while there is no significant relationship between IgM antibodies and pre-eclampsia. Another study proves the role of this parasite in raising blood pressure, which is an essential component of PE, Pregnant women who were treated with spiramycin because they suffer from *T. gondii* seroconversion had a lower risk of pregnancy-induced hypertension (PTH) later than women who did not receive treatment, as the rates of PTH were 0.5% and 5.2%, respectively, in the two groups.[16]

Numerous studies supported the results of the current study about the association of the presence of antibodies to phospholipids with cases of pre-eclampsia. Patabendige *et al*.[17] indicated that Antiphospholipid syndrome was associated with a case of severe pre-eclampsia in a teenage female patient. Other case report study found, APS is directly related to pre-eclampsia during pregnancy, and has resulted in stillbirth and placental abruption outcomes.[14] PE is an important marker for the diagnosis of APS in pregnant women,[18] Anti-phospholipid antibodies were discovered in 0%–5% of the general population and in 40% of women who had a history of stillbirth, recurrent pregnancy loss, intrauterine growth restriction, or PE.[19-21]

The elevation of IgM antibodies of phospholipids in the current study in PE patients with chronic toxoplasmosis group is consistent with what was reported by Petrikova *et al.*[22] in their study on the relationship of toxoplasmosis infection with autoimmune diseases, including the antiphospholipid antibody syndrome and the parasite considered as an environmental trigger or stimulus for the generation of autoimmune diseases.

The result of the current study depicts that Preeclampsia patients had more past abortions than the control group ($P < 0.01$). This result does not agree with a number of studies, as previous studies showed that old abortions have a protective effect against the risk of pre-eclampsia. In the study by Trogstad *et al*.,[23] no statistically significant differences were shown between the occurrence of prior abortions and the risk of pre-eclampsia. Both natural and artificial abortions were included in the study. Additionally, the quantity of prior abortions had no discernible impact. According to Mohamedain *et al*.[24] study, a prior spontaneous abortion decreased the incidence of PE by 59.0%.

The outcome of the ongoing study indicates that most cases of PE occur in the third trimester of pregnancy ($P < 0.0001$), which is consistent with the general definition of PE, which is high blood pressure after the twentieth week of pregnancy.[25] PE before 20 weeks of gestation is uncommon and is frequently related with trophoblastic disorders or antiphospholipid syndrome. In spite of this, previous studies have recorded cases of PE in pregnant women for a period of less than 20 weeks without other accompanying pathological conditions,[26] which allowed the discovery of new cases in early pregnancies, in this study, 10% of all cases were recorded in the first trimester.

The current study shows that there were significant differences ($P < 0.001$) between the number of pregnancies and the incidence of pre-eclampsia among the participants. The findings of Trogstad *et al*.[23] study demonstrate that previous induced abortions in primiparous women are also protected against pre-eclampsia, supporting the long-standing theory that a prior birth reduces the risk of pre-eclampsia in subsequent pregnancies.

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Conflicts of interest

There are no conflicts of interest.

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