

Potential role of latent toxoplasmosis in inducing thyroid disorders with relevance to autoimmune thyroid disease and interleukin-33 level during pregnancy

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Abstract

Background and Aim: Latent toxoplasmosis is the most frequently occurring parasitic infection worldwide, which causes hormonal and behavioral changes that seriously affect pregnant women. It has also been linked to several autoimmune diseases, including autoimmune thyroid disease (AITD). This study aimed to investigate the association between *Toxoplasma gondii* seropositivity and thyroid dysfunction, considering the impact of latent toxoplasmosis on the prevalence of maternal AITD and interleukin-33 (IL-33) levels in infected and non-infected pregnant women.

Materials and Methods: We conducted a cross-sectional study on 400 pregnant women aged 15–50 in the 8th–36th gestational week. Toxoplasma status was confirmed by detecting anti-Toxoplasma immunoglobulin (Ig)G antibodies. Recent and past chronic toxoplasmosis status was differentiated using the Toxoplasma IgG avidity test. Free triiodothyronine (FT3), free thyroxine, and thyroid-stimulating hormone (TSH) levels were determined to evaluate thyroid disorders. Antibodies against thyroid peroxidase, thyroglobulin, and TSH receptor were assessed to distinguish patients with autoimmune thyroid disorders from those with other thyroid diseases. We divided the subjects into four groups (Toxo+ and abnormal hormone level, Toxo– and normal hormone level, Toxo+ and normal hormone level, and Toxo– and abnormal hormone level) and evaluated their IL-33 levels to investigate its role during the infection. All the tests were performed using the enzyme-linked immunosorbent assay.

Results: The results showed that (205/400, 51.2%) samples were seropositive for anti-Toxoplasma IgG antibodies. Of these, (25/205, 12.2%) and (180/195, 87.8%) had recent and past chronic infections, respectively. High infection rates were reported among rural dwellers (150/400, 37.5%) and those in their 3rd trimester (110/400, 27.5%). Of the 205 seropositive patients, (131/205, 63.9%) had thyroid disorders, among which (69/205, 33.7%) and (119/205, 58.0%) had abnormal FT3 and TSH hormone levels, respectively. In contrast, out of 195 Toxoplasma seronegative samples, (99/195, 50.8%) had thyroid disorders; (48/195, 24.6%) and (90/195, 46.2%) had abnormal FT3 and TSH hormone levels, respectively. Groups with abnormal FT3 and TSH levels had significantly higher seropositive anti-toxoplasma IgG antibodies ($p = 0.01$). Women with seropositive anti-Toxoplasma IgG antibodies had a high hypothyroidism rate (115/205, 56.1%) compared with those with seronegative anti-Toxoplasma IgG antibodies (86/195, 44.1%). We found an association between toxoplasmosis and thyroid status ($p < 0.05$). Out of 400 samples, 85 (85/400, 21.25%) had AITD. Further, (58/205, 28.3%) of women with seropositive anti-toxoplasma IgG antibodies had AITD compared to (27/195, 13.85%) in the seronegative ones. We found a significant association between toxoplasmosis and AITD ($p < 0.05$). The IL-33 level was highest in the Toxo+ and abnormal hormone level group (210.86 ± 44.39 pg/mL) and lowest in the Toxo- and normal hormone level group (22.27 ± 8.41 pg/mL).

Conclusion: Our results suggest that latent toxoplasmosis was significantly associated with thyroid hormone secretion, which might stimulate the immune system, leading to the development of AITD among pregnant women. Furthermore, the *T. gondii* seroprevalence was positively correlated with pregnant patients who were rural dwellers and in their 3rd trimester.

Keywords: autoimmune thyroiditis disease, interleukin-33, pregnancy, thyroid hormones, toxoplasmosis.

Introduction

Toxoplasmosis, a life-threatening disease in all warm-blooded mammals, is caused by a coccidian

protozoan parasite called *Toxoplasma gondii* [1]. Many risk factors are linked with toxoplasmosis, such as social cultures, nutritional habits, geographical regions, contact with cats, and hygiene status [2]. Although toxoplasmosis is mostly asymptomatic, it has serious health implications during pregnancy and in immunocompromised patients, including HIV and cancer patients and transplant recipients [3]. During pregnancy, toxoplasmosis can lead to miscarriage, microcephaly, hydrocephaly, blindness, and neural disorders [4]. *Toxoplasma gondii* attacks the body's

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organs and glands, including the thyroid, which releases thyroid hormones, such as triiodothyronine (T3), thyroxine (T4), and calcitonin. These hormones are essential for metabolic processes, heart and muscle functions, and brain and bone development [5].

Hypothyroidism occurs when the thyroid gland cannot produce adequate thyroid hormones, causing weight gain, hair loss, and fatigue. In hyperthyroidism, the thyroid gland produces excessive thyroid hormones, resulting in weight loss, sweating, and fatigue [6]. Autoimmune thyroid disease (AITD) is a condition where “autoantibodies” are formed targeting the thyroid gland cells, which dysregulates the immune system and immune tolerance [7]. Autoimmune thyroid disease is represented by Hashimoto thyroiditis through primarily T-cell-mediated autoimmunity and Graves’ disease from humoral autoimmunity. During pregnancy, these disorders can cause miscarriage, premature delivery, and abnormal neural development [8]. A study shown that *T. gondii* infection and AITD are linked [9], probably due to the molecular similarities between thyroid antigens and the pathogen. Moreover, genetic and environmental factors such as pathogens, intake of substances, radiation, cytokines, sex, and other unknown factor increase the chances of AITD [10]. Interleukin-33 (IL-33), a recently discovered member of the IL-1 cytokine family, is expressed in several cells, including lungs, liver, central nervous system, smooth muscles, macrophages, endothelial tissues, and damaged and dead cells. Interleukin-33 acts as a damage-associated molecular pattern or alarming for activating immune cells [11].

Interleukin-33 controls *T. gondii* infection through activation and proliferation of macrophages, TH2 CD4 +T-cells, and production of interferons from natural killer cells [12]. Lack of IL-33 decreases immune cell responses and resistance toward *T. gondii* [12]. Increased IL-33 levels indicate autoimmune diseases, such as AITD, systemic lupus erythematosus, and rheumatoid arthritis [13]. Latent toxoplasmosis is a common illness that alters the immune system and hormonal profile. However, the potential association between latent toxoplasmosis, thyroid hormone disorders, and AITD in pregnancy is poorly understood. This study aimed to investigate the link between latent maternal toxoplasmosis, as revealed by immunological testing by evaluating IL-33 levels and AITD in pregnant women diagnosed by detecting antibodies against thyroid peroxidase (TPO), thyroglobulin (TG), and thyroid-stimulating hormone receptor (TSHR) and thyroid hormone levels. Our results can help raise awareness regarding the potential health implications of toxoplasmosis, thyroid disorders, and autoimmune conditions in pregnant women and their effects on mothers and fetuses.

Materials and Methods

Ethical approval and Informed consent

The study received approval from the Research Ethical Committee of the Directorate General of

Health, Duhok-Iraq (Approval No. 13072021-7/July 12, 2021). Informed written consent was obtained from all participants, and data collection was primarily conducted by administering a questionnaire to gather the necessary information.

Study period and location

The study was conducted from August 2021 to August 2022. This cross-sectional study used blood samples collected from pregnant women who visited the Gynecology and Obstetrics Hospital in Duhok city-Iraq.

Study design

A specific questionnaire was used to collect the participant’s information, including pregnancy period, demographic data, and any pre-existing medical conditions. Before the treatment, the serum samples were analyzed to diagnose the seroprevalence of immunoglobulin (Ig)G and screened for toxoplasma infection using the enzyme-linked immunosorbent assay (ELISA) IgG avidity assay.

Sample collection

We collected samples from 400 pregnant women by obtaining 5 mL of venous blood through vein puncture using a sterile disposable syringe. The blood samples were placed in a tube without anticoagulant and left standing for 20 min at room temperature (25°C) to clot. Then, each tube was centrifuged at 1509.3×g for 10 min to separate the sera, which were individually transferred into sterile 2 mL Eppendorf tubes and stored at –20°C until further use [14]. Toxoplasma IgG, TPO, TG, and TSHR antibodies and free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), and IL-33 levels were determined using ELISA [15]. Toxoplasma status was evaluated using anti-Toxoplasma IgG antibodies (Bioactiva diagnostic, Germany) and the Toxoplasma IgG avidity test (Novalisa, Germany). Free triiodothyronine, pg/mL, FT4, ng/dL, and TSH, μIU/mL were measured using AccuBind-Monobind (USA). The serum TPO (IU/mL), TG (IU/mL), TSHR (U/L) (Aeskulisa, Germany), and IL-33 (pg/mL) antibody levels were analyzed as per Elabscience (USA) according to the manufacturer’s instructions. The optical density was measured at 450 nm using an ELISA plate reader (BioTek, USA).

Inclusion criteria

Pregnant women at different stages of pregnancy were included in the study.

Exclusion criteria

We excluded pregnant women of uncertain gestational age, having other chronic or infectious diseases, immune-suppressed, and with thyroid disorders. Overall, 400 pregnant women were included, and no women were excluded due to suspected acute toxoplasmosis (tested negative for IgM antibodies against *T. gondii*).

Statistical analysis

The data were statistically analyzed using SAS software version 9.3 (<http://support.sas.com/>)

software/93/). Descriptive statistics were used to describe the data using mean \pm standard deviation (SD) and standard error for numerical variables. The frequency data were expressed as percentages (%). Statistical significance was set at $p < 0.05$.

Results

In this study, we enrolled 400 pregnant women in their 8–36th gestational weeks. Their mean (\pm SD) age was 28 ± 6.2 years (ranging from 15 to 50 years). Finally, (205/400, 51.3%) samples were seropositive for anti-Toxoplasma IgG antibodies. Of these, (25/205, 12.2%) showed low IgG avidity, indicating recent chronic infection (within 3 months), whereas (180/205, 87.8%) had high IgG avidity, suggesting past infection (more than 3 months ago). High infection rates were seen among women from rural areas (150/400, 37.5%) and in their 3rd trimester (110/400, 27.5%).

Table-1 shows the incidence of thyroid disorders and anti-IgG Toxoplasma antibodies seropositivity frequency among all examined pregnant women. Of the 205 women with seropositive anti-Toxoplasma IgG antibodies, (131/205, 63.9%) had thyroid disorders. Of the 195 Toxoplasma seronegative women, (99/195, 50.8%) had thyroid disorders. Further, (69/205, 33.7%), (68/205, 33.2%), and (119/205, 58.1%) samples with seropositive anti-Toxoplasma IgG antibodies had abnormal FT3, FT4, and TSH hormone levels, respectively. Among the samples with seronegative anti-Toxoplasma IgG antibodies, (48/195, 24.6%), (52/195, 26.7%), and (90/195, 46.2%) had abnormal FT3, FT4, and TSH hormone levels, respectively. There was no significant difference in FT4 hormone level and anti-IgG Toxoplasma antibodies seropositivity ($p = 0.15$). However, we found a significant difference ($p = 0.01$) between TSH hormone level and anti-IgG Toxoplasma antibody seropositivity.

Table-2 shows the thyroid status and anti-IgG Toxoplasma antibodies seropositivity frequency among all the subjects. Women with seropositive anti-Toxoplasma IgG antibodies had a high hypothyroidism rate

of (115/205, 56.1%) compared with those with seronegative anti-Toxoplasma IgG antibodies (86/195, 44.1%). We detected a significant association between toxoplasmosis and thyroid status ($p < 0.05$).

As shown in Table-3, TPO, TG, and TSHR antibody occurrence rates were higher in pregnant women with seropositive anti-Toxoplasma IgG antibodies than those with seronegative antibodies. Out of 400 samples, (85/400, 21.25%) had AITD. Of these, (58/205, 28.3%) women with seropositive anti-toxoplasma IgG antibodies screened positive for AITD, while (27/195, 13.85%) had seronegative anti-toxoplasma IgG antibodies. This indicates a significant association between toxoplasmosis and AITD ($p < 0.05$).

As shown in Table-4, we divided the pregnant women into four groups based on the presence of anti-Toxoplasma IgG antibodies, thyroid status, and IL-33 levels. We observed the highest IL-33 levels in women with seropositive Toxoplasma IgG antibodies with AITD, while the lowest levels were seen in healthy women. Further, the highest IL-33 level was seen in the positive control group (210.86 ± 44.39 pg/mL), while the lowest IL-33 levels were detected in the negative control group (22.27 ± 8.41 pg/mL).

Discussion

Here, we estimated the seroprevalence of anti-Toxoplasma IgG antibodies, phases of toxoplasmosis, and its link with AITD among pregnant women in Duhok City, Iraq. Our results on the prevalence of toxoplasmosis in women were consistent with previous studies by Pirali-Kheirabadi *et al.* [16] and Khan *et al.* [17] who reported 51.2% and 52.2%, respectively. However, they disagreed with other studies [18, 19] which reported only 10% and 21.1% prevalence, respectively. Regarding toxoplasmosis phases, our results agreed with other studies [20, 21] but disagreed with Csep *et al.* [22]. Women residing in rural areas had statistically higher infection rates, consistent with the results by Mizani *et al.* [23] but in contrast with those reported by Al-Qurashi *et al.* [24].

Table-1: Incidence of thyroid hormone disorders in pregnant women screened for Toxoplasma seropositivity.

Hormone	Hormone level of 400 samples	Toxo+205 (51.2%)	Toxo-195 (48.8%)	p-value
FT3	Normal	136 (66.3)	147 (75.4)	*0.04
	Abnormal	69 (33.7)	48 (24.6)	
FT4	Normal	137 (66.8)	143 (73.3)	0.15
	Abnormal	68 (33.2)	52 (26.7)	
TSH	Normal	86 (42)	105 (53.8)	*0.01
	Abnormal	119 (58.1)	90 (46.2)	

Toxo+/-: Women screened seropositive/negative anti-Toxoplasma IgG antibodies, *Statistical significance ($p < 0.05$), FT3=Free triiodothyronine, FT4=Free thyroxine, TSH=Thyroid-stimulating hormone

Table-2: Analysis of thyroid status among pregnant women.

Thyroid status	n = 400 (%)	Toxo+205 (51.2%)	Toxo-195 (48.8%)	p-value
Normal thyroid	170 (42.5)	74 (36.1)	96 (49.2)	*0.02
Hypothyroidism	201 (50.25)	115 (56.1)	86 (44.1)	
Hyperthyroidism	29 (7.25)	16 (7.8)	13 (6.7)	

Toxo+/-=Women screened seropositive/negative anti-Toxoplasma IgG antibodies, *Statistical significance ($p < 0.05$)

Table-3: Frequencies of pregnant women screened for autoimmune thyroid disorders according to Toxoplasma seropositivity.

Women Screened +/-	AITD+	AITD-	TPO+	TG+	TSHR+
Toxo+205 (51.25%)	58 (28.3%)	147 (71.7%)	38 (18.5%)	14 (6.8%)	6 (2.9%)
Toxo-195 (48.8%)	27 (13.85%)	168 (86.2%)	12 (6.1%)	11 (5.6%)	4 (2.1%)
Total 400	85 (21.25%)	315	50	25	10

AITD+/-=Women screened positive/negative for autoimmune thyroid disease in pregnancy, Toxo+/-=Women screened seropositive/negative anti-Toxoplasma IgG antibodies, (TPOAb, TGAb, and TSHRAb positivity and/or pathological TSH), TPOAb=Thyroid peroxidase antibodies, TGAb=Thyroglobulin antibodies, TSHRAb=Thyroid-stimulating hormone receptor antibodies

Table-4: Association between seropositive anti-Toxoplasma IgG antibodies, thyroid dysfunction, and interleukin-33 level in pregnant women.

Groups	Sample No. (%)	IL-33 Mean±SD (pg/mL)
Toxo+and abnormal hormone level	130 (32.5)	210.86±44.39
Toxo- and normal hormone level	95 (23.75)	22.27±8.41
Toxo+and normal hormone level	75 (18.75)	120.54±30.96
Toxo-and abnormal hormone level	100 (25.0)	62.18±19.04

IL-33=Interleukin-33, IgG=Immunoglobulin G

This might be due to the lack of hygiene measures in rural women who are in contact with cats, birds, and other domestic animals that feed and hunt freely, as speculated in the previous reports by Raissi *et al.* [25] and Agordzo *et al.* [26].

The occurrence rates of thyroid disorders in pregnant women were higher than those with normal thyroid conditions. Approximately (131/205, 63.9%) women with seropositive anti-Toxoplasma IgG antibodies had a thyroid disorder, specifically hypothyroidism, whereas (115/205, 56.1%) and (16/205, 7.8%) women had hyperthyroidism with a significant statistical association with toxoplasmosis and thyroid status, respectively (Table-2). These results are consistent with that reported by Valizadeh *et al.* [27] but disagree with the studies by Al-Khamesi [28] and Hashim *et al.* [29]. Abnormal FT3, FT4, and TSH hormone levels cause pregnancy complications, such as miscarriage, preterm delivery, placental abruption, and low birth weight [30]. Regarding thyroid autoimmunity, women with seropositive anti-Toxoplasma IgG antibodies had higher TPO, TG, and TSHR antibody levels than the Toxoplasma seronegative group, indicating a link between thyroid autoantibodies and toxoplasmosis, especially at high antibody levels [9, 27]. Further, (58/205, 28.3%) out of (85/400, 21.25%) women with AITD were positive for toxoplasmosis (Table-3), a condition that affects thyroid production, with elevated levels of TPO antibodies as [9]. This study agrees with Tozzoli *et al.* [30], who found that 65.5% of seropositive anti-toxoplasma IgG antibodies women had AITD. They also suggested that toxoplasmosis and AITD might be associated with thyroid dysfunction. Our current study demonstrated that the association between toxoplasmosis and thyroid disorder might arise from the production of autoantibodies due to abnormal thyroid hormone levels, as evidenced by the TPO, TG, and TSHR antibody seropositivity (Table-3). However, this finding disagrees with that of Shapira

et al. [10], possibly due to differences in the number of participants, seropositivity of anti-Toxoplasma IgG antibodies, the tests used, and geographical areas, as they did not find any effect of latent toxoplasmosis on thyroid hormones and AITD. Others reported that 22.6% of cases of latent toxoplasmosis exhibited no effect on thyroid hormones and AITD [31].

Autoimmune thyroid disease is known to cause miscarriage, preterm delivery, and low birth weight [32]. Our results showed that the serum IL-33 levels were higher in pregnant women with seropositive anti-Toxoplasma IgG antibodies coupled with AITD than in healthy women. The Toxo+ and abnormal hormone level group had the highest IL-33 level (210.86 ± 44.39 pg/mL), followed by Toxo+ and normal hormone level group (120.54 ± 30.96 pg/mL), while the lowest levels (22.27 ± 8.41) were seen in Toxo- and normal hormone level group (Table-4), consistent with the studies by Al-Shammaa [33] and Al-Aubaidi *et al.* [34].

Studies have indicated that IL-33 might contribute to the pathophysiology of different diseases, and it is considered a disease marker, especially in autoimmune disease pathogenesis [11]. Increased IL-33 levels were observed in the sera of women with anti-Toxoplasma IgG antibodies, abnormal thyroid hormones, and those with toxoplasmosis and AITD (Table-4). This might be because IL regulates and transfers information between various types of leukocytes during different stages of immune or inflammatory responses [12]. This finding further suggests that AITD might influence cytokine production, making IL-33 a potential therapeutic target [13].

This study has limitations, such as the small number of patients suffering from hypothyroidism and hyperthyroidism. It was also hard to follow-up with the pregnant women and their fetuses for further studies, which could have elucidated the process through which toxoplasmosis influences AITD.

Conclusion

It is necessary to control toxoplasmosis through health programs and hygiene awareness. Further, testing the anti-Toxoplasma antibody levels, Toxoplasma IgG avidity, thyroid hormone, and thyroid autoantibody levels in pregnant women is extremely important. Hence, pregnant women should be advised to visit a gynecologist to reduce the risks to the mother and her fetus. Further, toxoplasmosis might cause thyroiditis due to antigenic similarities between *T. gondii* and thyroid components, resulting in immune system cross-reactivity and AITD. Thus, further studies focusing on the molecular similarities between thyroid components and Toxoplasma antigens are required. Follow-up examinations should be done with the mothers and fetuses, if possible. Our study establishes that the IL-33 levels are elevated in response to toxoplasmosis, which might be involved in AITD pathogenesis. In addition to its role as a disease biomarker, IL-33 can be a potential therapeutic target for AITD.

Authors' Contributions

SHE and MAM: Proposed the idea, planned the study, wrote the original draft, and visualization. SHE and MAM: Writing-review and editing. MAM: Resources. SHE: Supervision. Both authors have read, reviewed, and approved the final manuscript.

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Competing Interests

The authors declare that they have no competing interests.

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