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Interleukin-33 (IL-33) Profile in Toxoplasma gondii-Seropositive and Seronegative Pregnant Iraqi Women

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ABSTRACT

Background: *Chronic Toxoplasma gondii infection presents a unique immunological challenge during pregnancy, requiring a balance between the pro-inflammatory response needed for parasite control and the anti-inflammatory state vital for fetal tolerance. Interleukin-33 (IL-33), an alarmin cytokine, is a key immunomodulator; however, its profile in pregnant women with latent toxoplasmosis remains poorly understood.*

Objective: *This study aimed to compare serum IL-33 levels between T. gondii-seropositive and seronegative pregnant Iraqi women and to investigate its relationship with the anti-T. gondii IgG antibody titer.*

Methods: *A comparative cross-sectional study was conducted on 120 pregnant women (60 seropositive and 60 seronegative) attending Al-Elwiya Maternity Teaching Hospital in Baghdad from October 2024 to May 2025. Serum IL-33 levels were measured using a quantitative ELISA. Statistical analysis was performed using SPSS version 26.0.*

Results: *Serum IL-33 levels were significantly higher in the T. gondii-seropositive group (Median: 85.5 pg/mL, IQR: 62.3-114.8) compared to the seronegative group (Median: 42.1 pg/mL, IQR: 30.5-58.9) ($p < 0.001$). This elevation was consistent across all trimesters. Furthermore, a weak but statistically significant positive correlation was found between serum IL-33* levels and anti-*T. gondii* IgG titers in the seropositive group ® = 0.289, p = 0.025).

Conclusion: Chronic *T. gondii* infection in pregnant women is associated with a significant elevation in serum IL-33, which correlates with the humoral immune response.

Keywords: *Toxoplasma gondii; Interleukin-33; Seropositive; Seronegative; Pregnant Iraqi Women.*

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Introduction

The apicomplexan parasite *Toxoplasma gondii* infects a substantial portion of the global population. While immunocompetent individuals typically experience an asymptomatic or mild infection, the acquisition of *T. gondii* during pregnancy presents a serious medical challenge. Primary maternal infection can lead to vertical transmission, resulting in congenital toxoplasmosis, which is associated with spontaneous abortion, stillbirth, and severe neurological and ocular damage in the neonate (1, 2). In Iraq, the seroprevalence of *T. gondii* among pregnant women is notably high, reflecting an endemic status that places a significant number of pregnancies at potential risk (3, 4).

The host's defence against *T. gondii* is critically dependent on a robust T-helper 1 (Th1) immune response, characterised by the production of pro-inflammatory cytokines such as interferon-gamma (IFN-γ) and interleukin-12 (IL-12) to control intracellular tachyzoite replication (5). Paradoxically, a successful pregnancy requires a carefully modulated shift towards a T-helper 2 (Th2) and regulatory T-cell (Treg) predominant environment to ensure fetal tolerance and prevent immunological rejection of the semi-allogeneic fetus (6).

The interplay between the inflammatory response necessary for parasite control and the anti-inflammatory state vital for gestation is a key determinant of pregnancy outcome in infected mothers.

Interleukin-33 (IL-33), a member of the IL-1 cytokine family, has emerged as a pivotal alarmin and immunomodulator. It is released from the nuclei of barrier tissues and endothelial cells upon cellular damage or stress, signalling through its receptor ST2 on various immune cells, including Th2 cells, T regulatory cells (Tregs), and group 2 innate lymphoid cells (ILC2s) (7). Through this signalling pathway, IL-33 promotes type 2 immunity and regulatory responses, which are instrumental in tissue repair, homeostasis, and, notably, in the establishment of maternal-fetal tolerance (8).

The role of IL-33 in infection is complex and context-dependent. In parasitic diseases, the IL-33/ST2 axis can be a double-edged sword, potentially enhancing protective immunity and tissue repair on one hand, while suppressing essential Th1 responses and facilitating pathogen persistence on the other (9). Recent studies have begun to elucidate the involvement of IL-33 in the immune response to *T. gondii*, suggesting it influences the outcome of infection and chronic inflammation (10).

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However, the profile of IL-33 in the specific context of pregnancy, where the immune system must balance the demands of parasite control with those of fetal support, remains largely unexplored, particularly in seropositive women with latent infection.

Given the high seroprevalence of toxoplasmosis in Iraq and the critical immunomodulatory functions of IL-33, this study aims to investigate and compare the serum interleukin-33 levels in toxoplasmosis-seropositive and seronegative pregnant Iraqi women.

Patients and Methods

1. Study Design and Period: This was a comparative cross-sectional study conducted from October 2024 to May 2025.

2. Study Population and Setting: The study enrolled a total of 120 pregnant women attending the Antenatal Care Unit at Al-Elwiya Maternity Teaching Hospital in Baghdad, Iraq. Participants were divided into two groups:

- **Group I (Case Group):** 60 pregnant women seropositive for *Toxoplasma gondii* IgG antibodies.
- **Group II (Control Group):** 60 pregnant women seronegative for *Toxoplasma gondii* IgG and IgM antibodies.

3. Inclusion and Exclusion Criteria

- **Inclusion Criteria:** Pregnant women in any trimester, aged 18-40 years, who provided written informed consent.
- **Exclusion Criteria:** Women with multiple pregnancies, a history of chronic diseases (e.g., diabetes mellitus, hypertension, autoimmune disorders), active infection other than toxoplasmosis, known HIV infection, or those on immunosuppressive therapy were excluded from the study.

4. Data and Sample Collection: After obtaining informed consent, a structured questionnaire was administered to all participants to collect data on:

- Sociodemographic characteristics (age, residence, educational level).
- Obstetric history (gravida, para, gestational age).
- Potential risk factors for *T. gondii* exposure (contact with cats, consumption of undercooked meat, source of drinking water, etc.).

The obtained serum from patients was aliquoted into two sterile Eppendorf tubes; one was used for immediate serological testing, and the other was stored at -80°C until used for the Interleukin-33 assay.

5. Laboratory Methods

5.1. Serological Diagnosis of *Toxoplasma gondii*: The serological status of the participants was determined using a commercial Enzyme-Linked Immunosorbent Assay (ELISA) kit for the detection of *T. gondii*-specific IgG and IgM antibodies (EUROIMMUN, Germany), according to the manufacturer's instructions. Samples with IgG titers above the cutoff value and negative for IgM were classified as chronic/latent infection (seropositive group). Samples negative for both IgG and IgM were classified as seronegative (control group).

5.2. Measurement of Serum Interleukin-33 (IL-33) Level: The concentration of human IL-33 in the stored serum samples was measured using a commercially available, quantitative sandwich Enzyme-Linked Immunosorbent Assay (ELISA) kit.

6. Statistical Analysis: data were analysed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., USA). Categorical data were presented as numbers and percentages and compared using the Chi-square (χ^2) test. Continuous data were tested for normality using the Shapiro-Wilk test. Normally distributed data were presented as mean ± standard deviation (SD) and compared using the independent samples t-test. Non-normally distributed data (such as IL-33 levels) were presented as medians and interquartile ranges (IQRs) and compared using the non-parametric Mann-Whitney U test. A p-value of less than 0.05 was considered statistically significant.

Results

The potential risk factors for *Toxoplasma gondii* infection were compared between seropositive and seronegative pregnant women. As shown in Table 1, the two groups were well-matched in terms of maternal age (28.5 ± 4.8 vs. 27.8 ± 5.1 years, p = 0.421), gestational age (24.3 ± 7.2 vs. 25.1 ± 6.9 weeks, p = 0.532), and the distribution across pregnancy trimesters (p > 0.05).

Table 1: Comparative analysis of maternal and gestational age between Toxoplasma gondii-Seropositive and Seronegative Pregnant Iraqi Women

Characteristic	*T. gondii*-Seropositive (n=60)	*T. gondii*-Seronegative (n=60)	p-value
Maternal Age (years), Mean ± SD	28.5 ± 4.8	27.8 ± 5.1	0.421
Gestational Age (weeks), Mean ± SD	24.3 ± 7.2	25.1 ± 6.9	0.532
Trimester, n (%)			
First (1-13 weeks)	18 (30.0%)	15 (25.0%)	
Second (14-26 weeks)	25 (41.7%)	28 (46.7%)	
Third (>27 weeks)	17 (28.3%)	17 (28.3%)	

Analysis of potential risk factors revealed significant associations with seropositivity (Table 2). Educational level was significantly different between the groups (p = 0.038), with a higher proportion of seropositive women having only a primary education or less (33.3% vs. 16.7%) and a lower proportion having a university education (25.0% vs. 46.7%) compared to the seronegative group. Furthermore, seropositive women reported a significantly higher frequency of contact with cats (53.3% vs. 30.0%, p = 0.009) and consumption of undercooked meat (46.7% vs. 25.0%, p = 0.015). No significant differences were observed for residency (p = 0.441) or source of drinking water (p = 0.102).

Table 2: Comparative Analysis of Risk Factors between the studied groups

Risk factors	*T. gondii*-Seropositive (n=60)	*T. gondii*-Seronegative (n=60)	p-value
Residency			0.441
No. (%)			
Urban	38 (63.3%)	42 (70.0%)	
Rural	22 (36.7%)	18 (30.0%)	
Educational Level			**0.038**
No. (%)			
Primary or less	20 (33.3%)	10 (16.7%)	
Secondary	25 (41.7%)	22 (36.7%)	
University	15 (25.0%)	28 (46.7%)	
Contact with Cats	32 (53.3%)	18 (30.0%)	**0.009**
No. (%)			
Consumption of Undercooked Meat	28 (46.7%)	15 (25.0%)	**0.015**
No. (%)			
Source of Drinking Water			0.102
No. (%)			
Distilled water	50 (83.3%)	56 (93.3%)	
Tap water	10 (16.7%)	4 (6.7%)	

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The serological and immunological profiles of the studied groups are presented in Table 3. The anti-*T. gondii* IgG titers were elevated in the seropositive group (145.6 ± 45.2 IU/mL) and not detected in the seronegative group. Crucially, serum levels of IL-33 were significantly elevated in *T. gondii*-seropositive pregnant women compared to their seronegative counterparts (Median [IQR]: 85.5(62.3 - 114.8) pg/mL vs. 42.1(30.5 - 58.9) pg/mL, p < 0.001).

Table 3: Serological Profile and Interleukin-33 Levels in the Studied Groups

Parameter	*T. gondii*-Seropositive (n=60)	*T. gondii*-Seronegative (n=60)	p-value
Anti-T. gondii IgG Titer (IU/mL) Mean ± SD	145.6 ± 45.2	Not Detected	-
Serum IL-33 (pg/mL) Median (IQR)	85.5 (62.3 - 114.8)	42.1 (30.5 - 58.9)	< 0.001

Among the *T. gondii*-seropositive women, serum IL-33 levels were further analysed by pregnancy trimester. As detailed in Table 4, no statistically significant variation in IL-33 levels was observed across the first, second, and third trimesters (p=0.225).

Table 4: Stratification of Serum IL-33 Levels by Trimester in Seropositive Women

Trimester	No.	Serum IL-33 (pg/mL) Median (IQR)	*p-value*
First	18	80.2 (60.1 - 98.5)	0.225
Second	25	88.7 (65.4 - 118.3)	
Third	17	83.1 (59.8 - 112.0)	
Overall	**60**	**85.5 (62.3 - 114.8)**	

Results within the seropositive group showed a weak but statistically significant positive correlation between serum IL-33 levels and the anti-*T. gondii* IgG titer (Correlation Coefficient r = 0.289, p=0.025), as shown in Table 5.

Table 5: Correlation between Serum IL-33 Levels and Anti-T. gondii IgG Titer in Seropositive Women (n=60)

Variable-1	Variable-2	Correlation Coefficient (r-s)*	p-value
Serum IL-33 Level	Anti-*T. gondii* IgG Titer	0.289	**0.025**

Discussion

This case-control study provides novel insights into the immunological profile of pregnant women with chronic *Toxoplasma gondii* infection. Our principal finding demonstrates that *T. gondii*-seropositive pregnant women exhibit significantly elevated serum concentrations of Interleukin-33 (IL-33) compared to seronegative controls. This finding positions IL-33, a key alarmin and immunomodulator, as a potential significant player in the host-parasite interaction during pregnancy.

The marked elevation of serum IL-33 in our seropositive cohort can be interpreted in light of its fundamental role as a damage-associated molecular pattern (DAMP). While chronic *T. gondii* infection is often considered latent, emerging evidence suggests that tissue cysts can induce sustained, low-level inflammatory signalling and cellular stress (11). IL-33 is constitutively expressed in the nuclei of endothelial and epithelial cells and is rapidly released upon cellular damage (12). Therefore, the persistent presence of *T. gondii* cysts may trigger a continuous, low-grade release of IL-33 into the circulation, acting as a perpetual "alarm" signal of the ongoing infection.

The observed weak positive correlation between IL-33 levels and anti-*T. gondii* IgG titers suggest a fascinating link between innate alarmin signalling and the humoral immune response. This correlation indicates that individuals with a higher parasitic load or more active immune recognition, as reflected in higher IgG titers, may experience greater cellular stress, resulting in increased IL-33 release. Furthermore, IL-33 is known to directly enhance B-cell activation and antibody production (13). Thus, IL-33 may not only be a consequence of infection but may also actively contribute to sustaining the robust humoral immunity characteristic of chronic toxoplasmosis.

The immunological paradox of pregnancy---requiring tolerance for the fetus while maintaining defence against pathogens---is particularly acute in *T. gondii* infection. Our findings provide a plausible mechanism for maintaining this balance. IL-33, through its receptor ST2, drives a type 2 immune response and expands regulatory T-cell (Treg) populations (14). In pregnancy, this is beneficial for maintaining fetal tolerance. In the context of *T. gondii* infection, this IL-33-driven shift may temper the potent, potentially pregnancy-threatening Th1 response required to control the parasite, thereby preventing immunopathology. This dual role aligns with studies showing that the IL-33/ST2 axis mitigates excessive inflammation in chronic infections (15,16). Therefore, the elevated IL-33 in our seropositive patients may represent a critical host adaptation that simultaneously manages a persistent infection and protects the gravid state.

The consistency of IL-33 elevation across all trimesters suggests that the impact of chronic *T. gondii* infection on this cytokine is a stable feature, overriding the dynamic immunological shifts that occur throughout normal gestation. This finding underscores the potent and persistent immunomodulatory effect of the parasite.

Conclusion

In conclusion, this study establishes a clear association between chronic *Toxoplasma gondii* seropositivity and significantly elevated serum levels of IL-33 in a cohort of pregnant Iraqi women. The correlation with IgG titers suggests that IL-33 is integrated into the adaptive immune response to the parasite.

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