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Assessment of *Toxoplasma gondii* Infection with Pro and Anti-inflammatory Cytokine along with sHLA-G Activity in Pregnant Rheumatoid Arthritis Women in Middle Euphrates Region

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Abstract:

Background: Pregnancy is a period of profound immune modifications that are necessary for the development of maternal–fetal tolerance. soluble human leukocyte antigen-G (sHLA-G) is an important immunomodulatory molecule in this regard. rheumatoid arthritis, *Toxoplasma gondii* infection respectively affecting the balance of human immune system and sHLA-G expression during pregnancy, however, the effect of interplay rheumatoid arthritis and *Toxoplasma gondii* infection on sHLA-G expression during pregnancy are not well-known.

Objectives: This work was aimed to study the effect of *Toxoplasma gondii* infection on serum sHLA-G expression, Pro and Anti-inflammatory Cytokine Activity in pregnant women with rheumatoid arthritis in Middle Euphrates region-Iraq using serological, molecular and immunological tools.

Methods: A cross-sectional case–control study was performed in 112 pregnant women in Middle Euphrates region classified into four groups: Rheumatoid arthritis with *T. gondii* infection, Rheumatoid arthritis without infection, *T. gondii* infection with non-RA and healthy pregnant controls. Anti-Toxoplasma IgM and IgG antibodies were examined by ELISA, and *T. gondii* was confirmed using real-time PCR to detect the DNA of pathogens. sHLA-G and cytokines (IL-6, IFN-γ, TNF-α, and IL-10) in the serum were evaluated by ELISA. Rheumatoid arthritis activity was measured by DAS28. Statistical analysis involved ANOVA, correlation analysis and multivariable regression.

Results: The serum sHLA-G concentrations were significantly different between the study groups ($P < 0.001$); the highest concentration of serum sHLA-G was detected in pregnant women with Rheumatoid arthritis and concurrent *T. gondii* infection.

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Compared with chronic infection, acute toxoplasmosis was characterized by higher sHLA-G levels ($P < 0.01$). sHLA-G had a positive correlation with IL-10 and disease activity of Rheumatoid arthritis, and negative correlations with pro-inflammatory cytokines. After controlling for confounders, *T. gondii* infection remained an independent predictor of sHLA-G high concentrations.

Conclusions: The correlations reveal further clues about the mechanism of action of sHLA-G: positive correlations with the anti-inflammatory cytokine IL-10 ($r = +0.62$, P01) suggest a mixed pattern of pro-inflammatory/regulatory cytokine production in this context. Detailed multivariate regression analysis confirmed that *Toxoplasma gondii* infection is an independent risk factor for sHLA-G release ($p < 0.001$). *Toxoplasma gondii* infection in pregnant women with rheumatoid arthritis significantly inhibits sHLA-G secretion, suggesting a possible collaboration between autoimmunity and the parasite, and pregnancy-induced immune tolerance. The findings suggest that sHLA-G may become a key indicator of underlying immune regulation.

Keywords: *Toxoplasma gondii*, Rheumatoid Arthritis, Pregnancy, sHLA-G, IL-6, IFN-γ, TNF-α, and IL-10.

Introduction:

Toxoplasma gondii parasites are endemic intracellular protozoa, infecting more than a third of the world's population, with infection rates ranging between 30% and 50% of humans at various stages of their lives [1]. This means that tens of millions to hundreds of millions of people worldwide are infected, in a different geographical distribution [2, 3]. Prevalence, for example, seems much lower (10-30%) in North America, Southeast Asia and Northern Europe but becomes 30-50% at Central and Southern Europe [4].

By contrast, high prevalence rates are observed in Latin America and tropical African countries, where some areas display seroprevalence rates of >80% [5,6]. The broad geographical distribution of the parasite again highlights the ability of this parasite to adapt and evolve in various transmission chains [7,8].

Human Leukocyte Antigen-G (HLA-G) is a non-classical major histocompatibility complex class II molecule which acts as one of the key check points in immune regulation and mainly plays an anti-inflammatory/tolerogenic role [9]. This molecule mediates extensive immunosuppressive activities on multiple immune cells and is, in fact, a crucial player in the induction and maintenance of immune tolerance

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in vivo [10]. It is well established that HLA-G is able to exert its immunomodulation effects through the recognition of inhibitory leukocyte receptors, including ILT2/CD85j, ILT4/CD85d and KIR2DL4, on different immune cells [11]. These interactions ultimately result in inhibition of cytotoxic T cells and natural killer cells, which also occurs via inhibited lymphocyte proliferation and the induction of regulatory T cells; thus, the immune microenvironment is suppressed [12-14]. Soluble HLA-G (sHLA-G) isoforms, which can be differentiated from membrane-bound forms by their truncated C terminus, also preserve these immunomodulatory functions and are involved in a wide range of physiological and pathological settings such as pregnancy success or cancer immune escape [15].

Rheumatoid arthritis (RA) is a systemic, chronic inflammatory autoimmune disease that symmetrically involves joints, first small articulations and then big articulations and finally multiple organ systems including the heart, eyes, skin, lung and kidneys, [16]. This debilitating disease affects about 1% of the world population and 1.5 million people in the United States, and is characterized by chronic inflammation accompanied by severe destruction of joints, cartilage disruption and erosion of bones [17,18]. This pathogenetic mechanism involves a complex interaction of genetic susceptibility, environmental effects including tobacco exposure, leading to chronic synovial inflammation and activation of inflammatory cytokines and proteinases that maintain joint destruction [19,20]. Left unchecked, this inflammation eventually results in permanent joint destruction, very high levels of disability and even organ failure in a minority of cases [20,21]. This study aimed to evaluate the impact of Toxoplasma gondii infection on serum sHLA-G levels in Iraqi pregnant women with Rheumatoid Arthritis using molecular and immunological methods.

Materials and methods:

Study Design: A cross-sectional case–control analytical study

Study Setting: Rheumatology and Obstetrics Departments of major Iraqi hospitals (Middle Euphrates region: Karbala, Babylon, Najaf, Diwaniyah hospitals)

Study Population: Pregnant women aged 18–47 years in their 2nd or 3rd trimester

Study Groups: the study distinguished four groups of participants:

Group I: Pregnant females with Rheumatoid arthritis and *T. gondii* infection

Group II: Rheumatoid arthritis maternal out of *T. gondii* infection

Group III: Pregnant women without Rheumatoid arthritis, *T. gondii*-infected.

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Group IV (Control): Healthy pregnant women; T. gondii infection negative, Rheumatoid arthritis negative

The size of samples were conserving what prey species they studied and the sample size per each one in terms of adjusting their results to estimate for instance the properties (biooperation capacity) of their graphs power and the size.

Inclusion standards: Confirmed pregnancy (2nd–3rd trimester) Iraqi Not individuals regarding RA diagnosis based upon ACR/EULAR requirements (for Rheumatoid arthritis groups) Agree to participate provide educated consent

Exclusion criteria: included other autoimmune diseases (e.g. HIV or hepatitis B/C infection, Diabetes mellitus or chronic kidney disease), any immunosuppressive therapy outside standard RA treatment (e.g., thalidomide) and multiple pregnancy (twins or more).

Data Collection

1. Clinical and Demographic Data: Age, gestational age, residence (urban/rural)**,** History of miscarriage or abortion. Rheumatoid arthritis duration and disease activity score (DAS28) **and** Current medications**.**

Laboratory Studies: A. Serology for *Toxoplasma gondii*. Anti-Toxoplasma IgG and IgM ELISA.

B. Soluble HLA-G (sHLA-G) Determination: Measurement of serum sHLA-G by ELISA.

C. Molecular Studies: DNA isolation from peripheral blood. Roche LightCycler® 480 qPCR-based assay for *T. gondii* DNA (targeting B1 or REP-529 gene)

D. Immunological Parameters: Pro-inflammatory cytokines: IL-6, IFN-γ, TNF-α and **Anti-inflammatory cytokine:** IL-10 Determined using ELISA in order to study the Influence of acute and chronic *T. gondii* infection on the sHLA-G levels

Statistical Analysis Software: SPSS v26 or similar Descriptive statistics: mean ± SD; frequency (%) Group comparisons: Kruskal–Wallis test or ANOVA; post-hoc tests Correlation: Pearson correlation coefficient or Spearman's rho. Multivariate regression for confounders. Significance: $P < 0.05$

Ethical Approval: Iraqi institutional ethics committee approval. Written informed consent from participants. Full information, informed consent, privacy and confidentiality! swift: type will be anonymized available ergate.

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Results:

Characteristics of the Study Population

The study was done in 112 pregnant Iraqi women divided into four groups of 28. The similar age distribution, gestational age and parity between groups demonstrated that there was no difference in the two matched groups, so these three variables are unlikely to have affected the immunological findings. On the other hand, all pregnant patient with Rheumatoid arthritis and *Toxoplasma gondii* infection, disease activity (DAS28) was significantly greater. These findings indicate that concurrent infection may exacerbate autoimmune inflammation in pregnancy. Size: 112 individuals (28 in each group). Age, 26.8 to 30.2 years; no significant difference (P = .41) Gestational age, residence, parity: no significant difference between groups (P > 0.05). RA duration & DAS28: both were significantly higher among Rheumatoid arthritis patients with Toxoplasma as comparison with Rheumatoid arthritis cases (P < 0.01)

Table 1. Clinical Characteristics and Demographics

Variable	Rheumatoid arthritis with Toxoplasma	Rheumatoid arthritis	Toxoplasma	Control	P value
Age (years)	29.6 ± 5.1	28.9 ± 4.7	27.8 ± 4.9	26.8 ± 4.9	0.41
Gestational age (weeks)	24.3 ± 3.8	23.9 ± 4.1	24.7 ± 3.5	25.1 ± 3.6	0.52
DAS28	4.8 ± 0.9	3.6 ± 0.8	—	—	<0.01

Evidence of *Toxoplasma gondii* Infection by Serological and Molecular Methods

Serological examination revealed acute and chronic toxoplasmosis was reversed, the status of pregnant women being characterized by high anti-Toxoplasma IgG antibodies rate. This is consistent with local and international studies supporting the prevalence of *T. gondii* exposure in endemic areas. Real-time polymerase chain reaction (PCR) detection of *T. gondii* DNA in a significant proportion of antibody-positive women indicates the presence of recent or active parasites in the blood, particularly in cases where IgM antibodies are present in the serum. This reinforces serological findings and demonstrates that the immune disturbances in these women are not solely related to prior exposure but are of a biological nature. Women with RA

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developed seropositive Rheumatoid arthritis More chronic infection than acute. Higher titers in RA infected compared to non-RA infected with $P < 0.05$ for IgG

Table 2. *T. gondii* Serology

Group	IgG positive (%)	IgM positive (%)
Rheumatoid arthritis with Toxoplasma	78.6	21.4
Toxoplasma	82.1	17.9

Study Group Comparisons in sHLA-G Levels

The most important result of the present work was exceeding changes in circulating sHLA-G levels that was manifested between four different groups. Lowest sHLA-G levels were found in healthy pregnant women, which reflects physiologic immune tolerance. Pregnant women with RA only showed moderately sHLA-G elevation, which could be interpreted as an attempt to counterbalance chronic autoimmune inflammation. In addition, sHLA-G levels were also increase in pregnant women with *T. gondii* infection without disease, thus parasitic infections that are generally responsible for immune-regulatory pathways may be considered.

The highest activity of sHLA-G was found in pregnant women suffering from RA with *T. gondii* infection, implying a synergistic action between autoimmunity and immune tolerance mechanisms induced by infection. This trend implies that sHLA-G is a risk responder to immunological stress reaction, playing a protective role during pregnancy. *T. gondii* DNA was detected with qPCR in 64.3% seropositive RA and 50% seropositive non-RA subjects. PCR positiveness was positively correlated with IgM positiveness ($P < 0.01$). Overall comparison of sHLA-G levels between groups: **$P < 0.001$**, qPCR positivity showed a **significant positive correlation with IgM seropositivity** (**$P < 0.01$**), also the Highest sHLA-G levels were observed in **Rheumatoid arthritis** with ***T. gondii*** group.

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Table 3. Study Group Comparisons in Serum sHLA-G Levels and *Toxoplasma gondii* Molecular Detection

Study Group	Clinical Description	sHLA-G Level (Mean ± SD, ng/mL)	Interpretation of sHLA-G Change	*T. gondii* DNA by qPCR (%)
Group I	Pregnant women with Rheumatoid arthritis with *T. gondii* infection	48.6 ± 9.4	Markedly elevated sHLA-G indicating synergistic immune regulation due to combined autoimmunity and infection	64.3%
Group II	Pregnant women with Rheumatoid arthritis	36.2 ± 7.8	Moderate elevation reflecting compensatory response to chronic autoimmune inflammation	—
Group III	Pregnant women with *T. gondii* infection	40.1 ± 8.2	Increased sHLA-G suggesting infection-induced immune tolerance mechanisms	50.0%
Group IV	Healthy pregnant controls	24.7 ± 6.5	Lowest physiological sHLA-G levels reflecting normal pregnancy immune tolerance	—

Acute and Chronic Toxoplasmosis

The difference between acute and chronic toxoplasmosis was significant ($P < 0.001$) with sHLA-G levels being much higher in patients with acute infection. An intense inflammation is enhanced by a sharp focal sHLA-G increase, which may play the role of limiting excessive immune activation and protecting maternal tissues during infection along with the fetus. Chronic infection, however, was characterized by lower but increased sHLA-G when compared to controls suggesting an efficient and stable immune balance between host and parasite. High significant difference among groups ($P < 0.001$).

Table 4. Serum sHLA-G Levels (ng/mL)

Group	Mean ± SD	Range	P value
Rheumatoid arthritis with Toxoplasma	48.6 ± 9.4	32–65	$P < 0.001$
Rheumatoid arthritis	36.2 ± 7.8	25–52	
Toxoplasma	40.1 ± 8.2	28–58	$P < 0.0001$
Control	24.7 ± 6.5	15–38	

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Cytokine Profile and Immune Balance

The proinflammatory cytokines (IL-6, IFN-γ and TNF-α) were more increased in pregnant women with RA and toxoplasmosis showing that the immune response is stimulated. Concomitantly, IL-10 was increased indicating a counter-regulatory anti-inflammatory activity. This combined cytokine profile is the result of immune balance in which inflammatory activity is required to contain infection and autoimmunity, whereas regulatory properties—such as IL-10 and sHLA-G-curtail immunomodulated tissue damage. Acute (IgM^+) showed higher sHLA-G as compared with chronic ($P < 0.01$)

Table 5. sHLA-G by Infection Stage

Infection stage	sHLA-G (ng/mL)	P value
Acute	55.2 ± 8.6	<0.01
Chronic	42.1 ± 7.4	<0.01

Correlation of sHLA-G with Cytokines and with Disease Phenotype

There was a positive correlation with IL-10, suggesting the involvement of sHLA-G in immune regulation and tolerance. Negatively related with pro-inflammatory cytokines, supporting an anti-inflammatory action. Favorable correlation with RA disease activity (DAS28), indicating that sHLA-G peaks when the inflammatory burden is high. These results suggest that sHLA-G is not proinflammatory but only reacts adaptively to inflammation. RA with toxoplasmosis enhanced IL-6, IFN-γ , TNF-αand IL-10 → combined pro-inflammatory/regulatory response.

Table 6. Cytokine Levels (pg/mL)

Cytokine	Rheumatoid arthritis with Toxoplasma	Rheumatoid arthritis	Control	P value
TNF-α	34.5 ± 6.9	28.1 ± 5.7	14.8 ± 4.3	<0.001
IL-6	41.7 ± 8.2	32.4 ± 6.5	16.3 ± 4.9	<0.001
IFN-γ	29.3 ± 5.8	22.9 ± 4.6	11.7 ± 3.8	<0.001
IL-10	18.9 ± 4.2	14.6 ± 3.7	8.2 ± 2.9	<0.01

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Independent Predictors of sHLA-G Elevation

After adjusting for confounders, multivariate regression analysis revealed that *Toxoplasma gondii* infection was still an independent predictor on higher levels of sHLA-G. This contributes to demonstrate that the observed increments in sHLA-G are directly related with infection and not by age, stage of pregnancy or duration of RA. sHLA-G with IL-10 : $r = +0.62$, $P < 0.001$. Also sHLA-G with TNF-α : $r = -0.46$, $P < 0.01$. while sHLA-G with DAS28 : $r = +0.55$, $P < 0.01$

Overall Interpretation

Together, they indicate that in pregnant rheumatoid arthritis and *Toxoplasma gondii* women an enhanced activation of immune tolerance pathways including sHLA-G expression is observed. The results indicate that sHLA-G is a key immunomodulator in supporting the maternal–fetal tolerance when there are increased immune challenges. T. gondii infection is a independent predictor of sHLA-G levels ($\beta = 0.41$; $P = 0.002$). RA disease activity also was independently correlated ($\beta = 0.35$, $P = 0.01$)

Discussion:

This study explored the potential role and association of *Toxoplasma gondii* infections, soluble HLA-G5 (sHLA-G) levels and rheumatoid arthritis (RA) in pregnancy complicated by RA in Middle Euphrates region pregnant women.

sHLA-G and Pregnancy with Autoimmunity

HLA-G is a nonclassical MHC class I with powerful immunosuppressive activities, involving in maternal–fetal immune tolerance by suppressing the killing functions of natural killer cells, cytotoxic T lymphocytes and antigen-presenting cell function [22,23]. High activity of sHLA-G in circulation has long been described as raised during normal pregnancy and regarded as pivotal for the protection against fetal rejection [23]. In the current study, pregnant women with RA had significantly higher serum sHLA-G expression than healthy controls. This finding is consistent with previous evidence of elevated sHLA-G levels in autoimmune conditions, such as RA, and further supports the idea of its role in compensating to inflammation that does not resolve [26], [33]. Similar findings were reported in European and Asian populations of RA, where high concentrations of sHLA-G correlated with a higher degree of disease activity and inflammation load [27;28].

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The Influence of Toxoplasma gondii Infection on the Concentration of sHLA-G

Interestingly, the higher sHLA-G production more characteristic of such RA pregnancy with concomitant T. gondii infection than for non-infected RA patients was a relevant finding of the present study . Intracellular parasite infection such as *T. gondii* has been shown to induce immune tolerance pathways for its escape from the immune system of the host and expression of HLA-G has been involved in this mechanism [29]. Prior studies have shown that *T. gondii* infection induces increased expression of immunoregulatory molecules in both placental and peripheral immune cells, especially at the time of pregnancy [31,32]. Araujo et al. found that *T. gondii* triggers tolerogenic abortogenic signal pathways in trophoblast cells, which might be responsible for the parasite persistence and immunological disbalance in the host [31]. The results expand this evidence by demonstrating that pre-existing autoimmune disease exacerbates this immunomodulation.

Acute Toxoplasmosis with Chronic Infection and Immunoregulation

The current study revealed that the expression of sHLA-G was significantly higher in patients with acute toxoplasmosis IgM+ than those showed signs of chronic infection. Acute *T. gondii* infection involves a strong Th1 response with high levels of TNF-α and IFN-γ [30]. Elevations of sHLA-G in acute HCV infection probably represent an attempt toward compensation to restrict excessive inflammation and tissue damage. Similar immune profiles have also been noticed in viral infection, for which higher blood sHLA-G activity were observed in the acute phase of the diseases than their chronic phase [25]. These observations imply that up-regulation of sHLA-G may be a general immune-regulatory response to increased inflammatory stress.

Correlation of sHLA-G with Cytokines and Disease Activity in CRADISC Patients

The strong positive correlation that we found between the expression of sHLA-G and IL-10 level in the present study is also supported by previous experimental data showing that IL-10 up-regulates HLA-G expression on antigen presenting cells, which leads to immunosuppression [24]. In contrast, negative relationships between sHLA-G and pro-inflammatory cytokines (IFN-γ and TNF-α) also confirm the anti-inflammatory function of sHLA-G. Of note, levels of sHLA-G were positively correlated with disease activity of RA in accordance to DAS28. This result is consistent with the findings of [27,29]. These findings are in agreement with those of [28]., who

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showed an association between higher sHLA-G expression and more severe RA, suggesting that increased concentrations of sHLA-G may constitute an endogenous response to chronic inflammation.

Molecular Confirmation and Diagnostic Relevance

T. gondii DNA in seropositive samples found by real-time PCR In many IgM positives, indicates usefulness of serologic and molecular tests as added value for pregnant woman and immune impaired individual. Molecular validation supports the diagnostic confidence and the physiological plausibility of immune changes, as shown also in parasitic immunology literature [30].

Clinical and Regional Implications

The fact that patients with rheumatoid arthritis have high serum sHLA-G levels also in pregnancy could allow for double-edge swords: these may facilitate the immunological modulation of the immune response that is necessary for fetal acceptance, and on the other hand to create an environment of immune suppression which not only might be beneficiary for survival of parasites but also accentuate autoimmune dysregulation. The study aims to make the novel discovery of immunological tolerance biomarkers during pregnancy, where little is known about their presence in certain geographical areas, like the Middle Euphrates region, where a high seroprevalence rates of toxoplasmosis.

Study Limitations and Directions of Future Research

Although they were great to have molecular confirmation and the ability to compare across multiple cohorts, this study is still just a cross-sectional so you cannot make any cause-and-effect conclusions with it. These results reinforce the conclusion that longitudinal studies are needed to investigate neonatal outcomes and variations of sHLA-G over time. Studies of placental tissue may also allow one to determine which local immunologic factors are responsible for these findings. [22,29].

Conclusion:

Soluble human leukocyte antigen-G (sHLA-G) production is the by-product of an unexpected multi-layered host response induced from an immunological interaction between a maternal *T. gondii* infection, autoimmunity and pregnancy. This reaction is observed in pregnant woman suffering from rheumatoid arthritis which is a typical case

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of sHLA-G expression [33]. More studies with larger longitudinal cohorts are needed to validate these findings and better assess the role of sHLA-G as a marker for immunological tolerance in high-risk pregnancies. SHLA-G levels are significantly higher in patients with acute Toxoplasmosis than in chronically infected ones. It implication as a defense mechanism against the strong inflammatory response mediated by Th1 through elevated levels of IFN-γ and TNF-α. These increases are similar to those of sHLA-G induction in acute viral infections, which is an adaptive response aiming at controlling overly exuberant inflammatory reactions and tissue injury.

Further insights concerning the sHLA-G action can be obtained through correlational studies. IL-10, the anti-inflammatory cytokine, has a positive correlation (r=+0.62P01), indicating that this framework both regulates and produces either pro-inflammatory or anti-inflammatory cytokines. Multivariate regression showed that the association between *T. gondii* infection and sHLA-G release remained significant after controlling for potential confounders (age, gestational age, duration since RA diagnosis). An important aspect of our results is that these also indicate the potential of sHLA-G to be used as a marker for acute toxoplasmosis and associated RA flares since its peak was detected early in the course of disease, thus distinguishing it from serum IgG levels against T. Prospective longitudinal investigations are needed to elucidate the predictive value and therapeutical goal of modulation in toxoplasma-associated inflammatory disorders. The role of *Toxoplasma gondii* in RA-pregnant ladies affecting the sHLA-G levels Here, it could be for example that sHLA-G consists of an immunoregulatory factor protecting the pregnant mothers with Toxoplasma co-infections from deleterious effects of RA.

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