Ukrainian Journal of Nephrology and Dialysis
Scientific and Practical, Medical Journal

Founder:
- National Kidney Foundation of Ukraine

ISSN 2304-0238;
eISSN 2616-7352

Journal homepage: https://ukrjnd.com.ua

Research article

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doi: 10.31450/ukrjnd.1(89).2026.03

Pregnancy-stratified IL-1β and IL-17A serum levels in women with recurrent urinary tract infections: An exploratory analysis of IL-1β and IL17A polymorphisms

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Citation: Al-Muswie RT, Nuhair RS, Chayan MA, Hami HJ. Pregnancy-stratified IL-1β and IL-17A serum levels in women with recurrent urinary tract infections: An exploratory analysis of IL-1β and IL17A polymorphisms. Ukr J Nephrol Dialys. 2026;1(89):17-24. doi: 10.31450/ukrjnd.1(89).2026.03.

Abstract. *Recurrent urinary tract infections (rUTI) are common among women and are influenced by anatomical, immunological, and physiological factors, particularly during pregnancy. Pro-inflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-17A (IL-17A) play important roles in host immune defense; however, their behavior in pregnant women with rUTI remains insufficiently explored.*

Methods. A total of 90 women, including 60 patients with rUTI and 30 healthy controls were included in this cross-sectional study. Participants were stratified by pregnancy and rUTI statuses. Serum levels of IL-1β and IL-17A were measured using ELISA. Genetic polymorphisms IL1B rs1143633 and IL17A rs2275913 were identified by PCR amplification followed by sequencing.

Results. Serum concentrations of IL-1β and IL-17A were significantly higher in women with RUTIs compared with controls regardless of pregnancy status ($p < 0.001$). Pregnant women with rUTI had lower levels of IL-1β than non-pregnant patients ($p = 0.025$). IL-17A levels did not significantly differ between pregnancy groups. Multivariate analysis showed that rUTI was independently associated with increased cytokine levels after adjustment for age, BMI, and comorbidities. Sequencing identified polymorphisms IL1B rs1143633 and IL17A rs2275913; however, there was no clear association between these variants and cytokine concentrations or disease status.

Conclusions. rUTI is associated with elevated serum IL-1β and IL-17A levels in women, regardless of their pregnancy status. Pregnancy appears to modulate IL-1β responses but does not significantly affect IL-17A expression. The investigated genetic polymorphisms showed no strong influence on inflammatory responses in this cohort. Our findings highlight the role of cytokine-mediated immunity in rUTI and support the need for further large-scale studies.

Key words: *genetic polymorphism, interleukin-1β, interleukin-17A, pregnancy, urinary tract infections.*

Article history:
Received December 26, 2025
Received in revised form February 03, 2026
Accepted February 05, 2026

Conflict of interest. The authors declare no conflict of interest.

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УДК: 616.61/63-022.7:618.2:612.017:575.17

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Концентрація IL-1β та IL-17A в сироватці крові жінок з рецидивуючою інфекцією сечовивої системи, стратифікована за вагітністю: описовий аналіз поліморфізмів IL-1β та IL17A

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Резюме. *Рецидивуюча інфекція сечової системи (рІСС) є надзвичайно поширеною серед жінок, що зумовлено анатомічними, імунологічними та фізіологічними чинниками, особливо під час вагітності. Прозапальні цитокіни, зокрема інтерлейкін-1β (IL-1β) та інтерлейкін-17A (IL-17A), відіграють важливу роль в імунному захисті організму; однак їх динаміка у вагітних жінок із рІСС залишається недостатньо вивченою.*

Методи. Це одномоментне дослідженні включало 90 жінок, з яких 60 пацієнток мали рІСС, а 30 становили групу здорового контролю. Учасниць стратифікували за наявністю вагітності та рІСС. Рівні IL-1β та IL-17A у сироватці крові визначали методом ІФА. Генетичні поліморфізми IL1B rs1143633 та IL17A rs2275913 ідентифікували за допомогою ПЛР з подальшим секвенуванням.

Результати. Сироваткові концентрації IL-1β та IL-17A були достовірно вищими у жінок з рІСС порівняно з контрольною групою, незалежно від статусу вагітності ($p < 0,001$). У вагітних жінок з рІСС рівень IL-1β був нижчим, ніж у невагітних пацієнток ($p = 0,025$). Рівні IL-17A суттєво не відрізнялися між групами вагітних і невагітних. Багатофакторний аналіз показав, що рІСС незалежно асоціювалась з підвищенням рівнів цитокінів після корекції за віком, індексом маси тіла та супутніми захворюваннями. Секвенування виявило поліморфізми IL1B rs1143633 та IL17A rs2275913; однак чіткої асоціації між цими варіантами та концентраціями цитокінів або рІСС не встановлено.

Висновки. рІСС асоціюються з підвищеними рівнями IL-1β та IL-17A у сироватці крові жінок незалежно від вагітності. Вагітність, імовірно, модулює відповідь IL-1β, але суттєво не впливає на експресію IL-17A. Досліджені генетичні поліморфізми не продемонстрували значного впливу на запальні реакції в цій когорті. Отримані результати підкреслюють роль цитокін-опосередкованого імунітету у пацієнток з рІСС та обґрунтовують необхідність подальших масштабних досліджень.

Ключові слова: *генетичний поліморфізм, інтерлейкін-1β, інтерлейкін-17A, вагітність, інфекції сечової системи.*

Introduction. Women often experience urinary tract infections (UTIs) at various ages. Due to the anatomy of the female lower urinary system and its closeness to the reproductive organs, women are more susceptible to UTIs than men [1]. UTIs affect approximately 60% of women, and about 30%–40% experience recurrent episodes [2]. Female urethras are shorter, which shortens the distance for bacterial entry into the bladder. In addition, conditions such as vulvar vestibulitis and vaginitis increase the vulnerability of the vulvar vestibule to infection. Sexual activity and excessive use of personal hygiene products can damage the normal vaginal flora [3].

Cytokines are the major mediators of immune responses. They control the activation of B and T lymphocytes, natural killer cells, monocytes, and granulocytes, and participate in pathways that regulate inflammatory processes [4]. Inflammation is involved in the onset and progression of many urological diseases [5].

Interleukin-17A (IL-17A) and interleukin-1β (IL-1β) are two important pro-inflammatory cytokines that play roles in host defense and tissue inflammation [6, 7]. IL-17A stimulates the activation of immune cells and enhances the secretion of pro-inflammatory mediators. IL-1β is crucial in mediating the innate immune response in UTI, particularly concerning stimuli from uropathogenic Escherichia coli [8, 9].

Pregnancy is a unique physiological condition characterized by hormonal changes, immune system modulation, and an increased tendency for UTI [10]. These factors may influence inflammatory cytokine production during infection and affect the host's immune defense. However, few studies have examined the influence of pregnancy on IL-1β and IL-17A expression in recurrent UTI (rUTI). Several studies have indicated that variations in cytokine genes, such as IL-1β, interleukin-1 receptor antagonist (IL-1RN), and tumor necrosis factor (TNF)-alpha, are associated with inflammatory diseases, cancer, and glomerulonephritis [9, 11,

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12]. The genes that encode the IL-1 family of proteins include IL-1α, IL-1β, IL-1 receptor types I and II, and IL-1RN. These genes are co-located on the 2q region of human chromosome 2 and exhibit polymorphism, meaning they can exist in several forms due to genetic diversity. Additionally, they are closely positioned on the chromosome [12]. Various genetic variations have been documented for IL-1β. Single-nucleotide polymorphisms (SNPs) may influence gene regulation and cytokine expression rather than altering protein structure. The *IL1B* gene has undergone extensive investigation in relation to malignancies, inflammatory conditions, and infectious disorders [11, 13, 14]. However, limited information is available regarding the relationship between *IL1B* and *IL17A* polymorphisms and circulating cytokine levels in pregnant women with rUTI.

Therefore, this study aimed to conduct pregnancy-stratified immunogenetic profiling of IL-1β and IL-17A by evaluating serum cytokine levels in relation to *IL1B* rs1143633 and *IL17A* rs2275913 polymorphisms in women with rUTI.

Materials and methods. *Study design and participants*. This cross-sectional study was carried out between February and April of 2024 at Al-Habobi Teaching Hospital in Thi-Qar Province, Iraq. Ninety women were recruited in the study, thirty of whom were healthy controls and sixty of whom had been diagnosed with rUTI. All participants provided written informed consent, and the study protocol was approved by the local ethics committee (Approval No. 3/11/903, June 2, 2022), in accordance with the principles of the Declaration of Helsinki.

rUTI was defined as the presence of three or more infection episodes within one year, confirmed by clinical symptoms and positive urine culture findings. Women without a history of UTI, no recent use of antibiotics within four weeks prior to enrollment, and no known inflammatory or chronic conditions made up the control group.

Participants were categorized based on pregnancy status at the time of sampling. Demographic and clinical information was collected for all women, including age, body mass index (BMI), place of residence, marital status, pregnancy status, and the presence of chronic diseases.

Blood sample collection and processing. Blood samples from rUTI patients were collected before initiation of antibiotic therapy. Five milliliters of venous blood were taken from each participant under aseptic conditions. Two milliliters were added to plain gel tubes for clotting at room temperature, which took about thirty minutes. Samples were centrifuged to separate serum that was kept at −20°C until it could be analyzed for cytokines.

The remaining three milliliters of blood were collected in EDTA tubes and immediately stored at −20°C for molecular analysis.

Determination of IL-1β and IL-17A. Serum concentrations of IL-1β and IL-17A were determined using enzyme-linked immunosorbent assay (ELISA) kits from a commercial source (Elabscience, China) according to the instructions provided by the manufacturer.

The detection range for IL-1β was 0.63–40 pg/mL with a sensitivity of 0.39 pg/mL; for IL-17A, it was 0.78–50 pg/mL with a sensitivity approximately equal to 0.49 pg/mL.

All serum samples and reagents were allowed to come to room temperature before use. Standards and samples (100 µL) were added to the wells and incubated for 90 minutes at 37°C. After removal of liquid, 100 µL biotin-conjugated antibody was added and incubated for an hour at 37°C, followed by washing steps then finally adding HRP-avidin solution (100 µL), which would also be incubated for another half an hour under the same conditions. The last wash was done; TMB substrate (90 µL) was added and kept in the dark for reaction development between 15 and 30 minutes. It was stopped with a stop solution of fifty microliters, then read absorbance at four hundred fifty nanometers using a microplate reader, Biotic USA. All samples were run in duplicate.

Extraction of DNA. DNA was extracted from whole blood using the phenol–chloroform extraction method with a volume of 2 mL. Briefly, blood samples were mixed with red blood cell lysis buffer and centrifuged to remove erythrocytes; the pellet obtained was lysed using nuclear lysis buffer, sodium dodecyl sulfate (SDS), proteinase K, and phenol.

Centrifugation followed by transfer of the aqueous phase into another tube mixed with chloroform–isoamyl alcohol (24:1). The precipitation process involves sodium acetate plus cold isopropanol wash in seventy percent ethanol, air drying before dissolving it in DNase/RNase-free water.

DNA concentration and purity were assessed using a spectrophotometer (NanoDrop, Thermo Fisher Scientific), and samples with A260/A280 ratios between 1.8 and 2.0 were selected for PCR amplification.

PCR amplification of IL1B and IL17A. PCR amplification was performed in a total volume of 25 µL, which contained 50–100 ng genomic DNA, 1× PCR buffer, 1.5 mM $MgCl_2$, 0.2 mM dNTPs, 0.5 µM of each primer, 1.25 U Taq DNA polymerase (Thermo Fisher Scientific, USA), and nuclease-free water. Primer sequences used for *IL1B* and *IL17A* amplification are presented in Table 1. Primer sequences used for *IL1B* and *IL17A* amplification are presented in Table 1.

Table 1

Primers used for PCR amplification

Gene	Primer sequences (5′ → 3′)	Product size	Reference
IL-1β	F: TTCAGTTCATATGGACCAGA R: GTTGTCATCAGACTTTGACC	245 bp	[21]
IL-17A	F: CAGAAGACCTACATGTTACT R: GTAGCGCTATCGTCTCTCT	344 bp	[22]

Thermal cycling conditions included initial denaturation at 94°C for 30 seconds followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing at 57°C for IL-1β and 61°C for IL-17A for 40 seconds and extension at 68°C for one minute with a final extension at this temperature for five minutes.

Gel electrophoresis and sequencing. The PCR products were separated on a gel consisting of an agarose solution at a concentration equal to that of the ethidium bromide-stained ladder (100 bp DNA ladder) under UV light.

Amplicons of expected size were purified using a PCR purification kit and subjected to Sanger sequencing in both forward and reverse directions (Bioneer, Korea). Sequence chromatograms were analyzed using Chromas software and aligned with reference sequences using NCBI BLAST. *IL1B* sequences were compared with GenBank accession NG_008851.1, and *IL17A* sequences with accession LC780105.1. SNPs were identified by comparison with the dbSNP database, confirming *IL1B* rs1143633 and *IL17A* rs2275913 variants.

Genetic analysis. Genotype frequencies were calculated and summarized descriptively. Because of the small sample size, genetic association analyses are treated as exploratory; hence, no definite risk estimates were derived.

Statistical analysis. Statistical analysis was performed using SPSS version 26. Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as numbers and percentages. Baseline characteristics were compared between groups using the independent sample t-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Serum levels of IL-1β and IL-17A showed non-normal distribution and were therefore analyzed using non-parametric tests. Comparisons between two groups were performed using the Mann–Whitney U test, while comparisons among more than two groups were conducted using the Kruskal–Wallis test.

Multivariable linear regression analysis using log-transformed cytokine values was applied to assess the independent association between rUTI and cytokine levels after adjustment for age, BMI, and comorbidities. A p-value less than 0.05 was considered statistically significant.

Results. *Characteristics of the study cohort*. Among 90 women included in the study, there were 52 (57.8%) pregnant women and 38 (42.2%) non-pregnant women. Of the pregnant participants, 43 (82.7%) had rUTI and 9 (17.3%) served as healthy controls. Among non-pregnant women, 17 (44.7%) had rUTIs and 21 (55.3%) were controls. There was no significant difference in age between rUTI patients and controls within either pregnancy group (Table 2).

Table 2

Baseline characteristics of participants according to pregnancy status and rUTI diagnosis

Variable	Pregnant women (n = 52)			Non-pregnant women (n = 38)		
	rUTI (n=43)	Control (n=9)	*p*-value	rUTI (n=17)	Control (n=21)	*p*-value
Age, years	32.7 ± 7.6	31.6 ± 3.7	0.581	31.6 ± 3.7	33.8 ± 6.6	0.235
Overweight, n (%)	35 (81.4%)	3 (33.3%)	0.009	14 (82.3%)	12 (57.1%)	0.113
Rural residency, n (%)	32 (74.4%)	3 (33.3%)	0.017	11 (64.7%)	6 (28.6%)	0.028
Married marital status, n (%)	37 (86.0%)	5 (55.5%)	0.036	13 (76.5%)	17 (80.9%)	0.744
Gestational age, weeks	26.4 ± 6.1	24.8 ± 5.3	0.412	–	–	–
Comorbidities, n (%)	9 (20.9%)	1 (11.1%)	0.501	4 (23.5%)	1 (4.7%)	0.091

As shown in Table 2, in pregnant women, overweight was significantly more common in those with rUTI compared with controls. A similar trend was observed in non-pregnant women, although the difference did not reach statistical significance. Rural residence was also more frequent among rUTI patients than controls in both pregnant women and non-pregnant women.

Among pregnant women, a higher proportion of rUTI patients were married compared with controls. In non-pregnant women, marital status did not differ significantly between rUTI patients and controls. Comorbid conditions were slightly more common in rUTI patients than in controls in both pregnancy groups. However, these differences were not statistically significant.

Serum IL-1β and IL-17A levels. Serum IL-1β concentrations were significantly higher in women with rUTI compared with controls in both pregnant and non-pregnant groups (Fig. 1A; $p < 0.0001$). Among rUTI patients, pregnant women showed slightly lower IL-1β levels than non-pregnant women ($p = 0.025$).

Similarly, serum IL-17A levels were markedly elevated in rUTI patients compared with controls regardless of pregnancy status (Fig. 1B; $p < 0.0001$). No significant difference in IL-17A concentrations was observed between pregnant and non-pregnant women with rUTI ($p = 0.971$).

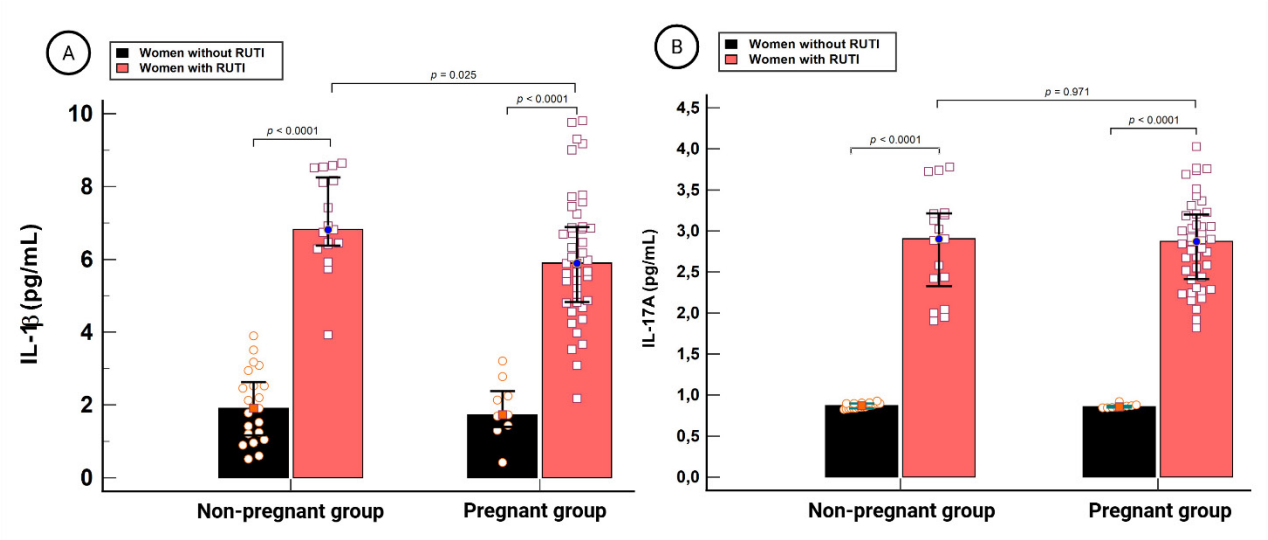

Fig. 1. Serum IL-1β and IL-17A concentrations in the studied cohort.

In multivariate linear regression using log-transformed cytokine values, rUTI remained significantly associated with higher IL-1β levels, after adjusting for age, BMI, and comorbidities ($p < 0.001$). The same pattern was observed for IL-17A. Log-transformed IL-17A levels were significantly higher in women with rUTI compared with controls after adjustment ($p < 0.001$), while age, BMI, and comorbidities showed no significant association.

Molecular detection and sequencing of IL1B and IL17A. PCR amplification of *IL1B* and *IL17A* genes produced fragments of 245 bp and 344 bp, respectively, that was confirmed by agarose gel electrophoresis. All samples generated clear, distinct bands, while the negative controls did not show any amplification.

Sequencing analysis of the PCR products demonstrated approximately 99% similarity with reference sequences in GenBank, confirming the identity of the amplified regions. *IL1B* sequences aligned with the reference sequence NG_008851.1, and *IL17A* sequences aligned with LC780105.1.

SNP was identified in each gene. In the *IL1B* gene, a G>A substitution at position 114 of the amplified fragment was detected and corresponded to rs1143633. Only homozygous genotypes (GG and AA) were observed, while the heterozygous genotype was not detected in the studied samples.

In the *IL17A* gene, an A>G substitution was identified within the 344 bp amplicon and corresponded to rs2275913. The heterozygous (AG) and minor homozygous (GG) genotypes were detected, whereas the major homozygous genotype (AA) was not observed.

The dbSNP database confirmed that these variants had been detected and verified their genomic positions: one in the intronic region of *IL1B* and another in the promoter region of *IL17A*. Due to the limited sample size, genetic findings were considered exploratory and require validation in larger cohorts.

Discussion. The present study aimed to characterize systemic inflammatory responses in women with rUTI by evaluating serum IL-1β and IL-17A levels. A key novel aspect of this work is the stratification by pregnancy status, which allowed assessment of how physiological changes during pregnancy influence immune responses to infection.

The main finding is that both IL-1β and IL-17A were significantly elevated in women with rUTI compared with healthy controls. We also found significantly lower levels of IL-1β in pregnant women with rUTI compared with non-pregnant patients. IL-17A levels remained similarly elevated in both groups. In multivariate regression analysis, rUTI was independently associated with increased IL-1β and IL-17A levels after controlling for age, BMI, and comorbidities. We believe that rUTI itself is a major driver of cytokine elevation; pregnancy and other host factors determine what specific inflammatory responses occur rather than the general activation of the immune system.

Elevated levels of IL-17A in patients with rUTI are an important mediator in mucosal defense through neutrophil recruitment during rUTI [15-17]. The fact that both pregnant and non-pregnant women have similar responses of IL-17A indicates that this pathway is not altered during pregnancy, which means antibacterial defenses will continue to operate effectively.

On the other hand, lower levels of IL-1β in pregnant women with rUTI compared to non-pregnant patients is a finding that makes biological sense since pregnancy involves immune modulation to avoid excessive inflammation that would damage a growing fetus [10]. It has been shown that pregnancy promotes immune tolerance through suppression of pro-inflammatory cytokine responses, including reduced stimulated IL-1β production, which protects maternal-fetal interfaces but may predispose to recurrent infections by attenuating early innate inflammatory defenses [18]. While this immune modulation may be protective for maternal-fetal health, it could predispose one to recurrent infections by not allowing early inflammatory responses.

Several demographic and clinical factors were associated with higher rUTI prevalence in this study. Increased BMI was more frequent among infected women, particularly in pregnant participants. Obesity is known to induce chronic low-grade inflammation and impair immune regulation, potentially reducing bacterial clearance [19-22]. Rural residency was also more common among rUTI patients, which may reflect environmental factors, hygiene conditions, and limited access to healthcare.

Pregnancy itself was strongly associated with rUTI occurrence, in agreement with previous reports highlighting the role of hormonal changes, urinary stasis, and anatomical modifications during gestation in promoting infection risk [23].

Chronic diseases were also more frequent among rUTI patients, as studies have shown that metabolic disorders compromise host immune defenses and facilitate bacterial persistence [24-27].

Molecular sequencing revealed rs1143633 in the *IL1B* gene and rs2275913 in the *IL17A* gene; both were previously reported in other populations [28-31]. Due to limited sample size and descriptive genetic analysis, clear associations with rUTI or cytokine levels could not be established. This study's inflammatory patterns seem mainly influenced by infection-related processes and physiological status rather than these specific genetic variants, thereby supporting a concept about rUTI based on complex immune and environmental interactions.

Several limitations should be considered when interpreting the present findings. First, the sample size was relatively small, especially in stratified subgroups, which has limited the power for detection of genetic associations and may also have an effect on the strength/stability of multivariable models. Second, the genetic analysis in this study was preliminary and limited to the identification of selected polymorphisms, without extensive genotyping or functional analysis. In addition, cytokine concentrations were assessed at a single sampling point, which does not allow evaluation of how inflammatory responses change over the course of infection or following therapy. Finally, data on the bacterial species and their antibiotic resistance were not included, although such factors may influence the cytokine levels. Future studies with larger cohorts, longitudinal sampling, and combined microbiological and genetic analyses are needed to clarify the dynamic immune responses in pregnant women with rUTI.

Conclusions. The present study demonstrates that rUTI was associated with increased levels of serum IL-1β and IL-17A independently of pregnancy status, age, BMI, and comorbidities. Although pregnancy is shown to be associated with a higher rate of recurrent infection, cytokine levels were mainly influenced by the presence of rUTI. IL-1β levels were lower in pregnant women with rUTI compared with non-pregnant patients.

No clear link was found between the identified SNPs and either cytokine levels or disease status, suggesting that inflammatory responses were mainly driven by clinical and physiological factors rather than by these genetic variations.

Overall, these findings emphasize the importance of inflammatory immune responses in the development of rUTI, particularly among high-risk groups such as pregnant women.

Conflict of interest. The authors declare no competing interests.

Findings. The authors received no financial support for the research.

Authors' contributions. All authors contributed equally to the conceptualization, data curation, investigation, methodology, project administration, resources, visualization, software, writing of the original draft, and writing – review & editing of the manuscript. All authors read and approved the final version of the manuscript.

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