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Recurrent implantation failure and inflammatory markers (TNF-α, IL-1β, IL-2, and IL-4) in serum and follicle fluid of women undergoing intracytoplasmic sperm injection

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Abstract
Background: Recurrent implantation failure (RIF), generally attributed to immunological abnormalities, represents a serious problem in ART. At the site of implantation, cytokines such as TNF-α, IL-1β, IL-2 and IL-4 modulate pro-inflammatory/anti-inflammatory responses. Disturbed balance could impair the embryo-endometrial interaction and result in IVF repeated failure.
Objective: To investigate the association between levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-2 and IL-4 in blood and follicular fluid of women with intracytoplasmic sperm injection (ICSI) who experienced recurrent implantation failure.
Methods: A cross-sectional analytic study was carried out in the Al-Nahrain University college of dentistry in Baghdad, from September 2024 to December 2025. There were 50 women who had a history of repeated implantation failure. Blood samples and follicular fluid were obtained on the day of oocyte retrieval. Concentrations of cytokines were determined by enzyme-linked immunosorbent assay (ELISA). Th1/Th2 ratios (IL-2/IL-4 and TNF-α/ IL-4) were evaluated to measure immune balance in compartment.
Results: Serum levels of Th1 and Th2 cytokines were found, with the highest circulating IL being that of TNF-α, demonstrating a systemically pro-inflammatory status. Follicular fluid demonstrated high levels of cytokines, the most abundant being IL-2, characterized by a strong Th1 proliferative signal. Elevated FF IL-4 and IL-1β levels point out to a local activation of FIG. In follicular fluid the IL-2/4 ratio was very gross and serum the TNF-α/IL-4, reflecting compartmentalised immunologic skews.
Conclusion: RIF women had distinct serum and FCF cytokine profiles. Systemic immunity responds mainly through inflammation, while Th1 and Th2 populate the ovarian microenvironment. These data demonstrate that individual cytokine profile in the compartments may potentially serve as a biomarker of predicting implantation and guide immunomodulatory treatments for ART.

Keywords: Recurrent implantation failure, cytokines, tumor necrosis factor-alpha (TNF-α), Interleukin-1beta (IL-1β), follicular fluid

Introduction
Repeated implantation failure (RIF) is, still now, one of the main obstacles in assisted reproductive technology (ART). It is commonly defined as failure to achieve clinical pregnancy after transfer of four high quality embryos in at least three cycles of IVF/ICSI [1]. RIF is a complex problem and occurs in 10-15% of couples receiving treatment. It is due to disorders in the uterus, in the quality of the embryos and of course: the lifestyle of the couple. Current evidence-based reviews are focusing more and more the attention on immunological dysregulation as a major driver, most notably in "idiopathic" situations, in which an impaired maternal immune modulating setup disrupts the complex dance between embryonic and endometrial cross-talk [2, 3]. Implantation only works if the pro-inflammatory state needed for the embryo to attach is reversed in an anti-inflammatory, tolerogenic field that permits maintenance [4]. The network of cytokines in the maternal-fetal interface is regulating at this step. The shift toward T-helper 1 (Th1) pro-inflammatory predominance, as reflected by elevations in TNF-α, IL-1β and IL-2 levels, is often associated with implantation failure. T-helper 2 (Th2) cytokines, such as IL-4, by contrast, favor the immune tolerance indispensable for pregnancy [5, 6]. Elevated TNF-α can cause local thrombosis and diminish trophoblast growth, excess IL-1β and IL-2 are linked to abnormal tissue remodeling and hyperactivated T-cell-mediated inflammation [7, 8].

To understand such mechanisms, scientists evaluate cytokine profiles in two distinct biological compartments: serum and FF. Plasma serum levels are non-invasive means of assessing the general immunological readiness of patient, and become a common use in RIF clinical biomarker tender [9, 10]. However, follicular fluid is the immediate microenvironment of the growing oocyte. Recent investigations have suggested that increased intrafollicular "tilt" towards an inflammatory state may impair oocyte competence and subsequent embryo viability, independent of transfer [11, 12]. Their detection in both compartments may be more comprehensive for diagnosis than an examination of serum alone. Although these signalling proteins are crucial, more attention should be given to the local and systemic ratio of cytokines (FF and serum) in respect to ICSI results. In this study, we aim to investigate and compare TNF-α, IL-1β, IL-2 and IL-4 levels in the serum and follicular fluid of ICSI-treated patients who fail to conceive with age-matched controls; to determine whether a correlation exists between these factors and recurrent implantation failure (RIF) as well as identify potential predictors for reproductive success.

Method

Study was carried out in the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University- Baghdad - Iraq. This is cross sectional analytical study. The study was carried out in collaboration with laboratories of clinical specialisation from September 2024 to December 2025. Enrollment and eligibility of the patients Fifty women were recruited by a systematic, consecutive approach. The majority of participants were selected on the basis of a history of Recurrent Implantation Failure (RIF: failed to get pregnant as a result of DAMEA three or more transfers with good quality embryos). To obtain a more homogenous sample and to limit confounding factors the following inclusion criterie were used: You are not older than 40 years. Not smoking. Menstrual periods that occur every 21 to 35 days. We obtained written informed consent and agreed to comply with the study protocols. Patients were, however, disqualified from participating if they had chronic inflammatory conditions such as systemic lupus erythematosus or rheumatoid arthritis, or had been taking immunosuppressants or anti-inflammatory drugs for a long time. Clinical and Laboratory Protocol: After signing up, every participant underwent a comprehensive clinical and obstetric assessment including measurement of their vital signs as well as Body Mass Index (BMI). Biological samples, peripheral blood (serum) and follicular fluid (FF), were collected at the time of ICSI. All cytokine biochemical assays were conducted in accredited laboratories with international quality assurance. Ethical Approval Study took place Museum Europe Body of the ethical principles laid down in the 1964 Declaration of Helsinki hasMeat been observed. Ethical approval was granted from the institutional research committee and informed verbal consent from all subjects was obtained according to the Iraqi Council of Medical Specializations. Analysis of Statistics. The data were analyzed using IBM SPSS (v29), and graphs were prepared with GraphPad Prism (v10. 5) were applied for the statistical analysis. Continuous variables are presented as mean ± sD. Spearman's rcoefficients were calculated to study the associations between cytokine levels in various compartments and implantation outcomes. P was less than 0.05, indicating statistically significance.

Results

In the current research, maternal and gynecological characteristics were surveyed in fifty patients studied here which indicated that mean age was 35.82±3.93 years old (range; 24 to 43 years) with mean body mass index as of 29.26±3.82 kg/m², representing that patients are generally overweight subjects. The mean FSH levelFSH (IU/L) on day 3 cycle was 7.01±2.27 IU/L, that is in the expected range for women of reproductive age indicating a preserved ovarian reserve. The average counted number of oocytes was 8.58±2.39, indicating an acceptable response to stimulation the ovary; and the mean available count of good-quality embryos was 2.10±0.88 such moderate output of viable embryos (Table 1).

Table 1: Assessment of maternal and gynecological parameters

Variables	Value
Number	50
Age (years)	35.82±3.926
BMI (kg/m^2)	29.26±3.815
FSH on day 3 (IU/L)	7.01±2.27
Number of aspirated oocytes	8.58±2.39
Good quality embryos	2.10±0.88

Data presented as mean ± standard deviation

In the present study, serum cytokine concentrations were determined in a cohort of fifty subjects, and the results demonstrated measurable levels of both Th1- and Th2-associated mediators. The mean concentration of IL-2 was 2.37±1.14 pg/mL, TNF-α was 4.56±2.26 pg/mL, IL-4 was 3.19±1.15 pg/mL, and IL-1β was 2.79±1.25 pg/mL. These findings indicate that TNF-α exhibited the highest circulating level among the cytokines assessed, reflecting a relatively stronger pro- inflammatory Th1 response. In contrast, IL-4 levels confirmed the presence of Th2 activity within the cohort. The overall cytokine profile suggests a balanced but slightly Th1-skewed immune status, with implications for immune regulation in the studied population (Table 2).

Table 2: Concentration of cytokines in serum

Variables	Value
Number	50
IL-2 (pg/mL)	2.37±1.14
TNF-**α** (pg/mL)	4.56±2.26
IL-4 (pg/mL)	3.19±1.15
IL-1**β** (pg/mL)	2.79±1.25

Data presented as mean ± standard deviation

In the present study, cytokine concentrations were measured in follicular fluid samples obtained from fifty subjects, and the results revealed elevated levels of both Th1- and Th2-associated mediators compared with serum values. The mean concentration of IL-2 was 27.30±4.72 pg/mL, TNF-α was 16.49±3.51 pg/mL, IL-1 was 14.51±2.87 pg/mL, and IL-1β was 14.86±4.51 pg/mL. These findings indicate that IL-2 exhibited the highest concentration among the cytokines assessed, reflecting a strong Th1-related proliferative signal within the follicular microenvironment. At the same time, IL-4 and IL-1β levels confirmed the presence of both Th2 and pro-inflammatory activity, as seen in Table 3.

Table 3: Concentration of cytokines in FF

Variables	Value
Number	50
IL-2 (pg/mL)	27.30±4.72
TNF-**α** (pg/mL)	16.49±3.51
IL-4 (pg/mL)	14.51±2.87
IL-1**β** (pg/mL)	14.86±4.51

Data presented as mean ± standard deviation

In the present study, Th1/Th2 cytokine ratios were calculated in both serum and follicular fluid samples from fifty subjects, and the results demonstrated distinct compartmental differences in immune balance. The IL-2/IL-4 ratio was 0.83±0.49 in serum compared with 1.99±0.60 in follicular fluid, indicating a stronger Th1 proliferative signal within the follicular microenvironment. The TNF-α/IL-4 ratio was higher in serum (1.64±1.00) than in follicular fluid (1.18±0.35), reflecting a relatively greater systemic inflammatory tone compared with the local ovarian milieu. Similarly, the IL-1β/IL-4 ratio was 0.99±0.55 in serum and 1.08±0.41 in follicular fluid, suggesting comparable pro-inflammatory activity in both compartments. Overall, these findings indicate that while serum cytokine ratios are skewed toward systemic inflammation, follicular fluid shows a more pronounced Th1 dominance over Th2, which may have implications for follicular development, oocyte maturation, and reproductive outcomes, as shown in Table 4.

Table 4: Th1/Th2 ratios in serum and follicle fluid

Variables	Serum	Follicular fluid
Number	50	50
IL-2/IL-4	0.83±0.49	1.99±0.60
TNF-α/IL-4	1.64±1.00	1.18±0.35
IL-1β/IL-4	0.99±0.55	1.08±0.41

Data presented as mean ± standard deviation

In the present study, correlations among serum inflammatory markers were analyzed, revealing distinct patterns of association between Th1- and Th2-related cytokines. IL-2 showed a strong positive correlation with its ratio to IL-4 (r = 0.825), while exhibiting inverse relationships with TNF-α (r = -0.486) and TNF-α/IL-4 (r = -0.498), suggesting that higher IL-2 levels are linked to reduced systemic inflammatory tone. TNF-α was positively correlated with its ratio to IL-4 (r = 0.778), reflecting its dominant contribution to inflammatory balance, but negatively associated with IL-1β (r = -0.241) and IL-2/IL-4 (r = -0.391). IL-4 demonstrated consistent inverse correlations with all Th1/Th2 ratios, including IL-2/IL-4 (r = - 0.448), TNF-α/IL-4 (r = -0.568), and IL-1β/IL-4 (r = -0.531), underscoring its role as a counter-regulatory cytokine. IL-1β was positively correlated with its ratio to IL- 4 (r = 0.785), indicating that its pro-inflammatory activity is proportionally reflected in Th1/Th2 balance. Collectively, these findings highlight that serum cytokine interactions are characterized by reciprocal regulation between Th1 and Th2 pathways, with IL-2 and TNF-α exerting opposing influences. At the same time, IL- 4 consistently acts as a balancing mediator in the systemic immune environment, as seen in Table 5.

Table 5: Correlation between various serum inflammatory marker

	IL-2	TNF	IL-4	IL1B	IL-2/IL-4	TNF/IL-4	IL1B/IL-4
IL-2	1	-0.486	0.061	0.181	0.825	-0.498	0.151
TNF		1	0.001	-0.241	-0.391	0.778	-0.201
IL-4			1	0.035	-0.448	-0.568	-0.531
IL1B				1	0.139	-0.207	0.785
IL-2/IL-4					1	-0.114	0.444
TNF/IL-4						1	0.174
IL1B/IL-4							1

Values indicate the correlation coefficient.

In the present study, correlations among follicular fluid inflammatory markers were examined, revealing distinct patterns of interaction between Th1- and Th2- associated cytokines. IL-2 demonstrated a positive correlation with IL-1β (r = 0.372), its own ratio to IL-4 (r = 0.588), and IL-1β/IL-4 (r = 0.423), while showing inverse associations with TNF-α (r = -0.594) and TNF-α/IL-4 (r = -0.332), suggesting that higher IL-2 levels are linked to reduced TNF-driven inflammatory activity. TNF-α was strongly correlated with its ratio to IL-4 (r = 0.718), confirming its dominant role in shaping local inflammatory balance, but was negatively associated with IL-2 and IL-4. IL-4 exhibited consistent inverse correlations with all Th1/Th2 ratios, including IL-2/IL-4 (r = -0.856), TNF-α/IL-4 (r = -0.708), and IL- 1β/IL-4 (r = -0.600), underscoring its role as a counter-regulatory cytokine within the follicular microenvironment. IL-1β showed a strong positive correlation with IL- 1β/IL-4 (r = 0.812) and a moderate association with IL-2/IL-4 (r = 0.245), highlighting its contribution to local pro-inflammatory signaling. Collectively, these findings indicate that follicular fluid cytokine interactions are characterized by reciprocal regulation, with IL-2 and IL-1β supporting Th1 dominance, TNF-α reinforcing the inflammatory tone, and IL-4 consistently acting as a balancing mediator in the ovarian milieu (Table 6).

Table 6: Correlation between various follicular fluid inflammatory markers

	IL-2	TNF	IL-4	IL1B	IL-2/IL-4	TNF/IL-4	IL1B/IL-4
IL-2	1	-0.594	-0.199	0.372	0.588	-0.332	0.423
TNF		1	-0.098	-0.116	-0.228	0.718	-0.156
IL-4			1	-0.128	-0.856	-0.708	-0.600
IL1B				1	0.245	-0.059	0.812
IL-2/IL-4					1	0.393	0.680
TNF/IL-4						1	0.235
IL1B/IL-4							1

Discussion

We identified a distinct complex immunomodulatory profile in RIF women with different expression of cytokines at both systemic and local reproductive level. RIF is thought to occur mainly as a consequence of imbalance in the Th1/Th2 cytokine profile rather than due to defective embryo quality or unfavourable uterine anatomy. The average BMI was 29.26 kg/m² and the mean age was 35.8 years in our study population. Elder *et al*. [13, 14] have linked increased mother age and BMI with reduced cumulative live birth rates, hence these are important baseline characteristics. Ovarian reserve in the study group as a whole (mean FSH 7.01 IU/L and adequate number of oocytes) is preserved; however, only a small number of high-grade embryos were obtained confirming the multifactorial nature of RIF [15, 16]. Endometrial receptivity and immunological modulation along with oocyte number probably have an important involvement of success [17]. Our results reveal a marked shift toward a pro-inflammatory Th1-polarized milieu, particularly in the FF. Successful implantation requires a controlled inflammatory response that proceeds to tissue remodeling, eventually giving way to an enduring transition in the local immune milieu from a Th1 to Th2 anti-inflammatory state where both mother and fetus can mutually tolerate each other [18]. This group also presented increased levels of proinflammatory cytokines TNF-α, IL-1β, and IL-2 that have been associated with the reduced trophoblast receptivity and apoptosis [19]. Moderately high amount of TNF-α and IL-1β were beneficial to invasion and vascularization of trophoblast while higher concentrations are detrimental [20, 21]. Follicular IL-2 levels were significantly higher in studies, suggesting a detrimental proliferative stimulus in ovarian micro-environs that could have adverse effects on oocyte maturation prior to pre-pregnancy [22]. Variation between compartments: serum versus

follicular fluid One important observation from our studies is the difference in peripheral and local immune antiretroviral statuses. The IL-2/IL-4 ratio was significantly higher in follicular fluid compared to that in serum, which may indicate a more pronounced degree of the local ovarian milieu being Th1-biased. By contrast, systemic TNF-α levels, even though measurable, were not as predictive and supported recent meta-analysis data that suggest serum cytokines are insufficiently sensitive for reliable RIF diagnosis [23, 24]. The IL-4 usually showed a negative association with Th1/Th2 ratios in both body cavities. A primary Th2 cytokine, IL-4 is a master counter-regulatory agent. Its deficiency in RIF patients leads to a reduced capacity for the body to end cytotoxic responses, thereby preventing the "immunological peace" required by the embryo to grow [25]. Data verify the notion that RIF is associated with perturbation of immune homeostasis. Existence of reciprocal regulation is evident, since IL-4 shows negative correlation with inflammatory ratios and suggests protective role. Clinically, these findings suggest that focusing on cytokine ratios (e.g. TNF-α/IL-4 or IL-2/IL-4) provides a stronger diagnostic tool than measuring individual cytokines alone. With respect to possible individualized immunomodulatory therapy or lifestyle changes targeting these imbalances, this may also remain an encouraging approach toward corrective actions toward ICSI successes in women with recurrent failures.

Conclusion

The results from this study indicate that some women with RIF display compartmentalised and distinct patterns of cytokine dysregulation. The serum picture reflects a pro-inflammatory disparity between systemic compartments and TH cells, via TNF-α. Furthermore, the FF environment consists of increased levels of IL2 (Th1 strong local proliferation). FF also has significantly higher levels of IL-2/IL-4, suggesting local Th1 predominance may be detrimental to oocyte and embryo-endometrium relations. These results suggest that RIF is a consequence of loss of immunologic tolerance. This demonstrates that the evaluation of systemic and local cytokine ratios is required for the identification of at-risk patients.

Conflict of Interest

Not available.

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Not available.

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