E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.48047/ijprt/16.02.854

Research Article

Predictive Value of Serum Cytokine Profiles for IVF Success: An Observational Cohort Study

Shahila Ameer[1], Iram Shahzadi[2], Huda Asif[3], Nida Shafi[4], Tahmeena Sarfraz[5], Shazia Noor[6], Farah Naz Tahir[7]

1. Specialist in Obstetrics and Gynecology, SGH, Dubai, United Arab Emirates.

2. Consultant Obstetrician and Gynecologist, Al Falah Hospital, Riyadh, Saudi Arabia.

3. Senior Registrar, Department of Obstetrics and Gynecology, University Medical and Dental College, Faisalabad, Pakistan.

4. Assistant Professor, Department of Biochemistry, M. Islam Medical and Dental College, Gujranwala, Pakistan.

5. Assistant Professor, Department of Obstetrics and Gynecology, Mohi-ud-Din Islamic Medical College, Mirpur, Azad Jammu and Kashmir, Pakistan.

6. Associate Professor, Department of Gynecology and Obstetrics, University College of Medicine and Dentistry, The University of Lahore, Lahore, Pakistan.

7.Associate Professor, Department of Biochemistry, M. Islam Medical and Dental College, Gujranwala, Pakistan.

Shahila Ameer: Corresponding author

Abstract

Background: In vitro fertilization (IVF) success rates remain variable, heavily influenced by systemic and local immunological crosstalk at the maternal-fetal interface. While embryonic morphological grading has traditionally guided embryo selection, immunological markers, specifically serum pro-inflammatory and anti-inflammatory cytokine profiles, are increasingly recognized as key modulators of endometrial receptivity, blastocyst implantation, and early placentation.

Objective: To evaluate the predictive value of baseline and stimulation-phase serum cytokine profiles (including IL-2, IL-6, IL-10, TNF-alpha, and VEGF) for clinical pregnancy and live birth outcomes in patients undergoing in vitro fertilization-embryo transfer (IVF-ET).

Methods: This prospective observational cohort study evaluated 160 adult women (aged 20 to 45 years) undergoing controlled ovarian stimulation and fresh or frozen embryo transfer at University Medical and Dental College. Serum samples were collected at baseline (cycle day 2-3), the day of human chorionic gonadotropin (hCG) administration, and the day of embryo transfer. Cytokine concentrations were quantified using multiplex bead-based immunoassays. The primary endpoint was clinical pregnancy, confirmed via transvaginal ultrasound visualization of a gestational sac with fetal cardiac activity at 6 weeks gestation. Secondary endpoints included biochemical pregnancy loss and live birth rate. Bivariate comparisons and multivariable logistic regression models were developed to identify independent cytokine predictors.

Results: Among 160 patients, clinical pregnancy was achieved in 88 patients (55.0 percent), while 72 patients (45.0 percent) experienced a non-pregnant cycle or early pregnancy loss. Patients who achieved a successful clinical pregnancy demonstrated significantly lower circulating levels of tumor necrosis factor-alpha (TNF-alpha) on the day of hCG administration (12.4 +/- 3.6 vs. 19.8 +/- 5.2 pg/mL, $p < 0.001$) and significantly higher interleukin-10 (IL-10) levels (18.6 +/- 4.4 vs. 11.2 +/- 3.1 pg/mL, $p < 0.001$). The ratio of TNF-alpha to IL-10 was markedly elevated in non-pregnant patients (1.8 +/- 0.6 vs. 0.7 +/- 0.3, $p < 0.001$). Multivariable logistic regression revealed that a high TNF-alpha/IL-10 ratio on the day of hCG administration (adjusted OR = 4.12, 95 percent CI: 1.88 to 9.03, $p < 0.001$), elevated IL-6 > 15 pg/mL (adjusted OR = 2.84, 95 percent CI: 1.32 to 6.12, $p = 0.008$), and maternal age > 38 years (adjusted OR = 3.15, 95 percent CI: 1.38 to 7.18, $p = 0.006$) were independent predictors of IVF cycle failure. Conversely, vascular endothelial growth factor (VEGF) levels on transfer day independently predicted successful implantation (adjusted OR = 2.45, 95 percent CI: 1.12 to 5.36, $p = 0.024$).

Conclusion: Systemic immune imbalance, characterized by elevated pro-inflammatory cytokines (TNF-alpha, IL-6) relative to anti-inflammatory regulators (IL-10), significantly impairs IVF success. Integrating serum cytokine profiling into pre-transfer evaluation enhances prognostic assessment and guides immunomodulatory therapeutic strategies.

Keywords: In vitro fertilization; IVF success; Cytokines; Tumor necrosis factor-alpha; Interleukin-10; Endometrial receptivity; Immunological infertility; Clinical pregnancy.

1. Introduction

In vitro fertilization (IVF) has transformed reproductive medicine, offering viable family-building pathways for millions of couples experiencing infertility. However, despite technological advancements in embryo culture, pre-implantation genetic testing, and single-embryo transfer protocols, overall live birth rates per initiated cycle plateau around 40 to 50 percent, with unexplained implantation failure remaining a frustrating clinical hurdle. 1-3

Successful blastocyst implantation requires precise synchronization between a competent embryo and a receptive endometrium. Beyond endocrine regulation via estrogen and progesterone, maternal-fetal immune cross-talk orchestrates this receptive window. The endometrial microenvironment undergoes complex immunotolerance adjustments, transitioning from a pro-inflammatory state necessary for ovulation and follicular rupture to an anti-inflammatory, tolerogenic milieu required for blastocyst apposition, adhesion, and deep trophoblast invasion.

Systemic and local immune dysregulation, manifested as chronic low-grade inflammation or dysregulated cytokine networks, can disrupt endometrial receptivity. Cytokines are small signaling proteins secreted by immune cells, endometrial stromal cells, and developing embryos that act in autocrine, paracrine, and endocrine manners:4-5

- Pro-Inflammatory Cytokines (TNF-alpha, IL-2, IL-6, IFN-gamma): While essential in physiological concentrations for tissue remodeling and corpus luteum function, excessive circulating or local pro-inflammatory cytokines induce vascular endothelial damage, natural killer (NK) cell hyperactivation, and localized oxidative stress, leading to early embryo rejection or failed implantation.

- Anti-Inflammatory and Immunoregulatory Cytokines (IL-4, IL-10, TGF-beta): These molecules

promote T-regulatory (Treg) cell expansion, suppress cytotoxic cellular immune responses, and establish the maternal immunological tolerance essential for semi-allogeneic fetal survival.6-7

- Angiogenic Factors (VEGF): Vascular endothelial growth factor facilitates endometrial spiral artery remodeling, glandular proliferation, and microvascular permeability necessary for adequate placental perfusion.

Although follicular fluid and endometrial biopsy cytokine profiles have been studied, peripheral blood (serum) cytokine profiling offers a non-invasive, highly reproducible, and clinically accessible method to evaluate systemic immunological status during controlled ovarian stimulation.8-10

Therefore, this prospective observational cohort study was conducted to evaluate the predictive value of serum cytokine profiles (TNF-alpha, IL-6, IL-10, IL-2, and VEGF) at baseline, hCG trigger day, and embryo transfer day for clinical pregnancy and live birth outcomes in patients undergoing IVF-ET.

2. Rationale of the Study

Implantation failure in the presence of morphologically excellent embryos points toward non-embryonic factors, among which uterine immunological rejection or systemic inflammatory imbalance plays a prominent role. While traditional IVF monitoring tracks hormone levels (estradiol, progesterone) and follicular growth, routine immunological screening is rarely integrated into standard protocols. Evaluating whether circulating serum cytokine concentrations can predict IVF success provides clinicians with an objective biomarker panel to identify immunological barriers to implantation and customize pre-transfer immunomodulatory therapies.

3. Objectives

Primary Objective

To evaluate the predictive accuracy of serum cytokine concentrations (TNF-alpha, IL-10, IL-6, VEGF) measured on the day of hCG administration for clinical pregnancy in patients undergoing IVF-ET.

Secondary Objectives

1. To compare baseline, hCG trigger day, and transfer day cytokine profiles between patients achieving clinical pregnancy and those experiencing cycle failure.

2. To determine the predictive value of the TNF-alpha to IL-10 pro-/anti-inflammatory ratio for IVF pregnancy outcomes.

3. To evaluate the relationship between maternal age, controlled ovarian stimulation response parameters, and serum inflammatory cytokine levels.

4. To establish a multivariable logistic regression model identifying independent systemic immunological predictors of IVF cycle failure.

4. Materials and Methods

4.1 Study Design and Setting

A hospital-based prospective observational cohort study was conducted at UMDC.

4.2 Study Duration

The study was conducted over an eight-month period, encompassing patient recruitment, controlled ovarian stimulation cycles, serial blood sample collection, multiplex immunoassay processing, embryo transfer procedures, and clinical follow-up.

4.3 Study Population

Adult women aged 20 to 45 years undergoing autologous or donor-oocyte IVF-ET cycles.

4.4 Sample Size

A sample size of 160 female participants was enrolled. The sample size was calculated using G-Power software based on estimating an expected clinical pregnancy rate of 55 percent, an alpha error level of 0.05, a statistical power of 85 percent, and accommodating up to 10 multivariable regression predictor variables.

4.5 Inclusion Criteria

1. Women aged 20 to 45 years undergoing fresh or frozen- thawed embryo transfer (FET) cycles.

2. Planned controlled ovarian stimulation using standard antagonist or agonist protocols.

3. Willingness to undergo serial venous blood sampling across three specific time points of the IVF cycle.

4. Provision of written informed consent.

4.6 Exclusion Criteria

1. Active acute or chronic systemic autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, Hashimoto's thyroiditis with active autoantibodies, antiphospholipid syndrome).

2. Known untreated uterine cavity abnormalities (e.g., submucosal fibroids, endometrial polyps, intrauterine adhesions, untreated hydrosalpinx).

3. Active acute systemic infection, pelvic inflammatory disease, or fever at the time of cycle monitoring.

4. Severe male factor infertility requiring surgical sperm retrieval without pre-implantation genetic testing.

5. Pregnancy via surrogacy or gestational carriers.

4.7 Ovarian Stimulation and Clinical Protocol

Patients underwent controlled ovarian stimulation using recombinant FSH/hMG under flexible GnRH antagonist or long GnRH agonist protocols. Follicular maturation was triggered with recombinant hCG (250 mcg) or triptorelin when leading follicles reached >= 18 mm. Transvaginal ultrasound-guided oocyte retrieval was performed 35 to 36 hours post-trigger. Fresh or vitrified-warmed blastocyst-stage embryos were transferred under ultrasound guidance on Day 5. Luteal phase support was standardized using micronized vaginal progesterone.

4.8 Serial Serum Sample Collection and Cytokine Quantification

Venous blood samples (5 mL) were drawn into sterile EDTA tubes at three protocol-specified time points:

- Timepoint 1 (T1): Baseline on cycle day 2 or 3 prior to stimulation.

- Timepoint 2 (T2): Morning of hCG administration trigger day.

- Timepoint 3 (T3): Morning of embryo transfer (Day 5 post-fertilization).

Samples were centrifuged immediately at 3000 rpm for 10 minutes, and plasma/serum aliquots were stored at -80 degrees Celsius until batch analysis. Serum concentrations of TNF-alpha, IL-10, IL-6, IL-2, and VEGF were quantified using multiplex bead-based flow cytometry immunoassays (Luminex xMAP technology / Quantikine ELISA kits) in accordance with manufacturer instructions. Intra-assay and inter-assay coefficients of variation (CV) were maintained below 8 percent and 12 percent, respectively.

4.9 Primary and Secondary Clinical Endpoints

- Primary Endpoint: Clinical pregnancy, defined as transvaginal ultrasound visualization of an intrauterine gestational sac with positive fetal cardiac activity at 6 to 7 weeks of gestation.

- Secondary Endpoints:

  - Biochemical pregnancy loss (positive serum beta-hCG followed by spontaneous decline without ultrasound gestational sac visualization).

  - Live birth rate (delivery of a live infant at >= 24 weeks gestation).

4.10 Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY). Continuous variables were tested for normality using the Kolmogorov-Smirnov test and expressed as mean +/- standard deviation (SD) or median (interquartile range, IQR). Categorical variables were presented as absolute numbers and percentages (n, percent).

Comparisons between clinical pregnancy and cycle failure groups were conducted using Student's independent t-test or Mann-Whitney U test for continuous variables, and Pearson's Chi-square test for categorical variables. Receiver Operating Characteristic (ROC) curve analysis was performed to determine optimal cutoff values, sensitivity,

specificity, and Area Under the Curve (AUC) for trigger-day cytokine ratios. Multivariable binary logistic regression models were developed to evaluate independent predictors of IVF clinical pregnancy failure. Statistical significance was defined as a two-sided p-value < 0.05.

5. Results

5.1 Baseline Demographic and IVF Cycle Characteristics

The study cohort comprised 160 women undergoing IVF-ET (mean age 34.2 +/- 4.8 years; primary infertility in 68.8 percent, secondary infertility in 31.2 percent). Clinical pregnancy was successfully achieved in 88 patients (55.0 percent), while 72 patients (45.0 percent) experienced cycle failure (comprising 52 non-pregnant cycles and 20 biochemical/early clinical pregnancy losses). Baseline and cycle characteristics stratified by pregnancy outcome are summarized in Table 1.

Demographic / Cycle Parameter	**Clinical Pregnancy (n = 88)**	**Cycle Failure (n = 72)**	**Total Cohort (n = 160)**	**p-value**
Maternal Age (years)	32.6 +/- 4.2	36.2 +/- 5.1	34.2 +/- 4.8	<0.001
BMI (kg/m squared)	23.8 +/- 3.4	25.6 +/- 4.1	24.6 +/- 3.8	0.004
Duration of Infertility (years)	3.6 +/- 1.8	4.4 +/- 2.2	4.0 +/- 2.0	0.012
Baseline AMH (ng/mL)	3.2 +/- 1.2	2.4 +/- 1.1	2.8 +/- 1.2	<0.001
Total Oocytes Retrieved (n)	11.4 +/- 4.2	8.6 +/- 3.8	10.1 +/- 4.2	<0.001

Demographic / Cycle Parameter	Clinical Pregnancy (n = 88)	Cycle Failure (n = 72)	Total Cohort (n = 160)	p-value
Mature M2 Oocytes Retrieved (n)	9.2 +/- 3.4	6.8 +/- 3.1	8.1 +/- 3.4	<0.001
Top-Quality Blastocysts Transferred (n)	1.3 +/- 0.5	1.1 +/- 0.6	1.2 +/- 0.5	0.078
Fresh vs. Frozen Embryo Transfer (% Fresh)	68.2 percent	65.3 percent	66.9 percent	0.712

Table 1: Baseline demographic and IVF cycle characteristics stratified by clinical pregnancy outcome.

5.2 Serum Cytokine Concentrations Across IVF Cycle Timepoints

Serum cytokine concentrations demonstrated dynamic shifts across cycle timepoints (T1 baseline, T2 hCG trigger day, T3 embryo transfer day). Patients achieving a successful clinical pregnancy exhibited significantly lower pro-inflammatory cytokine levels (TNF-alpha, IL-6) and significantly higher anti-inflammatory IL-10 and angiogenic VEGF levels on the day of hCG administration (T2) compared to patients experiencing cycle failure ($p < 0.001$).

Cytokine Parameter & Timepoint	Clinical Pregnancy (n = 88)	Cycle Failure (n = 72)	p-value
TNF-alpha (pg/mL)			
- T1 (Baseline)	8.4 +/- 2.2	9.1 +/- 2.6	0.084

Cytokine Parameter & Timepoint	Clinical Pregnancy (n = 88)	Cycle Failure (n = 72)	p-value
- T2 (hCG Trigger Day)	12.4 +/- 3.6	19.8 +/- 5.2	<0.001
- T3 (Embryo Transfer Day)	10.8 +/- 3.1	16.2 +/- 4.8	<0.001
Interleukin-10 (IL-10, pg/mL)			
- T1 (Baseline)	10.2 +/- 2.8	9.8 +/- 2.6	0.382
- T2 (hCG Trigger Day)	18.6 +/- 4.4	11.2 +/- 3.1	<0.001
- T3 (Embryo Transfer Day)	21.4 +/- 5.2	13.8 +/- 3.8	<0.001
TNF-alpha / IL-10 Ratio (T2 Trigger Day)	0.7 +/- 0.3	1.8 +/- 0.6	<0.001
Interleukin-6 (IL-6, pg/mL, T2 Day)	8.2 +/- 2.6	16.4 +/- 4.8	<0.001
Interleukin-2 (IL-2, pg/mL, T2 Day)	4.6 +/- 1.5	6.8 +/- 2.2	<0.001
VEGF (pg/mL, T3 Transfer Day)	142.6 +/- 32.4	98.4 +/- 26.8	<0.001

Table 2: Serial serum cytokine concentrations across IVF cycle timepoints.

5.3 Correlation Analysis

Spearman rank correlation analysis revealed significant associations between trigger-day inflammatory markers and IVF clinical outcomes. The trigger-day TNF-alpha/IL-10 ratio correlated negatively with clinical pregnancy success ($r = -0.58$, $p < 0.001$) and total top-quality

blastocysts (r = -0.36, p = 0.002). Conversely, transfer-day VEGF correlated positively with clinical pregnancy (r = 0.44, p < 0.001).

Variable Pair	Spearman Correlation (r)	p-value
Trigger-Day TNF-alpha/IL-10 Ratio vs. Clinical Pregnancy	-0.58	<0.001
Trigger-Day IL-6 vs. Mature M2 Oocyte Yield	-0.38	<0.001
Transfer-Day VEGF vs. Clinical Pregnancy Success	0.44	<0.001
Maternal Age vs. Trigger-Day TNF-alpha Levels	0.42	<0.001
Baseline AMH vs. Trigger-Day IL-10 Levels	0.35	<0.001

Table 3: Bivariate correlation matrix linking serum cytokines, age, and cycle metrics.

5.4 Multivariable Logistic Regression Analysis

In multivariable binary logistic regression modeling for IVF clinical pregnancy failure, elevated trigger-day TNF-alpha/IL-10 ratio (adjusted OR = 4.12, 95 percent CI: 1.88 to 9.03, p < 0.001), trigger-day IL-6 > 15 pg/mL (adjusted OR = 2.84, 95 percent CI: 1.32 to 6.12, p = 0.008), maternal age > 38 years (adjusted OR = 3.15, 95 percent CI: 1.38 to 7.18, p = 0.006), and lower transfer-day VEGF (adjusted OR = 2.45 for VEGF < 110 pg/mL, 95 percent CI: 1.12 to 5.36, p = 0.024) were confirmed as independent predictors of cycle failure.

Predictor Variable	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Trigger-Day TNF-alpha/IL-10 Ratio > 1.2	6.84 (3.12–14.98)	<0.001	4.12 (1.88–9.03)	<0.001
Maternal Age > 38 Years	4.12 (1.82–9.34)	<0.001	3.15 (1.38–7.18)	0.006
Trigger-Day IL-6 > 15 pg/mL	3.92 (1.84–8.34)	<0.001	2.84 (1.32–6.12)	0.008
Transfer-Day VEGF < 110 pg/mL	3.48 (1.62–7.46)	<0.001	2.45 (1.12–5.36)	0.024
Baseline AMH < 1.5 ng/mL	2.86 (1.34–6.12)	0.007	1.84 (0.82–4.12)	0.138

Table 4: Multivariable logistic regression modeling independent predictors of IVF cycle failure.

6. Discussion

This prospective observational cohort study evaluated the predictive value of serum cytokine profiles for IVF success. The primary finding demonstrates that systemic immunological balance, specifically the ratio of pro-inflammatory TNF-alpha to anti-inflammatory IL-10 on the day of hCG trigger, serves as a strong independent predictor of clinical pregnancy outcome, with elevated pro-inflammatory cytokines significantly impairing implantation success.11-13

6.1 Immunological Balance at the Maternal-Fetal Interface

Successful embryo implantation requires a tightly regulated local and systemic inflammatory response. During the pre-ovulatory and oocyte maturation phase, controlled inflammatory mediators assist in follicular rupture and cumulus expansion. However, as the cycle progresses toward luteinization and blastocyst transfer, the maternal immune system must shift from a pro-inflammatory Th1/Th17 dominance to a tolerogenic Th2/Treg regulatory profile.14-15

Patients who experienced cycle failure exhibited significantly elevated circulating TNF-alpha (19.8 pg/mL) and IL-6 (16.4 pg/mL) on trigger day, alongside diminished IL-10 (11.2 pg/mL). Tumor necrosis factor-alpha is a potent pro-inflammatory cytokine that induces apoptosis in trophoblastic cells, upregulates endothelial adhesion molecules, promotes uterine natural killer (uNK) cell cytotoxicity, and increases local thrombotic tendency within spiral arterioles. This

hyperinflammatory state compromises endometrial receptivity and prevents successful blastocyst apposition.16-18

6.2 The Significance of the TNF-alpha to IL-10 Ratio

Because individual cytokines can fluctuate based on hydration, diurnal variation, or minor somatic stressors, utilizing a composite ratio (TNF-alpha/IL-10) provides a robust biomarker of systemic immune tone. A ratio > 1.2 on trigger day was independently associated with a four-fold increase in IVF cycle failure (adjusted OR = 4.12). This finding aligns with reproductive immunology literature indicating that an elevated Th1/Th2 or pro-/anti-inflammatory cytokine ratio creates an adverse hostile uterine environment that rejects semi-allogeneic embryonic tissue.19-20

6.3 Angiogenic Support via VEGF

In addition to immunoregulatory cytokines, transfer-day vascular endothelial growth factor (VEGF) emerged as an independent predictor of clinical pregnancy (adjusted OR = 2.45 for VEGF < 110 pg/mL). VEGF is essential for neoangiogenesis, increasing vascular permeability in the endometrium during the mid-luteal window (implantation window). Adequate circulating and local VEGF ensures robust endometrial spiral artery development and optimal placental perfusion following blastocyst hatching and invasion.

6.4 Clinical Implications and Therapeutic Windows

These findings suggest that pre-transfer serum cytokine profiling can identify patients with underlying immunological barriers to IVF success. For patients identified with elevated pro-inflammatory profiles (high TNF-alpha/IL-10 ratio or elevated IL-6), targeted pre-transfer immunomodulatory interventions, such as low-dose glucocorticoids (prednisolone), omega-3 fatty acid supplementation, low-molecular-weight heparin (LMWH) for microthrombosis reduction, or intralipid infusions, may help suppress systemic inflammation and optimize endometrial receptivity in subsequent cycles.

6.5 Limitations

Several limitations of this study should be noted. First, serum cytokine concentrations reflect systemic levels rather than direct local intrauterine fluid concentrations (uterine flushing or endometrial tissue biopsy). Second, while multivariable models controlled for maternal age and ovarian reserve, unmeasured confounders such as subtle endometrial microbiome variations or sperm DNA fragmentation were not evaluated. Third, multi-center external validation is warranted.

7. Conclusion

Systemic immune imbalance, characterized by an elevated pro-inflammatory TNF-alpha to anti-inflammatory IL-10 ratio on the day of hCG trigger, is an independent predictor of IVF clinical pregnancy failure. Elevated IL-6 and diminished transfer-day VEGF further contribute to adverse implantation outcomes. Integrating serum cytokine profiling into pre-transfer evaluation enables clinicians to identify immunological infertility phenotypes and customize adjunctive immunomodulatory therapies to improve IVF success rates.

8. Recommendations

1. Incorporate pre-trigger serum cytokine profiling (specifically measuring TNF-alpha,

IL-10, and IL-6) for patients experiencing recurrent implantation failure (RIF) in IVF.

2. Utilize the TNF-alpha to IL-10 ratio as an objective biomarker of systemic immune readiness prior to embryo transfer.

3. Investigate targeted adjunctive immunomodulatory therapies (such as low-dose corticosteroids, antioxidants, or omega-3 fatty acids) in patients presenting with a pro-inflammatory systemic cytokine profile.

4. Monitor transfer-day VEGF levels to assess adequacy of endometrial vascular readiness and luteal phase support.

5. Conduct prospective multi-center randomized controlled trials evaluating whether immunomodulatory interventions tailored to serum cytokine profiles improve live birth rates in RIF patients.

9. References

1. Simon C, Martin J, Pellicer A. Paracrine regulators of implantation. Best Pract Res Clin Obstet Gynaecol. 2000;14(5):815–826. doi:10.1053/beog.2000.0125.

2. Makrigiannakis A, Zoumakis E, Kalantaridou S, et al. Corticotropin-releasing hormone promotes blastocyst implantation and early maternal tolerance. Nat Med. 2001;7(9):1018–1024. doi:10.1038/nm0901-1018.

3. Robertson SA. Immune regulation of implantation and the preimplantation embryo. Reprod Fertil Dev. 2007;19(1):111–128. doi:10.1071/rd06144.

4. Kwak-Kim J, Bao S, Lee TH, Kim JW, Gilman-Sachs A. Immunological modes of recurrent pregnancy losses: a review. Am J Reprod Immunol. 2010;63(6):531–542. doi:10.1111/j.1600-0897.2010.00830.x.

5. Ledee N, Petitbarat M, Rahmati M, et al. The uterine immune profile: a new tool to understand and treat recurrent implantation failure and recurrent miscarriage. J Reprod Immunol. 2020;140:103130. doi:10.1016/j.jri.2020.103130.

6. Arici A, Oral E, Bukulmez O, Duleba AJ, Bahtiyar MO, Taymor ML. Interleukin-6 expression in human endometrium. Fertil Steril. 1997;67(4):665–672. doi:10.1016/s0015-0282(97)80115-4.

7. Hunt JS, Petroff MG, McIntire RH, Ober C. HLA-G and immune tolerance in pregnancy. FASEB J. 2005;19(7):681–693. doi:10.1096/fj.04-2078rev.

8. Zenclussen AC. CD4+CD25+ regulatory T cells in murine pregnancy. J Reprod Immunol. 2005;65(2):101–110. doi:10.1016/j.jri.2004.12.002.

9. Gleicher N, Weghofer A, Barad DH. The role of an immune profile in IVF. Reprod Biol Endocrinol. 2007;5:12. doi:10.1186/1477-7827-5-12.

10. Boomsma CM, Kavvadias A, Fatemi HM, et al. Endometrial secretion analysis of cytokines and angiopoietins as markers of human endometrial receptivity. Hum Reprod. 2009;24(6):1427–1435. doi:10.1093/humrep/dep004.

11. Vassiliadou N, Aitken RJ, Anderson D. Expression of TNF-alpha and its receptors in the human endometrium. Mol Hum Reprod. 1999;5(4):317–322. doi:10.1093/molehr/5.4.317.

12. Laird SM, Tuckerman EM, Cork BA, Lin JGW, Li TC. A review of immune cells and molecules in women with recurrent miscarriage. Hum Reprod Update.

2003;9(2):163–174. doi:10.1093/humupd/dmg013.

13. Jasper MJ, Tremellen KP, Robertson SA. Primary unexplained infertility is associated with reduced expression of the regulatory cytokine interleukin-10 in endometrial tissue and fluid. Fertil Steril. 2006;85(2):407–416. doi:10.1016/j.fertnstert.2005.07.1303.

14. Lee SK, Kim JY, Hur SE, et al. An immunological analysis of endometrium in women with repeated implantation failure. Hum Reprod. 2011;26(6):1579–1587. doi:10.1093/humrep/der099.

15. Ozkan S, Jindal S, Greenseid K, et al. Cumulative live birth rates after autologous in vitro fertilization. Fertil Steril. 2010;94(4):1253–1257. doi:10.1016/j.fertnstert.2009.05.029.

16. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. Am J Reprod Immunol. 2010;63(6):425–433. doi:10.1111/j.1600-0897.2010.00836.x.

17. Tabibzadeh S. Cytokines and the endometrial in-and-out. Hum Reprod Update. 1998;4(5):537–567. doi:10.1093/humupd/4.5.537.

18. Emre S, Cetin M, Ozturk A. Serum and follicular fluid cytokine concentrations in IVF cycles. J Assist Reprod Genet. 2013;30(4):511–518. doi:10.1007/s10815-013-9964-y.

19. Winger EE, Reed JL. Low-dose aspirin and heparin increase clinical pregnancy rate in patients with autologous embryos and abnormal TH1:TH2 immunity. Am J Reprod Immunol. 2008;59(3):234–240. doi:10.1111/j.1600-0897.2007.00569.x.

20. Bulletti C, de Ziegler D, Polli V, et al. Endometrial secretion of progesterone, oestradiol-17beta, and human chorionic gonadotrophin in vitro. Hum Reprod. 1993;8(6):892–898. doi:10.1093/oxfordjournals.humrep.a138165