

Interleukin-6 as A Useful Predictor of Endometriosis-Associated Infertility: A Systematic Review

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Abstract

Endometriosis is a chronic inflammatory disease defined by the presence of endometrial-like tissue outside the uterine cavity. Several authors have reported on the association between changes in inflammatory marker levels and the maintenance or progression of endometriosis and associated infertility. Interleukin-6 (IL-6) is the most studied cytokine in endometriosis and has important functions in reproductive physiology. The aim of this study is to review systematically available evidence about altered IL-6 concentrations in endometriosis-related infertility. This is a systematic review including all studies until December 2022 in which IL-6 in serum, peritoneal fluid, follicular fluid, or endometrial biopsy specimens was measured and that correlated their findings with endometriosis-associated infertility. Fifteen studies were included in the systematic review. There seems to be a correlation between elevated serum and peritoneal fluid IL-6 concentrations and the occurrence of endometriosis-associated infertility. IL-6 may be a potential diagnostic or biomarker tool for the prediction of endometriosis-related infertility. However, the numerous biases affecting the available studies, and challenges in endometriosis research reproducibility must be considered. Future investigations should pay attention to factors that may affect the results, such as the choice of suitable control groups, and carefully consider other pathological conditions affecting the patients, endometriosis stage, and type of lesion.

Keywords: Endometriosis, Infertility, Interleukin-6

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Introduction

Endometriosis is a chronic inflammatory disease defined by the presence of endometrial-like tissue outside the uterine cavity (1, 2). It affects 5 to 10% of reproductive-age women (1, 2), causing low quality of life, depression, and various pain symptoms, including dysmenorrhea, dyspareunia, chronic pelvic pain, dyschezia, and dysuria (3, 4). Many authors have studied the association between this condition and infertility (3, 5). Several theories have been proposed to try to clarify the pathogenetic mechanisms underlying endometriosis. The most common involves pelvic and systemic inflammation stimulating the activation of immune cells and the secretion of cytokines and chemokines. Alterations in concentrations of these inflammatory mediators have been extensively described in women affected by this disease (6). Interleukin-6 (IL-6) is the most studied interleukin in endometriosis (4) and, considering its important functions in reproductive

physiology, altered concentrations in these patients may lead to fertility problems (7).

Given this, this study aims to review systematically the available papers documenting IL-6 levels in serum (S), peritoneal fluid (PF), follicular fluid (FF), or endometrial biopsy specimens (ES) in patients with endometriosis-associated infertility.

Material and Methods

A bibliographic search using Medline, Embase, Cochrane database of Systematic Reviews, and ClinicalTrials.gov to December 2022 was performed querying for randomized controlled trials and prospective studies evaluating IL-6 in patients with endometriosis-associated infertility.

We used the medical subject heading (MeSH) term interleukin-6 (MeSH Unique ID: D015850) in combination

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with: Endometriosis (MeSH Unique ID: D004715); and Infertility (MeSH Unique ID: D007246).

To be included, each study had to measure IL-6 levels in S, PF, FF, or ES samples from endometriosis patients and compare the data with the presence of endometriosis-related infertility. Only papers written in English were included. Commentaries, letters to editors, editorials, and conference abstracts were excluded.

A systematic review was performed to find any statistically significant difference between groups evidenced by the results of chi-squared tests, Student’s t tests, Mann-Whitney U-tests, Kruskal-Wallis tests, and Wilcoxon signed rank tests reported in the selected papers. Differences were expressed as means/median ± standard deviation (SD) and a P<0.05 was considered statistically significant. The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (8) (Fig.1).

One author (G.G.I.) independently screened titles and abstracts of each citation and included those for full-text review. Each retrieved full-text article was independently evaluated for inclusion by another author (F.D.G.). Any potential disagreement was solved by discussion by a third author (F.A.G.).

Results

Our systematic bibliographic research strategy

identified 656 articles. After screening of abstracts and titles and removal of 73 duplicates, 107 full-text records were assessed for eligibility. Finally, 15 studies were included in the systematic review (Fig.1).

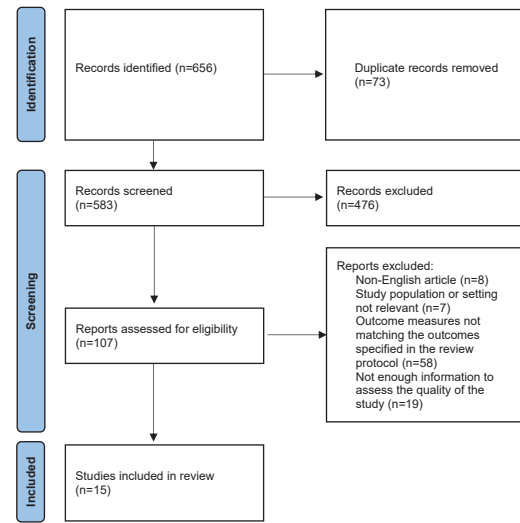


Fig.1: PRISMA flowchart.

IL-6 distribution among endometriosis-associated infertility and infertility without endometriosis, endometriosis without infertility, and non-endometriosis without infertility, respectively are displayed in Tables 1 (9-20), 2 (21, 22) and 3 (15, 23).

Table 1: Interleukin-6 distribution among women with endometriosis-related infertility and without endometriosis

Author, Year	E (n)	C (n)	C type	Type of sample	E IL-6	C IL-6	P value	Additional information
Buyalos et al. (9), 1992	10	10	Tubal infertility	FF		ns	αNA	
	10	10	Antisperm antibody	FF		ns	αNA	
Harada et al. (10), 1997	19	19	Diagnostic laparoscopy for infertility	PF	>	<	<0.05	
Iwabe et al. (11), 2002	53	40	Diagnostic laparoscopy for infertility	PF	>	<		
Jørgensen et al. (12), 2022	42	32	Diagnostic laparoscopy for infertility	ES		ns	0.99	
Kalu et al. (13), 2007	18	22	Diagnostic laparoscopy for infertility	PF	>	<	0.015	
	15	20	Diagnostic laparoscopy for infertility	S		ns	0.946	
Liu et al. (14), 2000	14	11	Diagnostic laparoscopy for infertility	PF	>	<	<0.01	
Moberg et al. (15), 2015	37	23	Diagnostic laparoscopy for infertility	PF	>	<	<0.0001	
Pellicer et al. (16), 1998	8	7	Diagnostic laparoscopy for infertility	S	<	>	<0.05	
	12	11	Assisted reproduction without endometriosis	FF	>	<	<0.05	
	8	7	Diagnostic laparoscopy for infertility	S	>	<	<0.05	Natural cycle
	12	11	Assisted reproduction without endometriosis	S	>	<	<0.05	Before HCG
	12	11	Assisted reproduction without endometriosis	S		ns	αNA	After HCG
Singh et al. (17), 2016	200	140	Tubal infertility	FF	>	<	<0.05	
	200	140	Tubal infertility	S	>	<	<0.05	
Skrzypczak et al. (18), 2005	28	20	Infertile without endometriosis	PF		ns	αNA	
	20	10	Fertile	PF		ns	αNA	
Wu et al. (19), 2017	17	17	Tubal, male, myoma or idiopathic infertility	FF	>	<	0.01	
Wunder et al. (20), 2006	47	279	Assisted reproduction without endometriosis	FF		ns	0.34	

Interleukin-6 (IL-6) levels for exposure groups were compared to those for controls reporting the higher or lower values between the two groups in case of statistical significance. αNA; α error not available, C; Control, E; Endometriosis, ES; Endometrial biopsy specimens, FF; Follicular fluid, ns; Non-significant, PF; Peritoneal fluid, S; Serum, and HCG; Human chorionic gonadotropin.

Table 2: Interleukin-6 distribution among women with endometriosis-related infertility and endometriosis without infertility

Author (References), Year	I (n)	C (n)	C type	Type of fluid	I IL-6	C IL-6	P value
Gica et al. (21), 2020	22	14	Diagnostic laparoscopy for endometriosis	S	>	<	0.00
Moberg et al. (15), 2015	37	28	Diagnostic laparoscopy for endometriosis	PF	>	<	<0.0001

Interleukin-6 (IL-6) levels for exposure groups were compared to those for controls reporting the higher or lower values between the two groups in case of statistical significance. C; Control, I; Infertility, n; Number, PF; Peritoneal fluid, and S; Serum.

Table 3: Interleukin-6 distribution among women with endometriosis-related infertility and non-endometriosis without infertility

Author (References), Year	E (n)	C (n)	C type	Type of fluid	E IL-6	C IL-6	P value
Ueki et al. (22), 1994	7	9	Fertile with myoma or ovarian cyst	PF	>	<	αNA
Wang et al. (23), 2018	55	30	Fertile without endometriosis	PF	>	<	<0.05

Interleukin-6 (IL-6) levels for exposure groups were compared to those for controls reporting the higher or lower values between the two groups in case of statistical significance. αNA; α error not available, C; Control, E; Endometriosis, n; Number, and PF; Peritoneal fluid.

One study reported higher values of S IL-6 in patients with endometriosis-related infertility than controls (17). Other authors compared women with endometriosis and controls, studying some patients with endometriosis in natural cycles to others in stimulated cycles. They concluded S IL-6 was increased in the natural cycles of patients with endometriosis and modulated by ovarian stimulation, showing a significant decrease in stimulated cycles and a significant increase just after human chorionic hormone administration (16). One study found no difference in S IL-6 levels between endometriosis-associated infertility patients and the control group (13).

All of the 6 included studies evaluating IL-6 concentration in PF found higher levels in the endometriosis-associated infertility group than in controls (10, 11, 13-15, 18). Interestingly, Harada et al. (10) found a statistically significant correlation between the American Fertility Society scoring system and the log-transformed IL-6 levels in PF from patients with endometriosis ($r=0.723$, $P<0.01$).

Higher FF IL-6 concentrations were found in three papers in which infertile women with endometriosis were compared to patients without endometriosis (11, 16, 17). Two studies found no difference in FF IL-6 concentrations between endometriosis-associated infertility patients and control groups (9, 20).

The only study evaluating IL-6 levels in ES between infertile patients with endometriosis and a control group failed to show any difference (12). Moreover, higher values of S (21) and PF (15) IL-6 were reported among patients with endometriosis-associated infertility compared with those who underwent diagnostic laparoscopy for endometriosis. Finally, higher values of PF IL-6 were shown among women with endometriosis-associated infertility compared to women without endometriosis or infertility (22, 23).

Discussion

The present systematic review reinforces the hypothesis that there is a correlation between elevated S and PF IL-6 concentrations and endometriosis-related infertility. However, there was no clear evidence of a correlation

between FF and ES IL-6 concentrations and endometriosis-associated infertility.

Nowadays 30 and 50% of patients with endometriosis develop infertility, and about 25 to 50% of infertile women are diagnosed with endometriosis (3, 21).

Several theories have been proposed to explain this pathogenesis and, currently, the chronic inflammation theory seems to be the most plausible (6). Therefore, research into inflammatory factors as a cause of endometriosis is growing. Many authors have stated that inflammatory markers are highly influential in endometriosis (21), and their evaluations represent non-invasive tests for this disease (24).

IL-6 is the most investigated interleukin concerning endometriosis and is an important pleiotropic cytokine for assisting with the diagnosis of this disease. It is secreted in response to injury by various immune cells (10), and participates in several immunological mechanisms (4, 25). Many studies have demonstrated higher S (26), PF (27) and FF (28) IL-6 concentrations in women with endometriosis. IL6 also plays an important role in reproductive mechanisms, such as the production of steroid hormones by the ovaries (10), folliculogenesis, and oocyte maturation by ovarian angiogenesis and enhancement of vascular permeability (7). IL-6 is an activator of macrophages (29), which can amplify angiogenesis and regulate the immune environment of the endometrium (5, 30). In this regard, IL-6 is felt to contribute to infertility often associated with endometriosis (3). IL-6 family proteins, especially leukemia inhibitory factor (LIF), also play an important role in the early stages of embryonic implantation (15, 31) and therefore one hypothesis is that their reduced expression may cause endometriosis-related infertility (15, 32). LIF, its receptor LIFR, and the IL-6 family signaling molecule glycoprotein (gp)130 are predominantly expressed in the mid-secretory endometrium, where embryo implantation occurs (15, 33, 34). The binding of LIF to the high-affinity receptor complex formed by LIFR and gp130 activates the intracellular signaling transduced mainly through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, which can be inhibited

by suppression of cytokine signaling 1 (SOCS1) (15, 35). The latter has been detected in the endometrium in both the proliferative and secretory phases (15, 34). LIF also has other functions in the endometrium, such as regulating the immune environment during implantation, controlling interactions between decidual leukocytes and the embryo, and altering the expression of glycans on the cell surface (36, 37). In mice, the intrauterine administration of anti-LIF has been shown to cause pregnancy blockage (38). In accordance with this, some authors found a lower expression of LIF in the mid-secretory endometrium of infertile women with endometriosis than in fertile women (32, 37), suggesting that altered endometrial expression of LIF, LIFR and gp130 may explain the higher rate of infertility in women suffering from endometriosis (14, 15).

Prima et al. (39) also showed a negative correlation between PF IL-6 levels and the Endometriosis Fertility Index (EFI) score, an indicator to predict pregnancy in patients undergoing surgery that combines patient history factors (age, duration of infertility and previous pregnancy history) and intraoperative findings (surgical factors). Contrary to the discordant studies included in this review relative to differences in FF IL-6 concentrations, Altun et al. (40) reported an increased likelihood of clinical pregnancies in women without endometriosis and with low FF IL-6 concentrations. Therefore, evaluating local and systemic IL-6 levels may be clinically useful to predict endometriosis-related infertility, especially in S and PF.

Factors that may limit the conclusions of this review are that the control groups differed among the included studies and that the results could have been influenced by the sample size, the presence of other inflammatory pathological conditions, and the use of hormones and therapies. The technical sensitivity of the assays used can be an additional confounding factor and it is possible that the IL-6 detected by some researchers may be non-functional or antagonized by anti-inflammatory cytokines or cytokine inhibitors. Another point to note is that IL-6 levels depend on the menstrual cycle phase, the endometriosis stage, and the type of lesion.

Conclusion

Local and systemic IL-6 levels may prove useful in the future as diagnostic or biomarker tools to predict endometriosis-related infertility. However, the numerous biases affecting the available studies, and challenges in endometriosis research reproducibility must be considered. Future investigations should pay attention to the choice of suitable control groups and carefully consider other pathological conditions affecting the patients, the endometriosis stage, and the type of lesion as these may affect the results.

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Authors' Contributions

G.G.I.; Conceptualization, Investigation, Methodology, Writing draft, Project administration, and Validation. F.D.G., F.A.G., F.G., D.B., C.L.; Investigation, Writing review, and Editing. M.P.; Supervision and Writing review. All authors read and approved the manuscript.

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