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The Role of Interleukin in Ectopic Pregnancy: A Systematic Review

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Abstract

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BACKGROUND: Ectopic pregnancy (EP) is the implantation of an embryo outside the eutopic cavity with the most location of EP is in the fallopian tube (FT), known as tubal EP (TEP). The FT of TEP expresses higher levels of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and IL-8.

AIM: The study aimed to look systematically into the current literature and carefully analyze the results to explore the role of IL in EP.

METHODS: Three independent reviewers conducted the literature search through some electronic databases searching for articles fulfilling inclusion and exclusion criteria. The lead author independently assessed the risk of bias of each of the 313 articles identified in database searching, 12 articles met the criteria for this review.

CONCLUSION: IL-6 and IL-8 have diagnostic significance in predicting EP with the cutoff levels of IL-6 and IL-8 which were 26.48 and 40 pg/mL. Further, research is needed for the role of other interleukins in EP.

Introduction

Ectopic pregnancy (EP) is the implantation of an embryo outside the eutopic cavity with the most location of EP is in the fallopian tube (FT), known as tubal EP (TEP). TEP is one of the most causes of maternal morbidity and mortality in the first trimester [1], [2], [3], [4]. The incidence of TEP is approximately 1–2% of all pregnancies in the US and Europe. In developing countries, the incident rate of TEP is higher and the mortality rate is about 10% [1], [5], [6], [7].

Increased levels of pro-inflammatory cytokines, induced by paracrine signaling from the embryo, characterize the endometrium during early implantation and are responsible for the activation of the proteins for embryo receptivity, adhesion, and trophoblast invasion. Interleukin (IL)-11 is obligatory for adequate decidualization and trophoblast invasion [1], [8], [9]. In the FT, pro-inflammatory cytokines caused by tubal damage from infection and/or smoking are believed to cause upregulation of cytokines that promote embryo receptivity, leading to EP. Pelvic inflammatory disease

(PID) is thought to be the main predisposing factor in about 50% of the patients with EP [1], [8], [10]. Cytokines are known to be pivotal in the communication of the FT and the developing embryo. Serum levels of various inflammatory cytokines and chemokines such as IL-1 β , IL-6, IL-8, interferon (IFN)- γ , tumor necrosis factor (TNF)- α , and granulocyte-macrophage colony-stimulating factor are higher in women with EP than in women with normal eutopic pregnancy [1], [2], [8], [11].

The inflammatory responses in the FT induce the activation of immune cells into the local sites [1]. These cells generate persistent tubal tissue damage by increasing the inflammatory responses and guide the embryo to migrate toward the inflammatory site by provoking the production of pro-inflammatory signals, as well as establish an environment conducive to embryo implantation by inducing implantation-associated molecules expression in the tubal epithelium. On the other hand, the inflammation affects tubal motility by reducing cilia beat frequency (CBF) and smooth muscle contraction, leading to embryo retention in FT [1], [12], [13], [14].

The FT tissue of TEP expresses higher levels of pro-inflammatory cytokines such as IL-1, IL-6, and IL-8 [1], [2], [8]. IL-1 plays a role in mediating the interaction between the FT and the implanting embryo, which regulates implantation. IL-1 is also reported to be produced by tubal epithelial cells in response to *Chlamydia trachomatis* infection and causes extensive destruction of the ciliated cells and with TNF- α stimulate IL-8 mRNA (which is a chemoattractant for neutrophils) and IL-6. This effect is reversed by the IL-1 antagonist, which confirms the direct toxic effects of IL-1. IL-8 mediates its effects on binding to two receptors, IL-8RA (CXCR1) and IL-8RB (CXCR2). IL-8 is associated with immune response-mediated tissue damage and chronic inflammatory diseases through the recruitment of leukocytes. IL-6 is a pro-inflammatory and immunoregulatory cytokine and is important for the activation of neutrophils, which mediate oxidative respiratory burst responses and induce the enzymatic degradation of tissue using metalloproteinases, serine proteinases, and their inhibitors. IL-6 also reduces the CBF of tubal epithelium, while anti-IL-6 restores the ciliary activity [1], [2], [8], [11].

Pro-inflammatory cytokines expressed by TP may play a role in diagnosing or predicting EP. The role of IL in EP has been reported and explained in various studies, but there was no systematic review of it. The study aimed to look systematically into the current literature and carefully analyze the results to explore the role of IL in EP.

Review of Literature

This systematic review was conducted by the Cochrane handbook for systematic reviews and is reported using the guideline of preferred reporting items for systematic review and meta-analysis [15], [16]. This systematic review follows five steps of systematic review: Framing questions for a review, identifying relevant work, assessing the quality of studies, summarizing the evidence, and interpreting the findings.

Scope of the review

Inclusion criteria:

1. Publication type:
 - Full-text articles discussing the role of IL in EP
 - Primary studies of every design (case study, case series, cross-sectional, case-control, cohort, and clinical trial).
2. Language of publication: English
3. Time of publication: January 2000–December 2020

4. Methodology: Studies included must explain the role of IL in EP.

Exclusion criteria:

1. Objective and outcome measures are not relevant (are not about the role of IL in EP)
2. Confounding variables are related to outcome in the role of IL in EP (such as had comorbidities or autoimmune disease history).

Literature search

A systematic search strategy was followed in these electronic databases: Cambridge Core, Clinical Key, EBSCO, Emerald Insight, JSTOR, Medline, Nature, ProQuest, PubMed, Science Direct, Scopus, and Springer Link. The search was conducted using the following keywords for title and abstract: (IL OR IL) AND (EP OR). The reference lists of retrieved papers were also examined to avoid missing any published data.

Data collection and analysis

Studies were selected for retrieval after two independent reviewers (AP and JB) had collected titles and abstracts identified in electronic searches. The results of the two reviewers were compared by a third independent reviewer (CH), and any differences of opinion were resolved by discussion. Full papers from potential studies were independently assessed by the investigators (AP, JB, and CP).

All studies selected for this systematic review were screened by two reviewers independently to validate the results (AP and JB). The data from all retrieved studies were presented in a summary table (Table 5) featuring key points of each study. The following data were collected: First author, country, and year; study design, sample, outcome measure, and result.

Quality assessment

The lead author independently assessed the quality assessment and risk of bias of each of the included studies and discussed their assessments with the other two authors to achieve consensus. Quality assessment and risk of bias within studies were assessed using criteria developed by Hawker *et al.* [17], [18]. Ratings were assigned (very poor, poor, fair, good, and not applicable) across nine different categories: Abstract and title; introduction and aim; method and data; sampling; data analysis; ethic and bias; result; generalizability; and implication and usefulness. The risk of bias potentially affecting the cumulative evidence across studies was determined by examining study methods, ethics committee approvals, study funding, and conflicts of interest [17], [18]. Newcastle–Ottawa scale adapted for

the cross-sectional study was also used to assess cross-sectional studies; interpretation of total score was: 9–10 points were considered in very good studies, 7–8 were considered in good studies, 5–6 points were considered in satisfactory studies, and 0–4 were considered in unsatisfactory studies [19], [20]. Newcastle–Ottawa scale for the case–control study was also used to assess case–control study; interpretation of total score was ≥ 7 points that were included in good studies, 5–6 points were included in fair studies, and < 5 points were included in poor studies. Newcastle–Ottawa scale for the cohort study was also used to assess prospective study; interpretation of total score was ≥ 7 points that were included in good studies, 5–6 points were included in fair studies, and < 5 points were included in poor studies [19], [21], [22], [23].

Results

Selection of articles for review

Figure 1 summarizes the identified, screened, and included articles for review. Initially, 305 peer-reviewed articles were identified from electronic databases and an additional eight articles were identified through other sources (search engine). After removing duplicates, 177 articles remained for the title and abstract screening. Articles that did not meet the inclusion and exclusion criteria were not further screened. Seventeen articles were screened for eligibility of which 12 articles met all the inclusion criteria.

Assessment of study validity (quality assessment and risk of bias)

All eligible studies were associated with the role of IL in EP. Table 1 provided quality assessment and risk of bias by Hawker *et al.* and all of the components are fair and good. Table 2 provided quality scores for cross-sectional study and all of the studies got 6–7 points that were considered satisfactory and good studies. Table 3 provided quality scores for the case–control study and all of the studies got 6–8 points that were considered in good and fair studies. Table 4 provided quality scores

for cohort study and all of the studies got 7 points that were considered in good studies.

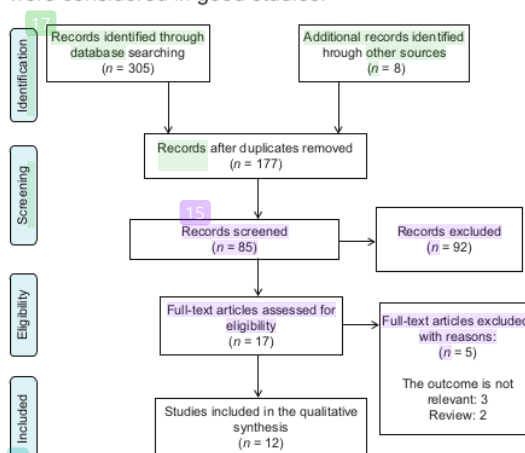


Figure 1: Preferred reporting items for systematic reviews and meta-analysis [16]

Study characteristic

Study characteristics for the included studies are shown in Table 5. The majority of the studies (7 of 12) were case–control studies. The studies reported the role of IL-1, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-11, IL-15, IL-17, and IL-22 in EP.

Discussion

The role of IL in EP

ILs are a group of cytokines with immunomodulatory function and regulate inflammatory responses in the human body and these cytokines also play a part in human conception. T-helper type 1 (Th1) cells produce various cytokines (such as IL-2, IFN, and TNF- α) that are involved in cell-mediated rejection processes while T-helper type 2 (Th2) cells mainly produce IL-4, IL-6, and IL-10; which inhibit cell-mediated immunity and enhance humoral immune responses, thereby promoting implantation [34]. IL-1,

Table 1: Quality assessment and risk of bias by Hawker *et al.* [18]

S. No.	First author, year	Abstract and title	Introduction and aim	Method and data	Sampling	Data analysis	Ethic and bias	Finding	Generalisability	Implication and usefulness
1.	Ashshi, 2016 [24]	Fair	Good	Good	Good	Good	Good	Good	Good	Good
2.	Balasuubramaniam, 2012 [8]	Good	Good	Good	Good	Fair	Good	Good	Good	Good
3.	Daponte <i>et al.</i> , 2013 [25]	Good	Good	Good	Good	Fair	Good	Good	Good	Good
4.	lyibozkurt <i>et al.</i> , 2010 [26]	Good	Fair	Fair	Fair	Good	Good	Good	Good	Good
5.	Huang <i>et al.</i> , 2005 [27]	Good	Good	Good	Good	Fair	Good	Good	Good	Good
6.	Lekovich <i>et al.</i> , 2015 [28]	Good	Good	Good	Fair	Good	Good	Good	Good	Good
7.	Lombardelli <i>et al.</i> , 2016 [29]	Good	Good	Good	Fair	Good	Good	Good	Good	Good
8.	Ma <i>et al.</i> , 2020 [30]	Good	Good	Fair	Fair	Good	Fair	Good	Good	Good
9.	Rajendiran <i>et al.</i> , 2016 [31]	Good	Good	Good	Fair	Good	Fair	Good	Good	Good
10.	Rango <i>et al.</i> , 2004 [32]	Fair	Good	Fair	Fair	Good	Good	Good	Good	Good
11.	Shao <i>et al.</i> , 2016 [33]	Good	Fair	Fair	Fair	Good	Good	Good	Good	Good
12.	Soriano <i>et al.</i> , 2003 [34]	Good	Good	Good	Fair	Good	Good	Good	Good	Good

secreted by cytotrophoblasts during first-trimester pregnancy, has a role in trophoblast invasion and tissue repair. IL-6, produced by decidual cell populations, and is a potent pro-angiogenic cytokine that stimulates the proliferation of endothelial cells *in vitro*, major regulators of endometrial receptivity and blastocyst implantation, and regulates the behavior of the female reproductive tract and gestational tissues. IL-8 is involved in the normal implantation process and is upregulated in the endometrium during decidualization and early pregnancy. IL-10, generated by cytotrophoblasts and decidual T cells, protect the fetal-placental interface by reducing the cytokine secretions of Th1 cells and macrophages [8], [24], [35].

Table 2: Newcastle–Ottawa scale adapted for cross-sectional study [20]

S. No.	First author, country	Selection				Comparability		Outcome		Total
		1	2	3	4	1	2	1	2	
1.	Lombardelli et al., 2016 [29]	*	*	**	*			*	*	7
2.	Shao et al., 2016 [33]	*	*	**	*			*	*	6

Notes for Table 2: Maximum points for selection number 4, comparability, and outcome number 1 were 2. Selection: (1) Representativeness of the sample, (2) sample size, (3) non-respondents, (4) risk factor measurement tool. Outcome: (1) Assessment of the outcome, (2) statistical test.

The role of IL-1 was explained in three studies [27], [28], [33]. More specifically related to mechanisms of implantation, the IL-1 system may be one of the major candidates for these molecular regulators in local intercellular interactions during embryonic implantation. The IL-1 system is a family of polypeptides composed of two agonists, IL-1 α and IL-1 β , and an inhibitor, IL-1 receptor antagonist (IL-1ra), as well as two receptors (type 1 and type 2).

Table 3: Newcastle–Ottawa scale (case–control study)

S. No.	First author, year	Selection				Comparability	Exposure		Total
		1	2	3	4		1	2	
1.	Ashshi, 2016 [24]	*	*	*	*		*	*	7
2.	Balasubramaniam, 2012 [8]	*	*	*	*		*	*	7
3.	Daponte et al., 2013 [25]	*	*	*	*		*	*	7
4.	Iyibozkurt et al., 2010 [26]	*	*	*	*		*	*	6
5.	Huang et al., 2005 [27]	*	*	*	*		*	*	7
6.	Ma et al., 2020 [30]	*	*	*	*		*	*	8
7.	Rajendiran et al., 2016 [31]	*	*	*	*		*	*	7

Notes for Table 3: The maximum point for comparability was 2. Selection: (1) Case definition, (2) representativeness, (3) selection of controls, (4) definition of controls. Exposure: (1) Ascertainment of exposure, (2) method.

Both IL-1 agonist and receptor antagonists are recognized by IL-1 receptor type 1 and trigger signal responses in target cells. IL-1ra is a specific inhibitor to IL-1 agonist, which competes with IL-1 for the binding site of IL-1 receptor type 1 and blocks signal transduction. IL-1 is also expressed in human endometrium and has been shown to play an integral role in local cellular interactions during implantation [28], [36], [37]. According to Huang *et al.*, an earlier upregulation of IL-1 receptor type 1 and downregulation IL-1 expression in human FTs was observed in TEP [27]. This suggests that the sequential cytokines expression maternally

Table 4: Newcastle–Ottawa scale (cohort study)

S. No.	First author, year	Selection				Comparability	Outcome			Total
		1	2	3	4		1	2	3	
1.	Lekovich et al., 2015 [28]	*	*	*	*		*	*	*	7
2.	Soriano et al., 2003 [34]	*	*	*	*		*	*	*	7

Notes for Table 3: Maximum point for comparability was 2. Selection: (1) Representativeness, (2) selection of non-exposed, (3) ascertainment of exposure, (4) demonstration that outcome was not present at the beginning. Outcome: (1) Assessment of the outcome, (2) follow-up long enough, (3) adequacy of follow-up.

direct human embryonic implantation independent of the location, either tubal or uterine, of the embryo. In addition, the ratio of IL-1 to IL-1ra in human endometrial stromal cells was statistically significantly increased in the presence of IL-1. It is interesting that, in the present study, a lower ratio of IL-1 agonist to IL-1ra was demonstrated in human FT with EP compared with normal controls, suggesting an inappropriate ratio of IL-1 agonist to antagonist may play a role in EP. IL-1 expression may play a crucial role in embryo-maternal interaction during the process of early embryonic implantation as embryos transverse the tube. This expression and an inappropriate ratio of agonist and receptor antagonist in FT may probably indicate an earlier dialogue between the early developing embryo and FT epithelium, predisposing the embryo to earlier implantation in the FT [27], [28].

IL-6 level had been reported to be significantly increased in EP in two studies, reported to have a diagnostic value for EP in two studies, and IL-6 genes expression level was increased in EP in one study [8], [24], [30], [31], [34]. The cutoff level of IL-6 level was 26.48 pg/ml with moderate accuracy (with a sensitivity of 53.57% and specificity of 80%). IL-6 level was also increased in women with intrauterine abortion, but the increasing level of IL-6 in EP was significantly higher than in intrauterine abortion patients [31]. Balasubramaniam *et al.* reported about the expression of IL-6 was significantly increased near the implantation site in FT with EP as compared with normal. In addition, there were significant differences in the level of expression of IL-6 and IL-8 in TEP near and away from the implantation site. This reflected that implantation affects the expression of IL-6 and IL-8 in the tubal epithelium locally and not throughout the FT. Balasubramaniam *et al.* were also demonstrated that IL-6, IL-8, and CXCR1 were upregulated in the epithelium of FTs with gestation and particularly near the implantation site, while IL-6Ra and CXCR2 are downregulated from the implantation site [8].

IL-8 level had been reported to be significantly increased in EP in two studies, reported to have a diagnostic value for EP in one study, and IL-8 genes expression level was increased in EP in one study [8], [30], [33], [34]. The cutoff level of IL-8 level was >40 pg/mL with a sensitivity of 82.4%, a specificity of 81.8%, and positive and negative predictive values (NPV) of 58.3% and 93.8% in combination, IL-8 and IL-6 cut points of 40 pg/mL and 16 pg/mL, predicted EP with a sensitivity of 70.6%, a specificity of 94.5%, a positive predictive value (PPV) of 80.0%, and a NPV of 91.2% [34]. Women with EP and free fluid in the pouch of Douglas had higher serum IL-8 levels than did other women with EP and this condition is related to cytokine hypersecretion by peritoneal macrophages involved in the local inflammatory process. Even after the exclusion of women with fluid in the pouch of Douglas, the EP group had higher serum IL-8 levels

Table 5: Study characteristic

S. No.	First author, country, year	Study design	Sample (n)	Outcome measure	Result
1.	Ashshi, Indian, 2016 [24]	Case-control	EP: 96 (22 positive CMV) Non-EP: 61 (5 positive CMV)	The role of IL-6 and its signaling molecules in CMV infection in EP	<ul style="list-style-type: none"> CMV-positive EP group showed the highest significant increase of the studied molecules by all techniques The expression in the non-infected EP group was significantly higher for IL-6 (p:0.004), IL-6Rα (p: 0.007), gp130 (p:0.006), and STAT3 (p:0.007) compared with control group The expression levels of IL-6, IL-8, and CXCR1 were significantly upregulated in the EP group (p<0.05) The expression levels of CXCR2 and IL-6Rα were not changed in comparison with the normal group (p>0.05) EP group had elevated significant IL-15 levels compared to other groups with a cutoff of 16 pg/mL and a negative predictive value of 99% with a sensitivity for diagnosing an EP of 92% (p<0.05) EP group had a lower level of anti-C1q Ab level but not statistically significant (p>0.05)
2.	Balasubramaniam, UK, 2012 [8]	Case-control	EP: 50 Non-EP: 25	The expression of IL-8, CXCR1, CXCR2, IL-6, and IL-6R α in EP	<ul style="list-style-type: none"> LIF levels increased significantly in the EP group (p: 0.002). Ranges of LIF were 15–300 and 70–1200 ng/ml for the IUP and EP groups There were no significant differences between IL-10 and IL-11 between groups (p>0.005) IL-1 mRNA expression was decreased, and IL-1RA and IL-1 receptor type 1 were increased in the EP group IL-1 receptor type 1 mRNA was statistically significantly increased in paraectopic tubes (p<0.05) There was a lower ratio of IL-1 to IL-1RA at mRNA in EP The mean IL-1b levels were higher in the EP group at cycle days 24 and 28 (127.1 pg/mL and 166.9 pg/mL, respectively) than other IVF outcome groups (15.8–55.3 pg/mL and 14.8–75.5 pg/mL, respectively) The IL-1b-to-IL-1RA ratio was 0.18 in the EP group versus 0.01–0.09 in the other groups at cycle day 24
3.	Daponte <i>et al.</i> , Greece, 2013 ²³	Case-control	EP: 30 MA: 30 IUP: 33	Diagnostic significance of IL-15 and anti-C1q Ab in EP	<ul style="list-style-type: none"> LIF levels increased significantly in the EP group (p: 0.002). Ranges of LIF were 15–300 and 70–1200 ng/ml for the IUP and EP groups There were no significant differences between IL-10 and IL-11 between groups (p>0.005) IL-1 mRNA expression was decreased, and IL-1RA and IL-1 receptor type 1 were increased in the EP group IL-1 receptor type 1 mRNA was statistically significantly increased in paraectopic tubes (p<0.05) There was a lower ratio of IL-1 to IL-1RA at mRNA in EP The mean IL-1b levels were higher in the EP group at cycle days 24 and 28 (127.1 pg/mL and 166.9 pg/mL, respectively) than other IVF outcome groups (15.8–55.3 pg/mL and 14.8–75.5 pg/mL, respectively) The IL-1b-to-IL-1RA ratio was 0.18 in the EP group versus 0.01–0.09 in the other groups at cycle day 24
4.	Ilybozkurt <i>et al.</i> , Turkey, 2010 [26]	Case-control	EP: 17 IUP: 19	The role of LIF, IL-10, and IL-11 in EP	<ul style="list-style-type: none"> LIF levels increased significantly in the EP group (p: 0.002). Ranges of LIF were 15–300 and 70–1200 ng/ml for the IUP and EP groups There were no significant differences between IL-10 and IL-11 between groups (p>0.005) IL-1 mRNA expression was decreased, and IL-1RA and IL-1 receptor type 1 were increased in the EP group IL-1 receptor type 1 mRNA was statistically significantly increased in paraectopic tubes (p<0.05) There was a lower ratio of IL-1 to IL-1RA at mRNA in EP The mean IL-1b levels were higher in the EP group at cycle days 24 and 28 (127.1 pg/mL and 166.9 pg/mL, respectively) than other IVF outcome groups (15.8–55.3 pg/mL and 14.8–75.5 pg/mL, respectively) The IL-1b-to-IL-1RA ratio was 0.18 in the EP group versus 0.01–0.09 in the other groups at cycle day 24
5.	Huang <i>et al.</i> , Taiwan, 2005 [27]	Case-control	EP: 5 Non-EP: 4	IL-1 system mRNA in EP	<ul style="list-style-type: none"> LIF levels increased significantly in the EP group (p: 0.002). Ranges of LIF were 15–300 and 70–1200 ng/ml for the IUP and EP groups There were no significant differences between IL-10 and IL-11 between groups (p>0.005) IL-1 mRNA expression was decreased, and IL-1RA and IL-1 receptor type 1 were increased in the EP group IL-1 receptor type 1 mRNA was statistically significantly increased in paraectopic tubes (p<0.05) There was a lower ratio of IL-1 to IL-1RA at mRNA in EP The mean IL-1b levels were higher in the EP group at cycle days 24 and 28 (127.1 pg/mL and 166.9 pg/mL, respectively) than other IVF outcome groups (15.8–55.3 pg/mL and 14.8–75.5 pg/mL, respectively) The IL-1b-to-IL-1RA ratio was 0.18 in the EP group versus 0.01–0.09 in the other groups at cycle day 24
6.	Lekovich <i>et al.</i> , USA, 2015 [28]	Retrospective cohort	307 with the following IVF outcomes: <ul style="list-style-type: none"> Live births: 103 Negative pregnancy tests: 80 Biochemical pregnancies: 52 EP: 47 Miscarriages: 25 	The role of IL-1b and IL-1b-to-IL-1RA ratio in EP (vs. cycle outcome)	<ul style="list-style-type: none"> LIF levels increased significantly in the EP group (p: 0.002). Ranges of LIF were 15–300 and 70–1200 ng/ml for the IUP and EP groups There were no significant differences between IL-10 and IL-11 between groups (p>0.005) IL-1 mRNA expression was decreased, and IL-1RA and IL-1 receptor type 1 were increased in the EP group IL-1 receptor type 1 mRNA was statistically significantly increased in paraectopic tubes (p<0.05) There was a lower ratio of IL-1 to IL-1RA at mRNA in EP The mean IL-1b levels were higher in the EP group at cycle days 24 and 28 (127.1 pg/mL and 166.9 pg/mL, respectively) than other IVF outcome groups (15.8–55.3 pg/mL and 14.8–75.5 pg/mL, respectively) The IL-1b-to-IL-1RA ratio was 0.18 in the EP group versus 0.01–0.09 in the other groups at cycle day 24
7.	Lombardelli <i>et al.</i> , Italy, 2016 [29]	Cross-sectional	EP: 6 Non-EP: 36	The role of IL-4, IL-17, and IL-22 in EP	<ul style="list-style-type: none"> LIF levels increased significantly in the EP group (p: 0.002). Ranges of LIF were 15–300 and 70–1200 ng/ml for the IUP and EP groups There were no significant differences between IL-10 and IL-11 between groups (p>0.005) IL-1 mRNA expression was decreased, and IL-1RA and IL-1 receptor type 1 were increased in the EP group IL-1 receptor type 1 mRNA was statistically significantly increased in paraectopic tubes (p<0.05) There was a lower ratio of IL-1 to IL-1RA at mRNA in EP The mean IL-1b levels were higher in the EP group at cycle days 24 and 28 (127.1 pg/mL and 166.9 pg/mL, respectively) than other IVF outcome groups (15.8–55.3 pg/mL and 14.8–75.5 pg/mL, respectively) The IL-1b-to-IL-1RA ratio was 0.18 in the EP group versus 0.01–0.09 in the other groups at cycle day 24
8.	Ma <i>et al.</i> , China, 2020 [30]	Case-control	TEP: 120 Non-TEP: 30	The role of cytokine genes in EP	<ul style="list-style-type: none"> LIF levels increased significantly in the EP group (p: 0.002). Ranges of LIF were 15–300 and 70–1200 ng/ml for the IUP and EP groups There were no significant differences between IL-10 and IL-11 between groups (p>0.005) IL-1 mRNA expression was decreased, and IL-1RA and IL-1 receptor type 1 were increased in the EP group IL-1 receptor type 1 mRNA was statistically significantly increased in paraectopic tubes (p<0.05) There was a lower ratio of IL-1 to IL-1RA at mRNA in EP The mean IL-1b levels were higher in the EP group at cycle days 24 and 28 (127.1 pg/mL and 166.9 pg/mL, respectively) than other IVF outcome groups (15.8–55.3 pg/mL and 14.8–75.5 pg/mL, respectively) The IL-1b-to-IL-1RA ratio was 0.18 in the EP group versus 0.01–0.09 in the other groups at cycle day 24
9.	Rajendiran <i>et al.</i> , India, 2016 [31]	Case-control	TEP: 28 Miscarriage: 31 IUP: 29	Diagnostic significance of IL-6 and IL-8 in TEP	<ul style="list-style-type: none"> LIF levels increased significantly in the EP group (p: 0.002). Ranges of LIF were 15–300 and 70–1200 ng/ml for the IUP and EP groups There were no significant differences between IL-10 and IL-11 between groups (p>0.005) IL-1 mRNA expression was decreased, and IL-1RA and IL-1 receptor type 1 were increased in the EP group IL-1 receptor type 1 mRNA was statistically significantly increased in paraectopic tubes (p<0.05) There was a lower ratio of IL-1 to IL-1RA at mRNA in EP The mean IL-1b levels were higher in the EP group at cycle days 24 and 28 (127.1 pg/mL and 166.9 pg/mL, respectively) than other IVF outcome groups (15.8–55.3 pg/mL and 14.8–75.5 pg/mL, respectively) The IL-1b-to-IL-1RA ratio was 0.18 in the EP group versus 0.01–0.09 in the other groups at cycle day 24
10.	Rango <i>et al.</i> , Germany, 2004 [32]	Descriptive	Non-EP: 84 EP: 8	The role of IL-11 in EP	<ul style="list-style-type: none"> LIF levels increased significantly in the EP group (p: 0.002). Ranges of LIF were 15–300 and 70–1200 ng/ml for the IUP and EP groups There were no significant differences between IL-10 and IL-11 between groups (p>0.005) IL-1 mRNA expression was decreased, and IL-1RA and IL-1 receptor type 1 were increased in the EP group IL-1 receptor type 1 mRNA was statistically significantly increased in paraectopic tubes (p<0.05) There was a lower ratio of IL-1 to IL-1RA at mRNA in EP The mean IL-1b levels were higher in the EP group at cycle days 24 and 28 (127.1 pg/mL and 166.9 pg/mL, respectively) than other IVF outcome groups (15.8–55.3 pg/mL and 14.8–75.5 pg/mL, respectively) The IL-1b-to-IL-1RA ratio was 0.18 in the EP group versus 0.01–0.09 in the other groups at cycle day 24
11.	Shao <i>et al.</i> , China, 2016 [33]	Cross-sectional	TEP: 36 IUP: 50 Non-pregnant: 139	The role of inflammatory cytokines in Chlamydia trachomatis infection in TEP	<ul style="list-style-type: none"> LIF levels increased significantly in the EP group (p: 0.002). Ranges of LIF were 15–300 and 70–1200 ng/ml for the IUP and EP groups There were no significant differences between IL-10 and IL-11 between groups (p>0.005) IL-1 mRNA expression was decreased, and IL-1RA and IL-1 receptor type 1 were increased in the EP group IL-1 receptor type 1 mRNA was statistically significantly increased in paraectopic tubes (p<0.05) There was a lower ratio of IL-1 to IL-1RA at mRNA in EP The mean IL-1b levels were higher in the EP group at cycle days 24 and 28 (127.1 pg/mL and 166.9 pg/mL, respectively) than other IVF outcome groups (15.8–55.3 pg/mL and 14.8–75.5 pg/mL, respectively) The IL-1b-to-IL-1RA ratio was 0.18 in the EP group versus 0.01–0.09 in the other groups at cycle day 24
12.	Soriano <i>et al.</i> , France, 2003 [34]	Cohort	EP: 17 Miscarriages: 22 IUP: 33	Diagnostic significance of IL-2R, IL-6, IL-8, and TNF- α in EP	<ul style="list-style-type: none"> LIF levels increased significantly in the EP group (p: 0.002). Ranges of LIF were 15–300 and 70–1200 ng/ml for the IUP and EP groups There were no significant differences between IL-10 and IL-11 between groups (p>0.005) IL-1 mRNA expression was decreased, and IL-1RA and IL-1 receptor type 1 were increased in the EP group IL-1 receptor type 1 mRNA was statistically significantly increased in paraectopic tubes (p<0.05) There was a lower ratio of IL-1 to IL-1RA at mRNA in EP The mean IL-1b levels were higher in the EP group at cycle days 24 and 28 (127.1 pg/mL and 166.9 pg/mL, respectively) than other IVF outcome groups (15.8–55.3 pg/mL and 14.8–75.5 pg/mL, respectively) The IL-1b-to-IL-1RA ratio was 0.18 in the EP group versus 0.01–0.09 in the other groups at cycle day 24

Ab: Antibody, C.: Chlamydia, CXCR: C-X-C chemokine receptor, EP: Ectopic pregnancy, gp: Glycoprotein, IFN: Interferon, IL: Interleukin, IUP: Intrauterine pregnancy, LIF: Leukemia inhibitory factor, MA: Missed abortion, NPV: Negative predictive value, PPV: Positive predictive value, R: Receptor, RA: Receptor antagonist, ROC: Receiving operating characteristic, STAT: Signal transducer and activator of transcription, TEP: Tubal ectopic pregnancy, TNF: Tumor necrosis factor.

than did those in the normal pregnancy and miscarriage groups [34]. The upregulation of IL-8 in TEP may create a receptive endometrial-like environment that encourages embryo implantation [8]. Rajendiran *et al.* reported about IL-8 level was decreased significantly in EP [31]. The probable explanation for this could be that IL-6 also has an anti-inflammatory effect in the early

phase of inflammation by decreasing the level of other pro-inflammatory cytokines like IL-8. Thus, in early inflammation, it can be expected that the levels of IL-6 be high but IL-8 to below. The decrease in IL-8 levels could also be due to differential expression of IL-8 due to tubal and peritoneal inflammation. Therefore, this underlying inflammation due to PID could have

further suppressed the IL-8 levels [31]. The difference in demography variance and sample size is likely contributed to the difference in the result.

EP group had elevated significant IL-15 levels compared to other groups with a cutoff of 16 pg/mL and a NPV of 99% with a sensitivity for diagnosing an EP of 92%. IL-15 expression is upregulated in placental tissue of disturbed human first-trimester pregnancy and trophoblast cells were detected as the main source for IL-15 in women with recurrent miscarriages. The trophoblast invasion in EP is different from normal pregnancies and this may explain differences related to IL-15 tissue expression and circulating levels of this cytokine. Trophoblast infiltrating the tube or the peripheral NK cells can be the source of the increased levels of IL-15 in EPs compared to IUPs, but this needs to be explored further. This is by the finding of increased IL-15 levels in EP which due to its protective effect and angiogenic role might explain the survival of trophoblasts while penetrating the tubal wall [25]. There was also a statistically increase of immunoregulatory cytokine levels of IL-4, IL-17, and IL-22 at the implantation site than the levels of these cytokines distant from the implantation site ($p < 0.05$) [29]. IL-4, IL-17, and IL-22 are known to increase in pregnancy [29], [35]. IL-17 also accumulates in both the decidua and the peripheral blood in patients with recurrent pregnancy loss [35].

A decrease in IL-10 level was observed in the TEP group with positive *C. trachomatis* infection compared to other groups with *C. trachomatis* infection [33]. In tubal abortions, IL-11 expression was reduced in EP abortion in comparison to other groups. IL-10 and IL-11 were known to increase the occurrence of implantation and pregnancy [32]. There was no statistically significant difference in IL-2R level ($p > 0.05$) [34]. There were no significant differences in IL-4, IL-6, IL-7, and IL-8 levels among *C. trachomatis*-positive or -negative women under pregnant and non-pregnant conditions ($p > 0.05$) [33]. There were no significant differences of IL-10 and IL-11 between groups of EP and normal pregnancy [26]. The difference of demography variance and minimum sample number may be contributed in this insignificant and the difference in this result.

Strength and limitation of the study

The present systematic review involved studies that reported 12 studies related to the role of IL in EP. Most of the studies were case-control studies (7 of 12) and reported about ten ILs.

The limitation of the study was the variance of the demography, confounding variable in each study (there were confounding variables that cannot be controlled in human subjects like the severity of the disease and care-seeking behavior), and also the limitation of study type (there was no experimental study and majority of the studies were retrospective

studies).

Future implication

The current systematic review is expected to be a scientific reading, material, and consideration to clinicians related to the role of IL in EP. Further research is needed for the cutoff value and genetic study (and genetic variance) in each of IL and optimization of the IL in early detection of EP so can minimize the complication of EP.

Conclusion

IL-6 and IL-8 have diagnostic significance in predicting EP with the cutoff levels of IL-6 and IL-8 which were 26.48 and 40 pg/mL. Further research is needed for the role of other ILs in EP.

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