INPLASY

Interleukin 6 for the prediction of Chorioamnionitis. A systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 September 2025 and was last updated on 27 September 2025.

INTRODUCTION

Review question / Objective Objective: To systematically review and meta-analyze the role of interleukin-6 (IL-6) in the prediction of histological chorioamnionitis (HCA), across various body fluids including amniotic fluid (AF), maternal plasma, and cervicovaginal fluid (CVF), and among distinct subgroups such as preterm premature rupture of membranes (PPROM) and preterm labor (PTL).

PICO/PECO Framework
- Population: Pregnant women with suspected chorioamnionitis, particularly those with PPROM or PTL
- Index Test: IL-6 levels measured in amniotic fluid, plasma, or cervicovaginal fluid
- Comparator: Histopathological examination of the placenta (gold standard)
- Outcome: Diagnostic accuracy parameters (sensitivity, specificity, diagnostic odds ratio, likelihood ratios, area under the ROC curve).

Rationale Interleukin-6 is a widely recognized inflammatory cytokine that has shown strong diagnostic performance for HCA in prior research, positioning it as a compelling biomarker candidate. Its clinical utility is enhanced by several critical advantages. First, IL-6 can be reliably detected in easily accessible, non-invasive biological compartments like CVF and plasma. The painless and repeatable nature of this sampling facilitates serial monitoring without procedural risks, making it ideal for dynamic assessment throughout high-risk pregnancies.

Furthermore, the recent advent of rapid point-of-care (POC) IL-6 testing addresses critical diagnostic limitations inherent in traditional approaches. Conventional lab-based assays (e.g., ELISA) require hours to days for results, delaying critical decisions. In contrast, POC platforms deliver results in under 30 minutes using CVF or plasma samples. This enables real-time risk assessment during initial patient presentation. This timeliness is particularly transformative in acute

settings like PPROM or PTL, where early intervention based on rapid results can significantly reduce neonatal morbidity.

Despite IL-6's established role in inflammation, existing systematic reviews fail to address critical gaps in its application for HCA prediction. Notably, this represents the first meta-analysis to evaluate the measurement of CVF IL-6 for HCA prediction—a significant advancement, as CVF sampling offers a non- invasive, POC procedure with high sensitivity. Prior meta-analyses focused on mixed outcomes (HCA and/or funisitis) and omitted CVF data. While subsequent studies have emerged, they have not been synthesized in a dedicated analysis. Significant challenges still persist in standardizing IL-6 measurement techniques and establishing universal cut-off values across varying gestational ages and clinical presentations. Therefore, this study aims to systematically review and synthesize updated literature, focusing exclusively on this biomarker across different biological compartments (AF, CVF, plasma) and distinct clinical scenarios (e.g., PPROM, PTL).

Condition being studied Chorioamnionitis is the infection that affects the fetal membranes, the amniotic fluid and the placenta and usually occurs due to PPROM without that being necessary. It is often multimicrobial and complicates an important proportion of births. In 1982, Gibbs et al suggested a set of criteria for the clinical diagnosis of chorioamnionitis that define that the diagnosis relies on clinical data, such as maternal fever, maternal leukocytosis, maternal or fetal tachycardia, uterine tenderness, and purulent vaginal discharge in combination with positive amniotic fluid Gram strain or culture. However these criteria are nonspecific and their low diagnostic accuracy raise significant limitations regarding prompt diagnosis and treatment to avoid complications. Histopathological chorioamnionitis (HCA) has been used to define the diffuse infiltration of neutrophils into the chorioamniotic membranes. The histological analysis of the placenta is regarded as the gold standard for diagnosing such kind of infections but this result can only be obtained postpartum.

HCA has profound implications for individual and public health. For neonates, it is a major risk factor for lifelong neurodevelopmental disabilities and preterm birth complications, driving NICU admissions and long-term healthcare costs. For mothers, untreated HCA may progress to sepsis or postpartum hemorrhage. At a population level, HCA contributes to global preterm birth rates, straining healthcare systems. Policy-wise, accurate prediction could optimize antibiotic stewardship, corticosteroid timing, and delivery planning, aligning with WHO goals for reducing preterm mortality.

METHODS

Search strategy

The following databases will be searched:

- PubMed
- Embase
- Cochrane Library
- ClinicalTrials.gov (CT.gov)

The following combination of keywords will be used: "((chorioamnionitis) OR (amnionitis) OR (intraamniotic infection) OR (intraamniotic inflammation) OR (HCA) OR (IAI) OR (intrauterine infection)) AND ((IL-6) OR (interleukine 6)) AND ((diagnosis) OR (diagnostic accuracy) OR (Sensitivity) OR (Specificity) OR (prediction) OR (accuracy) OR (PPV) OR (NPV) OR (cut-off) OR (prognosis))"

No language or other restrictions will be imposed in the initial search.

Participant or population

Preterm pregnant women whose cases were included in studies that:

– Measured interleukin-6 (IL-6) levels in either maternal or fetal compartments.

– Performed histological evaluation of the placenta after delivery.

Intervention

No intervention- DTA study.

Index Test: IL-6 levels measured in amniotic fluid, plasma, or cervicovaginal fluid.

Comparator Comparator: Histopathological examination of the placenta (gold standard).

Study designs to be included Studies were excluded from further evaluation if they were case reports or case series; however, any study design that compared the results of the index test with the reference standard and provided data suitable for the extraction of 2 × 2 data qualified for inclusion.

Eligibility criteria

- Studies involving pregnant women (particularly preterm pregnancies)
- Studies that measured IL-6 in amniotic fluid, plasma, or cervicovaginal fluid
- Studies that conducted histological evaluation of the placenta post-delivery as the reference standard

• Studies that provided sufficient data to construct 2×2 contingency tables
• All study designs that compared the results of the index test with the reference standard.

Information sources
The following databases will be searched:
• PubMed
• Embase
• Cochrane Library
• ClinicalTrials.gov (CT.gov)

The following combination of keywords will be used: "((chorioamnionitis) OR (amnionitis) OR (intraamniotic infection) OR (intraamniotic inflammation) OR (HCA) OR (IAI) OR (intrauterine infection)) AND ((IL-6) OR (interleukine 6)) AND ((diagnosis) OR (diagnostic accuracy) OR (Sensitivity) OR (Specificity) OR (prediction) OR (accuracy) OR (PPV) OR (NPV) OR (cut-off) OR (prognosis))"

No language or other restrictions will be imposed in the initial search.

Main outcome(s)
Data Items:
The following data will be extracted from each included study:
• First author, publication year
• Study design (prospective/retrospective)
• Sample type (AF, plasma, CVF)
• Sample size
• IL-6 cut-off value (pre-specified or optimal)
• Patient population (PPROM, PTL, or mixed)
• Gestational age
• Measurement method (ELISA, POC, etc.)
• Timing of sample collection
• 2×2 contingency table data (TP, FP, TN, FN)
• Method of placenta assessment and blinding of pathologist to IL-6 results

Primary Outcomes:
• Sensitivity and specificity of IL-6 for predicting HCA
• Area under the summary receiver operating curve (sROC)
Secondary Outcomes:
• Diagnostic odds ratio (DOR)
• Positive likelihood ratio (LR+)
• Negative likelihood ratio (LR-).

Data management
Selection Process:
• Two independent reviewers will conduct the study selection
• Disagreements regarding eligibility will be resolved through consensus discussion
• Reference lists of pertinent studies will be manually searched to identify further relevant studies
Data Collection Process:
• True positives, false negatives, true negatives, and false positives will be independently extracted by two investigators (ES and CM)
• Authors of studies with missing, ambiguous, or conflicting contingency table data will be contacted via email for clarification.

Quality assessment / Risk of bias analysis The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool will be used to assess the risk of bias of each study. Two reviewers (ES and CM) will conduct independent evaluations, with conflicts resolved through consensus.

Strategy of data synthesis
• Meta-analysis will be carried out if the number of studies in each index test category is ≥3
• The pooled sensitivity, specificity, DOR, LR+, LR-, and AUC will be estimated using bivariate meta-analysis with a generalized linear mixed-model approach
• 95% confidence intervals will be calculated for each metric
• R programming language and STATA/SE version 16 will be used for all statistical analyses
• Publication bias will be assessed using funnel plots and statistical tests if sufficient studies are available.
• Heterogeneity will be assessed using visual assessment methods and the I^2 statistic.

Subgroup analysis Subgroup analyses will be performed based on patient population (PPROM, PTL).

Sensitivity analysis In cases where subgroup analyses for PPROM and PTL are not feasible due to limited sample size or data constraints, sensitivity analyses will be conducted to assess whether excluding one subgroup alters the results compared to the overall population.

Language restriction No language or other restrictions will be imposed in the initial search.

Country(ies) involved Greece.

Keywords interleukins, IL-6, prediction, diagnostic accuracy, chorioamnionitis, HCA.

Contributions of each author
Author 1 - Eleni Solomou - ES: Designed the study, conducted the literature review, analyzed and curated the data, and drafted the manuscript.

Email: elenisol@med.uoa.gr
Author 2 - Kalampokas, EM - EK: Contributed to writing and refining the manuscript.
Author 3 - Michailides,CM - CM: Co-conceptualized the study, contributed to the literature review, and co-authored the manuscript.
Author 4 - Sergentanis,TNS - TNS: Performed data analysis and curation.
Author 5 - Kalampokas, T - TK: Supervised the research.