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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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THE SIGNIFICANCE OF INTERLEUKIN-22 AND HOMOCYSTEINE IN THE PROGNOSIS OF PREMATURE ANTEPARTUM RUPTURE OF MEMBRANES IN PREGNANT WOMEN

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Abstract.

Background: Premature preterm rupture of membranes (PPROM) is a leading cause of preterm birth and neonatal complications. Identifying reliable biomarkers such as interleukin-22 (IL-22) and homocysteine (Hcy) is critical for early diagnosis, prognosis, and improved maternal-fetal outcomes.

Objectives: To systematically evaluate the prognostic significance of IL-22 and Hcy in predicting PPROM, preterm birth, and related maternal and neonatal outcomes in pregnant women.

Methods: This systematic review (2015–2025) analyzed 10 studies on IL-22 and Hcy in PPROM. Literature was searched in PubMed, Cochrane Library, Europe PMC, ProQuest, and Google Scholar using PICO criteria. Data extraction was performed with an emphasis on reliability, and risk of bias was assessed with ROBINS-I.

Results: Ten studies from diverse countries with varying designs and sample sizes were included. IL-22 was consistently elevated in women with PPROM and preterm birth (PTB). One included study reported a diagnostic cut-off value of 23.86 pg/mL with 72% sensitivity, while other studies supported an overall trend of increased IL-22 levels without establishing a uniform threshold. IL-22 was also associated with vaginal microecological imbalance, inflammatory responses, and immune modulation, although correlations with neonatal outcomes were inconsistent. Hcy showed a significant association with adverse pregnancy outcomes. Elevated levels predicted PPROM, PTB, miscarriage, and reduced fertility. Hyperhomocysteinemia was additionally linked to low birth weight, neonatal intensive care unit admission, and vitamin B12 deficiency. Overall, IL-22 and Hcy demonstrated considerable potential as biomarkers for predicting pregnancy complications, however, standardized thresholds require further validation through large-scale studies and meta-analytical approaches.

Conclusion: IL-22 and Hcy are promising biomarkers for predicting PPROM, PTB, and adverse pregnancy outcomes. Elevated IL-22 reflects immune modulation, while high Hcy correlates with fetal risk and neonatal complications. These findings support their potential application in early diagnosis and risk stratification.

Key words. PPROM, IL-22, Hcy, preterm birth, biomarkers, maternal outcomes.

Introduction.

Preterm premature rupture of membranes (PPROM) is defined as rupture of the membranes before 37 weeks of gestation and is a major contributor to preterm birth (PTB), which remains a leading cause of neonatal morbidity and mortality worldwide [1-5]. Despite advances in maternal-fetal medicine, the global incidence of PTB has not significantly declined [6,7].

Current clinical predictors and management strategies for PPROM remain limited, as available markers lack sufficient accuracy and consistency [8,9]. Among emerging biomarkers, interleukin-22 (IL-22) and homocysteine (Hcy) have gained attention due to their roles in inflammation, immune regulation, and vascular homeostasis, making them biologically plausible candidates for PPROM prediction [10]. Rather than being independent findings, these biomarkers represent complementary pathways through which maternal immune status and metabolic balance may influence pregnancy outcomes. However, existing studies have primarily examined these biomarkers in isolation, and findings remain inconsistent: IL-22 shows both pro-inflammatory and protective effects in pregnancy [11], while elevated Hcy has been associated with multiple adverse outcomes but with variable strength [12,13]. This inconsistency underscores the need for integrative approaches that assess these biomarkers together, allowing researchers to clarify whether their effects are synergistic, antagonistic, or context-dependent in PPROM.

Therefore, this study aims to evaluate and compare the predictive value of IL-22 and Hcy in women with PPROM, with the primary endpoint of improving diagnostic accuracy and the secondary endpoint of informing timely clinical interventions. The expected practical value of integrating IL-22 and Hcy into risk prediction is to support individualized clinical decision-making: women at higher predicted risk could be prioritized for hospitalization, intensive monitoring, and timely delivery planning, while those at lower risk may avoid unnecessary interventions through safe outpatient observation.

Literature Review.

Epidemiology and Classification of PROM:

Preterm premature rupture of membranes (PPROM) occurs in approximately 2-3% of all pregnancies and contributes to nearly one-third of spontaneous preterm births, which remain among the leading causes of neonatal morbidity and mortality worldwide. PROM is classified based on the gestational age at rupture term PROM when it occurs at ≥37 weeks and preterm PROM (PPROM) when rupture occurs before 37 weeks. Earlier onset, particularly at previable gestations (<24 weeks), is associated with more severe outcomes, including higher rates of fetal loss, neonatal complications, and maternal morbidity [14].

This gradation in clinical outcomes illustrates that the timing of membrane rupture is not merely a descriptive classification but a critical determinant of maternal fetal prognosis. Recent evidence reinforces the importance of gestational timing in shaping outcomes. PPROM in extremely preterm infants is associated

with significantly increased risks of sepsis and respiratory complications, even after adjustment for confounders [15]. The survival following previable PPROM is markedly reduced, with prognosis heavily dependent on maternal and fetal risk factors. Taken together, these data suggest that PPROM should be conceptualized less as a single entity and more as a clinical spectrum, where biological, gestational, and maternal factors interact to determine outcomes. These findings highlight that PPROM is not a uniform condition but rather a spectrum where earlier rupture presents the most challenging clinical scenarios, underscoring the need for reliable tools to guide prognosis and management [16].

Maternal and Fetal Complications:

PPROM is associated with a wide spectrum of adverse outcomes for both the mother and fetus. For the fetus, complications include respiratory distress syndrome, intraventricular hemorrhage, cerebral palsy, intra-amniotic infection, and neonatal sepsis, all of which contribute significantly to perinatal morbidity and mortality [17,18]. The risk of adverse neonatal outcomes is particularly pronounced in extremely preterm infants, where survival is closely influenced by gestational age at rupture and latency period.

Maternal complications primarily arise from ascending infection and obstetric emergencies. Chorioamnionitis is the most frequent, but other serious conditions such as placental abruption, umbilical cord prolapse, postpartum hemorrhage, and sepsis may also occur, potentially escalating to life-threatening situations if timely interventions are not initiated [19,20]. These maternal and fetal risks highlight the urgency of early identification and risk stratification in PPROM, underscoring the need for reliable prognostic biomarkers that can guide clinical decisions on monitoring, hospitalization, and timing of delivery.

Established Biomarkers in PPROM:

Several biomarkers have been investigated for their predictive and diagnostic utility in PPROM. Among these, C-reactive protein (CRP), alpha-fetoprotein (AFP), and βhCG are the most widely studied [21-23]. These biomarkers provide insight into inflammatory status, placental function, and fetal well-being, but their predictive power remains inconsistent, limiting their use in routine clinical practice. It is worth noting that in other areas of medicine, biomarkers have been successfully applied to risk prediction and patient stratification, such as vitamin D in relation to hypothyroidism in adolescents, where cross-sectional studies have demonstrated their value for forecasting health outcomes [24-26]. This underscores their potential in obstetric forecasting, although specific evidence for PPROM remains limited.

Emerging Role of Interleukin-22 (IL-22):

IL-22, a cytokine involved in immune regulation and tissue homeostasis [27], has recently drawn attention in pregnancy-related research. Evidence suggests that IL-22 exerts a dual role. On one hand, it activates pro-inflammatory signaling, promoting synthesis of effector molecules such as IL-6 and TNF-α, which may contribute to tissue damage and premature rupture of membranes [28-30]. On the other hand, IL-22 supports mucosal protection, prevents microbial invasion, and enhances tissue repair, thereby helping to preserve the integrity of fetal membranes [31]. This functional duality indicates that the biological context in which IL-22 is expressed may be decisive in shaping its impact whether harmful or protective during pregnancy. The distinct positioning of IL-22 between immune activation and tissue protection has also been demonstrated in molecular and immunological assessments in other disease prevention contexts [32,33]. By situating PPROM within this broader immunological framework, it becomes evident that IL-22 should not be interpreted as a uniformly beneficial or detrimental factor, but rather as a dynamic mediator whose role is determined by the surrounding maternal–fetal environment. These contrasting functions highlight IL-22 as a promising but complex biomarker in PPROM.

Homocysteine (Hcy) and Pregnancy Outcomes:

Homocysteine (Hcy), a sulfur-containing amino acid, has been strongly linked to adverse pregnancy outcomes. Elevated Hcy levels are associated with spontaneous abortion, preeclampsia, PROM, placental abruption, and low birth weight [34]. Beyond pregnancy, hyperhomocysteinemia is recognized as a risk factor for cardiovascular and neurological disorders [35,36]. This broader clinical relevance strengthens the rationale for considering Hcy in obstetric research, as the same mechanisms driving vascular dysfunction and oxidative stress in systemic diseases may also predispose to adverse pregnancy outcomes. Moreover, similar biomarker-based approaches have been applied in gynecological and postpartum conditions such as stress incontinence, where Hcy and related markers have been utilized in risk assessment and prognostic evaluations [37-39]. By drawing on evidence across different clinical domains, researchers can better contextualize Hcy as a biomarker that links systemic metabolic imbalance with obstetric complications such as PPROM. The main biomarkers investigated in PPROM are summarized in Table 1, grouped by functional categories.

Knowledge Gaps and Future Directions:

Despite substantial research, no single biomarker has proven sufficiently reliable for clinical implementation in PPROM. Although CRP, AFP, and βhCG provide some predictive value, their sensitivity and specificity remain limited. Emerging markets such as IL-22 and Hcy show potential but have not been validated in combination. Furthermore, evidence on the direction of associations remains conflicting, with IL-22 demonstrating both protective and pathogenic roles and Hcy showing variable strength of association. Developing predictive algorithms that integrate these biomarkers could improve risk stratification, guide obstetric management, and reduce adverse maternal and perinatal outcomes [40-43]. This study directly addresses this gap by investigating IL-22 and Hcy both individually and in combination as prognostic markers for PPROM.

Objective.

To systematically evaluate the prognostic significance of L-22 and Hcy in predicting PPROM, PTB, and related maternal and neonatal outcomes in pregnant women.

Methodology.

Study Design:

This study was conducted as a systematic review covering the period from 2015 to 2025. All relevant studies were identified through a comprehensive literature search in electronic databases and were screened according to pre-defined inclusion and exclusion criteria. Figure 1 shows the PICO criteria applied in this systematic review, providing a structured framework for study selection and outcome evaluation.

Figure 2 presents the inclusion and exclusion criteria used for this review. These criteria ensured that only studies directly relevant to the research question and of acceptable quality were considered for further analysis.

Importantly, during study selection it was observed that no eligible study concurrently evaluated both interleukin-22 (IL-22) and homocysteine (Hcy) as combined biomarkers for PPROM or related pregnancy outcomes. As a result, this systematic review synthesizes evidence from separate studies investigating IL-22 and Hcy independently. This methodological constraint was considered during data interpretation and limits the ability to draw conclusions regarding their combined prognostic performance

Search Strategy:

This review involved a comprehensive search across multiple electronic databases to identify relevant studies. The following search keywords were used ("PROM" OR "PPROM" OR "Premature rupture of membranes") AND ("IL-22" OR "Interleukin-22" OR "Homocysteine"). This search was conducted in PubMed, Cochrane Library, Europepmc, ProQuest, and Google Scholar. The search was limited to studies published between 2015 and 2025 to ensure the inclusion of the most recent research. Duplicates were removed during the screening process, and irrelevant studies were excluded based on the title and abstract review.

Study Selection:

Figure 3 illustrates the systematic process employed in identifying [44], screening, and including studies for this review on the significance of IL-22 and Hcy in the prognosis of PPROM. Initially, a total of 15,397 records were identified from several databases, including PubMed (17), Cochrane Library (6,024), EuropePMC (477), ProQuest (4,519), and Google Scholar (4,360). Based on studies published between 2015 and 2025, 6,572 records remained. After removing duplicate records (932) and irrelevant studies (3,852), 29 records were screened. Of these, 19 were excluded due to being either unrelated to the relevant biomarkers or not focused on PPROM, leaving 10 studies eligible for further assessment. Ultimately, these 10 studies [45-54] were included in the review.

Data Extraction:

Data extraction for this systematic review was carried out using a structured and standardized approach to ensure consistency and accuracy. Key data points were extracted from each study, including study characteristics such as authors, publication year, study design, sample size, and population characteristics. Additionally, biomarkers studied, biomarker assay methods, and units of measurement were recorded. Outcomes measured included maternal outcomes, neonatal outcomes, and pregnancy-related outcomes. Key findings related to IL-22 and homocysteine levels were extracted, along with their prognostic value, including cut-off values and predictive metrics. Data was extracted by two independent reviewers from full-text articles, and discrepancies were resolved through discussion with a third reviewer. The extracted data was then organized into a database for further analysis, ensuring a comprehensive exploration of the relationship between IL-22, homocysteine, and pregnancy outcomes.

Inter-Observer Reliability:

Inter-observer reliability was quantified by two blind reviewers extracting data independently of each other in all included studies. The data extraction form was a predefined form of study characteristics including the biomarker information, measurements on outcomes and the important findings. All the differences in data extraction by the two reviewers were addressed by discussion. In cases where the agreement could not be reached, the opinion was obtained by a third reviewer who was involved in providing an additional opinion and ensure that there was a consensus. This way was used to eliminate bias and raise the reliability of the data extracted. The inter-observer reliability kappa value 0.85 was found to be nearly perfect.

Risk of Bias Assessment:

Figure 4 presents a traffic-light plot [55] using the ROBINS-I tool [56] to visualize the risk of bias across studies. Most studies showed low risk in areas like bias due to confounding and selection of participants, but some studies, such as Busse et al. 2020 and Eko et al. 2022, exhibited moderate and serious risks in bias in classification of interventions and measurement of outcomes. These risks were primarily linked to small sample sizes and measurement errors.

Figure 5 presents the summary plot, also assessed using the ROBINS-I tool, which corroborates the traffic-light plot findings. Most studies are classified as low risk, while a few show moderate and serious risks, particularly in selection bias and outcome measurement. This highlights potential concerns in data analysis and interpretation of results. Both plots emphasize the need to carefully consider study design and methodology when evaluating IL-22 and homocysteine as biomarkers for PPROM and other pregnancy complications.

Results.

Table 2 provides an overview of the study characteristics included in the review on the significance of IL-22 and homocysteine in the prognosis of PPROM in pregnant women. The studies span a range of countries, including Turkey, Canada, China, Germany, Italy, Iraq, India, and Indonesia, offering a diverse international perspective on the topic. The study designs vary from cohort, case-control, to cross-sectional, ensuring a broad approach to understanding the biomarkers' impact across different settings. The sample sizes range from 9 to 481, indicating the inclusion of both small-scale pilot studies and large cohort studies, which provide valuable insights with varying levels of generalizability. Several studies specifically target populations with PPROM, while others address conditions like inflammatory bowel disease

Table 1. *Established and emerging biomarkers investigated in PPROM prognosis.*

Block / Category	Biomarker	Studies	Main Findings
Inflammatory markers	C-reactive protein (CRP)	[21]	Elevated CRP reflects systemic inflammation but shows limited predictive accuracy in PPROM.
	IL-6, TNF-α	[28–30]	Pro-inflammatory cytokines; associated with tissue damage and PROM.
Placental/fetal markers	Alpha-fetoprotein (AFP)	[22]	Elevated AFP may reflect compromised membrane or placental integrity; inconsistent results.
	βhCG	[23]	Studied for diagnostic/prognostic role, but predictive power remains limited.
Cytokines with dual role	Interleukin-22 (IL-22)	[27,29–31]	Plays both pathogenic (induces IL-6/TNF-α) and protective (mucosal repair, anti-microbial) roles.
Metabolic markers	Homocysteine (Hcy)	[34–36]	Elevated Hcy linked to PROM, preeclampsia, placental abruption; mechanisms via oxidative stress and vascular dysfunction.

Table 2. *Characteristic of included studies.*

Author's / Year	Country	Study Design	Sample Size	Population
Behram et al. 2021 [45]	Turkey	Case-control	80	Pregnant women, 18-40 years, 24-34 weeks gestation
Wu et al. 2022 [46]	Canada	Cohort	87	Pregnant women with IBD and healthy controls
Xu et al. 2019 [47]	China	Case-control	84	Pregnant women with PPROM, healthy and non-pregnant women
Busse et al. 2020 [48]	Germany	Cohort	18	Pregnant women undergoing cesarean section (term or preterm)
Logiodice et al. 2019 [49]	Italy	Cohort	9	Women with successful pregnancy or recurrent abortion (URA)
Dawood et al. 2024 [50]	Iraq	Case-control	100	Pregnant women, single viable fetus, 240/7-366/7 weeks
Bala et al. 2022 [51]	India	Cohort	75	Preterm (PTB) and term infants, cord blood and placenta tissue
Zhan et al. 2025 [52]	China	Cohort	481	IVF/ICSI patients, categorized by serum homocysteine levels
Eko et al. 2022 [53]	Indonesia	Cross-sectional	70	Pregnant women, 20-<37 weeks gestation, including those with PPROM
Mishra et al. 2020 [54]	India	Cohort	100	Pregnant women, all three trimesters evaluated

*(**Note NR:** Not reported in the original study.)*

Table 3. *Biomarkers and Assay Methods.*

Authors / Year	Biomarker Studied	Biomarker Assay Method	Units of Measurement	Outcomes Measured
Behram et al. 2021 [45]	IL-22	Enzyme immunoassay	pg/mL	Maternal IL-22 levels, pregnancy outcomes
Wu et al. 2022 [46]	IL-22	ELISA	pg/mL	Cytokine levels, pregnancy-related outcomes
Xu et al. 2019 [47]	IL-22	ELISA	pg/mL	Vaginal microecology, serum IL-10, IL-22, NF-κB
Busse et al. 2020 [48]	IL-22	Flow cytometry	pg/mL	Cytokine levels in plasma, Breg cell frequency
Logiodice et al. 2019 [49]	IL-22	Multiplex assay	pg/mL	Cytokine production in CD4+ T cell clones
Dawood et al. 2024 [50]	Hcy	Serum levels measured	µmol/L	Maternal and neonatal outcomes (birth weight, NICU admission)
Bala et al. 2022 [51]	Hcy	ELISA, RT-PCR	µmol/L	Homocysteine, vitamin B12, gene expression in placenta
Zhan et al. 2025 [52]	Hcy	ELISA	µmol/L	Pregnancy rate, miscarriage, clinical pregnancy outcomes
Eko et al. 2022 [53]	Hcy	HPLC	µmol/L	Serum homocysteine, incidence of PROM
Mishra et al. 2020 [54]	Hcy	Biochemical investigations	µmol/L	Pregnancy progression and outcomes

Note: *IL-22 = Interleukin-22; Hcy = Homocysteine.*

Table 4. *Key Findings and Prognostic Value of Interleukin-22.*

Authors / Year	Key Findings	Prognostic Value
Behram et al. 2021 [45]	Higher in PPROM (60.34 ± 139.81 pg/mL vs. 20.71 ± 4.36 pg/mL, $p < 0.001$)	Associated with PPROM risk (cut-off 23.86 pg/mL, 72% sensitivity)
Wu et al. 2022 [46]	Elevated IL-22 linked to disease activity in UC and CD	T1 IL-22 associated with T2 disease activity for UC (cut-off 0.624 pg/mL)
Xu et al. 2019 [47]	Higher in PPROM (45.91 ± 7.13 pg/mL) compared to normal pregnancy and non-pregnant groups	Linked with vaginal microecological imbalance ($r = 0.692$)
Busse et al. 2020 [48]	Higher in PTB group vs TD group ($p < 0.05$)	Associated with PTB inflammatory changes
Logiodice et al. 2019 [49]	Higher in successful pregnancy compared to URA	Associated with Th2 (IL-4) in successful pregnancy and Th17 (IL-17A) in URA

Table 5. *Key Findings and Prognostic Value of Homocysteine.*

Author's / Year	Key Findings	Association / Risk Indication
Dawood et al. 2024 [50]	Elevated homocysteine levels significantly associated with PPROM risk	Homocysteine ≥28.85 nmol/mL linked to increased PPROM risk
Bala et al. 2022 [51]	PTB infants with hypHcy had higher homocysteine levels and lower vitamin B12	Fetal hypHcy associated with oxidative stress and inflammation, contributing to PTB
Zhan et al. 2025 [52]	Elevated female serum Hcy ≥12.43 µmol/L is a risk factor for early miscarriage (OR = 2.20)	Elevated serum homocysteine linked to reduced fertility and early miscarriage
Eko et al. 2022 [53]	Elevated homocysteine levels (Hcy >15 µmol/L) associated with PROM ($p = 0.001$)	Elevated Hcy associated with PROM in a cross-sectional study; predictive value cannot be inferred
Mishra et al. 2020 [54]	Hyperhomocysteinemia in early pregnancy is a risk factor for adverse pregnancy outcomes	Hyperhomocysteinemia is an independent risk factor, not a predictor of future events

Table 6. *Maternal and Neonatal Outcomes.*

Author's / Year	Biomarker Levels	Maternal Outcomes	Neonatal Outcomes	Clinical Implication
Behram et al. 2021 [45]	Significant difference between PPROM (high IL-22) and control	No significant correlation with pregnancy outcomes	No correlation with neonatal birth weight, Apgar scores	IL-22 associated with PPROM risk
Wu et al. 2022 [46]	Elevated IL-22 >0.624 pg/mL (UC) and IL-6 >0.648 pg/mL (CD)	Active disease in UC associated with elevated cytokines	No correlation with neonatal birthweight	Early IL-22 levels linked with disease activity in IBD
Xu et al. 2019 [47]	Elevated IL-10, IL-22, and NF-κB in PPROM group	Vaginal microecological imbalance	-	IL-22 and NF-κB **associated** with PPROM
Busse et al. 2020 [48]	Elevated IL-22 and IL-6 in PTB group	Increased B cell numbers, altered Breg cell function	Preterm infants had lower birth weight, higher cord pH	Breg cells and cytokine levels linked with PTB risk
Logiodice et al. 2019 [49]	IL-22 positively correlated with IL-4 in successful pregnancy	IL-22 associated with successful pregnancy	-	IL-22 and Th2 cytokines support pregnancy success
Dawood et al. 2024 [50]	Homocysteine levels higher in PPROM group	Folate deficiency linked to PPROM	Lower birth weight, lower Apgar scores, higher NICU admission	Homocysteine and folate associated with PPROM
Bala et al. 2022 [51]	High homocysteine (>2.0 µmol/L) in PTB group	Fetal homocysteine impacts placental inflammation and oxidative stress	PTB infants had lower birth weight, higher inflammation	Fetal hypHcy linked to PTB risk
Zhan et al. 2025 [52]	High serum homocysteine associated with lower pregnancy rate	Elevated Hcy linked to reduced pregnancy rate	No significant correlation with embryo quality	Elevated homocysteine associated with fertility outcomes in IVF/ICSI
Eko et al. 2022 [53]	Hcy >15 µmol/L as a major risk factor for PROM	Higher rates of PROM with elevated Hcy levels	Increased risk of preterm birth and complications	Homocysteine levels linked to PROM risk
Mishra et al. 2020 [54]	Vitamin B12 deficiency linked to LBW, hyperhomocysteinemia	Vitamin B12 deficiency and hyperhomocysteinemia associated with LBW	LBW most common adverse outcome (52%)	Vitamin B12 deficiency and Hcy associated with LBW risk

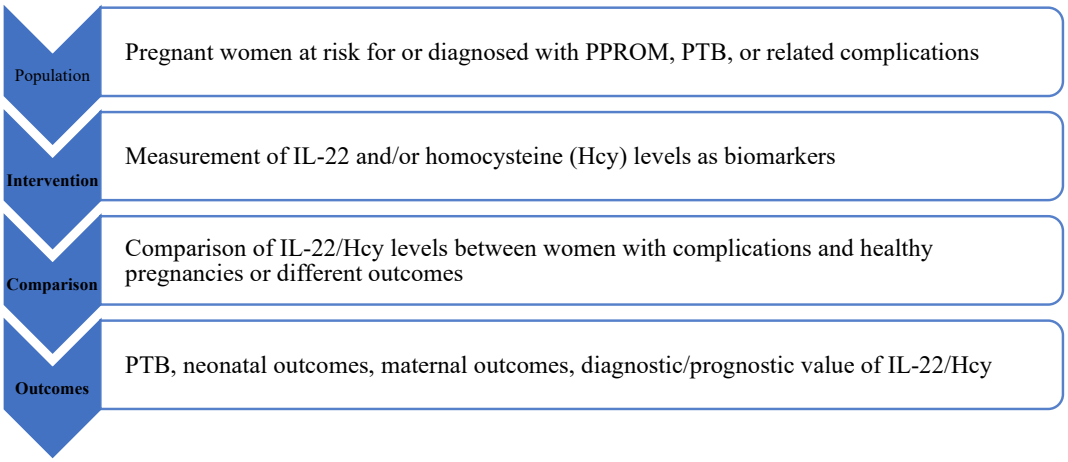

Figure 1. *PICO Criteria.*

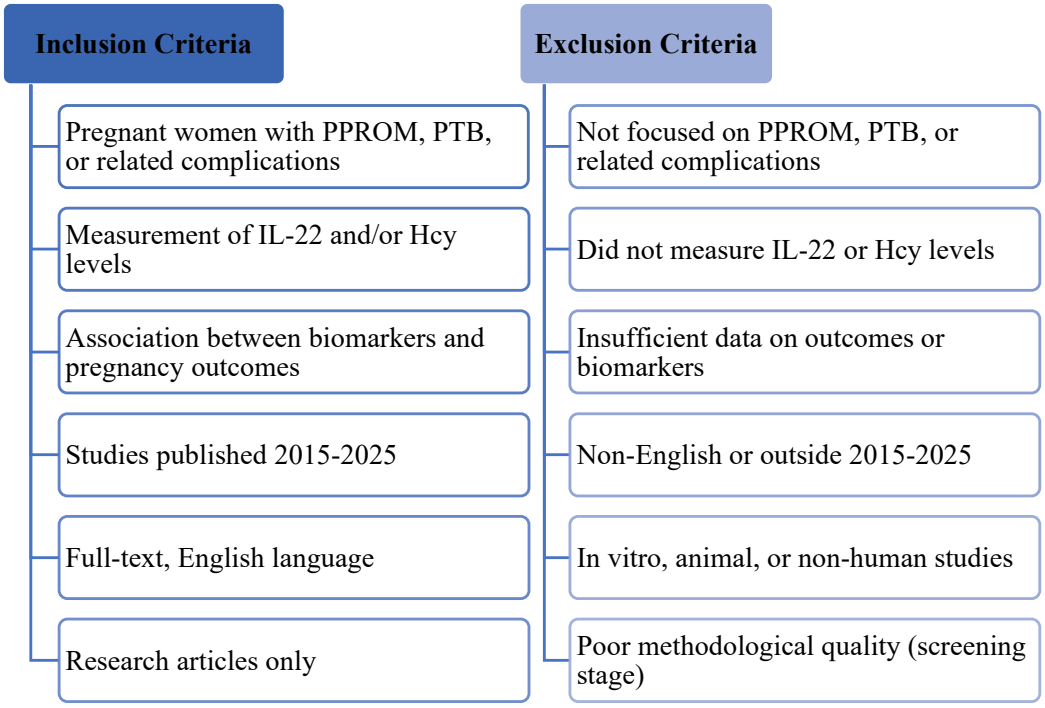

Figure 2. *Inclusion and Exclusion Criteria.*

(IBD), PTB, and single viable fetuses, thereby expanding the scope of analysis. However, findings derived from specialized populations, including pregnant women with IBD and patients undergoing IVF/ICSI, should be interpreted with caution, as underlying inflammatory conditions and reproductive therapies may independently influence cytokine and homocysteine levels and may not directly reflect PPROM risk in the general pregnant population. Additionally, some studies focus on fetal tissues such as cord blood and placenta tissue, allowing for a detailed examination of biomarkers in relation to pregnancy outcomes.

Table 3 outlines the biomarkers studied and the assay methods used to measure IL-22 and Hcy levels in various studies. The table highlights the use of different biomarker assay methods, including enzyme immunoassay, ELISA, flow cytometry, multiplex assays, and HPLC, across studies on IL-22 and Hcy. The units of measurement for IL-22 and Hcy are primarily given in pg/mL and μmol/L, respectively, reflecting standard practices in cytokine and serum biomarker analysis. The outcomes measured span a wide array of maternal and neonatal factors, such as pregnancy outcomes, cytokine levels, vaginal microecology, and incidence of PPROM, providing a comprehensive view of the biomarkers' roles in assessing risk of pregnancy-related complications. Studies on IL-22 mostly focus on its levels in maternal serum, and its correlation with pregnancy outcomes, cytokine production, and immune cell frequencies, while Hcy studies examine its levels in serum and their association with neonatal outcomes, including birth weight and NICU admission. These assays and outcomes form the basis for understanding the potential use of IL-22 and Hcy as biomarkers for risk evaluation in PPROM and other pregnancy complications, underlining their diagnostic and associative value in pregnancy-related research.

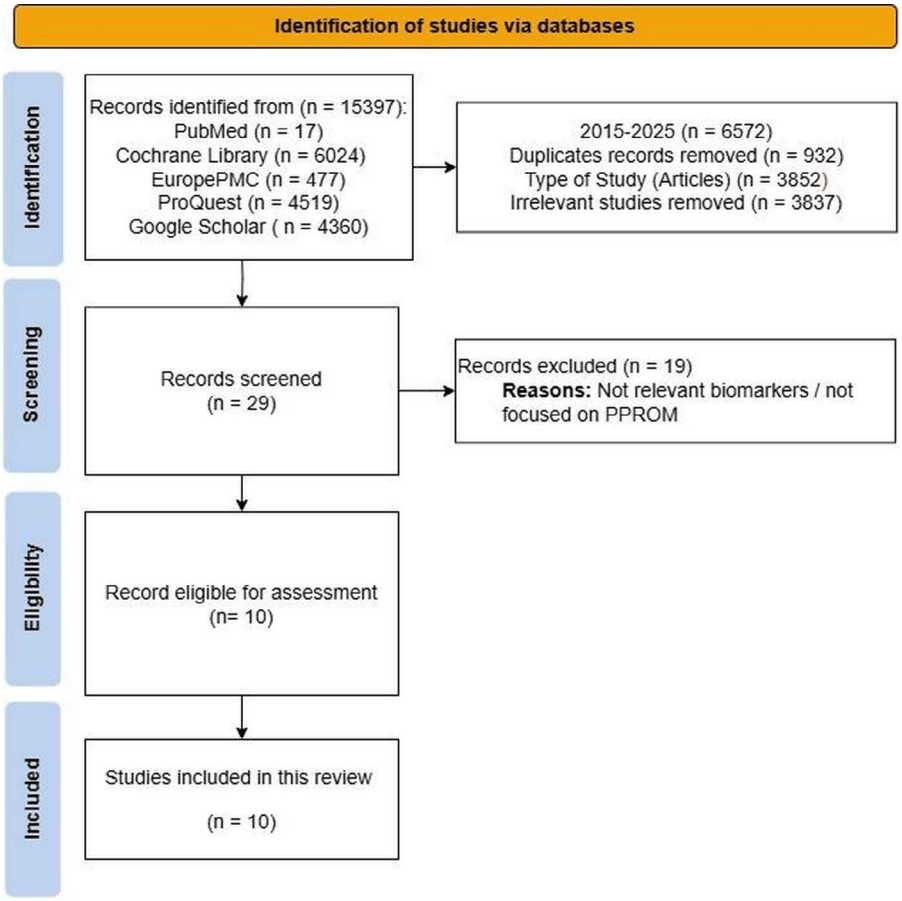

Figure 3. *PRISMA flow diagram.*

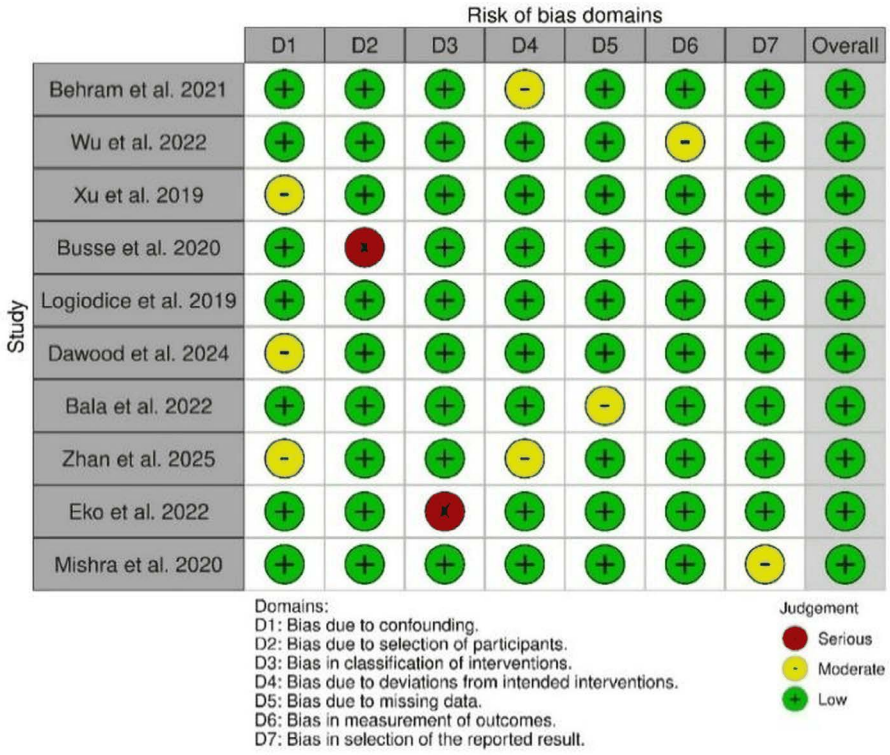

Figure 4. *Traffic-Light Plot of Risk of Bias in Included Studies.*

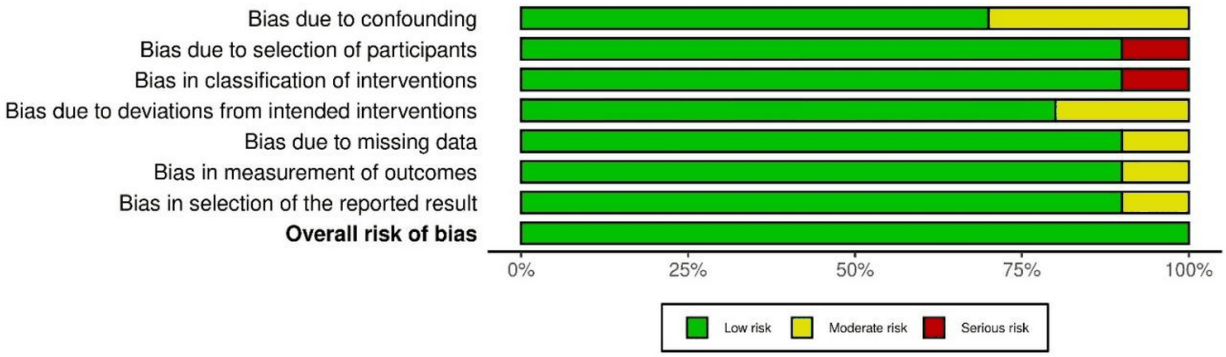

Figure 5. *Summary Plot of Risk of Bias in Included Studies.*

Table 4 summarizes the key findings and prognostic value of IL-22 in various studies related to PTB, PPROM, and other pregnancy outcomes. IL-22 levels were significantly higher in PPROM groups compared to healthy controls, suggesting its potential as a diagnostic marker for PPROM with a cut-off value of 23.86 pg/mL and 72% sensitivity. Elevated IL-22 was also linked to disease activity in conditions like ulcerative colitis (UC) and Crohn's disease (CD), with IL-22 at T1 predicting disease activity at T2 for UC. Higher IL-22 levels in the PPROM group correlated with vaginal microecological imbalance, indicating its role in immune responses related to pregnancy complications. Further, IL-22 was found to correlate with inflammatory changes contributing to PTB. In successful pregnancies, IL-22 was associated with Th2 cytokines, while in recurrent abortions, it linked to Th17 cytokines, underscoring its immune modulation role. IL-22 shows strong diagnostic and prognostic potential for pregnancy complications.

Table 5 summarizes the key findings and associations of Hcy in relation to PPROM, PTB, and other pregnancy complications. Elevated homocysteine levels were significantly associated with PPROM risk, with homocysteine ≥28.85 nmol/mL identified as a reliable indicator for PPROM. In PTB infants, higher homocysteine levels and lower vitamin B12 were linked to increased oxidative stress and inflammation, contributing to PTB. Elevated female serum Hcy ≥12.43 μmol/L was found to be a significant risk factor for early miscarriage, with higher homocysteine levels associated with reduced fertility and early miscarriage. Elevated Hcy levels were strongly associated with PROM, emphasizing its role as a risk factor for PROM in preterm pregnancies. Hyperhomocysteinemia in early pregnancy was also found to be an independent risk factor for adverse pregnancy outcomes. In conclusion, homocysteine is a key biomarker for assessing risk and association with PPROM, PTB, early miscarriage, and other pregnancy complications, making it crucial for risk evaluation in pregnant women.

Table 6 highlights the maternal and neonatal outcomes associated with IL-22 and Hcy levels in pregnancy. IL-22 was found to be significantly elevated in PPROM and PTB groups, yet its correlation with pregnancy outcomes like birth weight and neonatal Apgar scores remains unclear. Elevated IL-22 levels were linked to disease activity in UC and CD, with early IL-22 measurements potentially aiding disease management in IBD during pregnancy. Homocysteine levels, especially >15 μmol/L, were strongly associated with PPROM and PTB, correlating with lower birth weight and higher NICU admission rates. Fetal hypHcy was identified as a potential early indicator for PTB risk, while vitamin B12 deficiency and hyperhomocysteinemia were linked to LBW in neonates. Overall, these biomarkers demonstrate potential for predicting adverse pregnancy outcomes and improving maternal and neonatal care.

Discussion.

This review highlights the prognostic significance of IL-22 and homocysteine in pregnancy complications, particularly PPROM and PTB. Although the literature search spanned a decade (2015-2025) and incorporated the most recent evidence, the final inclusion of 10 studies reflects the limited availability of high-quality research addressing these biomarkers in this clinical context. Notably, none of the included studies simultaneously evaluated both IL-22 and homocysteine within a single cohort; therefore, the present conclusions are derived from a parallel synthesis of independent biomarker studies rather than from a combined predictive or analytical model. The included studies, conducted across diverse populations and employing various designs, provide both maternal and fetal perspectives, with sample sizes ranging from small pilot investigations to large cohorts. Such diversity enhances the generalizability of the findings while enabling nuanced insights into biomarker performance across different clinical contexts. Inflammation of the fetal membranes is a central driver of both PTB and PPROM through mechanisms involving senescence, oxidative stress, and matrix degradation. Within this framework, additional studies confirm the role of key inflammatory biomarkers such as interleukins, C-reactive protein (CRP), and other mediators that exacerbate localized tissue damage and transmit inflammatory signals to maternal uterine tissues. Recent evidence has identified IL-22 as a novel candidate biomarker, with potential utility for risk stratification rather than established prognostication. Collectively, these findings reinforce the concept that inflammation is not only a biological hallmark of parturition but also a promising target for identifying women at risk of adverse pregnancy outcomes [57-59]. Another retrospective biomarker studies emphasize the difficulty in predicting spontaneous PTB due to heterogeneity of causes but recognize placental function markers and inflammatory cytokines as key biological indicators. IL-22's role, alongside homocysteine's, adds depth to understanding inflammatory and vascular contributions to these pregnancy complications [60].

Interleukin-22 expression was significantly higher in women with unexplained recurrent pregnancy loss compared to those with unexplained infertility and healthy controls. Women with unexplained infertility showed intermediate levels, though differences with controls were not statistically significant. Immunoreactivity was localized to endometrial glands and stroma. Elevated interleukin-22 may contribute to impaired immune regulation and adverse pregnancy outcomes, warranting further investigation [61]. Another study demonstrated that IL-22 deficiency increased susceptibility to lipopolysaccharide (LPS)-induced abortion in mice by impairing endometrial regeneration through disruption of junctional proteins and collagen deposition. Administration of recombinant IL-22 (rIL-22) restored mucosal integrity and rescued pregnancies in a dose-dependent manner, although excessively high doses were harmful. These findings highlight the therapeutic potential of IL-22 in preventing inflammation-related pregnancy loss while underscoring the critical importance of dose regulation [62,63].

IL-22 consistently emerged as a potential risk-associated biomarker. Elevated levels were observed in PPROM and PTB, correlating with vaginal microecological imbalance and inflammatory processes. IL-22 plays a dual role in pregnancy, supporting immune tolerance through Th2 pathways in successful gestations while associating with Th17 responses in recurrent abortions. Based on the findings synthesized in this review, a plausible hypothesis is that IL-22 exerts protective, tissue-repair and epithelial-regenerative functions at physiological or moderately elevated concentrations, whereas excessive or dysregulated IL-22 expression particularly in the context of intra-amniotic infection or sustained inflammation may shift its activity toward pro-inflammatory signaling. This transition may promote extracellular matrix degradation, membrane weakening, and subsequent PPROM. Elevated IL-22, particularly in intra-amniotic inflammation, has been linked to preterm birth and neonatal complications. One study emphasized the complex pro-inflammatory and anti-inflammatory functions of IL-22 during gestation, reinforcing its potential as a marker for adverse pregnancy outcomes such as PTB and fetal injury [27]. Another review highlights that immune deviations such as impaired tolerance and premature immune activation along with vaginal microbiome imbalances play a critical role in spontaneous PTB. IL-22 is discussed as a potential biomarker reflecting these inflammatory and immune regulatory processes [64]. In immune-mediated conditions such as ulcerative colitis (UC) and Crohn's disease (CD), serum IL-22 and IL-22 binding protein levels are significantly reduced compared with healthy controls, with a more pronounced decrease observed in CD. Altered IL-22/IL-22BP ratios and their correlations with inflammatory markers suggest dysregulation of the IL-22 system, which may contribute to impaired mucosal repair and the pathogenesis of inflammatory bowel disease (IBD) [65,66]. Homocysteine demonstrated a similarly strong association with adverse outcomes. Elevated maternal and fetal Hcy levels were consistently associated with PPROM, PTB, early miscarriage, and low birth weight. Defined cut-off thresholds, such as Hcy ≥28.85 nmol/mL, provided risk indication for PPROM, while hyperhomocysteinemia in early pregnancy was identified as an independent risk factor for complications. In addition, fetal hyperhomocysteinemia and maternal vitamin B12 deficiency contributed to oxidative stress, placental inflammation, and impaired neonatal growth, underscoring the maternal-fetal metabolic connection. Elevated homocysteine levels during pregnancy have also been associated with placental vasculopathies and complications including fetal growth restriction, placental abruption, hypertensive disorders of pregnancy, recurrent pregnancy loss, and PTB. High maternal Hcy disrupts endothelial function in placental vessels, further contributing to these outcomes. Current evidence suggests that increased maternal Hcy in early gestation is an independent risk factor and may serve as an early predictor of placenta-mediated complications [67]. A case-control study of 100 pregnant women found significantly higher homocysteine levels in those with complications (26.4 μmol/L) compared to healthy controls (8.4 μmol/L). Elevated levels were most marked in eclampsia and abruption cases. Hyperhomocysteinemia correlated with poor pregnancy outcomes, suggesting a strong link with placental dysfunction. Vitamin supplementation may help prevent such complications [68]. Another study compared 70 women with early miscarriages to 54 healthy pregnancies. Homocysteine levels were significantly higher in all miscarriage groups (7.8-8.9 nmol/L) than in controls (4.8 nmol/L). Elevated levels, particularly in missed miscarriage, indicate increased risk for early pregnancy loss and may also predict later complications like preeclampsia and placental abruption [69]. A prospective cohort study in Nigerian women confirmed that elevated maternal Hcy concentrations in early pregnancy are associated with spontaneous PTB, antepartum fetal death, and delivery of LBW neonates, emphasizing the need for clinical monitoring of Hcy as a marker for at-risk pregnancies [70].

Additional observational studies support maternal Hcy as a determinant of vascular-related pregnancy complications including pre-eclampsia and small for gestational age infants. Folate supplementation reduces maternal Hcy but its direct impact on pregnancy outcome remains under investigation, especially post-folic acid fortification era when populations are generally folate replete [71]. Other research reveals that elevated maternal and fetal Hcy levels, in combination with deficiencies in essential cofactors such as folate, vitamin B6, and vitamin B12, impair methionine and folate cycle function. This dysregulation exacerbates placental dysfunction and fetal growth restriction, thereby linking hyperhomocysteinemia more clearly to adverse gestational outcome [72,73].

Taken together, IL-22 and homocysteine represent complementary biomarkers. IL-22 reflects immune dysregulation and inflammatory pathways, while homocysteine highlights metabolic and vascular risk factors. However, none of the included studies measured IL-22 and homocysteine concurrently within the same cohort, and no combined predictive or prognostic model incorporating both biomarkers currently exists. A 2025 study used multiplex cytokine profiling in urine samples from pregnant women and identified IL-22 as a central cytokine node in the network differentiating preterm from term deliveries. IL-22 was linked with macrophage-driven inflammatory mechanisms implicated in preterm labor and

PPROM, suggesting its role in pathophysiology and potential as a predictive biomarker [74-76].

Taken together, IL-22 and homocysteine reflect distinct but theoretically complementary biological pathways immune-inflammatory and metabolic-vascular, respectively. However, no study to date has concurrently measured these biomarkers within a unified cohort or integrated them into a combined predictive model. Therefore, their complementary clinical utility cannot be empirically confirmed and should be regarded as a hypothesis for future investigation rather than a conclusion supported by current evidence. Additional studies, though focused on broader immune-cytokine profiles in preterm labor or PPROM, have identified altered chemokine and cytokine patterns, supporting the involvement of inflammatory mediators like IL-22 in the etiology of these complications [77]. Future studies integrating IL-22 and homocysteine within a single predictive framework may help clarify whether combined biomarker models improve risk stratification in PPROM and PTB.

Limitation.

This review has several limitations. The included studies varied substantially in design, sample size, population characteristics, and biomarker assay methods, which may limit the generalizability of the findings. Some studies focused on specialized subpopulations, including pregnant women with inflammatory bowel disease or those undergoing assisted reproductive technologies, in whom inflammatory status and hormonal modulation may independently influence cytokine and homocysteine levels, thereby limiting direct generalizability to spontaneous PPROM risk in the general pregnant population. In addition, heterogeneity in outcome measures and the timing of biomarker assessment restricts direct comparison across studies. Future research should prioritize methodological standardization and include larger, multicenter cohorts to ensure more robust conclusions.

Conclusion.

In the current review, both IL-22 and Hcy demonstrate considerable potential as risk-associated biomarkers for PPROM and related pregnancy complications. Elevated IL-22 levels were consistently observed in PPROM and PTB groups, correlating with immune dysregulation, vaginal microecological imbalance, and inflammatory changes, while showing association patterns in successful compared with recurrent pregnancies. Similarly, elevated Hcy levels were strongly associated with PPROM, PTB, early miscarriage, and adverse neonatal outcomes, including low birth weight and increased NICU admissions. Maternal folate and vitamin B12 status influenced Hcy levels, underscoring their importance in modulating fetal outcomes. However, due to the absence of studies integrating both biomarkers within a single predictive model, conclusions regarding their combined prognostic value remain premature. Future research should focus on large-scale, prospective, longitudinal studies that integrate inflammatory and metabolic biomarkers to strengthen early identification and management of high-risk pregnancies.

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None

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