GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 6 (363) Июнь 2025

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

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.

GEORGIAN MEDICAL NEWS
No 6 (363) 2025

Содержание:

GEORGIAN MEDICAL NEWS
No 6 (363) 2025

MOLECULAR MECHANISMS OF OBSTETRIC APS

Madina Khalmirzaeva[1]*, Almagul Kurmanova[2], Damilya Salimbayeva[3], Gulfairuz Urazbayeva[4], Gaukhar Kurmanova[5], Zhanar Kypshakbayeva[6], Gaukhar Koshkimbayeva[7].

[1]*Obstetrician-gynecologist, Teacher, Department of Obstetrics and Gynecology, Al-Farabi Kazakh National University, Almaty, Kazakhstan.*

[2]*Doctor of Medical Sciences, Professor, Head of Obstetrics and Gynecology Department of NJSC "Al-Farabi Kazakh National University", Almaty, Kazakhstan.*

[3]*Candidate of Medical Sciences, Associate Professor, Head of Strategic Development and Science Department, Scientific Center of Obstetrics, Gynecology and Perinatology, Almaty, Kazakhstan.*

[4]*Candidate of Medical Sciences, Associate Professor, Head of Scientific Center of Obstetrics, Gynecology and Perinatology JSC, Almaty, Kazakhstan.*

[5]*Head of Department of General medical practice, Al-Farabi Kazakh National University, Almaty, Kazakhstan.*

[6]*Master, Obstetrician-gynecologist, Al-Farabi Kazakh National University, Almaty, Kazakhstan.*

[7]*Director of the Municipal State Enterprise "City Center for Human Reproduction" under the Public Health Department, Almaty, Kazakhstan.*

Abstract.

Introduction: Antiphospholipid syndrome is an autoimmune disease marked by antiphospholipid antibodies, causing thrombosis and obstetric complications.

Objectives: This study explores molecular mechanisms, endometrial receptivity, and clinical parameters linked to APS, focusing on pregnancy complications such as miscarriage, preterm delivery, recurrent implantation failure (RIF), and thrombosis.

Patients and Methods: A systematic review was conducted through Scopus, WoS, PubMed, Cochrane, and Google Scholar, including studies published between 2019 and 2024. 17 relevant original research studies were selected, focusing on clinical trials and observational studies. Narrative reviews and meta-analyses were excluded, with priority given to preeclampsia-specific studies to explore the immune and vascular dysfunction link in APS patients.

Results: Key findings include the correlations between elevated antiphospholipid antibodies (aPLs), including aCL and aβ2GPI, poor vascularization of the uterus, and recurrent pregnancy loss (RPL) reports. Preeclampsia is closely linked to APS, resulting in immune and vascular dysfunctions that exacerbate complications, including miscarriage, preterm delivery, and fetal death. ELISA, Doppler ultrasound, and genetic testing are some of the diagnostic methods applied. The aPL autoantibodies along with inflammatory markers like CRP and TNFSF13B, an increase in cytokine imbalance, are associated with many pregnancy complications such as early-stage miscarriage and preterm delivery. Deficient inflammation resolution and adequate uterine perfusion, abnormal uterine blood perfusion, and chronic infection significantly impact rates of perinatal illness and death which emphasizes the problem in identifying and managing APS.

Conclusion: This review focuses on the effects of the antiphospholipid syndrome on the endometrial receptivity and pregnancy outcomes, paying special attention to how early diagnosis and treatment can enhance the chances of a successful pregnancy and reduce complications.

Key words. Antiphospholipid syndrome, endometrial receptivity, pregnancy complications, autoantibodies.

Introduction.

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by the production of antiphospholipid antibodies (aPLs) that target phospholipid-binding proteins, leading to increased blood clot formation (thrombosis) and pregnancy complications such as miscarriage, preeclampsia, and intrauterine growth restriction. Obstetric APS specifically refers to APS manifestations that affect pregnancy outcomes, including recurrent pregnancy loss, fetal growth restriction, and preterm delivery [1].

Classification criteria are formal sets of clinical and laboratory findings used primarily for research to identify patients who truly have APS, while diagnostic criteria are used in clinical practice to diagnose and manage patients. Triple positivity refers to the presence of all three major aPLs lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti-β2 glycoprotein I antibodies (aβ2GPI) and is associated with higher risk for thrombosis and pregnancy complications. Complement activation in APS involves triggering the complement cascade, a part of the immune system that contributes to inflammation and tissue injury, further promoting clot formation and pregnancy loss. NETosis is a process by which neutrophils release web-like structures called neutrophil extracellular traps (NETs) composed of DNA and proteins, which can trap pathogens but also contribute to thrombosis and inflammation in APS [2-5].

APS is a diagnosis that stems from an autoimmune systemic syndrome resulting from autoantibodies forming an increased propensity for thromboembolic sequelae and poor pregnancy outcomes [6]. Preeclampsia is hypertensive disorder of pregnancy which poses severe risk to maternal health in patients with obstetric APS due to its associated complications such as preterm delivery and intrauterine fetal growth restriction. As a subtype of APS, obstetric APS is a notable global concern for reproduction and poses extensive consequences for obstetric care such as miscarriage, preeclampsia, and intrauterine growth restriction [7,8]. The recent advances associated with the molecular mechanisms of APS have opened new possibilities for intervention, including the endobiotic porous cavity, which frequently causes infertility and pregnancy complications [9], and some forms of reproductive challenges like genital

endometriosis have been linked to gene polymorphisms, which may intersect with immune-mediated infertility as seen in APS [10]. The ISTH's proposed criteria for the diagnosis in 2023 showcase the contemporary approach to formulating a diagnosis which includes non-criteria antibodies and molecular markers. The broader scope, which includes markers of preeclampsia, advances the understanding of its role in APS. It also underscores how critical such revision is, given the particularly precise and sensitive diagnosis required for the effective management of complications. Understanding these alterations and the shift in focus toward the diagnosis and treatment of APS emerges as clinically vital and highlights the need to critically analyze these changes [11]. The development of APS involves a genetic component, exposure to specific factors or infections, and dysregulation of the immune system. Some of the major contributory factors to APS include infections and preeclampsia [12,13].

The infections that are most likely able to induce a complete or partial autoimmune response involve those that are transmitted sexually; with these induced aPLs, the result is APS [14,15]. Additionally, preeclampsia has a bidirectional relationship with APS, acting both as a trigger and an outcome of APS-related immune and vascular dysfunctions. This complex situation involves both the vascular and immune systems [16]. On the molecular basis, APS is characterized by the clinical trial of endothelial dysfunction, ameliorated complement and altered decidualization, which adversely affect implantation [17]. The factors contributing to a successful pregnancy are altered in APS due to the increased pro-inflammatory cytokine concentration, reduced angiogenesis, and deranged intercellular signaling pathways. Exploring these molecular mechanisms would help to elucidate how the syndrome affects the reproductive outcome [18]. A growing body of research emphasizes the role of preeclampsia in modulating the inflammatory and thrombotic pathways of APS, exacerbating complications. Biomarkers like IFN-γ and TNF may provide diagnostic and therapeutic insights into APS-related conditions, underscoring the need for targeted interventions to mitigate reproductive complications [19]. The worldwide impact of obstetric APS indicates significant circles of differentiation in risk factor distribution, diagnostic protocols and treatment options. Countries with developed healthcare systems have devised timely identification and management strategies, and even non-criteria antibodies are employed [20-22]. On the other hand, there are problems with weighted diagnosing and standard care delivery in areas such as Kazakhstan, which stresses the importance of local investigations to fill such voids. Despite development, the healthcare system of Kazakhstan remains devoid of many tools and broad coverage of APS diagnostics, such as assays of non-criteria antibodies and advanced imaging technologies [23,24]. The diagnostic panorama of APS has undergone a great revolution, as non-criteria antibodies are being recognized in diagnosing obstetric APS. These include anti-phosphatidylserine/prothrombin complex antibodies, anti-domain I of β2-glycoprotein I, and others [25].

The inclusion of their components in revised criteria enhances the accuracy of diagnosis. However, their use in clinical practice is not achievable due to limited supply and cost issues in underdeveloped countries like Kazakhstan. Furthermore, I believe that the introduction of molecular diagnostics, such as endothelial dysfunction and immune activation biomarkers, will also be instrumental in improving the diagnosis of APS. It is also necessary to develop and validate these tools in different populations to allow international use [26]. The role of preeclampsia-specific markers, such as angiogenic and anti-angiogenic factors (e.g., sFlt-1 and PlGF), is emerging as a valuable addition to diagnostic protocols in obstetric APS. A comprehensive knowledge of the mechanisms involved in the impairment of endometrial receptivity in the aspect of obstetric complications, especially in patients with APS, is still lacking despite the advancements made forth [27]. The importance of accurate diagnosis is further underscored by efforts to reduce medical errors in obstetric care, as shown in expert decision tree analyses used to minimize diagnostic mistakes in high-risk pregnancies, which could be adapted for APS-related assessments [28]. Finally, socio-demographic and medical predictors of chronic autoimmune conditions like APS, especially in low-risk populations, also deserve attention. The integration of such factors can inform early screening and risk stratification [29]. This systematic literature review seeks to elucidate the molecular pathways and biomarkers linked to the impaired endometrial receptivity of patients with antiphospholipid syndrome, the clinical and diagnostic markers used to assess APS-related conditions such as recurrent pregnancy loss, recurrent failure of implantation, and thrombosis and the effect of APS on pregnancy outcomes like miscarriage, preterm birth, and placental abnormalities in the aspect of autoimmune activity and antiphospholipid antibodies.

Objectives.

This study explores molecular mechanisms, markers, and clinical parameters linked to APS, focusing on pregnancy outcomes, adverse events like miscarriage, preterm birth, and thrombosis.

Materials and Methods.

Study design:

This study employed a systematic review methodology guided by the PRISMA 2020 framework. The PRISMA guidelines were chosen for their rigour in ensuring transparency and reproducibility in the systematic review process. This approach was deemed appropriate as it provided a structured protocol to identify, evaluate, and synthesize evidence from the literature on the molecular mechanisms underlying impaired endometrial receptivity in patients with antiphospholipid syndrome.

Search strategy:

The search strategy for this systematic review focused on retrieving studies related to the molecular mechanisms of obstetric antiphospholipid syndrome (APS). Databases including Scopus, Web of Science (WoS), PubMed, Cochrane, and Google Scholar were searched using a combination of keywords "antiphospholipid syndrome" OR "APS" AND "Endometrial Receptivity" AND "Preeclampsia" OR "Infection" OR "Sexually Transmitted Infections" AND

"Autoantibodies" OR "Non-Criteria Antibodies." These keywords were carefully selected to capture original, empirical studies addressing the role of APS in pregnancy complications, focusing on autoantibodies, infection, and endometrial factors influencing pregnancy outcomes such as preeclampsia.

Inclusion and exclusion criteria:

This systematic review considered only original empirical studies, including randomized controlled trials, cohort studies, clinical trials, case-control studies, cross-sectional studies, and studies with quantitative or qualitative analysis.

Inclusion criteria:

1. Publications between 2019 and 2024.
2. Studies published in English.
3. Articles that were original research.

Exclusion criteria:

1. Review articles (e.g., narrative reviews, literature reviews).
2. Methodological articles without empirical data.
3. Expert opinion pieces, editorials, essays, and analytical reports without clearly described methods of data collection.
4. Articles published outside the specified range (2019-2024).
5. Articles in languages other than English.
6. Duplicate records.
7. Articles with titles and/or abstracts that did not specifically focus on molecular mechanisms or the endometrial receptivity of the targeted population.

Data extraction:

During the data extraction, the study systematically focused on particular variables critical to its objectives. For example, data variables covering the year of publication or the country/ region covered, type of publication design, sample size together with mean age (years), the title of the study, the type of APS, the risk factors considered, the infections studied, the non-criteria antibodies investigated, the diagnostic techniques employed, endometrial receptivity outcomes, the pregnancy rates, and also the markers of autoimmune activity were all extracted. The relevance of each study was further evaluated based on the parameters to identify diagnostic patterns, the means of endometrial receptivity in APS patients and moieties with immunological functions. This methodological outline facilitated systematic planning, data collection and assessment in a manner that would provide a valuable understanding of the condition.

Risk of bias assessment:

Figure 1 traffic light plot summarizing the risk of bias assessment across the included studies on the molecular mechanisms of Obstetric APS. The plot categorizes bias into seven domains: confounding, participant selection, intervention classification, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. The green circles represent low bias, while yellow indicates moderate bias. Most studies show low bias across all domains, with a few studies e.g., Álvarez et al. [30] and Junmiao Xiang et al. [31] exhibiting moderate risk in participant selection and

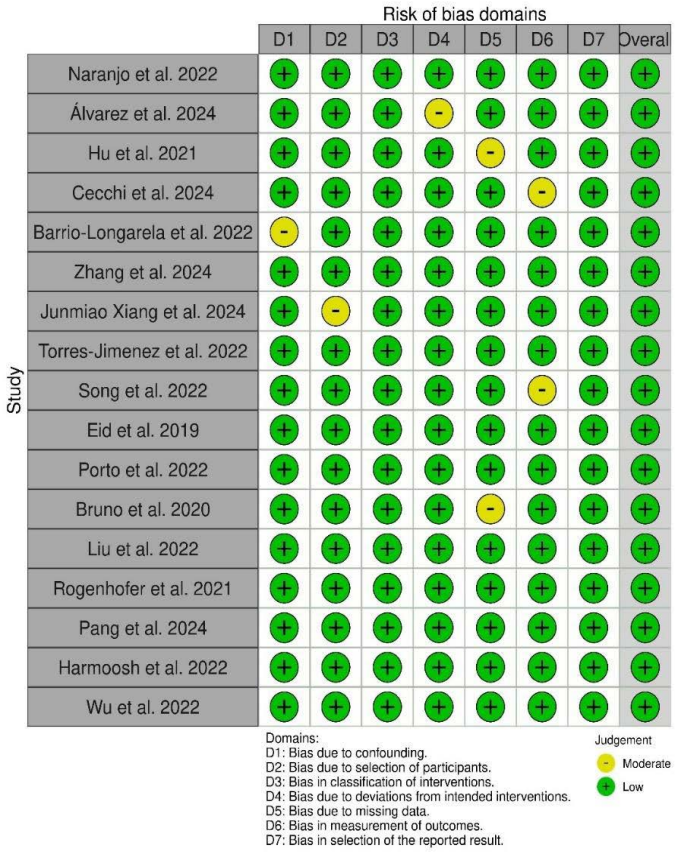

Figure 1. *Risk of bias assessment.*

intervention classification. The ROBINS-I tool was used for this assessment, specifically designed to evaluate the risk of bias in non-randomized studies.

Results.

Figure 2 in the PRISMA Flow Diagram visually represents the systematic review process for identifying highly relevant studies on the molecular mechanisms of obstetric antiphospholipid syndrome (APS). Initially, 510,370 records were identified through multiple databases, including Scopus, WoS, PubMed, Cochrane, and Google Scholar. After applying the inclusion and exclusion criteria, the year filter (2019-2024), and subject and document type filters, 134,319 records remained. Subsequently, 31,489 records were filtered by language, retaining only English-language studies. Following the removal of duplicate records, 20,142 studies remained, after which irrelevant records were excluded, reducing the total to 193. Finally, a thorough evaluation led to the inclusion of 17 [30-46] highly relevant studies for assessment. This flow diagram effectively illustrates the rigorous selection process, ensuring that only the most pertinent research on the molecular mechanisms of obstetric APS was included in the systematic review.

Table 1 presents the characteristics of the included studies, which vary in terms of country, study design, sample size, and participant age. The studies employed different designs, including cross-sectional (e.g., Naranjo et al. [32] with 303 participants), prospective (e.g., Álvarez et al. [30] with 68

Table 1. *Study Characteristics.*

Author's / Year	Country	Study Design	Sample Size	Mean Age (Years)
Naranjo et al. 2022 [32]	European	Cross-sectional	303	43.8 ± 13.2
Álvarez et al. 2024 [30]	Colombia	Prospective	68	36-51
Hu et al. 2021 [33]	China	Prospective cohort	152	36.3
Cecchi et al. 2024 [34]	Italy	Cross-sectional	112	48.5 ± 13.5
Barrio-Longarela et al. 2022 [35]	Spain	Retrospective	137	33.5 ± 4.8
Zhang et al. 2024 [36]	China	Retrospective	62	32.70 ± 4.51
Junmiao Xiang et al. 2024 [31]	China	Retrospective Cohort	1574	29
Torres-Jimenez et al. 2022 [37]	Mexico	Retrospective	32	11.75
Song et al. 2022 [38]	China	Retrospective	478	54
Eid et al. 2019 [39]	Egypt	Retrospective	94	20-38
Porto et al. 2022 [40]	Italy	Retrospective	64	40 ± 4.1
Bruno et al. 2020 [41]	Italy	Retrospective	71	34-36
Liu et al. 2022 [42]	China	Retrospective Cohort	347	42.4 ± 15.3
Rogenhofer et al. 2021 [43]	Germany	Case-Control	63	35 ± 3
Pang et al. 2024 [44]	China	Case-Control	214	31.13 ± 3.34
Harmoosh et al. 2022 [45]	Iraq	Case-Control	100	30.0 ± 6.86
Wu et al. 2022 [46]	China	Prospective cohort	132	20-40

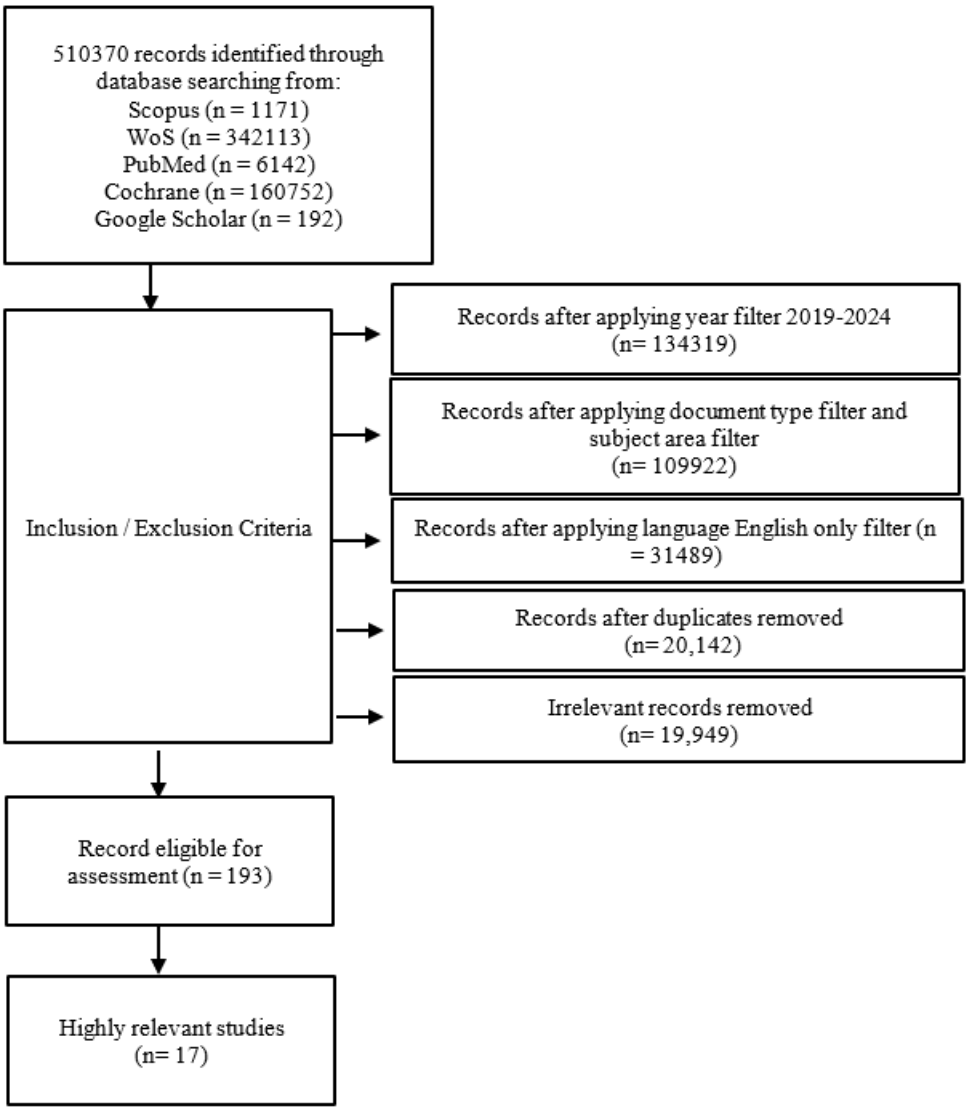

Figure 2. *PRISMA Flow Diagram.*

participants), and retrospective cohort (e.g., Junmiao Xiang et al. 2024 [31] with 1574 participants) designs. Sample sizes ranged widely from as few as 32 participants Torres-Jimenez et al. [37] to as many as 1574 participants Junmiao Xiang et al. 2024 [31]. The mean ages varied across studies, with the youngest participants 11.75 years in Torres-Jimenez et al. [37] and the oldest 54 years in Song et al. [38]. Most studies featured participants with mean ages ranging from 30 to 45 years, suggesting a broad demographic representation of APS patients in these studies.

The clinical and diagnostic findings presented in Table 2 reveal various associations between antiphospholipid syndrome (APS) and reproductive outcomes, as well as the diagnostic methods employed across different groups. For recurrent pregnancy loss (RPL), studies by Eid et al. [39] and Zhang et al. [36] reported that a history of ≥3 early miscarriages, ≥1 fetal death, or preterm birth due to placental insufficiency/preeclampsia was often diagnosed using ELISA for anticardiolipin antibodies and the dilute Russell viper venom time for lupus anticoagulant. In recurrent implantation failure (RIF), genetic analysis of the M2/ANXA5 haplotype and IVF/ICSI outcomes were used to identify risk factors, as highlighted by Rogenhofer et al. [43]. Thrombosis and hypercoagulability were linked to pregnancy morbidity rates of 44.7% in SPAPS and 78.2% in SNAPS, with diagnostic tests like AESKULISA® ELISA kits and the Russell viper venom test, as reported by Hu et al. [33] and Liu et al. 2022 [42]. Infections triggering recurrent pregnancy loss or implantation failure were diagnosed through serology for both criteria and non-criteria antibodies. Obstetric APS and ART outcomes were assessed using repeated aPL testing and Doppler ultrasound for uterine and placental blood flow, with studies by Porto et al. [40] and Bruno et al. [41] reporting elevated BMI and complement levels as key factors. Furthermore, systemic non-criteria APS (SNAPS) was diagnosed through aPL testing, including anti-β2GPI and aCL, with clinical assessment, as noted by Barrio-Longarela et al. [35]. Lastly, APS and autoimmune conditions such as systemic lupus erythematosus and cardiovascular risk factors were evaluated through ELISA testing for antiphospholipid antibodies and anti-dsDNA, as described by Cecchi et al. [34] and Liu et al. [42].

The results presented in Table 3 highlight various endometrial and pregnancy outcomes related to antiphospholipid syndrome (APS). Key findings include impaired endometrial receptivity due to reduced ANXA5 expression, which affects implantation, with an increased risk of recurrent implantation failure (RIF) in couples with the M2 haplotype [43,44]. Pregnancy complications such as miscarriage, preterm delivery, and pre-eclampsia were commonly observed, with elevated antiphospholipid antibodies (aPLs), including aCL and aβ2GP1, linked to pregnancy morbidity [32]. A 75% live birth rate was observed, but 37.2% of cases experienced adverse pregnancy outcomes (APOs) [35]. Further, elevated CRP, HLA-DRA, and TNFSF13B were associated with autoimmune responses leading to recurrent miscarriages, fetal death, and pre-eclampsia [36]. APS-related pregnancy complications also included fetal loss, preterm delivery, and cesarean sections, with elevated levels of ANA, C3/C4, and multiple aPLs contributing to these adverse outcomes [31]. Among women with APS, ongoing pregnancy rates were significantly higher in the early initiation group (81.2%) compared to the late initiation group (60.9%), indicating better outcomes with early treatment [39]. Additionally, a vascularization index (VI) linked to poor outcomes was identified in ANA-positive patients, and a higher miscarriage rate was observed in ANA-positive women, although potential improvements with LMWH in ANA-negative recurrent pregnancy loss (RPL) patients were noted

Table 2. *Clinical and Diagnostic Variables in Antiphospholipid Syndrome (APS) and Reproductive Outcomes.*

Group	Clinical Findings	Diagnostic Method	Authors/Year
Recurrent Pregnancy Loss (RPL)	History of ≥3 early miscarriages, ≥1 fetal death, or ≥1 preterm birth due to placental insufficiency/preeclampsia	ELISA for anticardiolipin antibodies, dilute Russell viper venom time for lupus anticoagulant	Eid et al., 2019 [39], Zhang et al., 2024 [36]
Recurrent Implantation Failure (RIF)	M2/ANXA5 haplotype as a potential risk factor, maternal and paternal haplotype carriage, endometrial factors	Genetic analysis of M2/ANXA5 haplotype, IVF/ICSI outcomes	Rogenhofer et al., 2021 [43]
Thrombosis and Hypercoagulability	Thrombosis, pregnancy morbidity (44.7% SPAPS, 78.2% SNAPS), microangiopathy, autoimmune hemolytic anemia	AESKULISA® ELISA test kits, Russell viper venom test for lupus anticoagulant	Hu et al., 2021 [33], Liu et al., 2022 [42]
Infections as Triggers	Infection as a trigger for recurrent pregnancy loss or implantation failure	Serology for criteria and non-criteria antibodies (e.g., anti-cardiolipin, anti-β2GPI, LA)	Junmiao Xiang et al., 2024 [31]
Obstetric APS and ART Outcomes	History of miscarriage, multiparity, elevated BMI, elevated complement levels, ANA positivity	IVF with repeated aPL testing Doppler ultrasound for uterine and placental blood flow	Porto et al., 2022 [40], Bruno et al., 2020 [41]
Systemic Non-Criteria APS (SNAPS)	Pregnancy morbidity, thrombosis, vascular abnormalities, idiopathic infertility, ART failure	aPL testing (including anti-β2GPI, aCL, aPS/PT) with ELISA testing and clinical assessment	Barrio-Longarela et al., 2022 [35]
APS and Autoimmune Conditions	Thrombosis, pregnancy complications, systemic lupus erythematosus, cardiovascular risk factors (obesity, smoking)	ELISA testing for antiphospholipid antibodies (aCL, aβ2GPI), Anti-dsDNA, anti-thyroid antibodies	Cecchi et al., 2024 [34], Liu et al., 2022 [42]

Table 3. *Endometrial Receptivity and Pregnancy Outcomes in Patients with Antiphospholipid Syndrome (APS).*

Group	Endometrial Receptivity Outcomes	Pregnancy Outcomes	Autoimmune Activity	Author(s) / Year
Endometrial Receptivity	Impaired due to reduced ANXA5 expression, affecting implantation	Increased RIF risk in couples with M2 haplotype	Altered ANXA5-related anticoagulant function, pro-thrombotic at implantation sites	Rogenhofer et al. 2021 [43], Pang et al. 2024 [44]
Pregnancy Complications	-	Pregnancy morbidity (miscarriage, preterm delivery)	Examined via aPLs, aCL, aβ2GP1, aPS, LAC	Naranjo et al. 2022 [32]
	-	History of pregnancy morbidity (gestational loss, preterm birth due to eclampsia or placental insufficiency)	Analysis of antiphospholipid antibodies, associations with thrombotic events and pregnancy complications	Hu et al. 2021 [33]
	-	75% live birth rate; 37.2% had adverse pregnancy outcome (APO)	Elevated aGAPSS for high risk	Barrio-Longarela et al. 2022 [35]
	-	Recurrent miscarriages, fetal death, pre-eclampsia	Increased CRP, HLA-DRA, and TNFSF13B associated with autoimmune response	Zhang et al. 2024 [36]
APS & Pregnancy	-	Fetal loss, preterm delivery, FGR, postpartum hemorrhage, cesarean section	Positive ANA, elevated C3/C4, multiple antiphospholipid antibodies associated with adverse outcomes	Junmiao Xiang et al. 2024 [31]
	-	Ongoing pregnancy rate higher in early initiation group (81.2% vs 60.9%); lower miscarriage	-	Eid et al. 2019 [39]
	Idiopathic infertility in 31.25%, ART success in 88.88%	Pregnancy achieved in 88.88%, live births 77.77%	70.31% showed autoimmune features (e.g., ANA positivity)	Porto et al. 2022 [40]
	Altered vascularization index (VI) linked to poor outcomes in ANA+ patients	Higher miscarriage rate in ANA+ women; potential improvement with LMWH in ANA- RPL patients	ANA positivity linked to impaired uterine and placental blood flow	Bruno et al. 2020 [41]
	-	Pregnancy morbidity in APS (SPAPS: 44.7%, SNAPS: 78.2%)	Positive associations found for aPLs with thrombosis (aPS/PT, aPS IgG, APhL IgG)	Liu et al. 2022 [42]
Uterine Perfusion & Inflammation	Impaired uterine perfusion with elevated PI (>2.6) and RI (>0.86)	-	Positive correlation between ACA-IgM levels and uterine artery RI ($r = 0.43$, $p < 0.01$)	Pang et al. 2024 [44]
	Decreased due to unbalanced Th1/Th2 and Th17/Treg ratios; elevated pro-inflammatory cytokines (e.g., IL-2, TNF-α)	Lower implantation rate, clinical pregnancy rate, and take-home baby rate in aPL-positive women	Elevated Th1 and Th17 cells, higher pro-inflammatory cytokines; decreased Th2 and Treg cells	Wu et al. 2022 [46]
Inflammation & Immunity	-	Recurrent miscarriages, fetal death, pre-eclampsia	Increased CRP, HLA-DRA, and TNFSF13B associated with autoimmune response	Zhang et al. 2024 [36]
	-	Fetal loss, preterm delivery, FGR, postpartum hemorrhage, cesarean section, adverse pregnancy outcomes	Positive ANA, elevated complement C3/C4, multiple antiphospholipid antibodies associated with adverse outcomes	Junmiao Xiang et al. 2024 [31]
	Decreased due to unbalanced Th1/Th2 and Th17/Treg ratios; elevated pro-inflammatory cytokines (e.g., IL-2, TNF-α)	Lower implantation rate, clinical pregnancy rate, and take-home baby rate in aPL-positive women	Elevated Th1 and Th17 cells, higher pro-inflammatory cytokines; decreased Th2 and Treg cells	Wu et al. 2022 [46]

[41]. The study also found significant associations between uterine perfusion, inflammation, and pregnancy outcomes, with impaired uterine perfusion and elevated inflammatory markers correlating with poorer implantation and pregnancy rates in aPL-positive women [46].

Integrative Pathophysiological Framework.

The molecular and clinical findings presented in Tables 1-3 indicate complex interactions between antiphospholipid antibodies (aPL), immune dysregulation, and placental function. Importantly, these pathways can be integrated under the unifying concept of "immunothrombosis," where aPL positivity initiates a cascade of inflammatory and thrombotic events within the placenta. In this model, aPL antibodies activate the complement system, particularly components C3 and C4, leading to endothelial injury and microvascular damage. This triggers recruitment of immune cells, such as Th1 and Th17 lymphocytes, and release of pro-inflammatory cytokines including IL-2 and TNF-α, creating a hostile environment for trophoblast invasion and placental development. Trophoblast dysfunction, impaired spiral artery remodeling, and local thrombosis collectively contribute to placental insufficiency and adverse pregnancy outcomes, including miscarriage, preeclampsia, fetal growth restriction (FGR), and preterm delivery. This integrative mechanism explains how complement activation, immune cell infiltration, and trophoblast failure converge to drive the pathogenesis of obstetric APS. Figure 3 illustrates this immunothrombosis model, depicting how aPL positivity initiates these cascading molecular events in the placenta, ultimately linking molecular mechanisms with the observed clinical complications.

Discussion.

Molecular Mechanisms:

Antiphospholipid syndrome (APS) is an autoimmune thrombotic disorder linked to aPL abnormalities and clinical manifestations such as thrombosis and recurrent abortions. Key molecular mechanisms involve impaired endometrial receptivity due to reduced annexin A5 (ANXA5) expression, complement activation, immune cell infiltration, and trophoblast dysfunction, which are unified under the pathophysiological framework of immunothrombosis. In this context, aPL antibodies initiate complement activation (especially C3/C4), leading to endothelial damage and immune cell recruitment. The ensuing inflammatory milieu, characterized by elevated IL-2 and TNF-α, further compromises trophoblast invasion and function, disrupting placental development

The current SLR included studies from multiple countries, such as Mexico, China, Egypt, Italy, Brazil, Germany, Sweden, the UK, Iraq, Spain, and Armenia. Sample sizes varied significantly, ranging from small cohorts to larger studies, with sample sizes as few as 32 participants to as many as 1574 participants. The mean age of participants also varied widely, from as young as 11.75 years to a range of 30-45 years in most studies. The SLR encompassed various study designs, including cross-sectional, prospective, and retrospective cohort studies, with some studies using genetic analysis to identify risk factors for recurrent implantation failure. Evidence from the review highlighted that couples with the M2 haplotype face higher risks of RIF due to reduced ANXA5 expression, while elevated aPLs, such as aCL and aβ2GP1, correlate with recurrent pregnancy loss, preterm delivery, and pre-eclampsia, all linked to impaired

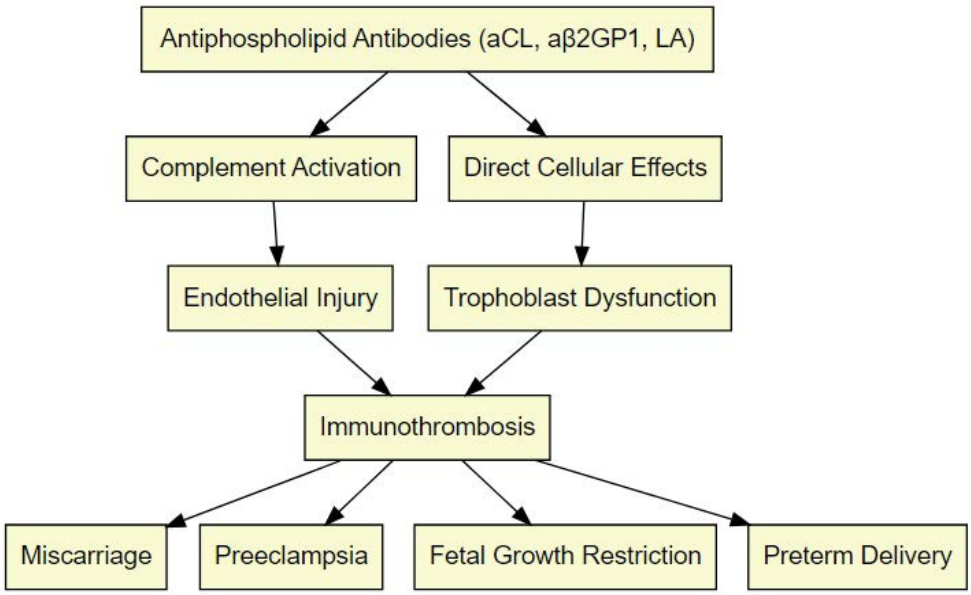

Figure 3. *Immunothrombosis Model Linking aPL to Placental Complications.*

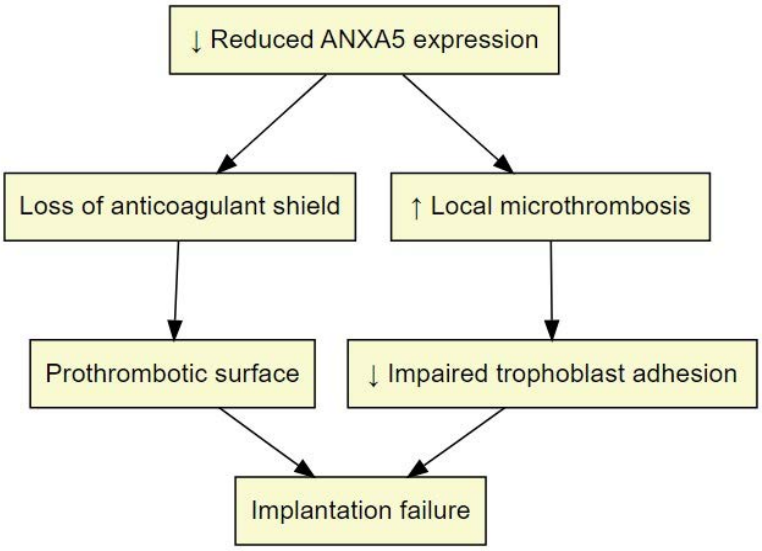

Figure 4. *Molecular Impact of Reduced ANXA5 on Implantation.*

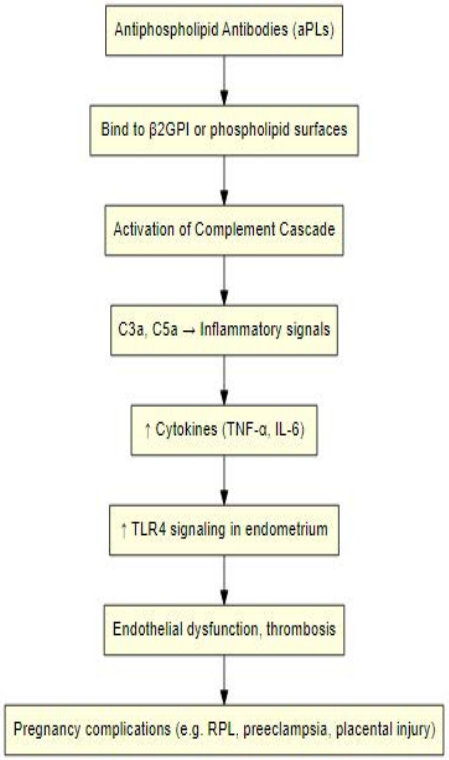

Figure 5. *Immune and Complement Activation in Obstetric APS.*

endometrial stromal cell function and increased inflammation. Figure 4 illustrates this molecular pathway, showing how reduced ANXA5 leads to local pro-thrombotic changes that impair trophoblast adhesion and implantation.

Additionally, elevated antiphospholipid antibodies (aPLs), such as aCL and aβ2GP1, were associated with recurrent pregnancy loss, preterm delivery, and pre-eclampsia, indicating their role in impaired endometrial stromal cell function, leading to increased inflammation and impaired decidualization. Notably, one study found that preeclampsia amplifies these effects by exacerbating inflammation and oxidative stress, further impairing decidualization through TLR4 signaling [47]. Figure 5 provides an overview of how aPLs activate complement cascades and inflammatory pathways, leading to pregnancy complications in APS.

aPLs activate the complement system, generating inflammatory mediators (C3a, C5a) that stimulate cytokine release and TLR4 signaling. These processes contribute to endothelial dysfunction, hypercoagulability, and adverse pregnancy outcomes in obstetric APS. These molecular mechanisms have

important clinical implications, as they suggest potential targets for therapy such as complement inhibitors, and indicate that biomarkers like ANXA5 levels or complement fragments may help identify patients at higher risk.

These findings highlight the necessity of understanding the molecular mechanisms underlying endometrial receptivity in APS patients. The same studies also examined how molecular factors and endometrium receptivity are involved. Furthermore, the application of PCR arrays in clinical research indicates that patients suffering from endometrial receptivity defects due to pathophysiological similarities with APS, such as polycystic ovary syndrome (PCOS), undergo drastic changes in endometrial gene expression LTC levels [48]. Clinically, these findings underscore the importance of investigating molecular mechanisms underlying endometrial receptivity in APS, as understanding these pathways can inform targeted therapeutic strategies. The studies collectively hypothesize that certain molecular patterns might drive impaired receptivity across diverse infertility contexts, highlighting the need for personalized approaches in managing APS-related reproductive complications.

Importantly, the interplay between aPL positivity, complement activation, immune cell infiltration (e.g., Th1/Th17 imbalance), and trophoblast dysfunction can now be understood under the unifying pathophysiological framework of "immunothrombosis." In this context, aPL antibodies initiate complement activation (especially C3/C4), leading to endothelial damage, which in turn triggers immune cell recruitment. The ensuing inflammatory milieu, characterized by elevated IL-2 and TNF-α, further compromises trophoblast invasion and function, disrupting placental development. This integration explains how immune dysregulation, endothelial injury, and placental insufficiency interact in a cascade-like manner, driving pregnancy complications in APS. Clinically, understanding these pathways may guide future trials investigating targeted treatments like complement inhibitors, and help develop prognostic models that integrate molecular and immunological markers to personalize therapy.

Hormonal Interactions:

Mechanistically, hormonal dysregulation plays a critical role in APS-related pregnancy complications, involving interactions between estrogen, progesterone, and immune mediators that influence endometrial receptivity. Imbalanced cytokine ratios and elevated pro-inflammatory cytokines (e.g., IL-2, TNF-α) contribute to altered uterine perfusion and implantation failure.

Evidence from the SLR shows elevated inflammatory markers and autoimmune responses, such as CRP, HLA-DRA, and TNFSF13B, in APS patients with pregnancy complications. Several studies stress the role of estrogens and specific cytokines in maintaining endometrial receptivity, emphasizing that hormonal imbalances disrupt embryo implantation and contribute to RIF [49,50]. Other research demonstrated that aPL can enhance inflammatory effects on the endometrium through TLR4 pathways [51]. aligning with the SLR's findings of aPL's negative impact on endometrial function. Studies on luteinization insufficiency indicate that variations in progesterone levels significantly influence endometrial functionality [52]. Emerging research also highlights how preeclampsia-associated hormonal imbalances disrupt progesterone and estrogen pathways critical for implantation.

Clinically, this underscores the necessity of monitoring hormonal profiles in APS patients. Recognizing hormonal and immune balance during early pregnancy is vital for preventing implantation failures and pregnancy loss. The insights from recent studies expand our understanding of how aPL influences decidualization and broader immune interactions in the uterine environment, informing therapeutic approaches to support reproductive success in APS.

Diagnostic Tools:

Mechanistically, APS-related pregnancy complications arise from aPL-mediated thrombosis, endothelial dysfunction, and immune dysregulation, necessitating precise diagnostic tools to identify patients at risk.

Evidence from the review clarifies the role of key diagnostic markers in APS. For recurrent pregnancy loss (RPL), elevated levels of aCL, aβ2GPI, and LA are frequently observed, correlating with miscarriage, preterm delivery, and pre-eclampsia. The M2/ANXA5 haplotype is linked to increased RIF risk, while elevated CRP, HLA-DRA, and TNFSF13B levels indicate autoimmune activity associated with pregnancy complications. Early treatment initiation results in significantly higher ongoing pregnancy rates (81.2%) compared to late intervention (60.9%) [53]. Doppler ultrasonography and ELISA are widely used, though variability exists regarding their sensitivity and specificity for predicting RPL. Integration of preeclampsia markers, such as sFlt-1/PlGF ratios, has shown promise in enhancing diagnostic precision.

Regarding RIF, studies identify genetic factors like the M2/ANXA5 maternal and paternal haplotype as pivotal contributors, alongside fertility problems. Complementary findings suggest immune profiling and Doppler ultrasound as standard diagnostic procedures; however, emerging literature advocates incorporating genetic susceptibility analysis to refine management interventions for individuals seeking ART services [54-56]. Notably, some studies propose that genetic predispositions could explain variability in treatment outcomes, whereas others argue that environmental and immune factors play a more dominant role [57]. This divergence underscores the need for multi-factorial investigations integrating genetic, environmental, and immunological assessments. Preeclampsia-associated cytokines, such as TNF-α and IL-6, have also been highlighted for their potential role in refining diagnostic criteria. The association between APS and thrombosis is characterized by elevated cytokines such as TNF-α and IL-6. Contrasting studies offer varying insights into the role of inflammatory markers. Some evidence highlights their diagnostic utility through ELISA for cytokine levels and other biomarkers for inflammation [58,59]. Meanwhile, other research critiques the variability and reproducibility of cytokine measurements, suggesting that laboratory monitoring alone may not reliably predict thrombotic risk [60].

Clinically, these findings emphasize the importance of comprehensive diagnostic protocols combining immunological assays, genetic testing, and vascular assessments to identify

high-risk APS patients. Standardizing assays for cytokine measurements and exploring new biomarkers is essential for accurately predicting thrombotic risk and tailoring individualized management strategies. Future research should focus on bridging gaps in diagnostic consistency and evaluating multi-marker approaches to improve outcomes in APS-related reproductive care.

Treatment Strategies:

Mechanistically, treatment strategies for APS focus on preventing thrombosis and managing immune dysregulation to protect pregnancy outcomes. Anticoagulation and immunomodulatory therapies target hypercoagulability and inflammation driven by aPLs and related immune pathways.

Evidence demonstrates that early treatment initiation substantially improves pregnancy outcomes, increasing ongoing pregnancy rates from 60.9% to 81.2%. LMWH has shown efficacy, especially in ANA-negative RPL patients. Regular monitoring of aPL levels, along with immunosuppressants and anticoagulants, is crucial for managing hypercoagulability, recurrent miscarriages, and preterm birth risks. Infections have been identified as potential triggers for APS flares, highlighting the importance of testing for transient versus persistent aPL elevations [53]. Obstetric APS significantly impacts ART outcomes, with ANA assays and Doppler ultrasonography aiding in assessing placental blood flow and fetal well-being [61]. Early recognition and management of preeclampsia are vital for improving maternal and fetal outcomes. Diagnosing SNAPS remains challenging, with recent studies advocating more inclusive criteria to identify atypical presentations [42,62]. APS often coexists with SLE, but positive serologies alone do not confirm SLE in the absence of clinical features [63,64]. Clinically, these insights underscore the necessity of individualized therapeutic strategies. Anticoagulation therapies, such as LMWH, along with close rheumatological monitoring, are essential for reducing miscarriage and preterm birth risks. Incorporating genetic, immunological, and inflammatory markers into patient care pathways ensures precise risk assessment and treatment planning. The review highlights the need for continued research into optimizing therapeutic interventions, refining diagnostic criteria, and addressing the complex interplay of APS with other autoimmune conditions.

In conclusion, the evolving landscape of APS diagnosis and management reflects ongoing research efforts aimed at refining clinical criteria and enhancing laboratory testing methodologies. The inclusion of preeclampsia-specific markers, such as sFlt-1 and PlGF, into diagnostic protocols has opened new avenues for early detection and intervention. The integration of genetic, immunological, and inflammatory assessments into routine diagnostics is crucial for improving patient outcomes. Future research should also focus on these relations and highlight all the factors inherent in the diagnosis of such a diverse syndrome. The current review focuses more on the relationship between antiphospholipid syndrome, molecular and clinical effects, receptivity of the endometrium and pregnancy-related complications. We established that recurrent implantation failure and miscarriages in ANA-positive women are a result of poor ANXA5 function, inadequate vascularization, and dysregulated cytokine activity. Preeclampsia, characterized by endothelial dysfunction and immune dysregulation, exacerbates these complications, further impairing pregnancy outcomes. High levels of aPLs, Th1/Th17 cytokines, and decreased endothelial stability are associated with poor pregnancy outcomes, including miscarriage, preterm birth, and placental complications. Once started early on, anticoagulation therapy optimizes pregnancy outcomes, while persistent inflammation and aPL positivity remain risk factors for impaired uterine blood flow and adverse outcomes. The same has been indicated to apply to women with APS who have been described to have endometrial poor receptivity due to various factors, including abnormalities in annexin A5 (ANXA5), a protein which plays an important role in the formation of placenta, resulting in RIF in addition to higher miscarriage rates in women with ANA positive [65,66].

Literature also reveals that diminished vascular density has been associated with decreased cytokine bipolarity and poor uterine blood flow, contributing to implantation failure [67]. The presence of preeclampsia in APS patients has been linked to aggravated vascular impairments, necessitating tailored management strategies. This is especially the case if the cytokines are of Th1 /Th2 ratios that promote immunity responses unfavorable for maintaining pregnancy in women. Antiphospholipid has been identified as a factor that significantly raises the chances of having a miscarriage and a preterm birth. It has been established that aPL positivity is indicative of a higher risk of these adverse outcomes; thus, pregnant women with aPL should be monitored and managed very closely [68]. Another comparative work highlights potential precursors to pregnancy complications in women with APA and prior adverse pregnancy history and shows that the possible predictors are age, APO, history, ANA titer, and steroid use; the possible preventers are LMWH use, rheumatology follow-up, and high serum C3 level [69].

The current review further demonstrates that aPL positivity is associated with a higher incidence of adverse outcomes, necessitating careful monitoring and management during pregnancy. Another study emphasizes that the presence of antiphospholipid antibodies correlates with increased risks of miscarriage and preterm birth [70]. Tailored therapeutic strategies that include addressing preeclampsia-related risks are essential for improving outcomes.

Practical recommendations emphasize early and thorough screening for aPL positivity in women with a history of RPL or RIF, using advanced immunological assays and Doppler ultrasonography to evaluate placental blood flow and endometrial receptivity. Screening for preeclampsia markers alongside aPL levels can enhance risk stratification and guide timely intervention. Incorporating genetic susceptibility testing, such as M2/ANXA5 haplotype analysis, can refine management strategies for patients undergoing ART. Monitoring inflammatory cytokine levels (e.g., TNF-α, IL-6) and vascular markers is crucial for assessing thrombotic risk and tailoring personalized treatment plans. Close management of pregnant women with APS, including the use of anticoagulation therapies such as LMWH and regular follow-ups with rheumatology specialists, is essential to minimize the risks of miscarriage and preterm birth. Furthermore, developing standardized and

inclusive diagnostic criteria for SNAPS is needed to improve the recognition and care of atypical APS cases. Future research should address gaps in diagnostic methodologies, explore the interplay between APS and other autoimmune conditions, and evaluate the long-term efficacy of current therapeutic strategies.

Conclusion.

The findings from the systematic literature review on the molecular mechanisms of impaired endometrium receptivity in patients with antiphospholipid syndrome underscore the critical role of immune system dysregulation and endothelial dysfunction in the impaired endometrial receptivity observed in APS patients. Preeclampsia, as both a contributor to and a result of APS, highlights the complex interplay of vascular and immune pathways in these patients.

The studies provide a deeper understanding of the molecular mechanisms underlying reproductive failure in APS and highlight the importance of early and effective diagnostic and therapeutic strategies. Future clinical research should explore whether complement inhibitors and molecular biomarkers can improve outcomes, paving the way for more personalized management in obstetric APS. This review emphasizes the need for further research into advanced diagnostic tools and treatment approaches, particularly those that can mitigate the impact of APS on pregnancy outcomes. APS is a multifactorial condition, with immune and genetic factors playing a central role in the pathogenesis of reproductive complications, and these findings provide a foundation for more targeted interventions in managing APS-related fertility issues.

Limitations of the study.

Another weakness of the research evidenced by this systematic literature review is that the studies include diverse designs, populations, and sizes that can influence the outcome generalization. Otherwise, a variety of geographic provenience, which may imply the differences in the healthcare systems and diagnostic criteria, may introduce the source of bias. Some also do not have a follow-up after treatment was given, hence failing to capture long-term reproductive changes. In addition, differences in the molecular markers and diagnostic methods used in different research also introduce some difficulties in defining and perfecting precise and generalizable diagnostic and therapeutic guidelines for predicting and managing APS-linked reproductive complications.

Suggestions for Future Research.

Future research on APS should look into the potential contribution of non-criteria antibodies and any new biomarker that may improve diagnostic accuracy. Specific attention should be paid to preeclampsia as a co-factor, with studies aimed at developing preeclampsia-focused diagnostic and therapeutic approaches in APS. Explorations of the genetic factors determining the endometrial receptivity and the pregnancy outcome may assist in achieving targeted, individualized therapies. More studies are needed that will profile the new anticoagulants and immunomodulatory therapies and their impact on a wide range of patients. In addition, further research is warranted examining how infections moderate aPL positivity in order to develop better strategies for prevention. Cost-effectiveness analysis and evaluation of the practicality of the use of such diagnostic devices as a genetic profiler and assays for cytokines can help their incorporation into some clinical practice. Lastly, combining expertise in immunology, genetics, and obstetrics will be beneficial.

Authors' contribution.

Gaukhar Koshkimbayeva Gaukhar Kurmanova

Conceptualization: Madina Khalmirzaeva, Gaukhar Kurmanova

Data curation: Almagul Kurmanova, Gulfairuz Urazbayeva

Formal analysis: Damilya Salimbayeva, Zhanar Kypshakbayeva

Funding acquisition: Madina Khalmirzaeva, Almagul Kurmanova

Investigation: Gulfairuz Urazbayeva, Damilya Salimbayeva

Methodology: Almagul Kurmanova, Gaukhar Kurmanova

Project administration: Madina Khalmirzaeva, Zhanar Kypshakbayeva

Resources: Gaukhar Koshkimbayeva, Gaukhar Kurmanova

Software: Damilya Salimbayeva, Gulfairuz Urazbayeva

Supervision: Zhanar Kypshakbayeva, Almagul Kurmanova

Validation: Madina Khalmirzaeva, Damilya Salimbayeva

Visualization: Gulfairuz Urazbayeva, Gaukhar Koshkimbayeva

Writing–original draft: Madina Khalmirzaeva, Almagul Kurmanova

Writing–review & editing: Gaukhar Koshkimbayeva, Zhanar Kypshakbayeva

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: 1023143) and Research Registry (UIN: reviewregistry1974) website.

Ethics Statement.

This study is a systematic literature review and adhered to the principles outlined in the Declaration of Helsinki. The authors fully complied with ethical standards, ensuring the absence of plagiarism, data fabrication, and double publication. Informed consent was obtained from all patients or their legal guardians prior to participation in the reviewed studies, and all participants were informed in advance about the objectives and procedures. Given the nature of this study, approval by the university's academic board was not required. This systematic review does not require ethics committee review, as it does not involve direct patient intervention or data collection.

Conflicts of interest.

The authors declare that there is no conflict of interest

Funding/Support.

This research was funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. AP19678324).

REFERENCES

1. Negrini S, Pappalardo F, Murdaca G, et al. The antiphospholipid syndrome: from pathophysiology to treatment. Clin Exp Med. 2017;17:257-267.

2. Barbhaiya M, Zuily S, Naden R, et al. The 2023 ACR/ EULAR Antiphospholipid Syndrome Classification Criteria. Arthritis and Rheumatology 2023;75:1687-702.
3. Laurent C, Ricard L, Nguyen Y, et al. Triple positive profile in antiphospholipid syndrome: prognosis, relapse and management from a retrospective multicentre study. RMD Open. 2023;9:e002534.
4. Vorobjeva NV, Chernyak BV. NETosis: Molecular Mechanisms, Role in Physiology and Pathology. Biochemistry (Mosc). 2020;85:1178-1190.
5. Chaturvedi S, Brodsky RA, McCrae KR. Complement in the Pathophysiology of the Antiphospholipid Syndrome. Front Immunol. 2019;10:449.
6. Mayer-Pickel K, Nanda M, Gajic M, et al. Preeclampsia and the Antiphospholipid Syndrome. Biomedicines. 2023;11:2298.
7. D'Ippolito S, Barbaro G, Paciullo C, et al. Antiphospholipid Syndrome in Pregnancy: New and Old Pathogenetic Mechanisms. Int J Mol Sci. 2023;24:3195.
8. Wulandari LP, Apsari DD, Hapsari A. Development of Educational Media for Adolescent Reproductive Health. Futur Med. 2023;2:17-2.
9. Bajpai K, Acharya N, Prasad R, et al. Endometrial receptivity during the preimplantation period: A narrative review. Cureus. 2023;15:e37753.
10. Malanchuk L, Martynyuk V, Malanchyn I, et al. Perspective management in the treatment of genital endometriosis in women with polymorphism of gens gstt1 and gstm1. Georgian Med News. 2017;272:33-37.
11. Barbhaiya M, Zuily S, Naden R, et al. The 2023 ACR/ EULAR antiphospholipid syndrome classification criteria. Arthritis Rheumatol. 2023;75:1687-702.
12. Chaiworapongsa T, Romero R, Gotsch F, et al. Preeclampsia at term can be classified into 2 clusters with different clinical characteristics and outcomes based on angiogenic biomarkers in maternal blood. Am J Obstet Gynecol. 2023;228:569.e1-569.e24.
13. Jung E, Romero R, Yeo L, et al. The etiology of preeclampsia. Am J Obstet Gynecol. 2022;226:S844-S866.
14. de Wit JBF, Adam PCG, den Daas C, et al. Sexually transmitted infection prevention behaviours: health impact, prevalence, correlates, and interventions. Psychol Health. 2023;38:675-700.
15. Bustamante JG, Goyal A, Rout P, et al. Antiphospholipid Syndrome. 2024. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
16. Lane LC, Owen CJ, Cheetham T. Pathophysiology, diagnosis, and management o autoimmune polyglandular syndromes in childhood and adolescence. In: Endocrinology. Cham: Springer International Publishing. 2023:1-46.
17. Alijotas-Reig J, Esteve-Valverde E, Anunciación-Llunell A, et al. Pathogenesis, diagnosis and management of obstetric antiphospholipid syndrome: A comprehensive review. J Clin Med. 2022;11:675.
18. Murvai VR, Galiș R, Panaitescu A, et al. Antiphospholipid syndrome in pregnancy: a comprehensive literature review. BMC Pregnancy Childbirth. 2025;25:337.
19. Loay C. The role of the immune system in the formation and development of diseases of the oral cavity. Futur Med. 2022;1:51-62.
20. Martínez-Taboada VM, Blanco-Olavarri P, Del Barrio-Longarela S, et al. Non-criteria obstetric antiphospholipid syndrome: How different is from Sidney criteria? A single-center study. Biomed. 2022;10:2938.
21. Pires da Rosa G, Bettencourt P, Rodríguez-Pintó I, et al. "Non-criteria" antiphospholipid syndrome: A nomenclature proposal. Autoimmun Rev. 2020;19:102689.
22. Sagindykova AA, Bazylbekova ZO, Sagindykova BA. Ways of Prognosis and Reduction of Obstetric and Perinatal Complications at Pregnancy Chronic Pyelonephritis. Biomed Pharmacol J. 2017;10:535-47.
23. Amagoh FE. Healthcare Policies in Kazakhstan: A Public Sector Reform Perspective. Healthcare Policies in Kazakhstan: A Public Sector Reform Perspective. 2021;1-110.
24. Semenova Y, Lim L, Salpynov Z, et al. Historical evolution of healthcare systems of post-soviet Russia, Belarus, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, Armenia, and Azerbaijan: A scoping review. Heliyon. 2024;10:e29550.
25. Liu T, Gu J, Wan L, et al. “Non-criteria” antiphospholipid antibodies add value to antiphospholipid syndrome diagnoses in a large Chinese cohort. Arthritis Res Ther. 2020;22:33.
26. El Hasbani G, Taher AT, Sciascia S, et al. Antiphospholipid syndrome: the need for new international classification criteria. Expert Rev Clin Immunol. 2021;17:385-394.
27. Knight JS, Erkan D. Rethinking antiphospholipid syndrome to guide future management and research. Nat Rev Rheumatol. 2024;20:377-388.
28. Franchuk VV, Myroshnychenko MS, Hnatjuk MS, et al. Implementation of the decision tree method in expert analysis of the medical errors in obstetric practice. Pol Merkur Lekarski. 2023;51:128-134.
29. Boyarchuk O, Komorovsky R, Kovalchuk T, et al. Socio-demographic and medical predictors of rheumatic heart disease in a low-risk population. Pediatr Pol. 2018;93:325-330.
30. Álvarez D, Winter HE, Velasquez Franco CJ, et al. Improving diagnosis in patients with obstetric antiphospholipid syndrome through the evaluation of non-criteria antibodies. Clin Transl Immunology. 2024;13:e70021.
31. Junmiao Xiang MM, XueKe Guo MM, Ruru Bao MM, et al. Non-criteria and criteria antiphospholipid antibodies and their association with pregnancy outcomes in women with a history of miscarriage: A retrospective study. J Reprod Immunol. 2024;165:104316.
32. Naranjo L, Stojanovich L, Djokovic A, et al. Circulating immune-complexes of IgG/IgM bound to B2-glycoprotein-I associated with complement consumption and thrombocytopenia in antiphospholipid syndrome. Front Immunol. 2022;13:957201.
33. Hu C, Li S, Xie Z, et al. Evaluation of the Diagnostic Value of Non-criteria Antibodies for Antiphospholipid Syndrome Patients in a Chinese Cohort. Front Immunol. 2021;12:741369.
34. Cecchi I, Radin M, Barinotti A, et al. Type I interferon pathway activation across the antiphospholipid syndrome spectrum: associations with disease subsets and systemic antiphospholipid syndrome presentation. Front Immunol. 2024;15:1351446.
35. Del Barrio-Longarela S, Martínez-Taboada VM, Blanco-Olavarri P, et al. Does Adjusted Global Antiphospholipid Syndrome Score (aGAPSS) Predict the Obstetric Outcome in

Antiphospholipid Antibody Carriers? A Single-Center Study. Clin Rev Allergy Immunol. 2022;63:297-310.
36. Zhang Y, Jin S, Tian W, et al. Proteomics of Serum Samples for the Exploration of the Pathological Mechanism of Obstetric Antiphospholipid Syndrome. J Proteome Res. 2024;23:289-300.
37. Torres-Jimenez AR, Ramirez-Nova V, Cespedes-Cruz AI, et al. Primary antiphospholipid syndrome in pediatrics: beyond thrombosis. Report of 32 cases and review of the evidence. Pediatr Rheumatol Online J. 2022;20:13.
38. Song X, Fan Y, Jia Y, et al. A novel aGAPSS-based nomogram for the prediction of ischemic stroke in patients with antiphospholipid syndrome. Front Immunol. 2022;13:930087.
39. Eid MI, Abdelhafez MS, El-Refaie W, et al. Timing of initiation of low-molecular-weight heparin administration in pregnant women with antiphospholipid syndrome: a randomized clinical trial of efficacy and safety. Int J Womens Health. 2019;11:41-47.
40. Del Porto F, Ferrero S, Cifani N, et al. Antiphospholipid antibodies and idiopathic infertility. Lupus. 2022;31:347-353.
41. Bruno V, Ticconi C, Martelli F, et al. Uterine and placental blood flow indexes and antinuclear autoantibodies in unexplained recurrent pregnancy loss: should they be investigated in pregnancy as correlated potential factors? A retrospective study. BMC Pregnancy Childbirth. 2020;20:44.
42. Liu X, Zhu L, Liu H, et al. Non-criteria antiphospholipid antibodies in antiphospholipid syndrome: Diagnostic value added. Front Immunol. 2022;13:972012.
43. Rogenhofer N, Markoff A, Ennerst X, et al. Maternal and paternal carriage of the annexin A5 M2 haplotype: a possible risk factor for recurrent implantation failure (RIF). J Thromb Thrombolysis. 2020;50:772-781.
44. Pang H, Xiao Z, Huang Z, et al. Correlation between serum markers and midluteal phase Doppler assessment of uterine arterial blood flow in unexplained recurrent pregnancy loss. Reprod Sci. 2025;32:158-167.
45. Harmoosh SK, Nori W, Hamed RM. Is there a change in platelet indices among pregnant with antiphospholipid syndrome? Immunopathol Persa. 2022;9:e32410.
46. Wu L, Fang X, Lu F, et al. Anticardiolipin and/or anti-β2-glycoprotein-I antibodies are associated with adverse IVF outcomes. Front Immunol. 2022;13:986893.
47. Tong M, Kayani T, Jones DM, et al. Antiphospholipid antibodies increase endometrial stromal cell decidualization, senescence, and inflammation via Toll-like receptor 4, reactive oxygen species, and p38 MAPK signaling. Arthritis Rheumatol. 2022;74:1001-1012.
48. Bai X, Zheng L, Li D, et al. Research progress of endometrial receptivity in patients with polycystic ovary syndrome: a systematic review. Reprod Biol Endocrinol. 2021;19:122.
49. Günther V, Allahqoli L, Deenadayal-Mettler A, et al. Molecular determinants of uterine receptivity: Comparison of successful implantation, recurrent miscarriage, and recurrent implantation failure. Int J Mol Sci. 2023;24:17616.
50. Mrozikiewicz AE, Ożarowski M, Jędrzejczak P. Biomolecular markers of recurrent implantation failure-A review. Int J Mol Sci. 2021;22:10082.
51. Zhang M, Xu T, Tong D, et al. Research advances in endometriosis-related signaling pathways: A review. Biomed Pharmacother. 2023;164:114909.
52. Sun B, Yeh J. Non-invasive and mechanism-based molecular assessment of endometrial receptivity during the window of implantation: Current concepts and future prospective testing directions. Front Reprod Health. 2022;4:863173.
53. Vandevelde A, Devreese KMJ. Laboratory diagnosis of antiphospholipid syndrome: Insights and hindrances. J Clin Med. 2022;11:2164.
54. Schreiber K, Hunt BJ. Managing antiphospholipid syndrome in pregnancy. Thromb Res. 2019;181:S41-S46.
55. Jarne-Borràs M, Miró-Mur F, Anunciación-Llunell A, et al. Antiphospholipid antibodies in women with recurrent embryo implantation failure: A systematic review and meta-analysis. Autoimmun Rev. 2022;21:103101.
56. Yang J, Liang M. Risk factors for pregnancy morbidity in women with antiphospholipid syndrome. J Reprod Immunol. 2021;145:103315.
57. Lopez-Pedrera C, Barbarroja N, Patiño-Trives AM, et al. New biomarkers for atherothrombosis in antiphospholipid Syndrome: Genomics and epigenetics approaches. Front Immunol. 2019;10:764.
58. Devreese KMJ. How to Interpret Antiphospholipid Laboratory Tests. Curr Rheumatol Rep. 2020;22:38.
59. Devreese KMJ. Laboratory testing for non-criteria antiphospholipid antibodies: Anti-phosphatidylserine/prothrombin antibodies (aPS/PT). Methods Mol Biol. 2023;2663:315-27.
60. Yasmeen F, Pirzada RH, Ahmad B, et al. Understanding autoimmunity: Mechanisms, predisposing factors, and cytokine therapies. Int J Mol Sci. 2024;25:7666.
61. Rhein AK, Rabinovich A, Abuhasira R, et al. Obstetric antiphospholipid syndrome carries an increased lifetime risk for obstetric and thrombotic complications-a population-based study. Res Pract Thromb Haemost. 2024;8:102430.
62. Caraiola S, Voicu L, Jurcut C, et al. Criteria and non-criteria antiphospholipid antibodies in antiphospholipid syndrome: How strong are they correlated? Biomedicines. 2023;11:2192.
63. Pengo V. Additional laboratory tests to improve on the diagnosis of antiphospholipid syndrome. J Thromb Haemost. 2020;18:1846-1848.
64. Devreese KMJ, Zuily S, Meroni PL. Role of antiphospholipid antibodies in the diagnosis of antiphospholipid syndrome. J Transl Autoimmun. 2021;4:100134.
65. Baiazid L, Hraib M. Effects of low-dose aspirin and heparin on the pregnancy outcome in women with antiphospholipid syndrome. Ann Med Surg (Lond). 2022;83:104807.
66. Neto A, Martins P, Capela S, et al. Ab0542 pregnancy outcomes in antiphospholipid syndrome: 8 year-experience from a multidisciplinary unit. Ann Rheum Dis. 2019;78:1732-3.
67. Branch DW, Lim MY. How I diagnose and treat antiphospholipid syndrome in pregnancy. Blood. 2024;143:757-768.
68. Saccone G, Berghella V, Maruotti GM, et al. Antiphospholipid antibody profile based obstetric outcomes of primary antiphospholipid syndrome: the PREGNANTS study. Am J Obstet Gynecol. 2017;216:525.e1-525.e12.

69. Li X, Deng X, Duan H, et al. Clinical features associated with pregnancy outcomes in women with positive antiphospholipid antibodies and previous adverse pregnancy outcomes: a real-world prospective study. Clin Rheumatol. 2021;40:193-204.

70. Chen J, Yue J, Lu Y, et al. Recurrent miscarriage and low-titer antiphospholipid antibodies. Clin Rheumatol. 2024;43:1327-1334.