

INPLASY

INPLASY2026100031

doi: 10.37766/inplasy2026.10.0031

Received: 7 October 2026

Published: 7 October 2026

Corresponding author:

Keyan Luo

814469682@qq.com

Author Affiliation:

Reproductive Medicine Center,
Affiliated Hospital of Zunyi Medical
University, Zunyi, China.

CD8⁺ T-cell and arginine–polyamine metabolic alterations in recurrent pregnancy loss: a systematic review, meta-analysis, and decidual transcriptomic integration protocol

Du, J; Liang, H; Yin, HL; Ren, TY; Luo, KY.

ADMINISTRATIVE INFORMATION**Support** - This review received no specific financial support.**Review Stage at time of this submission** - Preliminary searches.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100031**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 October 2026 and was last updated on 7 October 2026.**INTRODUCTION**

Review question / Objective This review aims to systematically evaluate CD8⁺ T-cell alterations and arginine–polyamine metabolic alterations in recurrent pregnancy loss (RPL). We will assess changes in CD8⁺ T-cell abundance, phenotype, activation and functional characteristics, as well as alterations in metabolites and related measures within the arginine–polyamine metabolic pathway. Evidence will be synthesized according to biological compartment, including peripheral blood, endometrium, decidua and other pregnancy-related tissues where applicable. Meta-analysis will be performed only when sufficient clinically and methodologically comparable data are available. We will further assess whether evidence for both CD8⁺ T-cell and arginine–polyamine metabolic alterations is present in human decidua. Finally, publicly available decidual transcriptomic datasets, with single-cell RNA sequencing as the primary approach, will be integrated to evaluate a prespecified arginine–polyamine metabolic

program within decidual CD8⁺ T cells and to explore its potential association with CD8⁺ T-cell functional states.

Rationale Recurrent pregnancy loss is a complex reproductive disorder in which disturbances of maternal immune tolerance and metabolic homeostasis have both been implicated. CD8⁺ T cells are important components of the maternal immune environment, and previous studies have reported alterations in their abundance, phenotype and functional state in women with RPL. In parallel, metabolomic and molecular studies have identified abnormalities involving arginine metabolism and related polyamine pathways. However, these two areas of evidence have largely been investigated separately, across different biological compartments and using heterogeneous methods. Recent single-cell studies have further demonstrated substantial heterogeneity and functional changes in decidual T-cell populations in RPL, while metabolic studies suggest that arginine-related pathways may also be altered at the maternal–fetal interface. Nevertheless, it

remains unclear whether the available evidence supports a potential relationship between arginine–polyamine metabolic alterations and decidual CD8⁺ T-cell states.

Therefore, this study will systematically synthesize the clinical evidence for CD8⁺ T-cell and arginine–polyamine metabolic alterations in RPL, examine their tissue-specific distribution, and integrate these findings with decidual transcriptomic data. This approach may provide a more coherent view of immune and metabolic alterations in RPL and generate testable hypotheses for future experimental studies.

Condition being studied Recurrent pregnancy loss (RPL), generally characterized by two or more pregnancy losses. This review focuses on women with RPL and investigates associated alterations in CD8⁺ T-cell immunity and arginine–polyamine metabolism. Studies of a single sporadic pregnancy loss will not be considered equivalent to RPL and will be handled according to the prespecified eligibility criteria.

METHODS

Search strategy PubMed/MEDLINE, Embase, and Web of Science will be systematically searched from database inception to the date of the final search. Two complementary search strategies will be used. The first will combine terms for recurrent pregnancy loss with terms related to CD8⁺ T cells. The second will combine terms for recurrent pregnancy loss with terms related to arginine–polyamine metabolism.

RPL-related terms will include “recurrent pregnancy loss”, “recurrent miscarriage”, “recurrent spontaneous abortion”, and relevant synonyms and controlled vocabulary. CD8-related terms will include “CD8”, “CD8-positive T lymphocytes”, “cytotoxic T lymphocytes”, and related terms. Metabolic terms will include “arginine”, “ornithine”, “citrulline”, “putrescine”, “spermidine”, “spermine”, “polyamine”, “arginine metabolism”, “arginine biosynthesis”, “polyamine metabolism”, and “polyamine biosynthesis”. Broader metabolomics-related terms may also be used to identify studies reporting relevant metabolites or pathways.

Search strategies will be adapted to the syntax and controlled vocabulary of each database. No publication-date restriction will be applied. Reference lists of included studies and relevant reviews will also be screened to identify additional eligible studies. The final search strategies and search dates for each database will be reported in the review.

Participant or population Women with recurrent pregnancy loss (RPL), recurrent miscarriage, or recurrent spontaneous abortion as defined by the original study. Studies using different historical or guideline-based definitions of RPL will be eligible, provided that the study population clearly represents recurrent rather than a single sporadic pregnancy loss. The number of previous pregnancy losses, whether losses were consecutive, gestational stage, and whether RPL was unexplained will be recorded where available. Evidence from peripheral blood, endometrium, decidua, villous/placental tissues, and other relevant biological compartments will be classified separately.

Intervention Not applicable. This review will primarily include observational studies evaluating CD8⁺ T-cell and/or arginine–polyamine metabolic alterations in women with RPL. The exposures of interest are RPL status and the associated immune or metabolic alterations rather than a therapeutic intervention.

Comparator Women without a history of recurrent pregnancy loss, including healthy pregnant women, women with normal pregnancies, or healthy fertile/non-pregnant women, as appropriate to the original study design and biological compartment. Comparator groups will be recorded and analyzed separately where clinically relevant. Studies comparing clinically relevant subgroups within RPL populations may also be included for qualitative synthesis where appropriate.

Study designs to be included Observational human studies, including cross-sectional, case-control, and cohort studies, will be included. Relevant baseline data from interventional studies may also be eligible if they provide extractable data for RPL and an appropriate comparator. Human tissue-based transcriptomic and single-cell studies relevant to the decidual integration will also be considered.

Eligibility criteria Studies will be eligible if they: (1) include women with RPL/recurrent miscarriage/recurrent spontaneous abortion as defined by the original study; (2) evaluate CD8⁺ T-cell abundance, phenotype or function and/or measures directly relevant to arginine–polyamine metabolism; and (3) provide an appropriate comparator or other data relevant to the planned systematic synthesis. Human studies using peripheral blood, endometrium, decidua, villous/placental tissue or other relevant biological samples will be

considered, with different compartments analyzed separately.

Studies limited to a single sporadic pregnancy loss without a clearly defined recurrent-loss population will be excluded from the primary RPL evidence synthesis. Animal-only and in vitro-only studies, reviews, editorials, conference abstracts without sufficient data, and studies without relevant CD8⁺ T-cell or arginine–polyamine outcomes will be excluded. Studies concerning protein arginine methylation without assessment of the arginine–polyamine metabolic pathway will not be considered metabolic evidence for this review.

Information sources The primary electronic databases will be PubMed/MEDLINE, Embase, and Web of Science, searched from inception to the date of the final search. Reference lists of included articles and relevant reviews will be manually screened for additional eligible studies. Where necessary, study authors may be contacted to clarify eligibility or obtain missing information. Publicly available transcriptomic datasets relevant to human decidua and RPL will be identified from repositories such as the NCBI Gene Expression Omnibus (GEO) and associated publications for the transcriptomic integration component.

Main outcome(s) The main outcomes will be: (1) alterations in CD8⁺ T cells in women with RPL compared with appropriate controls, including CD8⁺ T-cell abundance/proportion and, where available, phenotypic and functional characteristics; and (2) alterations in the arginine–polyamine metabolic pathway, assessed through individual metabolites and directly related metabolic measures, including arginine, ornithine, citrulline, putrescine, spermidine and spermine where reported.

Outcomes will be classified according to biological compartment and will not be pooled across peripheral blood, endometrium, decidua, villous/placental tissue or other biologically distinct samples. Different CD8⁺ T-cell measures and individual metabolites will also be analyzed separately. Meta-analysis will be undertaken only when at least two studies provide sufficiently comparable populations, biological compartments, outcomes and data.

Additional outcome(s) Additional outcomes will include CD8⁺ T-cell differentiation, activation, cytotoxicity, inhibitory/exhaustion and memory-related phenotypes, as reported by individual studies. CD4/CD8 ratio and other relevant CD8-associated immune measures will be considered separately. Tissue-specific evidence for CD8⁺ T-cell and arginine–polyamine alterations in human

decidua will also be summarized. For the transcriptomic integration, additional outcomes will include prespecified arginine–polyamine pathway/module scores in decidual CD8⁺ T cells and their associations with CD8⁺ T-cell functional states, including cytotoxicity, activation and exhaustion-related programs.

Data management Search results will be exported from each database and merged for deduplication. Two reviewers will independently screen titles and abstracts and subsequently assess potentially eligible full-text articles according to the prespecified eligibility criteria. Disagreements will be resolved through discussion and, if necessary, consultation with a third reviewer.

Data will be extracted using a standardized extraction form by one reviewer and independently verified against the original reports by a second reviewer. Extracted information will include study characteristics, participant characteristics, RPL definition, comparator, biological compartment, sample size, outcome definition, measurement method, numerical results, and information required for risk-of-bias assessment. For quantitative data, the original source location (table, figure, page or supplementary material), original reported values, any converted values, and the method of conversion will be recorded to maintain traceability.

Quality assessment / Risk of bias analysis Risk of bias will be assessed using the appropriate Joanna Briggs Institute (JBI) critical appraisal tools according to study design. Two reviewers will independently assess each eligible study, and disagreements will be resolved through discussion or consultation with a third reviewer when necessary. Assessments will be performed at the study or relevant result level where appropriate. Risk-of-bias judgments will be considered when interpreting the findings and in sensitivity analyses where sufficient studies are available. Transcriptomic datasets used for bioinformatic integration will additionally be evaluated for key methodological characteristics, including sample source, case/control definition, sample size, sequencing platform, data processing and availability of relevant metadata.

Strategy of data synthesis A structured qualitative synthesis will first be performed separately for CD8⁺ T-cell and arginine–polyamine metabolic evidence. Studies will be grouped according to biological compartment, including peripheral blood, endometrium, decidua and other relevant pregnancy-related tissues. Different

biological compartments will not be pooled together.

Meta-analysis will be performed only when at least two studies provide sufficiently comparable populations, comparators, biological compartments and outcomes. Individual CD8⁺ T-cell measures and individual metabolites will be analyzed separately. Continuous outcomes measured on the same scale will be pooled using mean differences, while standardized mean differences will be used when conceptually equivalent outcomes are measured using different scales. Random-effects models will be used when quantitative pooling is considered appropriate. Effect estimates will be reported with 95% confidence intervals. Statistical heterogeneity will be assessed using the I^2 statistic and, where appropriate, τ^2 .

Potential sources of heterogeneity, including RPL definition, biological compartment, gestational stage, comparator type, sample type and measurement method, will be explored through subgroup or sensitivity analyses when sufficient studies are available. Sensitivity analyses may exclude studies with high risk of bias or studies that require substantial data conversion. Publication bias will be assessed only when a sufficient number of studies are available.

For the transcriptomic integration, publicly available human decidual datasets will be analyzed separately from the clinical meta-analysis. Single-cell RNA-sequencing data will be used to evaluate the prespecified arginine–polyamine metabolic program within decidual CD8⁺ T cells and its association with CD8⁺ T-cell functional states. Independent decidual transcriptomic datasets will be used for validation where suitable data are available. Transcriptomic findings will be interpreted as associative and hypothesis-generating rather than causal evidence.

Subgroup analysis Where sufficient data are available, subgroup analyses will be considered according to biological compartment (e.g., peripheral blood, endometrium and decidua), RPL definition (e.g., two versus three or more previous losses), gestational stage, comparator type, sample type (e.g., serum versus plasma), and measurement method. For CD8⁺ T-cell outcomes, different phenotypic or functional subsets will be analyzed separately where appropriate. For metabolic outcomes, individual metabolites will be analyzed separately and will not be combined into a single arginine–polyamine effect. Subgroup analyses will only be performed when clinically meaningful and supported by an adequate number of studies.

Sensitivity analysis Where sufficient studies are available, sensitivity analyses will assess the robustness of pooled estimates by excluding studies at high risk of bias and by performing leave-one-out analyses. Additional sensitivity analyses may exclude studies requiring substantial statistical conversion of reported data, studies with markedly different RPL definitions or comparator groups, and studies identified as major contributors to heterogeneity. The characteristics of influential or outlying studies will be examined before considering exclusion, and studies will not be removed solely to reduce statistical heterogeneity.

Language restriction No language restrictions will be applied.

Country(ies) involved China.

Other relevant information The transcriptomic component is intended to complement, rather than replace, the systematic review and meta-analysis. It will be used to explore whether the prespecified arginine–polyamine metabolic program is altered within decidual CD8⁺ T cells and whether it is associated with relevant CD8⁺ T-cell functional states. These analyses will be considered exploratory and hypothesis-generating, and no causal inference will be made.

Keywords recurrent pregnancy loss; CD8⁺ T cells; arginine; polyamines; decidua; metabolomics; single-cell RNA sequencing; transcriptomics; systematic review; meta-analysis.

Dissemination plans The findings will be submitted for publication in a peer-reviewed journal and may also be presented at relevant scientific conferences. The systematic review and meta-analysis will be reported in accordance with the PRISMA 2020 statement.

Contributions of each author

Author 1 - Jing Du - Study coordination; literature search; independent study screening (Reviewer 1); data extraction; clinical assessment of RPL studies; interpretation of results; manuscript drafting.

Email: dujing.dr@gmail.com

Author 2 - Hong Liang - Independent study screening (Reviewer 2); full-text eligibility assessment; independent verification of extracted data; risk-of-bias assessment; methodological review; interpretation of results.

Email: hongliang.dr@gmail.com

Author 3 - Hongli Yin - Literature organization; assessment of CD8⁺ T-cell and immunological evidence; data checking and interpretation of results.

Email: hongli.yin@tum.de

Author 4 - Tianyuan Ren - Assessment of arginine–polyamine metabolic evidence; assistance with transcriptomic and bioinformatic analyses; result verification.

Email: apenotsmart@gmail.com

Author 5 - Keyan Luo - Study supervision; clinical and scientific oversight; resolution of disagreements when necessary; interpretation of findings; critical revision of the manuscript and final approval.

Email: 814469682@qq.com