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Meta-analysis

Endocrine interventions and live birth outcomes in women with recurrent pregnancy loss: a meta-analysis

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ABSTRACT

Recurrent pregnancy loss (RPL) is a multifactorial reproductive disorder for which endocrine therapies are frequently considered, although their effects on live birth remain uncertain. This meta-analysis assessed the effectiveness of progesterone and levothyroxine on pregnancy outcomes in women with RPL. Following PRISMA 2020 guidance, PubMed, the Cochrane Central Register of Controlled Trials, and Web of Science were searched from January 2015 to the final search date without language restrictions. Eight studies involving 7,749 participants were included in the systematic review; quantitative synthesis was restricted to randomized controlled trials with comparable data. Mantel-Haenszel fixed-effect meta-analyses generated pooled risk ratios (RRs) with 95% confidence intervals (CIs), heterogeneity was assessed using I^2, and risk of bias was evaluated with Cochrane RoB 2. For progesterone versus placebo, two large trials (PROMISE and PRISM; n=4,864) showed no statistically significant improvement in live birth (RR=1.03, 95% CI=1.00-1.07; I^2=0%; p=0.08). For levothyroxine, pooled analysis suggested a non-significant trend toward improved live birth (RR 1.25, 95% CI 0.90-1.73; I^2=74%), but substantial heterogeneity limited confidence in the estimate. Differences in thyroid status and study populations may explain part of this variability. Current evidence does not support routine empirical progesterone or levothyroxine use in unselected women with RPL. Progesterone may offer modest benefit in selected higher-risk subgroups, particularly women with multiple previous miscarriages; treatment should therefore be individualized according to clinical characteristics and endocrine profiles.

Keywords: Progesterone, Levothyroxine, Recurrent pregnancy loss, Live birth rate, Endocrine intervention, Meta-analysis

INTRODUCTION

Recurrent spontaneous abortion (RSA), also referred to as recurrent pregnancy loss (RPL), is commonly defined as the occurrence of two or more consecutive pregnancy losses prior to fetal viability, typically before 20-24 weeks of gestation.[1,2] It affects approximately 1-3% of couples attempting to conceive and represents a major clinical challenge in reproductive medicine.[1,3] Beyond its clinical implications, RSA is associated with significant psychological burden, including anxiety, emotional distress, and reduced quality of life among affected individuals.[2]

The etiology of RSA is complex and multifactorial, involving genetic, anatomical, immunological, thrombotic, metabolic, and endocrine factors.[1,2,4] Among these, endocrine dysfunction has received particular attention due to its potential reversibility and therapeutic relevance.[4,5] Hormonal disturbances may impair key reproductive processes, including ovulation, corpus luteum function, endometrial receptivity, implantation, trophoblast invasion, and early embryonic development.[4,5]

Progesterone is one of the most extensively studied endocrine interventions in this context. It plays a critical role in decidualization, maintenance of uterine quiescence, and modulation of immune tolerance at the maternal–fetal interface.[6] Based on the hypothesis of luteal phase deficiency, progesterone supplementation has been widely used in clinical practice, particularly in women with unexplained recurrent miscarriage or early pregnancy bleeding.[6,7] However, evidence from large randomized controlled trials, including the PROMISE trial and subsequent evaluations, suggests that while progesterone may confer a modest benefit, its overall effect on live birth rates remains limited and may be restricted to specific high-risk subgroups.[6,7]

Thyroid-related endocrine dysfunction represents another important area of investigation in RSA. Thyroid hormones are involved in multiple reproductive processes, including implantation, placental development, and fetal growth.[8] The presence of thyroid autoimmunity, particularly thyroid peroxidase antibodies (TPOAb), has been associated with an increased risk of pregnancy loss, even in euthyroid women.[9] Consequently, levothyroxine therapy has been proposed as a potential intervention. Nevertheless, recent high-quality evidence, including the T4LIFE trial, has not demonstrated a clear benefit of levothyroxine in improving live birth rates in euthyroid women with thyroid autoimmunity.[10] Although some studies suggest potential benefits in specific subgroups, particularly those with subclinical hypothyroidism, the overall evidence remains inconsistent.[11]

In addition to progesterone and levothyroxine, a variety of endocrine and endocrine-related interventions have been explored in RSA, including insulin-sensitizing agents, immunomodulatory therapies, and other adjunctive treatments.[12-17]

However, these interventions differ substantially in terms of mechanisms, patient populations, and clinical indications, contributing to heterogeneity in the available evidence and limiting direct comparisons across studies.

Importantly, RSA should not be considered a single disease entity but rather a clinical syndrome encompassing diverse underlying mechanisms.[1,2] As such, treatment effects may vary depending on patient characteristics, including the number of previous miscarriages, underlying endocrine conditions, and clinical presentation at the time of treatment.[18] Subgroup analyses are therefore essential to identify populations that may derive greater benefit from specific interventions.

Despite the growing body of research, the effectiveness of endocrine interventions in improving pregnancy outcomes in women with RSA remains uncertain. Previous studies have reported inconsistent findings, partly due to differences in study design, intervention protocols, and outcome definitions.[18,19]

In this context, the present systematic review and meta-analysis aim to evaluate the effectiveness of endocrine interventions, with a specific focus on progesterone and levothyroxine, on pregnancy outcomes in women with RSA. The primary outcome of interest is live birth rate. In addition, subgroup analyses are performed to explore whether treatment effects differ according to clinical and biological characteristics. By synthesizing the most robust available evidence, this study seeks to provide a clearer and clinically relevant understanding of the role of endocrine therapies in RPL and to support a more individualized, evidence-based approach to patient management.

METHODS

Study design

This study was conducted as a systematic review and meta-analysis in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Studies evaluating endocrine and endocrine-related interventions, including progesterone, levothyroxine, and other hormonal therapies, were considered for inclusion.

A qualitative synthesis was performed including all eligible studies regardless of design. However, quantitative synthesis (meta-analysis) was restricted to randomized controlled trials (RCTs) to ensure methodological consistency and minimize the risk of bias. Observational and retrospective studies were included in the systematic review but excluded from the pooled meta-analysis.

Study-level outcome data were extracted and used to calculate RRs with 95% confidence intervals (CIs) for pregnancy outcomes, primarily live birth. This protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420261322878) before the start of the study.

Inclusion criteria

The inclusion criteria are (1) randomized controlled trials and comparative non-randomized studies; (2) studies reporting outcomes of live birth rate, pregnancy loss rate or pregnancy continuation; (3) interventions involving progesterone (vaginal, oral, or intramuscular) or levothyroxine; (4) comparator groups consisting of placebo or no treatment; (5) participants with a history of RPL (≥2 consecutive miscarriages), RSA, or early pregnancy complications associated with increased miscarriage risk.

Exclusion criteria

Exclusion criteria included non-comparative studies (case series, case reports), editorials, reviews, and studies without extractable outcome data and studies involving

participants with chromosomal abnormalities, uterine malformations or known antiphospholipid syndrome. No language restrictions were applied; however, only studies with sufficient data for extraction were included. To ensure that the current clinical practice is reflected, the search was restricted to those studies published between January 2015 and December 2025.

Search strategy

A comprehensive literature search was conducted in electronic databases and trial registers, including PubMed (MEDLINE), the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. Additional studies were identified through manual screening of reference lists from included articles and relevant review papers. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords using Boolean operators. The main search terms included "recurrent spontaneous abortion," "recurrent pregnancy loss," "habitual abortion," "RSA," and "RPL," combined with terms related to randomized clinical trials and endocrine interventions. An example of the search strategy used in PubMed was as follows: (recurrent spontaneous abortion OR recurrent pregnancy loss OR habitual abortion OR RSA OR RPL) AND (randomized controlled trial OR RCT OR randomized OR placebo-controlled).

The final literature search was conducted before data extraction and study selection. No language restrictions were applied. To reflect contemporary clinical practice, only studies published between January 2015 and the date of the final search were considered eligible for inclusion.

Study selection

Titles and abstracts of all records retrieved were screened by two reviewers using a standardized form. Records that were potentially of interest were evaluated in their entire text based upon the preset inclusion and exclusion criterion. Conflicts were sorted out by discussing or consulting a third reviewer. The selection of the study was recorded through PRISMA flow diagram.[20]

Data extraction

Two reviewers who were independent of each other performed data extraction using a standardized form. Extraction variables entailed: first author, year of publication, country, study design, sample size, and participant demographic (age, number of previous miscarriages, patient subgroup), intervention information (type, dose, timing, duration), comparator, outcome definitions, and result data (number of events in intervention/control groups).

Risk of bias assessment

The Cochrane Risk of Bias Tool version 2.0 (RoB2) was used to assess the risk of bias of the included randomized controlled trials. The five domains that were assessed by two independent reviewers included bias that would arise out of the randomization process, bias due to the deviations of the intended interventions, bias due to the missing outcome data, bias due to the measurement of the outcome, and bias due to the selection of the reported outcome.[21] Each area was rated as a low risk, some concerns, or high risk, and an overall risk of bias was established in each study.

Statistical analysis

Statistical analyses were conducted using Review Manager (RevMan) version 5.4 (Cochrane Collaboration). Treatment effects were expressed as RRs with 95% confidence intervals (CIs). Meta-analyses were performed using the Mantel-Haenszel method. A fixed-effect model was applied in analyses with low statistical heterogeneity, whereas substantial heterogeneity was interpreted with caution. A random-effects model (DerSimonian-Laird method) was prespecified for analyses demonstrating important between-study variability.

Statistical heterogeneity was assessed using the I^2 statistic and Chi^2 test, with I^2 values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. A $p<0.10$ for the Chi^2 test was considered indicative of statistically significant heterogeneity.

Due to the limited number of studies included in each meta-analysis (<10 studies), publication bias was not formally assessed using funnel plots or Egger's regression test.

Subgroup analyses were predefined according to intervention type and patient characteristics. Quantitative subgroup synthesis was performed only when sufficient comparable data were available. Sensitivity analyses were conducted by excluding studies considered at high risk of bias. All statistical tests were two-sided, and a $p<0.05$ was considered statistically significant.

RESULTS

Study selection

The systematic literature search identified a total of 4,725 records across the selected databases. Of these, 4,421 records were retrieved from electronic databases and 304 from trial registers.

After removal of 350 duplicate records, 4,375 records remained for title and abstract screening. A total of 4,310 records were excluded at this stage due to irrelevance to the research question, non-randomized design, or failure to meet predefined eligibility criteria.

Sixty-five full-text articles were sought for retrieval, of which 5 reports could not be obtained. The remaining 60 full-text articles were assessed for eligibility.

Following full-text review, 52 studies were excluded for the following reasons: wrong population (n=18), wrong intervention (n=12), absence of comparator (n=5), non-endocrine-related intervention (n=7), ineligible study design (n=6), and insufficient outcome data (n=4).

Ultimately, 8 studies met the inclusion criteria and were included in the systematic review. Among these, only studies with comparable designs, interventions, and outcomes were included in the quantitative synthesis. The study selection process is summarized in Figure 1.

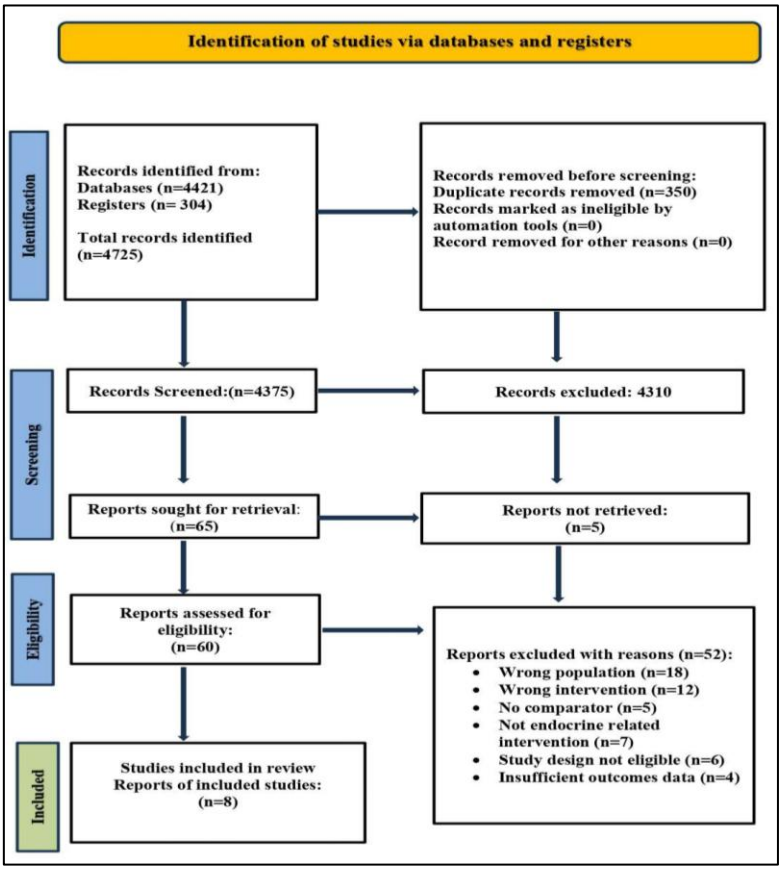

Figure 1: PRISMA 2020 flow diagram of study selection process.

Characteristics of included studies

The eight included studies comprised a total of 7,749 participants, with individual study sample sizes ranging from 60 to 4,153 participants. The studies were published between 2015 and 2025 across multiple geographical regions, including Europe (United Kingdom, Netherlands, Belgium, Denmark, Italy) and Asia (China, India).

In terms of study design, most studies were randomized controlled trials, although one retrospective cohort study and one prospective comparative study were also included.

Regarding interventions, 5 studies evaluated progesterone-based therapies, while three studies investigated levothyroxine treatment. In addition, one study evaluated a combined or non-endocrine-dominant intervention involving low molecular weight heparin (LMWH) compared with progesterone plus human chorionic gonadotropin.

Progesterone was administered either vaginally, orally, or intramuscularly, with dosages ranging from 200 mg to 400 mg twice daily in most studies, although higher daily doses (e.g., 600 mg/day) and alternative formulations such as dydrogesterone were also used. Levothyroxine was administered orally, either as a fixed dose (e.g., 50 µg/day) or as a weight-adjusted dose (0.5-1.0 µg/kg/day), with some studies using individualized dosing strategies.

The populations included in these studies varied considerably. Progesterone trials primarily involved women with unexplained recurrent miscarriage or early pregnancy bleeding, while levothyroxine studies focused on women with thyroid-related conditions, including thyroid peroxidase antibody positivity (TPO-Ab+) and subclinical hypothyroidism (SCH). One study included women with unexplained RSA treated with anticoagulant-based therapy.

The primary outcomes differed across studies. While live birth was the most commonly reported outcome, other outcomes included pregnancy loss, abortion rate, pregnancy continuation, bleeding cessation, pregnancy success rate, and treatment-related complications (Table 1).

Table 1: Characteristics of included studies.

Study (Year)	Country	Study design	Intervention	Dosage	Sample size (I/C)	Patient Subgroup	Primary Outcome
Agarwal et al[22] (2025)	India	Prospective comparative study (randomized within RPL group)	Oral micronized progesterone vs no progesterone	200 mg twice daily (oral)	60 (30/30) (within RPL group; +30 controls overall)	Women with unexplained RPL (≥3 miscarriages, ≤8 weeks gestation)	Abortion rate (3.5% vs 16.7%); cytokine levels (TNFα, IL-6); Pentraxin-3 (PTX3)
Xu et al[23] (2018)	China	Randomized controlled trial	Low molecular weight heparin (LMWH) vs progesterone + hCG	LMWH: 5000 IU subcutaneous once daily Control: progesterone 20 mg IM daily + hCG	120 (60 / 60)	Women with unexplained RSA (URSA)	Pregnancy success rate; pregnancy complications; adverse drug reactions
van Dijk et al[10] (2022)	Netherlands, Belgium, Denmark (multicenter international)	Multicenter double-blind RCT	Oral levothyroxine vs placebo	0.5–1.0 µg/kg/day (oral)	187 (94/93)	Women aged 18–42 years, TPO-Ab positive, euthyroid, with RPL (≥2 losses)	Live birth >24 weeks
Leng et al[11] (2022)	China	RCT	Levothyroxine (L-T4) vs control	50 µg daily (oral), initiated early in pregnancy	Not directly reported as I/C groups; total n=1736	Pregnant women with RPL and either subclinical hypothyroidism (SCH) or TPOAb positivity	Live birth rate; pregnancy loss rate
Kale et al[24] (2021)	India	RCT	Vaginal progesterone vs oral dydrogesterone	Vaginal progesterone 600 mg/day vs oral dydrogesterone 30 mg/day	200 (100/100)	Pregnant women ≤12 weeks gestation with ≥2 previous miscarriages and vaginal bleeding	Time to cessation of bleeding; pregnancy continuation to 24 weeks and term
Dal Lago et al[25] (2021)	Italy	Retrospective cohort study	Levothyroxine (L-T4) vs No treatment	Individualized low-dose levothyroxine (approximately 39–54 µg/day, adjusted according to TSH levels)	457 (227/230)	Euthyroid women with thyroid autoimmunity (TPOAb+) and recurrent miscarriage	Full-term pregnancy rate; miscarriage rate; ability to conceive
Coomarasamy et al[6] (2019)	UK	Multicenter double-blind RCT	Vaginal micronized progesterone vs placebo	400 mg twice daily (vaginal)	4153 (2079/2074)	Women 16-39 years with early pregnancy bleeding (≤12 weeks)	Live birth ≥34 weeks gestation
Coomarasamy et al[7] (2015)	UK and Netherlands (multicenter)	Multicenter double-blind RCT	Vaginal micronized progesterone vs placebo	400 mg twice daily (vaginal), from positive pregnancy test until 12 weeks gestation	836 (404/432)	Women aged 18-39 years with unexplained recurrent miscarriage (≥3 losses)	Live birth ≥24 weeks gestation

*I/C: Intervention/Control; RSA: Recurrent Spontaneous Abortion; RPL: Recurrent Pregnancy Loss.

Risk of bias assessment

The risk of bias of the included studies was assessed using the Cochrane Risk of Bias Tool version 2.0 (RoB 2).

Among the eight included studies, four were judged to have a low overall risk of bias, three presented some concerns, and one study was considered to have a high risk of bias due to its retrospective non-randomized design.

The major domains contributing to "some concerns" ratings included lack of blinding of participants and personnel, which could potentially introduce performance bias. However, most studies demonstrated low risk in terms of incomplete outcome data, with attrition rates generally below 10%.

The PROMISE and PRISM trials evaluating progesterone, as well as the T4LIFE trial assessing levothyroxine, were considered to have low risk of bias across all domains due to their robust randomized, double-blind, placebo-controlled designs.

Overall, the methodological quality of the evidence included in the meta-analyses was considered high.

A summary of the risk of bias assessment across studies is presented in Figure 2.

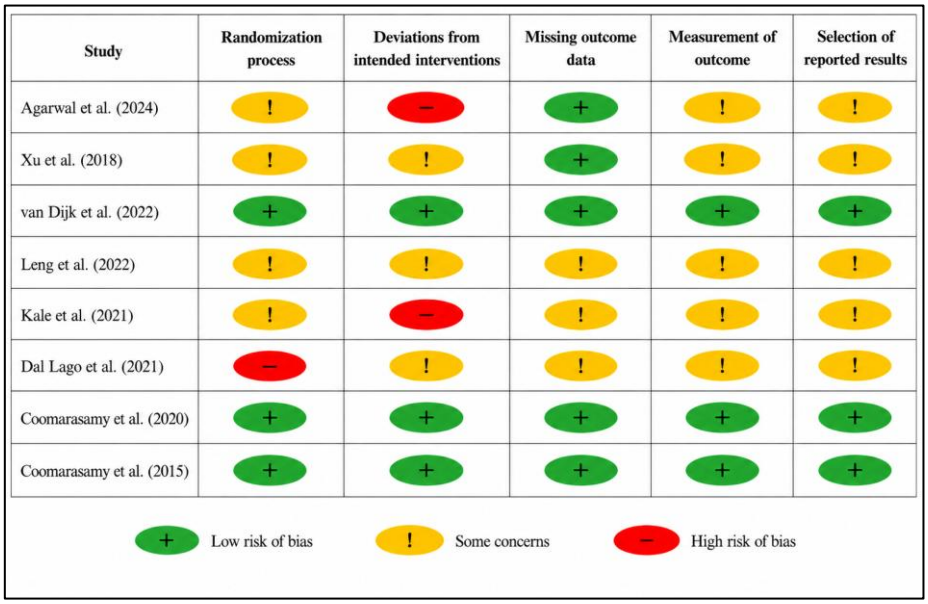

Figure 2: Summary of the risk of bias assessment across included studies using Cochrane risk of bias 2 (RoB 2) tool.

Results of individual studies

Progesterone studies

The PROMISE trial (Coomarasamy et al) was a multicenter, double-blind randomized controlled trial including 836 women with unexplained recurrent miscarriage. The study reported a live birth rate of 65.8% (266/404) in the progesterone group compared to 63.3% (273/432) in the placebo group, with no statistically significant difference observed (RR=1.04, 95% CI=0.94-1.15).[7]

The PRISM trial (Coomarasamy et al), which included over 4,000 women presenting with early pregnancy bleeding, reported live birth rates of 75% in the progesterone group and 72% in the placebo group. The estimated effect size was modest and not statistically significant (RR=1.03, 95% CI=0.99-1.07).[6]

Other progesterone-related studies included in the systematic review were not incorporated into the meta-analysis due to differences in intervention design (e.g., active comparators such as dydrogesterone), combined therapies, or non-comparable outcome measures.

Levothyroxine studies

The T4LIFE trial (van Dijk et al) was a multicenter, double-blind randomized controlled trial conducted in euthyroid women with thyroid autoimmunity and recurrent pregnancy loss. The study found no statistically significant difference in live birth rates between levothyroxine and placebo groups (RR=1.03, 95% CI=0.77-1.38).[10]

The randomized trial by Leng et al evaluated levothyroxine in pregnant women with subclinical hypothyroidism and TPOAb positivity. Subgroup data relevant to women with recurrent pregnancy loss were extracted for analysis.[11]

The retrospective cohort study by Dal Lago et al suggested a potential benefit of levothyroxine; however, due to its observational design, it was excluded from the primary

meta-analysis and considered only in sensitivity analyses.[25]

Quantitative synthesis (Meta-analysis)

Subgroup 1: Progesterone versus placebo

Two large randomized controlled trials (PROMISE and PRISM) were included in the meta-analysis, comprising a total of 4,864 participants.

Using a Mantel-Haenszel fixed-effect model, the pooled analysis showed no statistically significant improvement in live birth rates associated with progesterone therapy compared to placebo (RR=1.03, 95% CI=1.00-1.07).

Statistical heterogeneity was negligible (I^2=0%, Chi^2 p=0.88), indicating highly consistent results between studies despite differences in clinical populations.

The overall effect did not reach statistical significance (Z=1.77, p=0.08).

Subgroup 2: Levothyroxine versus control

Two studies evaluating levothyroxine interventions were included in the quantitative synthesis: the T4LIFE trial (van Dijk et al) and the randomized clinical trial by Leng et al.

The pooled analysis demonstrated a non-significant trend toward improved live birth outcomes in women receiving levothyroxine compared with control groups (RR=1.25, 95% CI=0.90-1.73).

However, substantial statistical heterogeneity was observed across studies (I^2=74%), indicating important differences in study populations, thyroid status, intervention protocols, and methodological characteristics.

Specifically, the T4LIFE trial, which focused on euthyroid TPOAb-positive women with recurrent pregnancy loss, demonstrated no statistically significant benefit of levothyroxine treatment. In contrast, Leng et al. reported more favorable outcomes in women with subclinical hypothyroidism and/or thyroid autoimmunity.

These discrepancies may reflect differences in endocrine profiles and baseline patient characteristics between study populations. Therefore, the pooled findings should be interpreted with caution, and current evidence remains insufficient to support the routine empirical use of levothyroxine in all women with the recurrent pregnancy loss.

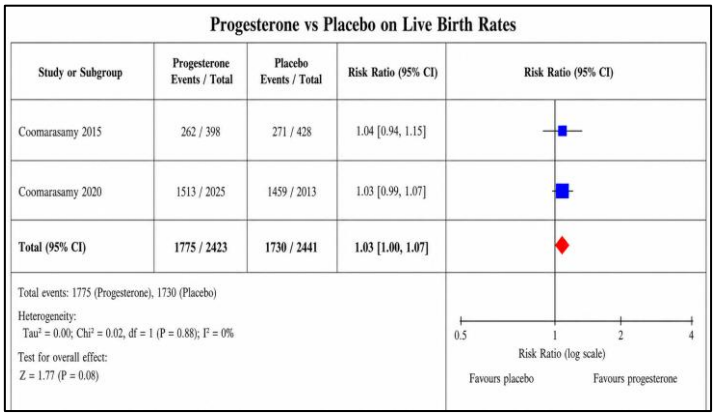

Figure 3: Forest plot of progesterone versus placebo for live birth rates.

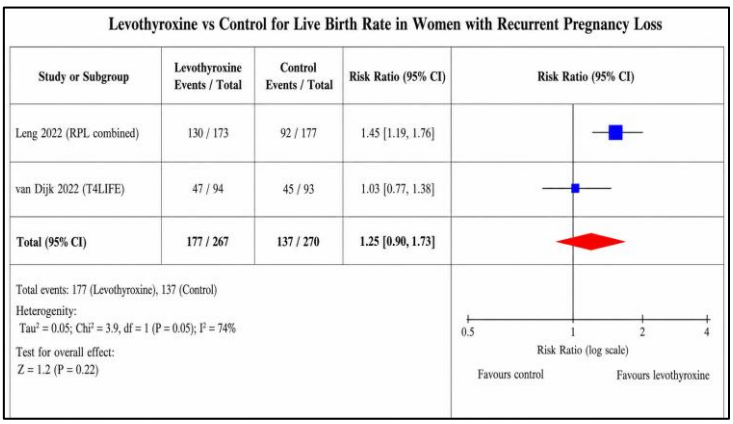

Figure 4: Forest plot of levothyroxine versus control for live birth rates in women with recurrent pregnancy loss.

Summary of effect estimates

Sensitivity analyses excluding non-randomized studies did not materially alter direction/magnitude of pooled estimates. Subgroup analyses from the PRISM trial indicated a potential benefit of progesterone in women with 3 or more previous miscarriages, suggesting that treatment effects may vary according to baseline risk. For levothyroxine, variability in treatment response appeared to be influenced by differences in thyroid status and study populations. Studies including women with subclinical hypothyroidism suggested more favorable outcomes compared with studies restricted to euthyroid TPOAb-positive women.

Table 2: Summary of meta-analysis results.

Study (in year)	Intervention	N	Outcome	Patient subgroup	RR (95% CI)
Coomarasamy et al[7] (2015)	Progesterone vs placebo	836	Live birth	Women with unexplained recurrent miscarriage	1.04 (0.94-1.15)
Coomarasamy et al[6] (2019)	Progesterone vs placebo	4153	Live birth	Women with early pregnancy bleeding	1.03 (1.00-1.07)
Pooled progesterone	Progesterone vs placebo	-	Live birth	All included populations	1.03 (1.00-1.07)
van Dijk et al[10] (2022)	Levothyroxine vs placebo	187	Live birth	TPO-Ab positive euthyroid women	1.03 (0.77-1.38)

Subgroup and sensitivity analyses

Subgroup analyses

Subgroup analyses were primarily derived from the PRISM trial, which provided prespecified analyses based on the number of previous miscarriages.

In this trial, a trend toward improved live birth rates with progesterone was observed among women with a history of three or more previous miscarriages, whereas no meaningful benefit was identified in women with fewer prior losses. This finding suggests that the effect of progesterone may vary according to baseline risk and clinical history.

For levothyroxine, subgroup analyses based on thyroid status (subclinical hypothyroidism versus isolated TPOAb positivity) did not demonstrate consistent modification of treatment effects. Although subgroup data from Leng et al suggested potential variability, these findings were not consistently supported by high-quality randomized evidence, particularly the T4LIFE trial.

Overall, subgroup analyses indicate that treatment effects may differ across specific patient populations, although the available evidence remains limited and should be interpreted with caution.

Sensitivity analyses

Sensitivity analyses were conducted to assess the robustness of the primary findings.

The retrospective cohort study by Dal Lago et al was excluded from the main meta-analysis due to its non-randomized design and higher risk of bias. When considered qualitatively, its findings did not substantially alter the overall interpretation of levothyroxine effects on live birth outcomes.[25]

Additionally, exclusion of studies with methodological limitations or non-comparable outcome measures did not materially change the direction or magnitude of the pooled estimates.

These results support the stability and robustness of the primary meta-analysis findings.

DISCUSSION

Principal findings

This systematic review and meta-analysis evaluated the effectiveness of endocrine interventions, specifically progesterone and levothyroxine, on pregnancy outcomes in women with RSA. A total of eight studies involving 7,749 participants were included in the qualitative synthesis, with a subset contributing to the quantitative analysis.

For progesterone supplementation, pooled analysis of two large, high-quality randomized controlled trials (PROMISE and PRISM; n=4,864) demonstrated a consistent but non-statistically significant effect on live birth rates (RR=1.03, 95% CI=1.00-1.07).[6,7] The magnitude of effect was small, corresponding to an absolute difference of approximately 2-3%. Notably, statistical heterogeneity was absent (I^2=0%), indicating a high level of consistency between studies despite differences in clinical populations.

Regarding levothyroxine, pooled analysis suggested a possible trend toward improved live birth outcomes; however, the effect did not reach statistical significance and was associated with substantial heterogeneity between studies. Differences in thyroid status, particularly between

euthyroid TPOAb-positive women and women with subclinical hypothyroidism, may partially explain the variability in treatment response. Therefore, the current evidence remains insufficient to support the routine empirical use of levothyroxine in all women with recurrent pregnancy loss.

Comparison with previous literature

The present findings are consistent with the broader body of evidence on endocrine interventions in recurrent pregnancy loss. For progesterone, previous randomized trials have similarly reported limited or non-significant overall effects on live birth outcomes.[6,7] However, subgroup analyses from the PRISM trial suggest a potential benefit in women with a history of three or more previous miscarriages, indicating that treatment effects may be more pronounced in higher-risk populations.[6]

The absence of heterogeneity (I^2=0%) between the PROMISE and PRISM trials strengthens the reliability of the pooled estimate and supports the consistency of the observed modest treatment effect.

In the case of levothyroxine, observational studies and some randomized data have suggested a possible benefit of thyroid hormone supplementation in selected women with thyroid autoimmunity or subclinical hypothyroidism. However, findings remain inconsistent across studies. The T4LIFE trial did not demonstrate a significant benefit in euthyroid TPOAb-positive women, whereas Leng et al. reported more favorable outcomes in women with subclinical hypothyroidism and/or thyroid autoimmunity. These discrepancies may reflect differences in patient selection and endocrine profiles.

Clinical implications

These findings have important implications for clinical practice in reproductive medicine.

Progesterone

The current evidence does not support the routine use of progesterone supplementation in all women with recurrent pregnancy loss. However, the observed trend toward improved outcomes, combined with a favorable safety profile, suggests that progesterone may still be considered in selected high-risk populations. In particular, women with a history of three or more miscarriages or those presenting with early pregnancy bleeding may derive greater benefit, as indicated by subgroup analyses.[6]

Levothyroxine

The available evidence does not support the empirical use of levothyroxine in euthyroid women with thyroid autoimmunity and recurrent pregnancy loss.[10] Treatment should instead be reserved for women with clinically significant thyroid dysfunction, in accordance with established clinical guidelines.[8]

Individualized approach

Overall, these findings reinforce the importance of a personalized approach to the management of recurrent pregnancy loss, taking into account patient-specific characteristics and underlying pathophysiology.[1,2]

Strengths

This study has several methodological strengths. It included high-quality randomized controlled trials, including large multicenter studies such as PROMISE, PRISM, and T4LIFE, which provide relatively robust evidence for clinical decision-making. The use of PRISMA 2020 guidelines enhanced the transparency and methodological rigor of the review process.[20] In addition, the use of the Cochrane RoB2 tool allowed a standardized and systematic assessment of study quality and risk of bias across randomized trials.[21]

Another important strength of this review is the comprehensive search strategy performed across multiple electronic databases and trial registers, which reduced the likelihood of missing relevant studies. Furthermore, the progesterone subgroup analysis demonstrated very low statistical heterogeneity (I^2=0%), supporting the consistency and reliability of the pooled findings for this intervention.

Limitations

Several limitations should be acknowledged. First, the number of studies included in each meta-analysis was relatively small, precluding formal assessment of publication bias using funnel plots or Egger's regression test. Second, some eligible studies could not be included in the quantitative synthesis because of differences in study design, comparators, interventions, or reported outcome measures, which may limit the overall generalizability of the findings.

In addition, important variability existed across study populations, particularly regarding thyroid status, underlying endocrine conditions, and clinical presentation, which may have affected comparability between studies. This variability was especially evident in the levothyroxine subgroup analysis, where substantial heterogeneity was observed (I^2=74%).

Long-term maternal and neonatal outcomes were not consistently reported across studies and therefore could not be adequately evaluated in this review. Finally, indirect comparisons between progesterone and levothyroxine interventions should be interpreted cautiously, as these therapies target different biological mechanisms and distinct patient populations.

CONCLUSION

This systematic review and meta-analysis evaluated the effectiveness of endocrine interventions, specifically progesterone and levothyroxine, on pregnancy outcomes in women with recurrent pregnancy loss.

Current evidence does not support the routine empirical use of progesterone or levothyroxine in unselected women with recurrent pregnancy loss. Although progesterone demonstrated a modest trend toward improved live birth outcomes, the effect did not reach clear statistical significance in the overall population. Similarly, levothyroxine showed a non-significant trend toward benefit, but substantial heterogeneity between studies limits the certainty of the pooled findings.

Differences in patient characteristics, particularly thyroid status and baseline miscarriage risk, may influence treatment response. Women with multiple previous miscarriages or specific endocrine abnormalities may potentially derive greater benefit from targeted interventions.

Overall, these findings support an individualized and evidence-based approach to the management of recurrent pregnancy loss. Future high-quality randomized controlled trials are needed to better identify patient subgroups most likely to benefit from endocrine therapies.

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REFERENCES

1. Turesheva A, Aimagambetova G, Ukybassova T, Marat A, Kanabekova P, Kaldygulova L, et al. Recurrent pregnancy loss etiology, risk factors, diagnosis, and management. Fresh look into a full box. J Clin Med. 2023;12(12):4074.
2. Cao C, Bai S, Zhang J, Sun X, Meng A, Chen H. Understanding recurrent pregnancy loss: recent advances on its etiology, clinical diagnosis, and management. Med Rev. 2023;2(6):570-89.
3. ESHRE Guideline Group on RPL, Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, et al. ESHRE guideline: recurrent pregnancy loss: an update in 2022. Hum Reprod Open. 2023;2023(1):hoad002.
4. Krog MC, Nielsen HS, Christiansen OB, Kolte AM. Reproductive endocrinology in recurrent pregnancy loss. Clin Obstet Gynecol. 2016;59(3):474-86.
5. Kaur R, Gupta K. Endocrine dysfunction and recurrent spontaneous abortion: an overview. Int J Appl Basic Med Res. 2016;6(2):79-83.
6. Coomarasamy A, Devall AJ, Cheed V, Harb H, Middleton LJ, Gallos ID, et al. A randomized trial of progesterone in women with bleeding in early pregnancy. N Engl J Med. 2019;380(19):1815-24.
7. Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, et al. A randomized trial of progesterone in women with recurrent miscarriages. N Engl J Med. 2015;373(22):2141-8.
8. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017;27(3):315-89.
9. Jansen S, Leduc-Robert G, AbdelHafez FF, Albert A, Mayer U, Bedaiwy MA. Temporal trends in thyroid-stimulating hormone and live birth rate in subclinical hypothyroid patients in a recurrent pregnancy loss population. Eur J Obstet Gynecol Reprod Biol. 2022;277:21-6.
10. van Dijk MM, Vissenberg R, Fliers E, van der Post JAM, van der Hoorn MP, de Weerd S, et al. Levothyroxine in euthyroid thyroid peroxidase antibody-positive women with recurrent pregnancy loss (T4LIFE trial): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2022;10(5):322-9.
11. Leng T, Li X, Zhang H. Levothyroxine treatment for subclinical hypothyroidism improves the rate of live births in pregnant women with recurrent pregnancy loss: a randomized clinical trial. Gynecol Endocrinol. 2022;38(6):488-94.
12. Morley LC, Tang T, Yasmin E, Norman RJ, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2017;11(11):CD003053.
13. Palomba S, Molinaro M, Ingargiola A, Aversa A. Recent developments in drug treatment strategies for infertility in patients with polycystic ovary syndrome. Expert Opin Pharmacother. 2024;25(16):2191-202.
14. Saadati S, Mason T, Godini R, Vanky E, Teede H, Mousa A. Metformin use in women with polycystic ovary syndrome: opportunities, benefits, and clinical challenges. Diabetes Obes Metab. 2025;27(3):31-47.
15. Shpakov AO. Improvement effect of metformin on female and male reproduction in endocrine pathologies and its mechanisms. Pharmaceuticals. 2021;14(1):42.
16. Zhou L, Qu H, Yang L, Shou L. Effects of GLP1RAs on pregnancy rate and menstrual cyclicity in women with polycystic ovary syndrome: a meta-analysis and systematic review. BMC Endocr Disord. 2023;23(1):245.
17. Ling Q, Xu J, Tian Y, Chen D, Mo C, Peng B. Effect of IVIG therapy on pregnant women with unexplained recurrent spontaneous abortion: a systematic review

and meta-analysis. Front Endocrinol. 2024;15:1381461.
18. Fang T, Ji X, Su Z, Zhang A, Zhu L, Tang J, et al. Risk factors associated with pregnancy outcomes in patients with recurrent pregnancy loss after treatment. BMC Pregnancy Childbirth. 2024;24(1):827.
19. Zhou X, Lai F, Chen W, Zhou C, Deng Y, Wang T, et al. The landscape of recurrent spontaneous abortion registered on ClinicalTrials.gov. Front Endocrinol. 2024;15:1460968.
20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Rev Panam Salud Publi. 2022;46:e112.
21. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
22. Agarwal N, Gupta S, Kulshrestha V, Yadav RK, Kriplani A, Kachhawa G, et al. Cytokines and pentraxin 3 levels in unexplained recurrent pregnancy loss: role of oral micronized progesterone therapy as immunomodulator on their levels and pregnancy outcome, a prospective comparative study. J Obstet Gynaecol India. 2025;75(1):59-66.
23. Xu GL, Hu XF, Han YM, Wei AW. Clinical efficacy of low molecular heparin on unexplained recurrent spontaneous abortion. Clin Lab. 2018;64(6):1037-40.
24. Kale AR, Kale AA, Yelikar K. A comparative, randomized control trial in patients of per vaginal bleeding comparing efficacy of oral dydrogesterone versus vaginal progesterone in successful pregnancy outcome for patients with recurrent pregnancy loss. J Obstet Gynaecol India. 2021;71(6):591-5.
25. Dal Lago A, Galanti F, Miriello D, Marcoccia A, Massimiani M, Campagnolo L, et al. Positive impact of levothyroxine treatment on pregnancy outcome in euthyroid women with thyroid autoimmunity affected by recurrent miscarriage. J Clin Med. 2021;10(10):2105.

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