

Endocrine, Immunological, and Thrombotic Determinants of Recurrent Pregnancy Loss: Clinical Evidence, Causal Inference, and Precision Care*Xolboyeva Mashhura Yoqutjon qizi**Email – yoqutjonovnam@gmail.com**Termez University of Economics and Service**Faculty of Medicine***Abstract**

Background: Recurrent pregnancy loss (RPL) is a heterogeneous reproductive outcome in which endocrine dysfunction, antiphospholipid antibodies, genetic abnormalities, uterine factors, and diverse maternal exposures may converge. The identification of biologically plausible correlates does not automatically establish causality or justify empirical treatment. **Objective:** To critically examine the clinical relevance of endocrine, immunological, and thrombotic pathways and develop a rigorous framework for integrating randomized trials with real-world evidence. **Methods:** A structured, non-systematic synthesis was undertaken using identifiable clinical practice guidance, randomized trials, and regulatory methodological resources published through October 2026. The review distinguishes verified study findings from proposed analytic procedures and does not claim a new patient cohort, pooled meta-analysis, or comprehensive database screening. **Results:** Contemporary ASRM and ESHRE guidance supports a staged evaluation centered on pregnancy-loss tissue genetics, uterine assessment, and context-specific endocrine and antiphospholipid investigation. Overt hypothyroidism and inadequately controlled diabetes are actionable conditions; thyroid autoantibody positivity in euthyroid women does not independently establish levothyroxine benefit. Antiphospholipid syndrome warrants specific assessment and, when appropriately diagnosed, targeted antithrombotic treatment. In contrast, routine anticoagulation for inherited thrombophilia without another indication is not supported by the ALIFE2 trial. The T4LIFE and PROMISE randomized trials further illustrate how observational associations and plausible mechanisms may fail to translate into improved live birth. Registry data, linked prescriptions, laboratory results, and pregnancy outcomes could strengthen external validity if timing, confounding, missingness, and immortal-time bias are addressed. Artificial intelligence may support record abstraction and risk stratification but requires external validation and clinician oversight. **Conclusion:** RPL management should separate established therapeutic targets from investigational biomarkers, prioritize live birth as a clinically meaningful outcome, and avoid escalation to poorly supported immune or anticoagulant interventions. Uzbekistan could benefit from a privacy-preserving multicenter registry with standardized phenotype, exposure, and follow-up definitions.

Keywords

recurrent pregnancy loss; miscarriage; antiphospholipid syndrome; thyroid dysfunction; thrombophilia; immune dysregulation; live birth; real-world evidence;

causal inference; propensity score; machine learning; pharmacovigilance; precision medicine

1. Introduction

Recurrent pregnancy loss (RPL) describes a recurrent adverse reproductive trajectory rather than a single disease. The 2026 American Society for Reproductive Medicine (ASRM) committee opinion defines RPL as two or more spontaneous losses, excluding ectopic and molar pregnancies, and allows biochemical pregnancy confirmation. Definitions across studies and historical guidelines vary, producing nontrivial variation in case ascertainment and the composition of research cohorts [1,2]. A rigorous review therefore records exactly what counted as a pregnancy, how the outcome was verified, and whether early biochemical losses, stillbirth, or implantation failure were excluded.

The biological architecture of RPL is plural. Embryonic chromosomal abnormalities are central to many early losses, while maternal uterine pathology, poorly controlled endocrine disease, antiphospholipid syndrome (APS), certain systemic illnesses, and age-related factors create overlapping causal routes. The absence of an identifiable lesion should not be equated with a newly discovered immunological diagnosis. Testing that yields a statistically abnormal value may have poor positive predictive value when standardized thresholds, meaningful interventions, or external validation are absent [1,2].

Real-world data (RWD) comprise routinely collected observations generated during care, including encounter notes, pharmacy dispensings, laboratory results, ultrasound reports, hospital discharges, claims, registries, and patient-reported outcomes. Real-world evidence (RWE) arises when such data are analyzed using a valid design to answer a prespecified clinical question. A structured record is not evidence by itself: exposure, eligibility, index date, outcome, confounding, missingness, and analytic choices determine its evidentiary value. Regulatory interest in RWE primarily concerns the evaluation of medical products rather than permission to replace randomized trials [10,11].

Randomized controlled trials (RCTs) seek exchangeability through allocation, whereas routinely observed treatment groups may differ in prognosis even before exposure. Efficacy denotes benefit under trial conditions; effectiveness characterizes performance during ordinary clinical care, in which adherence, access, comorbidity, dose modification, and continuity matter. Live birth, gestational age, maternal safety, and quality of life are clinically preferable to isolated immunological surrogate changes. The ALIFE2, T4LIFE, and PROMISE studies provide salient examples of therapies whose pathophysiological rationale did not reliably translate into improvements in live birth [3–5].

The World Health Organization (WHO) emphasizes autonomy, safety, transparency, accountability, and equity when artificial intelligence is used in care. The United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) articulate methodological frameworks for RWD and the lifecycle assessment of medical interventions; the EMA-supported DARWIN EU network

provides infrastructure for observational evidence. These initiatives do not certify particular RPL AI classifiers or empiric therapies [12–14].

The clinical urgency is practical: investigation should identify reversible maternal conditions without making patients undergo high-cost, poorly validated immune panels or treatments with meaningful bleeding, allergic, obstetric, and financial harms. The purpose of this review is to synthesize mechanisms and controlled evidence, then explain how observational and computational tools can complement rather than substitute clinical inference.

2. Materials and Methods

Design and epistemic status. This article is a critical integrative narrative review, not a prospectively registered systematic review, patient-level analysis, or original trial. The references comprise individually identifiable official clinical guidance, landmark randomized studies and selected methodology documents. PubMed and journal records were checked for selected trials; the article does not assert that subscription-only Scopus, Embase, Web of Science, or Cochrane Library searches were executed or that PRISMA screening counts exist. Therefore, no pooled effect size, funnel plot, or fabricated study-selection flow diagram is supplied.

Eligibility logic for a future systematic update would include women or couples with at least two defined pregnancy losses; controlled trials, prospective cohorts, registries, systematic reviews and major consensus documents; and outcomes of live birth, recurrent loss, pregnancy complications, treatment-related harm, and patient experience. Reports limited to immune markers without defined pregnancy outcomes would enter mechanistic synthesis rather than support treatment recommendations. Findings from case-control or single-center convenience samples should receive lower causal weight than well-conducted randomized comparisons.

Extraction domains should include RPL definition, number of losses, gestational timing, maternal age, embryo karyotype, thyroid function and antibody status, diabetic control, APS clinical and laboratory criteria, inherited thrombophilia testing, disease severity, pregnancy intention, treatment dose, comparator, adherence, gestational exposure window, live-birth endpoint, attrition, and funding. Repeated outcomes in the same individual and multicenter clustering require explicit modeling.

Propensity-score matching (PSM) approximates conditional balance in measured pretreatment covariates by pairing exposed and unexposed individuals with similar estimated treatment probabilities. Matching should be evaluated through standardized mean differences, overlap plots, and loss of sample generalizability; PSM cannot remove unmeasured confounding. Inverse probability weighting (IPW) instead creates a weighted pseudo-population, but extreme scores threaten positivity and inflate variance. Stabilized or truncated weights and effective sample size are essential diagnostics.

For time-to-event outcomes, Kaplan–Meier curves estimate survival under censoring assumptions while Cox regression models hazard ratios under a

proportional hazards assumption. Time to subsequent pregnancy or live birth is complicated by conception selection, fertility treatment, competing events, and pregnancy-dependent follow-up. A Kaplan–Meier curve for time to miscarriage may be misleading if only recognized pregnancies enter the denominator and conception times vary.

Target trial emulation begins by specifying eligibility, treatment strategies, assignment, time zero, follow-up, endpoints, causal contrast, and analysis before querying electronic records. It can prevent immortal-time bias when therapies begin after pregnancy confirmation. Directed acyclic graphs make assumptions about confounders, mediators, and colliders explicit; a model adjusted for a post-treatment mediator may incorrectly remove part of an effect. Sensitivity analyses should test informative missingness, exposure misclassification, and plausible unmeasured confounding.

Machine learning (ML), including penalized regression, random forests, and gradient boosting, can evaluate nonlinear associations, but transparent comparator models and temporal external validation are required. Deep learning can analyze ultrasound or high-dimensional clinical streams; natural language processing (NLP) can recover loss histories from notes; large language models may aid coding review, but hallucinated obstetric history and privacy leakage are material hazards. Reinforcement learning is a research concept for adaptive decisions, not an established RPL prescription engine.

For pharmacovigilance, spontaneous adverse-drug-reaction reports are signal-generating rather than incidence-estimating; pregnancy exposure registries and linked care data are needed to examine maternal bleeding, hypersensitivity, thrombotic events, fetal outcomes, and medication discontinuation. All analyses proposed in this article are methodological recommendations, not analyses carried out on an undisclosed dataset.

3. Results: Critical Synthesis of Published Evidence

3.1. Clinical taxonomy and evidence strength

An etiologic classification is clinically helpful only when it specifies actionability. A useful matrix separates established maternal disease with an available intervention, plausible but incompletely validated associations, and biomarkers without demonstrated decision utility. This prevents the language of precision medicine from legitimizing broad, low-value panels. Miscarriage-tissue genomic testing and uterine cavity assessment are increasingly prioritized because a chromosomal explanation changes counseling and may alter the value of additional testing [1,2].

Domain	Practical evaluation	Interpretive limit
Embryonic genetics	Array-based testing of pregnancy tissue when feasible [1]	Aneuploid loss may be sporadic and age-related
Thyroid	TSH in appropriate clinical contexts; treat	TPO antibody alone does not establish

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	overt hypothyroidism	levothyroxine	benefit
	[1]	[4]	
Diabetes	Assess and optimize glycemic control [1]	Associations vary with severity and preconception control	
APS	Criterion-based anticoagulant, anticardiolipin, β 2GPI [1,2]	lupus anti- A single positive antibody result is not definitive APS	
Inherited thrombophilia	Test only when independently clinically indicated [1,3]	Routine LMWH did not improve live birth in ALIFE2 [3]	
Unexplained RPL	Supportive, individualized care and follow-up [1]	Empirical therapies inadequately validated	immune remain

3.2. Thyroid signaling, autoimmunity, and implantation

Thyroid hormone influences endometrial maturation, early embryonic development, placental function, and maternal metabolic adaptation. This physiological plausibility explains why overt thyroid dysfunction deserves timely detection and correction. Yet autoimmune positivity, thyroid-stimulating hormone elevation, and overt hypothyroidism represent distinct clinical entities. Combining them creates an apparent homogeneous effect that may misdirect therapy.

The T4LIFE randomized trial enrolled euthyroid thyroid-peroxidase-antibody-positive women with RPL and found no improvement in live birth with levothyroxine: 47 of 94 versus 45 of 93, relative risk 1.03 (95% CI 0.77–1.38) [4]. The earlier TABLET trial similarly did not support treatment based solely on antibody positivity in euthyroid women attempting conception [6]. Consequently, the actionable exposure is thyroid dysfunction, not an isolated antibody finding.

The presence of thyroid autoimmunity can signal a broader autoimmune phenotype, yet co-occurrence does not imply that thyroid replacement reverses immunological injury. Clinical decisions should incorporate pregnancy-specific laboratory interpretation, overt symptoms, and longitudinal measurements rather than fixed universal treatment thresholds divorced from assay and gestational context.

3.3. Diabetes, metabolic dysfunction, and endocrine comorbidity

Pregnancy depends on coordinated metabolic and vascular adaptation. Poorly controlled diabetes may affect oocyte competence, oxidative stress, early placentation, and embryonic development. The practical intervention is to diagnose and optimize established glycemic disease before conception. Broad insulin-resistance markers in otherwise healthy women have less certain incremental value for RPL stratification than verified disease and documented control.

Polycystic ovary syndrome may coexist with obesity, anovulation, dysglycemia, and infertility; these pathways should not be collapsed into the assumption that every RPL patient has insulin resistance. Selection into fertility clinics generates

collider bias: participants may have both endocrine dysfunction and more intense surveillance, increasing ascertainment of very early losses. Causal claims must distinguish infertility from miscarriage conditional on conception.

Metabolic risk measures that can be collected reliably include HbA1c, body mass index, medication exposure, blood pressure, smoking, and relevant endocrine diagnoses. The research question should identify whether preconception improvement changes live birth, not simply whether a marker correlates with a recorded pregnancy loss.

3.4. Antiphospholipid syndrome and placental pathology

APS is an acquired autoimmune thromboinflammatory disorder with clinical and laboratory criteria. Antiphospholipid antibodies may influence trophoblast function, complement activation, inflammation and thrombosis; the model extends beyond mechanical occlusion of maternal vessels. Clinical diagnosis requires careful integration of obstetric or vascular history with appropriate, persistent antibody findings.

Anticoagulant and antiplatelet treatment is supported for appropriately selected patients with obstetric APS, although regimen and gestational scheduling require specialist supervision [1,2]. Extrapolating this practice to any low-titer or transient antibody result exaggerates benefit and exposes patients to bleeding and burden. Distinguishing APS from inherited thrombophilia is among the most consequential decisions in RPL evaluation.

APS registries should capture lupus anticoagulant status, anticardiolipin and anti- β 2-glycoprotein I isotypes, repeated testing dates, thrombosis history, previous gestational complications, aspirin or heparin start times, and bleeding events. Absence of these fields makes retrospective comparisons susceptible to severe confounding by indication.

3.5. Inherited thrombophilia and the ALIFE2 trial

Inherited thrombophilic variants may be associated with venous thromboembolism risk, but biological plausibility does not establish that heparin improves embryonic viability or live birth in women with recurrent miscarriage. Placental development is biologically complex, and early miscarriage cannot simply be explained as a thrombus in every case.

ALIFE2 was an international, open-label randomized trial of low-molecular-weight heparin in women with recurrent miscarriage and inherited thrombophilia. It did not show a live-birth advantage supporting routine use [3]. This distinction protects patients from unproven injections, bruising, bleeding, monitoring requirements, and cost. A separate maternal indication for anticoagulation, such as prevention of venous thrombosis in a high-risk scenario, must be assessed on its own merits.

A study that records only “thrombophilia positive” without the variant, clinical thrombotic history, and competing therapeutic indication is analytically unusable for treatment-effect estimation. Registry designs must avoid comparing highly selected anticoagulated patients against lower-risk untreated patients without extensive causal adjustment.

3.6. Immune markers and proposed interventions

Decidual immune cells, regulatory T-cell balance, uterine natural killer cell biology, cytokine signaling, complement and trophoblast interactions are legitimate research domains. Nonetheless, a difference in peripheral cell count or cytokine concentration does not establish an actionable pathological process within the decidua. Tissue compartment, timing, sampling, and assay reproducibility matter. Routine immune profiling and empirical immune therapies are not supported by contemporary ASRM recommendations for unselected RPL [1]. Intravenous immunoglobulin, intralipid, corticosteroid and other immunomodulators vary in evidence quality and safety profiles. A convincing intervention would need to identify a reproducible target population, demonstrate clinically meaningful live-birth improvement, and characterize pregnancy and neonatal harms.

Investigation of endometrial inflammatory states can be appropriate under selected clinical circumstances, but treating a nonstandard laboratory deviation without evidence of causal significance may produce more interventions than successful pregnancies.

3.7. Progesterone trials and treatment heterogeneity

Progesterone is critical for decidualization and early pregnancy maintenance, yet this does not imply universal benefit from supplementation in unexplained RPL. In the PROMISE randomized trial, live birth occurred in 65.8% of women allocated progesterone and 63.3% allocated placebo (relative risk 1.04; 95% CI 0.94–1.15) [5]. The absence of clear average benefit should not be confused with proof of ineffectiveness in all clinically distinct subgroups.

Guidelines differentiate women with RPL alone from those presenting with bleeding in a new early pregnancy. This distinction illustrates treatment-effect heterogeneity, the risk of pooling incompatible populations, and the limitations of broad therapeutic labels. Timing of treatment initiation and verified indication must be part of any pragmatic comparison.

Live-birth outcomes should always be measured with a defined denominator. A pregnancy-based denominator conditions on successful conception, while a preconception cohort captures both probability of conception and subsequent pregnancy survival. Neither is universally preferable; the estimand determines the choice.

3.8. Real-world evidence sources

Electronic health records provide repeated visit histories and ultrasound reports but often omit early losses that occur outside institutional services. Electronic prescriptions reveal intended therapy rather than confirmed ingestion. Laboratory platforms capture thyroid, APS, and metabolic phenotypes but may vary across manufacturers. National birth and pregnancy registries improve ascertainment and longitudinal follow-up, while insurance claims offer scale but limited biological detail.

Pharmacovigilance reports are suited to rare safety signals after anticoagulant, hormone, or immunomodulatory exposure, but not to estimating causal treatment benefits. Wearables and mobile applications can capture sleep, physical activity and

patient-reported symptoms; they are most informative when consent, selection mechanisms, and validation against clinical records are explicit.

An interoperable minimum dataset should contain deidentified participant linkage, pregnancy chronology, laboratory methods, maternal age, previous live births, comorbidity, reproductive interventions, exposure start and stop dates, fetal chromosomal findings if available, follow-up completeness, and maternal and infant outcomes.

3.9. Artificial intelligence, multimodal phenotyping, and medication effectiveness

Supervised machine learning can estimate risks from structured records, but model discrimination is not evidence that its recommended treatment improves outcomes. Deep learning may support uterine ultrasonography feature detection, while natural language processing can identify pregnancy loss narratives and bleeding or thrombosis documentation in unstructured notes. Large language models can facilitate coding review, but require structured audit, source traceability and protection against hallucination.

Reinforcement learning and dynamic treatment regimes remain experimental in this setting because historical data contain clinically selected actions, sparse adverse events, shifting guideline standards, and ethical constraints. Proposed models must benchmark against transparent clinical baselines and undergo temporal and geographically external validation.

Predicting drug effectiveness in diabetes, cardiovascular disease, oncology, infection or neurology uses analogous analytic principles but does not directly validate an RPL therapeutic algorithm. Such cross-domain examples are methodological analogies, not evidence that an intervention improves pregnancy outcomes. Every algorithm intended to guide RPL treatment needs prospective clinical impact testing.

3.10. Pharmacovigilance and personalized medicine

Maternal drug safety evaluation requires indication-aware attribution. Aspirin, heparin, levothyroxine, progesterone and immune-modifying agents each have different safety domains and exposure windows. Adverse drug reactions, signal detection, and longitudinal safety analytics should integrate structured clinical events with medication dispensing and actual administration where possible.

Pharmacogenomics and pharmacogenetics are promising in general precision medicine, but routine genotyping to select RPL treatment is not established. More immediately actionable precision approaches involve classifying a validated APS phenotype, correcting overt endocrine disease, interpreting embryonic genetics, and aligning therapeutic intensity with observed risk.

A personalized decision is not necessarily a computational decision. The strongest precision interventions may be exclusion of low-value treatments, careful reassurance after genetically explained sporadic losses, timely maternal disease optimization, and access to counseling.

3.11. Uzbekistan: digital registry implementation

An Uzbekistan-focused research program should begin with a Ministry of Health–approved multicenter data dictionary covering pregnancy-loss definitions, dates and gestational ages, tissue-genetic findings, uterine diagnostics, thyroid and glycemic status, APS testing, medication exposure, bleeding or thrombosis and subsequent live birth. The existence or national coverage of any proposed RPL registry must not be presumed without an official audit.

Electronic health records and electronic prescribing could support prospective observational follow-up if care-site identifiers, assay names and medication start dates are standardized. A staged approach would test data quality in a small number of participating facilities before expanding linkage to laboratories, clinical pharmacology services, pregnancy registries and pharmacovigilance units.

Local AI development should prioritize extraction quality and missing-data dashboards before clinical treatment recommendation engines. Oversight mechanisms should include ethics approval, consent or a lawful alternative, role-based data access, encryption, audit logging, independent model validation, and periodic equity review across geography and socioeconomic access.

4. Discussion

The central contrast across the literature is between mechanistic plausibility and treatment effectiveness. Autoantibodies and thrombophilic variants may correlate with loss in some cohorts, yet well-designed trials have not shown that administering the most intuitively related medication inevitably restores successful pregnancy. This does not diminish the scientific role of immune and vascular mechanisms; it calibrates their translational readiness.

The 2026 ASRM update places genetic and anatomical assessment at the core of evaluation and argues against routine inherited thrombophilia panels or empirical immunological treatments in unselected patients [1]. The ESHRE update likewise favors evidence-based, individualized investigations [2]. Differences in specific algorithms between societies may stem from evidence dates, health-system access, definitions and interpretation of conditional benefits. These differences should be acknowledged rather than collapsed into a false global consensus.

Data quality is not a secondary engineering problem. Incomplete pregnancy histories, losses treated outside health facilities, absent gestational dating, assay heterogeneity and unrecorded drug discontinuation can each reverse apparent treatment patterns. Multiple imputation presumes defensible missingness mechanisms; sensitivity analyses for missing-not-at-random outcomes and negative controls are particularly valuable.

Bias may enter through referral selection, confounding by severity, surveillance intensity, immortal-time exposure definitions, and conditioning on pregnancy after treatment initiation. Cox hazard models do not correct such biases by themselves. Target trial emulation can improve transparency but cannot guarantee identification when important predictors and treatment rationale are unmeasured.

Explainable AI techniques may expose feature attribution but not confer causal validity. Ethical AI requires accessible clinical explanations, calibrated uncertainty,

subgroup performance assessment, cybersecurity, and routes for clinician disagreement. Clinical decision support systems should display test indications, guideline exceptions and provenance, and never automatically order immunotherapy or anticoagulation on the basis of a proprietary probability score. Regulatory science provides an organizational framework, not an endorsement of every algorithm or observational estimate. The WHO emphasizes patient autonomy and governance; FDA evaluates fit-for-purpose data and evidence pathways; EMA DARWIN EU demonstrates networked real-world analytics [10–14]. Pregnancy studies require particularly careful benefit–risk assessment because maternal and fetal outcomes can diverge.

Key limitations of this review include its non-systematic search process, restriction to an explicitly identifiable set of sources, absence of independent risk-of-bias scoring for all eligible literature, no patient-level dataset and no new meta-analysis. The results are thus a critical evidence synthesis and research agenda—not original epidemiological estimates. The clinically strongest conclusions arise from contemporary guidance and the explicitly cited randomized trials.

5. Conclusion

Recurrent pregnancy loss should be evaluated as a heterogeneous syndrome requiring careful definition, genetic and uterine assessment, judicious endocrine investigation, and criterion-based testing for antiphospholipid syndrome. Evidence supports treatment of established maternal conditions and selected APS-associated pregnancy risk, but does not justify routine low-molecular-weight heparin for inherited thrombophilia or levothyroxine solely for euthyroid thyroid autoantibody positivity. Routine immune testing and empirical immune therapy remain insufficiently supported. High-quality real-world registries and externally validated computational tools may strengthen longitudinal research, provided that causal design and patient safety govern deployment. The primary endpoint must remain a healthy live birth, not correction of an isolated laboratory abnormality.

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Evidence integration addendum: newer studies and clinical boundaries

An additional systematic review of chronic endometritis and recurrent reproductive failure published in 2024 found a higher observed frequency of chronic endometritis in RPL groups than controls (37.6% versus 16.4%; pooled odds ratio 3.59, 95% CI 2.46–5.24) [14]. This is evidence of association, not proof that empirical antibiotic therapy improves live birth. Thresholds for CD138-positive plasma cells, biopsy timing and prior antimicrobial exposure differ across studies. Such variation can generate ascertainment heterogeneity sufficient to limit transportability of an apparent association. Histologic definitions should be explicitly established before prospective studies evaluate treatment effects.

Genomic investigations change the denominator of unexplained loss. A large 2022 series examined chromosomal microarray data from 24,900 products of conception, illustrating the feasibility of studying embryonic genomic alterations at scale [21]. However, referral-based products-of-conception repositories do not establish population prevalence, because pregnancy losses eligible for tissue collection and submitted to commercial laboratories are selected. Studies connecting molecular results to subsequent outcomes should adjust for maternal age and prior pregnancy trajectory, and they should distinguish prognostic stratification from demonstrably effective reproductive interventions.

A 2023 retrospective study of couples undergoing chromosomal microarray analysis followed subsequent reproductive outcomes in a subset, demonstrating the usefulness of longitudinal linkage [17]. Follow-up selection is itself an issue: couples who return, conceive, or use fertility treatment may differ from those who do not. Live-birth estimates should specify whether nonconception is counted, how subsequent pregnancies are identified, and whether assisted reproduction is considered a mediator or a distinct treatment strategy.

Contemporary RCOG guidance recommends thyroid evaluation in recurrent miscarriage but advises against routine immunological screening with nonvalidated cytokine, HLA, or natural killer cell assays [13]. Across scientific societies, different positions on thyroid autoantibody testing must be read alongside randomized evidence showing that levothyroxine does not improve live-birth outcomes in euthyroid antibody-positive patients [4,6]. A laboratory observation should not override a negative patient-important clinical trial.

The 2025 randomized trial combining prednisolone and intravenous immunoglobulin after assisted reproduction provides an important example of the continuing effort to test intensive immunological treatment in a defined population [15]. Its small single-center context and selection of ART-related recurrent loss make the question meaningfully different from unexplained RPL across all modes of conception. Such trials should be evaluated on their own eligibility, live-birth endpoint, precision, and safety; extrapolation to empirical immune treatment for every affected patient would be inappropriate.

The male contribution to recurrent loss is increasingly studied. A 2025 systematic review of male factors and RPL supports considering both partners as part of reproductive history [16]. Yet biomarker measurement and test-directed treatment are different questions. Semen DNA fragmentation tests can have variable assay methodology and cutoff values, and uncertainty about intervention benefit should be discussed explicitly when results are used for counseling.

The immunothrombotic evidence base cannot be summarized under the generic phrase “thrombophilia-associated miscarriage.” Recent systematic reviews on antiphospholipid-antibody-associated recurrent loss address aspirin and heparin combinations within an acquired autoimmune phenotype [19,20]. Trials of low-molecular-weight heparin in inherited thrombophilia address a distinct clinical population [3]. A separate 2026 synthesis of placenta-mediated complications

among APS patients without a recurrent-miscarriage history underscores how baseline obstetric phenotype modifies the relevant inference [24].

Precision diagnostics should ask whether a test changes what happens next. Chromosome analysis can explain an individual loss and shape counseling, but its value for treatment selection depends on what interventions are available and shown to work. Whole-exome findings may yield variant classifications of uncertain significance; such results cannot be interpreted as proof of causation or an indication for personalized medication without strong genotype-phenotype support and independent confirmation [18,26].

A 2026 synthesis of RPL etiologic categories reported substantial unexplained burden and exceptionally high between-study heterogeneity for several pooled estimates [23]. The lesson is not to import pooled categories uncritically into Uzbekistan or any other care setting. Instead, standardized reporting of diagnostic workup completeness, local fertility service access, maternal age distribution, fetal genetic testing uptake and laboratory thresholds is needed before valid epidemiological comparisons can be made.

For practice implementation, a registry should measure feasibility and completeness as well as medical outcomes: proportion with verified pregnancy dates, successful record linkage, known treatment start time, outcome ascertainment after transfer of care, and proportion with sufficient data for APS classification. These are proposed process measures without invented target percentages. Robustness would be assessed with prespecified source-verification samples, external chart adjudication, and missing-data sensitivity analyses.

Equity has clinical consequences. Women attending specialized referral units may be more likely to receive genetic testing, immune panels and longitudinal follow-up than women using district-level services. Models trained in tertiary centers can learn referral patterns rather than biology. Before use in clinical decision support, external validation should examine different referral routes, gestational ages, socioeconomic settings and language characteristics. Decisions should remain clinician-reviewed and anchored in current guidelines.

Finally, the literature favors transparent negative recommendations as strongly as affirmative prescriptions. A decision not to order routine immune markers, not to prescribe empiric heparin for inherited thrombophilia, or not to treat isolated thyroid antibodies in an otherwise euthyroid person is a clinically substantive decision based on controlled evidence. Such restraint is not an absence of care: it directs resources toward support, appropriate investigations, management of verified disease, and shared reproductive planning.