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AOGD BULLETIN

"Women's wellness-From tiny heartbeats to timeless strength"

THEME: REFRAMING RECURRENT PREGNANCY LOSS: A CALL FOR PATIENT-CENTERED, EVIDENCE-BASED CARE

AOGD SECRETARIAT
Department of Obstetrics and Gynaecology
Lady Hardinge Medical College & Associated Hospitals, New Delhi-110001
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Follicle Monitoring in Assisted Reproductive Technology (ART)

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Director Dr Pankaj Talwar IVF and Fertility Clinics Gurugram.

Academic Director, Clinical ART Program, SEART, Gurugram University.

Dean Department of Clinical Embryology & Reproductive Sciences **Shridhar University, Pilani.**

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Greetings from AOGD Secretariat!

The November chill has set in signalling a change in season and setting the mood for yet another eventful month.

October was a month of festivities and saw a slight drop in the number of activities. However, there were very impactful activities conducted -A HPV vaccination camp for specially abled children was conducted by the Community Health and Public Awareness Subcommittee and Webinar on Adolescent Health was conducted by Adolescent Health Subcommittee.

"Mission NEEeV" a vibrant educational program was conducted by Delhi Gynae Forum in association with AOGD on November 2, 2025. The mission was to educate and eradicate preventable maternal and neonatal mortality. The Mini Auditorium at LHMC was bursting with more than 350 delegates from various states , eager to learn and upscale their knowledge and with a mission to work towards zero preventable deaths .

We would like to draw your attention towards few important activities lined up this month. A CME on GDM is slated for 15th November and a FOGSI- JOGI PICSEP Workshop on Research Methodology will be held on 22nd November 2025, both activities will be held at LHMC. We invite you to please attend in large numbers as both these events will provide a wealth of information which will inspire and awaken your desire to learn . We will circulate the programs and I am sure the course content will generate interest in you .

The Urogynaecology subcommittee will be conducting cervical cancer vaccination camp and free surgical camps this month. These activities are regularly conducted by them and we highly appreciate their huge contribution towards public health awareness.

The November Bulletin is targeted toward " Recurrent Pregnancy Loss -A call for patient centred and evidence based care". Providing Quality Care cannot be overemphasized and this Bulletin will provide insights for better care. I congratulate the team headed by Dr Pikee for this impactful journal.

Best Wishes,,

AOGD Secretariat

From the President's desk

Dear AOGD Members,

Hope you all had a joyous and illuminous Diwali!

The clinical meeting for month of October was conducted by on 31st October 2025 at Deen Dayal Upadhyay Hospital. Three interesting emergencies were discussed which require prompt attention for early diagnosis and treatment. Ovarian malignancy with torsion, spontaneous bladder rupture and tuberculosis of spine were the final diagnosis but none were straightforward to diagnose.

The attendance was meagre once again, and I implore you all to join us on the virtual platform on last Friday of each month to learn from these interesting and unique presentations made.

November bulletin is on Recurrent Pregnancy Loss – A call for individualized and evidence based management. I congratulate Dr Pikee and her team for drawing our attention to treat each case as different and to inculcate evidence based practices'.

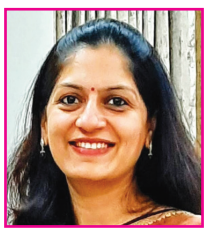
President AOGD

From the Editor's Desk

Dr Pikee Saxena

Dr Manisha Kumar

Dr Vidhi Chaudhary



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Reframing Recurrent Pregnancy Loss: A Call for Patient-Centered, Evidence-Based Care

Dear Readers,

Recurrent Pregnancy Loss (RPL) remains one of the most emotionally challenging and clinically complex experiences in reproductive medicine. Despite remarkable progress in diagnostics and therapeutics, the uncertainty surrounding its etiology often leaves both patients and clinicians grappling for answers. This issue of the AOGD Bulletin is dedicated to revisiting RPL through a patient-centered, multidisciplinary lens — one that values evidence-based medicine while recognizing the profound emotional dimension of loss.

In recent years, our understanding of RPL has evolved from a purely anatomical or endocrine perspective to a holistic one that integrates genetics, immunology, thrombophilia, endocrinology, and the psychological well-being of the couple. Advances in cytogenetic testing, evolving definitions of antiphospholipid syndrome (APS), and growing insights into immunological and endocrine dysfunctions are reshaping clinical paradigms. However, as this issue highlights, the key lies not merely in expanding our diagnostic armamentarium, but in applying it judiciously — ensuring that care remains individualized, empathetic, and grounded in sound scientific rationale.

The contributions in this edition provide an in-depth exploration of contemporary RPL management. Articles review the role of genetic testing, the impact of the revised ACR/EULAR criteria for APS, and the emerging understanding of immunological, endocrine, anatomical and metabolic factors in pregnancy loss. Together, they reflect a unified effort to transform RPL care from fragmented investigation to cohesive, compassionate management.

As clinicians, our mission extends beyond restoring fertility — it encompasses restoring hope. Patient-centered counselling, psychosocial support, and shared decision-making are as integral to outcomes as the laboratory results and imaging reports we rely upon.

I extend heartfelt thanks to all our esteemed contributors for their insightful work, and to the AOGD Secretariat for their continued support. May this issue inspire us to approach every couple with renewed sensitivity and scientific rigor, reaffirming that behind every loss is a story deserving of both compassion and clarity.

The Editorial Team

Role of Genetic Testing in Recurrent Pregnancy Loss (RPL) – What is clinically relevant?

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Introduction

Recurrent pregnancy loss (RPL) has traditionally been defined as three or more confirmed pregnancy losses; this has recently been modified to two or more (≥2) pregnancy losses before viability.[1,2] These losses can be consecutive or non-consecutive. RPL affects about 5% of pregnancies.[1] It continues to be a diagnostic as well as therapeutic challenge for clinicians. Up to 50% of RPL will not have an identifiable cause; the other half may be due to uterine anomalies, cervical incompetence, endocrinological causes like uncontrolled thyroid disorders, diabetes, thrombophilias, and genetic causes. Advancing maternal age and the number of previous miscarriages are both independent risk predictors for future recurrence risks.[3]

Genetic etiology in RPL

Genetic mechanisms contributing to RPL can range from parental chromosomal rearrangements to sporadic fetal aneuploidy, copy number variations (CNVs), and rarely single-gene mutations. Most pregnancy losses before 10 weeks are due to random numerical chromosomal abnormalities, primarily trisomies, which may be related to maternal and paternal age. However, in women with RPL, the risk of aneuploidy at each age is lower as compared to women who have sporadic miscarriages. Thus, karyotype on the products of conception, wherever available, is recommended in couples with RPL. Although the proportion of abnormalities in the POC is much higher than the proportion of chromosomal abnormalities in the parents, such a finding is of immense psychological benefit to the couple.[3] Couple karyotype in peripheral blood should be offered as 2-5% of couples with RPL will have a balanced reciprocal translocation or Robertsonian translocation in one of the partners.[3]

Types of genetic tests

There has been a dramatic change in the options available for genetic testing in the last decade; karyotype is increasingly being superseded by chromosomal microarray (CMA) and whole exome sequencing (WES). It is currently recommended that ultra-low-density microarray on products of conception should be offered in RPL. In addition to offering higher resolution, CMA also lowers culture failure rates compared to traditional karyotyping. Parental testing should be limited to karyotype and not microarray. A comparison of the various genetic tests currently available is given in table 1.

Table 1: Comparison of various genetic test available.

GENETIC TEST	ADVANTAGES	DISADVANTAGES	RESOLUTION	TAT	COST
FISH (Fluorescence In Situ Hybridization)	Quick targeted result	Requires prior knowledge of specific aneuploidies suspected Only common aneuploidies can be detected (18,13,21, Sex Chromosomal Aneouploidies)	0.5 MB	3-5 days	3000-5000
KARYOTYPE	Gold standard for aneuploidies Affordable	Cannot detect microdeletions, microduplications, low level mosaicism	>5-10 MB	3 weeks	4000-5000
CHROMOSOMAL MICROARRAY (315k/750k)	Higher resolution Detects copy number variation not visible on KT (>20 Kb) Additional 5-10% yield	Possibility of Variants of Unknown Significance (VOUS) Cannot detect balanced translocations	20 Kb losses 40 Kb gains	10-14 days	8000-15000
WHOLE EXOME SEQUENCING (WES)	Picks up known single gene disorders Indicated in the presence of structural anomaly with normal CMA	Possibility of VOUS Does not identify large CNV, triplet repeats, balanced translocations	Base pair level	3-4 weeks	12000-15000 per sample

Fetal chromosomal abnormalities may account for up to 40–50% of miscarriages in RPL. *Aneuploidy*, which results from meiotic nondisjunction, is more common with increasing maternal age. Typical aneuploidies include trisomy 16, 21, 22, monosomy X, and triploidy. RCOG (Royal College of Obstetrician of Gynaecology) recommends cytogenetic analysis of miscarriage tissue after three consecutive losses or any second-trimester miscarriage.

Copy number variants (CNVs), or submicroscopic chromosomal deletions and duplications detectable by chromosomal microarray (CMA) or next-generation sequencing (NGS), may account for up to 5% of euploid miscarriages. These often involve genes that are critical for implantation or early embryogenesis. However, many CNVs remain variants of uncertain significance (VOUS), requiring genetic counseling for interpretation.

Rarely**,** *single-gene mutations* may lead to RPL by affecting oocyte maturation, fertilisation, or embryonic development. However, routine gene panel testing is not recommended except in consanguineous couples or unexplained RPL cases after exclusion of common causes.

Parental Chromosomal Rearrangements

Balanced structural chromosomal rearrangements are found in 2–5% of couples experiencing RPL. These include balanced reciprocal and Robertsonian translocations. Carriers are usually phenotypically normal but have a higher likelihood of producing unbalanced gametes, leading to pregnancy loss or congenital anomalies. The risk of miscarriage is approximately 25–50%, but the overall live birth rate can reach 70–80% without assisted reproduction. Current guidelines recommend parental karyotyping when products of conception (POC) show an unbalanced rearrangement or when no POC is available. Routine parental karyotyping for all couples is not recommended.[3-5]

Routine testing for sperm DNA fragmentation, immune factors, or MTHFR (Methylenetetrahydrofolate Reductase) mutations is not indicated in genetically normal couples.

Assisted Reproductive Technologies (ART) and Genetics

Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR) enables the selection of chromosomally balanced embryos in couples with translocations or inversions. It reduces miscarriage rates per transfer but has a limited effect on overall live-birth rates due to low embryo yield.

Preimplantation Genetic Testing for Aneuploidy (PGT-A) detects aneuploid embryos before transfer. However, it has not consistently improved live-birth outcomes in unexplained RPL and should not be used routinely (RCOG Grade C).

Genetic Counselling and recurrence risk

If a genetic cause is identified in a couple experiencing RPL, genetic counseling is crucial as it offers explanations, risk assessment, and reproductive guidance. The likelihood of having a successful next pregnancy will depend on the chromosome involved and the type of rearrangement. Female carriers of balanced translocations have a 10–15% risk of an unbalanced conceptus resulting in a repeat miscarriage. This risk is 5-10% in male carriers.

Options for the couple include chorionic villus sampling (CVS) or amniocentesis in the next natural conception or in vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD) and transfer of unaffected embryos. However, there is insufficient data to suggest that IVF-PGD improves live birth rates in these couples.[5] Published literature suggests that couples with RPL and chromosomal abnormalities who conceive spontaneously have a good chance (63.4%) of a successful pregnancy.[6] Thus currently, routine preimplantation aneuploidy screening in patients with RPL is not justified.

Other reproductive options include use of a donor gamete and adoption. Psychological support is an essential part of care for couples with RPL.

Prognosis

The overall live-birth rate in a subsequent pregnancy in RPL is 70–75 %, depending on the parental age and the underlying cause. Prognosis improves if the preceding miscarriage was aneuploid and worsens with euploid losses.

Current recommendations

- Cytogenetic analysis should be offered on products of conception of the third and subsequent miscarriage(s) and in any second-trimester miscarriage.
- Peripheral blood karyotyping should be performed in couples in whom testing of the products of conception reported an unbalanced structural chromosomal abnormality. An abnormal parental karyotype should prompt referral to a clinical geneticist
- If genetic testing on POC fails or there is no pregnancy tissue available for testing, parental karyotyping should be offered.

Conclusion

Genetic causes of RPL encompass parental rearrangements, sporadic embryonic aneuploidy, and, less commonly, single-gene or epigenetic defects. Modern molecular tools enhance diagnostic precision but should be applied judiciously. The cornerstone of management remains personalised evaluation, informed counselling, and supportive care. Prognosis is favourable, and most couples eventually achieve a successful live birth with appropriate guidance and intervention.

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FOGSI – JOGI – PICSEP 2025

(Program for Inculcating Culture of Scientific Enquiry & Pursuit)

Workshop on Research Methodology

Organized by

Association of Obstetricians and Gynaecologists of Delhi

Date: **22nd November 2025** | *Time:* **9:00 am - 5:00pm**

Venue: **Ground Floor, Seminar Room, New Academic Block, LHMC, New Delhi**

The workshop is awarded 5 ICOG Credit Points

Dr Sunita Tandulwadkar
President, FOGSI

Dr Suvarna Khadilkar
Secretary General, FOGSI

Dr Sujata Dalvi
Editor- In- Chief, JOGI

Dr Arun Nayak
Associate Editor, JOGI

Dr Nidhi Gupta
National Faculty

Dr Reena Yadav
President, AOGD

Dr Ratna Biswas
Secretary, AOGD

Program

Time	Topic	Speaker	Chairperson
09:00 - 09:15am	Registration		
09:15 - 9:30am	Introduction to the Workshop & Editor – In – Chief Message.	Dr. Sujata Dalvi	
09:30 - 10:00am	Selection of a topic for research Guide's role Feasibility of a research topic Time management	Dr A G Radhika	Dr Ashok Kumar Dr Geeta Mediratta Dr Taru Gupta Dr Madhulika Monga
10:00 - 10:45am	Types of studies in research Interventional studies, RCTs Case control studies Cohort studies Cross sectional study Case Report, case series report Importance and relevance of each type Systematic Review	Dr Nidhi Gupta	Dr Manju Puri Dr Anupam Prakash Dr Archana Singh Dr Anuradha Singh
10:45 - 11:15am	Tea & Inauguration		
11:15 - 11:45am	The art and science of scientific writing Standard structure of a paper (IMRAD format) Representation of data (figures, graphs, tables) Language and style, common grammatical errors Authorship and plagiarism	Dr Ranadip Chaudhary	Dr Asmita Rathore Dr Sushma Nangia Dr Bindu Bajaj Dr K Aparna Sharma
11:45 - 12:30pm	Literature search and referencing Interactive demonstration of use of Pubmed and other search engines Use of online and offline referencing tools / AI	Dr Viswas Chhapola	Dr S.S Trivedi Dr Shailja Shukla Dr Rachna Aggarwal
12:30 - 01:00pm	Basics of medical statistics Calculation of sample size / Power of Study Selection of samples, confidence intervals, P value Application of various statistical tests to different types of data / Odd Ratio / Risk Ratio Simple exercises	Mr. V Ravi	Dr Ratna Biswas Dr Sameer Gulati Dr Sharda Patra
01:00 - 01:30pm	Critical evaluation of a journal article Use of PICO tool	Dr Anju Seth	Dr Rehan Dr Manoj Aindley Dr Kiran Aggarwal
01:30 - 02:15pm	Lunch		
02:15 - 2:45pm	Overview of evidence-based medicine and relevance to practice	Dr Reena Yadav	Dr S B Khanna Dr Gyan Saurabh Dr Saritha Shamsunder
02:45 - 03:15pm	The other side: What editors and reviewers want Editorial process and peer review What authors can do to improve their publications	Dr Pikee Saxena	Dr Vikram Dutta Dr Prabha Lal Dr Vidhi Chaudhary
03:15 - 03:45pm	Ethical principles guiding research Brief overview of GCP, IHC and ICMR guidelines Scientific Misdeeds, Misconduct, Authorship and Plagiarism	Dr Manisha Kumar	Dr Sumitra Bachani Dr Ekta Debnath Dr Aishwarya Kapur
03:45 - 04:15pm	Quiz & Distribution of Certificate & Vote of Thanks : Dr Ratna Biswas, Dr Anuradha Singh		

Changing diagnostic criteria of Antiphospholipid Antibody syndrome for RPL management: Guideline recommendations 2023 ACR/EULAR

Srilekha Thupili[1], Pikee Saxena[2]
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Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterised by recurrent arterial or venous thrombosis, pregnancy morbidity, and the persistent presence of antiphospholipid antibodies (aPL), including lupus anticoagulant (LAC), anticardiolipin antibodies (aCL), and anti-β2-glycoprotein I antibodies (anti-β2GPI).[1–3] APS may occur as a primary condition or secondary to other autoimmune diseases, most commonly systemic lupus erythematosus (SLE).[4] APS is a notable cause of recurrent pregnancy loss (RPL), contributing to 10–15% of unexplained miscarriages.[5,6] The pathogenic mechanism involves aPL-mediated thrombosis and inflammation of placental vasculature, leading to impaired placentation, fetal growth restriction, preeclampsia, and fetal loss.[6,7] Given the heterogeneity of clinical presentations and laboratory findings, accurate classification is critical for risk stratification, guiding therapy, and optimising obstetric outcomes. The 2023 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) form classification criteria introduce a weighted, domain-based approach that enhances specificity while refining the definition of obstetric APS.[2,8,9] These criteria prioritise clinically severe manifestations, incorporate temporal relationships between laboratory and clinical events, and exclude low-titre or IgM-only positive cases, thereby identifying high-risk populations more precisely.[2,9] For women with recurrent miscarriages, the updated criteria narrow formal APS diagnosis, which may exclude patients previously classified under older criteria despite potential clinical benefit from antithrombotic therapy.[6,7] This highlights the importance of individualised clinical judgment in managing RPL associated with aPL positivity.[4,6,7]

Historical Perspective: Evolution of APS Classification Criteria

1999 Sapporo and 2006 Revised Sydney Criteria

The original 1999 Sapporo criteria combined clinical (thrombosis or pregnancy morbidity) and laboratory (LAC, aCL) features with modest sensitivity and specificity.[8] The 2006 Revised Sydney criteria introduced higher specificity by adding anti-β2GPI antibodies and stipulating 12-week persistence of aPL.[1] Although an improvement, challenges remained in terms of classification consistency and the inclusion of non-thrombotic manifestations.[3,8]

2023 ACR/EULAR Criteria

The 2023 ACR/EULAR criteria were developed through a multiphase process involving international expert consensus, multicriteria decision analysis, and independent validation cohorts.[3, 2] This produced six clinical domains and two lab domains with weighted scoring to reflect risk and clinical relevance more faithfully.[2,9]

Evolution of APS Classification Criteria

Criteria Aspect	1999 Sapporo	2006 Revised Sydney	2023 ACR/EULAR
Clinical Domains	Thrombosis, pregnancy morbidity	Same, refined definitions	6 domains, including microvascular, cardiac valve, and hematologic
Laboratory Domains	LAC, aCL	Added anti-β2GPI	Weighted LAC, aCL, anti-β2GPI
Positivity Interval	≥6 weeks apart	≥12 weeks apart	≥12 weeks apart within 3 years of clinical event
Weighting	None	None	Weighted scoring system (≥3 points combined)
Sensitivity/Specificity	~98% / 80%	~98% / 86%	~84% / 99%

Entry Criteria[a]

At least one documented[b] clinical criterion listed below (domains 1-6)

plus

A positive antiphospholipid antibody (aPL) test
(a lupus anticoagulant test, or moderate-to-high titers of anticardiolipin or anti-β_2-glycoprotein-I antibodies [IgG or IgM])
within three years[b] of the clinical criterion

↓

If absent, do not attempt to classify as APS - If present, apply additive criteria

↓

Additive clinical and laboratory criteria[a]

Do not count a clinical criterion if there is an equally or more likely explanation than APS.
Within each domain, only count the highest weighted criterion towards the total score.

Clinical domains and criteria	Weight	Clinical domains and criteria	Weight
D1. Macrovascular (Venous Thromboembolism [VTE])		**D2. Macrovascular (Arterial Thrombosis [AT])**	
VTE with a high-risk VTE profile[c]	1	AT with a high-risk CVD profile[c]	2
VTE without a high-risk VTE profile[c]	3	AT without a high-risk CVD profile[c]	4
D3. Microvascular		**D4. Obstetric**	
Suspected (one or more of the following)	2	≥3 Consecutive pre-fetal (<10w) and/or early fetal (10w 0d -15w 6d) deaths	1
Livedo racemosa (exam)			
Livedoid vasculopathy lesions (exam)			
Acute/chronic aPL-nephropathy (exam or lab)			
Pulmonary hemorrhage (symptoms and imaging)		Fetal death (16w 0d – 33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features	1
Established (one of more of the following)	5		
Livedoid vasculopathy (pathology[d])			
Acute/chronic aPL-nephropathy (pathology[d])		PEC with severe features (<34w 0d) or PI with severe features (<34w 0d) with/without fetal death	3
Pulmonary hemorrhage (BAL or pathology[d])			
Myocardial disease (imaging or pathology)		PEC with severe features (<34w 0d) and PI with severe features (<34w 0d) with/without fetal death	4
Adrenal hemorrhage (imaging or pathology)			
D5. Cardiac Valve		**D6. Hematology**	
Thickening	2	Thrombocytopenia (lowest 20-130x10^9/L)	2
Vegetation	4		

Laboratory (aPL) domains and criteria[e]	Weight	Laboratory (aPL) domains and criteria[e]	Weight
D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])		**D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β_2-glycoprotein-I antibody [aβ_2GPI] ELISA [persistent])**	
Positive LAC (single – one time)	1	Moderate or high positive (IgM) (aCL and/or aβ_2GPI)	1
Positive LAC (persistent)	5	Moderate positive (IgG) (aCL and/or aβ_2GPI)	4
		High positive (IgG) (aCL or aβ_2GPI)	5
		High positive (IgG) (aCL and aβ_2GPI)	7

↓

TOTAL SCORE

Classify as Antiphospholipid Syndrome for research purposes if there are
at least 3 points from clinical domains AND at least 3 points from laboratory domains

Figure 1 2023 ACR/EULAR classification criteria.

Table 2. Implications of the 2023 APS Criteria for Recurrent Pregnancy Loss.

Aspect	2006 Criteria	2023 Criteria	Implication
Early pregnancy loss (<10 weeks)	3 consecutive losses required	3 losses = 2 points (low weight)	Many RPL cases were excluded
Late fetal death (>10 weeks)	≥1 fetal death	Weighted 3 points	Maintained
Preterm birth / placental insufficiency	<34 weeks with preeclampsia	Emphasis on severe features	Stronger association with placental pathology
aPL profiles	Any persistent aPL	High-titre, dual/triple only	Excludes low-titre/IgM only cases
Classification threshold	Any one clinical + lab	≥3 pts clinical + ≥3 pts lab	Narrower inclusion
Overall inclusion rate (RPL studies)	~10–15%	<5%	Reduced classification, greater specificity

The 2023 ACR/EULAR APS criteria introduce several important updates aimed at improving specificity and reflecting disease severity more accurately.[2,9] Clinical manifestations are now prioritised using hierarchical weighting, ensuring that more severe events are appropriately emphasised.[2] A temporal association has been incorporated, requiring that laboratory and clinical events occur within a three-year window to enhance relevance.[2,9] The clinical domains have been expanded to include microvascular thrombosis and cardiac valve involvement, broadening the recognised spectrum of APS manifestations.[2,4] Obstetric criteria have been refined to focus on severe placental insufficiency and preeclampsia occurring before 34 weeks, while isolated early fetal losses are de-emphasised.[2,5–7] Laboratory definitions have also been tightened, excluding low-titer and IgM-only positive cases to reduce overdiagnosis and improve diagnostic specificity.[2,9]

Obstetric APS is traditionally associated with recurrent fetal loss, unexplained stillbirth, and preterm birth due to placental dysfunction.[5–7] Under the 2023 ACR/EULAR criteria, diagnosis is now restricted to patients with more severe placentation disorders, in contrast to earlier criteria that included isolated early miscarriages.[2,9] This refinement has had a significant impact on classification rates among women with recurrent pregnancy loss. For example, Mercier et al. reported a reduction in the proportion of RPL patients meeting APS criteria from 14.5% under the Sydney criteria to 1.2% with the 2023 criteria, highlighting the increased specificity but lower sensitivity of the revised system.[6] These changes underscore the need for careful clinical evaluation, as many patients with milder or early pregnancy losses may no longer meet formal classification despite potentially benefiting from monitoring or intervention.[5–7,9]

The narrower definition of APS under the 2023 ACR/EULAR criteria has important implications for obstetric practice.[2,9] Fewer women with recurrent pregnancy loss are formally classified as having APS, emphasising that clinical judgment remains essential, as classification criteria are primarily designed for research and may not identify all patients who could benefit from treatment.[1,9] High-risk patients who meet the 2023 criteria require comprehensive multidisciplinary specialist care.[9], while those who are aPL-positive but unclassified should undergo individualised counselling regarding potential risks and treatment options, with close monitoring throughout pregnancy.[5–7,9]

Clinical Algorithm for RPL and APS Management

A practical clinical approach involves first excluding other causes of pregnancy loss, including genetic, anatomic, or endocrine factors.[5] Screening for antiphospholipid antibodies—lupus anticoagulant (LAC), IgG/IgM anticardiolipin (aCL), and anti-β2 glycoprotein I (anti-β2GPI)—should be performed on two occasions at least 12 weeks apart.[1] The 2023 criteria can then be applied using weighted clinical and laboratory scores to guide management.[2,9] Patients classified with APS should receive multidisciplinary care, with consideration of thrombo-prophylaxis where indicated.[6]. For aPL-positive but unclassified individuals, the potential benefits of treatment must be weighed against risks, with careful follow-up to ensure maternal and fetal safety.[7]

Patient counselling is an integral part of care, ensuring that women understand the distinction between classification and clinical diagnosis, the evolving nature of APS criteria, and the implications for monitoring and therapy.[9] Shared decision-making allows management to be tailored to individual risk profiles and preferences.[7] Despite these advances, challenges remain, including low sensitivity of the criteria that may fail to identify milder or purely obstetric presentations, and the need for validation in ethnically diverse and low-resource populations.[6,10] Future directions include the development of diagnostic criteria distinct from research-focused classification, integration of emerging biomarkers and risk scores, and revisiting treatment thresholds and guidelines to reflect the narrower APS definition.[9,10]

Conclusion

In conclusion, the 2023 ACR/EULAR APS classification criteria represent a robust, evidence-based refinement, offering higher specificity and more precise phenotyping.[2,9,10] For women with recurrent pregnancy

loss, these changes translate into tighter thresholds for formal APS classification, necessitating nuanced clinical interpretation.[5–7,9,10] Continued research will be critical to optimise management strategies and improve maternal and fetal outcomes in APS-related pregnancy morbidity.[6,7,9,10]

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Immunological Causesof Recurrent Pregnancy Loss: New Insights and Emerging Treatments

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Abstract

Recurrent pregnancy loss (RPL), which is defined as two or more failed pregnancies before 20 weeks of gestation, affects 1-5% of couples and remains unexplained in up to 50% of cases. Immunological dysregulation plays a pivotal role, which includes disruptions in feto maternal tolerance, an imbalance between the innate and the adaptive immune responses, and autoimmunity. Key mechanisms include elevated natural killer (NK) cell cytotoxicity, Th1/Th17 dominance over Th2/Treg responses, cytokine shifts toward inflammation (e.g., increased TNF-α, IL-17; decreased IL-10, TGF-β), HLA/KIR mismatches, and microbiome dysbiosis. Recent advances (2025), leverage single-cell sequencing and biomarker profiling to uncover heterogeneous immune profiles, enabling precision diagnostics. Emerging treatments focus on targeted immunomodulation, such as corticosteroids for autoantibody-positive cases, intravenous immunoglobulin (IVIG) for high-loss patients with cellular imbalances, and novel agents like TNF-α inhibitors or mesenchymal stem cells (MSCs). Guidelines from the American Society for Reproductive Medicine (ASRM), European Society of Human Reproduction and Embryology (ESHRE), and the 2025 American Society for Reproductive Immunology (ASRI) emphasize evidence-based approaches, recommending therapies only for confirmed immune abnormalities while cautioning against unproven interventions. This review emphasizes on the current insights, highlighting personalized strategies to improve live birth rates and decrease the overall burden of Recurrent Pregnancy Losses.

Introduction

Recurrent pregnancy loss (RPL) represents a significant challenge in reproductive medicine, encompassing emotional, physical, and economic burdens for affected

individuals. Historically viewed through genetic, anatomic, and endocrine lenses, the main etiologies and pathophysiologic approaches has increasingly shifted toward immunological perspectives, which identifies the fetus as a semi-allogeneic graft requiring maternal immune tolerance for successful implantation and gestation. Dysregulation in this tolerance thus can lead to repeated failures, particularly in unexplained cases where no chromosomal or structural anomalies are evident. The

immune system's role in pregnancy is multifaceted: it must suppress rejection while maintaining the defensive mechanism against pathogens. At the feto maternal interface, decidual immune cells orchestrate trophoblast invasion, spiral artery remodelling, and placental development. Imbalances pertaining to these mechanism such as overactive innate responses or skewed adaptive immunity—contribute to miscarriage. Immunological factors are implicated in 40-60% of idiopathic RPL, with overlaps in conditions like antiphospholipid syndrome (APS) and thyroid autoimmunity. Advancements in immunology, driven by technologies like single-cell RNA sequencing and liquid biopsies, have unveiled novel mechanisms and biomarkers. As of October 2025, research hotspots include immune cell heterogeneity, exosome-mediated regulation, and genetic-epigenetic influences on tolerance. These insights pave the way for emerging treatments, moving beyond empiric therapies to personalized immunomodulation. This article reviews immunological causes of RPL, integrates guidelines from ASRM (2012), ESHRE (2023 update), and ASRI (2025), and enlightens on new insights and treatments. It draws on recent literature to provide an informative synthesis for clinicians and researchers.

Definition and Epidemiology

RPL is clinically defined by the major societies with slight variations. The ASRM defines it as two or more failed clinical pregnancies (documented by ultrasound or histopathology), excluding ectopic, molar pregnancy, or biochemical losses.

ESHRE in line with this, specifies losses before 24 weeks and emphasizing non visualized pregnancies if confirmed by beta HCG.

The World Health Organization (WHO) requires three or more losses, but clinical practice often initiates evaluation after two. Primary RPL occurs without prior viable pregnancies, while secondary follows at least one success. Epidemiologically, RPL affects 1-2% of couples trying to conceive naturally, rising to 5% if including biochemical losses, and up to 10-15% in IVF cohorts.

Risk factors include advanced maternal age (>35 years, [OR] 2-4), obesity (body mass index >30, OR 1.5-2), smoking, and prior losses (risk escalates from 10% after one to 40% after three). Unexplained RPL constitutes 50% of cases, with immunological causes suspected in many. Global

incidence varies by region, higher in areas with vitamin D deficiency or autoimmune prevalence. Psychological impacts, including anxiety and depression, compound the issue, underscoring the need for holistic management.

Immunological Mechanisms

Successful pregnancy hinges on immune tolerance at the maternal-fetal interface, where the decidua hosts a unique milieu of cells modulating responses to paternal antigens. Dysregulation leads to RPL through failed implantation, placental insufficiency, or fetal rejection. Abnormal numbers, percentages, or activity of immune cells has been associated with RPL. (ASRI 2025)

- Natural Killer (NK) cells
  - uNK cells (in uterus): Involved in implantation.
  - pbNK cells (in peripheral blood): Often tested but less relevant to implantation.
  - Some studies suggest increased pbNK cells (or their activity) is associated with RPL.
- Th1/Th2 cells
  - Th1: Promote inflammation (involving cytokines IL-2, IFN-gamma, TNF alpha).
  - Th2: Anti-inflammatory (IL-4, IL-10).
  - A high Th1/Th2 ratio may indicate immune overactivation.
- Regulatory T cells (Tregs)
  - Promote immune tolerance and prevent over-inflammation.
  - Low Treg levels are linked to miscarriage and failed implantation.
- Th17 cells
  - Drive inflammation and autoimmunity.
  - High Th17 or high Th17/Treg ratio may increase RPL/RIF risk.
- Autoantibodies
  - Antiphospholipid antibodies (aPL): Cause clotting, miscarriage.

Innate Immunity

Uterine NK (uNK) cells, comprising 70% of decidual leukocytes, are pivotal for tolerance. In normal pregnancy, CD56(bright), CD16+, uNK cells secrete angiogenic factors (e.g., VEGF, PLGF) to facilitate trophoblast invasion and vascular remodelling.

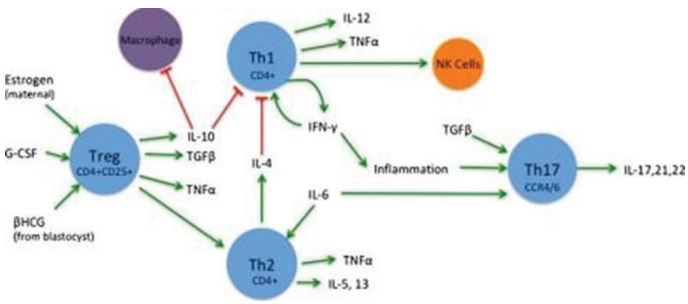
In RPL, levels peripheral NK (pNK) cells are elevated (>18% of lymphocytes), with heightened cytotoxicity via upregulated receptors (NKp30, NKp44, NKp46) and pro inflammatory cytokines (IFN-γ, TNF-α).

Decidual macrophages skew toward pro-inflammatory M1 phenotypes, reducing IL-10 and increasing CD80/CD86, impairing tolerance. Dendritic cells (DCs) show reduced tolerogenic subsets (e.g., ILT4+), leading to aberrant antigen presentation. Myeloid derived suppressor cells (MDSCs) levels decline, failing to suppress T-cell activation via STAT-3 signalling.

Adaptive Immunity

T-cell subsets play a pivotal role: Regulatory T cells (Tregs, CD4+, CD25+, Foxp3+) enhance tolerance through IL-10 and TGF-β. In RPL, Treg numbers fall, with Th17 dominance (IL-17, IL-21 secretion) fostering inflammation.

Th1/Th2 imbalance favours Th1 (TNF-α, IFN-γ), correlating with miscarriage risk. B cells increase in endometrium, potentially producing autoantibodies; reduced IL-10+ B cells exaggerate the issue further



Cytokine and Check point Dynamics

Pro-inflammatory cytokines (IL-6, IL-17, TNF-α) rise, while anti-inflammatory (IL-10, TGF-β) fall, disrupting Th1/Th2 and Th17/Treg ratios.

Immune checkpoints (PD-1/PD-L1, TIM-3) decrease, unleashing effector responses. HLA-G polymorphisms reduce soluble forms, impairing NK inhibition.

Genetic, Epigenetic, and Microbiome Influences

Polymorphisms in FOXP3, CTLA-4, and IL-17 genes predispose to immunological imbalances. Epigenetic modifications (DNA methylation) alter gene expression; miRNAs (e.g., miR-133a) downregulate HLA-G.Endometrial dysbiosis (reduced Lactobacillus, increased Gardnerella) triggers inflammation via IL-1β/IL-6.

Specific Immunological Causes

Immunological causes of RPL encompasses autoimmune and alloimmune etiologies, often overlapping with other factors. Anti-thyroid, antiphospholipid, lupus anticoagulant, anticardiolipin, antinuclear, anti-ssDNA, anti-dsDNA, and anti-histone are some of the important immunological factors.

Autoimmune Causes

Antiphospholipid syndrome (APS) is primary, with persistent antiphospholipid antibodies (APLA ,ACL, LAC,

anti-β2-glycoprotein) in 15-20% of RPL cases. These antibodies induce thrombosis, impair trophoblast function, and activate complement, leading to tissue necrosis and loss.Thyroid autoimmunity (anti-TPO/anti-TG antibodies) affects 10-15%, elevating Th17 and reducing cytotoxic T cells, even in euthyroid states.

Antinuclear antibodies (ANA) disrupt mitosis; celiac disease (anti-transglutaminase) impairs invasion via HLA-DQ2/DQ8. Systemic lupus erythematosus (SLE) and Sjögren's syndrome increase risks through low complement and autoantibodies.

Alloimmune Causes

HLA alleles are on chromosome 6. They are the human versions of MHC genes. Class I HLAs present peptides from within the cell. Class II present antigens outside of the cell. HLA-C also interacts with NK cells, and is responsible for the autologous recognition of the fetal tissue. They are expressed on the extravillous trophoblast and can bind to NK cells via the killer immunoglobulin like receptors (KIRs) and have been postulated to mediate trophoblast invasion. HLA-C1 allotypes inhibit KIR2DL2/3 and activate HIR2DS2 receptors. HLA-C2 allotypes inhibit KIR2DL1 and activate KIR2DS1 receptors

HLA/KIR mismatches (e.g., maternal KIR AA with fetal HLA-C2) activate NK cytotoxicity. Shared HLA alleles (>3) reduce tolerance; paternal antigen sensitization

leads to Th1-dominant responses. increased frequencies of identical HLA-A and HLA B alleles in families with higher rates of RPL. series of RPL patients and their HLA typing, found strong positive linkage disequilibrium between HLA-G14 insertion polymorphism, and HLA-A*01, -A*11, -A*31, -B*08, and DRB1*03. A strong negative linkage equilibrium was found between HLA G14 insertion and HLA-A*02, -A*03, and -A*24.

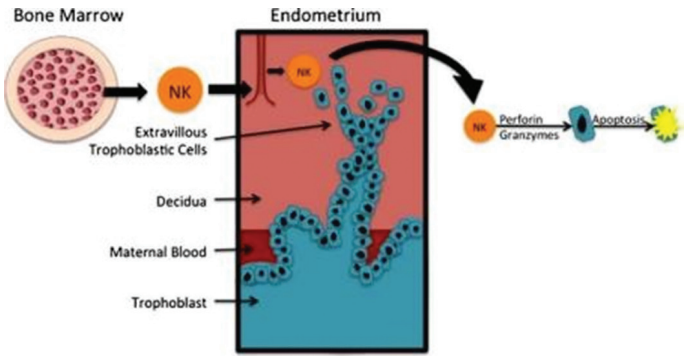
Human leukocyte antigen (HLA DP,DQ,DR), HLA–DRB1 and -DQB1 polymorphisms are associated with most autoimmune disorders and studies of HLA-DBB1 polymorphism in RPL patients are thus relevant. The clinically most important HLA class II loci are HLA-DRB1, -DQA1 and -DQB1. Polymorphisms in the HLA-G gene that may affect gene expression seem to play a role in several pregnancy complications such as recurrent pregnancy loss (RPL)The HLA-DRB1*07/*07 genotype was highly increased in patients with RPL compared with controls: OR 2.27

Cellular Imbalances

Uterine Natural Killer cells (uNK) comprise three subsets and are the most numerous immune cells found in the uterine mucosa at the time of implantation. They are thought to play an important role in successful pregnancy by regulation of extravillous trophoblast (EVT) invasion and spiral artery remodelling.

KIR2DL1/S1 and LILRB1 expression is lower in the reproductive failure group for both uNK (total uNK, uNK 2 and 3) and pNK. Degranulation activity is significantly reduced in total uNK, and that TNF-α production is lower in all uNK subsets in the reproductive failure group

Elevated uNK (>5%) and pNK with Th1/Th2 shifts; reproductive failure is associated with global reduction in expression of uNK receptors important for interaction with HLA-C and HLA-G on EVT during early pregnancy, leading to reduced uNK activation. low Tregs/high Th17 ratios; MDSC apoptosis via TRAIL.NKT and γδ T cells promote inflammation.



Other Associations

Vitamin D deficiency impairs Treg/NK function; obesity induces adipokine-driven inflammation; chronic endometritis via microbiota dysbiosis amplifies responses.

These causes highlight RPL's heterogenous nature, further stressing on targeted diagnosis and individualised treatment .

Diagnostic Approaches

Evaluation begins after two losses, per ASRM/ESHRE. Immuno logical testing is selective, focusing on unexplained cases.

Autoantibody Screening

Test for APLA, ACL, LAC (twice, 12 weeks apart); thyroid antibodies; ANA if autoimmune suspected. Celiac screening via anti-transglutaminase.

Cellular Immunity

Flow cytometry for pNK/uNK levels, cytotoxicity, Th1/Th2/Th17/Treg ratios Endometrial biopsy assesses uNK (>5%), macrophages.

Genetic/Epigenetic

HLA typing/KIR genotyping; miRNA profiling; single-cell sequencing for decidual immune landscape.

Microbiome and Biomarkers

Vaginal or endometrial swabs; liquid biopsies for exosomes and miRNAs.Technique uses 16S rRNA sequencing

Culture-dependent methods involve the cultivation of

microorganisms on various media to isolate and identify specific microbial species such as Lactobacillus species (crispate and gasserri), Gardnerella vaginalis, Candida species in the vagina or Bacteroides, Firmicutes, and Actinobacteria in the gut cytokine panels (IL-6, TNF α, IL-10);

By using light microscopy and bacterial culture, it was observed that women with RPL have a five-fold higher prevalence of aerobic vaginitis than healthy controls. Atopobiaceae bacteria (includes the species Fannyhessea vaginae) can be identified in over 80% of bacterial vaginosis patients. Together with Gardnerella vaginalis, both Fannyhessea vaginae and Prevotella are among the most found bacterial species in bacterial vaginosis – which is associated with other adverse pregnancy outcomes

For microbiome studies, an endometrial biopsy is most commonly performed during the mid-luteal phase (7 to 9 days after the LH surge). This timing, also known as the "window of implantation," is when the endometrium is hormonally primed for embryo implantation and a healthy, Lactobacillus-dominant microbiome is expected in fertile individuals.

In Frozen Embryo Transfer cycles, in a Hormonally prepared endometrium, sampling is preferably done after 5 days of starting of progesterone supplementation Challenges include assay standardization and cost; AI-integrated profiling may enhance detection in such cases.

New Insights

As of 2025, single-cell sequencing reveals decidual immune heterogeneity in RPL, showing aberrant decidual NK/macrophage subsets and ligand-receptor disruptions. Metabolites like succinic acid influence trophoblast via immunity. Ferroptosis/oxidative stress genes (PTPN6, GJA1) are emerging as biomarkers.

Exosomes regulate cytokines, offering non-invasive diagnostics; miRNAs (hsa-miR 4454) in sperm link male factors. IL-6R's role highlights therapeutic targets with safety profiles. Trends show multidisciplinary integration: encompassing immunology with genetics/coagulation/ART.

EMERGING TREATMENTS

Treatments target confirmed abnormalities, as per 2025 ASRI guidelines.

Drug/Dosage	Mechanism of Action	Duration of Treatment	Effect Mediated
Corticosteroids (10-20 mg/day prednisolone or 1 mg/day dexamethasone)	Decrease in peripheral NK cells and increase tolerogenic activity. Combined with aspirin in patients with autoimmune antibodies.	Till serum Beta HGC is positive	Decreased cytotoxicity. Increased implantation rate in IVF.
Low molecular weight heparin (LMWH) and Aspirin LMWH dosage is 20-40 mg/day s.c and aspirin 150 mg/day,	Decreases thrombotic risk in patients with antiphospholipid syndrome.	Post Embryo Transfer, To be continued till 16 to 20 weeks gestation in uncomplicated cases, whereas high risk cases may need to continue till 36 weeks gestation	Increased live birth rate in RPL patients with persistent thrombophilia and antiphospholipid antibodies . There are no significant differences in patients with inherited thrombophilia and heterogeneous pregnancy morbidity.
Vitamin D (2000-4000 IU/Day)	Deficiency in vitamin D is related to impaired immune response. Decreases the Th17 cell population	To Be continued for sustaining normal levels	Vitamin D deficiency is observed in RPL patients. Decreased vitamin D in antiphospholipid syndrome
Intravenous immunoglobulins (400 mg/kg every 1-3 weeks): For ≥4 losses	Inhibition of HLA antibodies decreases Fc receptor expression and modulates NK cells. NK/Th1 imbalances; elevated (> 12%) NK-cell percentage, elevated Th1/Th2	IVIG administration was continued every 4 weeks during pregnancy until 30–32 weeks of gestation with a dosage of 400 mg/kg body weight.	Increased pregnancy success. Better efficiency at high doses. Effective in women with immunological problems
Hydroxychloroquine (200 to 400 mg/day)	Anti-thrombotic and immunomodulatory properties. Combined with conventional treatment in antiphospholipid syndrome.	Dosage to be continued till serum beta HCG is positive,	Decreased pregnancy loss. Effect dependent on dose. Enhanced Tregs, diminished Th17.

Lymphocyte immunotherapy (LIT) (3 to 4 ml) and repeated every 3 to 4 weeks	For Th1/Th2 imbalance	Injecting lymphocytes from the male partner to induce maternal immune tolerance, around 80 to 100 ml of male partner blood sample collected and WBCs prepared are injected subcutaneously in female partner	Mixed RCT shows 68% LBR
Intralipid/Intravenous lipid emulsions IV nutritional supplement made of fats (typically soy or egg-based)	Suppression of NK cytotoxic function and probably T CD8 cells.	Two doses of 500 ml of 20% infusion during the treatment cycle;	Increased pregnancy rate in previously failed IVF. Probable decrease in uterine NK cells. No effect on pregnancy rate. Effective in patients with high Th1 in endometrial biopsy. No effect in patients with high endometrial NK cells
Calcineurin inhibitors (Tacrolimus, Sirolimus) 2 to 4 mg/day	Modulate Th1/NK immune response; elevated Th1/Th2 response (>10.3),Low-dose tacrolimus in women with immune disorders alone or combined with heparin. Low side effects. Sirolimus (rapamycin) inhibits the mTOR pathway that is altered in some RIF and RPL patients	Tacrolimus 2 to 4 mg daily starting two days before the ET till serum beta HCG is positive	Decreased Th1/Th2 ratio. Risk-benefit effect in endometriosis. Phase II clinical in altered Th17/Treg patients. Increased implantation and pregnancy success.
Granulocyte colony stimulating factor (G-CSF)300 mcg sc/day	Tolerogenic response. Increase in Tregs/IL10. Enhances receptivity of the endometrium; for persistent thin ET	Till optimal Endometrial Thickness (>8 mm) is achieved	Increased pregnancy success. Subcutaneous injections have a increased implantation success in RIF patients.
Alpha Thymosin (3.2mg/day) sc	Immune modulator agent	Alternate Day dosing starting from treatment cycle continued till ET	Treatment may be initiated from the luteal phase before ET and may potentially be continued till 9-10 weeks of gestation

Strongly Recommended

1. Corticosteroids (10-20 mg/day prednisolone or 1 mg/day dexamethasone): For immune abnormalities/ANA+, to be continued till serum beta HCG is positive; meta-analyses show OR 2.45 for live births.
2. Vitamin D (2000-4000 IU/day): If deficient; linked to reduced risk of RPL .
3. LMW Heparin/aspirin: For APS/APLA; dosage is 20-40 mg/day s.c and aspirin 150 mg/day, standard as per guidelines. To be continued till 16 to 20 weeks gestation in uncomplicated cases, whereas high risk cases may need to continue till 36 weeks gestation

Conditionally Recommended

1. IVIG (400 mg/kg every 1-3 weeks): For ≥4 losses with NK/Th1 imbalances; elevated (> 12%) NK-cell percentage, elevated Th1/Th2 ;IVIG administration was continued every 4 weeks during pregnancy until 30–32 weeks of gestation with a dosage of 400 mg/kg body weight. RCTs show increased live births (OR 2.24).
2. Lymphocyte immunotherapy (LIT): for Th1/Th2 imbalance, involves injecting lymphocytes from the male partner to induce maternal immune tolerance, around 80 to 100 ml of male partner blood sample collected and WBCs prepared are injected subcutaneously in female partner (3 to 4 ml) and repeated every 3 to 4 weeks , mixed RCTs (68% benefit).
3. Hydroxychloroquine (200-400 mg/day): For APS/inflammatory pathology; dosage to be continued till serum beta HCG is positive, 94% live births in studies.

Unclear Benefit/Emerging

1. Intralipids: Intravenous lipid emulsion (ILE) is an IV nutritional supplement made of fats (typically soy or egg-based) sometimes used off-label to modulate immune activity. It may reduce NK cell activity and inhibit Th1 cytokines. Dosage is two doses of 500 ml of 20% infusion during the treatment cycle; limited RCTs.

2. Calcineurin inhibitors (tacrolimus): Modulate Th1/NK immune response; elevated Th1/Th2 response (>10.3), Dosage is Tacrolimus 2 to 4 mg daily starting two days before the ET till serum beta HCG is positive.;small studies.
3. G-CSF: Enhances receptivity of the endometrium; for persistent thin ET dosage is 300 mcg sc injections can be repeated till optimal thickness achieved; has conflicting evidence
4. TNF-α inhibitors (adalimumab): Increase live births as evidenced by RCTs.
5. MSCs/Treg transfer: Restore tolerance; but it's a preclinical promise.
6. Exosome-based: Regulate immunity; only in the early stage.
7. Alpha Thymosin : Immune modulator agent, dosage is 3.2 mg sc injections every alternate day till ET. Dosing may be started in the luteal phase before embryo transfer and continued for a period of time after, potentially up to 9-10 weeks of gestation.

Personalized via biomarkers; trials (e.g., NCT04643117) trial. Guidelines: ASRM, ESHRE, and ASRI

ASRM's 2012 guideline recommends evaluation after two losses, including aPL testing but limited immunological workup; no routine NK/Treg testing; empiric progesterone/heparin for unexplained losses but cautions on immunotherapy.

ESHRE's 2023 update defines RPL as two losses, advises against routine immunotherapies (e.g., IVIG, LIT, glucocorticoids) due to insufficient evidence; supports aspirin/heparin for APS; conditional for progesterone in bleeding/high-risk; and emphasizes on psychological support.

ASRI's 2025 guidelines, first evidence-based for immunological RPL, recommend therapies only with biomarkers (e.g., uNK >5%, Th17/Treg imbalance); strong for corticosteroids and vitamin D therapies in identified abnormalities; conditional for IVIG/HCQ; unclear for intralipids/G-CSF; evidence from meta-analyses/RCTs, cautioning overuse of these therapies. Contrasts with ASRM/ESHRE by endorsing targeted immunomodulation.

Conclusion

Immunological RPL arises from a range of complex immune tolerance failures, with new 2025 insights emphasizing personalized profiling for better outcomes. Emerging treatments like targeted IVIG and biologics hold promise, guided by ASRI's evidence based framework. Future research should standardize diagnostics and conduct large RCTs to validate therapies, ultimately reducing the burden of RPL's impact.

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Endocrinological Disorders and RPL: From Diagnosis to Management

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Introduction

Endocrinological and metabolic disturbances are key contributors to reproductive dysfunction, affecting ovulation, fertilization, implantation, and the early maintenance of pregnancy. Hormonal imbalances—such as those involving thyroid hormones, prolactin, insulin, and progesterone—can create an unfavorable endometrial environment, leading to impaired embryo implantation and recurrent pregnancy loss (RPL). In addition, subtle metabolic abnormalities, including vitamin D deficiency and hyperhomocysteinemia, have been increasingly recognized for their influence on reproductive outcomes. The interplay between these endocrine factors is complex and often multifactorial, underscoring the need for a systematic approach to diagnosis and management. The following section explores the pathophysiological mechanisms, diagnostic approaches, and evidence-based management strategies for major endocrine and metabolic disorders associated with RPL.

Endocrine and Metabolic Causes

Thyroid Disorders

Pathophysiology

Thyroid hormones play a central role in reproductive physiology by influencing ovarian function, oocyte maturation, luteal phase adequacy, and placental development. Both hypo- and hyperthyroidism can disrupt the hypothalamic–pituitary–gonadal axis, alter gonadotropin release, and impair fertility. Abnormal thyroid hormone levels and elevated thyroid peroxidase antibodies (TPOAb) interfere with folliculogenesis, fertilization, and embryogenesis, thereby increasing susceptibility to pregnancy loss.[1] Autoimmune thyroid disease, particularly Hashimoto's thyroiditis, is frequently observed in women with RPL, even when thyroid function is within normal limits. Hyperthyroidism—predominantly caused by Graves' disease—affects about 0.1–0.4% of pregnant women, but a direct causal link to RPL has not been clearly demonstrated. Subclinical hypothyroidism is more commonly reported in RPL, though its etiological contribution remains debated.

Diagnosis

Screening for subclinical hypothyroidism is advised for women with RPL, given the high coexistence of thyroid autoimmunity in this group. Routine testing of TSH, free T4, and anti-TPO antibodies is considered a reasonable approach. A meta-analysis of 13 studies reported a statistically significant association between TPOAb positivity and RPL, suggesting that immune-mediated thyroid dysfunction may adversely affect early pregnancy outcomes.

Management

- Women with overt hypothyroidism should be promptly treated with levothyroxine to maintain TSH within trimester-specific reference ranges.
- The benefit of treating subclinical hypothyroidism (SCH) is still uncertain; while some studies suggest reduced miscarriage rates, others have found no significant effect on live birth outcomes.
- For women with SCH or thyroid autoimmunity, close monitoring of TSH every 4–6 weeks during early pregnancy (especially between 7–9 weeks) is recommended, initiating levothyroxine if hypothyroidism is confirmed.
- Levothyroxine is not recommended for euthyroid women with positive thyroid antibodies, as no consistent benefit on pregnancy outcomes has been demonstrated.
- Optimal iodine intake and avoidance of excessive supplementation are also essential components of management.:

TSH (mIU/L)	Interpretation	Recommended Intervention
< 2.5	Normal thyroid function	No treatment required; routine monitoring only
2.5 – 4.0	Mild/subclinical hypothyroidism zone	Check thyroid peroxidase (TPO) antibodies. If **TPO+** and RPL history → consider **levothyroxine**; if **TPO negative**, monitor TSH pre-conception and early pregnancy
> 4.0	Hypothyroidism likely	**Start levothyroxine**; aim for TSH < 2.5 mIU/L pre-conception and during early pregnancy
Overt hypothyroidism (↑TSH + ↓Free T4)	Established thyroid disease	**Initiate/adjust levothyroxine** immediately; close monitoring every 4–6 weeks
Normal TSH + TPO-positive	Thyroid autoimmunity without dysfunction	Routine levothyroxine **not universally recommended**; monitor TSH every 4–6 weeks in early pregnancy

Polycystic Ovary Syndrome (PCOS) and Insulin Resistance

Pathophysiology

PCOS represents a multifaceted endocrine disorder characterized by chronic anovulation, hyperandrogenism, and polycystic ovarian morphology. It is frequently associated with metabolic derangements such as insulin resistance, hyperinsulinemia, and obesity—all of which can adversely affect oocyte quality and endometrial receptivity. The relationship between PCOS and RPL remains ambiguous, as both share overlapping risk factors including obesity, hyperinsulinemia, LH hypersecretion, and androgen excess. Insulin resistance, more prevalent among women with RPL, may contribute to a pro-inflammatory state, endothelial dysfunction, and hypercoagulability, potentially compromising implantation and placental development.[2]

Diagnosis

Routine evaluation for PCOS and insulin resistance in RPL is not universally recommended. However, clinical features such as irregular cycles, hirsutism, or obesity may justify assessment using fasting glucose, fasting insulin, or HOMA-IR index. Despite these, current data suggest that insulin testing does not necessarily improve pregnancy outcomes.

Management

Metformin remains the cornerstone therapy for insulin resistance and type 2 diabetes mellitus. It improves insulin sensitivity, lowers androgen levels, and may enhance ovulation.[3] Several studies have shown that metformin reduces miscarriage rates and improves pregnancy outcomes in women with PCOS, possibly by restoring endometrial receptivity. However, the evidence remains insufficient to recommend its routine use as a preventive therapy in all RPL patients. Lifestyle modification—focusing on weight reduction, dietary management, and regular exercise—should be emphasized, as modest weight loss can restore ovulatory function and improve reproductive outcomes.

Hyperprolactinemia

Pathophysiology

Prolactin is vital for luteal function and progesterone synthesis, supporting the endometrial environment necessary for embryo implantation. Excess or deficiency in prolactin levels may disrupt gonadotropin secretion and luteal adequacy, predisposing to pregnancy loss. Studies examining serum and endometrial prolactin levels have reported conflicting results, often limited by small sample sizes and inadequate control groups. Li et al. observed that women who miscarried had significantly lower prolactin levels compared to those with successful pregnancies.[4] Nonetheless, the overall data remain inconclusive regarding a causal association between prolactin levels and RPL.

Diagnosis

Routine prolactin testing is not advised unless there are symptoms such as galactorrhea, menstrual irregularities, or infertility. Prolactin levels can also be influenced by stress, obesity, luteal phase defects, and PCOS, complicating diagnostic interpretation.

Management

Patients with confirmed hyperprolactinemia should be treated with dopamine agonists such as bromocriptine or cabergoline, which can restore ovulatory cycles and normal prolactin levels. In women with RPL and hyperprolactinemia, bromocriptine therapy has been associated with improved live birth rates in small studies, although larger trials are needed for validation.[5] MRI evaluation of the pituitary may be indicated in persistent cases to exclude microadenomas.

Luteal Phase Insufficiency (LPI)

Pathophysiology

Luteal phase insufficiency (LPI) is characterized by inadequate progesterone secretion from the corpus luteum, resulting in an endometrium insufficiently prepared for embryo implantation. Contributing factors include stress, PCOS, hyperprolactinemia, and thyroid dysfunction. Progesterone is essential for transforming the endometrium into a secretory state and for suppressing uterine contractility in early pregnancy.

Diagnosis

Accurate diagnosis remains challenging due to variability in criteria. Commonly used measures include:

- Mid-luteal serum progesterone <10 ng/mL.
- Sum of three serial luteal phase progesterone levels <30 ng/mL.
- Histological dating of endometrial biopsies, though this has poor reproducibility. Because progesterone secretion is pulsatile, a single measurement may not reliably indicate luteal function.

Management

Although LPI has historically been considered a cause of RPL, contemporary evidence does not confirm a strong link. Routine testing is not recommended. Similarly, progesterone supplementation or hCG administration has not consistently improved live birth rates in RPL attributed to LPI. Nonetheless, luteal phase support with vaginal or oral progesterone is commonly practiced empirically, especially in women undergoing assisted conception or those with documented luteal defects.

Vitamin D Deficiency

Pathophysiology

Vitamin D, beyond its skeletal role, functions as an immunomodulator in reproductive physiology. Deficiency has been associated with several obstetric complications, including preeclampsia, gestational diabetes, and preterm birth. Its receptors (VDR) are expressed in the endometrium, trophoblast, and placenta, underscoring its importance in implantation and immune tolerance.[6] Vitamin D regulates NK cell activity, promotes anti-inflammatory cytokine balance, and supports decidualization. Although studies have linked low vitamin D levels with higher rates of miscarriage, the evidence remains inconclusive.

Diagnosis

Routine screening for vitamin D levels in RPL is not recommended because of inconsistent findings. Nevertheless, assessment may be warranted in populations at risk for deficiency or in those with multiple pregnancy losses.

Management

Vitamin D supplementation during pregnancy is safe and widely endorsed. While conclusive evidence of its role in preventing RPL is lacking, maintaining optimal levels may contribute to favorable maternal and fetal outcomes. Most experts consider daily supplementation of up to 4,000 IU safe during pregnancy and lactation. Combined supplementation with calcium and vitamin D may further support placental health and bone metabolism.

Luteinizing Hormone (LH)

Elevated LH concentrations (≥10 IU/L) in the early to mid-follicular phase have been correlated with a higher risk of miscarriage following both spontaneous conception and assisted reproduction, particularly in PCOS patients.[7] Excess LH can impair folliculogenesis, leading to oocyte immaturity and altered corpus luteum function. Despite these associations, routine LH testing is not recommended in RPL workups, as therapeutic correction has not consistently improved outcomes.

Hyperhomocysteinemia

Pathophysiology and Clinical Significance

Hyperhomocysteinemia, resulting from deficiencies of folate, vitamin B6, or vitamin B12, or from genetic mutations such as MTHFR polymorphisms, is associated with endothelial dysfunction, thrombosis, and placental vasculopathy. Elevated homocysteine levels have been linked with adverse pregnancy outcomes, including neural tube defects, preeclampsia, intrauterine growth restriction, and placental abruption. These mechanisms may also contribute to RPL by disrupting implantation and placental development.

Diagnosis and Management

Although mild to moderate hyperhomocysteinemia may occur in women with PCOS or thyroid dysfunction, its routine testing in RPL is not supported due to inconsistent data. When identified, management includes dietary modification and supplementation with folic acid, vitamin B6, and vitamin B12, which effectively normalize homocysteine levels and improve vascular function.

Conclusion

Endocrinological factors are central to the successful establishment and maintenance of pregnancy. Identification and correction of underlying hormonal disturbances—whether thyroid, gonadal, adrenal, or metabolic—can markedly improve reproductive prognosis in women with RPL. A personalized, multidisciplinary approach integrating endocrinologic, immunologic, and reproductive expertise remains key to optimizing outcomes and reducing the burden of recurrent pregnancy loss.

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Endometrial Receptivity and Thin Endometrium in RPL: Diagnostic and Therapeutic Controversies

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Introduction

Recurrent pregnancy loss (RPL) and recurrent implantation failure (RIF) are devastating conditions for couples attempting to conceive. RPL remains one of the most challenging and poorly understood areas in reproductive medicine. This article summarizes the current understanding of the pathophysiological mechanisms underlying thin endometrium in association with RPL, and highlights diagnostic modalities and emerging therapeutic approaches. RPL affects approximately 3% of couples trying to conceive .[1] It is a multifactorial condition and despite available diagnostic tools, the etiology remains unidentified in more than 50% of RPL cases[2], giving rise to the term unexplained RPL.[3]

The disorder may be triggered by a spectrum of factors including chromosomal errors, immunological dysfunction, anatomical defects, autoimmune and endocrine disorders, thrombophilia, maternal infections, and endometrial abnormalities.[4]

Successful initiation of pregnancy depends on effective embryo implantation within a well-formed endometrium. Beyond the chromosomal integrity of the embryo, endometrial receptivity and thickness play crucial roles in reproductive outcomes and should not be overlooked in the context of RPL. Increasing evidence suggests that a dysregulated or non-receptive endometrium is significantly associated with reproductive failures, particularly RPL.[5]

Thin Endometrium

A thin endometrium—commonly defined as less than 7 mm in thickness[6]—indicates reduced endometrial receptivity. It is associated with lower implantation and pregnancy rates and may lead to recurrent miscarriages. In a study by Liu et al., the endometrium was significantly thinner in patients with RPL, who demonstrated reduced clinical pregnancy and live birth rates compared to those with normal endometrial thickness.[7]

Causes of Thin Endometrium

Persistently thin endometrium in RPL can have multifactorial origins.

1. Structural and Iatrogenic Damage

- Uterine scarring (Asherman's syndrome): Trauma to the basal endometrial layer following procedures such as dilation and curettage (D&C) or infections like genital tuberculosis can lead to intrauterine adhesions.
- Chronic endometritis: The condition often presents with non-specific or subtle symptoms, making clinical diagnosis challenging. Its pathogenesis involves a multifaceted interplay of microbial infection, immune dysregulation, and impaired endometrial receptivity. Often asymptomatic, persistent endometrial inflammation may cause fibrosis and impair the regenerative capacity of the endometrium.

2. Blood Flow and Vascular Factors

- Poor uterine perfusion: Sedentary lifestyle, fibroids, or vascular abnormalities can reduce blood supply to the uterus, impeding endometrial proliferation. Thin endometrium is often associated with reduced vascular endothelial growth factor (VEGF) expression, which compromises angiogenesis and vascular development necessary for a receptive lining.

3. Hormonal and Functional Factors

- Hormonal imbalances: Low estrogen levels due to aging, stress, or endocrine dysfunction—and impaired estrogen responsiveness—can lead to endometrial thinning.
- Excessive Clomiphene Citrate use: Prolonged or injudicious administration may adversely affect endometrial growth.
- Decreased stem cell activity: Dysfunction of endometrial stem/progenitor cells can hinder the regeneration of the functional layer.

4. Endometrial Immune Dysregulation

The endometrium hosts immune cells that promote maternal tolerance to pregnancy. Dysregulation in this immune environment may contribute to implantation failure in unexplained RPL.

5. Endometrial Receptivity Defects

Endometrial receptivity (ER) refers to the phase—known as the window of implantation (WOI)—when the endometrium is optimally prepared to support embryo implantation.[8] Deficiency or misalignment of this window can result in infertility or early pregnancy loss. Implantations outside the WOI are linked to early miscarriages.[9] Conversely,

an overly receptive "hyperfertile" endometrium may accept genetically abnormal embryos, predisposing to miscarriage.[10]

Association with RPL

Thin endometrium impairs receptivity and fails to support proper embryo growth due to:

- Poor vascularization: Reduced perfusion and downregulated VEGF lead to tissue hypoxia and atrophy, compromising placentation.
- Altered oxygen tension: Implantation near spiral arteries in a thin lining exposes the embryo to excessive oxygen, which may be detrimental.
- Inflammation and disrupted cellular signaling: Altered expression of adhesion molecules (β1-integrin, CD44), abnormal cytokine signalling, reduced natural killer (NK) cell activity—all impair embryo-endometrial communication.
- Epigenetic modifications: Aberrant DNA methylation and microRNA dysregulation affect genes critical for implantation.
- Defective decidualization: Impaired stromal cell transformation increases risks of delayed implantation and early placental failure, regardless of embryo ploidy.

Diagnostic Evaluation

- **Transvaginal Ultrasound (TVS):** Commonly used to assess endometrial thickness, pattern, volume, and vascularity. However, its predictive value for RPL remains inconsistent.[11]
- **Hysteroscopy**: Enables direct visualization of the uterine cavity to detect adhesions, polyps, or chronic endometritis. Though informative, it is invasive and less suitable for repeated assessments.[12]
- **Endometrial Biopsy / ERA Test**: A sample of the uterine lining can be collected to test for chronic endometritis or molecular markers associated with receptivity. Histopathological examination remains the gold standard for the diagnosis of chronic endometritis (CE). Characteristic microscopic findings and plasma cell infiltration within the stroma are regarded as the most specific and sensitive diagnostic hallmark. Despite their diagnostic value, both conventional hematoxylin and eosin (H&E) staining and immunohistochemical staining for CD138 (syndecan-1)—a reliable marker for plasma cells—have notable limitations. These include dependence on adequate endometrial sampling, variability in staining quality, interobserver subjectivity, inconsistency in the timing of biopsy collection across the menstrual cycle, and uncertainty regarding the clinical significance of minimal plasma cell infiltration (13). ERA provides more insight into endometrial receptivity beyond just thickness. It evaluates gene expression profiles related to receptivity and chronic inflammation. It helps to identify if the implantation window is displaced or if the endometrium is fundamentally non-receptive, even if the thickness is adequate. It is often recommended for patients with recurrent implantation failure aiding personalized treatment planning. However, its routine use in RPL or RIF remains debated.[14]
- **Radiomics**: An emerging AI-based imaging technique that extracts quantitative data from medical images to reveal microstructural patterns. A study conducted by Wendi et al.[15] demonstrated a significant association between unexplained recurrent pregnancy loss (RPL) and elevated endometrial radiomic scores during the window of implantation (WOI), underscoring the role of suboptimal endometrial receptivity as a potential contributing factor. These findings highlight the promise of radiomic scoring as a predictive tool for assessing the likelihood of ongoing pregnancy in RPL patients. It offers the potential to deepen our understanding of the endometrial environment and may enhance diagnostic precision and prognostic accuracy in RPL management.[16]

Treatment Approaches

Managing thin endometrium in RPL is challenging and often requires a multimodal strategy. Although thin endometrium correlates with poor reproductive outcomes, conception is still possible, and emerging therapies offer promise.

Treatment Approaches

Managing thin endometrium in recurrent pregnancy loss (RPL) remains a formidable challenge that often requires a **multimodal and individualized approach.** Although endometrial thinning correlates with poor reproductive outcomes, conception is still possible, and several emerging therapies offer promising prospects.

1. Endocrine and Drug Therapies

Hormonal Therapy:

Estrogen supplementation promotes endometrial proliferation, while progesterone supports luteal phase transformation. Estrogens may be administered orally, vaginally, or transdermally, with **transvaginal delivery achieving the highest serum concentrations** and endometrial growth.[17] In patients with reduced estrogen receptor activity, higher doses may be necessary; however, concurrent progesterone is essential to prevent hyperplasia. The mode of administration, dosage, and duration warrant standardization.

Growth Hormone (GH):

GH enhances endometrial thickness by improving uterine perfusion and upregulating insulin-like growth factor pathways. Meta-analyses have demonstrated improved implantation and live birth rates with GH supplementation.[18]

Human Chorionic Gonadotropin (hCG):

Intrauterine hCG instillation prior to embryo transfer stimulates cytokines such as VEGF and MMP-9, promoting angiogenesis and endometrial vascularization.[19]

Tamoxifen:

As a selective estrogen receptor modulator, tamoxifen may augment endometrial thickness when combined with hormone replacement therapy, although its clinical efficacy remains inconclusive.[20]

2. Improving Uterine Blood Flow

Low-Dose Aspirin:

Aspirin enhances uterine perfusion and endometrial morphology, indirectly improving implantation potential.[21]

Sildenafil Citrate:

This phosphodiesterase-5 inhibitor enhances nitric oxide–mediated vasodilation and has been shown to increase endometrial thickness and pregnancy rates, particularly with vaginal administration.[22]

3. Immunomodulatory Agents

Immunomodulatory strategies involve **anticoagulants, corticosteroids, intravenous immunoglobulin (IVIG),** and immunosuppressive agents. These therapies aim to correct immune dysregulation and prevent embryo rejection. Prednisone or prednisolone (10–20 mg/day) is typically tapered gradually. IVIG is administered intravenously at 0.4–2 g/kg body weight over several hours, with treatment frequency tailored to patient response.[23]

4. Regenerative and Innovative Therapies

Granulocyte–Macrophage Colony-Stimulating Factor (GM-CSF):

GM-CSF stimulates endometrial proliferation and neovascularization. Small studies report improvement in refractory thin endometrium. Gleicher et al. reported successful pregnancies in women with refractory thin endometrium following G-CSF infusion.[24]

Platelet-Rich Plasma (PRP):

PRP is defined as " the plasma component of autologous blood in which platelet concentration is four to five times the normal level" . It is obtained by centrifugation of autologous peripheral venous blood and contains various growth factors like VEGF , PDGF,EGF ,IGF1 and other cytokines which play a crucial role in cell proliferation , regeneration and differentiation .Intrauterine PRP therapy is being studied to improve endometrial thickness and receptivity, and it has shown promise in patients with thin endometria or a history of implantation failure. This therapy involves injecting a concentration of a patient's own platelets into the uterus either into the endometrial under hysteroscopic guidance or through a uterine catheter directly in the uterine cavity. The growth factors released by the platelets stimulate endometrial cell proliferation, and vascularization improving endometrial thickness .A prospective cohort study showed that intrauterine injection of PRP on day 10 of HRT cycle and on the day of progesterone administration is beneficial for improving endometrial thickness and clinical pregnancy rate.[25].

Stem Cell Therapy:

Stem cells possess the remarkable capacity to replace and regenerate damaged endometrial tissue and are therefore being explored as a potential therapeutic option for women refractory to conventional treatments. Based on their differentiation potential, stem cells are categorized as totipotent, pluripotent, multipotent, or unipotent. Among these, **mesenchymal stem cells (MSCs)—**the most widely studied type—exhibit high self-renewal capacity and multipotency. They can be derived from various sources, including bone marrow, adipose tissue, menstrual blood, umbilical cord, and endometrial tissue. Despite their promise, stem cell–based therapies present certain challenges. Harvesting procedures can be invasive, time-consuming, costly, and occasionally associated with discomfort. Nevertheless, clinical and experimental studies have demonstrated that MSCs can enhance endometrial thickness and potentially improve live birth rates. However, further research is required to establish the safety, efficacy, and long-term outcomes of this modality in clinical practice (26). A distinct class of pluripotent cells, **human embryonic stem cells (hESCs),** originates from the inner cell mass of the blastocyst during early embryonic development. Experimental studies have shown that hESCs can repair and regenerate endometrial tissue; however, their clinical application remains limited due to ethical concerns and tumorigenic concerns.[27]

Extracellular Vesicles (EVs) and Exosomes:

These bioactive vesicles facilitate tissue repair, immune regulation, stem cell support and cellular communication (28). Preliminary studies suggest intrauterine exosome therapy during the luteal phase may enhance endometrial receptivity, though dosing and efficacy require further evaluation.[28]

5. Procedural and Supplementary Interventions

Surgical Approaches:

Hysteroscopic correction of adhesions or anatomical defects facilitates endometrial regeneration, particularly in Asherman's syndrome.

Treatment of Chronic Endometritis:

Targeted antibiotic therapy has demonstrated encouraging effects on endometrial recovery and reproductive outcomes; however, further large-scale studies are warranted to establish standardized diagnostic and therapeutic protocols.[29]

Adjunctive and Lifestyle Interventions:

Antioxidants (vitamin E, melatonin), L-arginine, vitamin D, folic acid, and omega-3 fatty acids contribute to uterine health. Lifestyle measures—including regular exercise, adequate sleep, caffeine and nicotine reduction, and stress management through yoga or meditation—can enhance endometrial receptivity.

Endometrial Scratch:

A minor mechanical injury to the endometrium induces local inflammatory and regenerative responses, potentially improving implantation in selected cases.

6. Individualized Treatment and Pharmacogenomics

Therapeutic interventions should be **personalized** based on underlying pathology. **Pharmacogenomics**, integrating genetics, pharmacology, and clinical medicine, offers promise for individualized treatment—optimizing drug choice, dosage, and delivery according to genetic profiles.[30]

Conclusion

The endometrium plays a decisive role in implantation and pregnancy maintenance. A thin, non-receptive endometrium can undermine these processes, leading to recurrent pregnancy loss. Management encompasses hormonal modulation, improved perfusion, regenerative therapies, and lifestyle optimization. However, robust evidence supporting standardized treatment remains scarce. Future research should focus on elucidating molecular mechanisms, validating regenerative modalities, and integrating pharmacogenomic principles to establish **evidence-based and personalized therapeutic algorithms** for RPL associated with thin endometrium.

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Surgical Correction of Uterine Anomalies in Recurrent Pregnancy Loss: Controversy, Evidence, and Current Practice

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Endometrial Receptivity & Thin Endometrium

Congenital uterine anomalies (CUA) have long been associated with reproductive failure, including recurrent pregnancy loss (RPL). Surgical correction, primarily hysteroscopic metroplasty for septate uterus, has been widely practiced to improve reproductive outcomes. However, the magnitude of benefit remains controversial due to diagnostic variability and inconsistent evidence. This review critically examines the available literature on surgical correction of uterine anomalies in RPL, analyzing evidence, controversies, and current best practices. Observational studies consistently report significant reductions in miscarriage rates and improved live-birth outcomes following hysteroscopic septum resection in women with RPL. However, randomized and controlled data—most notably the 2021 Rikken et al. trial—question the routine benefit of surgery. Variability in diagnostic criteria, patient selection, and surgical technique further complicate interpretation. Major guidelines (ESHRE 2023; ASRM 2024) now recommend individualized, case-based management rather than universal surgical correction. Thus it can be concluded that Hysteroscopic metroplasty remains valuable in selected women with a confirmed septate uterus and recurrent loss, but current evidence does not support routine resection in all detected anomalies. Accurate diagnosis, standardized classification, and patient-centred counselling are essential. Well-designed randomized trials are urgently needed to clarify the true role of uterine correction in RPL.

Recurrent pregnancy loss, uterine septum, hysteroscopic metroplasty, congenital uterine anomaly, reproductive outcome, miscarriage

Introduction

Recurrent pregnancy loss (RPL) affects 1–2% of reproductive-age women and remains one of the most distressing challenges in reproductive medicine. Among multiple aetiologies, congenital uterine anomalies (CUA) have been identified as an important structural cause of miscarriage and adverse obstetric outcomes. The septate uterus, in particular, has been most consistently associated with recurrent early pregnancy loss and poor reproductive performance.[1–3] The presumed mechanisms include implantation on poorly vascularized septal endometrium, altered uterine contractility, and reduced cavity volume.[4] Surgical correction aims to restore a unified, vascular uterine cavity and improve implantation and gestational continuation. Despite decades of practice, however, the benefit of surgery remains controversial.

Types of Uterine Anomalies Relevant to RPL

Uterine anomalies arise from abnormal fusion or resorption of the Müllerian ducts during embryogenesis. Of these, the septate uterus (class U2 under ESHRE/ESGE) carries the strongest correlation with recurrent miscarriage [5]. Other anomalies—bicornuate, uni cornuate, didelphys, and arcuate uteri—show weaker or inconsistent associations, often contributing more to preterm labour or malpresentation than early pregnancy loss.[6,7]

Minor variants such as the arcuate uterus or subtle cavity indentations are frequent incidental findings and are rarely clinically significant. Overdiagnosis of these variants has contributed to unnecessary surgical interventions and subsequent complications.[8]

Diagnosis and Classification: The Core of Controversy

Accurate diagnosis of uterine anomalies is challenging and critical. Historically, diagnosis relied on hysterosalpingography and combined hysteroscopy–laparoscopy. Modern practice Favors 3D transvaginal ultrasound and MRI for non-invasive, high-resolution delineation of the uterine cavity and fundal contour [9].

Divergence between ASRM (2021) and ESHRE/ESGE (2016) classification systems adds confusion. The ESHRE/ESGE criteria, based on relative indentation depth and angle, tend to "over-diagnose" septate uterus compared with ASRM.[10] Fig 1 , 2. As a result, patient populations vary across studies, undermining comparability and leading to inconsistent evidence regarding the benefit of surgical correction.

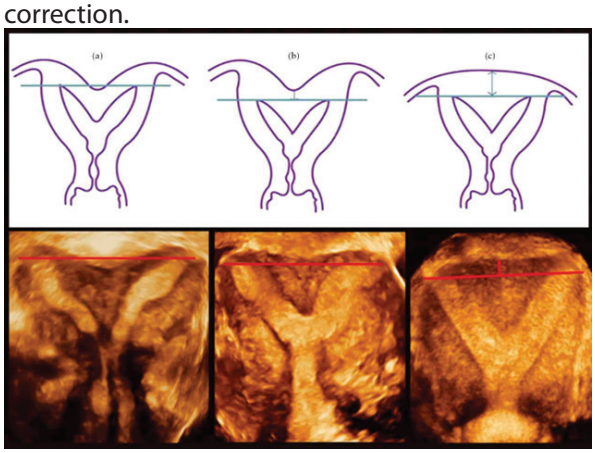

fig 1 – Septate vs bicornuate

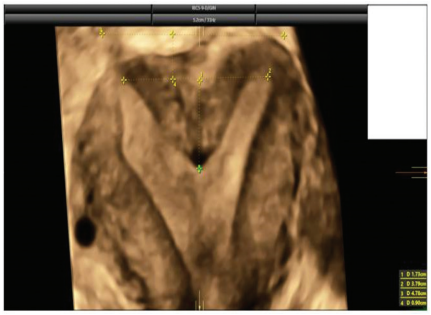

fig 2 – septate uterus

Surgical Techniques

Hysteroscopic Metroplasty

Hysteroscopic septum resection is the standard and minimally invasive method for correction of a septate uterus. Resection may be performed using micro scissors, monopolar/bipolar resectoscopes, or hysteroscopic morcellators under direct visualization. Intraoperative ultrasound or laparoscopic monitoring may reduce perforation risk.[11,12]

Postoperative measures, such as estrogen therapy or intrauterine balloon placement, are optional and variably practiced. Follow-up imaging is usually recommended after one to two menstrual cycles to exclude intrauterine adhesions or residual septum.[13]

Laparoscopic or Abdominal Metroplasty

These approaches are now rarely indicated, reserved for complex or mixed anomalies (e.g., partial septate–bicornuate uterus).[14]

Evidence on Reproductive Outcomes

Observational Evidence

Cumulative data from multiple retrospective and prospective cohort studies indicate improvement in reproductive outcomes following hysteroscopic septum resection among women with RPL. A 2023 meta-analysis by Omoto et al.[15] showed significantly higher take-home baby rates and reduced miscarriage rates after metroplasty compared to expectant management. Similarly, Zhang et al.[16] reported improved live-birth rates in over 800 cases of resected septum.

Controlled and Randomized Studies

Despite the encouraging observational evidence, controlled trials present a more nuanced picture. The multicentric randomized study by Rikken et al. (2021)[17] compared hysteroscopic septum resection with expectant management and found no significant difference in live-birth rates. While this study faced criticism for limited sample size and inclusion of women without severe reproductive histories, it challenged long-held assumptions about the universal benefit of septum resection.

Guideline Recommendations

The ESHRE Recurrent Pregnancy Loss Guideline (2023)[18] and ASRM Uterine Septum Practice Guidance (2024)[19] both recognize the limited high-quality evidence and recommend surgery primarily for women with a confirmed septate uterus and relevant clinical history (recurrent loss or implantation failure). They advise against routine correction of arcuate or minor anomalies.

Controversies and Challenges

1. Selection Bias and Study Design: Most supportive data arise from before–after cohort studies lacking control groups, which may overestimate benefit.[20]
2. Diagnostic Variability: Differing criteria lead to inconsistent patient populations and unclear external validity.[10]
3. Outcome Definitions: Miscarriage, clinical pregnancy, and live birth are variably reported, complicating meta-analysis.[21]
4. Surgical Risk: Though rare, uterine perforation, intrauterine adhesions, and later obstetric complications (e.g., placenta accreta) must be acknowledged.[22]
5. Cost-effectiveness and Access: Limited evidence exists regarding cost-benefit ratio, especially where imaging or skilled hysteroscopy resources are scarce.[23].

Practical Approach and Current Best Practices

1. Confirm Diagnosis using 3D ultrasonography or MRI before any intervention.
2. Select Candidates: Surgery should be considered for women with a true septate uterus and recurrent pregnancy loss, after excluding other causes.
3. Counselling: Patients must be informed about potential benefits, uncertain evidence, and procedural risks.
4. Surgical Execution: Hysteroscopic resection by an experienced surgeon under direct visualization with minimal trauma.
5. Postoperative Care: Imaging confirmation of cavity restoration before attempting conception (natural or ART).

Future Directions

Further large-scale randomized controlled trials are essential to determine which patient subgroups truly benefit from surgery. Standardized imaging and uniform definitions across ASRM and ESHRE are equally critical to harmonize diagnosis and reduce over-treatment. Long-term obstetric outcome data, particularly regarding uterine rupture or abnormal placentation, remain underreported and warrant systematic study.

Conclusion

Hysteroscopic metroplasty for septate uterus represents one of the most debated interventions in reproductive surgery. While decades of observational evidence suggest improved pregnancy outcomes in women with recurrent miscarriage, recent randomized data and evolving guidelines urge caution. The decision to operate should be individualized, guided by accurate imaging, careful exclusion of other RPL causes, and informed patient choice. The field now requires robust, standardized evidence to define the precise role of surgical correction in RPL management.

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Calendar for AOGD Monthly Clinical Meeting 2025-2026

31st October 2025	DDU Hospital
28th November 2025	MAMC & LNJP Hospital
26th December 2025	Sir Ganga Ram Hospital
30th January 2026	Dr RML Hospital
27th February 2026	UCMS & GTB Hospital
27th March 2026	LHMC & SSK Hospital
24th April 2026	Hamdard Institute of Medical Sciences and Research

Reframing Recurrent Pregnancy Loss: A Call for Patient-Centered, Evidence-Based Care

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Introduction

Recurrent pregnancy loss (RPL) is among the most distressing challenges faced by obstetricians and fertility specialists. It carries not only biological complexity but also profound emotional and social consequences for affected couples. Historically defined as the loss of three or more consecutive pregnancies before 20 weeks, this criterion was primarily statistical rather than biological. Contemporary definitions have evolved to reflect earlier recognition and patient-centred care. The European Society of Human Reproduction and Embryology (ESHRE, 2023) defines RPL as the loss of two or more pregnancies confirmed by serum or ultrasound, irrespective of sequence or gestational age.[1] The American Society for Reproductive Medicine (ASRM, 2023) provides a similar definition, while the Royal College of Obstetricians and Gynaecologists (RCOG, 2023) also recommend evaluation after two consecutive losses.[2, 3]

This paradigm shift recognises that recurrent miscarriage represents not a single disease but a spectrum of underlying disorders that warrant prompt evaluation after two events rather than delaying until three. Equally, modern management emphasises individualised, evidence-based, and empathetic care, acknowledging the psychosocial burden that accompanies the clinical process.

Epidemiology and Indian Scenario

Globally, RPL affects 1–2 % of couples when defined as three or more consecutive losses. If two or more losses are included, the prevalence rises to around 5 %.[4] In India, the true incidence may be underestimated because many early pregnancy losses occur at home, are unregistered, or unrecognised. In addition, regional factors such as genital tuberculosis, consanguineous marriage, nutritional deficiencies, and limited access to tertiary care further contribute to its burden.

Indian studies report that secondary RPL (occurring after a prior live birth) is more common than primary RPL, reflecting post-infectious endometrial pathology and advanced maternal age.[5] Sociocultural pressures—particularly the expectation of motherhood—compound the psychological toll, demanding a care model that integrates medical precision with empathy and cultural sensitivity.

Etiopathogenesis

RPL is multifactorial; multiple mechanisms may coexist in the same couple. Understanding these mechanisms provides the foundation for rational investigation and management.

1. Genetic Factors

Chromosomal anomalies account for nearly 50–60 % of sporadic first-trimester miscarriages, primarily due to de-novo embryonic aneuploidy.[6] Among couples with RPL, balanced reciprocal or Robertsonian translocations are found in 2–5 % of cases. Hence, parental karyotyping is recommended when there is a history of multiple losses or a previous child with chromosomal abnormality. Advanced maternal age increases meiotic nondisjunction and thus aneuploidy; miscarriage risk escalates from 15 % at age 30 to over 50 % beyond 40 years.[7]

Technologies such as chromosomal microarray analysis (CMA) or next-generation sequencing (NGS) on products of conception detect submicroscopic imbalances missed by karyotyping, although their utility in changing management is still debated. Pre-implantation genetic testing for aneuploidy (PGT-A) may reduce miscarriage in specific IVF populations but is not universally recommended in natural conceptions due to cost and limited evidence.[1]

2. Anatomical Factors

Congenital uterine anomalies—particularly septate uterus—and acquired defects such as intrauterine adhesions, submucous fibroids, and endometrial polyps impair implantation and placentation. Prevalence of structural anomalies in women with RPL ranges from 7 – 28 %, compared with 4–7 % in fertile controls.[8] Three-dimensional transvaginal ultrasound is the preferred diagnostic tool; hysteroscopy allows confirmation and simultaneous correction. Septum resection, polypectomy, myomectomy, and adhesiolysis have shown improvement in live-birth outcomes.[2]

In India, post-tubercular intrauterine adhesions (Asherman's syndrome) remain an important and under-recognised cause.

3. Endocrine and Metabolic Causes

Endocrine disturbances affect luteal function, endometrial receptivity, and trophoblastic support.

- Thyroid Disorders: Both overt and subclinical hypothyroidism are associated with miscarriage.

Treatment with levothyroxine is advised when TSH > 2.5 mIU/L in women planning conception.[1]

- Diabetes Mellitus and Insulin Resistance: Poor glycaemic control (HbA1c > 6 %) significantly increases miscarriage risk. Strict preconception optimisation is essential.
- Polycystic Ovary Syndrome (PCOS): Obesity, hyperinsulinaemia, and endometrial dysfunction in PCOS are linked to early pregnancy loss. Weight reduction and insulin-sensitising therapy (e.g., metformin) may improve outcomes.[9]
- Luteal Phase Deficiency: Once a popular explanation, it now lacks consistent diagnostic criteria; routine progesterone supplementation outside assisted reproduction remains controversial.
- Thyroid Autoimmunity: Presence of anti-thyroid antibodies is associated with RPL even in euthyroid women, though the causal link remains uncertain.

4. Thrombophilic and Immunologic Causes

Inherited thrombophilias (Factor V Leiden, prothrombin G20210A, protein C/S deficiency) have long been proposed in RPL, yet large studies fail to demonstrate a consistent association.

Guidelines[1,2] therefore advise against routine screening for inherited thrombophilias.

The major exception is antiphospholipid syndrome (APS)—the only thrombophilic condition with robust evidence. Diagnostic criteria include positive lupus anticoagulant, anticardiolipin IgG/IgM, or anti-β2-glycoprotein I antibodies, documented on two occasions 12 weeks apart, plus relevant obstetric or thrombotic events.[10]

Combination therapy with low-dose aspirin (75–100 mg daily) and low-molecular-weight heparin (40 mg daily) from conception through 36 weeks improves live-birth rates and carries a strong recommendation in all major guidelines.[1, 3]

Other proposed immunologic causes (HLA incompatibility, NK-cell activity, cytokine imbalance) currently lack reproducible evidence, and immunotherapies such as IVIG or steroids should be reserved for research protocols.

5. Infectious and Environmental Factors

Infections can disrupt implantation or induce chronic endometrial inflammation. While TORCH serology screening is not recommended, chronic endometritis confirmed by biopsy or hysteroscopy may contribute to RPL and responds to antibiotics (11). In India, genital tuberculosis remains a notable cause, leading to endometrial fibrosis and adhesions; high clinical suspicion is warranted. Lifestyle factors—smoking, alcohol, high caffeine intake (>200 mg/day), and environmental toxins—adversely affect pregnancy viability.

6. Unexplained RPL

Despite exhaustive testing, 40–50 % of couples have no identifiable cause (4). These couples should be counselled that the prognosis remains favourable: up to 60–70 % achieve a live birth in subsequent pregnancies with supportive care alone.[1] Empirical treatments without evidence—such as heparin in the absence of APS, immunoglobulins, or extensive thrombophilia panels—should be avoided.

Diagnostic Evaluation

A structured, stepwise evaluation is essential to balance thoroughness with cost-effectiveness. Investigations should only be pursued if results are likely to influence management.

1. Clinical Assessment

A comprehensive medical and reproductive history includes:

- Number, sequence, and gestational age of losses
- History of preterm delivery or stillbirth
- Mode of conception (natural/ART)
- Family or personal history of thrombosis
- Menstrual regularity, PCOS features, thyroid symptoms
- Surgical or infectious history (curettage, myomectomy, tuberculosis)
- Physical examination should assess BMI, blood pressure, thyroid enlargement, acanthosis nigricans, hirsutism, and signs of chronic disease.

2. Baseline Laboratory Investigations

- TSH and free T4 – target TSH < 2.5 mIU/L
- HbA1c – target <6.0 %
- Prolactin, LH/FSH, fasting insulin when endocrine causes suspected
- Antiphospholipid antibody panel (lupus anticoagulant, anticardiolipin, anti-β2 GP1)
- Parental karyotype when indicated
- CBC and vitamin D levels

3. Imaging for Uterine Pathology

Preferred sequence:

- 3-D transvaginal ultrasound for congenital anomalies
- Hysteroscopy for confirmation and correction
- MRI for complex malformations
- Hysterosalpingography if other modalities unavailable

4. Genetic Testing

If products of conception are available, chromosomal microarray can distinguish embryonic aneuploidy from maternal causes. Parental karyotyping is indicated when recurrent balanced translocations are suspected. Routine genetic testing of every miscarriage is unnecessary unless recurrent or structurally abnormal losses occur.

5. Thrombophilia and Immunology

Test for APS according to revised Sapporo criteria. Inherited thrombophilia testing, NK-cell assays, cytokine profiling, and sperm DNA fragmentation are not recommended for routine evaluation.[1]

6. Infectious and Environmental Work-up

Screen for genital tuberculosis, chronic endometritis, and sexually transmitted infections when clinically indicated. Address modifiable environmental factors such as smoking or occupational exposure to toxins.

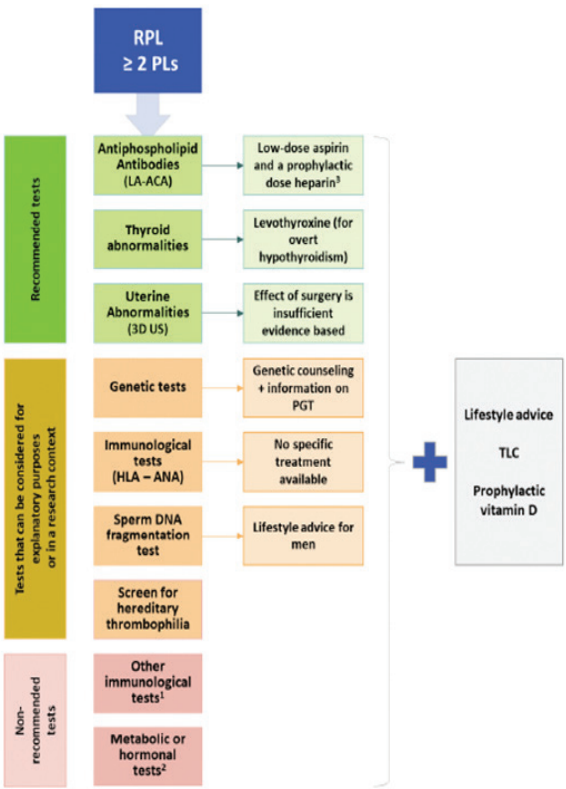

Figure 1: Summary of recommended tests and management of couples with RPL (1)

Management Strategies

Successful management of RPL requires integrating medical, surgical, and psychological interventions with preconception counselling.

Preconception Optimisation

- Weight management: Achieve BMI < 30 kg/m^2; even 5–10 % weight reduction improves outcomes.
- Glycaemic control: Maintain HbA1c < 6 %.
- Thyroid normalisation: Adjust levothyroxine dosage for euthyroid state.
- Folic acid 400–800 µg/day and vitamin D > 30 ng/mL supplementation.
- Lifestyle: Stop smoking, limit caffeine and alcohol, manage stress through mindfulness or therapy.

Targeted Therapies

1. Genetic counselling and assisted reproduction: Couples with translocations should receive genetic counselling; options include natural conception with prenatal diagnosis or IVF with PGT-SR.
2. Surgical correction: Septum resection, adhesiolysis, and polypectomy under hysteroscopy significantly improve live-birth rates.[2]
3. Endocrine/metabolic management: Metformin in PCOS, weight reduction, and thyroid correction form the cornerstone.
4. APS therapy: Combination of low-dose aspirin and LMWH from conception until 36 weeks is strongly recommended.[10]
5. Progesterone support: Vaginal or oral progesterone may reduce miscarriage risk in women with prior early losses, though evidence remains moderate.[12]
6. Treatment of chronic endometritis or tuberculosis: Appropriate antibiotics or anti-tubercular therapy where indicated.

Supportive and Empirical Care

Even in unexplained RPL, supportive care—regular early antenatal visits, early ultrasound reassurance, and emotional support—improves live-birth rates.[13] Psychological counselling should be integrated from the outset.

Antenatal Monitoring

Once pregnancy is achieved:

- Early ultrasound at 6–8 weeks
- Serial β-hCG if viability uncertain
- Screening for gestational diabetes at first visit and repeat at 24-28 weeks

- Growth and Doppler scans at 28 and 32 weeks

Women with prior APS require continued LMWH and close obstetric surveillance for placental complications.

Psychosocial and Patient-Centred Care

Beyond diagnostics and therapy lies the heart of modern RPL management: patient-centred care. Couples often experience grief, guilt, and fear of future loss. Repeated investigations without clear answers can deepen distress. Hence, clinicians must:

- Validate emotional experiences and avoid dismissive reassurances.
- Communicate results and uncertainties transparently.
- Engage both partners in decision-making.
- Coordinate multidisciplinary input (reproductive endocrinology, psychology, genetics).
- Provide culturally appropriate counselling, especially in societies where motherhood defines social identity.

Empathetic communication—phrases such as *"this was not your fault"* and *"you still have a strong chance of success"*—carry as much therapeutic value as medical prescriptions.

Future Directions

The landscape of RPL is shifting toward precision and prevention. Emerging frontiers include:

- Genomic and transcriptomic profiling of endometrium to identify implantation failure pathways.
- Endometrial microbiome analysis to detect dysbiosis linked to chronic inflammation.
- Artificial intelligence (AI) models predicting recurrence risk and guiding personalised management.
- Stem-cell and regenerative therapies for post-infectious or fibrotic endometrium.
- Global and Indian registries to strengthen epidemiologic data and generate region-specific protocols.

Conclusion

Recurrent pregnancy loss is not merely a sequence of miscarriages—it is a multifaceted disorder demanding both scientific precision and human compassion. The shift from a number-based definition to an individualised, patient-centred approach reflects the maturation of reproductive medicine.

Optimal care integrates:

1. Evidence-based diagnostics,
2. Targeted medical or surgical interventions, and
3. Holistic psychosocial support.

As clinicians, our task is not only to identify pathology but also to restore hope, resilience, and trust. By aligning with contemporary guidelines (ESHRE 2023, ASRM 2023, RCOG 2023) and applying them sensitively in the Indian context, obstetricians can provide care that is both scientifically sound and deeply humane.

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Transforming OB-GYN Care: Key Insights from the Latest Clinical Trials Levothyroxine in Euthyroid Thyroid Peroxidase Antibody Positive Women with Recurrent Pregnancy Loss (T4LIFE Trial): A multi-centre, randomised, double-blind, placebo-controlled, phase 3 trial

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Recurrent pregnancy loss (RPL) is a distressing reproductive condition affecting approximately 2% of women attempting conception[1]. Thyroid peroxidase antibody (TPO-Ab) positivity is associated with increased risk of miscarriage, subfertility, and obstetric complications[2–3]. The T4LIFE trial, a multicentre, randomized, double-blind, placebo-controlled phase 3 study published in *The Lancet Diabetes & Endocrinology* (2022), evaluated whether preconceptional levothyroxine improves live birth rates in euthyroid TPO-Ab positive women with RPL. This review summarizes and expands on T4LIFE, integrating mechanistic insights, comparative evidence, and implications for clinical practice. Despite sound biological rationale, levothyroxine failed to improve live birth rates compared with placebo, aligning with previous randomized trials. Routine levothyroxine use in euthyroid women with TPO-Ab positivity and RPL is therefore not recommended. The focus should instead shift toward immunological and endometrial mechanisms underlying RPL.

Introduction

Recurrent pregnancy loss (RPL), defined as two or more consecutive miscarriages before 20 weeks' gestation, represents a multifactorial reproductive disorder with substantial physical and psychological burden[4]. Among possible etiologies, autoimmune thyroid disease has emerged as a consistent factor even in the absence of overt hypothyroidism[5]. TPO-Ab positivity has been observed in 15–20% of women with unexplained RPL compared with 8–10% of the general population[6–7]. Mechanistic theories suggest that TPO-Ab positivity may predispose to subtle thyroid hormone insufficiency in early pregnancy or reflect generalized immune dysregulation at the maternal–fetal interface[8–9]. Levothyroxine therapy has thus been proposed as a prophylactic intervention to optimize thyroidal status and reduce immune-mediated pregnancy loss[10]. However, high-quality evidence has been lacking until the publication of the T4LIFE trial, which provides the most rigorous evaluation of this hypothesis to date[11].

Study Design and Methods

T4LIFE was an international, multicentre, double-blind, randomized, placebo-controlled, phase 3 trial conducted across 15 hospitals in the Netherlands, Belgium, and Denmark[11]. Eligible women were aged 18–42 years, positive for TPO-Ab, and had experienced at least two prior pregnancy losses. Participants with thyroid disease, antiphospholipid syndrome, or other autoimmune disorders were excluded. Randomization (1:1) assigned participants to levothyroxine or placebo, stratified by center. The levothyroxine dose (0.5–1.0 µg/kg/day) was individualized based on preconceptional TSH and body weight. Treatment began preconceptionally and continued throughout pregnancy. The primary endpoint was live birth beyond 24 weeks of gestation. Secondary outcomes included ongoing pregnancy, miscarriage before 20 weeks, preterm birth, and neonatal survival[11].

Table 1. Key Design Features of the T4LIFE Trial

Study Type	Randomized, double-blind, placebo-controlled, phase 3
Population	Euthyroid women (18–42 years) with ≥2 pregnancy losses and positive TPO-Ab
Intervention	Levothyroxine 0.5–1.0 µg/kg/day, preconception to delivery
Control	Matching placebo
Primary Outcome	Live birth ≥24 weeks gestation
Secondary Outcomes	Ongoing pregnancy, miscarriage, preterm birth, neonatal survival, adverse events

Results

Between January 2013 and September 2019, 187 women were randomized—94 to levothyroxine and 93 to placebo. Recruitment was discontinued early due to slow accrual (78% of target enrollment). Baseline demographic and clinical characteristics were comparable between groups[11].

Table 2. Primary and Secondary Outcomes of the T4LIFE Trial

Outcome	Levothyroxine (n=94)	Placebo (n=93)
Live birth ≥24 weeks	50% (47/94)	48% (45/93)
Miscarriage <20 weeks	23% (16/69)	33% (24/73)
Ongoing pregnancy at 12 weeks	68%	63%
Preterm birth <37 weeks	6%	4%
Adverse events	7%	8%

There were no statistically significant differences between groups in any primary or secondary endpoint. Subgroup analyses by preconception TSH (<2.5 vs ≥2.5 mIU/L) and number of previous losses (two vs ≥3) revealed no effect modification[11].

Discussion

The T4LIFE trial is the largest and most definitive study assessing levothyroxine in euthyroid TPO-Ab positive women with RPL. Contrary to earlier expectations, the study demonstrated no improvement in live birth rates with levothyroxine therapy[11]. These findings align with the TABLET trial (NEJM 2019)[12] and Wang et al. (JAMA 2017)[13], both of which reported null results in euthyroid women with thyroid autoimmunity. A 2021 meta-analysis including over 2200 women confirmed no significant effect on miscarriage (RR 0.93, 95% CI 0.76–1.14) or live birth (RR 1.01, 95% CI 0.89–1.16)[14]. The consistency of these findings across trials strengthens the conclusion that levothyroxine supplementation is not beneficial in this setting.

Several mechanisms may explain the lack of efficacy. First, most euthyroid TPO-Ab positive women maintain sufficient thyroid reserve to meet the increased hormonal demands of pregnancy[15]. Second, immunologic rather than endocrine mechanisms—such as Th1/Th2 imbalance, NK cell activation, or complement-mediated placental injury—likely drive miscarriage risk[16–17]. Third, heterogeneity in antibody assays, population selection, and timing of therapy initiation across studies may obscure small subgroup benefits[18]. Nonetheless, even modest hormonal adjustment appears insufficient to counteract immune dysregulation.

Clinical Implications

The results of T4LIFE directly inform current clinical practice guidelines. The 2018 European Society of Human Reproduction and Embryology (ESHRE) guideline advises against routine levothyroxine use in euthyroid women with RPL[19]. Similarly, the 2017 American Thyroid Association guideline acknowledges the lack of definitive benefit but allows individual discretion[20]. Given robust evidence from T4LIFE and preceding trials, the consensus now favors avoiding empirical levothyroxine in this group. TSH monitoring during pregnancy remains prudent, as TPO-Ab positivity predicts a higher risk of developing subclinical hypothyroidism[21].

Conclusion

The T4LIFE trial provides conclusive evidence that levothyroxine therapy does not increase live birth rates in euthyroid TPO-Ab positive women with RPL. Routine supplementation in this population is therefore unwarranted. Attention should shift toward elucidating immunological, genetic, and endometrial mechanisms underlying RPL, integrating personalized approaches rather than empirical hormone therapy.

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Quiz on Recurrent Pregnancy Loss (RPL)

Apoorva Kulshreshtha
Assistant Professor, Department of Obstetrics & Gynaecology, Lady Hardinge Medical college, New Delhi

"Test your clinical instincts and evidence-based understanding!"

Think you've mastered the mysteries of Recurrent Pregnancy Loss (RPL)?

Let's find out! This quiz challenges your grasp of the definition, evaluation, and management of RPL according to modern evidence and guidelines (ESHRE, ASRM, RCOG).

Choose the most appropriate answer for each question. (Answers and explanations are provided at the end.)

1. Definition

According to ESHRE, Recurrent Pregnancy Loss (RPL) is defined as:

A. Two or more ectopic pregnancies
B. Three or more consecutive first-trimester miscarriages
C. Two or more pregnancy losses from conception until 24 weeks of gestation
D. Three or more second-trimester losses

2. Molar Pregnancies and RPL Definition

What is the status of molar pregnancies in defining RPL?

A. Always included
B. Included only if after ART
C. Excluded if identified as such
D. Included only if spontaneous

3. Commonest Identifiable Cause

Which of the following is the most commonly identified cause of RPL?

A. Antiphospholipid syndrome
B. Chromosomal abnormalities
C. Uterine anomalies
D. Hormonal imbalances

4. Incidence

What is the approximate incidence of recurrent miscarriage in the general population?

A. 5–10%
B. 2–3%
C. ~1%
D. 10–50%, depending on age

5. Genetic Cause and Next Step

A couple has had three first-trimester losses. Karyotyping shows a balanced translocation in the male partner.

What is the next best step?

A. IVF with donor sperm
B. Expectant management
C. IVF with preimplantation genetic testing (PGT)
D. Surrogacy

6. Molecular Marker of Receptivity

Which endometrial marker, when reduced during the implantation window, has been linked to RPL in recent molecular studies?

A. VEGF
B. LIF (Leukemia Inhibitory Factor)
C. FSH receptor
D. Kisspeptin

7. Cytogenetic Abnormality with Highest Miscarriage

Which parental cytogenetic abnormality carries the highest theoretical risk of unbalanced gametes leading to miscarriage?

A. Robertsonian translocation between chromosomes 13 and 14
B. Pericentric inversion on chromosome 9
C. Balanced reciprocal translocation involving chromosomes 4 and 20
D. Mosaic Turner syndrome in the mother

8. Role of Endometrial Receptivity Array (ERA)

The Endometrial Receptivity Array (ERA) may be proposed in RPL cases primarily for which category?

A. Patients with uterine septum
B. Patients with proven thrombophilia
C. Patients with euploid embryo transfer failures in IVF
D. Patients with luteal phase defect

9. Inherited Thrombophilia

A 30-year-old with RPL and heterozygous Factor V Leiden mutation (no APS) seeks advice.

Which statement is correct?

A. Prophylactic LMWH + aspirin is mandatory
B. LMWH alone reduces miscarriage
C. Anticoagulants do not improve outcomes
D. She should avoid pregnancy

10. Postpartum Anticoagulation in APS

A woman with APS-associated RPL asks if she should continue heparin postpartum.

Best advice?

A. Stop heparin immediately after delivery
B. Continue for 6 weeks postpartum
C. Switch to warfarin immediately postpartum
D. Continue aspirin only

Answers

1.C, 2.C, 3.B, 4.C, 5.C, 6.B, 7.C, 8.C, 9.C, 10B

AOGD Clinical Meet from DDU Hospital held on 31st October 2025

Case 1

SILENT GROWTH TO SUDDEN CRISIS

Soma Mitra, Jyoti Prabha, Poonam Laul, Harvinder Kaur, Usha Yadav,

[1]SMO, [2]Specialist, [3]HOD and Consultant, [4,5]Senior Specialist

50 year old presented with pain and lump in lower abdomen since 6 months along with weight loss since 3 months. Patient underwent USG which was suggestive of large sub serosal fibroid. MRI and tumor markers were advised. After MRI patient reported with increased pain abdomen and syncopal attack and she was admitted in DDUH. On admission there was marked pallor , tachycardia and hypotension. On per abdominal examination distension with guarding and tenderness was seen. A hard, irregular, mass of around 20×14 cm felt in lower abdomen reaching up to umbilicus, more on right side, tender, fixed confirmed on P/V and P/R examination. Patient was resuscitated and exploratory laparotomy was done with multidisciplinary team. Hemoperitoneum of approx 3 litre was present, The Omentum was adherent to friable ruptured ovarian mass, Mass of approximately13 cm×9cm cm pushing sigmoid colon to right side and abutting the major vessels. Left ovary and tubes were normal. TAH with left salpingo-ophorectomy with excision of right tubo-ovarian mass with omentectomy with right internal iliac artery ligation. Pelvic packing was done to achieve hemostasis because of generalized oozing. blood and blood products were transfused. The patient was stabilized. After 24 hours pack removal done. MRI collected later suggestive of a large heterogenous solid cystic mass superior to fundus of uterus measuring 16cm× 14cm ×9.5cm compressing the urinary bladder and rectosigmoid colon extending to right adnexa not separate from the the right ovary and CA125 level was 51.9U/ml. On HPE high grade serous ovarian cancer (HGSOC) was diagnosed. Patient underwent CECT whole abdomen and Pelvis which was suggestive of an irregularly peripherally enhancing lesion in right adnexa with omental deposits. The Patient received 6 cycles of Carboplatin and Paclitaxel and 6 doses of GCSF injection. Patient underwent interval CRS (Pelvic peritonectomy + lymphadenectomy + small bowel serosa and mesenteric deposits excision) and R0 was achieved. On genetic screening she was positive for BRCA1. Adjuvant Chemotherapy with Injection Cisplatin was given in postoperative period. Whole family screening was advised. HGSOC is aggressive with high recurrence rates.Usually present with vague and nonspecific symptoms like abdominal pain, bloating, nausea, constipation, anorexia, diarrhoea and acid reflux .Treatment strategies for HGSOC are multifaceted and should respect patient diversity. Primary surgery could not achieve R0, but was mandatory as a life saving procedure for hemostasis followed by secondary cytoreduction after chemotherapy to achieve R0. Early recognition and imaging have life saving implications. This highlights the importance of suspecting cancer, timely resuscitation and surgery with multidisciplinary approach .

Case 2

Atypical Postpartum Decline: A Diagnostic Conundrum

[1]Aishwarya Nandakumar, [2]Urvashi Miglani, [3]Poonam Laul, [4]Ritu Goyal Mittal, [4]Usha Yadav

[1]Senior Resident, [2,5]Senior Specialist, [3]HOD and Consultant, [4]Consultant

The postpartum period, typically a time of recovery, can occasionally be complicated by severe and unexpected medical conditions. Such was the case of a 29-year-old multiparous woman, Mrs. X, who developed a rare complication following an otherwise uneventful full-term vaginal delivery.Mrs. X delivered a healthy male infant weighing 3 kg at a peripheral hospital on August 3, 2024, and was discharged in stable condition on the third postpartum day. On Day 6, however, she developed fever, abdominal pain, and foul-smelling vaginal discharge. Despite treatment, her condition worsened, and she developed difficulty passing urine, prompting referral to DDU Hospital.On admission, Mrs. X appeared ill, with mild abdominal distension and tachycardia. Examination revealed a gaping episiotomy wound with foul discharge and a contracted, non-tender uterus. A provisional diagnosis of puerperal sepsis was made, and broad-spectrum intravenous antibiotics with supportive care were initiated. Initially, her fever subsided and urine output remained satisfactory, suggesting improvement. However by Day 12, she developed high-grade fever, increasing abdominal distension, and pain. Imaging revealed multiple small splenic abscesses and loculated abdominopelvic collections, suggesting a persistent infective process. Peritoneal tapping and further investigations were pursued, with abdominal tuberculosis considered as a differential diagnosis. Despite aggressive management, her condition rapidly deteriorated with signs of septic shock—tachycardia, hypotension, hematuria, and worsening distension. An emergency exploratory laparotomy was undertaken by a multidisciplinary team. Intraoperatively, the peritoneal cavity contained pus flakes and approximately 600 ml of hemoperitoneum and pyoperitoneum. The most striking finding was a 2 × 3 cm defect at the fundus of the urinary

bladder, consistent with spontaneous bladder rupture (SBR). Meanwhile the ascitic fluid KFT report showed raised creatinine and negative CBNAAT. The bladder was repaired in two layers, and a suprapubic catheter was placed for continuous drainage and healing. Postoperatively, Mrs. X required intensive care, mechanical ventilation, and prolonged catheterization. Although she developed a surgical site infection, she gradually recovered with appropriate antibiotics and supportive management.

Spontaneous bladder rupture in the postpartum period is exceptionally rare but potentially life-threatening if unrecognized. In any postpartum woman with unexplained abdominal distension or deterioration despite antibiotics, SBR should be considered. CT scan remains the diagnostic investigation of choice, offering near-100% specificity. Early diagnosis and prompt surgical repair are crucial for survival and recovery.

Case 3

An Unexpected Turn – Revisiting an Old Foe in the Peri-partum Period

[1]Devi S, [2]Sunita Seth, [3]Seema Sheokand, [3]Harvinder Kaur, [4]Poonam laul

[1]Resident, [2]Head of Unit & Consultant, [3]Specialist, [3]Senior Specialist, [4]Consultant and Head of Department

Psoas abscess is rare during pregnancy. In India, TB spine remains the leading cause for psoas abscess. Diagnostic delay often occur due to overlapping symptoms with normal pregnancy related changes, posing significant maternal and fetal risks.

Mrs. X, 25-year-old, G2A1 at 39 weeks 6 days referred from Govt. peripheral hospital with complaints of left lower limb pain for three months, progressing to inability to walk in the last one month, and in early labour. Initial treatment at a peripheral centre attributed her lower limb pain to pregnancy. On examination, mild kyphosis with inability to move her left lower limb and in early latent labour with meconium grade II. She underwent emergency caesarean for meconium-stained liquor and non-reassuring NST. Postoperatively, DVT scan was normal, USG revealed bilateral psoas abscesses, and CECT findings revealed caries spine with pre and paravertebral collections, bilateral psoas abscess, 18 *10 *7 cm on right side and 10 * 5* 4 cm on left side, and erosion of left acetabulum and femoral head with collections extending into upper thigh and gluteal region. USG guided pigtail drainage of right psoas abscess and needle aspiration of left gluteal abscess done and Pus CBNAAT was positive for MTB with elevated ADA. Hence, she was started on ATT. Her condition gradually improved, with ATT and serial USG guided aspiration on left side and pig tail drainage on the right side (removed day 60) and at 2-month follow-up patient is able to walk comfortably.

Psoas abscess is the pus accumulation within the psoas compartment. It can be primary (haematogenous spread) or secondary (direct extension from nearby structures). In developing countries, Tuberculosis of spine is the leading cause especially in immunocompromised patients. The classical triad of back pain, fever, and limp is seen only in <30% of cases, often leading to delayed diagnosis. The abscess may spread locally to the pelvis, iliac fossa, gluteal region, or thigh via anatomical planes because of the close proximity of the psoas muscle with these structures. Imaging is vital, USG has an accuracy of 41–95%, while CT remains the gold standard (95–100%).

Mainstay of treatment is ATT and abscess drainage. Drainage can be percutaneous or surgical and is indicated for large abscesses (>2.3 cm transverse or >5 cm longitudinal), multi-loculated abscesses, neurological deficits, or poor response to ATT. Early diagnosis and imaging are vital for identifying rare causes like psoas abscess. Timely ATT initiation and drainage, coupled with multidisciplinary care, is necessary for good maternal and fetal outcomes.

Forthcoming Events

- Surgical camp will be conducted by Urogynaecology Subcommittee on 12th – 14th November, 2025 at Joginder Nagar
- PICSEP workshop will be conducted by Dept. of Obst. & Gynae at LHMC and AOGD on 22nd November,2025 at LHMC
- CME on " Enhancing Maternal and Fetal Health" will be conducted by Fetal Medicine and Genetics subcommittee on 17th December 2025 at Eros Hotel, Nehru Place.

AOGD Subcommittees Chairperson Election (2026-28)
Call for nominations

Nominations are invited from eligible AOGD members for the post of chairperson of following subcommittees:

1. Infertility & Reproductive Endocrinology Sub-committee
2. Community health & Public Awareness Sub-committee
3. Safe Motherhood Sub-Committee
4. Medico-legal sub-committee
5. Menopause and Geriatrics Subcommittee

Last date for submission of nominations is **15/12/2025**

- ✓ Applications by desirous candidates should be submitted on the prescribed form available on AOGD website (www.aogd.org) / bulletin / office, with due entry in the office register in a sealed envelope & through email aogdlhmc2025@gmail.com
- ✓ Nominations as per the eligibility criteria should reach AOGD secretariat: Department of Obst. & Gynae LHMC & SSK Hospital, New Delhi- 110001 (Phone no. 9717392924) by **15/12/2025.**

Dr. Ratna Biswas (Secretary AOGD , 9971372695

Important announcement : The chairpersons after being nominated have the responsibility to call for application for members of their respective subcommittee for up to a maximum of 10 members.

Eligibility Criteria for AOGD Sub-committee chairperson

1. The chairperson of a sub-committee should have been a member of the sub-committee in question for at least one term, with one term being equivalent to two years, prior to his/her appointment as chairperson of that sub-committee.
2. He/she should have been a member of the AOGD for fifteen years.
3. He/she should have experience in the field related to the subcommittee.
4. He/she should have completed at least fifteen years from the date of his/her registration as a medical practitioner. Further, he/she should have held a senior / faculty position for not less than that of associate professor, senior consultant or an equivalent there of in his/her respective organization, for a period of at least five years .
5. No person should hold chairperson ship of the same subcommittee for two consecutive terms with each term comprising of two years. Further, a person who has been chairperson of one subcommittee cannot be nominated as chairperson of another subcommittee unless separated by a duration equivalent to two terms of the subcommittee.
6. The Executive Committee may lay down additional criteria for the eligibility and pre-requisites for appointment as chairperson of each sub-committee from time to time.
7. An eligible member must send an application for nomination as chairperson of a sub-committee stating therein his/her previous experience in the field related to the sub-committee and future vision for furthering the goals of the AOGD through such sub-committee. One person shall not apply for chairpersonship of more than one sub- committee at a time. The application shall be scrutinized by the Executive Committee of AOGD for nomination as chairperson.
8. In the event of more than one application being received for appointment as chairperson of a subcommittee, and in the absence of unanimous decision of the Executive committee in this regard, the Executive Committee shall decide the nomination by cast of secret ballot.
9. The tenure of the chairperson of subcommittee shall be for a period of two years.

The Association of Obstetricians & Gynaecologists of Delhi

Nomination Form

Name:_____

Designation/Affilation_____

AOGD Membership no:_____

Official Address:_____

Residential Address:_____

Phone:_____Email:_____

Bio Sketch (Relevant to the Eligibility Criteria in 250words)

Post Applied for

Sub-committee Chairperson
2026-28

Subcommittee Name

Proposed by – Name AOGD Membership no. Signature

1.

Seconded by

1.

2.

Nominations should reach at AOGD Office
For any Query please call Mrs. Sarita : 9211656757, 9717392924

Prize Winners

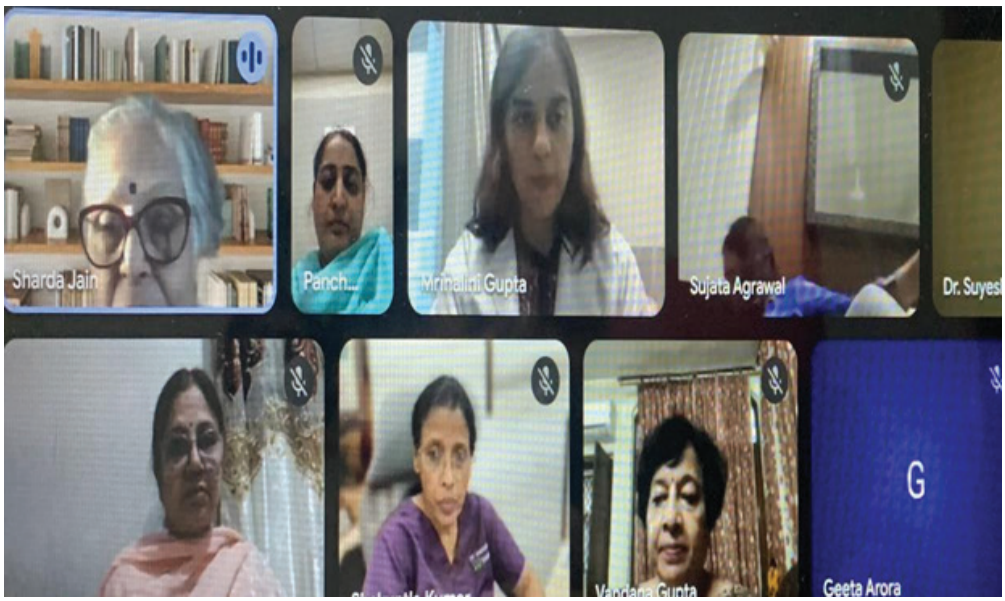
Competition Paper/ Free Paper/Poster/Quiz
47th Annual Conference AOGD
13th - 14st September, 2025

Category	Award	Name	Institute	Title
Dr Neera Agarwal's Medal for Best paper on theme topic: **Maternal Health**	**Gold Medal**	Dr Sampada Kundal	AIIMS	Muscle Fatigue and Motherhood: Myasthenia Gravis in Pregnancy
Dr Suneeta Mittal's Medal for Best paper on theme topic: **Population Stabilization**	**Gold Medal**	Dr Ayushi Hada	LHMC & SSK Hospital	Empowering Choices : Implants Reshaping the future of LARC
Dr U.P Jha & Raj Soni's Medal for Best paper on theme topic: **Endoscopy**	**Gold Medal**	Dr Ayushi Negi	AIIMS	Healing the Scar: Fertility restoration post -isthmocoele repair
Dr U.P Jha & Dewan Balakram's Medal for Best paper on theme topic: **Gynae - Oncology**	**Gold Medal**	Dr Jagriti Bajaj	MAMC	Effectiveness of Antepartum Health Education on Awareness and Acceptance of Human Papilloma Virus (HPV) Vaccine in Postpartum Period
Mr S. Bhattacharya & Dr Ganguli's Medal for Best paper on theme -**Miscellaneous Category**	**Gold Medal**	Dr Srishti	VMMC & SJH	A Prospective Study on Predictors and Outcomes of Surgical Site Infections Following Elective Caesarean Section
Best paper on theme topic: **Reproductive Endocrinology**	**Gold Medal**	Dr Sowmiya Rajendran	LHMC	Beyond Insulin-TyG Index as a Cost-Effective Marker of Insulin Resistance in PCOS
Poster Presentation	**Gold Medal (tie)**	Dr Garima Wadhwa	AIIMS	A Benign Masquerade of Malignancy: Diffuse Peritoneal Leiomyomatosis – A rare Case Report
	Silver Medal (tie)	Dr Monika Jain	MAMC	Recurrent Vulvar Aggressive Angiomyxoma with Hormonal Receptor Shift following Treatment Interruption- A Rare Case Report
		Dr Parul Kargwal	VMMC & SJH	Zoomed Zoned verified: The diagnostic leap from conventional to three ring vulvoscopy .
Slogan	**1st Prize**	Dr Kanika Chopra	LHMC & SSKH	
Research Paper- **Best Competition Paper**	**Gold Medal**	Dr Divya Khurana	SRHC NARELA	Rapid cycle improvement model as an effective quality tool for rationalizing oxytocin usage in third stage of labour
	Silver Medal	Dr Nisha Chopra	VMMC & SAFDARJUNG HOSPITAL	Grobman Score for Predicting Successful Trial of Labor After Cesarean in a North Indian Population
	Bronze Medal	Dr Megha	LHMC & SSK Hospital	Accuracy of Modified Cardiovascular Sequential Organ Failure Assessment (M-Cv Sofa) Score For Predicting The Duration of Critical Care Unit Stay in Maternal Sepsis
Dr Batra's Medal winner of **AOGD Quiz**	**Gold Medal**	Dr Saipriya & Dr Shivangi Singh		
	1st Runner Up	Dr Rahul & Dr Shagun		
	2nd Runner Up	Dr Nilufer & Dr Akanksha		
Dr S N Mukherjee **Rotating Trophy**	**Best AOGD Monthly Clinical Meeting**	VMMC & Safdarjung Hospital		

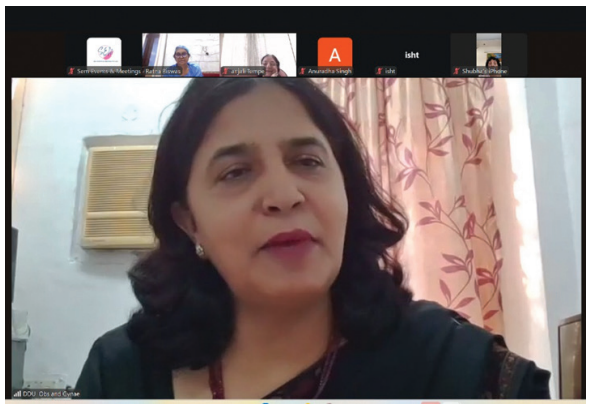
Events Held 2025

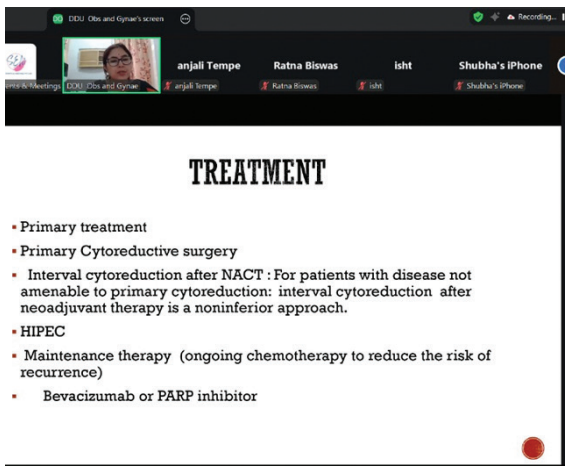
Webinar on " Mission Adolescent Health" conducted by

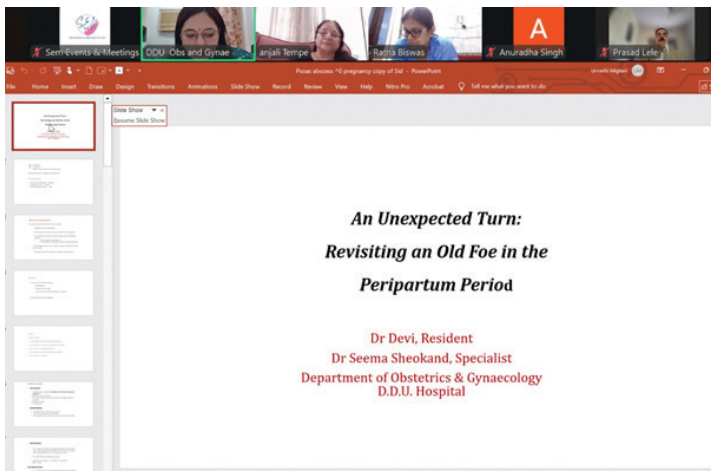
Adolescent Health Subcommittee in association with DGF on 14th October, 2025



The AOGD Monthly Clinical Meeting (virtual) conducted by the Department of Obst & Gynae, DDU Hospital on 31st October, 2025





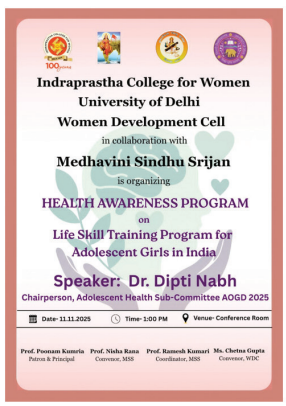


Program for 350 champions of Mission NEEeV conducted by DGF in association with AOGD at LHMC & SSK Hospital on 2nd November, 2025.

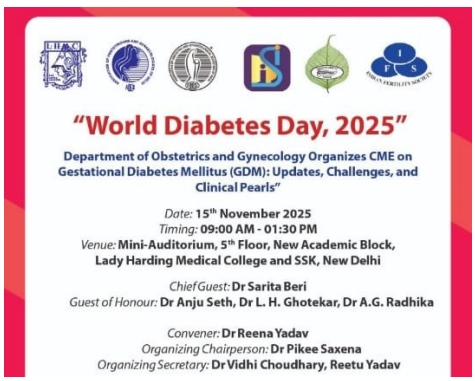
An awareness talk for Asha workers & General public conducted by Community Health and public awareness Subcommittee AOGD on 7th November, 2025 at Delhi Govt Dispensary (DGD) Vasundhara enclave.

Cervical and Breast Cancer Screening Camp conducted by Oncology committee AOGD and FOGSI on 11th November, 2025 at UCMS Health training Centre, Dilshad Garden

Life Skill Training Program for Adolescent Girls conducted by Adolescent Health Sub committee on 11 November, 2025 at IP College, University of Delhi



"World Diabetes Day, 2025" on 15 November, 2025 at Mini-Auditorium, 5th Floor, New Academic Block, Lady Harding Medical College and SSK, New Delhi



Association of Obstetricians & Gynaecologists of Delhi

MEMBERSHIP FORM

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Residence Ph. No. ..... **Clinical / Hospital Ph. No.** .....

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Gender: Male:..... **Female:**.....

Date of Birth: Date.....**Month** ..... **Year**.....

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Proposed by .....

Cheque/DD / No: .....

Cheque/Demand Draft should be drawn in favour of**: Association of Obstetricians and Gynaecologists of Delhi**

FOR ONLINE TRANSFER THROUGH NEFT/RTGS

Name of Account: Association of Obstetricians and Gynaecologists of Delhi
Account no: 5786412323
Name of Bank: Central Bank of India
Branch: LHMC & SSK Hospital
IFSC code: CBIN0283462
MICR code: 110016067

ASSOCIATION OF OBSTETR

12418708@cbin

BHIM UPI

For Life Membership	: Rs. 11,000 + Rs. 1,980 (18% GST applicable) = Rs. 12,980
For New Annual Membership*	: Rs. 2,000 + Rs. 360 (18% GST applicable) = Rs. 2,360
For Old Renewal Membership+	: Rs. 1,200 + Rs. 216 (18% GST applicable) = Rs. 1,416

Encl.: Attach Two Photocopies of All Degrees, DMC Certificate and Two Photographs (Self attested)

*** Annual Membership is for the calendar year January to December.**

*** In case of renewal, mention old membership number.**

Note: 18% GST will be applicable as FOGSI requires it.

Send Complete Membership Form Along With Cheque / DD and Photocopy of required documents to the secretariat.
For online transaction send scan copy of all documents with payment slip on given mail id

Secretariat
Department of Obstetrics and Gynaecology
Lady Hardinge Medical College & SSK Hospital, New Delhi-110001
Tel.: 011-23408297, (M): 9717392924 | Email Id: aogdlhmc2025@gmail.com

AOGD SECRETARIAT
Department of Obstetrics and Gynaecology
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