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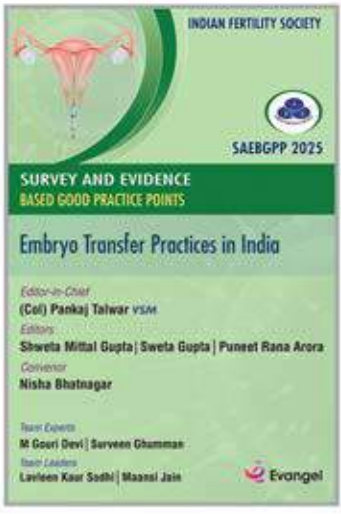
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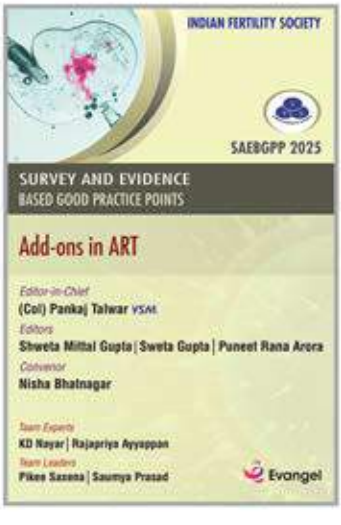
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Survey and Evidence Based Good Practice Points

Recurrent Pregnancy Loss

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Dedicated to

All gynecologists of India—those who continue to serve with compassion, courage, and commitment; those who balance science with empathy; those who stand by their patients through hope, uncertainty, and healing; and those who strive every day to raise the standards of women's health and reproductive care in our country.

Your tireless efforts inspire this entire initiative.

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Preface

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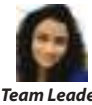

Team Leader
Niti Vijay

The SAEB (Survey and Evidence-Based) Good Practice Points initiative was conceived with the vision of bringing together clinicians, embryologists, researchers, and educators across India to create practical, implementable, and ethically sound guidelines that address real-world challenges in reproductive medicine. Each chapter in this compendium represents months of dedicated teamwork, data collection, expert deliberation, and collaborative refinement.

An important driving force behind this initiative has been the vision of the IFS President, who recognized the prevailing lacunae and knowledge gaps arising from the absence of India-specific recommendations. This endeavour reflects the commitment to develop guidance that is rooted in our own population data, clinical realities, and diversity of practice settings.

The strength of this work lies in its collective wisdom. By combining survey-driven insights with a rigorous evidence-based approach, we have attempted to bridge the gap between everyday clinical practice and evolving scientific knowledge. These GPP documents are not meant to replace existing guidelines; rather, they aim to complement them by offering context-specific recommendations tailored to the Indian ART landscape.

It is our hope that this consolidated effort will support clinicians in making informed decisions, encourage uniformity of care, and ultimately contribute to improved patient outcomes. We extend our gratitude to everyone who contributed to this initiative and made this work possible.

Acknowledgments

We extend our heartfelt appreciation to all the experts, clinicians, embryologists, and young team members who worked tirelessly on each of the eleven SAEB GPP projects. Your commitment to scientific rigor, your enthusiasm for learning, and your willingness to collaborate have been the foundation of this initiative.

We gratefully acknowledge the unwavering support of the team leaders and national coordinators who guided each group with clarity, patience, and vision. The completion of the surveys, the collection of adequate sample sizes, the detailed discussions, drafting, redrafting, and finalization of recommendations would not have been possible without your leadership.

We thank the reviewers, statisticians, and mentors who provided constructive feedback at every stage, ensuring that each chapter meets the highest academic and practical standards. Special appreciation is extended to the editorial and organizational teams whose behind-the-scenes efforts—coordination, communication, formatting, plagiarism checks, and preparation of final deliverables—were indispensable.

To every participant who contributed time, expertise, and passion: this work stands as a testament to your dedication to improving ART practice in India.

We are extremely thankful to Meyer Organics Pvt Ltd for providing academic support for this project.

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Recurrent Pregnancy Loss

INTRODUCTION

Recurrent pregnancy loss (RPL) is defined as the occurrence of two or more consecutive miscarriages before 20 weeks of gestation. It affects 1–2% of couples and has multifactorial causes including genetic, anatomical, endocrine, immune, thrombotic, and male factors. A systematic, evidence-based evaluation helps guide targeted management and improve outcomes.

PICO 1: DOES GENETIC SCREENING FOR CHROMOSOMAL ABNORMALITIES COMPARED TO NO SCREENING HELP IDENTIFY A POTENTIAL CAUSE OF MISCARRIAGE IN WOMEN WITH RPL?

Recommendations

- Offer parental chromosomal screening to couples with recurrent pregnancy loss (RPL) [>2 pregnancy losses]
- Extended genetic screening (e.g., CMA, NGS) [chromosomal microarray, next generation sequencing] may be considered in couples with normal karyotypes and persistent unexplained RPL
- Always incorporate genetic counseling in the evaluation process when chromosomal abnormalities are detected

Summary of Evidence

The European Society of Human Reproduction and Embryology (ESHRE) guideline Group 2018[1] and the American Society for Reproductive Medicine

(ASRM) Practice Committee 2020[2] recommend parental karyotyping and genetic counseling. Since the level of evidence is low, this is considered a Good Practice Point. A randomized controlled trial by Lindheim et al. 2020[3] showed PGT-SR reduced miscarriage in balanced translocation carriers and increased live birth rate per transfer. Level of evidence is moderate. Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR) in identified translocation carriers is optional as spontaneous conception may still result in a healthy live birth.

A systematic review and meta-analysis by Coomarasamy et al. 2021[4] supported personalized embryo transfer. Level of evidence is high. A systematic review and meta-analysis by Tiegs et al. 2021[5] found routine PGT-A does not consistently reduce miscarriage. Level of evidence is moderate. Observational studies by Rajcan-Separovic et al. 2020[6] and Tšuiko et al. 2020[7] reported CMA/WES (whole exome sequencing) may reveal novel variants but remain investigational. Since the level of evidence is low, these findings are not practice-changing.

Research Gaps

- Lack of large-scale RCTs evaluating chromosomal microarray and whole-genome/exome sequencing in idiopathic RPL, and long-term reproductive/psychological outcomes of PGT-SR.
- Limited cost-effectiveness data of routine genetic testing vs empirical management across healthcare settings.
- Insufficient integration of multiomics (genetic, immunological, endometrial) approaches in RPL protocols.
- Underrepresentation of male genetic factors and sperm DNA fragmentation.

Survey Question

Which genetic test you typically order for RPL patient?

Survey Results (Fig. 1)

The responses revealed that *parental karyotyping* remains the most commonly ordered test, selected by *51.12%* of clinicians. A significant proportion (*44.17%*) reported using a *combination of karyotyping and chromosomal microarray analysis (CMA)*. Only *3.23%* of respondents relied solely on CMA, while *NGS* was chosen by just *0.74%*, indicating its limited routine clinical adoption.

Choices	Percentage	Count
Parental karyotyping	51.23%	208
Combination of a and b	44.09%	179
Chromosomal microarray analysis	3.20%	13
Next-generation sequencing	0.74%	3
	Total	406
	Unanswered	3

Fig. 1: Genetic tests ordered for RPL patients

Good Practice Points after Integrating with Evidence

- Offer parental karyotyping to all couples with ≥2 pregnancy losses.
- If karyotype is normal yet RPL persists, consider extended testing (CMA/WES/NGS)—especially when fetal tissue is unavailable or losses ≥3.
- Incorporate pre- and post-test genetic counseling for interpretation and emotional support.
- Do not use advanced molecular panels routinely outside research or selected cases.

PICO 2: DOES PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY (PGT-A), IMPROVE PREGNANCY OUTCOMES COMPARED TO NATURAL CONCEPTION IN WOMEN WITH UNEXPLAINED RECURRENT PREGNANCY LOSS?

Recommendations

- *Women <35 years with unexplained RPL and good reserve:* PGT-A is not routinely recommended due to inconsistent benefit, potential discard of viable embryos, and cost/time.[8-10]
- *Women ≥35 years with unexplained RPL:* PGT-A may be considered with IVF to reduce miscarriage and potentially increase live birth per transfer/patient.[8-11]
- *Integrate genetic counseling:* Discuss aneuploidy risk, limitations (mosaicism), costs, alternatives. [12,13]

Summary of Evidence

The ESHRE 2023 guideline[14] states PGT-A may be considered in older women with RPL. Since the level of evidence is low, this is a conditional recommendation. Systematic reviews by Mumusoglu 2025,[8] Adamyan 2024,[9] and Liang 2023[10] show reduced miscarriage in women ≥35 years. Level of evidence is moderate. A retrospective cohort by Li et al. 2025[15] found mixed results, while Kato 2023[16] showed benefit in older women. Level of evidence is low.

Research Gaps

No high-quality RCTs directly compare IVF+PGT-A vs expectant natural conception in unexplained RPL; most evidence derives from IVF cohorts.

Survey Question

If an abnormality is found in the parental karyotyping, how will you typically manage it?

Survey Results (Fig. 2)

98.00% of respondents reported opting for *genetic counseling and discussion of potential reproductive options*, such as *IVF with Preimplantation Genetic Testing for Aneuploidy (PGT-A)*. This reflects a proactive and evidence-based approach that prioritizes personalized reproductive planning and genetic risk mitigation.

Only *1.25%* indicated they would *recommend no further action unless additional losses occur,*.

Choices	Percentage	Count
Genetic counseling and potential reproductive options (e.g., IVF with PGT-A)	98.01%	395
Recommend no further action unless additional losses occur	1.24%	5
	Total	403
	Unanswered	6

Fig. 2: Management approach when parental karyotyping shows abnormality

Good Practice Points after Integration with Evidence

- When a structural chromosomal rearrangement is detected, offer targeted genetic counseling about reproductive risks, natural conception, and ART options.
- PGT-SR can be offered to reduce miscarriage and increase live birth per transfer, with informed discussion on limitations, costs, and alternatives.
- Couples with low reproductive risk or who decline IVF can attempt natural conception with supportive follow-up.

PICO 3: IN WOMEN WITH A HISTORY OF RPL, DOES THE PRESENCE OF IMMUNE FACTORS INCREASE THE RISK OF FUTURE PREGNANCY LOSS COMPARED TO THOSE WITHOUT IMMUNE FACTORS?

Recommendations

- It is not recommended to do routine testing for immune factors in patients with RPL [14]
- Antinuclear antibodies (ANA) testing could be considered[14] for explanatory purposes.

Summary of Evidence

ESHRE guidelines 2023[14] do not recommend immune factors screening in RPL. Review by Moffett & Hiby 2015[17] highlighted immune dysregulation in RPL. Since the level of evidence is low, it is considered experimental. Prospective intervention by Meng 2022[18] showed improved outcomes in immune-positive women. Level of evidence is moderate. Network meta-analyses by He 2023[19] and Liu 2022[20] supported immunotherapy in immune-positive subsets. Level of evidence is moderate but indirect.

Research Gaps

- Lack of standardized immune profiling protocols and assay cut-offs; limited RCTs directly stratifying immune-positive vs immune-negative RPL cohorts.
- Insufficient exploration of genetic immune markers (e.g., KIR/HLA-C) in large diverse cohort.
- Long-term outcomes following personalized immunomodulation strategies remain understudied.

Survey Question

Which immunological factors are commonly associated with RPL

Survey Results (Fig. 3)

Antiphospholipid syndrome (APS) was the most frequently identified factor, chosen by *49.88%* of respondents. *Thyroid autoimmunity* ranked second, reported by *24.32%* of respondents, reflecting growing recognition of its potential contribution to early pregnancy failure through immune-mediated mechanisms. *All of the above* were selected by *22.58%*, indicating that some clinicians view RPL as a *multifactorial immunologic condition*, rather than being driven by a single entity. *NK cell dysfunction* and *Lupus* were cited by *1.49%* and *0.99%* respectively.

Choices	Percentage	Count
Antiphospholipid syndrome (APS)	50.00%	203
Thyroid autoimmunity	24.14%	98
All of the above	22.66%	92
NK cell dysfunction	1.48%	6
Lupus	0.99%	4
	Total	406
	Unanswered	3

Fig. 3: Immunological factors commonly associated with RPL

Good Practice Points after Integration with Evidence

Routine immune factor testing is not recommended in women with RPL.

Selective testing (e.g., ANA) may be considered in cases with clinical suspicion of autoimmunity or after other causes have been excluded. Antiphospholipid antibody syndrome (APLA) testing is recommended when there are ≥2 pregnancy losses.

PICO 4: IN WOMEN WITH A HISTORY OF UNEXPLAINED RPL, DOES THE TREATMENT WITH IMMUNOTHERAPY IMPROVES LIVE BIRTH RATES AND REDUCE MISCARRIAGE RATE COMPARED TO NO TREATMENT?

Recommendations

- *Lymphocyte immunotherapy (LIT):* Not recommended for routine use in recurrent pregnancy loss (RPL) management due to lack of consistent evidence of benefit.[14]

- *Intravenous immunoglobulin (IVIG):* Routine administration is not advised in cases of unexplained RPL.[14]
- *Selective use:* In highly selected cases, particularly those with more than four consecutive pregnancy losses, IVIG may be considered as a conditional therapeutic option after thorough evaluation and counseling.[14]

Summary of Evidence

Systematic review by Cavalcante 2021[21] showed higher live birth with LIT. Level of evidence is low to moderate. The ESHRE 2023 guideline[14] advises against the routine use of lymphocyte immunotherapy (LIT) in unexplained RPL, as studies have shown inconsistent benefit and there are concerns about safety and standardization. Since the level of evidence is low, this is considered a Good Practice Point.

IVIG, ESHRE 2023 also recommends against general use in unexplained RPL. However, the guideline notes that repeated, high doses of IVIG administered very early in pregnancy may improve live birth rates in women with ≥4 unexplained losses. The level of evidence is low to moderate, therefore this is considered a conditional recommendation for highly selected cases. RCT by Yamada 2022[22] and meta-analysis by Shi 2022[23] showed improved pregnancy with IVIG in ≥4 losses. Level of evidence is moderate. Safety study by Kling 2006[24] and cohort by Sarno 2019[25] confirmed low adverse effects. Level of evidence is low. RCT by Meng 2016[26] showed intralipid had similar outcomes to IVIG. Level of evidence is low.

Research Gaps

- Heterogeneous protocols and definitions; need modern RCTs incorporating immune diagnostics.
- Identify responders via immune biomarkers.
- Clarify long-term maternal/offspring safety.

Survey Question

How often do you recommend Immunotherapy for women with unexplained RPL and abnormal immune parameters?

Survey Findings (Fig. 4)

- Nearly *half (48.7%)* of clinicians occasionally recommend immunotherapy, suggesting selective or case-based use.
- Around *29%* never recommend it—reflecting alignment with *ESHRE 2023*, which discourages routine use.
- *21.5%* always recommend it, possibly reflecting belief in immunologic contribution to RPL in specific patient subsets.

Choices	Percentage	Count
Occasionally	49.00%	197
Never	28.86%	116
Always	21.39%	86
	Total	402
	Unanswered	7

Fig. 4: Immunotherapy recommendation frequency

Good Practice Points after Integrating with Evidence

Immunotherapy (including IVIG, LIT, or intralipids) should not be routinely offered to women with unexplained RPL.

IVIG may be considered selectively in women with repeated (≥4) consecutive pregnancy losses and documented immune dysfunction after thorough counseling regarding uncertain benefits and limited evidence.

Survey Question

Preferred first-line immunomodulatory therapy for RPL with suspected immune dysfunction.

Survey Results (Fig. 5)

- *Low-dose corticosteroids* (prednisolone) emerged as the most commonly chosen first-line option (32%), reflecting clinician comfort with its safety profile and cost-effectiveness.
- 24% refrain from any immunotherapy, consistent with guideline recommendations.
- *LIT (14%)*, *IVIG (7.8%)*, and *intralipid (17.6%)* were used by subsets of practitioners, mainly in immune-positive or refractory RPL.
- *TNF-α inhibitors* are rarely used (2.7%), due to limited evidence and safety concerns.

Good Practice Points after Integrating with the Evidence

Use of corticosteroids in RPL remains experimental/conditional rather than standard of care. As per ESHRE. *LIT, IVIG, and intralipids* should be *restricted to research settings* .

Choices	Percentage	Count
Low-dose corticosteroids (e.g., prednisolone)	32.25%	129
Do not use	24.50%	98
Intralipid therapy	17.50%	70
Lymphocyte immunotherapy (LIT)	14.00%	56
Intravenous immunoglobulin (IVIG)	8.25%	33
TNF-alpha Inhibitors	2.75%	11
	Total	400
	Unanswered	9

Fig. 5: TNF -α inhibitors IVIG

PICO 5: IN WOMEN WITH A HISTORY RPL AND THROMBOPHILIA, DOES THE TREATMENT WITH LOW-MOLECULAR-WEIGHT HEPARIN (LMWH) AND ASPIRIN IMPROVES LIVE BIRTH RATES AND REDUCE MISCARRIAGE RATE COMPARED TO NO TREATMENT?

Recommendations

For APS-related RPL, offer low-dose aspirin plus prophylactic heparin to improve live birth over aspirin alone, which has to be started early (preconception aspirin; heparin at positive test).[14,27]

For inherited thrombophilia without APS, routine LMWH (even with aspirin) is not supported; consider only within research or for VTE indications.[14,28,29]

Summary of Evidence

The ESHRE 2023 guideline[14] recommends aspirin + LMWH in APS. Since the level of evidence is moderate, it supports clinical use. Meta-analysis by Shi 2021[27] confirmed benefit of aspirin+LMWH in APS. Level of evidence is moderate. ALIFE2 RCT by Quenby 2023[28] showed no benefit of LMWH in inherited thrombophilia. Level of evidence is high. Meta-analysis by Leslie 2016[29] also found no benefit. Level of evidence is moderate.

Research Gaps

- Small or outdated RCTs in inherited thrombophilia; there is a need for thrombophilia-type–specific analyses.
- Optimal timing/dose for LMWH unclear.
- Limited long-term safety data for mothers and infants.

Survey Question

Treatment approaches for hereditary thrombophilia in RPL.

Survey Results (Fig. 6)

- *Majority (63%)* of clinicians use *prophylactic LMWH alone*, showing a strong inclination toward anticoagulation even beyond APS.
- *31%* of clinicians combine *LMWH + aspirin*.
- Very few (3.7%) treat only if there's a history of thrombosis, and only *1.24%* use aspirin alone.
- The survey reflects that many clinicians continue empirical LMWH use even in *inherited thrombophilia*, despite limited evidence.

Choices	Percentage	Count
Prophylactic low-molecular-weight heparin (LMWH)	62.41%	254
Combination of LMWH and aspirin	31.94%	130
Only treat in cases with prior thrombosis history	3.69%	15
Low-dose aspirin alone	1.23%	5
	Total	407
	Unanswered	2

Fig. 6: Treatment approaches for hereditary thrombophilia in RPL

Good Practice Points after Integrating with Evidence

In women with *APS-related RPL*, use *low-dose aspirin (75–150 mg/day)* and *prophylactic LMWH* beginning from a positive pregnancy test to improve live birth outcomes.

For *inherited thrombophilia without APS or VTE history, routine anticoagulation is not recommended*; consider LMWH only for concurrent VTE risk factors after counseling.

PICO 6: IN WOMEN WITH A HISTORY OF RPL AND SUBCLINICAL HYPOTHYROIDISM (SCH), DOES THE TREATMENT WITH L-THYROXIN IMPROVES LIVE BIRTH RATES AND REDUCE MISCARRIAGE RATE COMPARED TO NO TREATMENT?

Recommendations

SCH means that thyroid stimulating hormone >2.5 mIU with normal free T3 and free T4.[14]

If women with subclinical hypothyroidism and RPL are pregnant again, TSH level should be checked in early gestation (7–9 weeks gestational age), and hypothyroidism should be treated with levothyroxine.[14]

Summary of Evidence

Treatment of SCH may reduce miscarriage risk; potential benefit should be balanced against risks as per ESHRE 2023.[14]

There is conflicting evidence regarding levothyroxine treatment and effect for women with subclinical hypothyroidism and RPL.[14,30]

Research Gaps

Need large, well-designed RCTs in RPL with SCH using uniform diagnostic criteria, standardized LT4 protocols, and live birth as primary endpoint.

Survey Question

Screening for TPO-Ab in RPL

Survey Results (Fig. 7)

61% of clinicians routinely screen for thyroid peroxidase antibodies, while *39% of clinicians* do not screen thus emphasizing that majority screen for TPO-Ab.

Choices	Percentage	Count
Yes	60.49%	245
No	38.77%	157
	Total	**405**
	Unanswered	4

Fig. 7: Screening for TPO Antibodies In RPL

Survey Question

TSH Cut-off for Treatment in RPL

Survey Finding (Fig. 8)

91.75% of clinicians reported using a *TSH cut-off ≥ 2.5 mIU/L* for initiating treatment thus emphasizing tighter thyroid control in women planning pregnancy or with a history of losses. *5.25%* of clinicians considered a *cut-off of 4 mIU/L*, while only *2.25%* used a *cut-off of 5 mIU/L*.

Choices	Percentage	Count
>=2.5	91.81%	370
4	5.21%	21
5	2.23%	9
	Total	403
	Unanswered	6

Fig. 8: TSH Cut-off for Treatment in RPL

Good Practice Points after Integrating with the Evidence

In women with *RPL and subclinical hypothyroidism (TSH >2.5 mIU/L)*:

- Check *TSH early in next pregnancy (7–9 weeks)*.
- Start *L-thyroxine therapy*, especially if *TPO Ab positive* to reduce miscarriage rate
- Monitor every 4–6 weeks to avoid overtreatment.

PICO 7: DOES SCREENING FOR UTERINE ANOMALIES COMPARED TO NO SCREENING HELP IDENTIFY A POTENTIAL CAUSE OF MISCARRIAGE IN WOMEN WITH RPL?

Recommendation

It is recommended to evaluate uterine cavity in all women with recurrent pregnancy loss. [31,32]

Summary of Evidence

Uterine anomalies are identified in ~13–25% of women with RPL, with septate

uterus most frequently associated with early miscarriage; evaluation with high-quality imaging (3D TVUS or hysteroscopy) is recommended according to both ESHRE 2017 and ASRM 2023 guidelines.[32,31]

Research Gaps

There is a need for good randomized trials to test whether universal screening reduces miscarriage and improves live birth in RPL.

Survey Question

Preferred Investigation for Acquired Uterine Anomaly

Survey Results (Fig. 9)

For *acquired uterine anomalies,* the majority of clinicians (*57.18%*) reported using *3D transvaginal ultrasound (3D USG)* as the first-line investigation. This reflects the growing consensus that 3D USG offers excellent diagnostic accuracy for identifying intrauterine pathology such as adhesions, fibroids, and polyps, while being noninvasive and easily available. About *23.5%* of clinicians still rely on *2D ultrasound*, particularly in centers where 3D imaging is not routinely available. *Hysteroscopy* was preferred by *14.36%* of clinicians mainly for its dual diagnostic and therapeutic potential in cases of intrauterine adhesions or suspected polyps. A smaller proportion (*4.2%*) of clinicians selected *MRI*, generally reserved for complex or inconclusive cases, especially when deep myometrial involvement or structural distortion is suspected.

Choices	Percentage	Count
3D USG	57.25%	233
2D Ultrasound (USG)	23.34%	95
Hysteroscopy	14.50%	59
MRI	4.18%	17
	Total	407
	Unanswered	2

Fig. 9: Preferred investigation for acquired uterine anomaly

Survey Question

Diagnostic modality for congenital uterine anomalies.

Survey Results (Fig. 10)

For *congenital uterine anomalies,* nearly half of the clinicians (*48.76%*) favored *combined diagnostic laparoscopy and hysteroscopy* as the most definitive evaluation method, allowing simultaneous diagnosis and, where indicated, surgical correction can be done. *3D ultrasound* was the second most preferred modality (*28.86%*), increasingly recognized for its ability to accurately delineate uterine morphology and differentiate between septate and bicornuate configurations. *MRI* was chosen by *17.91%*, mainly for complex or ambiguous cases where further anatomical detail is needed. A small proportion still used *HSG (2.99%)* and *saline infusion sonography (0.75%)*, reflecting declining reliance on older techniques due to limited specificity and inability to distinguish uterine subtypes precisely.

Choices	Percentage	Count
Diagnostic Laparoscopy with hysteroscopy	48.40%	196
3D Ultrasound study	29.14%	118
Magnetic resonance imaging (MRI)	17.78%	72
Hysterosalpingogram (HSG)	3.21%	13
Saline infusion sonography (SIS)	0.74%	3
	Total	**405**
	Unanswered	4

Fig. 10: Diagnostic modality for congenital uterine anomalies

Good Practice Points after Integration with Evidence

All women with *RPL* should undergo *systematic uterine evaluation*.

- *3D transvaginal ultrasound* is the preferred initial test.
- *Hysteroscopy ± laparoscopy* reserved for confirmation or correction in the same sitting

- MRI may be used as an adjunct in complex or inconclusive cases.

PICO 8: IN WOMEN WITH A HISTORY OF RPL WITH UTERINE ANOMALIES, DOES THE CORRECTION OF ANOMALIES IMPROVES LIVE BIRTH RATES AND REDUCE MISCARRIAGE RATE COMPARED TO NO TREATMENT?

Recommendation

Septate uterus: Offer hysteroscopic septum excision to patients with a septum and a history of recurrent miscarriage because of probable benefit.[33]

Other Uterine Malformations

Consider hysteroscopic metroplasty in dysmorphic (class U1) uteri; (T-shaped uterus.[34]

Surgical correction is not recommended for bicorporal/bicornuate with normal cervix, nor for unicornuate uterus (except excision for functional rudimentary horn).[34,35]

Summary of Evidence

Meta-analysis by Jiang 2023[33] showed septum excision improved outcomes. Level of evidence is moderate. Systematic review by Garzon 2020[34] found benefit in metroplasty in T-shaped uterus. Level of evidence is moderate. Review by Bailey 2015[35] found limited benefit in bicornuate/unicornuate uteri. Level of evidence is low. TRUST trial by Rikken 2021[36] and Cochrane review by Kowalik 2011[37] found insufficient evidence to support that hysteroscopic metroplasty improves fertility or pregnancy outcomes compared to no treatment. Level of evidence is low.

Research Gaps

Need multicenter RCTs on septum excision in RPL and better data for fusion anomalies/abdominal metroplasty.

PICO 9: DOES SCREENING OF MALE PARTNER IN A COUPLE WITH RPL FOR DNA FRAGMENTATION (DFI) HELPS IDENTIFY A POTENTIAL CAUSE OF MISCARRIAGE IN WOMEN WITH RPL THAN WITHOUT SCREENING?

Recommendations

Assessing sperm DNA fragmentation in couples with RPL could be considered for diagnostic purposes.[14]

Summary of Evidence

The ESHRE 2023 guideline[14] allows sperm DNA fragmentation testing in RPL. Since the level of evidence is low, this is a Good Practice Point.

Meta-analysis by Inversetti 2025[38] confirmed higher SDF in RPL. Level of evidence is moderate.

Research Gaps

Need high-quality RCTs to determine the role of DFI in RPL and standardized SDF assays/thresholds.

Survey Question

Do you screen for sperm DNA fragmentation in women with unexplained RPL?

Survey Results (Fig. 11)

A majority (*63.5%*) of clinicians do *selective DFI screening*—mainly when risk factors such as advanced paternal age, varicocele, abnormal semen parameters, or unexplained RPL exist. Only *18%* of clinician screen all RPL cases routinely, while *17%* do not do DFI testing, reflecting ongoing debate about its routine utility.

Choices	Percentage	Count
Selectively (if risk factors exist)	63.05%	256
Routinely	18.47%	75
No	17.73%	72
	Total	**406**
	Unanswered	3

Fig. 11: Sperm DNA fragmentation screening in RPL

Good Practice Points after Integrating with Evidence

In couples with *unexplained RPL*, screen for *sperm DNA fragmentation* selectively—especially when male age ≥40, abnormal semen parameters, oxidative stress factors, or prior ART failures exist.

For routine population-wide screening is *not recommended.*

PICO 10: IN WOMEN WITH A HISTORY OF RPL WITH HIGH DFI (DNA FRAGMENTATION) IN MALE PARTNER, DOES REDUCING THE DFI IMPROVES LIVE BIRTH RATES AND REDUCE MISCARRIAGE RATE COMPARED TO NO TREATMENT?

Recommendations

Antioxidant treatment is not recommended in couples with high DFI and RPL.[14]

Summary of Evidence

According to ESHRE 2023,[21] antioxidants for men have not been shown to improve the chance of a live birth. The AUA/ASRM 2024 guideline[39] recommends male lifestyle optimization and varicocele repair in patients with high DFI. Since the level of evidence is low, this is a Good Practice Point. Cochrane review by de Ligny 2022[40] and meta-analysis by Agarwal 2023[41] showed antioxidants may lower SDF but impact on live birth is uncertain. Level of evidence is low. Meta-analyses by McQueen 2019,[42] Tan 2019,[43] and Busnelli 2023[44] confirmed association of high SDF with miscarriage. Level of evidence is moderate. Consider 3–6 months antioxidants with shared decision-making; avoid mega doses/multisupplement stacks.

Research Gaps

- RCTs in RPL cohorts testing SDF-lowering strategies with live birth/miscarriage as primary outcomes are needed.
- Standardization of SDF assays and thresholds.
- Studies linking in-cycle SDF reduction (biologic effect) to hard outcomes. (live birth rate/mortality rate)

Survey Question

Treatment for High DFI in RPL couples.

Survey Results (Fig. 12)

82% of the clinicians use a *combination of ICSI + antioxidants*, *14%* rely on *ICSI alone*, while very few employ *TESA (1.5%)*, *antioxidants alone (1.2%)*, or *lifestyle changes (0.5%)*.

Choices	Percentage	Count
Both (a and b)	81.98%	332
ICSI (Intracytoplasmic Sperm Injection)	14.07%	57
TESA (Testicular Sperm Aspiration)	1.48%	6
Antioxidants	1.23%	5
Lifestyle modification	0.49%	2
	Total	405
	Unanswered	4

Fig. 12: Treatment for High DFI in RPL

Good Practice Points after Integrating with Evidence

- In men with *high SDF and RPL*, optimize *lifestyle factors* (stop smoking, reduce BMI, avoid heat/toxins) and treat *correctable causes* (e.g., varicocele).
- *Antioxidants* may be considered for *3–6 months* with shared decision-making; avoid high-dose or multisupplement regimens as high DFI is associated with miscarriage rates.
- *ICSI or testicular sperm retrieval (TESA)* can be considered when persistently high SDF is associated with failed conceptions.
- Routine antioxidant therapy for all cases is *not recommended*.

KEY GOOD PRACTICE POINTS

1. Parental chromosomal screening should be offered to all couples with more than two pregnancy losses, while extended genetic testing, such as CMA or NGS, may be considered only when parental karyotypes are normal, and RPL remains unexplained, with genetic counseling provided whenever abnormalities are identified.
   The Indian survey showed that parental karyotyping remains the most widely used test (51.12%), followed by a combination of karyotyping and CMA (44.17%), whereas only 3.23% used CMA alone and 0.74% opted for NGS, reflecting the limited routine adoption of advanced genomic platforms. In line

with current evidence, advanced molecular genetic panels should not be used routinely and must be reserved for research settings or carefully selected cases where standard evaluation is inconclusive.

2. In women under 35 years with unexplained RPL and good ovarian reserve, PGT-A is not routinely recommended due to inconsistent benefit, possible discard of viable embryos, and additional financial and temporal burden, whereas in women aged 35 years or older, PGT-A may be considered with IVF to reduce miscarriage rates and potentially improve live birth outcomes. Genetic counseling should accompany all decision-making, including discussion of aneuploidy risk, mosaicism, limitations, costs, alternatives, and—when structural chromosomal rearrangements are present—specific counseling on natural conception versus ART options such as PGT-SR.
   The Indian Survey findings reveal that 98.00% of clinicians already provide such counseling and reproductive planning options, while only 1.25% adopt a wait-and-watch approach. Overall, PGT-SR may be offered to reduce miscarriage risk in translocation carriers, while couples with low reproductive risk or those declining IVF can opt for natural conception with appropriate follow-up.

3. Routine immune factor testing is not recommended in women with recurrent pregnancy loss, although ANA testing may be selectively considered when autoimmune disease is suspected, and APLA testing remains essential in women with more than two pregnancy losses.
   The Indian Survey findings indicate that APS is the most commonly recognized immune factor (49.88%), followed by thyroid autoimmunity (24.32%), while fewer clinicians identified NK cell dysfunction (1.49%) or lupus (0.99%), and 22.58% selected multiple immune contributors, reflecting the perception of RPL as a multifactorial condition. Immune testing should remain selective.

4. Lymphocyte immunotherapy (LIT) is not recommended for routine management of unexplained recurrent pregnancy loss, and similarly, IVIG and intralipids should not be routinely offered in cases of unexplained RPL, with IVIG reserved only for highly selected women with ≥4 consecutive losses and documented immune dysfunction after detailed counseling.
   The Indian Survey findings show that 48.7% of clinicians occasionally recommend immunotherapy, 29% never recommend it in alignment with ESHRE guidance, and 21.5% always recommend it, reflecting variability in perceived immunologic contribution to RPL. Integrating current evidence with survey insights reinforces that immunotherapies should remain limited to exceptional, carefully evaluated cases rather than routine practice.

5. For APS-related recurrent pregnancy loss, low-dose aspirin (75–150 mg/day) combined with prophylactic LMWH—initiated as preconception aspirin and heparin from a positive pregnancy test—is recommended to improve live birth outcomes compared with aspirin alone.
   The Indian Survey data show that 63% of clinicians use LMWH alone in inherited thrombophilias and 31% use the combination therapy, while very few treat only when thrombosis is present (3.7%) or use aspirin alone (1.24%), reflecting ongoing empirical anticoagulation practices even in inherited thrombophilia despite limited evidence. Integrating guidelines and survey findings underscores that combined aspirin + LMWH therapy should be reserved for APS-related RPL, whereas routine anticoagulation for inherited thrombophilia without APS or VTE history is not supported and should only be considered when additional VTE risks exist.

6. In women with RPL and subclinical hypothyroidism (TSH >2.5 miu/L), check TSH early in the next pregnancy (7–9 weeks) and start L-thyroxine therapy, especially if TPO Ab positive to reduce miscarriage rate and monitor every 4–6 weeks to avoid overtreatment.
   The Indian survey data show that 91.75% of clinicians reported using a TSH cut-off ≥ 2.5 miu /L for initiating treatment, thus emphasizing tighter thyroid control in women planning pregnancy or with a history of losses. 5.25% of clinicians considered a cut-off of 4 miu /L, while only 2.25% used a cut-off of 5 miu/L. The data also showed that 61% of clinicians routinely screen for thyroid peroxidase antibodies, while 39% of clinicians do not screen, thus emphasizing that the majority screen for TPO-Ab.

7. It is recommended to evaluate the uterine cavity in all women with recurrent pregnancy loss.
   The Indian survey data findings regarding preferred investigation for acquired uterine anomaly show that the majority of clinicians (57.18%) reported using 3D transvaginal ultrasound (3D USG) as the first-line investigation. This reflects the growing consensus that 3D USG offers excellent diagnostic accuracy for identifying intrauterine pathologies such as adhesions, fibroids, and polyps, while being noninvasive and easily available. About 23.5% of clinicians still rely on 2D ultrasound, particularly in centers where 3D imaging is not routinely available. Hysteroscopy was preferred by 14.36% of clinicians mainly for its dual diagnostic and therapeutic potential in cases of intrauterine adhesions or suspected polyps. A smaller proportion (4.2%) of clinicians selected MRI, generally reserved for complex or inconclusive cases, especially when deep myometrial involvement or structural distortion is suspected.

The Indian survey data findings regarding the diagnostic modality for congenital uterine anomalies show that nearly half of the clinicians (48.76%) favored combined diagnostic laparoscopy and hysteroscopy as the most definitive evaluation method, allowing simultaneous diagnosis and, where indicated, surgical correction can be done. 3D ultrasound was the second most preferred modality (28.86%), increasingly recognized for its ability to accurately delineate uterine morphology and differentiate between septate and bicornuate configurations. MRI was chosen by 17.91%, mainly for complex or ambiguous cases where further anatomical detail is needed. A small proportion still used HSG (2.99%) and saline infusion sonography (0.75%), reflecting declining reliance on older techniques due to limited specificity and inability to distinguish uterine subtypes precisely.

8. In the women with mullerian duct anomalies it is prudent to offer hysteroscopic septum excision to patients with a septum and a history of recurrent miscarriage because of probable benefit. Consider hysteroscopic metroplasty in dysmorphic (class U1) uteri (T-shaped uterus). Surgical correction is not recommended for bicorporal/bicornuate with a normal cervix, nor for unicornuate uterus (except excision for functional rudimentary horn.

9. Assessing sperm DNA fragmentation in couples with RPL could be considered for diagnostic purposes, in couples with unexplained RPL, screen for sperm DNA fragmentation selectively—especially when male age ≥40, abnormal semen parameters, oxidative stress factors, or prior ART failures exist.
   The Indian survey data findings showed that the majority (63.5%) of clinicians do selective DFI screening—mainly when risk factors such as advanced paternal age, varicocele, abnormal semen parameters, or unexplained RPL exist. Only 18% of clinicians screen all RPL cases routinely, while 17% do not do DFI testing, reflecting ongoing debate about its routine utility.

10. Antioxidant treatment is not recommended in couples with high DFI and RPL
    ICSI or testicular sperm retrieval (TESA) may be considered only in cases of persistently high DNA fragmentation and repeated failed conceptions. Routine use of ICSI for all RPL cases is not recommended. The Indian survey data findings showed that 82% of the clinicians use a combination of ICSI + antioxidants, 14% rely on ICSI alone, while very few employ TESA (1.5%), antioxidants alone (1.2%), or lifestyle changes (0.5%) for the treatment of high DFI in RPL couples.

SURVEY QUESTIONNAIRE OF RECURRENT PREGNANCY LOSS

Basic Demographic Questions

1. Which part of India do you practice in?
   a. North
   b. South
   c. East
   d. West
2. Do you practice in:
   a. Corporate Sector
   b. Private Practice
   c. Government Institutional Sector

Survey Question

1. How do you define Recurrent Pregnancy Loss (RPL) in your clinical practice?
   a. Two or more consecutive pregnancy losses
   b. Three or more pregnancy losses
   c. Case-by-case definition based on risk factors
   d. Unexplained recurrent miscarriage regardless of number
2. Do you include biochemical pregnancies in the diagnosis of RPL?
   a. Yes, always
   b. No, I exclude biochemical pregnancies
   c. I am not sure
3. What do you consider the most common known cause of RPL in your practice?
   a. Uterine anomalies
   b. Chromosomal abnormalities
   c. Thrombophilia
   d. Unexplained
4. How often do you suspect immune-related factors (e.g., NK cells, cytokines) contribute to RPL?
   a. Frequently
   b. Occasionally
   c. Rarely
5. Do you believe psychological support should be a routine part of RPL care?
   a. Yes, all patients should have access to psychological support
   b. Yes, but only for patients showing signs of distress
   c. No, psychological support is not routinely necessary
6. Which genetic tests do you typically order for RPL patients?

a. Parental Karyotyping
b. Chromosomal microarray analysis
c. Next-generation sequencing
d. Combination of a & b

7. If an abnormality is found in parental karyotyping, how do you typically manage this?
   a. Genetic counseling and potential reproductive options (e.g., IVF with PGT-A)
   b. Recommend no further action unless additional losses occur
8. For RPL in women with advanced maternal age, which prognostic tool(s) would best predict pregnancy chances?
   a. Ovarian Reserve Testing [Anti Mullerian Hormone] (AMH)
   b. PGT-A
   c. Semen Analysis
   d. AMH + PGT-A
9. Which immunological factors are most commonly associated with RPL?
   a. Antiphospholipid syndrome (APS)
   b. Lupus
   c. Thyroid autoimmunity
   d. NK cell dysfunction
   e. All of the above
10. How often do you recommend Immunotherapy for women with unexplained RPL and abnormal immune parameters?
    a. Always
    b. Occasionally
    c. Never
11. Preferred first-line immunomodulatory therapy for RPL with suspected immune dysfunction:
    a. Low-dose corticosteroids (e.g., prednisolone)
    b. Lymphocyte immunotherapy (LIT)
    c. Intravenous Immunoglobulin (IVIG)
    d. Intralipid therapy
    e. TNF-alpha inhibitors
    f. Do not use
12. Treatment approaches for hereditary thrombophilia in RPL
    a. Prophylactic low-molecular-weight heparin (LMWH)
    b. Low-dose aspirin alone
    c. Combination of LMWH and aspirin
    d. Only treat in cases with prior thrombosis history

13. Do you routinely test Vitamin D levels in RPL patients?
    a. Yes
    b. No
14. Do you screen for TPO AB (Thyroid Peroxidase Antibody) in RPL patients?
    a. Yes
    b) No
15. Cut-off TSH level for thyroid treatment in RPL patients:
    a. >= 2.5
    b. 4
    c. 5
16. Preferred investigation for RPL with acquired uterine anomaly:
    a. 2D Ultrasound (USG)
    b. MRI
    c. Hysteroscopy
    d. 3D USG
17. Diagnostic modalities for congenital uterine anomalies in RPL patients:
    a. Hysterosalpingogram (HSG)
    b. 3D Ultrasound study
    c. Saline infusion sonography (SIS)
    d. Magnetic resonance imaging (MRI)
    e. Diagnostic Laparoscopy with Hysteroscopy
18. Do you screen for sperm DNA fragmentation in women with unexplained RPL?
    a. Routinely
    b. Selectively (if risk factors exist)
    c. No
19. Treatment for high DFI in RPL couples:
    a. Antioxidants
    b. Lifestyle modification
    c. Both (A & B).
    d. ICSI (Intracytoplasmic Sperm Injection)
    e. TESA (Testicular Sperm Aspiration)

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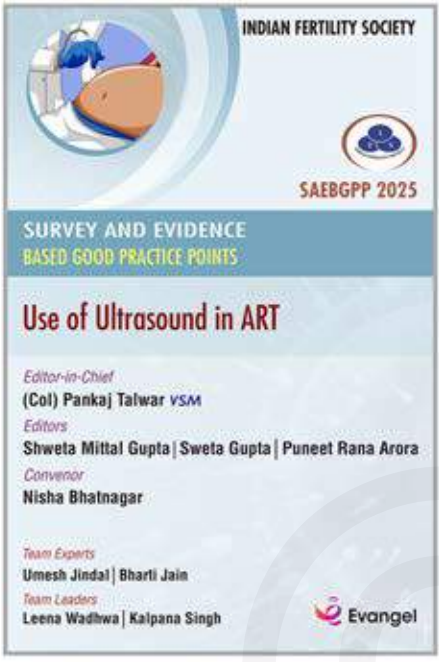
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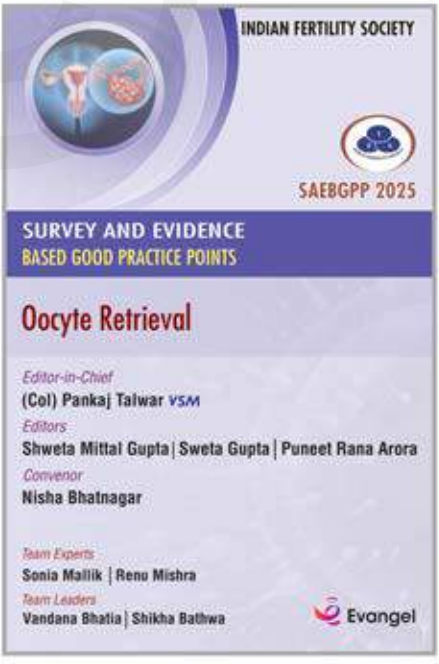
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