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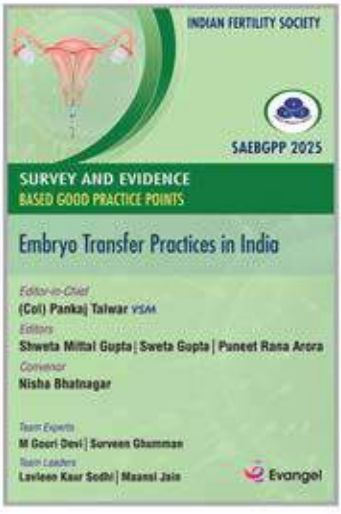
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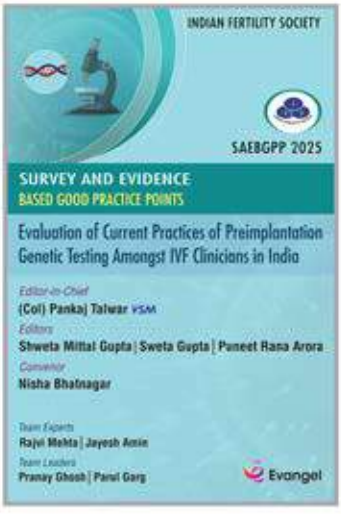
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Survey and Evidence Based Good Practice Points

Add-ons in ART

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SAEBGPP 2025

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Editor-in-Chief

(Col) Pankaj Talwar *VSM*

MD PhD
President, Indian Fertility Society (2024–26)
Director
Talwar Fertility and Men's Clinic
Academic Director, Clinical ART Program
SEART, Gurugram University
Dean
Department of Clinical Embryology
Shridhar University
Director, i-Ceat Academy of ART
Head, GE Healthcare 3D/4D Ultrasound Training School
Gurugram, Haryana, India

Editors

Shweta Mittal Gupta

Fellowship National Board Reproductive Medicine MD DNB MNAMS MBBS
Co-Director and Unit Head
Department of Centre of IVF and Human Reproduction
Sir Ganga Ram Hospital
New Delhi, India

Sweta Gupta

MD (Obs and Gyne) FRCOG (UK) MRCOG (UK) DFSRH (UK) MSc (Reproduction and Development, UK) Fellowship in ART (London)
Director
Department of IVF
Max Healthcare Ltd, Noida
Max Healthcare Ltd
New Delhi, India

Puneet Rana Arora

MBBS MS (Obs and Gyne) FRCOG (UK) MSc Reproduction
Senior Consultant-Gynecologist and Reproductive Medicine Specialist (IVF)
Founder and Director
Department of In Vitro Fertilization
CIFAR IVF Centre
Gurugram, Haryana, India

Convenor

Nisha Bhatnagar

MBBS MD
Medical Director
Department of Reproductive Medicine
Aveya IVF and Fertility Center, Rajouri Garden
New Delhi, India

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Evangel Publishing

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Team Experts

KD Nayar
MBBS DGO MD Dip in Obstetrics (Ireland) FICOG
Chief Consultant and Head
Akanksha IVF Centre
Mata Chanan Devi Hospital
New Delhi, India

Rajapriya Ayyappan
MD DNB MRCOG FRCOG FRM
Managing Director
Department of Obstetrics, Gynecology and Fertility
Srinivas Priya Hospital
Chennai, Tamil Nadu, India

Team Leaders

Pikee Saxena
FICOG MNAMS FMAS FIMCH PGCC (Hospital Management)
PGDCR (Clinical Research)
Director Professor and In-Charge of
Assisted Reproductive Services
Department of Obstetrics and Gynecology
Lady Hardinge Medical College and Smt Sucheta
Kriplani Hospital
New Delhi, India

Saumya Prasad
MBBS MS FMAS DMAS ICOG Certified
Senior Consultant
Matritava Advanced IVF and Maternity Centre
Gurugram, Haryana, India

Team Members

Seema Mittal

Madhupriya Ananthakrishnan

Kirti Gupta

Taruni Sharma

Syed Sajjad Hussain

Vandana Mohan

Utkarsha Agarwal

Supriya Kumari

Padmaja Veeramachaneni

Akshay Kumar Mahapatro

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.

Contributors

Akshay Kumar Mahapatro MD (Obs and Gyne) Postdoc Fellowship in Reproductive Medicine
Medical Director
Department of Reproductive Medicine
Shreya IVF Centre Pvt Ltd
Bhubaneswar, Odisha, India

KD Nayar MBBS DGO MD Dip in Obstetrics (Ireland) FICOG
Chief Consultant and Head
Akanksha IVF Centre
Mata Chanan Devi Hospital
New Delhi, India

Kirti Gupta MBBS MS (Obs and Gyne) Fellowship in Reproductive Medicine
Senior Fertility Consultant
Department of Fertility Clinic
Crysta IVF Fertility Centre
Kanpur, Uttar Pradesh, India

Madhupriya Ananthakrishnan MBBS DNB MRCOG
Clinical Director
Department of Reproductive Medicine
Nova IVF Fertility and Shree Clinic
Chennai, Tamil Nadu, India

Nisha Bhatnagar MBBS MD
Medical Director
Department of Reproductive Medicine
Aveya IVF and Fertility Center, Rajouri Garden
New Delhi, India

Padmaja Veeramachaneni MBBS MD (Obs and Gyne) (AIIMS, New Delhi) FCGP FMAS FICOG
Founder Chairperson-Chapter of ISAR Andhra Pradesh
Department of Obstetrics and Gynecology
Medcy Hospitals
Vijayawada, Andhra Pradesh, India

(Col) Pankaj Talwar *VSM* MD PhD
President, Indian Fertility Society (2024–26)
Director
Talwar Fertility and Men's Clinic
Academic Director, Clinical ART Program
SEART, Gurugram University
Dean
Department of Clinical Embryology
Shridhar University
Director, i-Ceat Academy of ART
Head, GE Healthcare 3D/4D Ultrasound Training School
Gurugram, Haryana, India

Pikee Saxena FICOG MNAMS FMAS FIMCH PGCC (Hospital Management) PGDCR (Clinical Research)
Director Professor and In-Charge of Assisted Reproductive Services
Department of Obstetrics and Gynecology
Lady Hardinge Medical College and Smt Sucheta Kriplani Hospital
New Delhi, India

Puneet Rana Arora MBBS MS (Obs and Gyne) FRCOG (UK) MSc
Reproduction
Senior Consultant-Gynecologist and Reproductive Medicine Specialist (IVF)
Founder and Director
Department of In Vitro Fertilization
CIFAR IVF Centre
Gurugram, Haryana, India

Rajapriya Ayyappan MD DNB MRCOG FRCOG FRM
Managing Director
Department of Obstetrics, Gynecology and Fertility
Srinivas Priya Hospital
Chennai, Tamil Nadu, India

Saumya Prasad MBBS MS FMAS DMAS ICOG Certified
Senior Consultant
Matritava Advanced IVF and Maternity Centre
Gurugram, Haryana, India

Seema Mittal MBBS MD
Gynecologist
Department of Infertility Obstetrics and Gynecology
Lalita Memorial Hospital
Rewari, Haryana, India

Shweta Mittal Gupta Fellowship National Board Reproductive Medicine MD DNB MNAMS MBBS
Co-Director and Unit Head
Department of Centre of IVF and Human Reproduction
Sir Ganga Ram Hospital
New Delhi, India

Supriya Kumari MBBS (AFMC) MD DNB MNAMS DM (Reproductive Medicine) (AIIMS, New Delhi)
Consultant (Fertility and IVF)
Department of Reproductive Medicine
Motherhood Hospital
Chandigarh, India

Sweta Gupta MD (Obs and Gyne) FRCOG (UK) MRCOG (UK) DFSRH (UK) MSc (Reproduction and Development, UK) Fellowship in ART (London)
Director
Department of IVF
Max Healthcare Ltd, Noida
Max Healthcare Ltd
New Delhi, India

Syed Sajjad Hussain MBBS MD (Physician) PGDHM DARM Diploma in ART and Reproductive Medicine (Germany) MSc Reproductive Medicine and IVF (London) Fellowship in Embryology and ART (PGD Academy, UK)
Managing Director, Chief IVF and ART Specialist
MED AGE
Srinagar, Jammu and Kashmir, India

Taruni Sharma MBBS MD (Safdarjung Hospital) DNB FNB (Oasis, Hyderabad)
Medical Director
Department of Obstetrics, Gynecology and IVF
Thakur Heal Care Hospital
Manwal, Punjab, India

Utkarsha Agarwal MBBS MS (Obs and Gyne) DNB (Obs and Gyne) FRM FCG FFM
Director and Centre Head
Department of IVF and Stem Cells
Ravi Women's Hospital and Indira IVF
Noida, Uttar Pradesh, India

Vandana Mohan MBBS MS DNB (Obs and Gyne) Dip in Clinical ART
Consultant
Department of Assisted Reproductive Technology (ART)
Nova Southend Fertility and IVF Centre
New Delhi, India

Preface

Editor-in-Chief
(Col) Pankaj Talwar *VSM*

Editor
Shweta Mittal Gupta

Editor
Sweta Gupta

Editor
Puneet Rana Arora

Convenor
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Team Expert
KD Nayar

Team Expert
Rajapriya Ayyappan

Team Leader
Pikee Saxena

Team Leader
Saumya Prasad

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 endeavor 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.

Contents

Add-ons in ART

INTRODUCTION

Add-ons in assisted reproductive technology (ART) refer to adjunctive procedures, interventions, or technologies that are offered in addition to standard in-vitro fertilization (IVF) protocols with the aim of improving outcomes. These may range from laboratory-based innovations such as time-lapse embryo imaging, assisted hatching, and preimplantation genetic testing (PGT), to pharmacological strategies, endometrial receptivity testing, immunological therapies, or complementary interventions. The rationale behind their introduction is to enhance implantation rates, optimize embryo selection, or improve live birth outcomes—areas where conventional IVF still faces limitations.

The use of add-ons has grown substantially over the past decade, largely driven by patient demand, technological advancement, and the desire to maximize the chances of success in a single cycle. For patients, each add-on represents not only an additional tool but also an extension of hope in what is often a physically and emotionally challenging journey. For clinicians, however, the integration of add-ons poses a complex responsibility: balancing innovation with scientific rigor, ensuring transparency in counseling, and safeguarding patients from unnecessary interventions.

Despite their increasing use, there remains a significant gap in high-quality evidence supporting many add-ons. Several interventions have been introduced into practice without robust randomized controlled trials or consistent data demonstrating improved live birth rates. International bodies, including the Human Fertilization and Embryology Authority (HFEA) in the United Kingdom, have published traffic-light style ratings to help patients and clinicians evaluate add-ons, but such structured frameworks remain absent in India. To date, there

are no national guidelines or consensus recommendations specifically addressing the role of add-ons in Indian ART practice. This absence of standardized direction has led to wide variability in clinical adoption, with practices differing not only between centers but also among individual practitioners.

Recognizing this critical gap, we conducted a comprehensive survey across India, involving approximately 630 ART specialists. The survey was designed to assess how clinicians in India perceive, define, and utilize add-ons, and for what clinical purposes these interventions are most often employed. The responses reflected the diversity of practices and the significant interest among clinicians in adopting add-ons despite the lack of unifying guidelines. Importantly, this exercise has enabled the compilation of data specific to the Indian context—addressing cultural, economic, and clinical realities unique to our population. Based on these insights, new recommendations tailored for Indian practice have been formulated, providing a framework for clinicians to adopt a more standardized and evidence-informed approach to add-ons in ART.

Thus, this chapter represents not only an overview of add-ons in ART but also the first attempt to contextualize their use within India through collective expert input. It aims to bridge the gap between innovation and evidence, while emphasizing the importance of transparency, patient-centered care, and scientific responsibility. The subsequent sections will present the survey findings and outline recommendations that may serve as a foundation for national consensus and future research in this evolving domain of reproductive medicine.

PICO 1: WHAT IS THE AIM OF USING AN ADD-ON IN ASSISTED REPRODUCTIVE TECHNOLOGY?

Recommendations

Add-ons are supplementary treatment options in addition to the standard fertility procedures, which aim to enhance live birth rate, to mitigate the risk of miscarriage, and to expedite the time to achieve pregnancy.

Summary of Evidence

ESHRE Add-Ons Working Group, 2023 defines add-ons in ART as—several supplementary laboratory techniques, additional clinical procedures, or adjuncts, commonly known as add-ons, have been introduced in fertility clinics and offered to patients on top of standard IVF/ICSI, and often at an additional cost to patients. These options **aim** to enhance pregnancy or LBRs, mitigate the risk of miscarriage,

or shorten the time to achieving pregnancy.[1] Add-ons are the procedures, medicines, or techniques that may be considered non-essential but are usually used in attempts to improve the probability of conception and live birth rates. In 2017, an online survey was distributed via social media to women in Australia who had undergone IVF. A total of 1590 eligible responses were analysed. Overall, 82% of women had used one or more add-ons, and these usually incurred an additional cost (72%).[2]

Research Gaps

- There is no globally accepted, evidence-based definition of ART add-ons, leading to inconsistency in clinical reporting and research design.
- Disagreement exists on what level of evidence is needed for a technique to be considered part of routine ART versus an add-on.

Survey Results from India (Fig. 1)

- 83% (n = 545) reported using add-ons to achieve all aims (LBR improvement, reduced miscarriage, faster pregnancy).
- 10% (n = 63) use add-ons specifically to enhance live birth rates.
- 3% (n = 22) to expedite time to pregnancy.
- 2% (n = 16) to mitigate miscarriage risk.
- 1% (n = 11) reported not using add-ons.

Choices	Percentage	Count
All of the above	82.95%	545
Enhance Live Birth Rates (LBRS)	9.59%	63
Expedite time to pregnancy	3.35%	22
Mitigate the risk of miscarriage	2.44%	16
Not using add-ons	1.67%	11
	Total	657
	Unanswered	8

Fig. 1: PICO 1: Survey findings

Integration with Evidence and Good Practice Points (GPP)

The majority of Indian ART specialists (83%) aim to use add-ons broadly, aligning with perceived benefits. However, ESHRE 2023 highlights limited evidence of benefit, showing that practice patterns may outpace supporting data.

PICO 2: WHICH AMONG THESE IS INCLUDED AMONG ADD-ONS IN ASSISTED REPRODUCTIVE TECHNOLOGY?

Recommendation

Add-ons include a diverse array of supplementary options encompassing tests, including drugs, equipment, complementary or alternative therapies, laboratory procedures, or surgical interventions.

Summary of Evidence

As per different studies available, add-ons in ART are defined as interventions or adjuncts offered in addition to standard IVF/ICSI with the intent of improving outcomes, though many lack robust evidence of benefit. ESHRE Add-ons Working Group (2023) states that add-ons in ART are "supplementary laboratory techniques, additional clinical procedures, or adjuncts, commonly known as add-ons, that have been introduced in fertility clinics and offered to patients on top of standard IVF/ICSI, often at an additional cost".[1] IVF add-ons are procedures, techniques, or medicines considered nonessential to IVF, but usually used in attempts to improve the probability of conception and live birth.[2] The term 'add-on' is also used to describe interventions, tests, or treatments that lack sufficient high-quality evidence; once substantial evidence accumulates, an add-on may no longer be categorized as such.[3]

Based on current literature and consensus statements, add-ons can be broadly grouped as follows:[4]

- *Diagnostic tests:* Screening hysteroscopy, endometrial receptivity assays (ERA), immunological tests, immunomodulating therapies.
- *Laboratory tests and interventions:* Artificial oocyte activation (AOA), mitochondrial replacement techniques (MRT), in-vitro maturation (IVM), sperm DNA fragmentation testing, sperm selection methods (IMSI, PICSI, MACS), growth factor–supplemented embryo culture media, assisted hatching, time-lapse imaging (TLI), mitochondrial DNA load assessment.
- *Clinical management interventions:* Platelet-rich plasma (PRP), double stimulation (duostim), adjuvants during ovarian stimulation (metformin,

growth hormone, testosterone, DHEA, aspirin, indomethacin, sildenafil), intravaginal/intrauterine culture devices, endometrial scratching, intrauterine G-CSF, stem-cell-based therapies, antioxidant supplementation.

ASRM 2021 has also highlighted similar categories, noting that while some (such as PGT-A for specific indications) may have a selective benefit, many other add-ons remain experimental and should be offered with careful counselling and transparency.[5]

Research Gap

Add-ons are inconsistently evaluated in the available trials, and there is a lack of evidence-based use and global or national regulatory frameworks to guide safe and effective ART add-ons.

Survey Results from India (Fig. 2)

- 79% (n = 521) reported using all categories of add-ons (drugs, equipment, complementary therapies, laboratory procedures, surgical interventions).
- 12% (n = 78) specifically use drugs.
- 4% (n = 28) complementary/alternative therapies.
- 2% (n = 14) equipment.
- 2% (n = 11) laboratory procedures.
- 1% (n = 5) surgical interventions.

Choices	Percentage	Count
All of the above	79.30%	521
Drugs	11.87%	78
Complementary/Alternative therapies	4.26%	28
Equipment	2.13%	14
Laboratory procedures	1.67%	11
Surgical interventions	0.76%	5
	Total	657
	Unanswered	8

Fig. 2: PICO 2: Survey findings

Integration with Evidence

Most Indian ART specialists (79%) reported use of diverse modalities, whereas evidence emphasizes the need for individualized evaluation. The wide uptake contrasts with limited regulatory guidance and variable evidence quality.

PICO 3: WHAT IS THE ROLE OF SCREENING HYSTEROSCOPY AS AN ADD-ON IN ART?

Recommendations

Screening hysteroscopy is not recommended routinely for women undergoing their first ART cycle. It may be performed for women with previous implantation failure or suspected intrauterine pathology.

Summary of Evidence

ESHRE 2023-Screening hysteroscopy is currently not recommended for routine
Clinical use: Screening hysteroscopy can be considered in patients with recurrent implantation failure.[1] A recent RCT confirmed a similar LBR when hysteroscopy was performed before IVF treatment or not (23.9% versus 19.3%; n¼171; P¼0.607) (Ben Abid et al., 2021).[6] A meta-analysis focusing on patients with RIF reported a significantly higher LBR after hysteroscopy compared to patients with RIF that did not have hysteroscopy (RR 1.29; 95% CI 1.03 to 1.62; 2 RCT and 2 cohort studies; n¼2247; P¼0.046) (Cao et al., 2018).[7]

Research Gap

- Currently, there is limited data on first-cycle ART in asymptomatic women.
- Due to heterogeneity and poor quality of the included studies, more high-quality RCTs are needed in the future to corroborate the results of this systematic evaluation and to provide high-quality, evidence-based medical evidence for the treatment of infertile women to improve pregnancy outcomes.

Survey Results from India (Fig. 3)

- 46% (n = 303) use hysteroscopy for RIF.
- 45% (n = 299) for RPL.
- 5% (n = 30) as routine practice.
- 2% (n = 15) do not use.
- 2% (n = 11) use in tubal factor infertility.

Integration with Evidence

Survey data of Indian ART specialists show widespread use in RIF/RPL, but not as routine practice. This reflects ESHRE's stance: hysteroscopy is not recommended routinely, though it may be considered in implantation failure cases.

Choices	Percentage	Count
Recurrent implantation failure (RIF)	46.05%	303
Recurrent pregnancy loss (RPL)	45.44%	299
Routine clinical Use	4.56%	30
Not used	2.28%	15
Tubal factor	1.67%	11
	Total	658
	Unanswered	7

Fig. 3: PICO 3: Survey findings

PICO 4: WHAT IS THE ROLE OF ENDOMETRIAL RECEPTIVITY TESTS IN ART?

Recommendation

The currently available endometrial receptivity tests are not recommended in routine clinical practice.

Summary of Evidence

ESHRE add-ons working group 2023 states that, inconclusive effect on clinical LBR. Limited data on safety according to Good practice recommendations on add-ons in reproductive medicine.[8] A systematic review and meta-analysis (2023) including 1 RCT and 9 cohort studies. It was observed that there was no significant difference in the primary outcome of clinical pregnancy rate between the 2 groups in unselected patients [RR = 1.07; 95% confidence interval (CI), 0.87–1.30; P = 0.53; I^2 = 89%].[2] The most recent and largest RCT is a double-blind, random ized clinical trial at 30 sites in the USA, including 767 women who had at least one cryopreserved euploid blastocyst. In the women with at least one cryopreserved euploid blastocyst, the use of endometrial receptivity testing to guide the timing of frozen ET did not significantly improve LBR as compared with standard ET [58.5% (223/381) versus 61.9% (239/386); RR 0.95; 95% CI 0.79 to 1.13] (DoyLe et al., 2022).[9] For the RIF group, the study by Hashimoto et al. (2017) showed some benefit of endometrial receptivity tests and pET with regard to PR.[10]

Research Gap

- There is heterogeneity in tests, timing, and thresholds, and a lack of high-quality RCTs demonstrating improved live birth outcomes.
- Multicentric, adequately powered RCTs need to be conducted to establish their efficacy and cost-effectiveness for clinical use.

Survey Findings (Fig. 4)

- 44% (n = 289) use ERA in RPL.
- 40% (n = 261) in RIF.
- 13% (n = 88) do not use ERA.
- 3% (n = 19) reported routine use.

Choices	Percentage	Count
RPL	43.99%	289
RIF	39.73%	261
Not using	13.39%	88
Routine Clinical Use	2.89%	19
	Total	657
	Unanswered	8

Fig. 4: PICO 4: Survey findings

Integration with Evidence

Most Indian ART specialists reserve ERA for RIF/RPL, with very limited routine use. This mirrors ESHRE guidance, which discourages routine ERA due to inconclusive benefit.

PICO 5: WHICH OF THESE IMMUNOLOGICAL TESTS AND TREATMENTS ARE CONSIDERED AS ADD-ONS?

Recommendations

- These tests and treatments include steroids, lipid emulsion (intralipid) infusion, intravenous immunoglobulin (IVIG), leucocyte immunization

therapy (LIT), tacrolimus, anti-tumour necrosis factor (anti-TNF) agents, G-CSF, and hydroxychloroquine.
- Peripheral blood tests for immune parameters and uNK-cell testing are not recommended.
- KIR and HLA genotyping is currently not recommended for routine use in ART
- Immunomodulation treatments, such as Intralipid, IVIG, rh-LIF, PBMCs, and anti-TNF, are not recommended due to a lack of robust evidence for efficacy, and their safety is not well established.

Summary of Evidence

ESHRE add-ons working group 2023 states that, benefit—on LBR or miscarriage rate is unclear due to a lack of understanding of the mechanisms.[1] In a systematic review and meta-analysis including 60 studies, Von Woon E et al evaluated uterine natural killer cells number and function in implantation failure and recurrent miscarriage. The uNK level in the endometrium of women with RIF compared with controls showed significantly higher levels in women with RIF. However, there was no difference in pregnancy outcome in women with RM/RIF stratified by uNK level, and no significant correlation between pNK and uNK levels in women with RM/RIF.[11] A recent meta-analysis and systematic review of interventional studies that were considered very low to low quality came to the conclusion not to recommend any of these immune treatments in ART (Melo et al., 2022).[12]

Research Gap

There is a lack of adequately powered RCTs, inconsistent testing protocols, heterogeneous patient populations, poor reporting on long-term safety outcomes, or neonatal follow-up after immunomodulatory therapies to recommend immunologic testing and treatments for use in ART.

Survey Results from India (Fig. 5)

- 79% (n = 517) reported not using immunological add-ons.
- 9% (n = 61) use Intralipid.
- 6% (n = 40) use IVIG.
- 4% (n = 24) use Tacrolimus.
- 2% (n = 14) use LIT.

Integration with Evidence

Immunological therapies are rarely adopted by Indian ART specialists, reflecting skepticism. Evidence also finds no robust benefit, reinforcing the cautious uptake.

Choices	Percentage	Count
None of the above	78.81%	517
Intralipid	9.30%	61
IVIG	6.10%	40
Tacrolimus	3.66%	24
LIT	2.13%	14
	Total	656
	Unanswered	9

Fig. 5: PICO 5: Survey findings

PICO 6: WHICH OF THESE SPERM SELECTION TECHNIQUES IS REOMMENDED FOR ROUTINE CLINICAL USE?

Recommendation

- Microfluidics can be considered in ICSI for male factor infertility.
- Artificial sperm activation is recommended for patients with primary or secondary total asthenozoospermia which are not the result of axonemal structure defects, and is currently not recommended for routine clinical use.

Summary of Evidence

ESHRE add-ons working group states that Sperm hyaluronic binding assay, sperm DNA damage testing, physiological ICSI, magnetic-activated cell sorting, intracytoplasmic morphologic sperm injection (IMSI) is currently not recommended for routine clinical use.[1] **A narrative review** of sperm selection technology for assisted reproduction techniques by Charles et al., 2024 suggests that advanced methods like magnetic-activated cell sorting (MACS) and microfluidic sorting have emerged as more precise tools for selecting sperm with better genetic integrity, although they face challenges in terms of their standardization, cost, and clinical adoption.[13] Emerging technologies such as artificial intelligence (AI) and Raman spectroscopy offer the potential for more automated, accurate sperm selection, minimizing human error and variability.[14]

Research Gap

The integration of these into clinical practice requires further validation through large-scale and long-term studies to assess long-term safety and cost- cost-effectiveness.

Survey Results from India (Fig. 6)

- 75% (n = 488) reported not using sperm selection add-ons.
- 10% (n = 64) use microfluidics/sperm sorting.
- 7% (n = 45) use microfluidics + PICSI.
- 4% (n = 29) use IMSI/MSOME.
- 2% (n = 14) use PICSI.
- 2% (n = 13) use all techniques.

Choices	Percentage	Count
None of the Above	74.73%	488
Microfluidics/Sperm sorting	9.80%	64
A+B	6.89%	45
IMSI/MSOME	4.44%	29
PICSI	2.14%	14
All of the above	1.99%	13
	Total	**653**
	Unanswered	12

Fig. 6: PICO 6: Survey findings

Integration with Evidence

Survey suggests that Indian ART specialists have limited uptake of sperm selection add-ons. This aligns with evidence showing no proven routine benefit, though emerging technologies are being explored.

PICO 7: DO YOU OFFER PGT-A TO PATIENTS UNDERGOING ART?

Recommendations

Pre-implantation genetic testing for aneuploidy is not recommended for routine clinical use.

Summary of Evidence

ESHRE add-ons working group 2023; states that—current available data for PGT-A for genetic analysis indicate limited improvement in LBR. The supposition that PGT-A reduces miscarriages or time-to-pregnancy in specific patient groups as maternal age, is based on post hoc analyses (Munne et al., 2019) and requires further assessment to establish its validity.[15] A Systematic review and network meta-analysis of 10 RCTs in 2021 indicated that PGT-A did not improve live-birth rates per patient in the general population since there were no benefits in younger women.[16] 10 meta-analysis in 2022 representing 2630 embryo transfers was included, and they found no significant difference in the reproductive outcome.[17] KIR and HLA genotyping is currently not recommended for routine use in ART.

Survey Results from India (Fig. 7)

- 74% (n = 478) offer PGT-A sometimes.
- 23% (n = 151) do not offer.
- 3% (n = 18) offer routinely.

Choices	Percentage	Count
Yes, sometimes	73.88%	478
No	23.34%	151
Yes, for all	2.78%	18
	Total	647
	Unanswered	18

Fig. 7: PICO 7: Survey findings

Integration with Evidence

Most Indian ART specialists use PGT-A selectively, rarely routinely. This aligns with ESHRE evidence that PGT-A does not improve LBR across all patients, but may help in selected groups.

PICO 8: SHOULD TIME-LAPSE IMAGING ON EMBRYOS BE ROUTINELY ADVISED IN ART?

Recommendations

Time-lapse imaging is not recommended as a tool to improve live birth rates.

Summary of Evidence

ESHRE add-ons working group 2023 states that there is no evidence of benefit on LBR or miscarriage rate, also there is no evidence or rationale for harm.[1]

The most recent Cochrane systematic review and meta-analysis on TLI concluded there is insufficient good-quality evidence of differences in LBR/ongoing PR (OPR) (OR 0.91; 95% CI 0.67 to 1.23; 3 RCTs; n¼ 826; I2 ¼ 33%; low-quality evidence), miscarriage (OR 1.90; 95% CI 0.99 to 3.61; 3 RCTs; n¼ 826; I2 ¼ 0%; low-quality evidence) and stillbirth (OR 1.00; 95% CI 0.13 to 7.49; 1 RCT; n¼ 76; low-quality evidence) to choose between TLI, with or without embryo selection software, and conventional incubation.[18]

Research Gap

More long-term, quality evidence is required to show improvement in cumulative LBR or OPR.

Survey Results from India (Fig. 8)

- 80% (n = 522) do not use TLI, citing lack of benefit.
- 11% (n = 73) would use it if available.
- 8% (n = 54) sometimes use.
- 1% (n = 5) routinely use.

Choices	Percentage	Count
No- doesn't offer benefit	79.82%	522
Not used, but will offer if available	11.16%	73
Yes, sometimes	8.26%	54
Yes, for all	0.76%	5
	Total	654
	Unanswered	11

Fig. 8: PICO 8: Survey findings

Integration with Evidence

Survey reflects low adoption of time-lapse imaging by Indian ART specialists due to limited evidence. This aligns with current guidance, which does not recommend TLI for routine use.

PICO 9: SHOULD PRP BE ROUTINELY ADVISED IN ART?

Recommendations

Intrauterine and intraovarian administration of platelet-rich plasma is not recommended in routine clinical practice.

Summary of Evidence

ESHRE add-ons working group 2023 states that PRP is administered as an intrauterine infusion for women with thin/refractory endometrium or RIF and as an intraovarian injection in women with poor ovarian response or POI.

There is evidence of benefit on CPR, but no evidence of an effect on the miscarriage rates of intrauterine PRP in RIF or with thin/refractory endometrium. Recently, the intervention has also been applied to women with RPL.[1] In a systematic review, including three RCTs and four cohort studies with women undergoing IVF/ICSI, a significantly higher probability of CPR was reported with PRP as compared to controls receiving no, or another, active intervention (RR 1.79; 95% CI 1.37 to 2.32; 7 studies; n¼ 625; I2 ¼ 16%; P < 0.001). There was no difference between women regarding miscarriage (RR 0.72; 95% CI 0.27 to 1.93; 3 studies; n¼ 217; I2 **¼ 0%;** P¼ 0.51).[19]

A systematic review of four studies (one case-control and three uncontrolled studies involving 696 women) concluded that intraovarian PRP infusion increases the mature oocyte yield, fertilization rates, and good-quality embryo formation rate (Panda et al., 2020).[20]

Research Gap

Although intrauterine and intraovarian PRP appear to be promising, further validation is warranted through additional large-scale, high-quality, multicenter, and rigorously designed studies for establishing efficacy and safety.

These studies involved small sample sizes, heterogeneous patient populations, and there is a possible overrepresentation of one research group in the data.

Survey Results from India (Fig. 9)

- 77% (n = 501) do not use PRP.

- 13% (n = 85) use intrauterine PRP.
- 6% (n = 41) use both intrauterine + intraovarian PRP.
- 4% (n = 27) use intraovarian PRP only.

Choices	Percentage	Count
Not used	76.61%	501
Yes (Intrauterine)	13.00%	85
A+B	6.27%	41
Yes (Intraovarian)	4.13%	27
	Total	654
	Unanswered	11

Fig. 9: PICO 9: Survey findings

Integration with Evidence

Indian ART specialists rarely use PRP, despite emerging studies. Evidence highlights promise but insufficient validation, consistent with cautious uptake.

PICO 10: SHOULD ADJUNCTS BE ROUTINELY ADVISED IN ART? WHICH OF THE FOLLOWING ADJUNCTS IS MOST FREQUENTLY USED DURING OR BEFORE OVARIAN STIMULATION?

Recommendations

Adjuncts (metformin, growth hormone, testosterone, DHEA, aspirin, indomethacin, and sildenafil) before or during ovarian stimulation are not recommended.

Summary of Evidence

ESHRE add-ons working group 2023 states that current evidence does not support the routine use of adjuncts such as metformin, growth hormone,

testosterone, DHEA, aspirin, indomethacin, and sildenafil before or during ovarian stimulation.

Furthermore, there are serious safety concerns with the use of some of these adjuncts, such as sildenafil.

However, the use of these adjuncts based on individual patient characteristics or in specific clinical circumstances may warrant further investigation.

Further research is needed to better understand the efficacy and safety of these adjuncts in the context of ovarian stimulation.[1]

Research Gap

Further research is needed to better understand the efficacy and safety of these adjuncts in the context of ovarian stimulation.

Survey Results from India (Fig. 10)

- 83% (n = 544) reported using DHEA.
- 8% (n = 50) CoQ10.
- 7% (n = 43) testosterone.
- 2% (n = 15) growth hormone.

Choices	Percentage	Count
DHEA	83.44%	544
CoQ10	7.67%	50
Testosterone	6.60%	43
Growth hormone	2.30%	15
	Total	652
	Unanswered	13

Fig. 10: PICO 10: Survey findings

Integration with Evidence

High DHEA use by Indian ART specialists contrasts with evidence, which does not recommend routine adjuncts. This suggests reliance on empirical practice rather than strong evidence.

PICO 11: WHAT IS THE EFFECTIVENESS OF ANTIOXIDANTS ?

Recommendations

Antioxidant therapy is not recommended in ART.

Summary of Evidence

ESHRE add-ons working group 2023; states that antioxidant therapy does not have evidence demonstrating a significant enhancement in LBRs. Antioxidants are a group of organic nutrients that including minerals, vitamins and polyunsaturated fatty acids, which are suggested to reduce oxidative damage and balance the negative outcomes related to OS (deterioration of sperm count, motility, morphology, fertilization, and embryo development and risk of infertility, miscarriage, and RIF).[21] Cochrane systematic review for female infertility was uncertain whether oral antioxidants (1–3 cycles) improve LBR compared with placebo or no treatment/ standard treatment (OR 1.81;95% CI 1.36 to 2.43; 13 RCTs; n¼ 1227; I2 ¼ 29%; P <0.001; very low-quality evidence).[2] Cochrane review for male subfertility reported that oral antioxidants (3–12 months) may lead to increased LBRs compared to placebo or no treatment (OR 1.43; 95% CI 1.07 to 1.91; 12 RCTs; n ¼ 1283; I2 ¼ 49%; very low-quality evidence).[22] 2024, 20 RCT, 2618 patients were included for analysis suggesting antioxidant therapy is an effective and safe complementary strategy during IVF for women with ovarian aging. The optimal treatment regimen for CoQ10 was 300 mg/d for 3 months before the controlled ovarian stimulation cycle, and women with diminished ovarian reserve clearly benefited from the treatment, especially those of young reproductive age.[23]

Research Gap

Most of the studies showed a small sample size and retrospective design, used various com- binations of antioxidants, and semen parameters or DFIs were used as surrogate success parameters rather than the PR itself.

Survey Results from India (Fig. 11)

- 81% (n = 530) use antioxidants in some patients.
- 15% (n = 97) use for all patients.
- 4% (n = 29) do not use antioxidants.

Integration with Evidence

Antioxidants are widely used by Indian ART specialists, though evidence remains uncertain. This highlights a gap where clinical optimism surpasses data strength.

Choices	Percentage	Count
Yes, for some	80.79%	530
Yes, for all	14.79%	97
No	4.42%	29
	Total	656
	Unanswered	9

Fig. 11: PICO 11: Survey findings

PICO 12: WHICH OF THOSE INTRAUTERINE INFUSION TECHNIQUES IS RECOMMENDED FOR ROUTINE CLINICAL USE IN ART?

Recommendations

Intrauterine administration of hCG and G-CSF is not recommended for routine clinical use in ART.

Summary of Evidence

ESHRE add-ons working group 2023 states that current evidence for the efficacy of intrauterine administration of hCG is conflicting. The evidence for its benefits in specific patient subgroups (RIF) is also inconclusive. Some evidence of benefit for cleavage stage (not blastocyst) transfer at >500 IU. Current evidence concerning the intrauterine administration of G-CSF is also inconclusive. In RIF: No evidence of benefit on LBR, in thin endometrium: may improve ET.[1] A Cochrane systematic review and meta-analysis summarized studies evaluating intrauterine administration of hCG and its effect on reproductive outcomes in women undergoing IVF treatment. To overcome the heterogeneity of the data, results were reported by day of transfer and hCG dosage. LBRs in women having Day 3 ET with intrauterine hCG at a dose <500 IU were similar to controls without hCG administration (RR 0.76; 95% CI 0.58 to 1.01; 1 RCT; n¼ 280; I2 **¼ 0%; very** low- quality), but LBR was higher with a higher dosage of hCG (500 IU) compared to controls (RR 1.57; 95% CI 1.32 to 1.87; 3 RCTs; n¼ 914; I2 ¼ 0%; moderate-quality evidence). For blastocyst transfer with intrauterine hCG (500 IU) compared to controls having blastocyst transfer without hCG, no significant

difference in LBR was observed (RR 0.92; 95% CI 0.80 to 1.04; 2 RCTs; n¼ 1666; I2 ¼ 0%; moderate-quality.[24] Two recent RCTs evaluated intrauterine administration of hCG (dosage 1,000 IU and 500 IU, respectively) immediately after OPU, rather than at ET as in the other studies. The study using the higher dosage reported no benefit with regards to LBR or any other outcome, while the trial using the lower dosage reported an increased CPR (49%) compared to saline intrauterine infusion (22.9%).[25,26]A meta-analysis of randomized controlled trials, miscarriage rate was significantly lower (OR 0.57; 95% CI 0.33–0.99) with intrauterine hCG administration as compared to controls, but this was not reported in other reviews Gao et al.,[27] The most recent review, including two RCTs with good prognosis patients, two RCTs with at least one implantation failure, and one RCT with thin endometrium patients, reported that intrauterine G-CSF may result in a higher LBR/OPR than placebo or no intervention (RR 1.52; 95% CI 1.11 to 2.10; 5 RCT; I2 ¼ 12%), although the certainly of the evidence was found to be low.[28]

Research Gap

Considering the safety concerns with hCG (Ectopic PRs), further studies are necessary because of the study's small sample sizes and mixed cleavage and blastocyst transfer in both fresh and frozen cycles in the G-CSF group. Further research is needed to better understand its potential efficacy and safety.

Survey Results from India (Fig. 12)

- 77% (n = 504) do not use intrauterine infusion add-ons.
- 17% (n = 108) use G-CSF.
- 6% (n = 41) use hCG.

Choices	Percentage	Count
None	77.18%	504
G–CSF	16.54%	108
hCG	6.28%	41
	Total	**653**
	Unanswered	12

Fig. 12: PICO 12: Survey findings

Integration with Evidence

Limited use of intrauterine infusion reflects uncertainty in evidence. Current data show inconsistent benefits, supporting the restrained adoption.

PICO 13: SHOULD ENDOMETRIAL SCRATCHING BE ROUTINELY ADVISED IN ART?

Recommendations

Endometrial scratching is currently not recommended for routine clinical use.

Summary of Evidence

ESHRE 2023 states that inconclusive data on the benefit of LBR with no effect on the miscarriage rate.[1] Recent Cochrane systematic review and meta-analysis included a total of 37 RCTs (8786 women) concluded that endometrial scratching was performed by pipelle biopsy in the luteal phase of the cycle before an IVF cycle. The primary analysis was restricted to studies with low risk of bias (Lensen et al., 2021c). The effect of endometrial scratching on LBR was unclear as the result was consistent with no effect, a small reduction, or an improvement (OR 1.12; 95% CI 0.98 to 1.28; 8 RCTs; n¼ 4402;I2 ¼ 15%; moderate-quality evidence). Similarly, the effect of endometrial scratching on CPR was unclear (OR 1.08; 95% CI 0.95 to 1.23; 8 RCTs; n¼ 4402; I2 ¼ 0%; moderate-quality evidence). It was concluded that endometrial scratching probably results in little to no benefit in risk of miscarriage (OR 0.88; 95% CI 0.68 to 1.13; 8 studies; n¼ 4402; I2 ¼ 0%; moderate-quality evidence).[29]

Research Gap

- Large heterogeneity among studies in methodology and timing of the intervention.
- Subgroup analyses also failed to identify patient groups that would benefit from endometrial scratching.

Survey Results from India (Fig. 13)

- 79% (n = 519) sometimes perform endometrial scratching.
- 15% (n = 96) do not use it.
- 3% (n = 22) use routinely.
- 3% (n = 19) rarely use it.

Integration with Evidence

Survey shows frequent but non-routine use by Indian ART specialists. This diverges

from evidence, which concludes that scratching offers little to no benefit, indicating clinical inertia.

Choices	Percentage	Count
Sometimes	79.12%	519
No	14.63%	96
Yes	3.35%	22
Rarely	2.90%	19
	Total	656
	Unanswered	9

Fig. 13: PICO 13: Survey findings

PICO 14: SHOULD STEM CELL TREATMENT BE ROUTINELY ADVISED IN PATIENTS UNDERGOING ART?

Recommendations

Stem cell therapy for premature ovarian insufficiency, diminished/poor ovarian reserve, or thin endometrium is not recommended.

Summary of Evidence

Stem cells have been found to have the ability of self-renewal and multi-directional differentiation potential, with broad prospects for the treatment of tissue damage involving the uterine cavity. Allogeneic stem cells have easy access and are convenient, and are widely used in experiments. ESHRE 2023 states that the rationale for stem cell therapy in women with POI, diminished/poor ovarian reserve, or thin endometrium is unclear.[1] Systematic review and meta-analysis in 2022 was done, which included 10 studies for the analysis, reporting 116 participants with intrauterine adhesions, 72 of them received autologous therapy, and 44 of them received allogeneic therapy. Improvements in endometrial thickness and pregnancy rates increased more after autologous stem cell IUA treatment (mean difference, 1.68; 95% confidence interval [CI]: 1.30-2.07; $P < 0.00001$), and the pregnancy rate was also improved (relative risk, 1.55; 95% CI:

1.19-2.02, P < 0 001). No obvious and serious adverse reactions were observed during stem cell therapy in either group.[30]-2024 RCT 152 patients with mild to moderate intrauterine adhesions. 72 patients received bone marrow stem cells, and 68 were in the control group. The ongoing pregnancy occurred in 45/72 (62.5%) participants in the bone marrow stem cells-scaffold group, which was significantly higher than that in the control group (28/68, 41.2%) (RR = 1.52, 95%CI 1.08-2.12, P = 0.012). The situation was similar in live birth rate (bone marrow stem cells-scaffold group 56.9% (41/72) vs. control group 38.2% (26/68), RR = 1.49, 95%CI 1.04-2.14, P = 0.027). Participants in the bone marrow stem cells-scaffold group, when compared with the control, showed more menstrual blood volume in the 3rd and 6th cycles and maximal endometrial thickness in the 6th cycle after hysteroscopic adhesiolysis.. In conclusion, transplantation of bone marrow stem cells-scaffold into the uterine cavities of the participants with severe intrauterine adhesion increased their ongoing pregnancy and live birth rates, and this therapy was relatively safe.[31]

Research Gap

- The available data on efficacy are limited and primarily derived from observational studies with small sample sizes.
- More importantly, there are serious safety concerns regarding the long-term effects of injections of stem cells and the risk of tumorigenesis with this technique.
- Further preclinical studies are necessary to assess the relevance and potential efficacy of this technique.

Survey Results from India (Fig. 14)

- 87% (n = 572) never use stem cells.
- 11% (n = 71) use sometimes.
- 1% (n = 7) use both/all approaches.
- 1% (n = 5) use routinely.

Integration with Evidence

Stem cell add-ons are almost never used by Indian ART specialists, consistent with evidence cautioning against routine application due to unclear safety and efficacy.

Choices	Percentage	Count
Never	87.33%	572
Sometimes	10.84%	71
Both of the above	1.07%	7
Yes	0.76%	5
	Total	655
	Unanswered	10

Fig. 14: PICO 14: Survey findings

KEY GOOD PRACTICE POINTS

1. Add-ons are supplementary treatment options in addition to the standard fertility procedures, which aim to enhance live birth rate, to mitigate the risk of miscarriage, and to expedite the time to achieve pregnancy
   The majority of Indian ART specialists (83%) aim to use add-ons broadly, aligning with perceived benefits. 9.5% to increase live birth rate, 3.5 % to expediate time to pregnancy, 2.4 % to mitigate the risk of miscarriage. However, ESHRE 2023 highlights limited evidence of benefit, showing that practice patterns may outpace supporting data.

2. Add-ons include a diverse array of supplementary options encompassing tests, including drugs, equipment, complementary or alternative therapies, laboratory procedures, or surgical interventions.
   Most Indian ART specialists (79%) reported use of diverse modalities,11.87 % only drugs, 4.26 % complimentary /alternative therapies, 2.13 % equipment, 1.67 % on laboratory procedures, 0.76% on surgical interventions whereas evidence emphasizes the need for individualized evaluation. The wide uptake contrasts with limited regulatory guidance and variable evidence quality.

3. Screening hysteroscopy is not recommended routinely for women undergoing their first ART cycle. It may be performed for women with previous implantation failure or suspected intrauterine pathology.
Survey data of Indian ART specialists show widespread use in RIF 46.05 %/ RPL 45.44%, but not as routine practice. Routine clinical use was in 4.56 %. 2.28% not used. This reflects ESHRE's stance: hysteroscopy is not recommended routinely, though it may be considered in implantation failure cases.

4. The currently available endometrial receptivity tests are not recommended in routine clinical practice.
Most Indian ART specialists reserve ERA for RIF 43.9 %/RPL 39.7 %, 13.9 % not using, 2.89% has routine use. This mirrors global evidence, which discourages routine ERA due to inconclusive benefit.

5. Immunological treatments include steroids, lipid emulsion (intralipid) infusion, intravenous immunoglobulin (IVIG), leucocyte immunization therapy (LIT), tacrolimus, anti-tumour necrosis factor (anti-TNF) agents, G-CSF, and hydroxychloroquine. Peripheral blood tests for immune parameters and uNK-cell testing are not recommended.

6. Microfluidics can be considered in ICSI for male factor infertility. Artificial sperm activation is recommended for patients with primary or secondary total asthenozoospermia that are not the result of axonemal structure defects, and is currently not recommended for routine clinical use.
Survey suggests that Indian ART specialists have limited uptake of sperm selection add-ons. 74.7 % did not use any, 9.8 % used microfluids/sperm sorting, both in 6.89 %, IMSI/MSOME in 4.4 % , PICSI in 2.14 % and in 1.9 % in all of the above. This aligns with evidence showing no proven routine benefit, though emerging technologies are being explored.

7. Pre-implantation genetic testing for aneuploidy is not recommended for routine clinical use.
Most Indian ART specialists use PGT-A selectively, rarely routinely. 73.8 % sometimes, 23.34 % not used. This aligns with the global evidence that PGT-A does not improve LBR across all patients, but may help in selected groups.

8. Time-lapse imaging is not recommended as a tool to improve live birth rates.
   Survey reflects low adoption of time-lapse imaging by Indian ART specialists due to limited evidence. 79.8 % concluded no benefit, 11.16 % had not used but will offer if available, 8.26 % sometimes use, 0.76 % yes for all. This aligns with current guidance, which does not recommend TLI for routine use.

9. Intrauterine and intraovarian administration of platelet-rich plasma is not recommended in routine clinical practice.
   Indian ART specialists rarely use PRP, despite emerging studies. 76.6 % not used, 13 % used intrauterine, both in 6.27 % and intraovarian in 4.23 %. Evidence highlights promise but insufficient validation, consistent with cautious uptake.

10. Adjuncts (metformin, growth hormone, testosterone, DHEA, aspirin, indomethacin, and sildenafil) before or during ovarian stimulation are not recommended.
    High DHEA use (83.44 %) by Indian ART specialists contrasts with evidence, which does not recommend routine adjuncts. 7.67 % used CoQ, testoserone on 6.6 %, 2.3 % Growth hormone. This suggests reliance on empirical practice rather than strong evidence.

11. Antioxidant therapy is not recommended in ART.
    Antioxidants are widely used by Indian ART specialists 80.79 % for some, 14.79% for all and 4.42 % do not use, though evidence remains uncertain. This highlights a gap where clinical optimism surpasses data strength.

12. Intrauterine administration of hCG and G-CSF is not recommended for routine clinical use in ART.
    Indian survey shows 77.18 % do not use, G-CSF use in 16.54 %, hCG in 6.28 %. Current data show inconsistent benefits, supporting the restrained adoption.

13. Endometrial scratching is currently not recommended for routine clinical use.
    Survey shows frequent but non-routine use by Indian ART specialists. 79.12 % use sometimes, 14.63 % do not use, yes in 3.35 % and rarely in 2.9 %. This diverges from evidence, which concludes that scratching offers little to no benefit, indicating clinical inertia.

14. Stem cell therapy for premature ovarian insufficiency, diminished/poor ovarian reserve, or thin endometrium is not recommended.
Stem cell add-ons are almost never (87.33 %) used by Indian ART specialists, 10.84 % use sometimes, both in 1.07 %. This consistent with evidence cautioning against routine application due to unclear safety and efficacy.

SURVEY QUESTIONNAIRE OF ADD-ONS IN ART

Basic Demographic Details

1. Age
2. Years of Practice
3. Organization Type
   a. Government Organization
   b. Individual Clinic
   c. Corporate Hospital
   d. Others

Survey Questions (Based on PICO Framework):

1. What is your aim for using add-on treatments in IVF
   a. Enhance Live Birth Rates (LBRs)
   b. Expedite time to pregnancy
   c. Mitigate the risk of miscarriage
   d. Not using add-ons
2. Which treatment modalities do you use as add-ons in your clinical practice?
   a. Drugs
   b. Complementary/Alternative Therapies
   c. Equipment
   d. Laboratory Procedures
   e. Surgical Interventions
3. Do you include screening hysteroscopy as an add-on in your clinical practice during ART?
   a. Recurrent Implantation Failure (RIF)
   b. Recurrent Pregnancy Loss (RPL)
   c. Routine Clinical Use
   d. Not Used
   e. Tubal Factor
4. In which cases do you perform endometrial receptivity array (ERA) as add-ons in ART?

a. Routine clinical use
b. RIF
c. RPL
d. Not using

5. Which of the following immunological therapy do you use in your practice?
   a. Intralipid
   b. IVIG
   c. Tacrolimus
   d. LIT
   e. None of the above
6. Which of these Sperm selection techniques do you utilize for clinical use?
   a. PICSI
   b. Microfluidics/sperm sorting
   c. IMSI/MSOME
   d. None of the above
   e. All of the above
   f. A+B
7. Do you offer PGT-A in patients undergoing ART?
   a. Yes for all
   b. Yes sometimes
   c. No
8. Do you offer time lapse imaging (TLI) in patients undergoing ART?
   a. Yes for all
   b. Yes sometimes
   c. No, as it doesn't offer any benefit
   d. Not used but will offer if available
9. Do you offer PRP in patients undergoing ART?
   a. Yes (Intrauterine)
   b. Yes (Intraovarian)
   c. Not used
   d. A +B
10. Which of the following adjuncts is most frequently used during or before ovarian stimulation in POR?
    a. DHEA
    b. Testosterone
    c. Growth Hormone
    d. CoQ 10
11. Do you use antioxidants for women undergoing ART?
    a. Yes for all
    b. Yes for some

   c. No
12. Which of these intrauterine infusion techniques do you use in clinical practice?
   a. G-CSF
   b. hCG
   c. None
13. Do you perform endometrial scratching in patients undergoing ART?
   a. Yes
   b. No
   c. Sometimes
   d. Rarely
14. Do you offer Stem cell treatment in patients undergoing ART?
   a. Yes
   b. Sometimes
   c. Never

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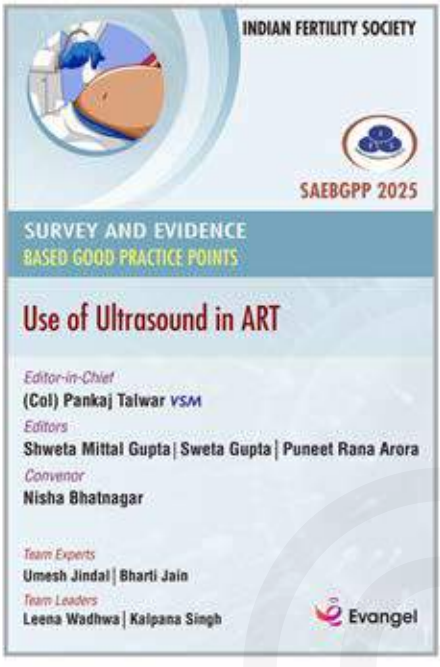
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Prof (Col) Pankaj Talwar *VSM*, is a renowned Fertility Specialist and Director, Talwar Fertility and Men's Clinic, Gurugram, Haryana, India. Recipient of the Vishisht Seva Medal from the President of India, he has performed over 17,000 IVF cycles with a success rate exceeding 60%. A PhD in Embryology and pioneer of ovarian cortex freezing in India, he has established 29 ART units globally and trained over 2,500 gynecologists across 34 countries.

He serves as Academic Director, Clinical ART Program, SEART, Gurugram University; Dean, Department of Clinical Embryology, Shridhar University; Director, i-Ceat Academy of ART; Head, GE Healthcare 3D/4D Ultrasound Training School; and Advisor, DocInfra Solutions.

Author of 10 books and over 100 scientific publications, he is currently the President of the Indian Fertility Society (IFS).

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FLAT NO. 302, 3RD FLOOR, KAILASH BUILDING 26. KASTURBA GANDHI MARG, C.P. NEW DELHI-110001

+91 9899308083 (MS FARAHA KHAN) +91 11 40018184

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