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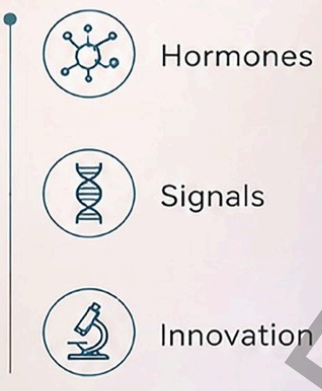
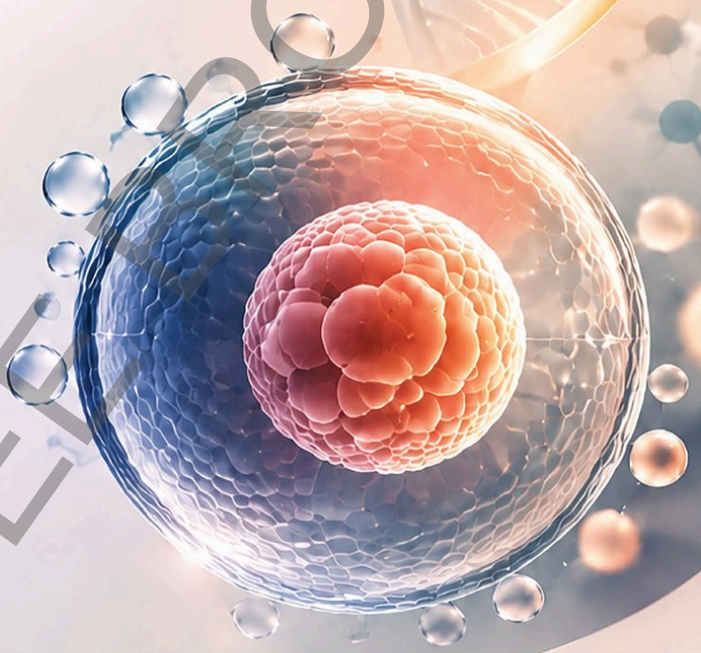
Next Gen Reproductive Medicine

Hormones, Signals and Scientific Innovation





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CHAPTER

20 Advances in Assisted Reproductive Technology and the Modern IVF Laboratory: Current Concepts, Emerging Technologies, and Future Perspectives

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OVERVIEW

Since the birth of the first in vitro fertilization (IVF) baby in 1978, assisted reproductive technology (ART) has evolved into one of the most rapidly advancing fields in medicine. Continuous innovations in ovarian stimulation, embryology, cryobiology, reproductive genetics, and laboratory technologies have significantly improved fertilization, implantation, and live birth rates while enhancing patient safety and treatment efficiency. The modern IVF laboratory has become a highly specialized environment where precision, quality control, and technological advancements are central to achieving optimal reproductive outcomes. This chapter provides a concise overview of the major advances in the ART and the modern IVF laboratory, highlighting current evidence, emerging technologies, and future perspectives that are shaping the practice of reproductive medicine.

LEARNING OBJECTIVES

- Understand the evolution and recent advances in ART and the modern IVF laboratory.
- Describe contemporary approaches to ovarian stimulation, gamete handling, fertilization, and embryo culture.
- Explain recent developments in embryo selection, preimplantation genetic testing (PGT), and cryopreservation.
- Discuss advances in endometrial receptivity assessment and implantation strategies.
- Recognize the applications of artificial intelligence (AI), automation, and quality management in IVF laboratories.
- Appreciate emerging technologies and future directions in the reproductive medicine, along with their clinical significance.

OVARIAN STIMULATION: PERSONALIZATION, SAFETY, AND EMERGING ADVANCES

Controlled ovarian stimulation (COS) is the cornerstone of ART, aiming to recruit multiple mature oocytes while minimizing treatment burden and the risk of ovarian hyperstimulation syndrome (OHSS). Over the past three decades, ovarian stimulation has evolved from standardized treatment protocols to a highly individualized approach based on patient characteristics, ovarian reserve, and predicted ovarian response. This shift has significantly improved treatment safety, optimized oocyte yield, and enhanced cumulative live birth rates.

Gonadotropin Formulations and Biosimilars

The recombinant gonadotropins provide highly purified, consistent, and reliable preparations compared with the traditional

urinary-derived gonadotropins. Recombinant follicle-stimulating hormone (rFSH) is now widely used because of its excellent batch-to-batch consistency, ease of subcutaneous administration, and predictable ovarian response.

An important advancement has been the development of *corifollitropin alfa*, a long-acting rFSH analog capable of stimulating follicular growth for approximately 7 days following a single injection. This significantly reduces the number of injections required during the early stimulation phase and improves patient convenience without compromising treatment outcomes. The availability of *biosimilar FSH preparations* has further expanded access to IVF by reducing treatment costs while maintaining comparable efficacy and safety to the reference recombinant products.

Interest has also grown in *luteinizing hormone (LH) supplementation*. Adequate LH activity is essential for steroidogenesis and normal follicular maturation, giving rise to the concept of the *"LH therapeutic window"*. Supplementation with recombinant LH or human menopausal gonadotropin (hMG) may benefit selected patients, particularly women of advanced maternal age, poor ovarian responders, or those with profound LH suppression during stimulation. However, routine LH supplementation in all IVF patients is not recommended and should be individualized.

Individualized Ovarian Stimulation: "One Protocol does not Fit All"

Before initiating stimulation, every patient should undergo assessment of ovarian reserve using:

- Anti-Müllerian hormone (AMH)
- Antral follicle count (AFC)
- Maternal age
- Body mass index (BMI)
- Previous ovarian response

These biomarkers allow prediction of ovarian response and facilitate individualized gonadotropin dosing aimed at maximizing mature oocyte yield while minimizing the risk of OHSS. Validated prediction models such as the *CONSORT* and *OPTIMIST* algorithms integrate AMH, AFC, age, and body weight to estimate the optimal starting dose of gonadotropins. Increasingly, these models are being incorporated into electronic clinical decision-support systems to standardize stimulation protocols and improve clinical outcomes.

POSEIDON Classification: Redefining Low Prognosis Patients

The management of poor ovarian responders has evolved considerably with the introduction of the *POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number)* classification **(Table 1)**. Unlike the Bologna criteria, which classify all poor responders as a single group, the POSEIDON system incorporates age, ovarian reserve markers (AMH and AFC), and previous ovarian response to better estimate the likelihood of obtaining at least one euploid embryo. The POSEIDON classification enables more realistic prognosis and personalized treatment strategies, particularly for women undergoing IVF.

GnRH Antagonist Protocols and Prevention of OHSS

The transition from conventional long gonadotropin-releasing hormone (GnRH) agonist protocols to *GnRH antagonist protocols* represents one of the most important advances in ovarian stimulation.

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TABLE 1: POSEIDON classification.

Group	*Characteristics*	*Treatment goal*
Group 1	<35 years, normal ovarian reserve, and unexpected poor/suboptimal response	Increase mature oocyte yield
Group 2	≥35 years, normal ovarian reserve, and unexpected poor/suboptimal response	Maximize euploid embryo number
Group 3	<35 years and low AMH/AFC	Optimize ovarian stimulation
Group 4	≥35 years and low AMH/AFC	Individualized counseling and fertility planning

(AFC: antral follicle count; AMH: anti-Müllerian hormone)

Antagonists provide rapid and reversible suppression of premature LH surges, resulting in shorter treatment duration, lower gonadotropin requirements, and greater patient convenience.

Advantage of antagonist protocols are as follows:

- Permit final oocyte maturation to be triggered using a *GnRH agonist*, producing a physiological endogenous LH surge instead of prolonged human chorionic gonadotropin (hCG) exposure.
- When combined with *elective embryo cryopreservation (freeze-all strategy)*, GnRH agonist triggering has dramatically reduced the incidence of severe OHSS, transforming this once life-threatening complication into a largely preventable condition.
- The combination of GnRH antagonist stimulation, GnRH agonist trigger, and freeze-all strategy has reduced severe OHSS to exceptionally low levels in experienced IVF centers, with reported rates of <0.1%.

Progestin-primed Ovarian Stimulation

Progestin-primed ovarian stimulation (PPOS) is a relatively recent addition to ovarian stimulation protocols in IVF. Unlike conventional protocols that use GnRH antagonists to prevent a premature LH surge, PPOS uses oral progestins such as medroxyprogesterone acetate or dydrogesterone during stimulation to suppress ovulation. Oral medication replaces daily antagonist injections, making treatment more patient-friendly, less expensive, and easier to administer. Clinical studies have shown that PPOS achieves comparable oocyte yield, embryo development, and pregnancy outcomes to conventional antagonist protocols.

Since progesterone exposure during stimulation adversely affects endometrial receptivity, fresh embryo transfer is not possible, and all embryos are cryopreserved for subsequent frozen embryo transfer (FET). Therefore, PPOS is particularly useful in planned freeze-all cycles, PGT cycles, fertility preservation, oocyte donation programs, and patients at high risk of OHSS.

Kisspeptin: A Novel Ovulation Trigger

Kisspeptin is an endogenous hypothalamic neuropeptide that stimulates physiological GnRH release and subsequent endogenous LH secretion. Unlike hCG, kisspeptin induces a shorter and more physiological LH surge, thereby markedly reducing the

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risk of OHSS while maintaining satisfactory oocyte maturation. Early clinical studies have demonstrated encouraging fertilization and pregnancy outcomes, particularly in women at high risk of OHSS, including those with polycystic ovary syndrome (PCOS). Although promising, kisspeptin-triggered oocyte maturation remains an emerging strategy and is not yet routinely adopted in clinical practice.

Follicular and Luteal Phase Stimulation

Conventional ovarian stimulation is initiated during the early follicular phase. However, the recognition that multiple waves of follicular recruitment occur during a menstrual cycle has challenged this traditional concept. *Luteal phase stimulation* has demonstrated comparable oocyte maturity and developmental competence to follicular phase stimulation and is increasingly used for fertility preservation and poor ovarian responders **(Table 2)**.

Double Ovarian Stimulation

Double ovarian stimulation (DuoStim) involves two consecutive ovarian stimulation cycles within the same menstrual cycle—one during the follicular phase followed by another during the luteal phase. This strategy is particularly beneficial for women with diminished ovarian reserve, poor ovarian response, advanced maternal age, or those requiring urgent fertility preservation before gonadotoxic cancer treatment. By exploiting multiple follicular recruitment waves, DuoStim increases the total number of retrieved oocytes within a shorter period. Although DuoStim consistently improves cumulative oocyte yield, evidence regarding improvements in live birth rates remains limited, and patient selection remains essential.

Pharmacogenomics and Precision Reproductive Medicine

Pharmacogenomics represents an emerging frontier in ovarian stimulation. Genetic polymorphisms affecting gonadotropin receptors, particularly the *FSH receptor (FSHR) Asn680Ser polymorphism*, influence ovarian sensitivity to exogenous FSH and may partly explain variability in ovarian response among women with similar ovarian reserve. Although genotype-guided ovarian stimulation is not currently recommended for the routine clinical practice, ongoing studies suggest that pharmacogenomic-guided dosing may improve the ovarian response while reducing cycle cancellation and excessive stimulation. AI and

TABLE 2: Follicular versus luteal phase stimulation.

Feature	*Follicular phase*	*Luteal phase*
Initiation	Day 2–3 of menstrual cycle	After ovulation
Primary indication	Routine in vitro fertilization (IVF)	Fertility preservation, poor responders, and double ovarian stimulation (DuoStim)
Oocyte competence	High	Comparable to follicular stimulation
Fresh embryo transfer	Possible	Usually not performed
Freeze-all strategy	Optional	Usually required

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TABLE 3: Summary of major advances in ovarian stimulation.

Major advances	*Clinical impact*
Recombinant FSH	Consistent dosing and improved patient convenience
Corifollitropin alfa	Reduced injection burden with sustained follicular stimulation
Biosimilar gonadotropins	Improved affordability and wider access to IVF
GnRH antagonist protocols	Shorter stimulation and reduced OHSS risk
Progestin-primed ovarian stimulation (PPOS)	Patient-friendly oral alternative for pituitary suppression in freeze-all IVF cycles
GnRH agonist trigger	Near elimination of severe OHSS in high responders
AMH/AFC-guided dosing	Personalized stimulation with optimized oocyte yield
POSEIDON classification	Better stratification and management of low-prognosis patients
Follicular and luteal phase stimulation	Greater flexibility and expanded fertility preservation options
DuoStim	Increased cumulative oocyte retrieval in poor responders
Kisspeptin trigger	Emerging physiological trigger with excellent safety profile
Pharmacogenomics (FSHR genotyping)	Potential future genotype-guided ovarian stimulation
AI-assisted stimulation planning	Emerging precision medicine approach

(AFC: antral follicle count; AI: artificial intelligence; AMH: anti-Müllerian hormone; DuoStim: double ovarian stimulation; FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; IVF: in vitro fertilization; OHSS: ovarian hyperstimulation syndrome; POSEIDON: Patient-Oriented Strategies Encompassing Individualized Oocyte Number)

machine-learning algorithms are expected to complement pharmacogenomics by integrating clinical, hormonal, ultrasonographic, and genetic data to develop highly individualized stimulation protocols. Summary of major advances in the ovarian stimulation are mentioned in **Table 3**.

Future Directions

Emerging technologies are expected to further personalize ovarian stimulation. These include:

- AI-based stimulation planning
- Machine learning prediction of ovarian response
- Pharmacogenomic-guided gonadotropin dosing
- Digital monitoring of follicular growth
- Biomarker-based prediction of embryo yield
- Integration of ovarian reserve biomarkers with AI-driven clinical decision support

Key Clinical Messages

- Ovarian stimulation has evolved from standardized protocols to personalized treatment based on ovarian reserve, age, and predicted ovarian response.
- GnRH antagonist protocols combined with GnRH agonist triggering and freeze-all strategies have dramatically reduced the incidence of severe OHSS.
- The POSEIDON classification provides a clinically meaningful approach to managing low-prognosis IVF patients.

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- DuoStim and luteal phase stimulation have expanded treatment options for poor responders and women requiring urgent fertility preservation.
- Kisspeptin represents a promising physiological ovulation trigger, while pharmacogenomics and AI are expected to further personalize ovarian stimulation in the future.
- AMH predicts the quantity of oocytes retrieved but not their quality. Maternal age remains the strongest predictor of embryo euploidy and live birth.
- Recombinant FSH remains the first-line gonadotropin for most IVF cycles, while LH supplementation should be reserved for carefully selected women rather than used routinely.

RECENT ADVANCES IN LUTEAL PHASE SUPPORT

Luteal phase support (LPS) remains an essential component of ART, particularly following COS and FET cycles, where endogenous progesterone production may be inadequate. Traditionally, a uniform approach using vaginal progesterone was employed for most patients. However, recent advances have shifted practice toward a more individualized strategy **(Table 4)**. One of the most important developments has been the recognition of the role of serum progesterone monitoring, particularly in hormone replacement therapy (HRT)-FET cycles. Measurement of progesterone levels before or around the time of embryo transfer allows identification of patients with inadequate luteal support and enables timely rescue supplementation.

In addition, newer formulations such as oral dydrogesterone and subcutaneous progesterone have improved patient convenience and compliance while providing pregnancy outcomes comparable to conventional vaginal or intramuscular preparations. Increasingly, clinicians are adopting personalized LPS, tailoring the route, dose, and duration of progesterone according to patient characteristics, treatment protocol, and hormonal profile. Overall, the focus of modern LPS has shifted from a standardized approach to a more individualized and evidence-based strategy aimed at optimizing implantation and live birth rates while improving patient comfort.

GAMETE ASSESSMENT AND OPTIMIZATION

Successful ART depends not only on obtaining an adequate number of gametes but also on selecting those with the highest developmental competence. Conventional assessment relies largely on morphological evaluation; however, morphology alone cannot accurately predict fertilization potential, embryo quality, or live birth. Recent advances in imaging technologies, sperm selection techniques, molecular diagnostics, and AI have enabled a more objective and functional assessment of both oocytes and sperm, improving laboratory decision-making and supporting personalized treatment strategies.

Oocyte Quality Assessment and Optimization

The human oocyte is the largest and most metabolically active cell in the body, containing not only the maternal genome but also the organelles, messenger ribonucleic acids (RNAs), proteins, and mitochondria required to support fertilization and early embryonic development until activation of the embryonic genome. Consequently, oocyte quality is one of the strongest determinants

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TABLE 4: Summary of recent advances in luteal phase support.

Advance	*Principle*	*Clinical impact*	*Current status*
Individualized progesterone supplementation	Tailoring luteal support according to serum progesterone levels	Optimizes implantation and live birth rates, particularly in HRT-FET cycles	Increasingly adopted in clinical practice
Serum progesterone monitoring	Measurement of progesterone during the luteal phase or on embryo transfer day	Identifies patients requiring additional luteal support	Emerging standard of care, especially in artificial FET cycles
Rescue progesterone supplementation	Addition of IM, SC, or vaginal progesterone in patients with low serum levels	Improves outcomes in patients with inadequate luteal progesterone exposure	Increasing clinical use
Subcutaneous progesterone	Aqueous progesterone administered subcutaneously	Provides effective luteal support with improved patient convenience and reduced injection pain	Established clinical alternative
Oral dydrogesterone	Oral progestogen with high receptor selectivity and bioavailability	Comparable pregnancy outcomes to vaginal progesterone with better patient acceptability	Widely used
Combination progesterone regimens	Use of multiple progesterone routes (oral, vaginal, IM, or SC)	Enhances luteal support in selected high-risk patients	Common in selected clinical scenarios
GnRH agonist luteal support	Administration of GnRH agonist during the luteal phase to stimulate endogenous LH secretion	May improve corpus luteum function and implantation	Selective clinical use
Personalized luteal phase support (pLPS)	Individualization of route, dose, and duration according to patient and cycle characteristics	Precision medicine approach to optimize reproductive outcomes	Emerging strategy
Luteal support optimization in modified natural FET cycles	Tailoring progesterone supplementation according to corpus luteum function	Avoids unnecessary treatment while maintaining pregnancy outcomes	Area of active research
AI-assisted luteal support algorithms	Use of predictive models incorporating hormonal and clinical variables	Potential future individualized treatment planning	Experimental
Biomarker-guided luteal support	Use of hormonal, molecular, or endometrial biomarkers to guide treatment	May identify patients requiring intensified support	Research stage
Long-acting progesterone formulations	Development of sustained-release progesterone preparations	Reduced treatment burden and improved compliance	Emerging technology

(AI: artificial intelligence; FET: frozen embryo transfer; GnRH: gonadotropin-releasing hormone; HRT: hormone replacement therapy; IM: intramuscular; LH: luteinizing hormone; SC: subcutaneous

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of IVF success. Usually, embryologists assess oocytes at the metaphase II (MII) stage before intracytoplasmic sperm injection (ICSI). Morphological evaluation includes assessment of:

- First polar body morphology
- Zona pellucida thickness and regularity
- Perivitelline space
- Cytoplasmic appearance (granularity, inclusions, and vacuoles)
- Oocyte shape and size

Although these features provide valuable information regarding oocyte maturity, several studies have demonstrated that morphology alone has limited ability to predict fertilization, embryo development, or live birth. To overcome these limitations, several advanced technologies have been introduced **(Table 5)**.

Spindle Imaging

The meiotic spindle plays a critical role in chromosome segregation during fertilization. Polarized light microscopy (PolScope® and Oosight®) allows noninvasive visualization of the spindle without damaging the oocyte. Studies have shown that the presence of a well-organized spindle is associated with higher fertilization rates, better embryo quality, and lower risk of chromosomal abnormalities. Some IVF laboratories use spindle imaging to optimize the timing and orientation of ICSI.

Polar Body Assessment

Polar body biopsy followed by next-generation sequencing (NGS) can assess maternal meiotic chromosomal errors before fertilization. Although technically feasible, its clinical use remains limited because it cannot detect paternal chromosomal abnormalities or mitotic errors that occur after fertilization.

Assessment of Cytoplasmic Maturation

Nuclear maturity (MII stage) does not always reflect cytoplasmic competence. Emerging research focuses on evaluating mitochondrial function, metabolic activity, and intracellular biomarkers to identify oocytes with greater developmental potential. Although promising, these techniques remain largely investigational.

Artificial Intelligence in Oocyte Grading

Artificial intelligence, particularly convolutional neural network (CNN)-based image analysis, is emerging as a valuable adjunct in oocyte assessment. AI algorithms analyze microscopic images and objectively evaluate multiple morphological characteristics with greater consistency than conventional visual assessment.

These systems evaluate:

- Zona pellucida thickness and symmetry
- Cytoplasmic texture and granularity
- Meiotic spindle visualization
- Cytoplasmic vacuoles
- First polar body morphology

AI-assisted grading reduces interobserver variability and improves reproducibility of oocyte assessment. Although early studies are encouraging, AI currently serves as a decision-support tool rather than a replacement for experienced embryologists.

Clinical Pearl

Oocyte morphology should always be interpreted together with maternal age, ovarian reserve, and clinical history. A morphologically normal oocyte does not necessarily indicate chromosomal competence.

Advanced Sperm Selection Technologies

Since the introduction of ICSI in 1992, fertilization rates in severe male factor

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TABLE 5: Summary of the recent advances in oocyte assessment.

Technology	*Principle*	*Clinical utility*	*Current status*
Conventional morphology assessment	Evaluation of oocyte maturity, cytoplasmic appearance, zona pellucida, and polar body morphology	Selection of mature (MII) oocytes for intracytoplasmic sperm injection (ICSI)	Current standard of care
Polarized light microscopy (PolScope)	Visualization of meiotic spindle and zona pellucida birefringence using polarized light	Assessment of nuclear maturity and optimal timing of ICSI	Available in selected centers and limited routine use
Time-lapse imaging of oocyte maturation	Continuous monitoring of meiotic events without disturbing culture conditions	Dynamic assessment of maturation kinetics and developmental competence	Emerging clinical application
Artificial intelligence (AI)-based image analysis	Machine learning algorithms analyze oocyte morphology and developmental features	Objective prediction of oocyte quality and embryo potential	Experimental to early clinical adoption
Cumulus cell transcriptomics	Analysis of gene expression in surrounding cumulus cells	Indirect molecular assessment of oocyte competence	Primarily research use
Follicular fluid metabolomics	Identification of metabolic biomarkers associated with oocyte competence	Prediction of developmental potential and implantation outcomes	Research stage
Mitochondrial function assessment	Evaluation of mitochondrial activity and cellular energy production	Assessment of oocyte quality and aging-related decline	Research stage
Hyperspectral imaging	Analysis of endogenous metabolic signatures using multiple wavelengths of light	Noninvasive prediction of oocyte viability and competence	Experimental
Fluorescence lifetime imaging microscopy (FLIM)	Measurement of cellular metabolic activity through endogenous fluorophores	Assessment of mitochondrial metabolism and oocyte health	Experimental
Raman spectroscopy	Label-free biochemical characterization using light scattering patterns	Evaluation of intracellular biochemical composition	Experimental
Polar body genetic analysis	Chromosomal assessment through analysis of the polar body	Detection of maternal aneuploidy in selected cases	Limited clinical application
Proteomics of follicular fluid or cumulus cells	Identification of protein biomarkers associated with developmental competence	Potential biomarker-based oocyte selection	Research stage
Holotomography and quantitative phase imaging	Three-dimensional label-free visualization of intracellular structures	Detailed assessment of organelle distribution and morphology	Experimental
Multiomics integrated with AI	Integration of imaging, genomics, transcriptomics, proteomics, and metabolomics data	Future precision approach for individualized oocyte selection	Future technology under development

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TABLE 6: Advanced sperm selection techniques.

Technique	*Principle*	*Advantages*	*Limitations*
PICSI	Hyaluronic acid binding	Selects mature sperm with better chromatin integrity	No consistent improvement in live birth
IMSI	Ultra-high magnification microscopy	Detects subtle nuclear abnormalities	Time-consuming and limited evidence
MACS	Removal of apoptotic sperm	Improves sperm viability	Benefit mainly in selected patients
Microfluidic selection	Physiological migration through microchannels	Lower ROS, reduced DNA fragmentation, no centrifugation	Increasing clinical use and long-term evidence evolving

(DNA: deoxyribonucleic acid; IMSI: intracytoplasmic morphologically selected sperm injection; MACS: magnetic-activated cell sorting; PICSI: physiological intracytoplasmic sperm injection; ROS: reactive oxygen species)

infertility have improved dramatically. However, conventional sperm selection relies primarily on motility and morphology, which do not always reflect chromatin integrity, deoxyribonucleic acid (DNA) quality, or functional competence. Consequently, several advanced sperm selection techniques have been developed to identify sperm with superior fertilizing potential **(Table 6)**.

Physiological Intracytoplasmic Sperm Injection

Physiological intracytoplasmic sperm injection (PICSI) utilizes hyaluronic acid (HA) binding to select mature spermatozoa. Mature sperm expressing HA receptors generally exhibit lower DNA fragmentation, better chromatin packaging, and greater nuclear maturity than nonbinding sperm. Although PICSI may improve selected laboratory outcomes in specific patient populations, high-quality randomized controlled trials have not consistently demonstrated improvements in cumulative live birth rates. Therefore, its routine use is not universally recommended, and patient selection remains important.

Intracytoplasmic Morphologically Selected Sperm Injection

Intracytoplasmic morphologically selected sperm injection (IMSI) employs ultra-high magnification microscopy (up to 6,000–8,000×) to identify subtle sperm nuclear vacuoles that may be associated with DNA damage and poor embryo development. Despite promising results in selected couples with recurrent implantation failure (RIF) or severe teratozoospermia, current evidence does not support routine IMSI for all IVF patients.

Magnetic-activated Cell Sorting

Magnetic-activated cell sorting (MACS) separates viable sperm from apoptotic sperm by removing cells expressing phosphatidylserine using annexin V-coated magnetic beads. Several studies have reported improvements in embryo quality and clinical pregnancy in selected patient groups. However, consistent improvements in cumulative live birth rates have not been demonstrated and routine clinical use remains controversial.

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Microfluidic Sperm Selection

Microfluidic sperm selection is one of the most promising recent developments in male infertility treatment. These "lab-on-a-chip" devices mimic the physiological environment of the female reproductive tract, allowing highly motile sperm to migrate through microchannels without centrifugation. Compared with conventional density-gradient centrifugation, microfluidic devices reduce oxidative stress, minimize reactive oxygen species (ROS) generation, and enrich sperm with lower DNA fragmentation and better mitochondrial function. Although clinical evidence continues to evolve, microfluidic technology is increasingly being incorporated into IVF laboratories, particularly for men with elevated sperm DNA fragmentation (SDF).

Clinical Pearl

Among currently available sperm selection methods, microfluidic sperm sorting shows considerable promise because it selects sperm under physiological conditions while minimizing oxidative stress.

Sperm DNA Fragmentation Testing

Routine semen analysis provides limited information regarding sperm genomic integrity. Assessment of SDF has therefore become an important adjunctive investigation in couples with recurrent IVF failure, recurrent pregnancy loss, unexplained infertility, and severe male factor infertility. A high DNA fragmentation index (DFI), particularly a *DFI >25–30%*, has been associated with reduced fertilization, impaired blastocyst development, recurrent pregnancy loss, and lower pregnancy rates **(Table 7)**. In selected couples with persistently elevated DNA fragmentation despite medical management, use of surgically retrieved testicular sperm for ICSI may improve reproductive outcomes.

The four most used assays **(Table 8)** include:

1. *Terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay:* Direct detection of DNA strand breaks
2. *Sperm chromatin structure assay (SCSA):* Measurement of DFI
3. *Sperm chromatin dispersion (SCD) test:* Halo-based assessment of DNA integrity

TABLE 7: Clinical interpretation of sperm DNA fragmentation.

DNA fragmentation index (DFI)	*Interpretation*	*Suggested clinical approach*
<15%	Excellent DNA integrity	Routine assisted reproductive technology (ART) management
15–25%	Mild DNA damage	Lifestyle modification, antioxidant therapy, and treat underlying causes
25–30%	Moderate DNA fragmentation	Consider advanced sperm selection (e.g., microfluidics); repeat testing if indicated
>30%	Severe DNA fragmentation	Evaluate for varicocele, oxidative stress, and infection; lifestyle modification, antioxidant therapy, treat underlying causes, consider advanced sperm selection, and consider testicular sperm retrieval [testicular sperm extraction (TESE)] for selected intracytoplasmic sperm injection (ICSI) cases

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TABLE 8: Comparison of common sperm DNA fragmentation tests.

Test	*Principle*	*Measures*	*Advantages*	*Limitations*	*Clinical utility*
Terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL)	Labels DNA strand breaks using fluorescent nucleotides	Direct DNA fragmentation	High sensitivity and specificity and widely validated	Requires specialized equipment and technical expertise	Recurrent implantation failure (RIF), recurrent pregnancy loss (RPL), unexplained infertility, and male factor infertility
Sperm chromatin structure assay (SCSA)	Flow cytometry using acridine orange staining	DNA fragmentation index (DFI) and high DNA stainability (HDS)	Highly reproducible; standardized; and rapid analysis	Expensive instrumentation and requires flow cytometer	Excellent prognostic test; DFI >25–30% associated with poorer assisted reproductive technology (ART) outcomes
Sperm chromatin dispersion (SCD) test (halo test)	Acid denaturation followed by halo formation around intact DNA	DNA fragmentation	Simple, inexpensive, easy to perform	Observer-dependent; semi-quantitative	Routine clinical laboratories and infertility work-up
COMET assay (single-cell gel electrophoresis)	Electrophoretic migration of fragmented DNA forming a "comet tail"	Single- and double-strand DNA breaks	Highly sensitive; detects extent and type of DNA damage	Technically demanding; lacks standardization; mainly research use	Detailed evaluation of sperm DNA damage, especially in research settings

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4. *COMET assay:* Sensitive single-cell electrophoresis technique for quantifying DNA damage

Clinical Practice Points

- Conventional morphology remains the cornerstone of gamete assessment but has limited predictive value for embryo competence.
- AI-assisted oocyte grading improves objectivity and reproducibility but currently complements rather than replaces embryologist expertise.
- PICSI, IMSI, and MACS may improve selected laboratory parameters in specific clinical situations; however, routine use is not recommended because consistent improvements in cumulative live birth have not been demonstrated.
- Microfluidic sperm selection represents one of the most promising innovations in sperm preparation owing to its physiological and noninvasive approach.
- SDF testing should not replace conventional semen analysis but should be used as a complementary test in selected patients, particularly those with recurrent IVF/ICSI failure, recurrent pregnancy loss, unexplained infertility, varicocele, advanced paternal age, or persistently abnormal semen parameters.

FERTILIZATION AND EMBRYO CULTURE SYSTEMS

The IVF laboratory provides the environment in which fertilization, early embryonic development, and blastocyst formation occur. Unlike natural conception, where embryos develop within the protected environment of the female reproductive tract, embryos cultured in vitro are highly susceptible to fluctuations in temperature, pH, osmolality, oxygen concentration, light exposure, and volatile organic compounds (VOCs). Even minor deviations from optimal conditions may adversely affect embryo metabolism, implantation potential, and long-term developmental outcomes. Consequently, continuous refinement of fertilization techniques, embryo culture systems, and laboratory equipment has become central to improving IVF success.

Advances in Fertilization Techniques

Since its introduction in 1992, ICSI has transformed the management of male factor infertility and has become an integral part of modern ART. In conventional ICSI, a single sperm is immobilized and injected directly into the cytoplasm of a mature oocyte using a fine glass micropipette. This technique bypasses many of the barriers to fertilization and has enabled successful treatment of conditions that were previously considered untreatable. Recent innovations in ICSI have focused on minimizing oocyte trauma, improving procedural precision, and reducing operator-dependent variability **(Table 9)**.

Piezo-ICSI

Piezo-assisted ICSI uses brief piezoelectric pulses to facilitate penetration of the zona pellucida and oolemma with minimal mechanical force. Compared with conventional ICSI, this technique causes less oocyte deformation and reduces cytoplasmic injury during injection. Early studies suggest improved oocyte survival and potentially better embryo development, particularly in fragile oocytes and difficult injection cases. Although widely adopted in some regions, particularly in East Asia, its routine clinical use is still expanding globally.

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TABLE 9: Summary of advances in fertilization and embryo culture.

Technology	*Principle*	*Clinical utility*	*Current status*
Intracytoplasmic sperm injection (ICSI)	Direct injection of a single sperm into the oocyte cytoplasm	Overcomes severe male factor infertility and fertilization failure	Standard clinical practice
Physiological ICSI (PICSI)	Selection of mature sperm based on hyaluronan binding ability	Potential selection of genetically mature sperm with lower DNA fragmentation	Selective clinical use
Intracytoplasmic morphologically selected sperm injection (IMSI)	High-magnification sperm selection based on detailed morphology	May benefit selected cases of recurrent ICSI failure or severe male factor infertility	Limited clinical use
Artificial oocyte activation (AOA)	Calcium ionophore-induced activation following ICSI	Improves fertilization in globozoospermia and previous fertilization failure	Established in selected indications
Microfluidic sperm selection	Mimics natural sperm migration to select highly motile sperm with lower DNA damage	Improved sperm quality for in vitro fertilization (IVF) and ICSI	Increasing clinical adoption
Sequential culture media	Culture media composition changes according to embryo developmental stage	Supports embryo development from cleavage to blastocyst stage	Widely used
Single-step culture media	Continuous culture without media change throughout embryo development	Reduced embryo handling and stable culture environment	Widely used
Low oxygen embryo culture (5% O_2)	Mimics physiological oxygen concentration in the female reproductive tract	Improved blastocyst development and embryo quality	Current standard practice
Time-lapse incubation (TLI) systems	Continuous embryo monitoring without removing embryos from incubator	Stable culture conditions and morphokinetic assessment	Widely adopted
Artificial intelligence (AI)-assisted embryo assessment	Machine learning analysis of static and time-lapse images	Objective embryo grading and implantation prediction	Early clinical adoption
Automated embryo annotation	Computer vision-based developmental stage identification	Improved standardization and reduced observer variability	Emerging technology
Microfluidic embryo culture systems	Dynamic culture environment mimicking in vivo conditions	Potential improvement in embryo development and implantation	Experimental
Noninvasive embryo metabolomics	Analysis of spent culture media metabolites	Prediction of embryo competence without biopsy	Research stage
AI-integrated embryology laboratories	Integration of AI, automation, and laboratory analytics	Standardization and optimization of IVF laboratory processes	Future technology

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Robotic and Semiautomated ICSI

Advances in AI, computer vision, and robotic micromanipulation have led to the development of semiautomated ICSI systems. These platforms assist embryologists by standardizing critical procedural steps such as sperm immobilization, pipette positioning, injection angle, and penetration depth. By reducing the technical variability, robotic systems may improve reproducibility and laboratory efficiency. At present, these technologies remain largely confined to research settings and highly specialized IVF laboratories. Nevertheless, they represent an important step toward automation and standardization in clinical embryology.

Advances in Embryo Culture Media

Embryo culture media have evolved considerably over the past three decades as our understanding of embryo physiology and metabolism has improved. Human embryos have changing nutritional requirements throughout development. During the cleavage stage, embryos rely predominantly on pyruvate and amino acids for energy production, whereas glucose utilization increases during blastocyst formation. Modern culture systems are designed to accommodate these changing metabolic needs and generally follow one of two approaches:

1. Sequential media, in which embryos are transferred to different media formulations as development progresses.
2. Single-step media, which contain all required nutrients throughout culture and eliminate the need for media replacement.

Large randomized trials and systematic reviews have not demonstrated clear superiority of one strategy over the other. Consequently, most IVF laboratories select the approach that best aligns with their laboratory workflow, culture philosophy, and quality assurance practices. Contemporary culture media frequently include additional components such as amino acids, antioxidants, hyaluronan, chelating agents, and recombinant human albumin to optimize embryo development and reduce oxidative stress.

Physiological Oxygen Tension

One of the most important advances in embryo culture has been the widespread adoption of low oxygen culture conditions (approximately 5% oxygen), which more closely resemble the environment within the fallopian tube and uterus. Reduced oxygen tension decreases the production of ROS and oxidative stress, contributing to improved blastocyst development, embryo quality, and implantation potential. Low oxygen culture is now considered standard practice in many IVF laboratories worldwide.

Benchtop Incubators: Enhancing Culture Stability

The introduction of benchtop incubators has significantly improved the stability of embryo culture conditions. Unlike conventional front-opening incubators, which expose all embryos whenever the door is opened, benchtop systems use individual culture chambers that isolate embryos from unnecessary environmental fluctuations. This design offers several important advantages:

- Improved temperature stability during handling
- Reduced pH fluctuations
- Faster recovery of gas concentrations following chamber opening
- Lower exposure to VOCs
- Reduced risk of contamination

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- Improved laboratory workflow and efficiency

Many benchtop incubators also incorporate time-lapse imaging technology, allowing continuous embryo monitoring without the need to remove embryos from the controlled culture environment.

Time-lapse Incubation and Morphokinetic Assessment

Time-lapse incubation represents one of the most important technological advances in modern embryology laboratories. By integrating high-resolution imaging within the incubator, these systems allow continuous monitoring of embryo development without disturbing culture conditions. Images are captured at regular intervals, generating a complete developmental record from fertilization through blastocyst formation. Commonly used platforms include EmbryoScope®, GERI®, and MIRI® time-lapse. Continuous monitoring enables assessment of important morphokinetic events such as:

- Pronuclear fading
- Timing of cleavage divisions
- Morula compaction
- Blastocyst formation
- Hatching dynamics

Time-lapse systems can also identify abnormal developmental patterns that may be missed during routine static observations, including direct cleavage, reverse cleavage, and asynchronous blastomere division. Recognition of these events may assist in embryo selection and prioritization.

Artificial Intelligence and Embryo Selection

The integration of AI into time-lapse systems represents the next major step in embryo assessment. Algorithms such as *KIDScore*™ and *iDAScore*® analyze large numbers of embryo images and developmental patterns to generate objective implantation scores and embryo rankings. These tools have the potential to reduce interobserver variability and improve consistency in embryo selection. However, current evidence suggests that although time-lapse imaging and AI-assisted assessment enhance workflow and provide valuable developmental information, they have not consistently demonstrated improved live birth rates in unselected IVF populations.

Consequently, the use of time-lapse technology should be guided by laboratory infrastructure, patient characteristics, and clinical objectives rather than by expectations of universally improved outcomes. Overall, the future of embryo culture is moving toward increasingly physiological culture conditions, reduced embryo handling, and data-driven embryo selection through the integration of advanced imaging, AI, and laboratory automation.

Clinical Practice Points

- Maintaining stable culture conditions remains one of the most important determinants of successful embryo development in IVF laboratories. In embryo culture, environmental stability is often more important than changes in culture media composition. Even minor temperature fluctuations may adversely affect spindle integrity and embryo development.
- Low oxygen culture (5% O_2) more closely replicates the physiological environment of the fallopian tube and uterus and is associated with improved blastocyst development and embryo quality.
- Benchtop incubators minimize fluctuations in temperature, pH, and gas concentrations and have become the preferred

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culture system in many modern IVF laboratories.

- Time-lapse imaging provides valuable morphokinetic information and improves laboratory workflow and embryo assessment; however, consistent improvements in live birth rates have not been demonstrated across all patient populations.
- AI currently serves as a decision-support tool that enhances embryo selection and standardization but does not replace clinical judgment or embryologist expertise.

Preimplantation Genetic Testing: Current Practice and Emerging Technologies

Preimplantation genetic testing (PGT) has become one of the most significant advances in ART, enabling genetic evaluation of embryos before embryo transfer **(Table 10)**. The primary objective is to improve reproductive outcomes by selecting embryos with normal chromosomal complements or those free from specific inherited genetic disorders. By reducing the transfer of affected or chromosomally abnormal embryos, PGT has improved implantation rates in selected patients, reduced miscarriage rates associated with aneuploidy and minimized the risk of transmitting serious genetic diseases. Based on the indication, PGT is classified into three major categories:

- *PGT-A*—preimplantation genetic testing for aneuploidy (selection of chromosomally normal embryos)
- *PGT-M*—preimplantation genetic testing for monogenic (single-gene) disorders. Initially developed for a limited number of inherited disorders, PGT-M is now routinely used for hundreds of monogenic diseases, including cystic fibrosis, β-thalassemia, sickle cell disease, spinal muscular atrophy, Huntington disease, and BRCA1 and BRCA2-associated hereditary cancer syndromes. Modern single nucleotide polymorphism (SNP)-based haplotyping and linkage analysis have simplified assay development, making testing feasible for nearly any inherited disorder when appropriate family DNA is available.

TABLE 10: Recent advances in preimplantation genetic testing.

Technology	*Advantages*	*Current status*
Trophectoderm biopsy	High DNA yield; minimal embryo damage	Standard practice
Next-generation sequencing (NGS)	High-resolution chromosome analysis	Standard platform
Mosaic embryo reporting	Improved embryo utilization	Selected clinical use
Noninvasive preimplantation genetic testing for aneuploidy (PGT-A)	Avoids embryo biopsy	Investigational
Long-read sequencing	Better detection of structural variants	Emerging
Whole-genome sequencing	Comprehensive genomic analysis	Under investigation
Polygenic risk scoring [preimplantation genetic testing for polygenic risk (PGT-P)]	Estimates complex disease susceptibility	Investigational

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- *PGT-SR*—preimplantation genetic testing for structural chromosomal rearrangements is indicated for couples carrying balanced reciprocal or Robertsonian translocations and other structural chromosomal rearrangements. By identifying embryos with balanced or normal chromosomal complements, PGT-SR reduces miscarriage risk and improves reproductive outcomes.

Embryo Biopsy Techniques

Embryo biopsy has evolved considerably over the past two decades. Earlier cleavage-stage biopsy, performed on day 3 embryos by removing a single blastomere, has largely been abandoned because of concerns regarding embryo viability and diagnostic accuracy. Today, trophectoderm (TE) biopsy at the blastocyst stage is considered the standard technique. Approximately 5–10 cells are removed from the TE, which later forms the placenta, while the inner cell mass destined to become the fetus remains undisturbed. This approach provides sufficient DNA for reliable genetic analysis with minimal impact on embryo developmental potential. The widespread adoption of vitrification and freeze-all strategies has further improved PGT workflows. Following biopsy, embryos are cryopreserved while genetic analysis is completed, allowing transfer of a selected embryo in a subsequent optimized cycle.

Next-generation Sequencing and Modern Genetic Platforms

The introduction of NGS has transformed PGT. Compared with the earlier technologies such as fluorescence in situ hybridization (FISH), array comparative genomic hybridization (aCGH), and SNP arrays, NGS offers greater resolution and improved sensitivity. Following whole-genome amplification of DNA obtained from TE biopsy, low-pass NGS generates a comprehensive chromosomal copy number profile, enabling embryos to be classified as:

- Euploid
- Aneuploid
- Mosaic

Next-generation sequencing has become the preferred platform for PGT-A because it accurately detects whole-chromosome abnormalities and many segmental chromosomal imbalances.

Mosaic Embryos

Embryonic mosaicism, characterized by the coexistence of euploid and aneuploid cell lines within the same embryo, remains one of the most challenging areas in reproductive genetics. Current evidence indicates that carefully selected low-level mosaic embryos may result in healthy live births when no euploid embryos are available. However, such transfers require comprehensive genetic counseling and confirmation with prenatal diagnostic testing.

Noninvasive Preimplantation Genetic Testing

Conventional PGT-A requires embryo biopsy, which is technically demanding and invasive. This has stimulated the development of *noninvasive PGT-A (niPGT-A)*, which analyses cell-free embryonic DNA released into spent embryo culture medium or blastocoel fluid. Recent improvements in DNA extraction, whole-genome amplification, and bioinformatic analysis have increased concordance between niPGT-A and TE biopsy results. Nevertheless, contamination from maternal cells, sperm DNA, and limited quantities of embryonic

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DNA remain important challenges. Although niPGT-A is an exciting development, *current European Society of Human Reproduction and Embryology (ESHRE) and Preimplantation Genetic Diagnosis International Society (PGDIS) guidelines do not recommend its routine clinical use as a replacement for TE biopsy*, and it should still be regarded as an investigational technology.

Emerging Technologies

Polygenic Risk Scoring (PGT-P)

One of the newest developments is preimplantation genetic testing for polygenic risk (PGT-P), which estimates an embryo's inherited susceptibility to complex multifactorial diseases such as coronary artery disease, type 2 diabetes, and certain cancers. Although technically feasible, PGT-P remains investigational. Its clinical utility, predictive accuracy, ethical implications, and potential for unintended bias continue to be actively debated. At present, routine clinical application is not recommended.

Long-read Sequencing

Emerging long-read sequencing, technologies permit improved detection of structural genomic variants, repetitive DNA regions, and complex chromosomal rearrangements that are difficult to identify using conventional short-read sequencing. Although promising, these platforms remain primarily research tools.

Whole-genome Sequencing

Whole-genome sequencing (WGS) has the potential to provide comprehensive genomic analysis of embryos by identifying chromosomal abnormalities, monogenic disorders, and potentially pathogenic variants simultaneously. However, technical limitations, interpretation of variants of uncertain significance, ethical concerns, and cost currently preclude routine clinical implementation.

Clinical Practice Points

- TE biopsy combined with blastocyst vitrification is currently the preferred and most widely adopted approach for PGT.
- NGS has become the technology of choice for PGT-A owing to its high accuracy, comprehensive chromosome assessment, and ability to detect chromosomal mosaicism.
- Transfer of low-level mosaic embryos may be considered in selected cases after appropriate genetic counseling, particularly when no euploid embryos are available.
- niPGT-A is a promising development but currently lacks sufficient validation to replace conventional embryo biopsy in routine clinical practice.

NONINVASIVE EMBRYO ASSESSMENT: THE FUTURE OF EMBRYO SELECTION

One of the major goals of modern IVF is to identify embryos with the highest implantation potential without compromising embryo viability. Conventional embryo selection relies on morphology, morphokinetics, and, when indicated, invasive TE biopsy for PGT. Recent advances in molecular diagnostics have led to the development of noninvasive embryo assessment, which aims to evaluate embryo competence by analyzing substances naturally released into the culture medium, thereby avoiding embryo biopsy. Although many of these technologies remain investigational, they represent one of the fastest-growing areas of

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TABLE 11: Emerging noninvasive embryo assessment technologies.

Technology	*Principle*	*Potential clinical application*	*Current status*
Cell-free DNA (cfDNA)	Analysis of embryonic DNA released into spent culture medium	Noninvasive preimplantation genetic testing for aneuploidy (PGT-A)	Investigational
Metabolomics	Measurement of nutrient consumption and metabolite production	Assessment of embryo viability	Research/ emerging
Proteomics	Identification of embryo-secreted proteins	Biomarkers of implantation potential	Research
Secretome analysis	Evaluation of cytokines and growth factors secreted by embryos	Prediction of embryo competence	Research
Extracellular vesicles (EVs)	Analysis of exosomes containing proteins and RNA	Embryo quality and embryo–maternal communication	Emerging
Raman spectroscopy	Optical assessment of biochemical composition	Noninvasive embryo selection	Investigational
Hyperspectral imaging	Optical imaging of embryo metabolism and mitochondrial function	Artificial intelligence (AI)-assisted embryo assessment	Emerging

reproductive medicine and have the potential to complement or even replace invasive embryo assessment in the future **(Table 11)**.

Cell-free DNA

Embryos release small quantities of *cell-free DNA (cfDNA)* into the surrounding culture medium during development. Analysis of this DNA forms the basis of *niPGT-A*. Improvements in DNA isolation, whole-genome amplification, and bioinformatics have enhanced diagnostic accuracy. However, contamination from maternal cells, sperm DNA, and the limited quantity of embryonic DNA remain major challenges. At present, niPGT-A should be regarded as an investigational technique and is not recommended as a replacement for TE biopsy.

Metabolomics

Embryo metabolism reflects its developmental competence. Metabolomic analysis evaluates the consumption and production of metabolites such as glucose, pyruvate, amino acids, and lactate in spent culture medium. Differences in metabolic profiles have been associated with embryo viability and implantation potential. Although encouraging, standardized clinical protocols are still lacking.

Proteomics and Secretome Analysis

Developing embryos secrete a variety of proteins, cytokines, growth factors, and signaling molecules into the culture medium, collectively referred to as the embryonic secretome. Proteomic analysis aims to identify biomarkers associated with embryo competence, implantation, and ongoing pregnancy. Candidate molecules include cytokines, angiogenic factors, and implantation-related proteins, although no biomarker has yet demonstrated sufficient clinical validity for routine use.

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Extracellular Vesicles

Embryos also release extracellular vesicles (EVs), including exosomes and microvesicles, which contain proteins, messenger RNA (mRNA), microRNA (miRNA), lipids, and other signaling molecules. These vesicles play an important role in embryo–maternal communication and may provide valuable biomarkers for embryo quality. Research into EV-based embryo assessment is expanding rapidly but remains at an early stage.

Raman Spectroscopy

Raman spectroscopy is a label-free optical technique that evaluates the biochemical composition of spent culture medium by analyzing molecular vibrations. Changes in amino acids, lipids, and other metabolites may correlate with embryo developmental potential. Although promising, further validation is required before routine clinical implementation.

Hyperspectral Imaging

Hyperspectral imaging is a completely noninvasive imaging technology that captures metabolic and biochemical information from embryos without the use of fluorescent dyes or contrast agents. By analyzing intrinsic optical signatures, hyperspectral imaging can assess mitochondrial activity, oxidative stress, and cellular metabolism. When combined with AI, it has shown encouraging results for predicting embryo viability and chromosomal status.

Clinical Pearl

Noninvasive embryo assessment is likely to complement rather than replace conventional morphology, time-lapse imaging, and PGT soon. Large multicenter validation studies are still required before routine clinical adoption.

CRYOPRESERVATION: RECENT ADVANCES AND FUTURE DIRECTIONS

Cryopreservation has transformed ART by enabling flexible treatment strategies, fertility preservation, embryo banking, and elective single embryo transfer. It has become an integral component of modern IVF, supporting freeze-all protocols, PGT, fertility preservation for medical and social indications, and donor gamete programs. Recent advances have focused on improving survival rates, reducing cryoinjury, and standardizing laboratory procedures while maintaining excellent clinical outcomes **(Table 12)**.

Advances in Vitrification

Ultra-rapid vitrification has replaced conventional slow freezing as the preferred cryopreservation method for oocytes and embryos. By preventing intracellular ice crystal formation, vitrification achieves excellent postwarming survival, with blastocyst survival rates exceeding 95% in experienced laboratories. Mature oocyte vitrification has also become an established option for fertility preservation, with clinical outcomes comparable to those achieved using fresh oocytes.

Recent research has focused on optimizing cryoprotectant formulations by reducing their concentration and toxicity while maintaining effective vitrification. Novel cryoprotective agents, including ice-binding (antifreeze) proteins, are being investigated to minimize cellular injury during freezing and warming.

Closed versus Open Vitrification

Open vitrification systems provide extremely rapid cooling rates but expose specimens

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As Clinical Director of Ova Fertility and Women Care, Thane, Maharashtra, she has guided thousands of families through the journey to parenthood—bringing to each couple not only clinical precision but also the empathy and holistic understanding that she considers inseparable from good reproductive care. Her published works include the *Oncofertility Manual* and authored chapters in established fertility reference texts. She is also the author of *When Hope Meets Science and Soul Conceives*, reflecting her conviction that fertility care must address the whole person—the biology, the psychology, and the spirit.

A certified Life Coach and NLP Practitioner, she integrates mind–body science, neuroplasticity-based tools, and vagal tone modulation into her clinical work—recognizing that the stress physiology of the patient is as relevant to reproductive outcomes as her hormone profile. She is a Reviewer for the International Journal of Reproduction and Fetal Medicine and a sought-after Faculty Member at national and international conferences, fertility training programs, and oncofertility workshops.



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