Indian Society for Assisted Reproduction

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Utility of Advanced Semen Tests

New ESHRE Guideline

Number of Embryos to Transfer

Clinical Applications of PGT-A

From The Editor's Desk

Dear readers,

The Indian Society for Assisted Reproduction (ISAR) has always encouraged research, publications, training and development. As part of our academic endeavours, we are pleased to bring you the first newsletter of the new ISAR year.

The ISAR year began with the ISAR Annual Conference held in Bhubaneswar from 02-04 February where the new President Dr Ameet Patki was installed. This scientific extravaganza had a record attendance and was graced by eminent faculty from India and overseas.

We also had the first ever Indian College of Reproductive Medicine (ICRM) Convocation where a host of eminent seniors and international luminaries were conferred the ICRM Fellowships.

The focus area for the ISAR year is Male Infertility and the various events, publications and training programmes during the year will focus on the same.

In this newsletter, we have three scientific articles contributed by ISAR Executive Committee members – New ESHRE Guidelines on Number of Embryos to Transfer by Dr Pratik Tambe, Clinical Applications of PGT by Dr Priya Kannan and Utility of Advanced Semen Testing by Drs Randhir and Monica Singh.

Of late, there has been considerable focus on the issues of iatrogenic multifetal gestations with the consequent fetal and neonatal morbidity and mortality with specific attention to the emotional trauma and financial burden to prospective parents. The new ESHRE Guideline addresses these issues and is therefore particularly topical and relevant to clinical practice.

PGT is one of the prescribed interventions in patients suffering from recurrent losses and recurrent implantation failure but is not widely accessible or available in our country. In keeping with the theme for the year, the focus on semen testing and recommendations and interpretation of advanced semen tests is another thought provoking article which may of use to beginners and practising clinicians alike.

There is a multitude of events being planned in the months to follow and we would exhort you to register for as many of them as possible. ISAR has always maintained the highest standards of scientific content at it's events and this year will be no different!

I would like to thank the ISAR President Dr Ameet Patki and Secretary Dr Asha Baxi for giving me the opportunity to be the Editor for the first ISAR Newsletter of the year. We hope you enjoy reading the articles and we welcome your suggestions for future focused articles in the forthcoming issues of the ISAR Newsletter.

We would also like to acknowledge the efforts of our publishers M/s Krishers Publishing and Sabarish Menon. We are indebted to our academic partners who have contributed generously, enabling us to print this newsletter and participated in the distribution of the same as well.

Dr Pratik Tambe
Editor

CONTENT

President's Message

Dear ISARians,

It is with great pleasure that we bring you the first ISAR Express Newsletter of the year 2024. This year has witnessed scorching heatwaves and climate change thanks to a multiplicity of factors.

The theme for the ISAR year is Focus on Male Infertility and I am sure you will agree that similarly, climate change, stress, lifestyle factors and endocrine disruptors are at play in the plummeting sperm counts worldwide. During the year we hope to conduct activities and educational events on this focus area to bring widespread awareness regarding the latest techniques and scientific evidence available to combat male infertility.

The ISAR Annual Conference 2024 held in Bhubaneswar was one of the finest scientific meetings organised by ISAR and was graced by a host of senior eminent national and international faculty in the field of reproductive medicine. I had the pleasure of meeting several ISAR members and interacting with them during the conference and the feedback from all of them was excellent and positive regarding the scientific deliberations.

We have a series of wonderful conferences being planned this year including the ISAR regional meet in Shirdi where this newsletter will be released, the ISAR regional south in Bengaluru, the ISAR ASPIRE Conference in Pune the ISAR Embryology in Chandigarh, the FUSION Conference in Jaipur and the Yuva ISAR in Patna later this year. Please take advantage of the early bird registrations for all of these and register in large numbers. Our online activities and physical CMEs will also continue countrywide regularly as usual.

Finally, I would request you to encourage more of your colleagues, friends, embryologists and juniors to become ISAR members, increase our strength and participate in the academic activities of this rapidly growing organisation.

I congratulate the Editor Dr Pratik Tambe and the publishers M/s Krishers Publishing House for compiling an excellent ISAR Express and please stay tuned for more from ISAR in the months to come!

Dr Ameet Patki
President, ISAR 2024-26

Secretary General's Message

Dear esteemed members, it's with great honor that I serve as Secretary General alongside President Dr Ameet Patki, leading our prestigious society. Our ISAR Express Newsletter stands as a testament to our collective dedication, continually engaging and articulating the perspectives of our ISAR community with flair. I urge all members to immerse themselves in its pages and to extend the invitation to colleagues far and wide. Furthermore, I encourage you to share your scientific endevours for publication consideration. Together, let's enrich our field with knowledge and collaboration.

Warm regards.

Dr Asha Baxi
Secretary General, ISAR 2024-26.

Meet The Team

Dr Ameet Patki,
MD DNB FCPS FICOG FRCOG (UK)
President, ISAR (2024-26)

Dr Ameet Patki, the current ISAR President is a multifaceted, multi-talented eminent stalwart in the field of Reproductive Medicine.

He has a number of unique distinctions to his credit. He was the 61st President of the Mumbai Obstetric and Gynaecological Society in 2014-15. He is the Medical Director of IKAN Fertility Associates - Centre for Assisted Reproduction in Mumbai. Previously, he has held the post of Medical Director, ReGenesis – Centre for Assisted Reproduction, Endoscopy and Fetal Medicine, Reliance Life Sciences, Mumbai. He was also an Honorary Associate Professor at the K.J. Somaiya Medical College, Hospital & Research Centre Mumbai. Presently he is Consultant Obstetrician & Gynaecologist at Hinduja Healthcare Hospitals & Surya Mother and Child Hospitals Mumbai.

Hailing from a family of architects, it was widely expected that Dr Ameet Patki would also follow in his forefathers' footsteps and become a successful architect like them. His family is credited with building several landmark buildings in Mumbai city, including the Jaslok and Bombay Hospitals and the Don Bosco High School in Matunga. But fate willed otherwise and to fulfil the wishes of his grandparents, Dr Ameet Patki after completing his education in Don Bosco School and SIES College in Sion enrolled for MBBS at the Lokmanya Tilak Municipal General Hospital and Medical College in 1982.

He chose Obstetrics and Gynaecology as his specialty of choice since this is one of the few areas of medicine not associated with sickness but with the joy of bringing new life into the world. Few are aware that in 1987 in his first year of MD, he was diagnosed with a deadly brain tumour which required urgent surgery. He was back at work within four weeks and a couple of years later had completed his MD, which is testament to his tenacity.

After completing his postgraduation, he worked as a lecturer for a year at the mecca of Obs Gyn, the Nowrsojee Wadia Maternity Hospital which brought him into close association with several eminent personalities and the who's who of the field. It was at this time that he received a call from the Royal College of Obstetrics and Gynaecology (RCOG) and travelled to the UK at short notice to complete his MRCOG in 1994.

A four year post-doctoral fellowship in Infertility and High Risk Obstetrics at the famous St Bartholomew's Hospital and Portland Hospital for Women and Children and Homerton hospitals. Incidentally, even though he was offered a Consultant post in the UK, Dr Ameet Patki chose to return to India with a strong desire to set up world class institutions in infertility to serve the common masses of the country.

In 1997, when he returned to his homeland, fertility clinics were few and far between, advanced infertility treatments were available to a small proportion of the population and the costs were exorbitant – beyond the reach of the common man. He therefore helped to establish the ReGenesis Centre in March 2001, where he served as its Medical Director. This ISO 9001 accredited centre also treated couples from overseas including from the UK, USA, Africa and the Far East. Thanks to the strong foundation laid by eminent seniors like Dr Shirish Daftary, Dr Duru Shah, Dr Shyam Desai, Dr Adi Dastur and Dr Usha Saraiya, Dr Ameet Patki rose through the ranks to become the 61st President of the Mumbai Obstetric and Gynaecological Society (MOGS) in 2014. His theme for the year was "Be Global, Touch Local" and even today, there is an annual MOGS Award with the same name which was instituted by him when he completed his tenure as MOGS President. This is presented at the inauguration of the MOGS Annual Conference to an eminent personality who has embodied the principle - Be Global, Touch Local.

Dr Ameet Patki has over 50 textbook chapters to his credit and edited three books on the specialty. He was part of the Embryonic Stem Cell Research team at the Reliance Life Sciences. He has two international patents to his credit for work in infertility and embryonic stem cell research.

He has served as Chairperson, Perinatology Committee of FOGSI and was on the Governing Council of ICOG (Indian College of Obstetricians and Gynecologists) for over 12 years. He has been Chairperson, West Zone India RCOG for 5 years when he conducted the first ever India Day at the Royal College in London drawing over 200 Obs Gyns from India and UK. He has been elected as Country Representative to ASPIRE (Asia Pacific Initiative Reproductive Endocrinology) 2021-23. He has been a TEDx speaker since 2017, the first gynaecologist & infertility specialist from Mumbai.

He has been the receipient of several awards at national and international level. These include the FOGSI Corion Award 2003 for Best Research, MOGS Young Scientist Award 2005 and MOGS Dr Ganatra Charitable Medical Centre Award for Commitment, Promotion and Services rendered to the cause of Women's health in 2015. He has also received the Dina Patel Gold medal for standing first at the FCPS exams.

He has won both the Dr Indumati Jhaveri Prize in the Junior category for Best Paper at Nagpur AICOG in 1990 and the Dr CS Dawn Award in the Senior category at AICOG Chennai 2015. He has been awarded the prestigious Asia-Oceania Federation of Obstetrics and Gynecology (AOFOG) Dr SS Ratnam Young Gynecologist Award at Seoul, Korea in 2005. He was conferred a Fellow of the Royal College, London in September 2008.

During the Presidential tenure the theme "Empowering Parenthood- leaving no one behind " speaks for equality of treatment to all classes religions and strata of society.

Male infertility is a much neglected aspect in management and treatment of couples. ISAR intends to focus on increasing awareness and screening of men and advise them to lead a healthy and fitter life.

Finally, Dr Ameet Patki has the unique distinction of being the President of MOGS who oversaw the shifting of the MOGS Office from the old premises at Jacob Circle to Kamala Mills Compound in Parel. It is also during his tenure as President of ISAR that the ISAR Office premises moved from a shared office with ISPAT in the Elco Arcade in Bandra to a modern, spacious new office space at Kamala Mills.

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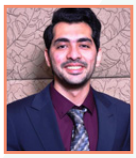

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Utility of Advanced Semen Tests

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Introduction

Semen analysis is an integral component of the evaluation and management of subfertile men. Although it is important for patient counselling and clinical-decision making, a conventional semen analysis cannot reliably predict the chance of pregnancy or differentiate between fertile and infertile men. Advanced sperm functional tests may provide additional discriminatory and prognostic power but further research is needed to determine how to best incorporate these tests into modern clinical practice. Therefore, the primary application of a conventional semen analysis to judge the severity of infertility, estimate the effects of future therapy, and measure the response to current therapy, is very important.

The Present and the Future

Semen analysis (SA) represents the most basic evaluation of male infertility. Recent scientific advances in the understanding of sperm DNA fragmentation (SDF), seminal oxidative stress (OS), and reactive oxygen species (ROS) testing have shed additional light on the prognosis of reproductive outcomes in terms of natural conception and assisted reproductive technology (ART). Since chromosomal abnormalities and gene mutations often underlie a diverse spectrum of male infertility, genetic and genomic testing are gaining attention. Some other tests used in research settings are sperm acrosome reaction, functional analysis of transmembrane ion flux and transport in sperm, and methods for the evaluation of chromatin condensation.

Evolution of Semen Testing

1. The Advancement in Basic Examination of Semen

- The evaluation of **semen odour** has been added, and "urine or putrefactive odours may be of clinical interest". However, the evaluation of semen odour is subjective and the standardization of this parameter very complicated. Furthermore, assessment of this parameter can lead to the respiratory transmission of viruses.
- the categorization of **sperm motility** has reverted to fast progressively motile, slow progressively motile, non-progressively motile, and immotile (grade a, b, c, or d, respectively). For the evaluation of sperm count, semen dilutions have been simplified, but 200 spermatozoa per replicate should be counted.
- the assessment of **sperm vitality** is recommended when total sperm motility is below 40%.
- **Sperm morphology** assessment using a systematic approach and micrographs of spermatozoa from unprocessed semen samples are analysed and classified as normal, borderline, or abnormal. The evaluation of the morphological anomalies of the head, intermediate piece, and tail should be carried out and the recording of the presence of large cytoplasmic droplets is significant.

WHO 2010 (5th Edition) and WHO 2021 (6th Edition) lower the fifth percentile (with 95% confidence interval) of semen parameters from men in couples who start a

pregnancy within one year of unprotected sexual intercourse leading to a natural conception.

	WHO 2010	WHO 2021
Semen volume (mL)	1.5 (1.4–1.7)	1.4 (1.3–1.5)
Total sperm number (106 per ejaculate)	39 (33–46)	39 (35–40)
Total motility (%)	40 (38–42)	42 (40–43)
Progressive motility (%)	32 (31–34)	30 (29–31)
Non-progressive motility (%)	1	1 (1–1)
Immotile sperm (%)	22	20 (19–20)
Vitality (%)	58 (55–63)	54 (50–56)
Normal forms (%)	4 (3–4)	4 (3.9–4)

2. Extended Examination of Semen

The importance of Sperm DNA Fragmentation and genetic evaluation in the context of male infertility has been elaborated in recent times. Elevated SDF is associated with prolonged time to pregnancy, lower chance of spontaneous pregnancy, and lower live birth rates. Sperm aneuploidy is more frequent in infertile men, in male partners of couples experiencing recurrent pregnancy loss, and recurrent failure of assisted reproductive technology (ART). These tests can, therefore, provide important information to guide the management and counseling of infertile couples to optimize reproductive outcomes.

Genetic and Genomic Tests

Unselected infertile men, as well as men with SDF, Robertsonian, and reciprocal translocation, and those with a history of recurrent pregnancy loss, are at increased risk of producing aneuploid sperm. FISH is commonly used in the assessment of chromosomal aneuploidy involving chromosomes 13, 18, 21, X, and Y, which usually result in viable but defective births. Additionally, FISH is used in the assessment of the male partner's chromosomal abnormalities in cases of recurrent pregnancy loss or ART failure.

Sperm DNA Fragmentation

Different methods of SDF testing, including the TUNEL assay, sperm chromatin dispersion assay, Comet assay, and acridine orange flow cytometry assay.

Evolution from Simple to Advanced Examination of Semen

1. Semen Analysis

- **Semen Analysis** is a simple test and is essential to be done by all men as a first-line investigation for infertility. If a previous test has been done and it is over a year ago, the test needs to be repeated. A 2-3 days period of sexual abstinence is required before the test.

Semen analysis examines the following sperm **parameters:**

A) Semen volume

B) Sperm concentration

C) Sperm motility, which provides information on how the sperm is moving & evaluates the percentage of spermatozoa that are moving vigorously.

D) Sperm morphology, which provides information on the shape and the size of spermatozoa and evaluates the percentage of spermatozoa that look normal.

E) The presence of any white or red blood cells within the sample, which could indicate an infection.

2. Sperm DNA Fragmentation Test (DFI)

A DNA sperm fragmentation test is performed on a semen sample to assess the level of DNA damage in sperm. This test gives important information about the integrity of the DNA in the sperm and represents an evaluation tool for the assessment of your sperm's quality.

Various studies have shown that increased levels of sperm DNA damage are associated with unexplained infertility, unsuccessful IUI or IVF treatments, and recurrent miscarriages.

For couples proceeding with an IVF treatment, when the sperm DNA fragmentation level is high, a urological opinion is advisable and ICSI should be used instead of IVF for the fertilisation of the eggs, even if the sperm's parameters are all normal.

3. Sperm Aneuploidy Test (SAT)

SAT is a diagnostic test that analyses the sperm with a technique called FISH (Fluorescence in situ hybridization) to identify the percentage of spermatozoa with chromosomal abnormalities. It evaluates in particular, the chromosomal abnormalities, which are mostly implicated in spontaneous miscarriages or male infertility (chromosomes 13, 18, 21, X and Y).

The results of the test are available within 2 weeks and can prove a useful tool for the management of couples who have suffered recurrent miscarriages, unsuccessful IVF treatments, or a previous pregnancy with a chromosomal abnormality.

4. Advanced Infection Screen Test

The presence of bacteria, such as chlamydia, or other pathogenic microorganisms in the sperm may remain undetected, as it is often asymptomatic. When these pathogens are present in the sperm can compromise sperm quality, leading to infertility.

Sometimes these pathogenic microorganisms may be located inside the spermatozoa (intracellular) and subsequently transferred inside the embryo, leading to miscarriage. Newer sensitive tests, unlike conventional methods can additionally detect intracellular inside spermatozoa, using immunofluorescence and flow cytometry techniques. This test allows for the prompt diagnosis and treatment of sperm infections with the use of targeted antibiotics/antivirals.

5. Anti-sperm Antibodies (MAR)

MAR test is used to identify an immunological cause of infertility by looking for anti-sperm antibodies in the semen. These antibodies when present may reduce the ability of the sperm to penetrate the egg, preventing fertilization and causing infertility.

6. Oxidative Stress Test for Reactive Oxygen Species

The concept of OS was developed by Helmut Sies in 1985. Due to the production of excessive amounts of ROS in numerous medical conditions, including varicocele, leukocytospermia, diabetes mellitus, and obesity, seminal OS develops. Consequently, OS negatively affects all sperm functions, including sperm DNA integrity and thereby the fertilization process and reproductive outcomes.

Excessive production of reactive oxygen species in the sperm results in oxidative stress, as the available antioxidants in the sperm cannot efficiently neutralise the excessive amount of the reactive oxygen species. Oxidative stress damages the sperm and existing evidence suggests that is one of the major causes of male infertility, especially in cases of unexplained infertility or when abnormal semen parameters are found.

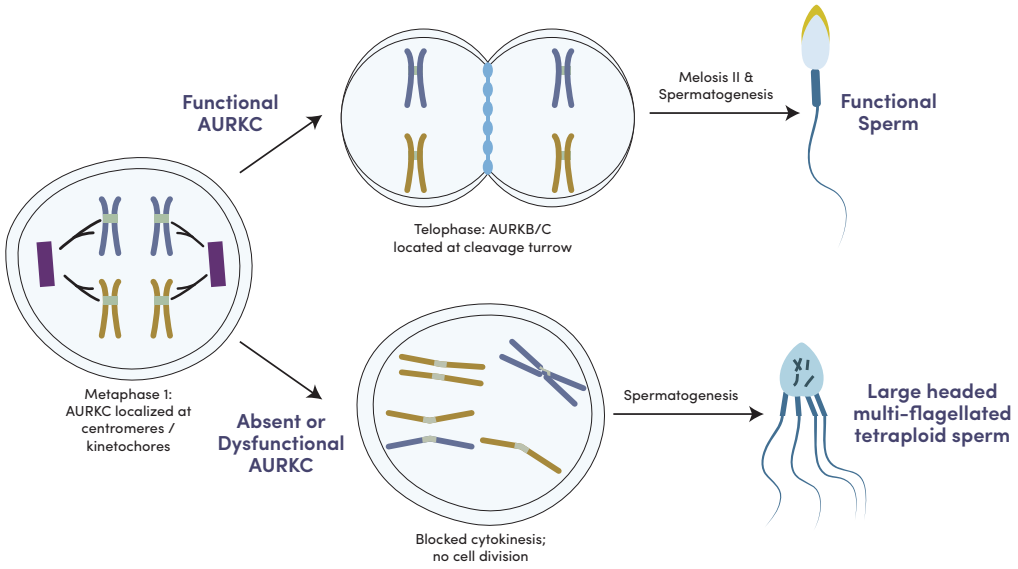

Figure 1: Macrozoospermia results from damaging mutations in aurora kinase C (AURKC). When AURKC is mutated, there is premature chromosome segregation, and cytokinesis is blocked during meiosis, resulting in large, headed multitailed, polyploid sperm formation. The c.144delC mutation is common in men of European and North African origin with macrozoospermia. For these men, intracytoplasmic sperm injection-in vitro fertilization is not recommended because the chances of a normal pregnancy are slim. AURKB/C = aurora kinase B/C.

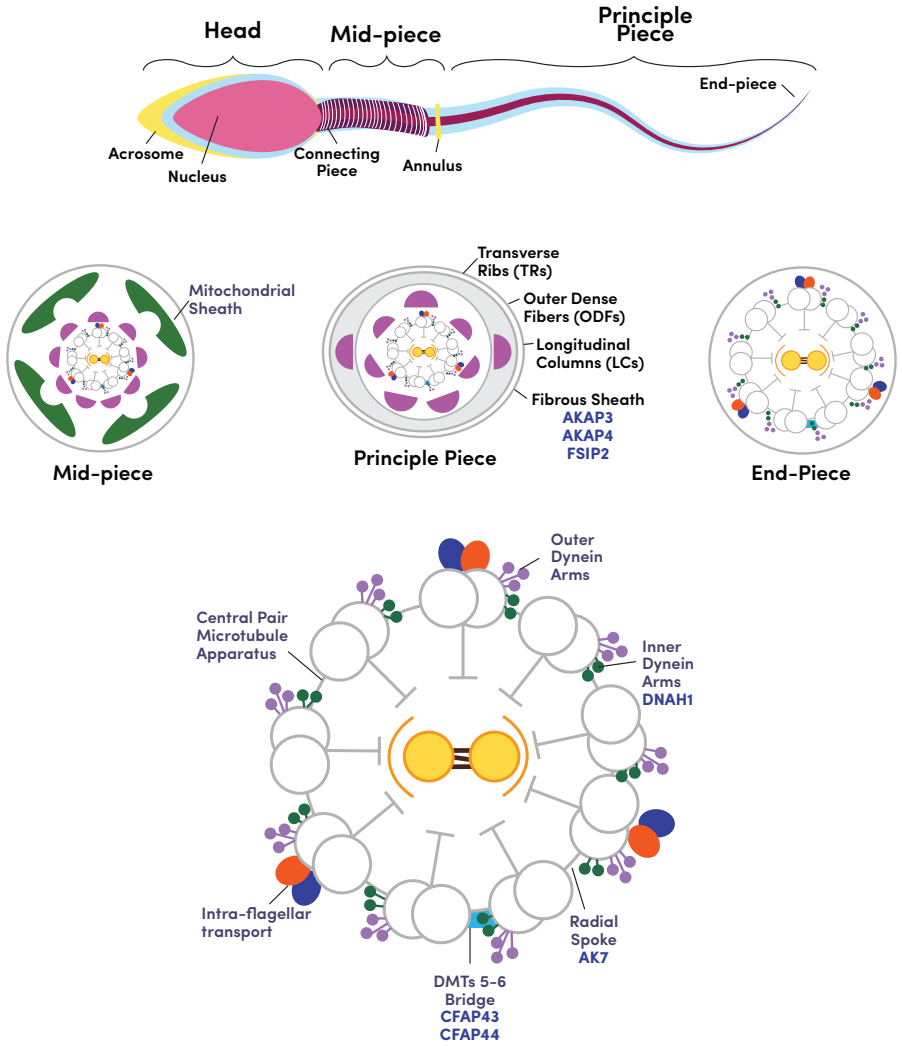

Figure 2: Multiple morphological anomalies of the sperm flagella (MMAF) refer to sperm morphology anomalies usually associated with asthenoteratozoospermia. In men with asthenoteratozoospermia, there is a relatively high frequency of mutations. As a result, structural defects of the centriole assembly, peri-axenome structure, and the axenome can be present.

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Clinical Applications of PGT-A

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Introduction

Pre-implantation Genetic Testing (PGT) is defined as a test performed to analyse the DNA from oocytes (polar bodies) or embryos (cleavage stage or blastocyst) for HLA typing or for determining genetic abnormalities. PGT was previously referred to as Preimplantation Genetic Screening (PGS) or Preimplantation Genetic Diagnosis (PGD).

Currently, three different types of PGT exist –

PGT – A: Screening of embryos of Chromosomal aneuploidy (previously referred to as PGS), eg Downs Syndrome, Turner Syndrome

PGT – M: Screening of embryos for a known monogenic or single gene defects (Previously referred to as PGD), eg Cystic Fibrosis,

PGT –SR: screening of embryos for a chromosomal structural rearrangement, eg, Robertsonian Translocations, inversions

Why PGT?

Many previous publications have suggested and is now widely accepted that the incidence of chromosomal abnormalities found in cleavage-stage embryos produced in vitro is about 50% to 70%, depending on maternal age. This is considerably higher than the incidence of aneuploidies seen in spontaneous abortions or prenatal samples from chorionic villus sampling or amniocentesis. Hence, we can safely infer that chromosomally abnormal embryos either do not implant or are eliminated before the time of prenatal testing.

The fact that the majority of the embryos created in vitro are aneuploid, irrespective of maternal age and morphology, has been demonstrated time and again through many publications. This was attributed as the reason for the low implantation rate of human embryos. Morphological assessment of embryos and extended culture till day 5 were some of the methods that were used for embryo selection to enhance implantation rates.

However, it has also been demonstrated that selecting embryos based on morphology alone can only slightly improve the probability of selecting a chromosomally normal embryo for transfer and aneuploidy is also prevalent in good-grade blastocysts. Hence, it was postulated that PGT in combination with other selection techniques may provide a benefit by accurately identifying euploid embryos, leading to improved ART outcomes.

History

The very first embryo biopsy was performed in 1968 by Richard Gardner, a student of Robert Edwards who used a holding pipette to position rabbit blastocysts and biopsied the trophectoderm using a pair of iridectomy scissors and aspirated the small pieces of trophectoderm into a fine pipette. In humans, Handyside and colleagues reported the first unaffected child born following PGT performed for an X-linked disorder in 1989.

In the 1990s and early 2000s, blastomere biopsy was the method of choice, and fluorescence in situ hybridization (FISH) was used as the technique of genetic analysis. The limitation of FISH is its ability to detect a reduced number of chromosomes. The Aneuploidy screening was called Preimplantation genetic screening (PGS). A landmark publication by Mastenbroek et al. in 2011, concluded that ´There is no evidence of a beneficial effect of PGS as currently applied on the live birth rate after IVF. On the contrary, for women of advanced maternal age PGS significantly lowers the live birth rate. Technical drawbacks and chromosomal mosaicism underlie this inefficacy of PGS". This ushered in the end of PGS 1.0. The advent of technological innovations mostly involving advancements in genetic analysis (such as NGS) & a shift to trophectoderm biopsy led to PGS 2.0, which is the currently applied version rechristened as PGT-A.

Indications for PGT-A

PGT-A is preimplantation genetic testing of embryos for chromosomal aneuploidy.

ESHRE PGT Consortium published the good practice guidelines for PGT in 2019. It recommended that PGT be applied only when the genetic diagnosis is technically feasible, and the reliability of the diagnosis is high. It also recommended that each centre should be aware of their error rates and suggested including this information in their informed consent and reports in open communication with the patient.

The application and indications for PGT-A have been one of the most debated topics. Presently the acceptable indications for PGT-A include the following:

- Women of advanced maternal age
- Male partner with severe male factor infertility
- Couples with repeated IVF failure
- Couples with normal karyotype with experience of recurrent pregnancy loss

Advanced maternal age (AMA)

Data from oocyte donation showed that the decline in pregnancy in women of advanced maternal age is largely caused by failing oocyte quality rather than unreceptive uterine lining. Based on publications by Munne and group, it is widely accepted that the principal reason for reduced oocyte competence is aneuploidy, the incidence of which increases dramatically with advancing maternal age.

An RCT in 2008 by Hardarson and group which aimed at demonstrating the use of PGS in women with AMA undergoing IVF, was terminated early as the interim analysis showed that the use of PGS for AMA patients decreased the clinical pregnancy rate.

A meta-analysis by Santiago Munne et al in 2019 concluded that PGT-A did not improve pregnancy outcomes in all women, however, they noted a significant increase in ongoing pregnancy rates per embryo transfer with the use of PGT-A in women aged between 35–40 years who had two or more embryos for biopsy. A recent meta-analysis by Simopoulou et al. concluded that PGT-A did not improve live-birth rates per patient in the general population however in women over 35-year-old, PGT-A seems to improve live-birth rates. They also noted a statistically significant lower miscarriage rate following PGT-A in the general population, while the subgroup analysis did not show a statistically significant difference in miscarriage rates in younger women and women over 35 years. The study concluded that “PGT-A does not seem to improve clinical pregnancy rate irrespectively of age group, it improves ongoing pregnancy and live-birth rates in the over 35-year-old age group, as well as decreasing miscarriage rate”. They also inferred that PGT-A improves the chances of sustaining a pregnancy leading to live-birth in women over 35-year-old. They dogmatically concluded that PGT-A performed on D5, employing CCS and accompanied with frozen D5 ET, enhances live-birth rates in women above 35 years.

Male partner with severe male factor infertility

Various genetic defects have been associated with male factor infertility such as Klinefelter syndrome, Robertsonian translocations, Y chromosome microdeletions, androgen receptor mutations, and other autosomal gene mutations. It is also a well-established fact that there is a risk of transmission of genetic mutations to the progeny. However, PGT-A does not seem to be associated with increased live-birth per transfer in couples with severe male factor infertility.

Couples with repeated IVF failure

The recent consensus has suggested defining RIF based on failure to conceive after the transfer of three euploid embryos. However, the efficacy of PGT-A in RIF has conflicting results with most studies concluding that the intervention has not shown statistically significant improvement in live birth rates or miscarriage rates (Kato et al., 2020) while some studies have shown improved clinical pregnancy rates in younger patients with RIF (Du et al., 2023).

Recurrent pregnancy loss

It was reported by Pellicier et al in 1999 that the incidence of aneuploid embryos was higher in couples with RPL than in couples without RPL.

Sato et al in 2020 concluded from their study that PGT-A could improve the live-birth rate per IVF transfer in RPL cases with a history of POC aneuploidy. The same was inferred in a large retrospective study published in 2021, where data was collected by the Society of Assisted Reproductive Technologies Clinical Outcomes Reporting System (SART-CORS) for IVF-FET cycles between the years 2010 through 2016 to assess the utility of PGT-A in couples with RPL undergoing FET, concluded that use of PGT-A improved live birth rates in couples with recurrent pregnancy loss undergoing frozen embryo transfer.

Challenges in clinical practise

1) Perception of patient

Patients typically fail to understand the limitations of genetic screening. Each type of analysis performed has its limitations & has to be extensively explained to the patient. It has to be mentioned with clarity to couple that PGT-A would not attempt to detect

monogenic or single-gene disorders. Moreover, there are no established diagnostic tests presently that can confirm the results of PGT-A.

The challenge is patient education. It has been suggested that the patient education leaflets for PGT should be written at or below a fifth-grade reading level for easy understanding (Early et al., 2020). Hence extensive genetic counselling is warranted for all couples undergoing PGT., even if the law does not mandate it. ESHRE PGT consortium has provided technical recommendations for each test, regulations, and laboratory requirements. Such recommendations can ensure that PGT patients receive the best care possible.

2) Mosaicism

Mosaicism is prevalent in preimplantation embryos. Several studies have been published where a transfer of mosaic embryos had resulted in non-notable healthy babies. Self-correction during differentiation and proliferation is a plausible explanation for this. This means that the biopsied cell from PGT-A may not accurately represent the embryo and thus lead to false-positive or false-negative results. The suggested new terminology for mosaicism is “intermediate copy number”.

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New ESHRE Guideline:
Number of Embryos to Transfer

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Governing Council member, ICRM (2024-26)
Managing Council member, MOGS, ISAR, MSR

Background

A new ESHRE guideline has been published on the number of embryos to transfer during IVF/ICSI. It has been developed to provide infertility care practitioners with the best available evidence and recommendations on how many embryos to transfer during IVF/ICSI, after assessing 17,700 scientific papers.

This guideline provides 35 recommendations and good practice points to help clinicians reach the ultimate objective of an infertility treatment: a healthy pregnancy and birth. The guideline outlined the clinical and non-clinical factors that should or should not be considered when deciding on the number of embryos to transfer. It has also taken into consideration patient preferences and experiences regarding embryo transfer. Furthermore, the guideline development group developed some real-life scenarios as examples to help both infertility care practitioners and patients make decisions.[1]

Why did we need a new guideline?

Transferring multiple embryos during the embryo transfer procedure is correlated with a higher rate of multiple pregnancies, leading to a subsequent increase in complications for both mother and babies. These complications include preterm birth, low birth weight, and other adverse perinatal outcomes.

To mitigate the risks associated with multiple pregnancies, eSET is now recommended by international and national professional organizations as the preferred approach in ART. This is especially true in a low-resource country like India where neonatal care and subsequent neurological deficits can place significant financial and emotional burdens on families.[2]

Key questions and recommendations[3]
Which pregnancy-related risks and issues should be considered before the transfer of more than one embryo?

Medical risks that should be considered before the transfer of more than one embryo are the higher rates of maternal, foetal, and neonatal complications. (strong 3/4)

The GDG recommends that whenever the transfer of >1 embryo is considered, the patient should be provided with clear information about the higher risk of pregnancy loss, ectopic pregnancy, pre-eclampsia, gestational diabetes, antepartum and postpartum haemorrhage, Caesarean section, stillbirth, preterm birth, low birth weight, neonatal intensive care admission, and neonatal death associated with multiple pregnancies. The GDG also recommends that the patients sign an additional consent form if >1 embryo is transferred. (GPP)

Financial issues of multiple pregnancy/birth

It is recommended to consider the increased direct costs related to obstetric care of multiple pregnancies and paediatric care of twins and triplets (strong 3/4)

The GDG recommends that cost-related information should be provided and discussed with the patient(s) at the treatment planning stage. (GPP)

Psychological issues of multiple pregnancy/birth

Clinicians should consider the possible complications of multiple pregnancies with regards to mental health

postpartum, emotional distress, and marital problems on the mental health of parents and offspring regardless of the number of children born. (strong 2/4)

The GDG recommends that information on possible psychosocial complications should be provided to patients at the treatment planning stage. (GPP)

Social, legislative, and economic factors

The GDG encourages legislative and health insurance policies that promote the practice of eSET. (GPP)

Which clinical criteria should be considered as factors when deciding to apply double embryo transfer (DET) instead of (E)SET for couples/individuals undergoing ART?

The decision to perform DET instead of eSET should not be based on the number of previous unsuccessful ART treatments. (strong 1/4)

The decision to perform DET instead of eSET should not be based on the duration of infertility. (strong 1/4)

The decision to perform DET instead of eSET should not be based on previous pregnancies or live births from ART. (strong 1/4)

The decision to perform DET instead of eSET should not be based on female age. (strong 2/4)

For normal responders, eSET is recommended. (strong 1/4)

The GDG recommends eSET in patients with low or high ovarian response. (GPP)

The decision to perform DET instead of eSET in fresh or frozen embryo transfer cycles should not be based on endometrial characteristics. (strong 1/4)

Only eSET should be practised for patients undergoing ART with donor oocytes. (strong 3/4)

Only eSET should be practised for patients undergoing ART with donated embryos. (strong 1/4)

Only eSET should be practised for gestational carriers. (strong 1/4)

Which embryo-related criteria should be considered as factors in deciding to apply DET instead of (E)SET for couples/individuals undergoing ART?

In fresh cleavage-stage embryo transfer, the decision to perform DET instead of eSET should not be based on embryo criteria. (strong 3/4)

In fresh blastocyst transfer cycles, the decision to perform DET instead of eSET should not be based on blastocyst morphology/quality. (strong 3/4)

The GDG recommends cryopreserving one embryo per device in order to facilitate the practice of SET and for traceability purposes. (GPP)

In cryopreserved-warmed cleavage-stage embryo transfer cycles, the decision to perform DET instead of SET should not be based on embryo criteria. (strong 3/4)

In vitrified-warmed blastocyst transfer cycles, SET should be applied regardless of the quality of the vitrified blastocyst. (strong 1/4)

Recent advances

Time-lapse imaging-derived parameters for embryo selection should not be considered a factor in performing DET instead of eSET. (strong 1/4)

Outcomes of preimplantation genetic testing for aneuploidies should not be considered when deciding to perform DET instead of eSET. (strong 1/4)

In any patient undergoing ART, should the transfer of more than two embryos be applied?

Transfer of more than two embryos is not recommended. (strong 1/4)

Fetal reduction

In patients who conceived higher-order multiples (HOM) following multiple embryo transfers, a foetal reduction can be considered to reduce the risk of maternal complications. (conditional 1/4)

Which issues are crucial for decision-making regarding the number of embryos to transfer and how should they be discussed with the patients?

The GDG strongly recommends that healthcare professionals discuss with the patient a number of issues related to the number of embryos to transfer. (GPP)

Discussion

The new ESHRE guideline universally espouses the cause of single embryo transfer given the multiple maternal and perinatal complications which are associated with double and multiple embryo transfers. These evidence-based recommendations were presented to 19 reviewers from 15 countries and a total of 71 comments were received which were incorporated into the final set of recommendations.

The guideline notes that the evidence indicates DET is not associated with a higher cumulative live birth in poor prognosis patients. However, transferring two embryos to patients is sometimes opted for in cases where patients present multiple poor prognostic factors including advanced age, poor-quality embryos, and a lack of live birth from previous ART cycles.

Nevertheless, patients for whom DET is considered should be counselled not only regarding the chances their treatment will be successful but also regarding short-and long-term medical risks, and social and economic factors. This should preferably be done as part of shared decision-making.3

Conclusions

While the complications of multiple iatrogenic pregnancies are well known, best practices related to single embryo transfer are not yet widely established in ART programs in the Indian subcontinent. The new ESHRE guideline provides yet another set of evidence-based recommendations that will reduce the burden of issues associated with multifetal gestations if appropriately implemented.

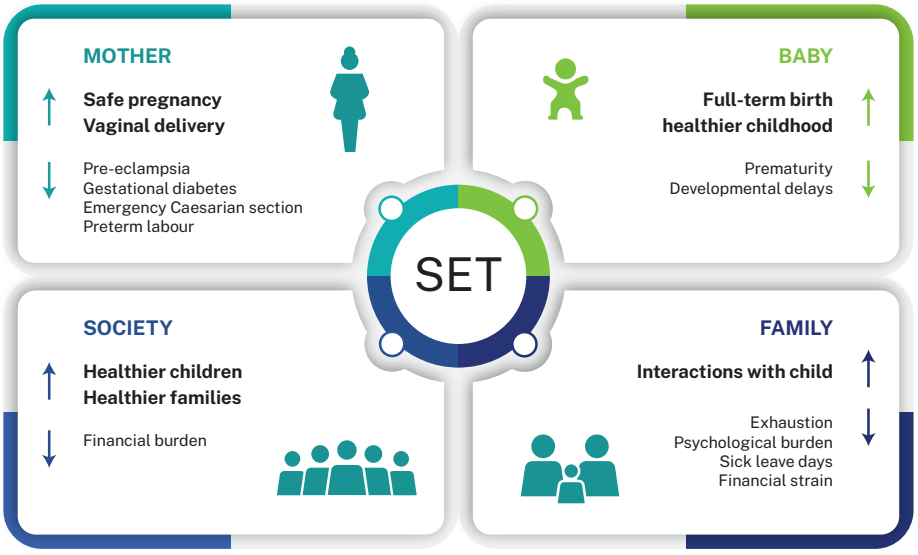

Figure 1: Single Embryo Transfer benefits[2]

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Report of ISAR 2024 Bhubaneshwar

The 28th Annual Conference of Indian Society of Assisted Reproduction (ISAR) 2024 was held in Bhubaneswar, the state capital of Odisha, also well known as temple city from 2nd Feb till 4th Feb in the most beautiful state of art venue, Hotel Mayfair Lagoon and Convention. The conference theme was 'Navigating the new normal in ART which focused on the innovations in the field of artificial Reproductive Technology. It was a green conference with minimal use of paper paying respect to mother earth. The conference was organized by Odisha chapter of ISAR under the guidance of ISAR president, Dr Nandita Palshetkar and Hon.Secretary General, Dr Sujata Kar with guidance of stalwarts in the field of ART like Prof P.C. Mohapatra and Dr Monu Pattnaik. The Organizing Chairperson was Dr Sujata Kar and organizing secretary was Dr Madhumita Mohanty.

The academic extravaganza included 2 days of extensive lectures, orations, panels, free papers and one full day of ten workshops, involving 1,700 plus delegates across the whole country 500 plus trade and pharma participants. With 596 faculties including 15 international faculties. The International faculties were

Anuja Dokras	USA
Rashida Begum	Bangladesh
Yutaka Osuga	Japan
Atsushi Tanaka	Japan
Louise Hull	Australia
Sergio Haimovich	Spain
Georg Griesinger	Germany
Amr Othman Abdelkareem	Egypt
Mohammad Ahmad	Egypt
Hatem Abo Elftooh Hassan Awaga	Egypt
Mohd Faizal Bin Ahmad	Malaysia
Jared Robins	USA
Kurt Barnhart	USA
Paula Amato	USA
Rachel Chin	Malaysia
Steve Levett	UK

There was a grand inaugural ceremony where the incoming president Dr Ameet Patki and his team of Office Bearers were installed. Eminent social activisit Namrata Chadda graced the ceremony as Chief Guest and gave an excellent deliberation on womens liberelisation. The inaugural ceremony was followed by an enthralling cultural program in which approximately 10 state chapters participated performing skits and local dance forms.

The highlights of the scientific programme were the ISAR Orations- Late Dr Sudesh Kamat Oration by Dr Jaydeep Tank, Late Dr B.N. Chakravarty Oration by international faculty Georg Griesinger, Dr Nandita Palshetkar Oration by Dr Nandita Palshetkar, Dr Rishma & Dr Hrishkesh Pai Oration by Dr Ameet Patki and Dr Jaideep Malhotra Yuva Oration by Dr Sumavarsha Krishnamshetty. There were many interesting panels, symposias and deep dive sessions and also debate and controversy sessions. On 3rd February evening there was a gala banquet and musical night in another state of art venue, Hotel Trident.

A nation wide ISAR quiz was conducted prior to the conference online in all four zones (East, West, North, South). The finalists appeared for the final round which took place on 2nd Feb and the winners were awarded cash prize which was very much appreciated by the awardees.

On 4th February 10 very interesting workshops were conducted by state and national faculties where apart from lectures, there were live videos and hands on.

Workshop	No. of delegates
1. The female pelvis-enhancing reproductive function	125
2. The intelligent sperm –basic & advanced male factor infertility	117
3. Mandatory sonography for reproductive medicine practice – basic & advanced	157
4. Navigating the new normal – art & surrogacy act	110
5. Starting life frozen	36
6. The lab of 2024	92
7. Research methodologies	18
8. Ovulation induction & IUI	139
9. OPU/ET hands-on workshops	119
10. Sexual medicine and Infertility	51

60 plus pharmaceutical and instrument companies participated and there was a huge stall exhibit area with small entertaining events. There was a stall of Odisha handloom which showcased various accessories directs from the weavers. The food that was served all there days was multicuisine with great taste & flavor.

The entire Organizing Committee of ISAR 2024 is grateful for getting this opportining to host this event and feel proud for the grand success of 28th ISAR 2024.


2024
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LH
Growth Hormone
Prolactin
production of high density lipoproteins and
bone resorption
decreases - decreases
TEAM A
SOUTH ZONE
TEAM B
WEST ZONE
TEAM C
EAST ZONE


Navigating
the new normal
in ART
ISAR
2024


the new normal
in ART

Report of ICRM Convocation 2024

The first ever convocation ceremony of the Indian College of Reproductive Medicine (ICRM) was held during the ISAR 2024 Annual Conference at Bhubaneswar on Friday, 02nd February, 2024. The ICRM Governing Council and Office Bearers were installed and the Founder members of ISAR, ISAR Office Bearers and ISAR Past Presidents were awarded Fellowships during the glittering ceremony. Honorary Fellowships were also awarded to several distinguished international faculty including Drs Paula Amato, President ASRM, Jared Robins, CEO ASRM, Georg Griesinger, Sergio Haimovich, Kurt Barnhart, Anuja Dokras, Budi Wiweko, Atsushi Tanaka and Yutaka Osaga.

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Padma Shri (Dr) Shanti Roy
Organising Chairperson
Dr. Pragya Mishra Choudhary
Organising Secretary


29th Annual Conference of
Indian Society for Assisted Reproduction
ISAR 2025
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