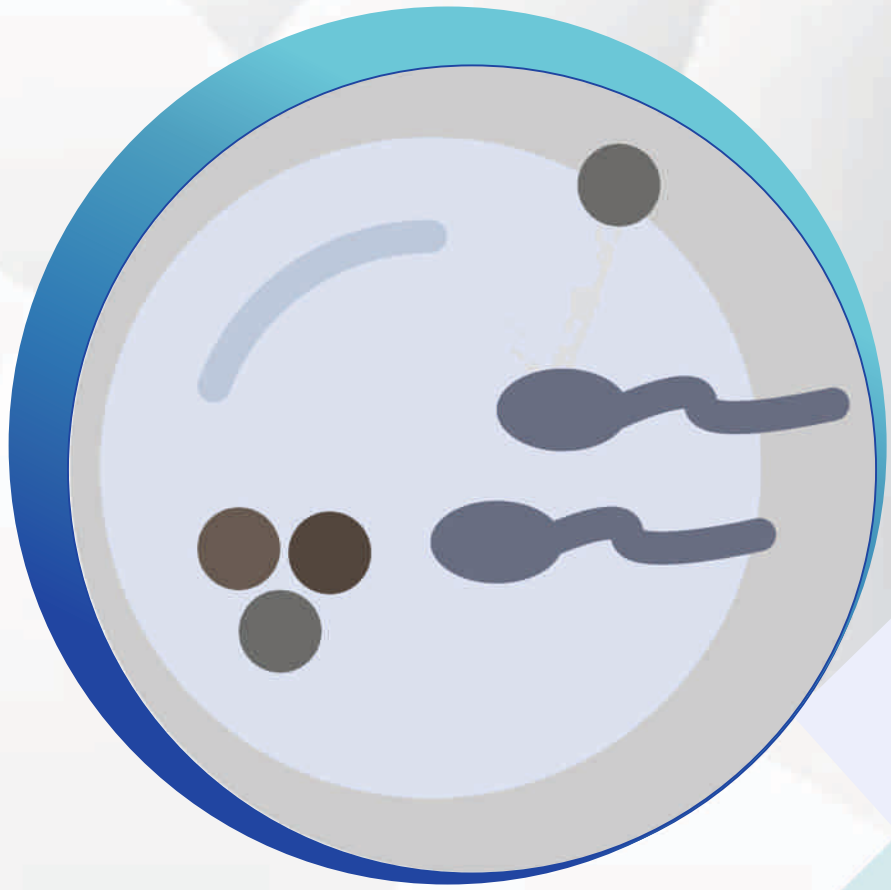
# IFS CONVERSATIONS

## Volume 15

## Recent Advances in Sperm Selection Techniques for IVF

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## MESSAGE FROM THE PRESIDENT DESK

**Dr Sudha Prasad**
President - IFS

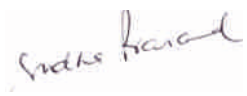
**Dear Friends,**

It is indeed a pleasure to address you all on this issue of IFS Conversations.

After the very successful virtual "Fertivision 2020" , I invite you all for "Fertivision 2021" which would be in a hybrid mode on 10th ,11th,and 12th December with 12 pre conference workshops on 4th and 5th December 2021 .

In this IFS conversation we have dealt with detailed analysis of the sperm factor in infertility and recurrent pregnancy loss. The editorial team and the authors have worked very hard towards it. Hope you all will find it very useful. The conversation also showcase various recent academic activities conducted by our extremely enthusiastic and committed members spread over 27 chapters across India and abroad.

Wishing you all a very Happy New Year!



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# MESSAGE FROM THE SECRETARY DESK

**Dr Neena Malhotra**
Secretary - IFS

**Dear Members and Friends**

Indian fertility society has progressed over the past few years with almost 3500 members and 28 chapters. We are a very academically oriented society with monthly publications of newsletters and quarterly publication of IFS conversation. Even during the past 1.5 years when the whole world came to a standstill due to unprecedented corona pandemic, IFS was very active in continuing the knowledge updation through its various online academic activities.

This time the IFS conversation has focused on role of sperm DNA fragmentation in unexplained infertility and recurrent pregnancy loss. Also, there is a review on various latest sperm selection techniques. I congratulate the editorial board for their tireless efforts in bringing these publications throughout the corona pandemic.

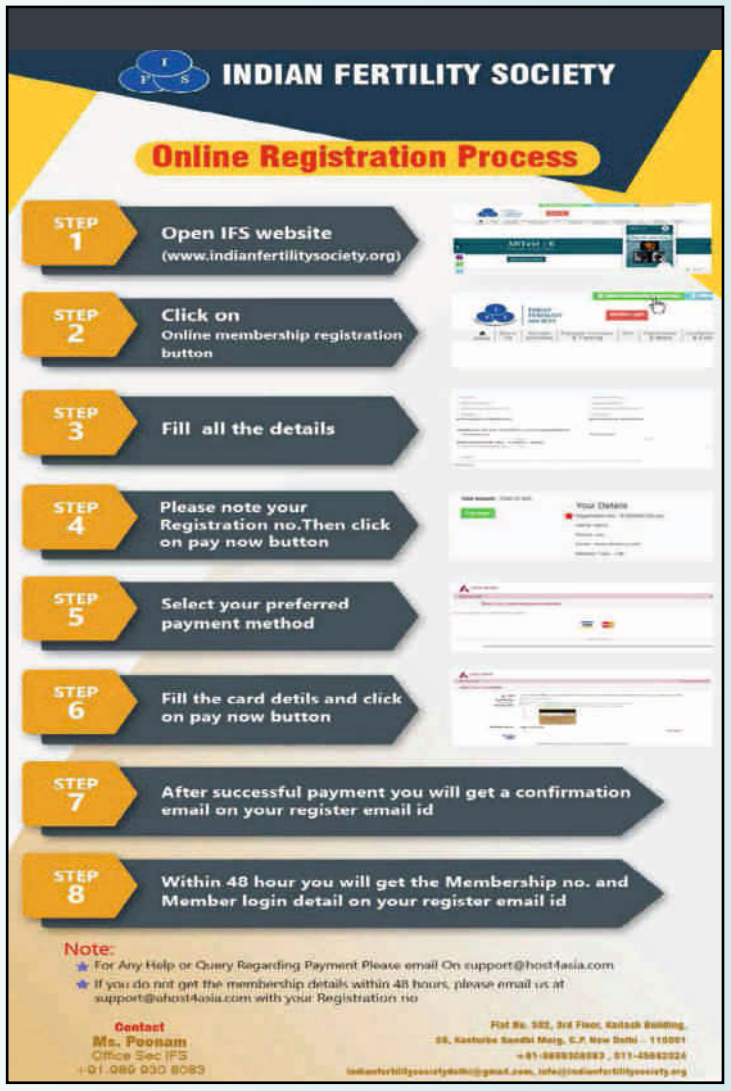
I also take this opportunity to welcome you all for the 17th Annual National Conference, "Fertivision 2021"

I hope the knowledge provided in this issue of IFS conversation will be useful to you in your clinical practice.

Wish you all a very happy new year!

Neena Malhotra

**Dr. Neena Malhotra**
Secretary - IFS

# MESSAGE FROM THE EDITOR'S DESK

**Dr. Shweta Mittal Gupta**
Editor - IFS

**Dr Rashmi Sharma**
Jt. Editor - IFS

**Dear Friends,**

Greetings from team IFS

In this issue of IFS conversation, we present to you a very important, though often neglected aspect of infertility treatment, that is role of sperm testing beyond the routine semen analysis. Sperm is a contributor of 50% genetic material in an embryo. There have been recent studies focusing on role of sperm DNA integrity in successful implantation and beyond. In this issue, we present a case report with 2 times poor quality embryos followed by successful IVF with sperms selection via microfluidic technique. We have also reviewed the literature on role of sperm DNA fragmentation in cases of unexplained infertility and recurrent implantation failure. There is also an in-depth article focusing on latest sperm selection technology like Microfluidics , MACS, IMSI etc .

We are a very academically active society. This issue also highlights all the academic activities undertaken in last 3 months from our state chapters , SIG's , vibrate webinars etc .

We sincerely thank all our authors for their wholehearted contribution towards this issue of IFS conversation . We would love to hear your comments and suggestions and also encourage all our readers to contribute in our forth coming issues of IFS conversations.

We look forward to meeting you all at Fertivision 2021 .

**Dr. Shweta Mittal Gupta**
Editor, IFS

**Dr. Rashmi Sharma**
Joint Editor, IFS

# INVITED ARTICLES

## Sperm DNA Fragmentation: A cause of repeated IVF- ICSI failure: A case report

**Dr. Rashmi Sharma**
**Director, Origyn Fertility and IVF**
**Joint Editor, Indian Fertility Society**

### Introduction

Infertility is a major issue among the couples . 1 out of 6 couples suffer from it. IVF has revolutionised the treatment of infertility but still there are many technical challenges to its success . Failure of IVF is a challenging situation. And if it occurs repeatedly it can have a major impact both on the patients treating doctor. Overall success rate of IVF is between 30%-40 %(1).

The pregnancy outcome after ART procedures has been unpredictable because several possible factors were involved in the process. Routine semen parameters, like semen concentration, motility and the percentage of normal sperm morphology are insufficient to predict pregnancy outcome after ART procedures(2).

Recent studies have shown that the integrity of genetic material in the sperm is essential for successful fertilisation and development of a healthy pregnancy . Sperm DNA fragmentation is a term used to denote abnormal genetic material within the sperm, which in turn may lead to male subfertility, implantation failure and miscarriages . Sperm DNA fragmentation (SDF) testing measures the quality of sperm as a DNA package carrier, and it therefore is more significant than the parameters analysed in conventional semen analyses.(3)

DFI, known as sperm DNA fragmentation index, was established to evaluate sperm chromatin integrity, and has gained increasing application for its diagnostic capabilities of male fertility potential and pregnancy outcome (4, 5)

While fully protaminated sperm DNA is highly stable and resistant to damage, deficiencies in protamination leave the DNA poorly compacted and more prone to damage (6)

Higher SDF is correlated with poor embryo development, lower implantation rate, and higher miscarriage rate in non-male factor infertility intracytoplasmic sperm injection cycles. Since defects in sperm may be hidden, the SDF test may bring additional information to the sperm quality evaluation of men with unknown infertility history(7).

Repeated implantation failure (RIF) is diagnosed when good-quality embryos repeatedly fail to implant after transfer in multiple IVF treatment cycles. There is as yet no universally accepted definition for RIF, despite There is as yet no universally accepted definition for RIF, despite many publications on this topic (8). RIF may be due to defects with either endometrium or embryo . There have been lot of focus on female part of it but since embryo is 50% male contribution , there have been recent focus in evaluating the role of sperm DNA fragmentation in RIF

### Case report

A young couple with married life of 5 years came to Origyn fertility and IVF centre, Pitampura with primary infertility. The wife was 35 years old and husband 36 years. wife had regular cycles coming at an interval of 25- 30 days and normal flow.

Her baseline showed an endometrial poly of 12x8 mm size. AMH was 2.3 ng/ml, other investigations were normal . HSG showed bilateral patent tubes.

Husband had grade 3 varicocele .His semen analysis showed severe oligoasthenospermia with sperm count < 1 million, 12 % showing forward motility and 2% morphologically normal sperms.

Repeat semen testing again showed sperm count< 1 million , 11% forward motility and 2 % morphologically normal sperms.

Hysteroscopic polypectomy was planned for wife followed by IVF- ICSI .

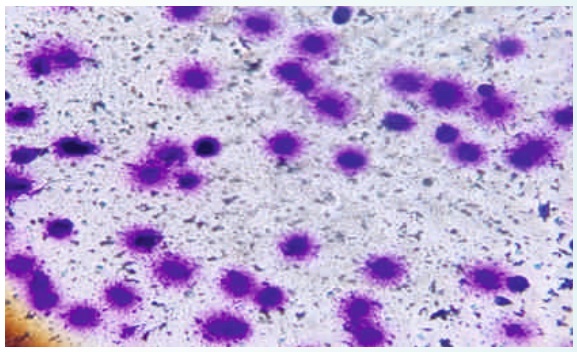
In the first cycle, ovarian stimulation was achieved with an antagonist protocol. On cycle day 2, recombinant FSH and human menopausal gonadotrophins administration was started. Their doses were adopted according to the number of ovarian follicles and their growth rates in vaginal ultrasonography. Gonadotropin-releasing hormone antagonist (GnRH antagonist) was initiated on 6 th day and continued up to the day when at least three follicles reached a diameter of ≥18 mm. Dual trigger was given and after 35 hours , OPU was performed. 13 oocytes - 5 M1 AND 8 M2 oocytes were obtained . ICSI was done and 5 grade B embryos were seen on day 3 , only 1 blastocyst could be transferred on day 5 . Beta HCG 12 days later confirmed negative result. Patient came back after second IVF failure from a different centre . In this cycle also in spite of good number of M II oocytes , only 1 not so good blastocyst was available for transfer .

Both these cycles resulted in poor quality embryos.

Sperm DNA fragmentation test was done after 2 IVF failures with a high DFI score of 72.2% where normally it should be <30%. Husband underwent varicocele surgery after consultation with a urologist . He also was put on antioxidants for 3 months. After 4 months – DFI score again was high at 60% along with continuing poor sperm count and motility .

Patient underwent third cycle of IVF – ICSI with sperm selection with the help of microfluidic chamber . This time we could obtain good quality 7 embryos ( vitrified on day 4 – compaction stage in 3 straws)

2 grade A compaction stage embryos were transferred in the subsequent FET cycle with successful ongoing singleton pregnancy .



### Discussion

Implantation is one of the most critical steps in reproduction. Recurrent implantation failure (RIF) is the absence of implantation after repeated embryo transfers. While this clinical phenomenon is commonly encountered and there is vast literature on the subject, there is no universally accepted definition.

Apart from the well-known causes for RIF still sometimes the cause remains not known. Studies at molecular level can explain many unexplained causes of RIF. Sperm DNA fragmentation is one on them.

Many studies have shown varying results between sperm DNA fragmentation and recurrent IVF failure with some studies saying it is not the cause and some saying it to be important cause of RIF (9)

Study by Coughlan C et al., do not support the hypothesis that sperm DNA fragmentation is an important cause of RIF or Recurrent miscarriages, or that sperm DNA integrity testing has value in such patients(10).

Study by Jhao J et al., indicate that assays detecting sperm DNA damage should be recommended to those suffering from recurrent failure to achieve pregnancy. Selection of sperm without DNA damage for use may improve the clinical outcome of ART(11).

Debate still goes on . For our patient very high sperm DNA fragmentation appears to be important cause of repeated failure to obtain good quality embryos and IVF failure . Selecting sperms with probably intact DNA through the use microfluidic chamber in this case seems to have helped the couple.

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# Sperm DNA fragmentation: A hidden cause of unexplained Infertility and recurrent pregnancy loss

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## Introduction

Unexplained infertility and recurrent pregnancy loss are two areas in the field of ART which if presents can bring much stress to both the treating doctor and the patient.

When in an infertile couple the results of a standard infertility evaluation i.e., semen evaluation, tubal tests and ovulatory studies are normal, a diagnosis of unexplained infertility is made. The likelihood that all such test results for an infertile couple are normal (i.e., that the couple has unexplained infertility) is approximately 15% to 30% (1).

Recurrent pregnancy loss (RPL) is defined as the loss of two or more pregnancies. The exact prevalence of RPL is difficult to estimate, but most studies report that RPL affects 1–2% of women [2].

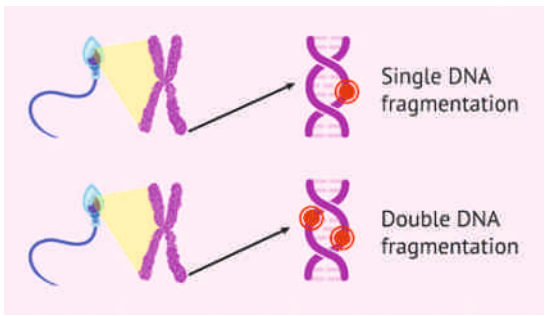
Sperm DNA fragmentation denotes abnormal genetic material within the sperm, which in turn may lead to male subfertility, implantation failure and miscarriages. Since the male gametes lack many DNA repair mechanisms, sperm DNA is especially susceptible to damage by oxidative stress from neighbouring immature sperm, leukocytes, and other environmental exposures.

DNA damage, such as fragmentation and denaturation, can have an untoward effect on fertilization and embryo development and can cause infertility and even recurrent pregnancy losses [3]. Sperm DNA fragmentation (SDF) testing measures the quality of sperm as a DNA package carrier, and it therefore is more significant than the parameters analysed in conventional semen analyses [4]. Sperm DNA integrity testing has therefore been proposed to be a test with promising potential to compliment the standard semen analysis [5].

This review of literature focuses on sperm DNA integrity testing in the evaluation of unexplained infertility and recurrent pregnancy loss.

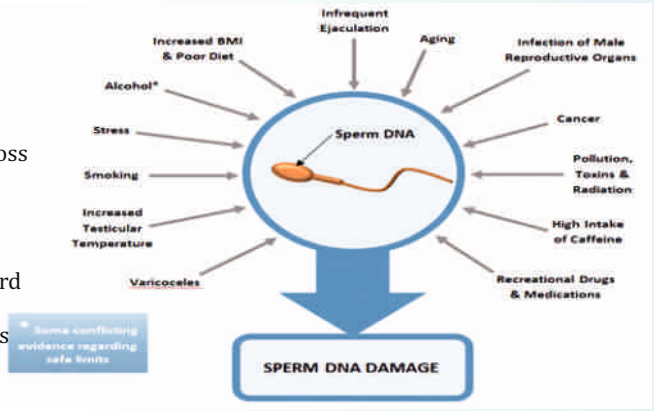
## What is sperm DNA fragmentation and why it happens?

To simplify, sperm DNA fragmentation occurs when there is a change in the bases or a physical break in one or both of the DNA strands of the chromosomes contained within the sperm. Besides single standard DNA breaks (SS-DBs) and double standard DNA breaks (DS-DBs), chromatin damage includes altered chromatin configuration and defective nuclear protein.




Sperm DNA integrity is essential for the birth of healthy offspring [6]. Increasing documentation shows that sperm DNA fragmentation (SDF), a sign of damaged chromatin, has an independent and remarkable role in male infertility and reproductive success [7].

The causes of sperm DNA damage are numerous, of complex nature and could be testicular or post-testicular [8]. These may include defects in spermatogenesis (e.g., genetic or developmental abnormalities) and testicular or post-testicular injury (e.g., gonadotoxins, hyperthermia, oxidants, and endocrine abnormalities). It has been suggested that protamine deficiency (with consequent aberrant chromatin remodeling), reactive oxygen species and abortive apoptosis may be responsible for sperm DNA damage [9].




Not all the patients require sperm DNA fragmentation. It is mainly warranted in couples with

- Unexplained infertility
- Arrested embryo development
- Poor blastocyst development
- Multiple failed IVF/ICSI treatments
- Recurrent miscarriage
- Advanced chronological age
- Varicocele
- Poor semen parameters
- Exposure to harmful substances

## What Does Testing for Sperm DNA Fragmentation involve?

There are many different tests for sperm DNA fragmentation, but the most commonly studied ones are

1. The sperm chromatin structure assay (SCSA)

2. The deoxynucleotidyl transferase-mediated dutp nick end labelling assay (TUNEL)

3. The single-cell gel electrophoresis assay (COMET)

4. The sperm chromatin dispersion test (SCD).

These tests provide an estimate of the degree of DNA damage present in a semen sample.

## Sperm DNA fragmentation testing warranted in unexplained infertility and recurrent pregnancy loss patients

It is found that in recurrent pregnancy loss and unexplained infertility patients, sperm DNA fragmentation examination could help to identify the cause of the infertility or pregnancy loss and guide the possibly therapeutic strategies.

Various studies have shown varying results regarding using sperm DNA integrity testing in infertility workup.

## Unexplained infertility

When infertile couples or individuals have undergone all appropriate tests and no cause for their infertility is found, they are diagnosed with unexplained infertility. As already stated earlier about 15- 30 percent of infertile couples are diagnosed with unexplained infertility, also referred to as idiopathic infertility.

Unexplained infertility most likely involves issues with poor egg or sperm quality, or problems with the uterus or fallopian tubes that aren't identifiable in routine infertility tests. Studies at molecular level have found out that DNA fragmentation can be the underlying hidden causes in some of these couples.

A study by Oleszczuk et al was done to investigate the prevalence of high DFI in male partners of unexplained infertile. In this study, The percentage of couples with diagnosis 'unexplained infertility' in which the male partner has DFI >20% or DFI >30% was calculated. In the group diagnosed with 'unexplained infertility' 17.7% of the men (95% CI 10.8-24.5) presented with DFI between 20 – 30% and 8.4% (95% CI 3.40-13.4) had DFI ≥30%. A significant part of men diagnosed as unexplained infertility according to traditional diagnostic methods had remarkably high degrees of fragmented sperm DNA [10].

A review article by Alaa hamada et al, on unexplained Male infertility: diagnosis and management, concluded that further tests are certainly required beyond semen analysis for evaluating sub fertile couples where cause remains unknown. The time has come for technological developments in the field of andrology to bring robust and cost-effective clinically useful tests to look for sperm DNA fragmentation to fix the shortcomings of the routine semen analysis [11].

Study by Kim GY et al concluded that physicians and researchers working with ART must continue to make efforts to obtain healthy sperm with nuclear DNA integrity to minimize the adverse effects that may arise in offspring conceived from sperm with DNA damage [12].

A review of literature by Pandruvada S et al says that though semen analysis is the cornerstone of evaluating male infertility, it is imperfect and insufficient to diagnose male infertility. As a result, about 20% of infertile males have undetermined infertility, a term encompassing male infertility with an unknown underlying cause[13].

Thus we see that it may be advisable to offer sperm DNA fragmentation testing in couples with unexplained or idiopathic infertility. An abnormal test result may indicate that fragmented sperm chromatin might be the cause of infertility. In an age when a small quantity of sperm can lead to pregnancy through in vitro fertilization or intracytoplasmic sperm injection, selecting healthy sperm is important. In couples with unexplained or idiopathic infertility and elevated sperm DNA fragmentation, a reproductive andrologist evaluation is warranted to assess underlying causes of DNA fragmentation.

## Recurrent pregnancy loss

Recurrent pregnancy loss is a devastating experience for a couple and their caregivers. The aetiopathogenesis of recurrent pregnancy loss (RPL) is heterogeneous.

Various causes such as uterine anatomical anomalies, genetic factors, and infectious and endocrine disorders have been reported for RPL. However, approximately 50% of the causes are unknown, which can be due to male factors. Several studies have been done on semen parameters to determine the unknown causes and risk factors for miscarriages, however, only studying common semen parameters have not been sufficient.

Two very recent comprehensive reviews on sperm DNA fragmentation tests [14,15] have reopened the debate over their usefulness in improving pregnancy outcome.

In this regards, two aspects need to be seen. First, spermatozoa are not simply carriers of paternal chromosomes, but play a role beyond fertilization. For instance, the spermatozoon transcribes genes critical for early embryonic development, inferring that integrity of sperm genome is essential for a successful gestation. Second, if sperm factors play a role in early embryonic development, are sperm DNA integrity tests useful as diagnostic and prognostic markers, especially in the context of recurrent pregnancy loss (RPL)? [16]

A systematic review and metanalysis by McQueen DB et al concluded that there was a link between sperm DNA fragmentation and recurrent pregnancy loss. Fifteen prospective studies were included in the review. Pooled data from 13 studies suggest that male partners of women with a history of recurrent pregnancy loss have a significantly higher rate of sperm DNA fragmentation compared to the partners of fertile control women: mean difference 11.91, 95% CI 4.97-18.86. However, given the significant heterogeneity between studies and lack of prospective pregnancy outcome data, they said that further large prospective studies are needed [17].

A study was carried out by Carlini T et al to investigate the male factor in Italian couples experiencing RPL following natural conception. The results suggested a correlation between increased SDF and impaired reproductive capacity in terms of both fertilization and pregnancies carried to term but they concluded that high SDF cannot yet be considered a predictive factor for the risk of RPL [18].

A meta-analysis was conducted of 12 prospective and 2 retrospective studies involving 530 men with a history of RPL by Tan J et al. In the study it was found that Couples with a history of idiopathic RPL demonstrated higher levels of SDF than fertile couples (average mean difference 11.98, $P < 0.001$). Results supported the diagnostic value of SDF over standard semen analysis, as well as a possible paternally derived genetic origin of unexplained RPL [19].

Recurrent pregnancy loss (RPL) is pathogenically complicated. So far, studies on the aetiology of RPL have focused on women and little attention has been paid to the role of sperm in the development and progression of the disease. Half of the genomes in the embryo are provided by sperm. RPL may be induced by abnormal number and structure of sperm chromosomes and sperm DNA integrity, gene mutations, and epigenetic abnormalities. This review presents an overview on the advances in the studies of the role of sperm genetic abnormality in RPL, hoping to give some help with the prediction, diagnosis and treatment of the disease.

**Conclusion**

Sperm DNA fragmentation testing has become an important test for evaluating male fertility though the relationship between DNA fragmentation in idiopathic recurrent pregnancy loss (RPL) and unexplained infertility remains a topic of ongoing debate.

There are studies to suggest that sperm DNA fragmentation testing should be offered to the couples of recurrent pregnancy loss and unexplained infertility in an effort to find hidden causes. In future more comprehensive studies may increase the scope of providing SDF testing to infertile couples for better clinical management.

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# Sperm DNA fragmentation: A hidden cause of unexplained Infertility and recurrent pregnancy loss


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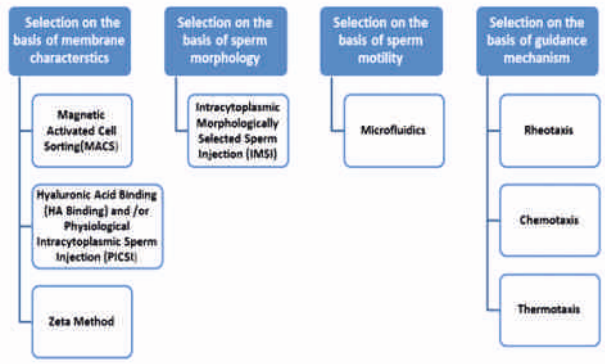
## INTRODUCTION

Out of the millions of sperms that are ejaculated, only a few hundred of those make it to the ampulla, where they encounter the egg and fertilization takes place. Presumably, the selection of this subpopulation of sperms through the oviduct is done in a way that only the ones with highest fertilization capacity and all the required features to support embryo development are selected to fertilise the egg.

One of the reasons for the low efficacy of ART has been credited to the lack of appropriate methodology and technique for the in-vitro selection of subpopulation of sperms with all the required features. Therefore, in order to overcome these shortcomings, techniques that are simple, economical, ensure the enrichment of sample with best quality sperms which are devoid of leukocytes and bacteria, as well as toxic or bioactive substances like reactive oxygen species (ROS)are required. So, the techniques that meet all these requirements and are the most extended techniques for the preparation of sperms are Swim-Up (SU) and Density Gradient Centrifugation (DGC). Both these methodologies are used all around the world prior to IVF and ICSI, but the one of the major disadvantages of these procedures is that, the selection is only on the basis of the motile capacity of the sperms which does not necessarily mean that the sperms are of highest quality. Therefore, the need of the hour are those sperm selection methods that are based on sperm characteristics which not only focus on the motile capacity of the sperm but also its morphology and fertilization ability.

Therefore, different sperm selection techniques are available, these includes PICSI, IMSI, MACS and MFSS. The application of these techniques depends upon sperm concentration, motility and




### Principle

The head of a mature sperm possesses a hyaluronan-specific ligand receptors which facilitates the mature sperm devoid of any aneuplodies and abnormal DNA integrity to unite to hyaluronan. This precisely is the principle of Physiological Intracytoplasmic Sperm Injection (PICSI) wherein an embryologist chooses the sperms which are mature, competent and biochemically active. This modus operandi mimics one of the most crucial steps in the innate fertilization course of action, that is, the binding of the sperm to the cumulus-oocyte complex.

### History and Evidence

According to a study, the relative reduction in Sperm DNA Fragmentation (SDF) after PICSI was found to be 67.9% (2). Though according to another randomised control trial PICSI did not shown any benefit over ICSI and no significant difference in the implantation rate and the pregnancy rate was found but it did show a reduction in the miscarriage rate (7.0% vs 4.3%, p-0.003). Studies also revealed that HA-ICSI decreased the miscarriage per woman randomly assigned: 7% chance of miscarriage with ICSI versus 3% to 6% chance with HA-ICSI and per clinical pregnancy: 20% chance of miscarriage with ICSI compared to 9% to 16% chance with HA-ICSI (3)

### Technique (1)

Currently, two ready-to-use systems specifically designed for sperm-HA binding selection are available:

1. Plastic culture dish with HA hydrogel attached to the bottom of the dish (PICSI® Sperm Selection Device, MidAtlantic Diagnostic - Origio, Måløv, Denmark)
   a) PICSI dishes are conventional plastic dishes pre-prepared with 3 microdots of powdered HA which are then re-hydrated with ~5ul of fresh culture media
   b) Then, a 2ul droplet of prepared sperm sample is then connected to the culture medium droplet along with the drops of Polyvinylpyrrolidone (PVP) are also placed elsewhere on the dish at this time for the manipulation of the sperms.
   c) The PICSI dish is then incubated under oil; within 5 min the bound spermatozoa are attached by their head to the surface of the HA-microdots and start spinning around their head. Finally, an ICSI injecting needle is used to pick up the best motile HA-bound sperms in order to inject them into the oocytes.

2. A viscous medium containing HA (Sperm Slow™, MediCult – Origio)

This requires a specific method of droplet preparation in order to allow selection of sperms bound to HA. It is more versatile than PICSI as it can also be used on a glass bottom culture dish for higher magnification sperm evaluation.

### Advantages

More filtered way of selecting the most competent sperms for fertilisation process. In this, the choice of sperm is completely based on its ability to fertilise and perform the role job

### Disadvantages

There are no such drawbacks of this technique except for the fact that in case of TESA samples or immotile sperms wherein PICSI cannot be employed. It also cannot be employed in cases of patients with occasional spermia where sperm count is ≤1million/ml

## Intracytoplasmic Morphologically selected Sperm Injection(IMSI)

**Principle**

IMSI is a technique which involves the use of MSOME in conjunction with ICSI, the sperm selection criteria is based upon the various approaches used in studies to assess the sperm morphology through SEM(Scanning Electron Microscope) and TEM(Transmission Electron Microscope).The microscopic examination of sperms involves the assessment of six subcellular organelles, wherein, in case of sperm head, three important characteristics taken into consideration are the shape, the presence of vacuoles and the base. So, MSOME does provides an accurate description of the sperm abnormalities, particularly the presence of head vacuoles (5). However, there has been no consensus on normal or abnormal MSOME criteria, despite being essential to transposing MSOME analysis into routine evaluation of male infertility (6).

**History and Evidence**

So, to overcome the limitations of the conventional magnification (sperm evaluation at ICSI is a maximum 400x), Bartoov et al (1994, 2001, 2002) introduced a new approach involving real-time high magnification observation of unstained spermatozoa called **M**otile **S**perm **O**rganelle **M**orphology **E**xamination **(MSOME)** and incorporation of this technique together with micromanipulation gave rise to a modified ICSI termed as **I**ntracytoplasmic **M**orphologically selected **S**perm **I**njection **(IMSI).** This method involves the use of an inverted light microscope equipped with high power Nomarski optic enhanced by digital imaging to achieve a magnification of up to 6300X.

But, according to a systemic review published in 2013 there is no evidence of effect of IMSI on live birth or miscarriage and the evidence that IMSI improves clinical pregnancy is also of very low quality. (9)

**Technique**

The analysis of the sperm involves the use of interference phase contrast inverted microscope with the optics of Nomarski. The final image obtained on the screen is a result of a combination of the magnification of the objective, the camera adaptor, ratio between the diagonal screen size (mm), diagonal of the camera chip size(mm), and internal magnification of the microscope. So, depending upon these specific characterstics of the IMSI system, the final magnification varies from 6000X to 6600X

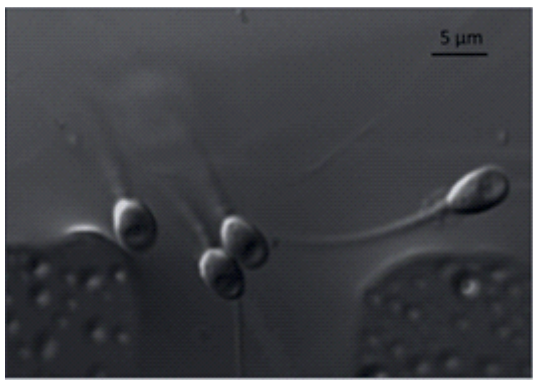



**Fig 3: Human spermatozoa with head vacuoles observed using MSOME, at ×6600 magnification** (6)

***Preparation of IMSI dish***

The dish used for IMSI is usually a glass bottom dish in which three types of droplets are made.

a) Observation droplets: These droplets of sperm culture medium might contain PVP ranging from 0% to 10% depending upon the intensity of motility of the sperms.

b) Clean droplets of clean sperm culture medium: After the sperm cells have been evaluated, they are transferred to these droplets.

c) Clean droplets of PVP 10%: These are 1ul droplets created parallel to the droplets containing spermatozoa. It is recommended to create bridges between these two droplets as it eases the detection of spermatozoa as it helps capture the head of mature sperms.

***IMSI in practice***

a) 1ul of prepared sperm sample droplet is placed inside the observation droplet of the pre-prepared IMSI dish.

b) Sperms with morphological abnormalities are omitted and not aspirated while the other motile sperms are transferred to the fresh PVP droplets and classified in accordance with classification published by Perdrix et al. (2012):

- **Type 0:** spermatozoa without vacuole.
- **Type 1:** spermatozoa with vacuoles occupying 0–5.9% of the nuclear surface.
- **Type 2:** spermatozoa with vacuoles occupying 5.9–12.4% of the nuclear surface.
- **Type 3:** spermatozoa with vacuoles occupying over than 12.4% of the nuclear surface.

Finally, individual sperm cell is then placed in appropriate droplet based on the type in the IMSI dish

| **Advantages** |
|---|
| IMSI helps select live sperms in real time, therefore helps separate sperms |
| It allows for an accurate visualisation of sperm cells and is around 15 times more powerful than conventional microscopes used in IVF or ICSI |
| **Disadvantages** |
| It is very time consuming |
| Long exposure of sperm to the heated stage of microscope increases vacoulation in the sperm head and also affects the sperm cytoplasm |

## Magnetic Activated Cell Sorting (MACS)

**History and Evidence**

Evidence from various studies suggest that normal spermatozoa used for ICSI can have negative impact on ART outcomes. The methodologies like swim-up and Density Gradient Centrifugation do not take into account certain important molecular features such as apoptosis and/or sperm DNA fragmentation. Therefore, development of new technologies was required in order to allow better gamete selection. So, following this rationale, MACS was applied as a sperm preparation method in order to remove apoptotic cells using Annexin V. Overall, it is a method of separating cells of interest from a mixed cell population.

**Principle**

MACS method is based on using of paramagnetic Annexing V-conjugated microbeads. It involves the conjugation of magnetic micro beads with specific antibodies or proteins on the target cell's membrane. It has been proposed as a safe method to select non-apoptotic and viable spermagnetic(12). Annexin V has a strong affinity for phosphatidyl serine but cannot pass through the intact sperm membrane. Colloidal superparamagnetic beads (~50 nm in diameter) are conjugated to highly specific antibodies to annexin V and used to separate dead and apoptotic spermatozoa by MACS. Annexin V binding to spermatozoa indicates compromised sperm membrane integrity.

**Technique**

1) A 100 µL sperm sample is mixed with 100 µL of MACS microbeads and incubated at room temperature for 15 minutes.
2) The mixture is loaded on top of the separation column which is placed in the magnetic field [0.5 Tesla (T) between the poles of the magnet and 1.5 T within the iron globes of the column];1 Tesla = 10,000 gauss.
3) The column is rinsed with buffer. All the unlabeled (annexin V-negative) non-apoptotic spermatozoa pass through the column.
4) The annexin V-positive (apoptotic) fraction is retained in the column.
5) The column is removed from the magnetic field, and annexing V-positive fraction is eluted using the annexin V-binding buffer.

**Fig 5: Magnetic Activated Cell Sorting(MACS)**

| **Advantages** |
|---|
| MACS acts at the molecular level as opposed to routine sperm preparation techniques that rely on sperm density and motility. |
| **Disadvantages** |
| Viable spermatozoa ought to be separated from all substances in the ejaculate such as apoptotic spermatozoa, leukocytes, and seminal plasma. MACS, which removes apoptotic spermatozoa, needs to be used in conjunction with other techniques such as density gradient centrifugation to remove the other substances. |

## MICROFLUIDICS

**History and Evidence**

The silicon microfluidics device was used in mid 1990s for selection of motile sperm (Kricka et al., 1993). Human semen was firstly processed in year 2003 and motile sperm isolation was done with impending therapeutic efficacy (Schuster et al., 2003). Cho et al., 2003 designed special parallel microchannel maintained by gravity driven pumping mechanism in microfluidics device and Schulte et al., 2007 reported that microfluidic sperm processing could significantly decrease the percentage of sperm with DNA damage and provide high motility sperm. Then, a microfluidic device was developed by Nosrati et al., 2014 to isolate progressively motile sperm in 500 parallel microchannel and also sperms with high DNA integrity and motility (15)(16).

**Principle**

Microfluidics helps sort sperms in a faster and a gentler way that closely mimics the natural sperm selection and avoids all the detrimental elements of current sperm sorting techniques. Microfluidics sperm sorter (MFSS) is a technique used to separate motile and morphologically good sperm with normal DNA integrity. It is a fluid dynamics-based model with sub microliter channels. The raw semen sample is used in this technique without any centrifugation, in order to avoid the generation of ROS. The geometry and flow involved in microfluidic platform closely mimics the natural in vivo locomotion of sperm at sub-microlitre level in micro confined environment of female reproductive tract.

**Technique**

Given below is the protocol of a cyclo-olefin polymer-based microfluidics sperm sorting chip manufactured by Menicon Co, which is approved by U.S. Food and Drug administration (Qualis Sperm Sorter, Menicon Life Science)(17).

1) Dilute the semen sample 1:1 with sperm washing media and maintain 37 degrees before using MFSS.
2) The sample is poured in the chamber A and the medium is dispensed into B which is parallel to each other and withdrawal to their specific outlet A-to-D and B-to-C. This technique helps to sort good spermatozoa collected in chamber C and immotile spermatozoan flow into the chamber D.
3) Firstly, fix the chip in 60 mm dish and load 100µl media in the given 4 chambers A, B, C and D. By this loading of media, streamlines are made.

4) Remove media from all the four chambers. Further, load 20 µl media in the chamber C and D, while 100 µl media in chamber B. Then, gently load 65 µl of suspended semen sample in chamber A.
5) The best motile spermatozoan move and get collected in chamber C within 30 to 35 minutes (25-30 µl).
6) While immotile spermatozoa, dead spermatozoa and debris accumulate in chamber D.
7) Sperm can be collected from chamber C and used accordingly for IVF/ICSI.

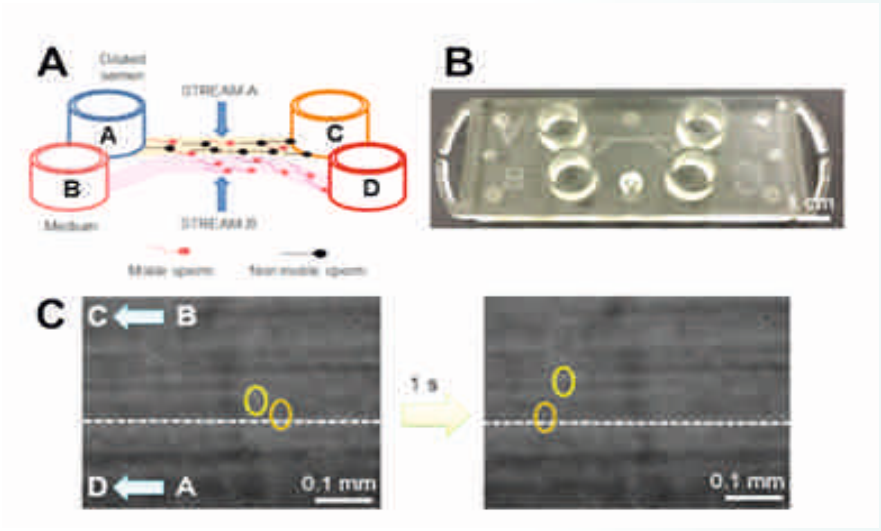



**Fig 6: (A) Schematic of the mechanism of microfluidic sperm sorting devices; (B) Chip device made of cyclo-olefin polymer (Menicon Co. Ltd.); (C) Microscope images during sperm sorting; Yellow and orange circles show human sperm swimming across the interface of the two laminar flows** (18)

## Microfluidic sperm sorting approaches can generally be sorted into three categories:

**Type 1: Microfluidic devices that isolate only motile sperm**
This device employs the technologies that improve the swim up method by translating the process of motility screening to a microfluidic system and is one of the largest microfluidics devices.

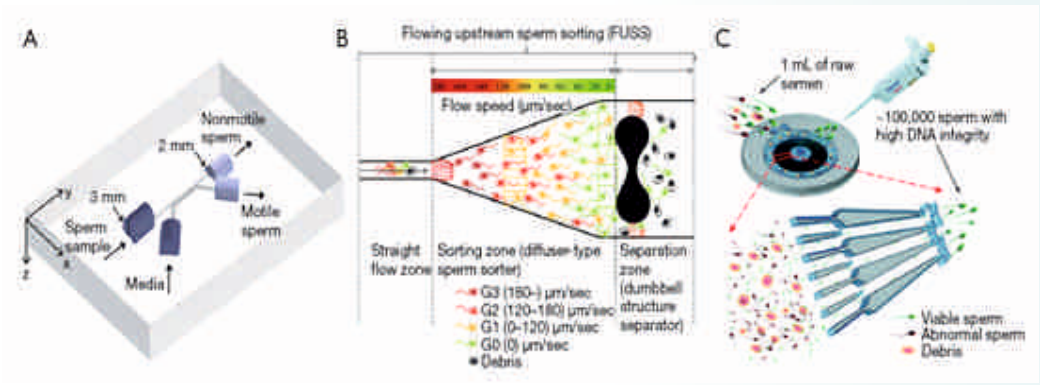



**Fig 7: Type 1- Microfluidic systems designed for separation of sperm based on sperm motility. (A) Motile sperm can be selected from immotile sperm due to their ability to swim across channel width** (19)**; (B) motile sperm are selected and sorted by swimming speed using the imposed velocity gradient** (20)**; (C) a series of parallel, long narrow channels are used to select motile, viable sperm** (15)

**Type 2: Microfluidic devices that isolate sperm cells without relying on sperm motility**
The selection mechanism of these microfluidics devices relies upon sperm shape, size, and/or other physical biomarkers instead of sperm motility. The primary focus of these systems is not on capturing an improved sperm sub-population, rather these systems focus more on the potential to retain the full fertilization capability of a sub-fertile semen sample by indiscriminately capturing sperm cells

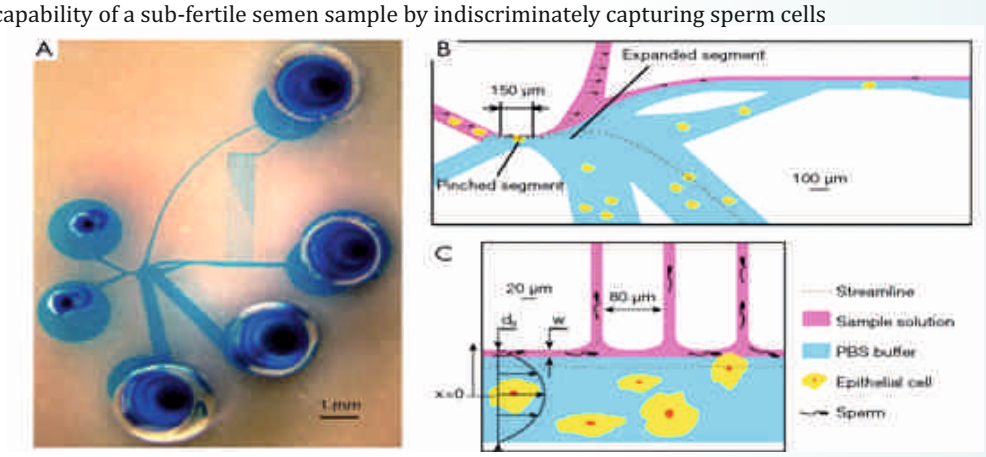



**Fig 8: Type 2- This figure depicts a microfluidic system designed for rapid separation of sperm from epithelial cells with application in forensics related to sexual assaults. (A) A picture of the actual device; (B) the cell mixture is aligned against the top wall in the pinched segment, and then the position difference of different sized cells is amplified in the expansion region; (C) sperm recovery rate is improved in the parallel capillary tubes**

**Type 3: Microfluidic devices for the observation and selection of individual sperm.**

These microfluidic devices take advantage of the ability of microfluidics to capture and non-invasively investigate the characteristics of a single sperm cell while maintaining sperm viability. An emerging area of research which focusses on isolation of a single sperm cell uses microfluidics sperm sorting system combined with Raman spectroscopy, a type of vibrational spectroscopy that relies on inelastic scattering of monochromatic light by the molecular structure of a system to determine the constituents of the system.

| Advantages |
|---|
| Spermatozoa are separated without centrifugation that aids in reducing centrifugation induced ROS generation. |
| Spermatozoa separated have better DNA integrity. |
| **Disadvantages** |
| Can only work in progressive motility spermatozoa samples. |

## CONCLUSION

The efficiency of Assisted Reproductive Technology (ART) still has a scope of improvement. Sperm selection is one of the most important factors on which the success of IVF and ICSI lies, especially in the cases where the cause of infertility is the male factor. However, the methodologies widely and commonly used have not proven to be useful and are effective in only certain cases of infertility.

But the various novel methodologies discussed above which are based on physiological selection operating in vivo and on microfluidic environment have given promising results.

But further studies are still required to get a better understanding of their advantages and limitations, in order to improve the ART outcome.

# IFS ACTIVITIES 2021

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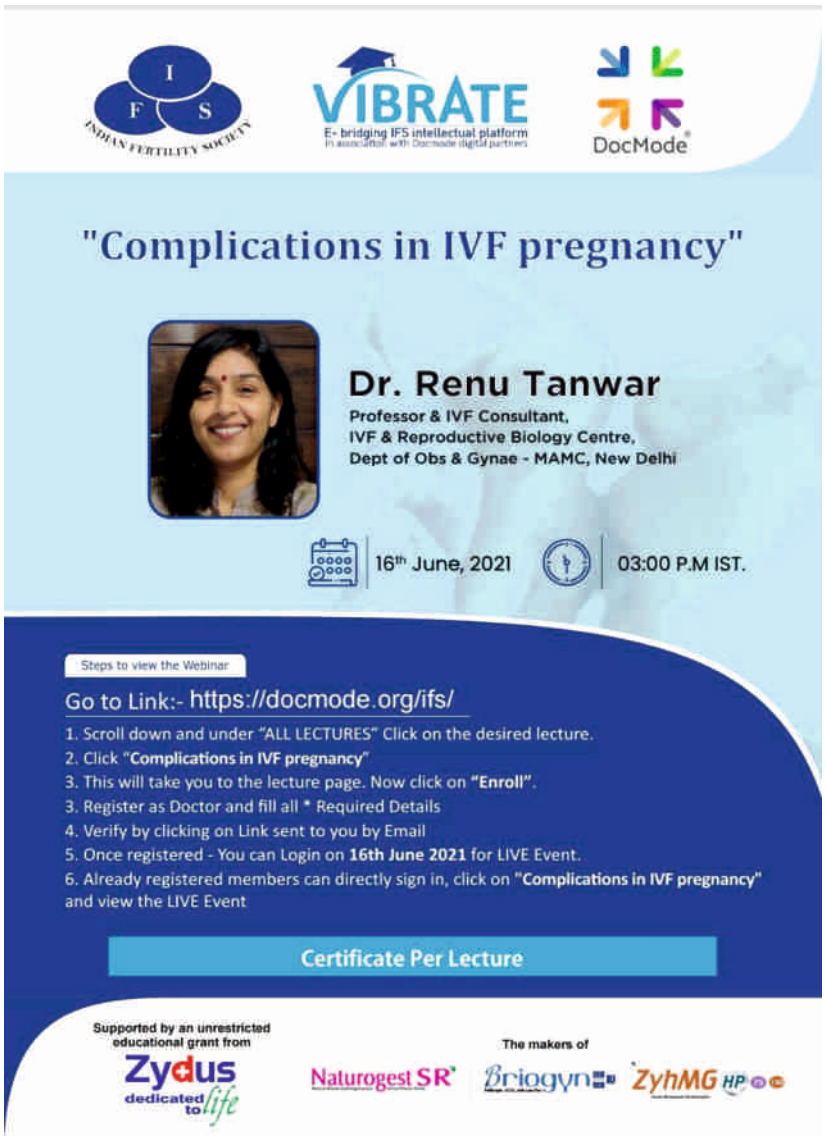


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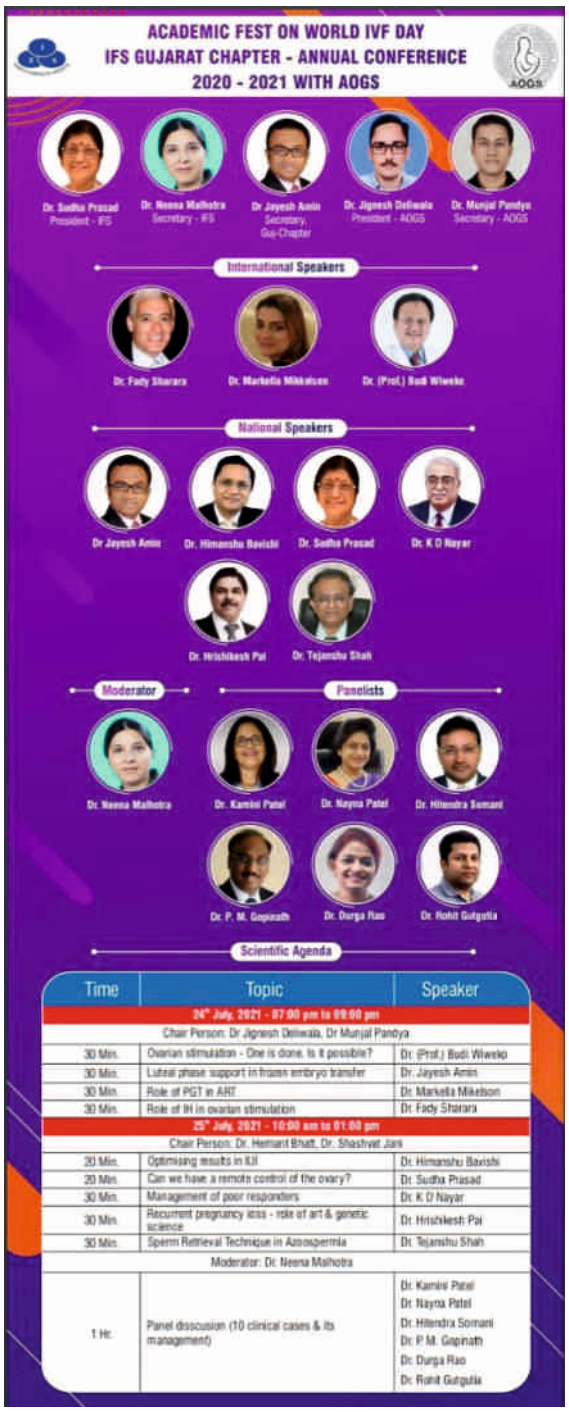


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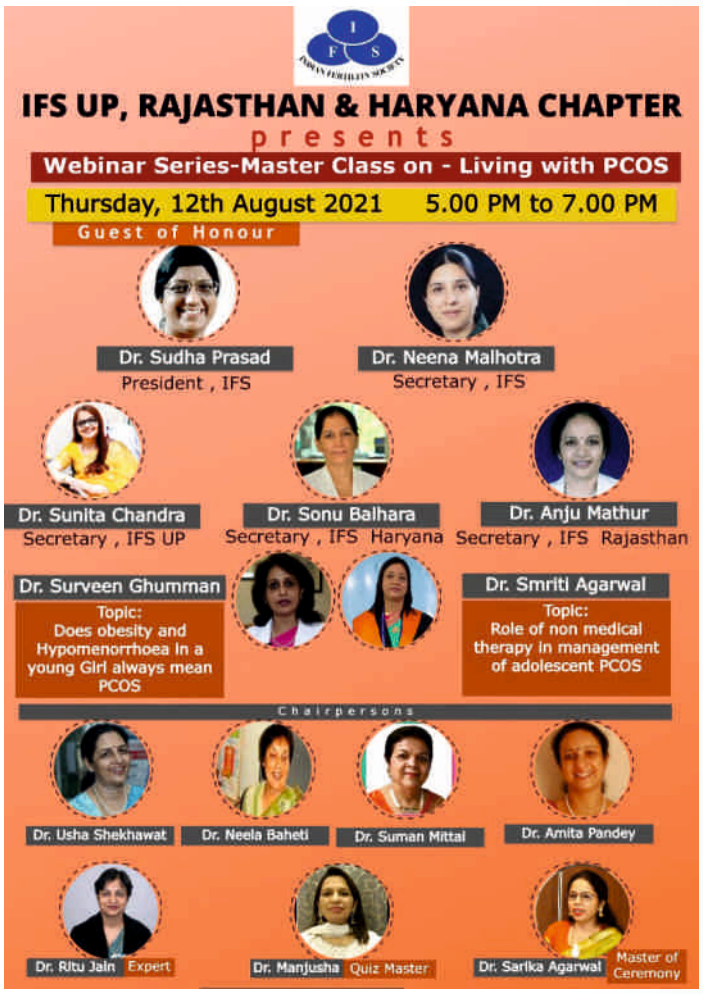


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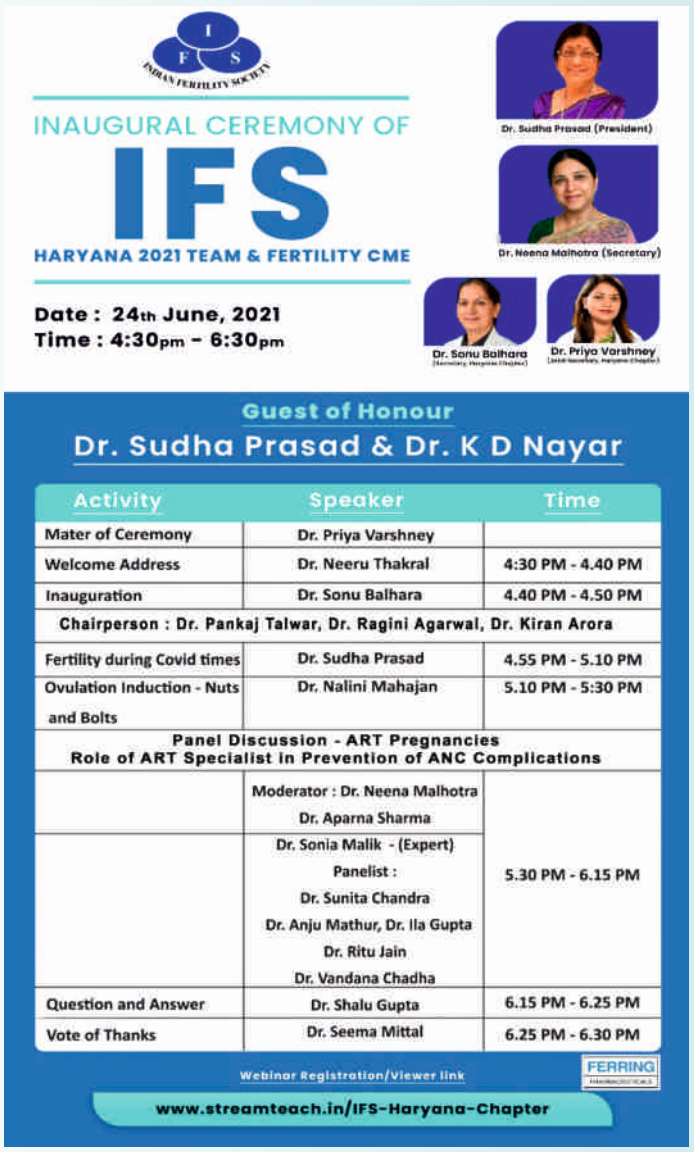

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# MISCELLANEOUS



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**Abstract Submission Closes on 30th November, 2021**

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| Foreign Delegates | $ 50 |

**For More Information Call Mr Vikas Sharma**
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