IFS CONVERSATIONS

Volume 16

Theme

Tackling Thin Endometrium

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MESSAGE FROM THE
PRESIDENT DESK

Dr K D Nayar
President - IFS

Dear Friends,

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

In this IFS conversation we have dealt with detailed Tackling Thin Endometrium. 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 member. .

Wishing you all a very pleasant reading of this issue of IFS Conversation!

Dr. K D Nayar
President- IFS

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MESSAGE FROM THE SECRETARY DESK

Dr Surveen Ghumman
Secretary - IFS

Dear Friends

Indian fertility society is an academic society which focusses on academics. It has a pan India presence with 29 chapters and over 3600 members. This year the theme of year is Quality Research and academics.

One of the initiatives is IFS surveys and the first one is online on FET . Please go on the website to answer and contribute to data collection.

With the new team taking over and COVID cases being low, we have now gone on to physical meetings from this year and hope to meet all our members more often. This year our Annual Conference “Fertivision - 22” is from the 9th to 11th December. We look forward to see you in Hyderabad for it.

IFS Conversation is the official newsletter of our Society, which informs the members about activities by the society all over India. It also deals with recent topics and debates in the field of ART. This particular issue has focused on thin endometrium, the dilemmas it causes for an ART specialist and methods of tackling it

Hope you enjoy reading this issue of IFS Conversations. The editorial team has put in lot of hard work to make it an interesting read

Best Wishes

Dr. Surveen Ghumman
Secretary - IFS

MESSAGE FROM THE EDITOR'S DESK

Dr. Sweta Gupta
Editor - IFS

Dr Rupali Bassi Goyal
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
Tackling thin endometrium. An Article on role of GCF is written highlighting its role. In this issue , we present two in-depth articles on stem cells and platelet rich plasma treatment for thin endometrium.

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.

Dr. Sweta Gupta
Editor, IFS

Dr. Rupali Bassi Goyal
Joint Editor, IFS

INVITED ARTICLES

Systematic review of role of Granulocyte Colony Stimulating Factor in treatment of thin endometrium in IVF

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Abstract

Introduction: A functioning and receptive endometrium is crucial for embryo implantation. Thin and unresponsive endometrium is difficult to treat and contributes to implantation failure. The cross-talk between the endometrium and the developing embryo is mediated by many substances, including cytokines. Granulocyte colony-stimulating factor a cytokine marketed as filgrastim has been used for improving endometrial thickness and receptivity. We planned this study to investigate evidence available whether use of G-CSF is able to improve endometrial thickness and pregnancy outcomes in women with thin endometrium in IVF.

Material And Method: We searched in PubMed Central database in last 5 years using keywords (Granulocyte colony stimulating factor) AND (Thin endometrium) AND (IVF) AND (RIF).

Result: A total of five studies, 3 RCTs, 1 systematic review and 1 metanalysis.Discussion: In the three RCTs one RCT result is pending the other two shows no significant difference in endometrial thickness or pregnancy rate in the trial group compared to control group. Systematic review shows increase endometrial thickness as well as increased pregnancy rate in cases of RIF. Metanalysis done in RIF shows increased pregnancy rate but inconclusive about endometrial thickness.

Conclusion: The evidence in the literature suggests a positive influence of G-CSF for improving pregnancy rates. But the evidence in favor of endometrial thickness is either no effect or insignificant effect.

So, there is need of a more controlled RCT involving larger sample size and focusing on thin endometrium only with standard route, time and dose of administration.

Introduction:

A functioning and receptive endometrium is crucial for embryo implantation. During the menstrual cycle the endometrium undergoes both morphologic and biologic changes that prepare it for interaction with the embryo, and ultimately for successful implantation. Once all biological changes occur, the embryo can attach, invade the endometrium and finally implant. This crucial stage lasts for a few days and is referred to as the “window of implantation”. Several studies have reported a strong association between endometrial thickness and successful implantation

However, others failed to confirm such an association. The minimal adequate endometrial thickness for successful implantation, as measured in the late proliferative phase, varies between studies, with a range of 6–8 mm. However, although rare, some investigators have reported

successful implantation in an endometrium of no more than 5 mm thickness

Thin and unresponsive endometrium is difficult to treat and contributes to implantation failure

Several approaches have been implemented to increase endometrial thickness, and presumably prepare it for the “window of implantation”. Treatment with high dose oral estrogen or vaginal estradiol is one approach. Treatment with low dose Aspirin or Sildenafil by increasing blood flow to the uterus Is another approach.

The cross-talk between the endometrium and the developing embryo is mediated by many substances, including cytokines (IL1, IL6 and its product LIF), integrins, adhesion molecules, growth factors and hormones etc. such as hCG, all of which support the process of apposition, adhesion and invasion

Exploration of stages of the complex process of implantation has inspired researchers to use some of the mediators to facilitate implantation for example hCG or by local injury resulting from a uterine endometrial biopsy catheter or uterine infusion of G-CSF or platelet rich plasma protein or autologous endometrial mesenchymal stromal cell infusion or bone marrow mesenchymal stem cell infusion or even systemic use of G-CSF.

Another interesting development is use of Neuromuscular electrical stimulation (NMES) combined with other modalities for improving endometrial thickness.

Granulocyte colony-stimulating factor (G-CSF or GCSF), also known as colony-stimulating factor 3 (CSF 3), is a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream. G-CSF is produced by endothelium, macrophages, and a number of other immune cells.The pharmaceutical analogs of naturally occurring G-CSF is the recombinant human G-CSF (rhG-CSF) synthesised in an E.coli is called filgrastim marketed as Neupogen. Another form of rhG-CSF called lenograstim is synthesised in Chinese Hamster Ovary cells (CHO cells)

The various medical uses of GCSF are

1. Chemotherapy induced neutropenia
2. Use in drug-induced neutropenia
3. Before blood donation: G-CSF is also used to increase the number of hematopoietic stem cells in the blood of the donor before collection by leukapheresis for use in hematopoietic stem cell transplantation
4. Stem cell transplants
5. For increasing endometrial receptivity/thickness: In 2011 Gleicher et.al. first used intrauterine G-CSF in four patient undergoing IVF with thin endometrium after standard endometrial preparation all the patients successfully underwent ET and conceived.

Since then G-CSF alone or in combination with other modalities has been experimented for improving endometrium and possibly pregnancy rate.

There is no standardised dose, route and time of treatment schedule. The various protocol used by different researchers in various literature are:

Local: 30 ml of GCSF gel through slow infusion into the uterine cavity under hysteroscopic guidance or without on day of hcg injection, or at the time of oocyte retrieval or on day of ET and

4thday of ET Systemic injection: s.c. 300µg one hour before ET or s.c.300µg on day of hcg or s.c.1.5mg /kg/d from tranfer to day of hCG test,and if positive the treatment was continued for other 40 days.

We planned this study to investigate evidence available whether use of G-CSF is able to improve endometrial thickness and pregnancy outcomes in women with thin endometrium in IVF.

Material And Method

This systematic review study included papers published in english literature investigated the use of intra uterine/sub cutaneous G-CSF in thin endometrium. As there was paucity of literature on thin endometrium only, we included RIF and IVF.

We searched in PubMed Central database in last 5 years using keywords (Granulocyte colony stimulating factor) AND (Thin endometrium) AND (IVF)AND(RIF).

Our primary outcome measure was endometrial thickness and secondary outcome measure was pregnancy rate.

Result

List of the studies that evaluated the use of G-CSF in women submitted to assisted fertilization, which held thin endometrium and repeated failures

First author/Year Geographic Region	Study Type	Participants number	criteria	G-CSFmethod of use Date	Endometrium thikness after G-CSF (average)	Pregnancy rates (%)
Ziya Kalem et al.,2020	RCT	TG: 82 CG: 75	RIF	TG: 300 mcg IU GC: Saline	No difference	No difference
Linjiang Song et al.,china 2021	-RCT	TG: 56 CG: 43	Thin endometrium	TG:300mcg IU+TEAS CG:300mcgl U	No difference	not significantly improved
Xaiona Lin et al.,China 2020	R CT	TG: 48 CG: 48	Thin endometrium	300 mcg IU	Result pending	Result pending
Ling Zhang et al.,China 2018	Meta analysis	Io RCTs TG:521 CG:495	Infertile women under ART	Both local and systemic	inconclusive	Increased PR
Mylena et al;Brazil2019	Systematic review	10 studies 475 participants	GCSF and repeated implantation failure with thin endometrium	local	Increased thickness in8/10 studies	Increased PR

RCT: Randomized clinical trial.

IU: intrauterine;
CT: Clinical trial;.
TG: Treated Group;
CG: Control Group;
PR: pregnancy rate.

Discussion:

We included five papers, three RCTs, one metanalysis, and one systemic review. These papers were published in last 5 years in which thin endometrium and repeated failure in assisted reproductive technique to whom G-CSF was employed.

In the three RCTs one RCT result is pending the other two shows no significant difference in endometrial thickness or pregnancy rate in the trial group compared to control group. A systemic review by Mylena et al;Brazil 2019 shows increased endometrial thickness in eight out of ten studies. This review was done from 2008 to2018 in English Spanish and Portuguese it also showed increased overall pregnancy rate but the cases selected were recurrent implantation failure with thin endometrium.

One robust metanalysis done by Ling Zhang et al., China 2018 consisting of ten RCTs involving 1016 IVF-ET cycle concluded that G-CSF administration has a beneficial role on the clinical outcome after embryo transfer by both routes of local infusion and systematic administration, especially for the cases with RIF. Further RCTs are needed to investigate the role of G-CSF in thin endometrium patients.5

Conclusion

The evidence in the literature suggests a positive influence of G-CSF for improving pregnancy rates. But the evidence in favor of endometrial thickness is either no effect or insignificant effect.So, there is need of a more controlled RCT involving larger sample size and focusing on thin endometrium only with standard route, time and dose of administration.

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5. Therapeutic role of granulocyte colony-stimulating factor (G-CSF) for infertile women under in vitro fertilization and embryo transfer (IVF-ET) treatment: a meta-analysis Ling Zhang 1, Wei-Hai Xu 1, Xiao-Hua Fu 1, Qiong-Xiao Huang 1, Xiao-Yan Guo 1, Lin Zhang 1, Shi-Shi Li 1, Jing Zhu 2, Jing Shu 3

INVITED ARTICLES

REVIEW OF ARTICLE – ROLE OF STEM CELLS IN THIN ENDOMETRIUM

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The endometrium of uterus in human is a very complex and dynamic tissue, which undergoes periods of growth and turn over in every menstrual cycle , during wide resection, parturition, and in postmenopausal women who receive estrogen substitution therapy(1). The endometrium consists of two type of cells ; i.e., epithelial cells (containing luminal and glandular cells) and supporting mesenchymal cells(2) . From a functional point of view, the endometrium has two different layers; i.e., the outer functionalis layer and the inner basalis layer. The functionalis is composed of compact glandular tissue and a slack connective stroma, whereas the stroma forms the main part of inner basalis layer. During each cycle of the menstrual period, the functionalis and a small part of the basalis are shed (3). The rebuilding of the functional layer is very important for the expansion of a tissue, which is responsible for implantation and menstruation(4) . The regeneration of surface epithelial in endometrium occur as a result of stromal cells that are differentiated & is not a direct development of the remains basal epithelial glands(5,6).

Sometimes the sheded endometrium is not able to regenerate itself & may be due Defective function of endometrial stem/progenitor cells which results in incompetent thin endometrium (< 7 mm). Sufficient growth of the endometrium is one of the essential factors required for prosperous implantation.

Thin endometrium is a cause of worry as it is related to lower implantation and pregnancy rates. A number of treatments have been tried to increase endometrial growth , but none has been validated up to now.

The most popular ongoing treatments are intra-uterine granulocyte colony-stimulating factor, extended estrogen support, human chorionic gonadotropin priming in the follicular phase, and drugs that increase endometrial blood flow which includes Pentoxyfilline, tocopherol, sildenafil, and l-arginine(7) .

Cell-based therapies using endometrial stem/progenitor cells hold promising role in restoring poor endometrium.

Stem cells are undifferentiated cells that have the potential to multiply as a stem cell in undifferentiated form (self-renewal) and to mature and differentiated cells. Stem cells can be classified based on their capability to produce various types of cells: totipotent, pluripotent, multipotent, and unipotent(8).

Considering the self-renewal and the capacity of multi-lineage differentiation, stem cells therapy can be useful in the treatment of many degenerative diseases and situation that therapeutic choices are limited or do not exist. Stem cells have the potential of substituting damaged cells in the endometrium. In addition, multipotent and pluripotent stem cells has shown beneficial paracrine effects, which can decrease cell death and provide growth/trophic support to host cells and reformative activities in the host tissues. It is commonly approved that transplanted cells can provide morphological and functional benefits through multiple mechanisms including, but not restricted to, trophic support, cell replacement, regeneration of endogenous cells, immunosuppression/anti-inflammation, stimulation, and regulatory interactions with endogenous cells(9). The scope of stem cell therapy is quickly developing and, today clinical trials have begun to investigate the use of stem/progenitor cells in the therapy of degenerative diseases, cancer, and the renovation of damaged or lost tissues(8).

A concise review of the current clinical applications of stem cell therapy in endometrial disorders will be discussed here.

YEAR	TYPE OF STUDY	CONDUCTED BY	SIZE	TITLE	POPULATION/INCLUSION CRITERIA	OUTCOME
2018	Prospective non – controlled phase 1 clinical trial	Caoetal	26	26 Allogeneic cell therapy using umbilical cord MSCs on collagen scaffolds for patients with recurrent uterine adhesion: a phase I clinical trial	Female with secondary infertility or embryo transfer failure due to recurrent intrauterine adhesion formation & age < 45 years	Total 10 patients became pregnant by the end of 30-month follow-up period out of which 8 patients had given live birth (6 term & 2 preterm), 1 patient was still in the third trimester of pregnancy (in august 2017)and 1 patient suffered from spontaneous abortion . All babies were healthy, including the two preterm babies(10).
2020	Observational study	Maetal	12	Intrauterine transplantation of autologous menstrual blood stem cells increases endometrial thickness and pregnancy potential in patients with refractory intrauterine adhesion	Female in age grp (22 – 40 yrs) with refractory intrauterine adhesions ,endometrial thickness < 6 mm after traditional treatment,infertility > 1 yr.	5 patients conceived including 4 pregnancies after embryo transfer and 1 via sexual intercourse (11).
2021	Pilot study	Zhangetal	18	Unresponsive thin endometrium caused by Asherman syndrome treated with umbilical cord mesenchymal stem cells on collagen scaffolds	Female in age grp of 20–40 years, infertile female received (ART) and had frozen embryos in store , patients who underwent at least hysteroscopic adhesiolysis (HSA) twice and the uterine cavity returned to normal , women with ET < 5.5mm with the use of 6–8 mg/ day estradiol valerate combined with at least 1 round of treatment with aspirin, granulocyte colony stimulating factor (G-CSF), heparin, vaginal sildenafil, or Chinese traditional medicine	Significant increase in endometrial thickness from 4.08 ± 0.26mm to 5.87 ± 0.77mm , 3 female got pregnant out of which 2 gave birth to live child & 1 had miscarriage @ 25 weeks(12).
2020	Systemic review & meta - analysis	Zhaoetal	8 studies	Clinical Efficacy and Safety of Stem Cell-Based Therapy in Treating Asherman Syndrome	Patients having Asherman syndrome and received conventional hysteroscopy adhesiolysis or hormone replacement treatment, but with no obvious alleviation, Patients administrated with MSC-based stem cell therapy , data containing base line after conventional treatment and outcomes concerning the MSC-based treatment , Outcomes included menses improvement, endometrial thickness changes, side effect reports, or pregnancy outcome , Internal control, prospective follow-up studies ,Written in English.	stem-cell based therapy was safe and effective in improving Asherman syndrome patients' conditions.To be specific patients has improved their menstrual volume, increased endometrial thickness, and restored regular menstrual cycles to some extent, which made it possible to provide a suitable environment for nurturing a baby. combination of stem cell transplantation and hormone was wildly recognized to play an adjuvant role in maintaining the necessary estrogen level, which is needed for restoring endometrium.Thus, these results lend support to stem cell therapy as a therapeutic strategy that can enhance the prognosis of Asherman syndrome, especially for those failing conventional treatment(13).

Conclusion

Endometrium plays an important role in reproductive and maternal health, and therefore it is important to maintain a physiological structure of endometrium & to eliminate the defects, and restore the damage. Stem cells have been the subject of intense research because of their beneficial functions.Actively research is going on in this field & from the researches done in this field it can be concluded that stem cells can be a important therapy to remedy degenerative diseases, cancer, and renovation of damaged tissues for which there are limited or no therapeutic choices. Hope has been kept alive that stem cell therapy can treat many diseases, especially in diseases such as Asherman syndrome and thin endometrium. Stem cells derived from bone marrow, endometrium, menstrual blood, and cord blood can help in regeneration of the endometrium. Different approaches have already been tried to boost survival of transplanted cells in the stem cell therapy . Some forms of biomaterials like scaffolds, hydrogel, and nanostructure lipid carrier are tried to promote stem cell/drug delivery; thus, these novel biomaterials can improve the outcome of the cell therapy.hUCMSCs are best for regenerating the endometrium because features like easy accessing, having faster self-renewal properties, harvesting by non-invasive procedures in abundance, and weakly immunogenic effects. Certainly, other types of stem cells like menSC, hAMSC, and MSC have beneficial characters and can be useful in this area. We have gained much information in this field , many concerns still remain like in the field of endometrium repair, EnSCs are involved in the pathogenesis of several gynecological diseases such as endometrial cancer, endometrial hyperplasia, endometriosis, and adenomyosis. Another concern in this area is that stem cells, in addition to being involved in proliferation, also stimulate angiogenesis through secreting growth factors. Furthermore, the major obstacle that prevents the clinical development of embryonic stem cells is teratomas.

From all the studies we can conclude that stem cell and hormone combination therapy have superior therapeutic effects in improving menstruation duration, pregnancy outcome, and endometrial

thickness. Moreover, this kind of therapy was also concluded with a favorable safety profile. However, further studies with large sample sizes are needed to establish more

solid evidence for administrating this therapy in clinic.

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INVITED ARTICLES

ROLE OF PLATELET-RICH PLASMA (PRP) IN THINENDOMETRIUM

INTRODUCTION

Implantation is the most important and vital process in reproduction. Endometrial thickness is directly related to endometrial receptivity and is a good predictor of success in assisted reproduction technology. Management of thin endometrium in ART has always been challenging and various options like estrogen, vitamin E, Ecosprin, Sildenafil, GCSF are available for its management.

Endometrial scratching is a procedure done in luteal phase to improve endometrial receptivity a successful implantation of the embryo.

Stem cell therapy and platelet rich plasma (PRP) has emerged as a new promising treatment modalities in patients with repeated ivf failure due to thin endometrium.

PRP has been used in many medical specialities as it stimulates and causes regeneration of tissues such as mucosa, skin fat and even in promoting healing responses of dieases of bones and tendons.

PRP is prepared from autologous fresh whole blood which have a high concentration of various cytokines and growth factors such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), transforming growth factor (TGF), fibroblast growth factor (FGF), Interluekin – 8, fibronectin and various other factors that initiate healing process.

Recently few studies have been done showing improvement in thickness of endometrium after PRP treatment in repeated ivf failure with history of thin endometrium but complete efficacy and treatment yet need to be established.

METHOD OF PREPARATION:

PRP is autologous blood plasma containing concentrated platelets prepared from autologous whole blood by centrifugation method. In this process blood is collected by venipuncture in tubes containing anticoagulants such as acid citrate dextrose (ACD).

PRP is prepared by two methods:

1. Double centrifugation PRP method

In this method PRP is prepared by double centrifugation method. Whole blood collected in tube with anticoagulant is centrifuged which make three different layers.The top most layer contains high concentration of platelets, middle layer known as buffy coat layer with WBCs and bottom layer mostly with RBCs. Upper layer with buffy coat is then transferred into a sterile tube and second centrifugation is done.There is formation of platelet pellets at the bottom of the tube which is lower one third is PRP and upper 2/3rd is platelet-poor plasma (PPP). PPP is removed and the platelet pellets is suspended in a minimum quantity of plasma (2-4 mL) by gently shaking the tube.

2. Buffy coat method

In the buffy coat method, the whole blood is centrifuged at "high velocity" with subsequent collection of only the middle layer containing mainly white blood cells and platelets. The resulting whole blood is stored at 20 °C to 24 °C and then centrifuged at a high speed, resulting in three layers: a bottom layer consisting of red blood cells; a middle layer consisting of platelets and white blood cells; and a top layer containing PPP.

The top layer is discarded from the tube. The "Buffy-coat" layer is transferred to another sterile tube. The aspirate is re-centrifuged at a low rate to cause white blood cell separation or a leukocyte filtering filter is used.

SIDE EFFECTS:

As PRP is prepared from patient own whole blood, minimal side effects are expected with intrauterine instillation of platelet rich plasma (PRP). Occasionally there can be small bruises or irritation on injection site.

MODE OF ACTION:

PRP contains highly concentrated platelets which release various growth factors from alpha granules of platelets, which stimulate and enhance natural healing process in different clinical applications.

Platelet causes release of various growth factors such as platelet derived growth factor, vascular endothelial growth factor (VEGF), Fibroblast growth factor (FGF), connective tissue growth factor, insulin like growth factor (IGF-1) ,chemokines and other cytokines that stimulate proliferation and growth.

Activation of growth factors lead to activation of a cascade of an intracellular signal proteins that causes the expression of a genes leading to cellular proliferation, matrix formation, osteoid production and collagen synthesis leading to initiation and acceleration of the natural healing process.

PRP stimulates endometrial cell proliferation , migration, endometrial regeneration and repair. When endometrial lining is still thin i.e less than 7 mm even after standard hormonal therapy in a stimulated cycle of ART , PRP is injected into the uterine cavity on the tenth day of the HRT cycle and can be repeated 2-3 times if endometrial thickness does not increase after 72 hrs of PRP infusion.

REVIEW OF LITERATURE:

Zadehmodarres et al. in a pilot study showed the role of PRP on endometrial growth and they found in all the participants that after two PRP infusions in all patients who had a history of cycle cancellation due to the thin endometrium (1).

Siddhartha Nagireddy et al. conducted a non randomized single arm trial on effect of autologous PRP for the management of thin endometrium in frozen embryo transfer cycle.

All women who presented with thin endometrium in FET cycles were included in their study and intra uterine PRP was infused on day 11 of HRT cycle. They concluded that autologous PRP significantly improves endometrial thickness in cases of thin endometrium in FET cycles and reduces cycle cancellation rate (2).

A prospective cohort study was conducted by Y. Chang et al on 42 cycles of 34 patients to evaluate the effectiveness of platelet-rich plasma (PRP) in women with thin endometrium in frozen embryo transfer cycles(FET).

PRP was infused intrauterine on the 10th day in HRT cycle and progesterone administration day in patients with thin endometrium with thickness less than 7 mm. They concludes that PRP played an vital role in promoting endometrium proliferation and improving embryo implantation rate(3).

The PRP has also been listed for the management of thin endometrium in assisted reproduction of the clinical guideline published in July 2019 from the Canadian Fertility and Andrology Society, but the level of evidence recommended is just weak. (4)

Another prospective study was done by A. Morad et al to establish the efficacy of PRP in thin endometrium on thirty anovulatory PCOS women with CC failure for 3 cycles and found that Intrauterine infusion of PRP could be a promising agent to increase endometrial thickness and endometrial blood flow and thus improved clinical pregnancy rate.(5)

A Prospective interventional study was done by Kim H et al in 2019 to study the effect of PRP in 24 FET patients with history of two or more failed IVF cycles and refractory thin endometrium .They concluded that PRP improved implantation, pregnancy and live birth rate and it was able to improve some aspects of endometrial receptivity (6) .

A randomized clinical trial was done by Maryam eftekhar Research and Clinical Center for Infertility, Yazd, Iran to establish that autologous platelet rich plasma expands endometrial thickness and improve pregnancy rate during frozen-thawed embryo transfer cycle.

They included 33 patients with thin endometrium and instilled intrauterine PRP on 13th day of HRT in patients with endometrial thickness less than 7 mm. they concluded that though statistical difference were not significant PRP seemed to have lower cancellation rate and higher pregnancy rate.

Conclusion

PRP is an autologous cell therapy containing many bioactive growth factors that are involved in the treatment of chronic wounds, severe burns, chronic joint diseases. Though endometrial thickness management is still a challenge in ART to treating infertility specialist many studies and randomized control trials have proved efficacy of PRP in improving endometrial rejuvenation and thus increasing the implantation potential and pregnancy rate.

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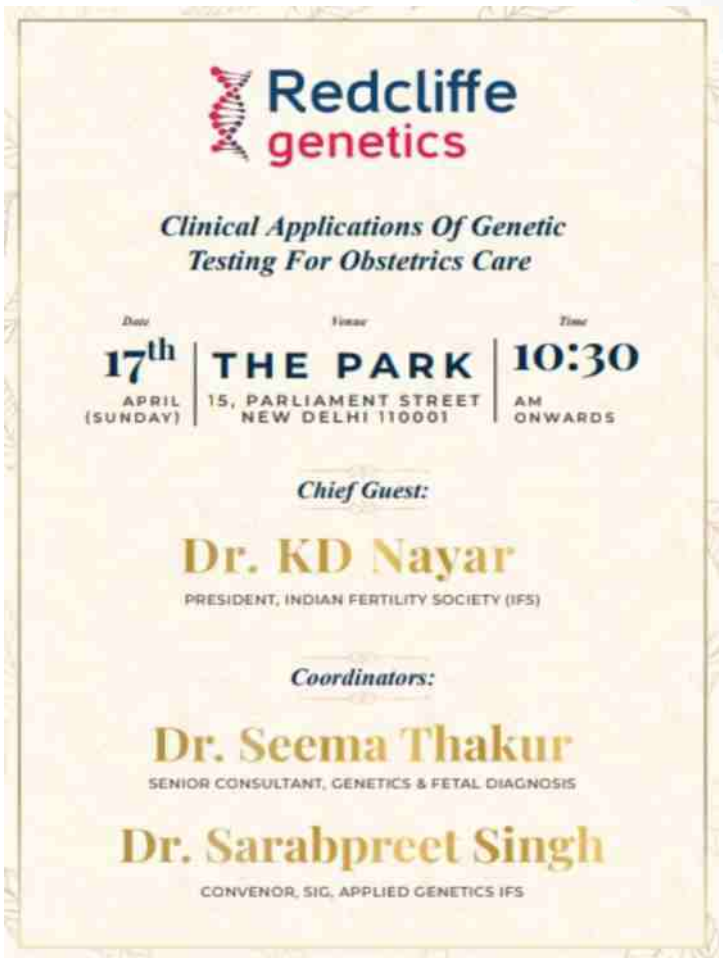

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Chapter Activity

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Time : 6.30pm onwards

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President IFS

Dr. Neena Malhotra
General Secretary IFS

Dr. KD Nayyar
President Elect

Guest Speaker

Dr. Geetendra Sharma

Dr. Sarabjeet Singh
Chapter Secretary
Punjab IFS

Dr. Sukriti Bansal
Jt. Secretary
Punjab IFS

Dr. Jasleen Randhawa
Treasurer
Punjab IFS

Time	Topic	
06:30 pm	Inaugration by Dr. Sudha Prasad (President IFS)	
06:35 pm	Lohri greetings by Dr. Neena Malhotra (General Secretary IFS)	
06:40 pm - 07.10 pm	ART Act by Dr. Geetendra Sharma	
07:10 pm - 08.00 pm	Genes & Genetics in Reproductive Medicine: Panel discussion	
	Expert Panelists	**Moderators**
	Dr. Umesh Jindal	Dr. Sarabjeet Singh
	Dr. KD Nayar	Dr. Sukriti Bansal
	Dr. Sangeeta Khattar	
	Dr. Sheetal Jindal	
	Dr. Sanjeev Kumar	

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Faculty

Dr. Umesh Jindal

Dr. Sangeeta Khatter

Dr. Sheetal Jindal

Dr. Sanjeev Kumar

Indian Fertility Society (Haryana) & Rewari Obs Gyn Society

present

RECURRENT IVF FAILURE
HOW TO IMPROVE RESULTS

Tuesday, Jan 18, 2022 | 4:30 PM – 6:00 PM

Guest of Honour

Dr Sudha Prasad
Director Mainstone, Advanced IVF & Training Centre, New Delhi
President Indian Fertility Society

CONVENORS

Dr Sonu Balhara Ahlawat
Unit Head Reproductive Medicine
Artemis Hospital Gurgaon
Secretary Haryana chapter IFS

Dr Seema Mittal
Director Lalita Memorial Hospital & Infertility Center Rewari
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DIFFICULTIES ENCOUNTERED DURING OPU & ET

Speaker

Dr Sonia Malik
Director & HOD
Nova Southend Fertility & IVF New Delhi
Past President
Indian Fertility Society

Chairpersons

Dr Neeru Thakral
Director Morpheus Thakral IVF Center & Hospital Gurgaon
Past President Haryana chapter IFS

Dr Shalu Gupta
Associate Director
Cloud 9 hospital Gurgaon

CLINICAL APPROACH TO IMPROVING THE ENDOMETRIUM: EVIDENCE BASED EVALUATION

Speaker

Dr Abha Majumdar
Director Center of IVF & Human Reproduction
Sir Ganga Ram Hospital
New Delhi

Chairpersons

Dr Priya Varshney
Sr. Consultant IVF
Cloud 9 hospital Gurgaon
Jt. Secretary Haryana IFS

Dr Reema Goel
Director & Infertility Consultant
Vaishnavi Nursing Home Gurgaon
Secretary Mission Pink Health

BETTER IVF OUTCOME FOLLOWING IMPROVED LAB AMBIENCE

Speaker

Dr KD Nayar
Sr. Consultant & HOD
Akanksha IVF Centre
Mata Chanan Devi Hospital Delhi
President Elect
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Dr. Pooja Sinha
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Meeting held with
Madam Geeta Nararaynan
Joint Secretary and

Mrs Kavitha Scientist E of DHR
on 11.2.22 at 3.00 PM

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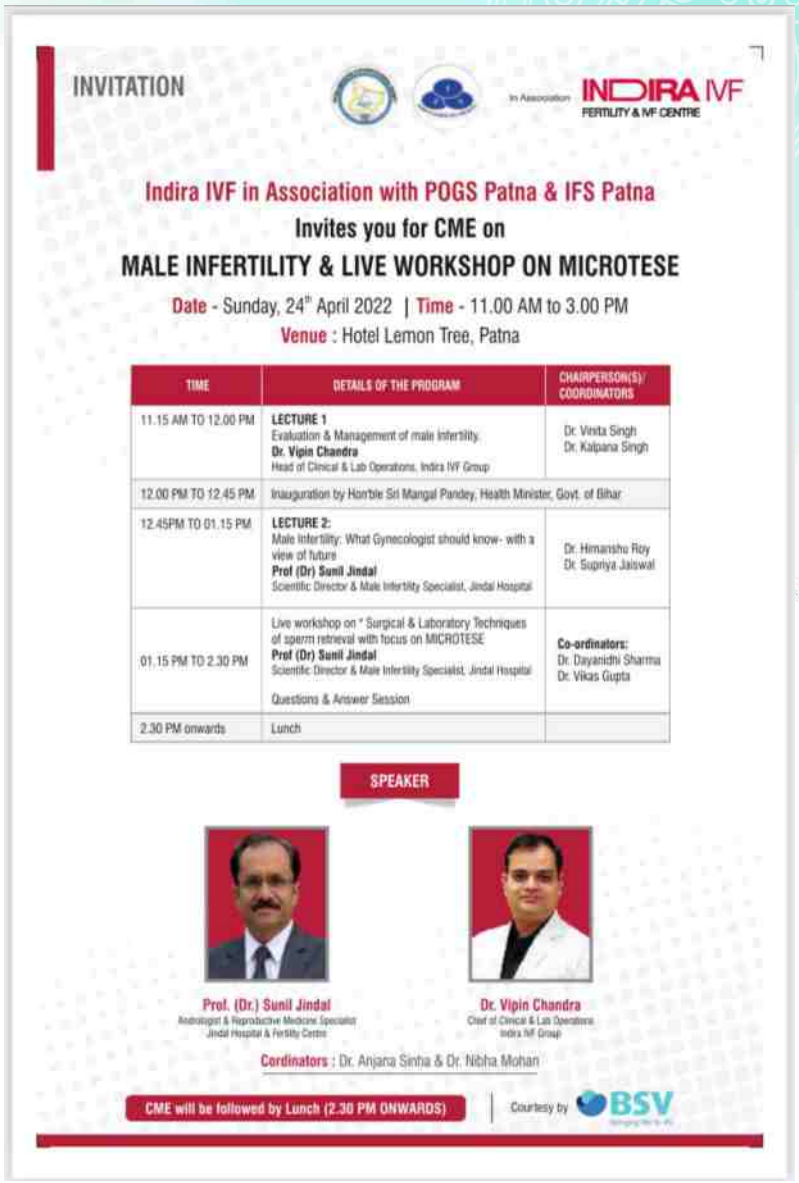

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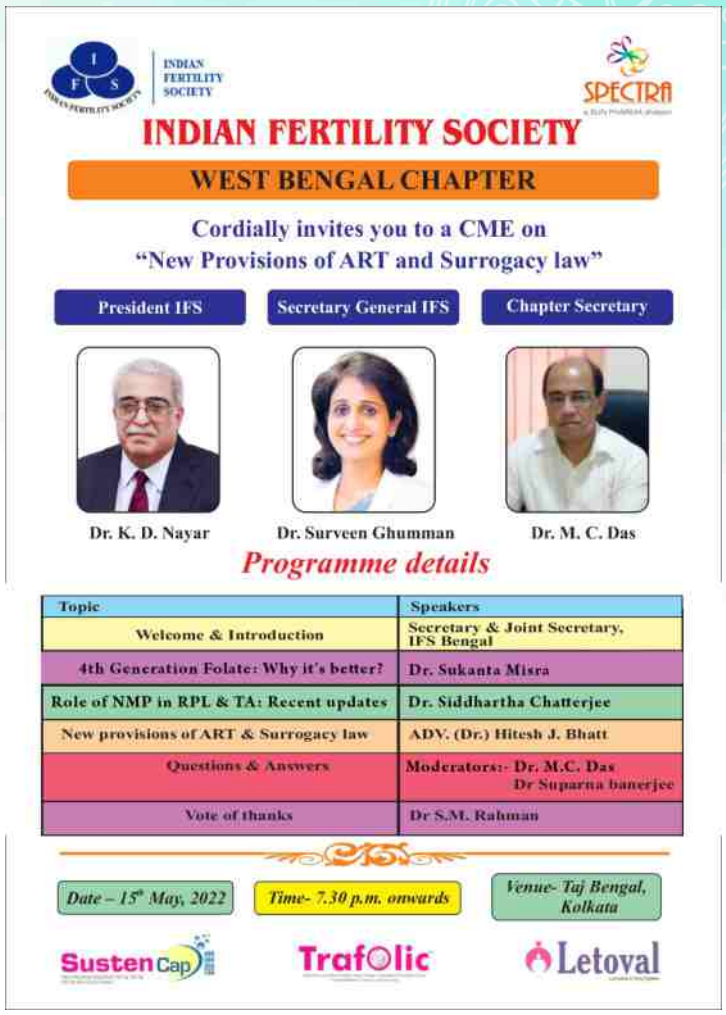

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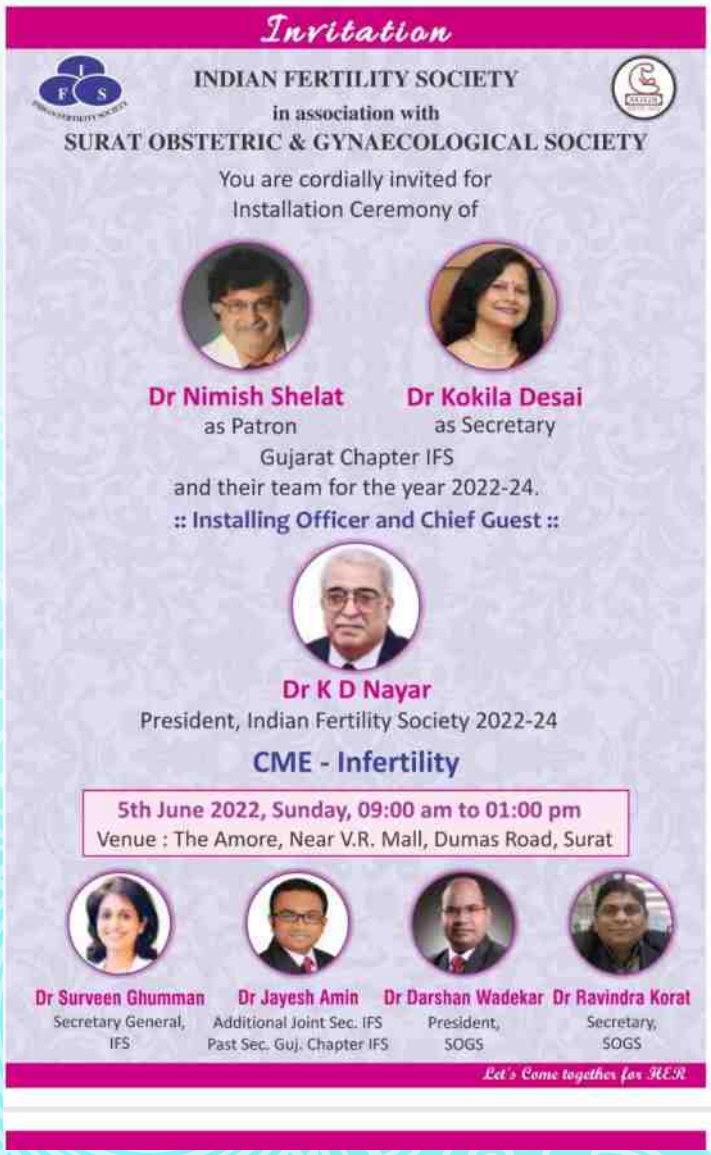

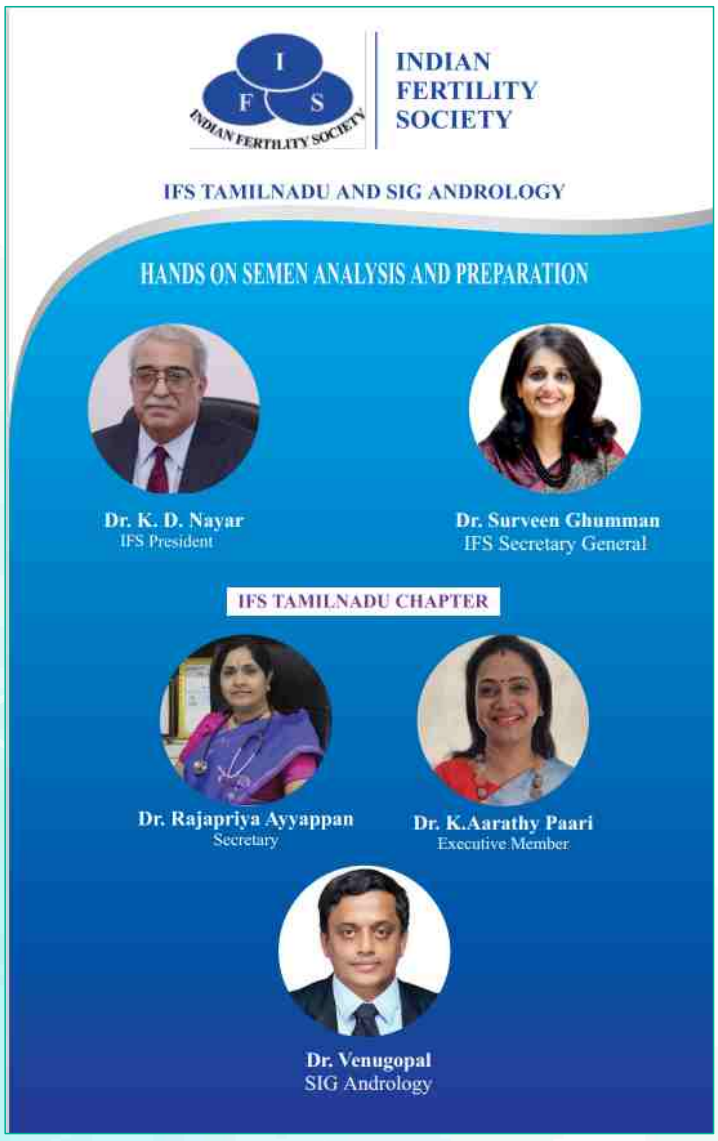

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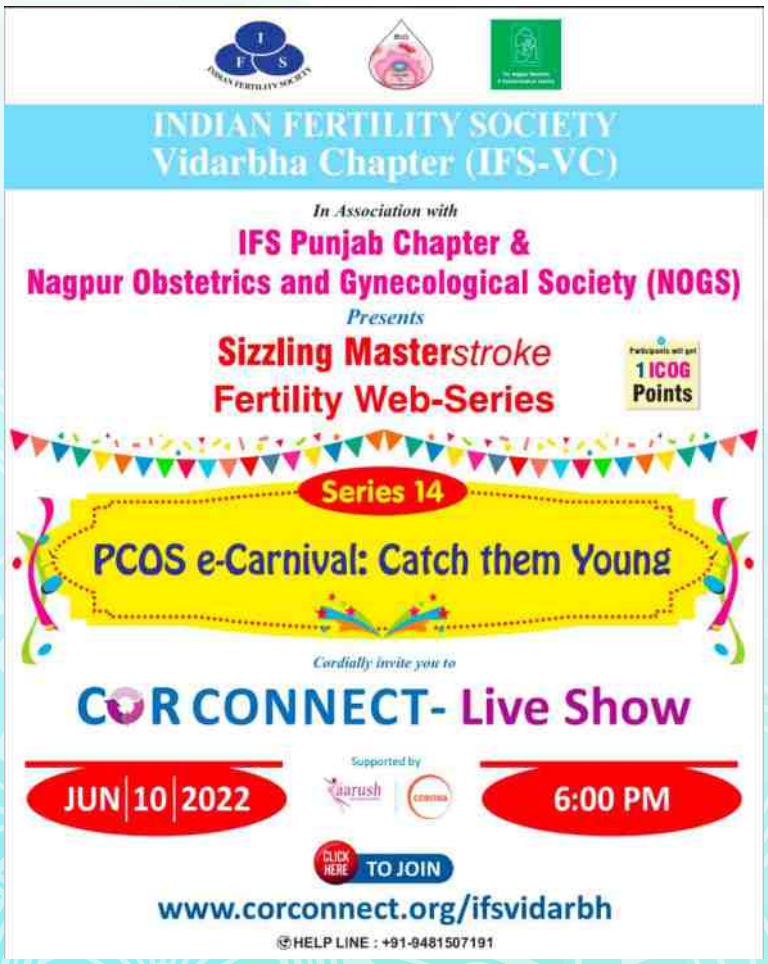


IFS ACTIVITIES
Newsletter

MAY 2022

Indian Fertility Society
FERTILITY NEWS
On
LATEST INNOVATION
NEW MICRO DEVICE FOR ICSI: COULD BE A GAME CHANGER

MAY 2022
(Volume 1)



Dr. KD Nayar
President, IFS

Dr. Surveen Ghumman
Secretary General, IFS

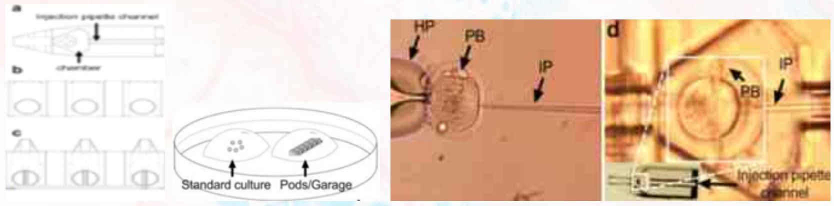
Dr. Sweta Gupta
Editor, IFS

Can there be better device to modify current ICSI treatment ?

Introduction: Continued innovation in the IVF lab will not only improve success for patients but also cost and improved access. ICSI hasn't changed since its discovery 30 years ago. ICSI is a slow and difficult procedure which involves the injection of a single sperm into an egg for fertilization and it can only be carried out by experienced embryologists.

Summary: Dr Dunning, from the University of Adelaide's Robinson Research Institute[1] fabricated a micrometre scale device that houses the oocyte, minimizes oocyte manipulation and requires only one micromanipulator for microinjection. They investigated the use of the device (Pods and Garage) by assessing biocompatibility and embryo culture performance within the device; using the device to microinject presumptive zygotes and to investigate the potential for high-throughput microinjection and improved tracing of injected vs non-injected oocytes.

This new technology, smaller than a pinhead in size holds up to 10 eggs in segregated positions for quicker injection, making it easier for embryologists to track and avoid the risk of errors. By removing the need for the pipette that normally holds the unfertilized egg in position during ICSI, this device simplifies the injection process, reduces dependency on a high level of technical experience and will dramatically improve embryo



Conclusion: Microinjection within this device minimizes the requirement for an experienced operator for handling and manipulation, may improve embryo production and that they may form a precursor to automated ICSI. The device is expected to undergo global clinical trials in 2022. This require less training for embryologists with less expensive equipment.

Reference: 1. Yagoub, S.H., et al. (12th May 2022) Fabrication on the microscale: a two-photon polymerized device for oocyte microinjection. Journal of Assisted Reproduction

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JUNE 2022

Indian Fertility Society
Fertility SIG Newsletter
June, 2022
SIG ANDROLOGY

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Mr. Gaurav Kant
Co Convenor, SIG Andrology

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Varicoceles: Recommendations and Practical Considerations.

Dr KK Gopinathan MD DGO
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Dr Parasuram Gopinath MS FICOG
Sr Consultant and Scientific Director,
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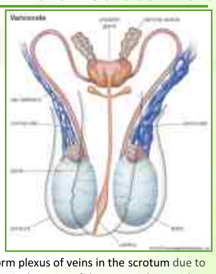


Image 1: Anatomy of the venous drainage from the testes (Jenson CF Nature Reviews Urology 2017

Varicocele is the abnormal enlargement of the pampiniform plexus of veins in the scrotum due to retrograde flow or impaired drainage of the testicular vein. It is the veins of the testes, along with tributaries from the epididymis, converge to form the pampiniform plexus[1].

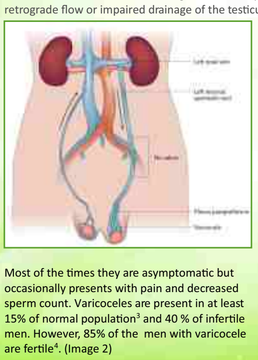
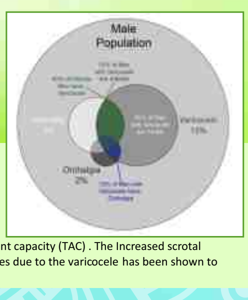


Image 2
Varicocele predominantly occurs on the left side. It is suspected that this is related to the indirect drainage of the testicular vein to the IVC through the left renal vein (Image 1). Bilateral and right-sided varicoceles account for approximately 10% to 15% of varicoceles.[2]

Most of the times they are asymptomatic but occasionally presents with pain and decreased sperm count. Varicoceles are present in at least 15% of normal population[3] and 40 % of infertile men. However, 85% of the men with varicocele are fertile[4]. (Image 2)



Pathophysiology of varicocele

Although varicocele pathogenesis is multifactorial, oxidative stress seems to have a central role. Increased oxidative stress can be a result of the combination of increased Reactive oxygen species (ROS)and decreased total antioxidant capacity (TAC) . The Increased scrotal temperature, hypoxia and reflux of toxic metabolites due to the varicocele has been shown to contribute to the oxidative stress.[2]

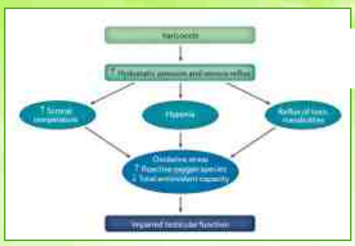


Image 3: Pathophysiology behind Varicocele Induced male infertility Jenson CF Nature Reviews Urology 2017

Diagnosis and Grading

Physical examination of the male partner gives the most valuable information regarding varicocele and its management and it shall never be neglected.
In addition to diagnosis of varicocele, it also gives valuable clue regarding testicular function. Only clinically palpable varicoceles have been clearly associated with infertility.. The accepted clinical grading of varicocele is as follows (Image 4). [2]

Varicocele grade	Clinical features
Subclinical	Examined with Doppler ultrasonography and defined as reverse venous blood flow during Valsalva manoeuvre or ectasia of the spermatic vein (>3 mm)
1	Only palpable during Valsalva manoeuvre
2	Palpable without Valsalva manoeuvre
3	Visible and palpable without Valsalva manoeuvre

Image 4: Grading of varicoceles on men in an upright position

Scrotal Ultrasonography is not recommended for the diagnosis of varicocele and is only to be done in case of an inconclusive physical examination of scrotum.

Recommendation by ASRM & AUA for Imaging for the diagnosis of varicocele[5] :

- Scrotal ultrasound should not be routinely performed in the initial evaluation of the infertile male. (Expert Opinion)
- Clinicians should not routinely perform abdominal imaging for the sole indication of an isolated small or moderate right varicocele. (Expert Opinion)

Recommendations for treatment of varicocele

Various professional bodies have put forward their recommendations for treating varicocele.
Recommendation by ASRM & AUA published in 2021 for varicocele surgery in male infertility are [5]

- Surgical varicocelectomy should be considered in men attempting to conceive who have palpable varicocele(s), infertility, and abnormal semen parameters, except for azoospermic men. (Moderate Recommendation; Evidence Level: Grade B)
- Clinicians should not recommend varicocelectomy for men with non-palpable varicoceles detected solely by imaging. (Strong Recommendation; Evidence Level: Grade C)
- For men with clinical varicocele and NOA, couples should be informed of the absence of definitive evidence supporting varicocele repair prior to ART. (Expert Opinion)

Further, the ASRM committee in 2014 goes on to state that an adult male not seeking conception now but with palpable varicocele, abnormal semen parameters, desiring future fertility and/or pain related to varicocele is also a potential candidate for treatment. Adolescent males with varicocele and objective evidence of testicular damage may also be considered for surgery according to ASRM. The difference in testicular volume is the most important indicator of the need for surgical intervention in such individuals.[6]

Similarly, the European Association of Urology (EAU) guideline has been revised in 2021 and recommend the following.[7]

- Treat infertile men with a clinical varicocele, abnormal semen parameters and otherwise unexplained infertility in a couple where the female partner has good ovarian reserve to improve fertility rates. (Strong)
- Treat varicocele in adolescents with ipsilateral reduction in testicular volume and evidence of progressive testicular dysfunction. (Weak)
- Do not treat varicocele in infertile men who have normal semen analysis and in men with a sub-clinical varicocele. (Weak)
- Varicocelectomy may be considered in men with raised DNA fragmentation with otherwise unexplained infertility or who have suffered from failed of assisted reproductive techniques, including recurrent pregnancy loss, failure of embryogenesis and implantation. (Weak)

Preferred Surgical Method for Varicocele

Sub inguinal microsurgical approach is the most accepted method of repair as it least invasive, cause minimal pain and has less chances of hydrocele and recurrence (1-2%). High ligation approaches (retroperitoneal, laparoscopic) are less preferred due to high recurrence rates up to 15%. [8]

Outcomes of varicocele repair techniques.

Technique	Pregnancy rates	Recurrence	Hydrocele
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	
	[illegible]	[illegible]	[illegible]

Controversies and Practical considerations

Despite all guidelines and recommendations, it is still controversial if varicocele repair improves fertility status. Varicocele repair for Non obstructive azoospermia and hypogonadism sparks in further debate. Unlike popular belief, we believe that varicocele is the sole reason for infertility only in a very small subset of infertile men, perhaps only 10%. Even a man with very severe OAT can be fertile and another with normal semen sample can be infertile (owing to high DFI) and hence it is impossible to define a threshold for semen parameters below which a man can be labelled infertile.

In the literature, most studies have considered only semen parameters and endocrine parameters, but approach to an infertile couple should be holistic and the management should be based on the following factors

- Degree of OAT and Testicular damage
  - Varicocele correction is ineffective in severe OAT and already damaged testicles as the insult is permanent and irreparable.
- Female factors
  - In couples with advanced female age, reduced ovarian reserve, or other female factors needing ART it is better the best treatment is provided at the earliest rather than a varicocele repair

Emerging evidence to recommend varicocele surgery in men having borderline or normal semen parameters with high DNA fragmentation and palpable varicocele. This needs to be further evaluated and substantiated in proper randomised control studies

Conclusions

We recommend varicocele repair only in following subset of infertile couple
a) Couple with reasonable trying time
b) Only moderate OAT with normal testicular size, FSH levels and palpable varicocele
c) Exclusion of other causes of OAT
d) Normal female factors with emphasis on ovarian reserve

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Any Suggestions / Queries May Be Sent to
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"Challenges and Innovations in ART"
zoom


HALL - A
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17th Annual Conference of Indian Fertility Society
FERTIVISION 2021
New Delhi | India
Workshops: 4 & 5 December
Conference: 11 - 12 December
"Challenges and Innovations in ART"
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zoom


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FERTIVISION 2021
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Workshops: 4 & 5 December
Conference: 11 - 12 December
"Challenges and Innovations in ART"
zoom


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Quiz - FERTIVISION 2021
Anviti
Y.A.Bhavya
Chandana
26896
29 out of 32
23059
24 out of 32
22644
24 out of 32
Kahoot!
Runners-up
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INTAS
FERRING PHARMACEUTICALS
SUN PHARMA
CooperSurgical
Abbott
MERCK
BSV
Emcure
COOK InterMedics
Shivani
SAMARTH
Mankind
Organised by
INDIAN FERTILITY SOCIETY
JAGSONPAL
AstraZeneca
Cryo Bio System
STORZ
KARL STORZ – ENDOSKOPE
Organised by
INDIAN FERTILITY SOCIETY


MERCK
MERCK


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Conference: 10 - 12 December
"Challenges and Innovations in ART"

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10:57

HALL - A
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HALL - B
09:21
zoom

HALL - A

HALL - A
zoom

HALL - A
zoom

FERTIVISION 2021
WINNERS

1st Prize:

Anviti Saraf

2nd Prize:

Y. Annapurna Bhavya Reddy

3rd Prize:

Chandana.S.Bhat

Dr. Kuldeep Jain- Best Clinical Paper(<40 yrs)

Dr. Reeta Mahey **Dr Bhawani Shekhar**

Dr. Kuldeep Jain- Best Embryology Paper(<40 yrs)

Dr. Monika Rajput

Dr. K.D. Nayar - Best Clinical Paper(>40 yrs)

Dr. Reeta Bansiwal

Dr. K.D. Nayar - Best Embryology Paper(>40 yrs)

Mr. Akhil Garg **Dr. N Sujatha Reddy**

Brig R.K. Sharma- Best Poster (<40 yrs)

Dr. Sana Naqash

Brig R.K. Sharma- Best Poster above (>40 yrs)

Dr. Vasanthi Palanivel

Dr. Gouri Devi Prize- 1st Team in Quiz Competition

Dr Bhawani Shekhar

Dr. Gouri Devi Prize- 2nd Team in Quiz Competition

Dr. Nidhi Tripathi

Dr. Umesh Jindal Best Paper Among Current Batch of IFS fellows

Dr. Prabhneet Kaur

Dr. Kriti Singh

Dr. Sonia Malik Prize Best Clinical IFS Fellow (1st in exit exam)

Dr. Jaya Kumari

Dr. Sonia Malik Prize 2nd Best Clinical IFS Fellow (2nd in exit exam)

Dr. Ruchika Sood

Dr Abha Majumdar Best Published Original Research Paper 2021

Dr. Nidhi Sharma