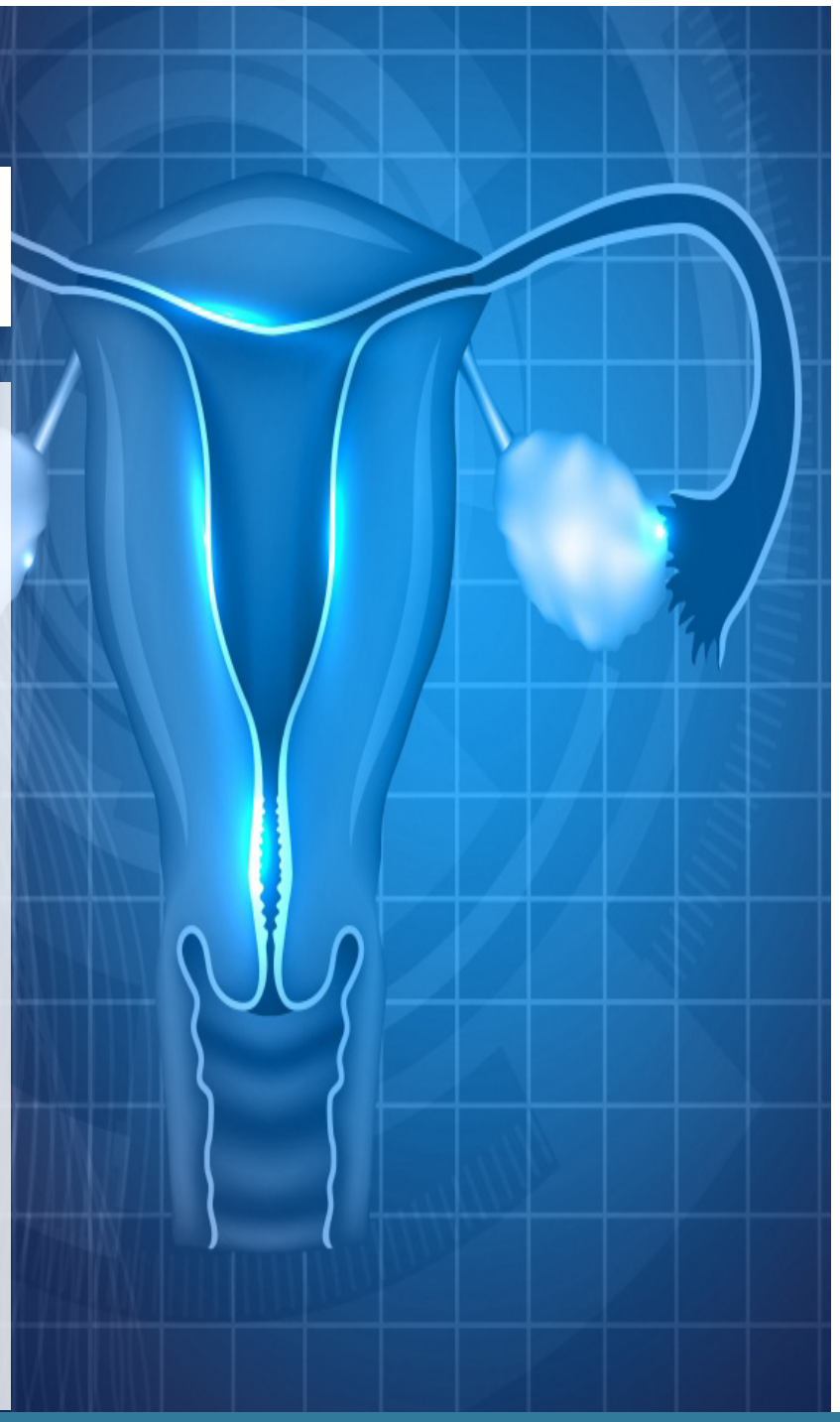
IFS CONVERSATION

Volume 4 : November 2017

UTERINE FACTOR INFERTILITY



CONTENTS

IFS SECRETARIAT

Akanksha IVF Centre

A-3/7, Janak Puri, New Delhi-110058

T: +91 9899308083, 45682024

E: indianfertilitysocietydelhi@gmail.com

W: www.indianfertilitysociety.org

MESSEGE FROM THE PRESIDENT DESK

Dear Friends,

Although traditionally "Uterine Factors" are considered to represent only 3 to 5 % of all infertility causes, it is well accepted now, that intra-uterine lesions are much more common in infertile women (40-50%). These lesions can interfere with spontaneous fertility and also can compromise pregnancy rates in assisted reproduction. Therefore, evaluation of the uterine cavity is one of the basic investigations in infertility workup. Classically, transvaginal sonography and hysterosalpingography are most commonly used investigations for this purpose. However, Hysteroscopy, with the development and miniaturization of equipment, is currently a simple and cost-effective technique. While hysteroscopy is now a widely accepted practice, the benefits of routine use of hysteroscopy in the initial assessment of infertility or even before trying first IVF cycle in all cases, remain unclear. The treatment of uterine factors is equally challenging, leaving "Surrogacy" as the only option to enjoy parenthood in a number of patients. Uterine transplant, although still far away from being a routine surgery at the present time, brings a fresh ray of hope in the medical science.

I congratulate Dr Surveen Ghumman for selecting this extremely important topic for the present issue of "IFS Conversations". I am sure readers will benefit from the scholarly articles written by renewed experts in this field, and find the information useful in their daily practice.

Since our last edition of "IFS Conversations" - Volume 3 August 2017, all IFS Executive Members, including various Chapter Secretaries and members have continued to work very hard and organized several excellent CMEs across the country. I congratulate and thank each one of them for their most sincerely valued contributions. The high quality e-bulletin "NEXUS" launched in June 2016, has now published its 6th volume, dedicated to the topic of "Vitrification". Our second e-bulletin - "ARText" which was released in July 2017 with its inaugural issue on "Hydrosalpinxin Assisted Reproduction", is now ready with its second volume focused on "Endometriosis in ART". Both these e-bulletins are available on our website without any cost to all our readers. Our "Special Interest Groups (SIG)" members have also been working very hard and organized several outstanding CMEs and public awareness programs in different parts of our country. I sincerely thank each one of them for their hard work and continued dedication towards IFS.

All our educational courses – "Embryology Preparatory Certification Course for ESHRE Exam" and two separate one year courses – "Diploma in Clinical ART" and "Diploma in Clinical Embryology" (both Diploma Courses are now accredited by prestigious Amity University) are running very successfully, and the procedure and dates for next entrance test for these courses are available on our website.

I sincerely thank Dr Surveen Ghumman , Dr Bharati Dhorepatil and all contributors for this excellent edition and wish all members an enjoyable reading. Your feedback and suggestions are always most welcome. Please do visit our website www.indianfertilitysociety.org regularly for all updates.

I look forward to your active participation in the 13th Annual Conference of IFS on 8-10 December 2017, which not only is sure to enrich your knowledge and expertize further, but it is also a pleasant opportunity to meet and bond with each other as proud IFS family members.

With warm regards and best wishes,

Dr. Sohani Verma
President – IFS

MESSEGE FROM THE SECRETARY DESK

Dear Friends,

Wish you all a very happy, healthy & festive season. As the end of 2017 approaches, we are continuing to work toward finalizing details of the our 13th Annual conference , Fertivision 2017. On behalf of the Organizing Committee of the 13th Annual Conference of Indian Fertility Society I have the immense pleasure to welcome you at Hotel Pullman , Aerocity, New Delhi on 8th, 9th and 10th December 2017. To provide the participants with the best and the latest, a galaxy of international and national stalwarts representing the best in Reproductive Medicine are scheduled to address the conference, which includes not only the customary orations, free papers, symposia but also interactive workshops, point-counterpoint debates and also a quiz and entertainment programme.

Over the last years, we have been focused on increasing the value of IFS to all its members. Today the Society is noted for its high quality and innovative Continuing Medical Education programs including the launch of this quarterly News bulletin ,IFS Conversations focusing on " Uterine factor Infertility". I congratulate Dr.Surveen Ghumman and her team for their tireless efforts for bringing out this informative newsletter. Uterine factor infertility refers to the anatomical or physiological inability of a uterus to sustain gestation, affecting 3-5% of population.

A new beginning has also been made about IFS initiative of collaborating with ESHRE and from 2018, ESHRE Certification Examination for Embryologists will be conducted simultaneously in New Delhi as the only Centre outside of Europe.

Looking forward to see you in New Delhi

With Warm Regards,

Dr. K.D. Nayar
Secretary General - IFS

THE EXECUTIVE MEMBERS

PRESIDENT
Dr. Sohani Verma
M: 9810116623 E: drsohaniverma@gmail.com
SECRETARY GENERAL
Dr. K.D. Nayar
M: 9810398765 E: kdnayar@usa.net
PATRON
Dr. M. Kochhar
M: 9810018277 / 24352514 / 24356615 E: drmkochhar@yahoo.com
FOUNDER PRESIDENT
Dr. Mangala Telang
M: 9811030476/25822454 E: drmangalatelang@gmail.com
PRESIDENT ELECT
Dr. M. Gouri Devi
M: 9810023111 E: gouri48@ridgeivf.com
VICE PRESIDENTS
Dr. Sushma Sinha
M: **9810068543** E: sinha_sushma@hotmail.com
Dr. Sudha Prasad
M: 9968604341 E: drsprasad@yahoo.com
PAST PRESIDENT
Dr Abha Majumdar
M: 9810315807 E: abhamajumdar@hotmail.com
Dr Nalini Mahajan
M: 9810087666 E: dr.nalinimahajan@gmail.com
Dr Kuldeep Jain
M: 9810018951, 22443069 E: jainravi6@rediffmail.com
Dr Sonia Malik
M: 9810122337 E: sm_doc@southendivf.com
JOINT SECRETARY
Col. (Dr.) Pankaj Talwar
M: 9810790063 E: pankaj_1310@yahoo.co.in
TREASURER
Dr. Neena Malhotra
M: 9891557707 E: malhotraneena@yahoo.com
JOINT TREASURER
Dr. Rashmi Sharma
M: 9810252619 E: drrashmisharma73@gmail.com
EDITOR
Dr. Bharati Dhorepatil
M: 26682070/09822043112 E: bharatidp@yahoo.co.in
JOINT EDITOR
Dr. Surveen Ghumman
M: 9810475476 E: surveen12@gmail.com
WEB EDITOR
Dr. leena Wadhwa
M: 9910933447, 9818145296 E: drleena_123@yahoo.co.in
EXECUTIVE MEMBERS
Dr. Gita Radha Krishnan
M: 9891178410 E: gita.radhakrishnan@gmail.com
Dr. Neeta Singh
T: 011-27519006/9810218812 E: drneetasingh@yahoo.com
Dr. Shweta Mittal
M: 9910303056 E: mshwets@hotmail.com
Dr. Ritu Jain
M: 9873183030 / 9999600410 E: vmcgurgaon@gmail.com
Dr. Renu Misra
M: 9811147217 E: drrenumisra@gmail.com
Dr. Tanya Buckshee
M: 9910003731 E: tanyabrohatgi@gmail.com
Dr. Sweta Gupta
M: 8130140007 E: swetagupta06@yahoo.com
Dr. Rupali Bassi Goyal
M: 9818331760 E: rupalibassi@hotmail.com
EXECUTIVE ADVISORS
Dr. Umesh Jindal
M: 9876130501, 0172-2703222 E: drunjindal@gmail.com
Dr. S.N. Basu
M: 9810119072 E: ssndbasu@gmail.com
Dr Sandeep Talwar
M: 9810306455 E: sonutalwar2001@yahoo.co.in
CHAPTER SECRETARIES
Dr. Ritu Khanna (UP)
M: 9415226900 E: ritukhannayogesh@yahoo.co.in
Dr. Kumud Pasricha (Punjab)
M: 9876709795 E: kumudpasricha@hotmail.com
Dr. Illa Gupta (Haryana)
M: 9811456056 E: ila_gupta007@yahoo.co.in
Dr. Manoj Chellani (Chattisgarh)
M: 9826611688 E: drmanoj22@gmail.com
Dr. Kishore Pandit (Maharashtra)
M: 9860080000 E: drkishorepandit@hotmail.com
Dr. Namita Kotia (Rajasthan)
M: 9829069228/01412370271 E: namitakotia2000@yahoo.co.in
Dr. Shalini Gainder (Greater Chandigarh)
M: 9815555732 / 172-2772871 E: shalinilakhanpal@rediffmail.com
Dr. Rohini Dravid (Vidharba)
M: 93731006542, 0712-2426071 E: mvdravid@yahoo.com
Dr. Randhir Singh (MP)
M: 9303133385 E: bttbcentre@gmail.com
Dr. Anila Koul (Jammu)
M: 9419133575 E: dr.anilakoul@gmail.com
Dr. Kunjimoideen (Kerala)
M: 9895983376 E: drkmideen@gmail.com
Dr. P.M. Gopinath (Tamil Nadu & Pondicherry)
M: 04426163884, 9840888878 E: dgopinath@yahoo.com
Dr. Anita Singh (Bihar)
M: 9334111925 E: anitasinghob@gmail.com
Dr. Konkon Mitra (West Bengal)
T: 9830150438 E: konkonmitra@gmail.com
Dr. Alok Sharma (Himachal)
M: 9418477725 E: md.alok@gmail.com
Dr. Mujibur Rehman (North East)
M: 9435070660 E: mrahman567@gmail.com
Dr. Uma Shrivastava (Nepal)
M: 9851074477/977-4471077/4785087 E: dr.ushrivastava@gmail.com
Dr. Jayesh S.Amin (Gujarat)
M: 9824302671/9825050565 E: dramin@wingshospitals.com
CO-OPTED MEMBERS
Dr. Alka Kriplani
M: 9810828717 E: kriplanialka@gmail.com
Dr. Urvashi Jha
M: 9811029310 / 9350550669 / 9971780385 E: urvashipjha@yahoo.com
Dr. R.K. Sharma
M: 9810442301 E: dr_sharma1957@yahoo.co.in

MESSEGE FROM THE EDITOR DESK

Dear All,

Greetings!!

We bring to you another issue of IFS Conversations, our quarterly newsletter. It has always been our endeavor to get the latest and most relevant topics in the field of ART. We look forward to being connected to you through this news letter.

In the field of ART success depends highly on the wellbeing of the uterus. Hence, we decided to review 'Uterine Factor Infertility' in this issue. Extremely relevant topics and controversies, like fibroid removal before IVF and impact of Mullerian anomalies are discussed. Dealing with difficult situations in infertility related to uterus like thin endometrium, intrauterine adhesions and tuberculosis are reviewed. Imaging of uterus related to the clinical decision making is appraised.

IFS, as usual, has been active in the academic front. All chapter activities CMEs, workshops, public forums and quiz competitions are enlisted. Besides that on the international front IFS has partnered with ESHRE to hold the ESHRE embryology certification exam in India. Delhi center will be second center for ESHRE Embryology certification and the only center outside Europe. This partnership is a big step to standardize embryology procedures in India to international levels.

We have seen IFS progress to a member strength of 1780 members in 18 state chapters all over the country. Recently 2 new chapters, were inaugurated, first international chapter in Nepal and the new chapter in the state of Gujrat. This progress has been made steadily over the last 13 years. There are many publications in the form of e-bulletins and a journal - Fertility science and Research which is taken out regularly. With its stress on academics IFS has evolved as a well recognized national academic body.

We thank all the contributors for their interesting articles for this issue and for giving this newsletter its academic content. Their timely submission of articles made it possible to put this together as scheduled and give it the face it has. In the next issue of IFS conversations we would include some topics on uterine factor infertility not covered in this isuue like endometrial polyp and adenomyosis.

The release of this newsletter coincides with IFS annual conference, Fertivision 2017 being held in Delhi. This conference is an academic conglomeration of 16 international faculty and numerous national pioneers in ART. It is a platform for scientists to share their work, debate controversies and formulate clinical guidelines in this field. We hope to see you there!

With Warm Regards,

Dr. Bharati Dhorepatil
Editor - IFS

Dr. Surveen Ghumman
Joint Editor - IFS

GOVERNING COUNCIL

President	Dr. Sohani Verma
President Elect	Dr. Gouri Devi
Vice President	Dr. Sudha Prasad Dr. Sushma Sinha
Secretary General	Dr. K.D. Nayar
Joint Secretary	Dr. Pankaj Talwar
Treasurer	Dr. Neena Malhotra
Joint Treasurer	Dr. Rashmi Sharma
Editor	Dr. Bharati Dhorepatil
Joint Editor	Dr. Surveen Ghumman
Web Editor	Dr. Leena Wadhwa

Dr. Sohani Verma

Dr. Gouri Devi

Dr. Sudha Prasad

Dr. Sushma Sinha

Dr. K.D. Nayar

Dr. Pankaj Talwar

Dr. Neena Malhotra

Dr.Rashmi Sharma

Dr. Bharati Dhorepatil

Dr. Surveen Ghumman

Dr. leena Wadhwa

TEAM IFS

President	Dr. Sohani Verma	
Secretary General	Dr. K.D. Nayar	
Patron	Dr. M. Kochhar	
Founder President	Dr. Mangla Telang	
President Elect	Dr. M. Gauri Devi	
Vice Presidents	Dr. Sudha Prasad Dr. Sushma Sinha	
Past President	Dr. Abha Majumdar Dr. Nalini Mahajan Dr. Kuldeep Jain Dr. Sonia Malik	
Joint Secretary	Dr. Pankaj Talwar	
Treasurer	Dr. Neena Malhotra	
Jt. Treasurer	Dr. Rashmi Sharma	
Editor	Dr. Bhaati Dhorepatil	
Jt. Editor	Dr. Surveen Ghumman	
Web Editor	Dr. Leena Wadhwa	
Executive Members	Dr. Neeta Singh Dr. Gita Radhakrishnan Dr. Shweta Mittal Dr. Ritu Jain Dr. Renu Mishra Dr. Tanya Buckshee Dr. Sweta Gupta Dr. Rupali Bassi Goyal	
Chapter Secretaries	Dr. Ritu Khanna	UP
	Dr. Kumud Pasricha	Punjab
	Dr. Illa Gupta	Haryana
	Dr. Manoj Chellani	Chattishgarh
	Dr. Kishore Pandit	Maharashtra
	Dr. Namita Kotia	Rajasthan
	Dr. Shalini Gainder	GR. Chandigarh
	Dr. Rohini Dravid	Vidharba
	Dr. Randhir Singh	MP
	Dr. Anita Koul	Jammu
	Dr. Kunjumoideen	Kerala
	Dr. P.M. Gopinath	Tamil Nadu
	Dr. Anita Singh	Bihar
	Dr. Konkon Mishra	West Bengal
	Dr. Alok Sharma	Himachal
	Dr. Mujibur Rehman	North East
	Dr. Uma Shrivastava	Nepal
	Dr. Uma Shrivastava	Gujarat
Co-opted Members	Dr. Alka Kriplani Dr. Urvashi Jha Dr. R.K. Sharma	

ESHRE & IFS PAGE

A New Era In Field Of Embryology

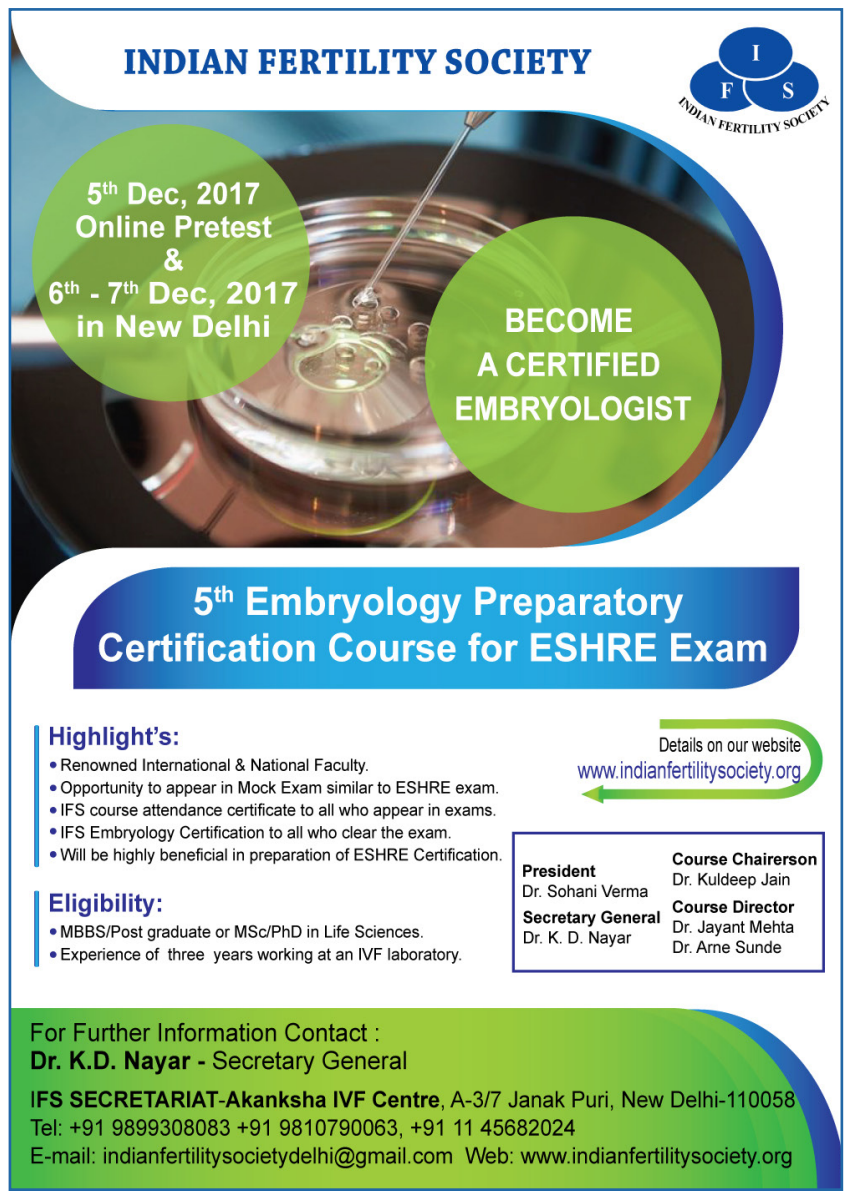
DR KULDEEP JAIN

Director, JIVF and Laparoscopy Centre Delhi
Program Director, Asian- KJIVF, Faridabad
Past President, IFS
Chairperson, Endometriosis Committee, FOGSI
Editor, Fertility Science and Research

Indian fertility society has crossed another great milestone by collaborating with European society of human reproduction on a pilot project bringing the prestigious ESHRE Embryology certification to Delhi, India . This is the first time that candidates aspiring to appear in certification exam would be able to take up the Exam without actually going to Barcelona. Delhi center will be second center for ESHRE Embryology certification and the only center outside Europe. Exams will be conducted online in sink with Barcelona exams at the same time. This will save cost as well as traveling so more and more embryologist from Indian subcontinent can now look forward to get certified. This project is seen as a great initiative of IFS with ESHRE collaboration which will help to standardise the practice of Embryology in India and Asian countries.

To start with, 40 seats are open for online exam at New Delhi and last date for application is 15 th Dec 2017 . For more details, candidates can log on to ESHRE.eu or Indian fertility society website.

It is important to know that exercise to standardise the Embryology practice in India started 5 years back with the introduction of Embryology preparatory course for ESHRE exams by Indian fertility Society with Dr Arne Sunde, Norway ,Past chair, ESHRE and DrJayant Mehta, UK, as course director and DrKuldeep Jain as course Chairperson. The effort and support put in by both course directors was tremendous and the course became a popular yearly event for embryologists in India. The course is a flagship program of IFS and one the most popular Embryology course available in India and currently 5th course is being organised on 6-7 thdec. many of students have cleared the ESHRE certification in last 4 years and this exercise became instrumental in Initiation of this landmark collaboration between IFS and ESHRE.



INVITED ARTICLES

Is Myomectomy Needed Before IVF ?

DR SOHANI VERMA
Sr. Consultant Obstetrics & Gynaecology
Infertility & ART Specialist
Clinical & Academic Coordinator
Dept. of IVF, Indraprastha Apollo Hospitals, New Delhi
President Indian Fertility Society
Immediate Past Chairperson North Zone
AICC RCOG (2012-2017)

Uterine leiomyomas, or fibroids, can occur in up to 60% of women before the age of 40, and 80% of women before the age of 50 (Baird DD et al 2003). These are described to be directly or indirectly associated with 5-10 % of all cases of infertility. The effect of uterine fibroids on fertility is largely dictated by their location and size. Despite a clear biological rationale to support a causal relationship between fibroids and subfertility, large observational studies are inconclusive, mainlybecause of methodological limitations.

It is widely accepted that the presence of fibroids significantly reduces the success of IVF treatment. The threat that myomas impose on the outcome of IVF cycle lies mainly in one of the two fields: the myometrial contractility and the endometrial receptivity. A 2009 review by Pritts et al found that fibroids causing intracavitary distortion result in decreased rates of clinical pregnancy, implantation and ongoing pregnancy / live birth, as well as an increased rate of spontaneous miscarriage. By contrast, there is controversy as to whether fibroids that do not cause distortion of the uterine cavity have any effect on fertility. However, in the same review, Pritts et al. found that patients with fibroids with no intracavitary involvement (particularly intramural fibroids), when compared with controls without fibroids, had decreased rates of implantation and ongoing pregnancy/live birth, and an increased rate of spontaneous miscarriage. Proposed etiologies for such effects of fibroids without intracavitary involvement include alterations of uterine peristalsis and vascular flow as well as disruption of sperm and ovum transportation, fertilization and embryo implantation. No evidence was found that subserosal fibroids decreased any measure of fertility. The data provide compelling evidence that there may be situations in which surgical removal of nonsubmucosal fibroids is indicated in the infertile patient.

Another important consideration while making a decision regarding treatment of fibroids before ART, is the effect, fibroids may have on pregnancy. Pregnancy complications related to fibroids have been reported to include: degeneration and associated pain in 10-15%, an increased risk of miscarriage, abruption, placenta previa, intrauterine growth restriction, malpresentation and cesarean section (Somigliana E. et al 2008). It is essential to consider both - the negative impact fibroids seem to have on fertility, as well as the possible pregnancy complications, when deciding upon surgical management of fibroids before ART.

In women with infertility, an effort must be made to adequately evaluate and classify fibroids, particularly those impinging on the endometrial cavity, using transvaginal ultrasound, hysteroscopy, hysterosonography, or magnetic resonance imaging (Grade III-A recommendation by SOGC). Preoperative assessment of submucoal fibroids should include, in addition to an assessment of fibroid size and location within the uterine cavity, evaluation of the degree of invasion of the cavity and thickness of residual myometrium to the serosa. A combination of hysteroscopy and transvaginal ultrasound or hysterosonography are the modalities of choice (III-B). A hysterosalpingogram is not an appropriate exam to evaluate and classify fibroids (III-D).The choice of surgical method will depend upon the size, site and type of such myomas. The staging first described by Wamsteker et al. (1993), is widely used to classify submucous fibroids at hysteroscopy and also during ultrasound examination. More recently, the ESGE / FIGO leiomyoma classification system is recommended to avoid inconsistency in reporting (Munro MG et al 2011).
Once a patient has been diagnosed with submucosal, intramuralor subserosal fibroids, a decision must bemade about management. Although there are many medicaltreatments available to help alleviate symptoms from fibroids,none are recommended for infertility patients as they can actuallydelay appropriate and timely management. The surgicaloption available to patients desiring fertility is myomectomy.

Observational studies suggest a fertility benefit for the surgical removal of fibroids.Myomectomy is however not without risk and can result in serious complications. One such study by Bulletti et al. (2004) allowed patients diagnosed with intramural or subserosal fibroids to choose whether to undergo myomectomy after counseling. Patients were then divided into two groups based on their decision (n = 84 each). Delivery rates were significantly higher in the group undergoing myomectomy (25 vs 12%; p=0.01). While this study was not randomized, the results are compelling for the efficacy of myomectomy.

There are a variety of surgical methods to remove fibroids including laparotomy, laparoscopy, Robotic assisted surgery and hysteroscopy. The relative advantages and disadvantages of these modalities in terms of efficiency and side effects are unknown. The greatest risks for an abdominal myomectomy are intraoperative hemorrhage, postoperative pain, and adhesive disease (up to 94% posteriorly and 55% anteriorly), which can further decrease fertility (The Practice Committee of ASRM 2008). The other recent surgical trend is laparoscopic myomectomy andthe latest surgical modality is that of Robotic assisted laparoscopic myomectomy. Although laparoscopic removal of fibroids has not been shown to confer additional fertility benefits over laparotomy, there is significant reduction in hospital stay and febrile morbidity. A decision to perform myomectomy will depend upon weighing the possible positive impact on implantation rate following IVF and also on the course of pregnancy, against the potential risks of the surgery.

In order to rationalize, if myomectomy is needed before IVF in a given case or not, we can divide uterine fibroids into 3 groups-

1. Submucosal and Intramural fibroids that protrude into the endometrial cavity.
2. Intramural fibroids Not distorting the uterine cavity.
3. Subserosal fibroids

Group I – Submucosal and Intramural fibroids that protrude into the endometrial cavity:

With regards to in vitro fertilization (IVF) treatment, submucosal and intramural fibroids that protrude into the endometrial cavity, have been reported to be associated with decreased pregnancy rates and implantation rates (Bernard et al., 2000). Studies have shown that IVF outcome is markedly improved in women with cavity-distorting submucosal fibroids following myomectomy (Surrey et al., 2005). It is recommended that submucoal fibroids strongly interfere with conception (OR for delivery of 0.3 [a 70% reduction], 95% Cl 0.1-0.8) and these should be removed (Sunkara SK et al 2010).

There is general consensus that type 0 and type 1 fibroids, where at least 50% of the fibroid is within the uterine cavity, are best removed hysteroscopically, whereas the removal of type 2 fibroids, where more than 50% is within the myometrium, is more complex. Type 2 fibroids larger than 40 mm may need two to three surgical procedures to ensure completeness of resection, thus increasing the risk of endometrial damage and complications. A suitable alternative is to remove such fibroids laparoscopically (or by laparotomy), should this be deemed necessary. The management of multiple submucous fibroids or multiple uterine fibroids with submucous lesions is unclear.

Group-II- Intramural fibroids Not distorting the uterine cavity:

Even intramural fibroids not distorting the endometrial cavity have been reported to result in a reduction in live birth rate (LBR) (OR for LBR of 0.79 [a 21% reduction], 95% Cl 0.70-0.88) (Sunkara SK et al 2010). However, a Cochrane Database Syst Review in 2012 by Metwally M et al. concluded that there was insufficient evidence to draw any conclusion regarding the effect of intramural fibroids on treatment outcomes.

While there is fair evidence to recommend against myomectomy in women with intramural fibroids (hysteroscopically confirmed intact endometrium) and otherwise unexplained infertility, regardless of their size (Grade II-D recommendation), there are conflicting opinions when the couple is undergoing IVF treatment, and more so, when they have 1 or more previous failed IVF attempts. Several studies have shown a detrimental effect of fibroids without intracavitary involvement on IVF outcomes, particularly when myomas are larger than 4 or 5 cm size (Sunkara SK et al 2010,), although other

studies refute this evidence (Bozdag G et al 2009). It has been proposed that the presence of deep intramural fibroids physically disrupts the Endo-myometrial Junctional (EMJ) Zone and alters the steroid receptors, leading to implantation failure (Tocci A et al 2008). In such cases, benefits of myomectomy should be weighed against the risks, and management of intramural fibroids should be individualized (III-C).

Group- III- Subserosal fibroids:

Although subserosal fibroids are not believed to alter IVF outcome, there may be a few circumstances in which the patients would likely benefit from myomectomy. For example, women with subserosal fibroids in such a location that egg retrieval must be performed using a trans-myometrial approach, may be best served by myomectomy prior to IVF. In addition, many authors ascribe to the general consensus that it is reasonable to proceed to myomectomy once a fibroid is greater than 10 cm in diameter regardless of location. There is no evidence that subserosal (FIGO L5 to L7) fibroids decreased any measure of fertility (Purohit P et al 2016). The patients should be informed that although myomectomy in such cases may help to alleviate symptoms, there is no strong evidence that surgery for large subserosal fibroids will improve IVF results or pregnancy outcome in terms of reducing the risk of prematurity.

Conclusion:

In conclusion, the role of myomectomy prior to IVF depends on the clinical situation.There is insufficient evidence from RCTs to evaluate the role of myomectomy to improve fertility. A thorough evaluation of the patient prior to proceeding with surgical management of fibroids is recommended. If fibroids are identified on transvaginal ultrasound, then sonohysterogram, hysteroscopy and/or MRI should confirm the specific location and size.

The available data support that subserosal fibroids do not necessitate removal unless transvaginal oocyte aspiration cannot easily be performed because of anatomic distortion. Submucous fibroids or intramural fibroids with a submucous component (FIGO L0-L2) reduce IVF success rates and should be removed. Hysteroscopic myomectomy is the preferred technique if greater than 50% of the fibroid is intracavitary. However, laparotomy or laparoscopy or Robotic assisted surgery (depending upon surgeon's expertize) and myomectomy may be needed for intramural fibroids that have a minor submucous component. The management of intramural fibroids should be individualized on a case to case basis. It remains controversial if the women with deep intramural fibroids larger than 4 cm size that distort the junctional zone should bethe candidates for removal before IVF, specially after 1 or more previous failed IVF attempts with no other obvious reason for infertility. In such cases, benefits of myomectomy should be weighed against the risks, and management should be individualized.

Reference:

1. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol. 2003;188:100–7.
2. Bernard G, Darai E, Poncelet C, Benifla JL, Madelenat P. Fertlity after hysteroscopic myomectomy: effect of intramural myomas associated.Eur J Obstet Gynecol Reprod Biol 2000;88:85–90.
3. Bozdag G, Esinier I, Boynukalin K, Aksu Gunalp S, Gutgan T. Single intramural leiomyoma with normal hysteroscopic findings does not have deleterious effect on ICSI-ET outcome. Reprod Biomed Online 2009; 19:276–280.
4. Bulletti C, DE Ziegler D, Levi Setti P, Cicinelli E, Polli V, Stefanetti M.Myomas, pregnancy outcome, and in vitro fertilisation. Ann N Y Acad Sci 2004; 1034:84–92.
5. Metwally M, Cheong YC Horne AW. Surgical treatment of fibroids for subfertility Cochrane Database Syst Review 2012; 11: CD003857.
6. Munro, MG, Critchley, HO, Fraser, IS. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertil. Steril 2011; 95(7), 2204–2208 .
7. Pritts EA Fibroids and infertility: a systematic review of the evidence. Obstet Gynecol surv 2001; 56 (8): 483-491.
8. Pritts EA, Parker WH, Olive DL, Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 2009; 91(4): 1215-1223.
9. Purohit M and Vigneswarn. Fibroids and Infertility. Curr Obstet Gynacecol Rep 2016;5:81-88
10. Ramzy AM, Sattar M, Amin Y, Mansour RT, Serour GI, Aboulghar MA.Uterine myomata and outcome of assisted reproduction. Hum Reprod 1998;13:198–202.
11. SOGC Clinical Practice Guideline No. 321, March 2015 J Obstet Gynaecol Cab 2015;37(3) : 277-285.
12. Somigliana E, Vercellini, Benaglia L. Abbiati A, Barbara G, Fedele L. The role of myomectomy in fertility enhancement. Curr Opin Obstet Gynecol 2008;20:379-385.
13. Sunkara, SK, Khairy, M, El-Toukhy, T, Khalaf, Y, Coomarasamy, A. The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. Hum. Reprod 2010;25(2), 418–429.
14. Surrey ES , Minjarez DA, Stevens JM, Schoolcarft WB. Effect of myomectomy on the outcomes of assisted reproductive technologies. Fertil Steril 2005: 83 (5);1473-1479.
15. The Practice Committee of the American Society for Reproductive Medicine. Myomas and reproductive function. Fertil Steril 2008; 90(30): S125-30.
16. Tocci A, Greco E, Ubaldi FM. Adenomyosis and 'endometrial-subendometrial myometrium unit disruption disease' are two different entities. Reprod Biomed Online. 2008;17:281–291
17. Wamsteker K, Emanuel MH, de Kruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: resultsregarding the degree of intramural extension. Obstet Gynecol 1993; 82:736–740.

Mullerian Abnormality in Infertility

DR GOURI DEVI
President Elect - IFS
Director - Gouri Devi Hospitals Limited
Director, Ridge IVF, New Delhi

Müllerian anomalies serve as a fascinating prism through which we examine both the embryologic development and normal functioning of the female reproductive tract. Deviation in the development of the female reproductive organs from the normal has been shown to impact greatly on fertility, obstetrical outcomes and gynaecologic health. Besides the physical health, Müllerian anomalies often bring with them adverse psychological effects for these women.

Embryology

Whereas genetic sex in humans is determined at the time of fertilisation, the male or female phenotype is not exhibited until after the 6th week of development. Normal development of the female reproductive tract requires: mullerian duct elongation, fusion, canalization, and septal resorption; failure of any part of this process can result in a congenital anomaly. This process occurs in close association with development of the urinary tract; thus, anomalies of the kidney and ureter are commonly identified in females with mullerian anomalies. Gonadal development occurs as a separate process, beginning by 7 weeks of gestation; therefore, women with mullerian anomalies usually have normal ovaries and ovarian hormone production.

The paired mullerian (paramesonephric) ducts are identifiable by week 6 of development, and arise from coelomic epithelium along the lateral walls of the urogenital ridge. These solid tissue structures elongate caudally, cross the Wolffian (mesonephric) ducts medially, and fuse in the midline to form the primitive uterovaginal canal. By 10th week, the caudal end of the fused mullerian ducts connects with the urogenital sinus. Subsequently, the internal canalization of the mullerian ducts occurs, resulting in two channels divided by a septum. The septum is subsequently resorbed in the caudal to cephalad direction; this is completed by week 20. The fused caudal portion of the mullerian ducts becomes the uterus and upper vagina, and the unfused cephalad portion becomes the fallopian tubes.

The lower vagina has a different embryologic origin. Upon contact between the mullerian ducts and the urogenital sinus, sinovaginal bulbs originate and proliferate toward the caudal end of the uterovaginal canal, forming a solid vaginal plate. The lumen of the lower vagina is formed by degeneration of cells at the center of the vaginal plate; this process occurs in a caudal to cephalad direction and is

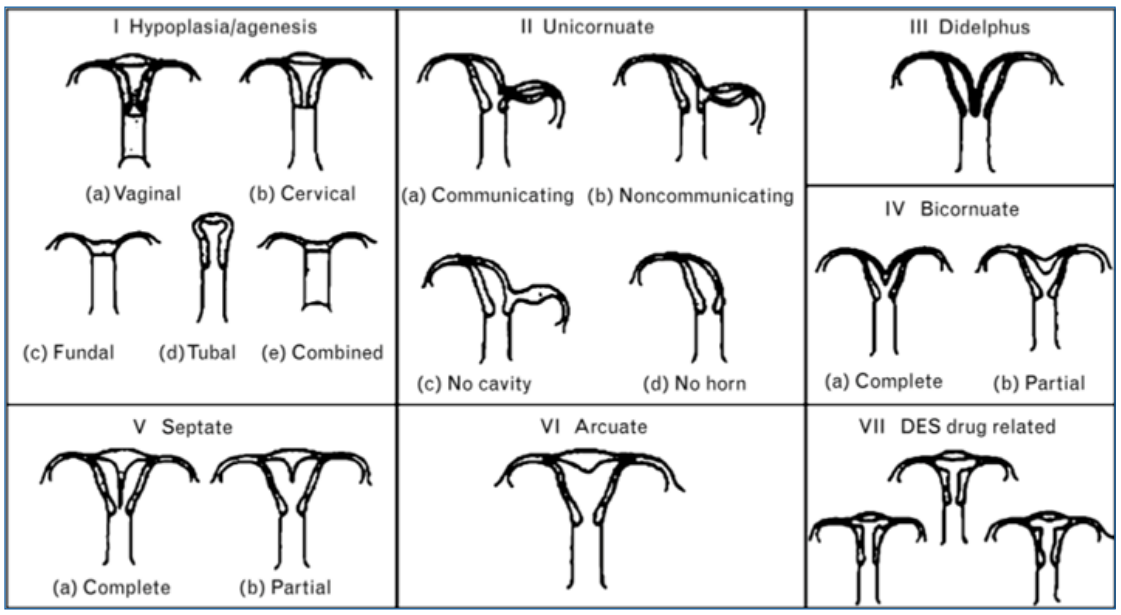
complete by week 20. The hymenal membrane separates the vaginal lumen from the urogenital sinus. The central epithelial cells of the hymenal membrane usually degenerate prior to birth, and the hymen persists as a thin fold of mucus membrane at the introitus. The HOX series of genes have been identified as playing a critical role in determining the positional identity along the axis of the developing paramesonephric duct. [1]

Classification System

Congenital anomalies of the female reproductive tract are typically classified into three main categories: agenesis and hypoplasia, lateral fusion defects, and vertical fusion defects. A fourth group is composed of women exposed to diethylstilbestrol (DES) in utero. Agenesis and hypoplasia can occur with any or multiple mullerian structures. Lateral fusion defects occur due to failure of migration of one mullerian duct, fusion of the mullerian ducts, or absorption of the intervening septum between the ducts. This is the most common category of mullerian defect, and can result in symmetric or asymmetric and nonobstructed or obstructed structures. Vertical fusion defects result from abnormal fusion of the mullerian ducts with the urogenital sinus, or problems with vaginal canalization.

There is no universally accepted standard classification for congenital anomalies of the female reproductive tract. In 1979, Buttram and Gibbons proposed a classification system for müllerian anomalies based on the type and degree of failure of normal development of the female genital tract-which was subsequently revised by the American Society for Reproductive Medicine in 1988***(Fig.1).***[2]

Figure.1 American Society for Reproductive Medicine Classification System for Müllerian Anomalies



Inheritance

Müllerian anomalies are most typically noted as de novo congenital abnormalities without significant hereditary distinction. Karyotypes are normal (46XX) in 92% of women with mullerian anomalies, and abnormal in 7.7% of these women.[3] The majority of these developmental abnormalities are infrequent and sporadic, and are thus attributed to poly- genic and multifactorial causes.

Presentation

Congenital uterine anomalies are often incidentally discovered in the workup for common obstetrical complications and gynaecologic complaints. Often patients present in adulthood, when repeated pregnancy loss, persistent menstrual irregularities or issues related to fertility lead to an unexpected diagnosis.Müllerian anomalies associated with obstruction, such as MRKH, unicornuate uterus with rudimentary horn, or uterine didelphys with obstructed hemivagina, often present with pelvic pain secondary to haematometra, haematocolpos or endometriosis.Patients with hydro or haematocolpos may present with a painful mass on bimanual examination.

Non-obstructive anomalies may be discovered on routine gynaecologic examination. Patients with segmental hypoplasia or agenesis often present with primary amenorrhoea. Similarly, hypomenorrhoea may occur if there is present, but minimal endometrium.

Uterine anomalies are associated with diminished cavity size, insufficient musculature, impaired ability to distend, abnormal myometrial and cervical function, inadequate vascularity, and abnormal endometrial development leading to obstetrical complications.

Diagnostic Evaluation

Ultrasound, whether through the trans-abdominal, trans-vaginal or trans-perineal approach, provides valuable information regarding both internal and external uterine contour while at the same time allowing for evaluation of the kidneys and confirming presence of the ovaries. Three-dimensional ultrasound allows for definition of the uterine and surrounding anatomy and offers a non-invasive, reliable method for differentiating similar internal anomalies with variable external appearance.[4]

Hysterosalpingography (HSG) is an excellent method of evaluating the uterine cavity; however, definitive diagnosis often requires evaluation of the external uterine contour, which is poorly defined by HSG.

Magnetic resonance (MR) imaging, less invasive than laparoscopy but both sensitive and specific for nearly all anomalies, has become for some the new 'gold standard' for definition of uterine and surrounding anatomy.MR imaging is helpful in delineating endometrium, detecting uterine horns, as well as in defining aberrant gonadal location or renal anatomy.[5]

Types of Anomalies :

Cervical Anomalies

Most cervical abnormalities accompany vaginal or uterine anomalies; they are rarely isolated, so an MRI is necessary to define the anatomy. Cervical anomalies include agenesis, atresia, abnormal length or width, obstruction and hypertrophy. Cervical atresia is a rare anomaly.

Successful pregnancies have occurred after utero-vaginal anastomosis for cervical atresia. Surgical correction of obstructive cervical anomalies, however, rarely results in a patent passage and is associated with a high risk of ascending infection; a hysterectomy is often necessary.[6] The ovaries should be preserved, hence pregnancy can be achieved with IVF and a gestational carrier.

Vaginal Anomalies

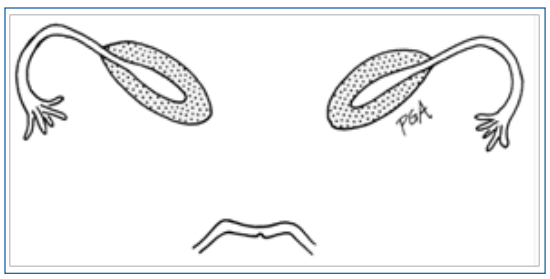
Vaginal anomalies include a transverse vaginal septum (a vertical fusion defect), a longitudinal septum, and an imperforate hymen. Although the transverse septum and imperforate hymen are not associated with other mullerian anomalies, the longitudinal vaginal septum often occurs with uterine anomalies such as a septate or didelphic uterus.

Each vaginal anomaly requires careful assessment of pelvic anatomy to make the correct diagnosis, and surgical repair is necessary in the presence of an obstructive anomaly. A transverse vaginal septum results from failure of fusion between the mullerian ducts and the urogenital sinus or abnormal vaginal canalization, and requires excision of the septum and vaginal anastamosis. A longitudinal vaginal septum may cause dyspareunia, difficulty with tampon placement, or obstructed labor, and should be excised if symptomatic or if the woman desires restoration of a normal vaginal canal. An imperforate hymen occurs due to incomplete degeneration of the central portion of the hymen, and requires excision of the excess hymenal tissue.

Vaginal agenesis is an uncommon condition, and most frequently occurs as congenital absence of the vagina with variable uterine development (Mayer-Rokitansky- Kuster-Hauser syndrome). This developmental anomaly occurs due to agenesis or hypoplasia of mullerian duct development. The incidence of this abnormality is one in 5000 female births.[7] These women have a 46XX karyotype, and normal ovaries, ovarian function, female external genitalia, and secondary sexual characteristics, but experience primary amenorrhea.

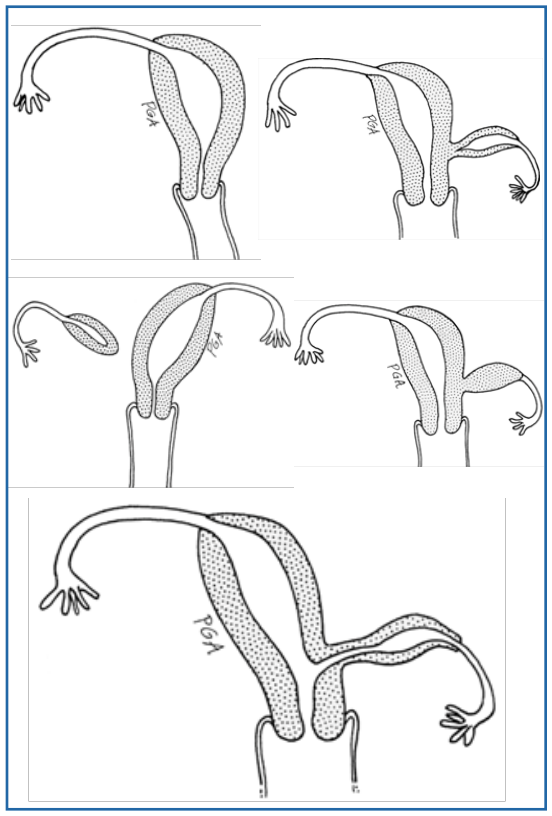
Patients with MRKH syndrome face significant reproductive challenges. Most patients with this anomaly have at least one normal ovary; ovulation induction, retrieval and subsequent transfer to a gestational carrier offer the opportunity for patients with MRKH to have genetically related offspring. These women respond to gonadotropin stimulation similarly to women with normal pelvic anatomy.[8] To enable sexual intercourse, a neovagina can be created with vaginal dilators or surgery; several successful approaches are available.

Research has suggested that congenital absence of the uterus and vagina are not commonly transmitted to offspring in MRKH surrogate pregnancies.[9] Uterine transplantation remains an option.



Unicornuate Uterus

During embryogenesis, the failure of one mullerian duct to develop and elongate results in a unicornuate uterus. This asymmetric lateral fusion defect usually results in a functional uterus with a normal cervix and fallopian tube, and varying configurations of abnormal mullerian development on the contralateral side: agenesis, or a rudimentary uterine horn (74%). This rudimentary horn may be noncommunicating (70 – 90%) or communicating with the unicornuate uterus, and may have no endometrial cavity or some functional endometrium. Although rudimentary horns are commonly asymptomatic, an obstructed horn with active endometrium can result in cyclic or chronic pelvic pain, endometriosis, or a horn gestation.

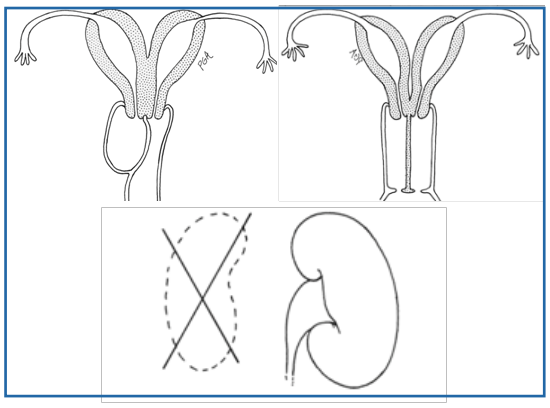


Unicornuate uterus, with its compromised uterine mass and sometimes associated uterine horns, brings with it considerable reproductive hurdles but mostly obstetric complications rather than infertility. Unicornuate uterus has been implicated in IUGR, miscarriage, malpresentation, preterm labour and cervical incompetence.

Uterine Didelphys

Complete failure of fusion of the two müllerian ducts results in duplication of the cervix in addition to the uterus. Patients with uterine didelphys often present earlier for clinical evaluation due to problems such as obstructed hemivagina, which usually occurs on the side of a renal anomaly and is referred to as OHVIRA (obstructed hemivagina with ipsilateral renal anomaly).[10]

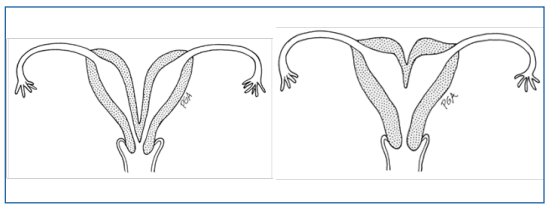
Uterine didelphys has a relatively good prognosis for achieving pregnancy; an infertility rate of 13% has been reported from a study of 49 women with a mean follow-up of 9 years. [11] A review of 114 patients with untreated uterine didelphys who had a total of 152 pregnancies exhibited a mean miscarriage rate of 32.9% and preterm delivery rate of 28.9%, with a live-birth rate quoted as 56.6%. Strassman reunification should not routinely be undertaken, except in circumstances of repeated pregnancy loss or preterm delivery in the absence of other aetiologies.



Bicornuate Uterus

This results from incomplete fusion of the two müllerian ducts, leading to varying degrees of separation between two uterine cavities. Complete bicornuate uterus results when two uterine horns are divided down to the internal os of the cervix with no communication between the two uterine cavities. Partial bicornuate uterus lies between these two extremes, with a more profound indentation between the two uterine horns than in arcuate uterus but with lateral fusion and a central cavity prior to the level of the internal OS.

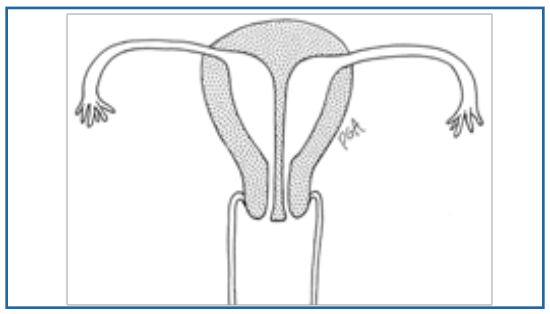
In patients with repeated pregnancy loss in whom other causes have been excluded, laparoscopic or abdominal metroplasty serves as a viable treatment modality to improve obstetric outcomes. We do not recommend metroplasty at the time of diagnosis for patients with primary infertility, given that fertility rates are not significantly reduced from the norm and successful pregnancies without intervention are common.



Septate Uterus

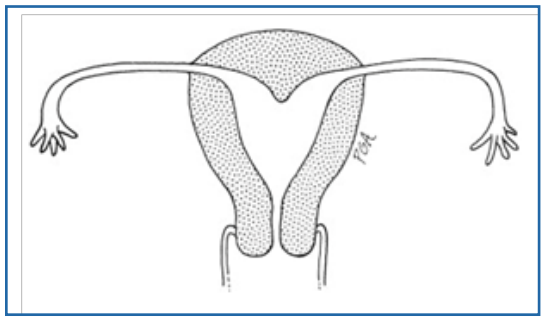
Septate uterus occurs when lateral fusion of the two müllerian ducts has occurred, allowing for a normal-appearing uterine surface, however, with failure of resorption of the internal septum between the two uterine cavities. This failure of resorption can be complete, wherein two cavities separated by a fibromuscular division, or can be incomplete, with a central caudal cavity divided cephalad into two upper compartments by a vestigial uterine septum.Impaired apoptosis associated with the Bcl-2 regulatory protein has been implicated in failed regression of the uterine septum. [12]

Prophylactic hysteroscopic metroplasty in infertile women or women without a history of adverse reproductive outcomes is a controversial procedure since many women with a septate uterus can have reasonable pregnancy outcomes, and there is no established causal relationship between a septate uterus and infertility.



Arcuate Uterus

Based on the minimal deviation from normal anatomy represented by arcuate uterus, that patients with this malformation enjoy reproductive outcomes relatively similar to those women with normal uteri. Several studies have implicated arcuate uterus as being associated with poor obstetric outcomes, although such claims remain controversial. Cited rates of live birth vary widely, from as low as 45% to as high as 82.7%.[13] Women with such anomalies do not benefit from surgical intervention in the absence of other anomalies, and such patients should be reassured of their high likelihood for successful reproduction.



Diethylstilbestrol Exposure

DES is a synthetic estrogen that was used between the 1940s and 1971 for the treatment of RPL, premature delivery, and other complications of pregnancy. If a woman was exposed to DES in utero, the T-shaped uterine cavity was the most common abnormality (70%); other anomalies include a hypoplastic uterus, midfundal constriction rings, intrauterine filling defects, and endometrial cavity adhesions. DES exposure was also associated with cervical abnormalities such as cervical hypoplasia, hoods, collars, and pseudopolyps, and vaginal abnormalities such as adenosis, vaginal ridges, and transverse septa.

Uterine anomalies due to in-utero DES exposure are associated with an increased risk of adverse reproductive outcomes.

Fertility and Mullerian Anomalies

In general, the reproductive challenges associated with patients having Müllerian anomalies lies in pregnancy maintenance rather than conception. Controversy exists over the impact of intrauterine defects and their impact on the potential for implantation. Earlier studies suggested that women with Müllerian anomalies undergoing in vitrofertilisation (IVF) for myriad infertility diagnoses had similar clinical pregnancy rates as women with normal uteri undergoing IVF.[14] Other, more recent, studies have called into question whether subtle factors affecting the intrauterine milieu, such as small residual septa subsequent to metroplasty, have detrimental effects on implantation.[15] One study comparing ART pregnancy rates in sterile women with untreated uterine malformations to the general sterile population did reveal significantly lower implantation and pregnancy rates. As with any patient undergoing assisted reproduction, care should be taken to optimise the endometrial cavity and restore normal anatomy prior to any major treatment.

To summarise, it is important to recognise the wide variation in degree of uterine anomalies and the unique impact of each anomaly on female reproductive success; counseling should be catered to the patient's unique anatomy. The clinician should keep in mind the embryologic origins of congenital uterine malformations, combined with the appro-

priate application of modern imaging techniques, can lead to the diagnosis of other associated anomalies. It is important to remember that many women with congenital Müllerian anomalies are likely to enjoy reproductive success without ever being labeled with a diagnosis.

References

1. H.S. Taylor. The role of HOX genes in the development and function of the female reproductive tract. Semin Reprod Endocrinol. 2000;18(1):81-89.
2. American Fertility Society. The American Fertility Society classification of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, müllerian anomalies and intrauterine adhesions. Fertil Steril. 1988;49(6):944-955.
3. Harger JH, Archer DF, Marchese SG, et al. Etiology of recurrent pregnancy losses and outcome of subsequent pregnancies. Obstet Gynecol 1983; 62:574 –581.
4. T. Ghi, P. Casadio, M. Kuleva, et al. Accuracy of three-dimensional ultrasound in diagnosis and classification of congenital uterine anomalies. Fertil Steril. 2008;92(2):808-13.
5. J.S. Pellerito, S.M. McCarthy, M.B. Doyle, et al. Diagnosis of uterine anomalies: relative accuracy of MR imaging, endovaginal sonography, and hysterosalpingography. Radiology. 1992;183(3):795-800.
6. Lin PC, Bhatnagar KP, Nettleton GS, Nakajima ST. Female genital anomalies affecting reproduction. Fertil Steril 2002; 78:899–915.
7. Petrozza JC, Gray MR, Davis AJ, Reindollar RH. Congenital absence of the uterus and vagina is not commonly transmitted as a dominant genetic trait: outcomes of surrogate pregnancies. Fertil Steril 1997; 67:387–389.
8. J.S. Sanfilippo, N.G. Wakim, K.N. Schikler, et al. Endometriosis in association with uterine anomaly. Am J Obstet Gynecol. 1986;154(1):39-43.
9. J.C. Petrozza, M.R. Gray, A.J. Davis, et al. Congenital absence of the uterus and vagina is not commonly transmitted as a dominant genetic trait: outcomes of surrogate pregnancies. Fertil Steril. 1997;67(2):387-389.
10. H. Dabirashrafi, K. Mohammad, N. Moghadami-Tabrizi. Ovarian malposition in women with uterine anomalies. Obstet Gynecol. 1994;83(2):293-294.
11. P.K. Heinonen. Clinical implications of the didelphic uterus: long-term follow-up of 49 cases. Eur J Obstet Gynecol Reprod Biol. 2000;91(2):183-190.
12. P. Acien. Reproductive performance of women with uterine malformations. Hum Reprod. 1993;8(1):122-126.
13. S. Marcus, T. al-Shawaf, P. Brinsden.The obstetric outcome of in vitro fertilization and embryo transfer in women with congenital uterine malformation. Am J Obstet Gynecol. 1996;175(1):85-89.
14. R. Pabuccu, V. Gomel. Reproductive outcome after hysteroscopic metroplasty in women with septate uterus and otherwise unexplained infertility. Fertil Steril.2004;81(6):1675-1678.
15. Wood EG, Batzer FR, Corson SL. Ovarian response to gonadotrophins, optimal method for oocyte retrieval and pregnancy outcome in patients with vaginal agenesis. Hum Reprod 1999; 14:1178–1181.

Imaging of Uterus

DR RITU KHANNA
M.B.B.S; M.S. (Gold Medalist)
Endoscopic Surgeon & ART Specialist
Director of Khanna Test Tube Baby Centre, Varanasi
Secretary -IFS UP Chapter

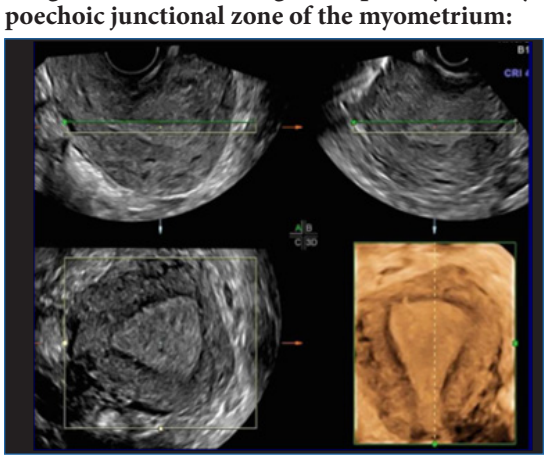
Hysterosalpingography is the oldest investigation used to assess the uterus. Todate USG (TVS, TAS) is the first line diagnostic armamentarium for imaging the uterus and can be coupled with color Doppler and 3D/4D scan. 3D ultrasound is a useful complement to 2D ultrasound particularly in suspicion of Mullerian duct anomalies.

Three-dimensional ultrasound is a new imaging modality introduced into clinical practice, been proved to be a very highly reproducible technique. With 3-D ultrasound, a volume of a region of interest can be acquired and stored. This volume can be further analyzed in several ways, such as navigation, multiplanar display and surface rendering or volume calculation. Power Doppler ultrasound, in combination with 3-D ultrasound, allows for a whole assessment of relevant vessels and quantitative assessment of vessel density and perfusion within a specified area. A whole evaluation is then possible for endometrial and subendometrial vascularization and also for ovarian stromal vascularity.

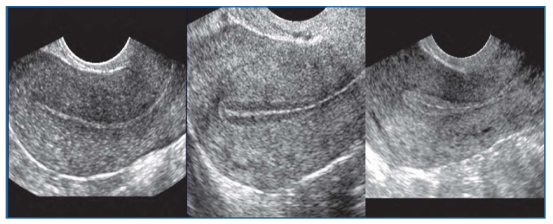
MRI has an established role in the pre- and post-procedural assessment for uterine artery embolization, diagnosis of adenomyosis, staging of known endometrial and cervical carcinoma, evaluation of suspected müllerian ductal anomalies.[1] Sonohysterographyused to evaluate uterine pathology because of its excellent diagnostic accuracy, has become a sensitive technique for detecting endometrial and myometrial pathology e.g. uterine synechiae, endometrial polyps, submucosal leiomyomas alongwith its role in documenting tubal patency.

Uterine Assessment

Fig. 1 The three orthogonal planes sagittal, transverse, and coronal planes as well as the rendered image. The coronal image also portrays the hypoechoic junctional zone of the myometrium:

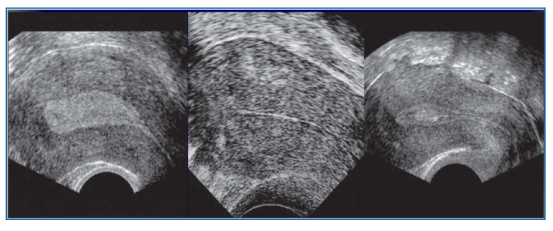


Endometrium: Spectrum of Appearances *(Fig:2):* Transvaginal scans. **A**, Normal, thin,early-proliferative endometrium. **B**, Normal, late-proliferative endometrium with triplelayerappearance. Central echogenic line is caused by opposed endometrial surfacessurrounded by a thicker hypoechoic functional layer, bounded by an outer echogenicbasal layer. **C**, Normal, early-secretory phase endometrium. The functional layersurrounding the echogenic line has become hyperechoic.[2]



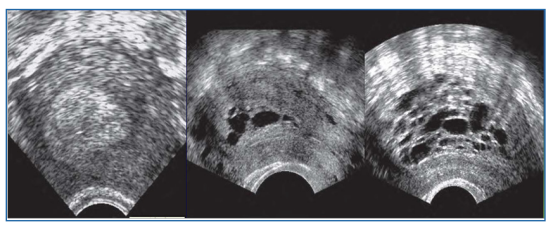
A B C

Endometrium: Spectrum of Appearances: **D**, Normal, thick,hyperechoic late-secretory endometrium. **E**, Normal, thin,postmenopausal endometrium. **F**, Oval, well-defined polyp that is morehyperechoic than surrounding periovulatory endometrium.



D E F

Endometrium: Spectrum of Appearances: **G**, Thickened endometrium caused by multiple small polyps confirmed on sonohysterogram. **H**, Thick, cystic endometrium caused byhyperplasia in patient taking tamoxifen. **I**, Thick, cystic endometrium caused by large polypin patient receiving tamoxifen.



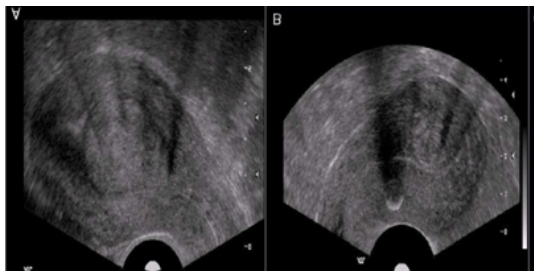
G H I

Fibroids

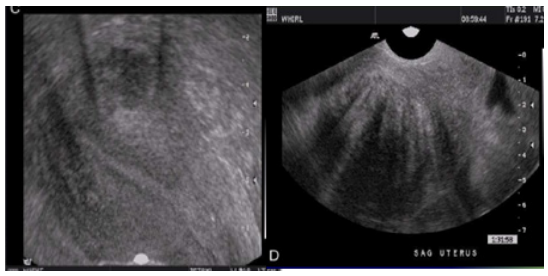
Uterine fibroids are the commonest benign uterine tumors and are seen in 20-40% of women of child bearing age. When assessing fibroids by ultrasound the number, site, size and their relation to the endometrial cavity are noted. Fibroids are seen as distinct, well circumscribed usually heterogeneous lesions arising from the myometrium. They may be hypoechoic, hyperechoic or show signs of calcification. Occasionally, they will be undergoing cystic degeneration and this is seen as hypoechoic areas within a hyperechoic lesion. Fibroids should then be categorized as intramural, those confined within the myometrium, subserous, when greater when 50% protrudes through the serosal surface and submucosal when they distort the endometrial cavity.

Fig (A-D) fibroids which compromise the contours of the endometrial cavity . Refraction artifactsresulting from tissue density interfaces and

the texture of the fibroids often aid in their identification.[3-5]



A B



C D

Saline infusion Sonography (SIS) offers the advantage of delineating the endometrial cavity and helps in diagnosing submucous fibroids . It is comparable to hysteroscopy in detecting the presence of submucous fibroids , and enables measurements to be taken. However, its value in determining the extent of protrusion into the endometrial cavity is limited. Using 3D SIS allows for a more accurate assessment of the cavity from the visualization of coronal plane. The degree of protrusion into the cavity can be calculated by measuring both the section of the fibroid protruding into the cavity **(A)** and the part confined to the myometrium **(B)** and calculating the protrusion ration as A/(A+B) x 100. These measurements have been shown to have good reproducibility amongst operator and can be used to predict the likelihood of successful hysteroscopic surgery. Color flow or Doppler can be used to look for vascularization and is usually seen as capsular flow with a vascular rim around the fibroid, though degenerated fibroids may show internal vascularity. The use of 3D ultrasound is largely improving mapping of fibroid localization prior to surgery.

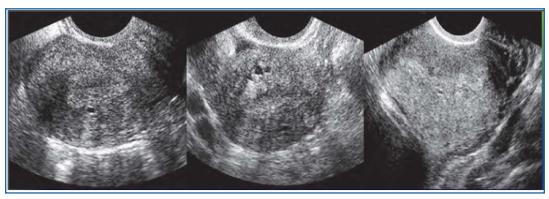
Adenomyosis—Diagnostic criteria

Bromley et al (2000) 2 or more of the followings:

1. Mottled heterogeneous myometrial texture: All cases.
2. Globular uterus: 95% of cases.
3. Small myometrial lucent areas: 82%.
4. "Shaggy" indistinct endometrial strips: 82%.

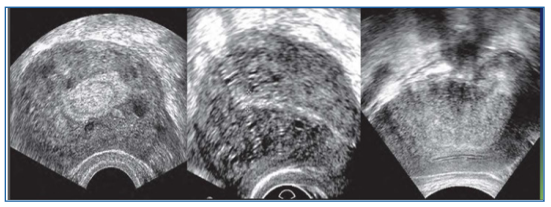
The most predictive: ill-defined heterogeneousechotexture within the myometrium (Brosen et al, 2004)

Adenomyosis on transvaginal scans: spectrum of appearances: A, Subendometrial cyst. **B** Cysts and heterogeneity in anterior myometrium with poorly defined anterior endometrial border . **C** Myometrial heterogeneity with poorly defined endometrial borders.[2]



A B C

Adenomyosis on transvaginal scans: spectrum of appearances: **D**, Multiple subendometrial cysts and echogenic nodules. **E**, Diffuse heterogeneous myometrium with multiple cysts and poorly defined endometrial borders. **F**, Large area of myometrial heterogeneity producing a focal mass effect and displacing endometrium.Adenomyosis leads to diffuse or focal thickening of the endomyometrial JZ, which can be seen on ultrasound as the subendometrial halo or hypoechoic area seen below the endometrial basal layer. The 3D ultrasound finding with the most sensitivity for adenomyosis are a JZmax of greater thanor equal to 8mm, and JZ difference greater than or equal to 4 mm and JZ alternation.However, Although 3D ultrasound has a greater sensitivity, it is not more specific then 2D ultrasound in the diagnosis of adenomyosis . Doppler ultrasound adds the diagnostic ability with finding of vessels traversing straight through areas of adenomyosis in contrast to peripheral rim of vasculature as seen in fibroids. TVUS is as efficient as MRI for the diagnosis of adenomyosis in women without myoma, while MRI could be recommended for women with associated leiomyoma.[6]

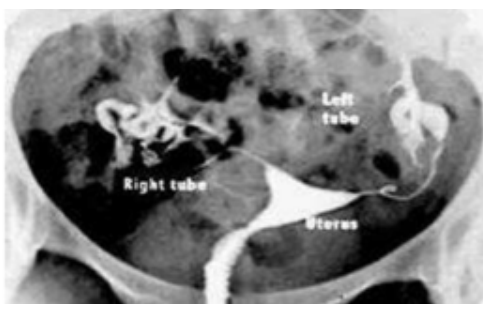


D E F

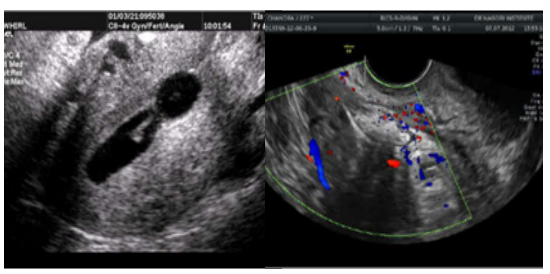
The Evaluation Of The Uterine Cavity:

Hysterosalpingography opacifies the endometrial cavity and both fallopian tubes at a time and also shows spill if the tube is patent. More over it is a static picture and fimbrial condition can not be assessed ***(fig:1A)***.

Sonohysterosalpingography(SSG) was an answer for assessment of fallopian tubes by ultrasound Sensitivity of SSG is 97.3% for open tubes and specificity of 92% and of HSG is 94.5 % but with a specificity of only 84%.[7] ***(Fig:1B)***. Adding colour doppler may increase the efficiencyand accuracy of SIS for assessment of tubalpatency.[8] ***(Fig:1C)***. Diagnostic accuracy of SSG is comparable with that of hysteroscopy. Although hysteroscopy enables visualizationand evaluation of the uterine cavity only, SSG allows evaluation of both the uterus and adnexa.[9]

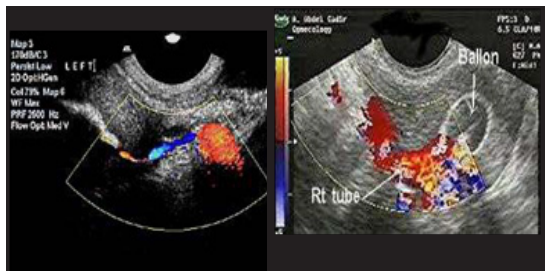


A

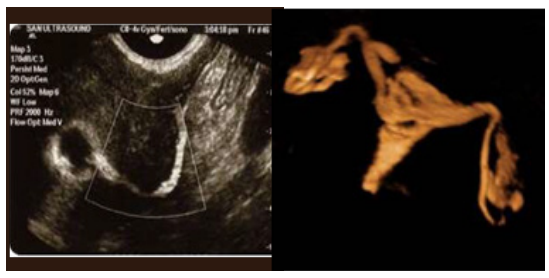


C D

The HyCoSy (Hysterosalphingo-contrast –sonography) method is an acceptable, timeefficientand well-tolerated alternative to HSG;it has been found to have comparableaccuracy in the assessment of the uterinecavity and tubal patency ***(Fig:2 A-C)***.[10] Modified HyCoSy with application of 3D-PD (3D HyCoSy) and post processing software technique allows simultaneous visualization of uterine cavity and Fallopian tubes and may potentially increase the diagnostic accuracy ***(Fig:2D)***. Sensitivity and specificity of HSG is 91 % & 71 % as compared to HyCoSy which is 87% and 84 %.[11]



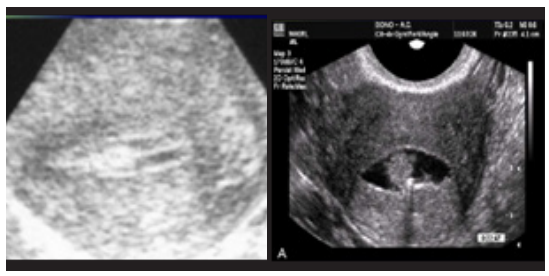
A B



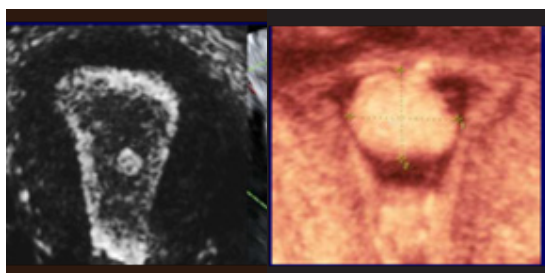
C D

Endometrial Polyps

Imaging On transvaginal ultrasonography (TVUS) an endometrial polyp typically appears as a hyperechoic lesion with regular contours within the uterine lumen, surrounded by a thin hyperechoic halo. Cystic spaces may be seen within the polyp, or the polyp may appear as a nonspecific endometrial thickening or focal mass within the endometrial cavity.[12] The addition of color-flow or power Doppler respectively may improve the diagnostic capability of TVUS. Color-flow Doppler may demonstrate the single feeding vessel typical of endometrial polyps.[13] Power Doppler is reported to increase sensitivity to 91% and 97% in patients with and without symptoms patients, respectively. Specificity may be increased to 95%, when color-flow Doppler is added to grayscale TVUS to identify the feeding vessel ***(Fig:1E)***

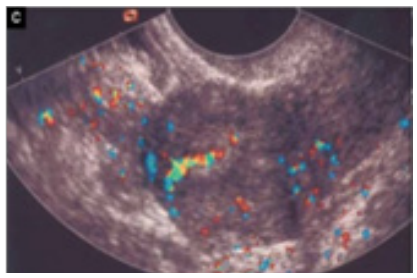


A B



C D

E



The addition of intrauterine contrast by saline infusion sonography (SIS) may outline small endometrial polyps missed on grayscale TVUS and is likely to improve diagnostic accuracy. When compared with hysteroscopy with guided biopsy, SIS has a sensitivity of 58% to 100%, specificity of 35% to 100%, ***(Fig:1A-D)***.

Congenital Uterine Anomalies

The anomalies may be divided into those associated with canalization defects –arcuate, subseptate and septate and those associated with unification defects bicornuate and unicornuate with or without rudimentary horn. Traditionally, these are classified according to the American Fertility Society (AFS) guidelines, although these are dependent on individual clinician interpretation. HSG has a low accuracy in assessing the endoluminal contour only, and not the external contour. Thus, has no potential to discriminate between the septate and bicornuate uterus, two entities with radically different prognosis and treatment. It was reported with a 44.4% sensitivity [8] and 55% accuracy.[14]

This is undoubtedly the area where 3D ultrasound has contributed the most and has become the current gold standard for diagnosis of these anomalies. The main benefit of 3D ultrasound for diagnosing anomaly is that is allow us to image both internal and external (serosal surface) contour of the uterine fundus simultaneously in the coronal plane, which is frequently impossible to obtain using 2D ultrasound. 3DUS overcomes all limitations, by providing the coronal view of the uterus, which can rarely be seen so clearly, even when using MRI (due to the relatively small size of the normal uterus). The coronal view enables the clinician to examine both the endometrial cavity and uterine fundus, thus providing all information necessary for a complete assessment of uterine morphology without resorting to the invasive surgery or more invasive diagnostic options such as saline infusion sonohysterography.[15] The characteristic of multiplanar capability, rotation and magnification, enabling an unlimited number of scan planes for detailed exploration of the uterine cavity; delineates the entire cervical canal.

Color flow or power Doppler interrogation may help by verifying the anticipated vascularity of the fundal myometrium of a bicornuate uterus, whereas septae are typically relatively avascular. Three dimensional sono HSG allows volumetric data to be re-interrogated in many planes, although the coronal plane appears to the most informative in identifying the anatomic relationships. SIS has been suggested as a method for diagnosing rudimentary horns as saline can be clearly seen in the unicornuate uterus, with no passage into the rudimentary horn. Magnetic resonance (MR) imaging is typically reserved for complex or indeterminate cases.Conventional methods (HSG , Hysteroscopy , Laparoscopy) should be restrained as second line investigations, due to the circumstance that all these methods are invasive, involving the subjective impression of the operator performing the test.

Adhesions

Ultrasound may be utilized with (sonohysterography) or without (standard) injection of sterile saline into the uterine cavity. Adhesions characteristically appear as "bridging bands" of tissue that distort the cavity. Flimsy adhesions are described as thin, undulating membranes that are most easily seen on real time scanning . Transvaginal ultrasound can also be useful in measuring the thickness of the endometrial lining.

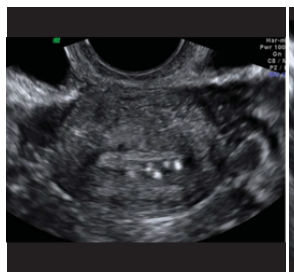


Fig.1: Echogenic foci visible within the

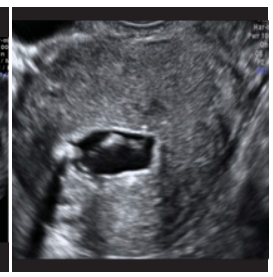


Fig.2: SIS demonstrating intra-uterine adhesion.

HSG and SSG both returned a sensitivity of 75.0% and a positive predictive value of 50.0% and42.9% respectively. 3D ultrasound allows for real time visualisation and provides more accurate assessment than traditional 2D ultrasound imaging.Sensitivity was calculated using hysteroscopy as the gold standard. 100% of pre-operative 3D imaging was found to be consistent with hysteroscopy results in assessing severity of disease, compared to 66.7% for HSG. It provided a more precise map of intrauterine adhesions and also enabled differentiation between severe intrauterine disease and outflow tract obstruction. The benefit of which allows more accurate prediction of prognosis and fertility outcomes. This could possibly be done in combination with SSG to further improve diagnostic accuracy. **(Fig:1 &2)**

Magnetic resonance imaging (MRI) has been suggested as a diagnostic tool. Thus far, there is little evidence in the literature supporting the use of MRI.

References

1. Behr et al. Imaging of Müllerian Duct Anomalies. RadioGraphics 2012; 32:E233–E250. Bermejo et al. Three-dimensional ultrasound in the diagnosis of Mullerian duct anomalies and concordance with magnetic resonance imaging.Ultrasound Obstet Gynecol 2010; 35: 593–601.
2. Carol M. Rumack, MD, FACR. Dignostic Ultrasound, Fourth Edition 2011 by Mosby, Inc., an affiliate of Elsevier Inc.)
3. Chizen, D, Pierson, R, Glob. libr. women's med., (ISSN: 1756-2228) 2010; DOI 10.3843/GLOWM.10326.
4. S.M.Kelly et al. investigation of infertile couple—A one stop ultrasound based approach. Human reproduction vol.16, No12 pp2481-2484, 2001.
5. C.K. Chen, H.M. Wu, Y.K. Soong. Clinical Application of Ultrasound in Infertility: From Two-dimensional to Threedimensional J Med Ultrasound 2007;15(2):126–133.
6. Marc Bazot. Ultrasonography compared with MRI for the diagnosis of adenomyosis:correlation with histopathology.- Human Reproduction vol.16,-No.-11pp.2427-2433,2001.
7. HajishafihaM, Zobairi T, et elJ Ultrasound Med.2009 Dec;28(12):1671-7.Diagnostic value of sonohysterography in the determination of fallopian tube patency as an initial step of routine infertility assessment.
8. Saunders RD, Shwayder JM, Nakajima ST. Current methods of tubal patency assessment. Fertil Steril 2011; 95: 2171–2179.
9. Martinez-Perez O, Perez-Medina T, Bajo-Arenas J. Ultrasonography of endometrial polyps. Ultrasound Rev Obstet Gynecol. 2003;3:43.
10. Jakab A, Ov_ari L, Juh_asz B, Birinyi L, Bacsk_o G,T_oth Z. Detection of feeding artery improves the ultrasound diagnosis of endometrialpolyps in asymptomatic patients. Eur J Obstet Gynecol Reprod Biol. 2005;119:103–107.
11. Reuter KL, Daly DC, Cohen SM (1989) Septate versus bicornuate uteri: errors in imaging diagnosis. Radiology 1989;172: 749-752.
12. Saravelos SH, Cocksedge AK, Li TC (2008) Prevalence and diagnosis of congenital uterine anomalies inwomen with reproductive failure: a critical appraisal. Human Reproduction Update 2008; 14: 415-429.

Non Surgical Treatment of Fibroids and its impact on Fertilty

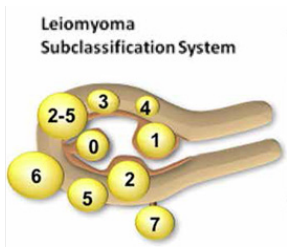
DR KISHORE PANDIT
Medical Director
Aundh Institute of Medical Sciences, Pune
Secretary - IFS Maharashtra Chapter

Uterine fibroids, myomas, or leiomyomata are smooth muscle cell tumours and being the most common benign gynaecologic tumour in women of reproductive age, fibroids affect 20–50 % of these women.

Hence, their relation with infertility although controversial, is always a great concern to the clinician as well as the patient. The evidence base in relation to fibroids and infertility is complex, with an overrepresentation of observational data and a lack of well-designed controlled trials. Moreover, the heterogeneity in patient populations and fibroid disease and multifactorial aetiology of infertility mean that it is often difficult to plan and successfully execute large scale multi-centre randomised controlled trials.

Published literature signifies the need for myomectomy to improve reproductive outcomes, though it depends on the location of fibroid. (Figure 1) Submucosal fibroids lower fertility rates, and by removing such fibroids; there is an improvement in both conception and live birth rates. On the other hand, there appears a very little causation linking subserosal fibroids and infertility. Therefore, unless there are other indications, a myomectomy to remove subserosal fibroids for infertility is not evidence based. With regard to intramural fibroids, both the evidence and consensus for myomectomy, purely for infertility, is weak.

Figure.1: The FIGO leiomyoma sub-classification system (2011)



S - Submucosal	0	Pedunculated Intracavitary
	1	<50% Intramural
	2	≥ 50% Intramural
O - Other	3	Contacts endometrium; 100% Intramural
	4	Intramural
	5	Subserosal ≥50% Intramural
	6	Subserosal < 50% Intramural
	7	Subserosal Pedunculated
	8	Other (specify eg. cervical, parasitic)
Hybrid Leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a dash. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities respectively.

Primary Assessment in Infertility and Fibroids

The two critical factors for assessing the need for treatment are determining causal aetiologies as well as predicting the overall chance of conception, whether natural or otherwise. All patients need to complete preliminary investigations to ascertain causation of infertility; the important domains being assessment of ovarian reserve, ovulation, as well as seminal fluid analysis. Tubal patency tests are invasive, and in the presence of fibroids are inaccurate.

Accurate fibroid mapping, i.e. description of size, location and nature of fibroids, using ultrasound scan is a critical step in such an assessment. Saline infusion sonography (SIS) can be used to rule out submucosal involvement, and MRI reserved for complex cases or to differentiate from adenomyosis.

SURGICAL THERAPIES

Well-designed surgical intervention trials for myomectomy and infertility are sparse, with a single RCT published to date which demonstrated an improvement in spontaneous conception rates after the surgical removal of submucosal fibroids, but no significant effect on pregnancy rates group of women with intramural-subserosal fibroids.Pritts et al also demonstrated similar findings in a recent meta analysis.[1] It is therefore imperative that surgical management of fibroids for infertility be undertaken only when there is evidence to support improvement in pregnancy outcomes through surgical intervention.

Surgical approach to fibroids can be either vaginal or abdominal. The abdominal approach may be either by laparotomy or laparoscopy depending on fibroid size and location and on skill of the practitioner. The decision to proceed with myomectomy should be weighed against the patient'sclinical fertility history, subsequent plans for fertility treatment, and estimated fecundability with or without myomectomy.

Hysteroscopic Myomectomy

Hysteroscopic myomectomy is the least invasive surgical approach to fibroid removal. It is most effective for patients with submucosal fibroids completely within the uterine cavity (Type 0) (Figure 1) or with at least 50% of the fibroid volume within the uterine cavity (Type I). Fibroids with less than 50% of the fibroid volume in the cavity (Type II) are much more difficult to resect completely and are more often associated with the need for repeated procedures, more so if larger than 3 cm. Camanni et al. demonstrated that hysteroscopic approach issuitable for fibroids measuring up to 5 cm in diameter.[2] The risk of endometrial damage and intrauterine adhesions, and its subsequent effect on conception and pregnancy outcomes, has to be discussed with the patient during pre-operative counselling.

Late complications that may further impair fertility after hysteroscopic myomectomy, and of these intrauterine adhesions are the most concerning. Postoperative adjuvant therapy, including estrogen therapy for 4 to 8 weeks or insertion of an intrauterine device, pediatric Foley catheter, or other balloon for 1 week postoperatively, have all been used to prevent further adhesion development. However, there is scant evidence to support the use of these postoperative therapies.

Whilst it is perfectly reasonable to perform resection of large L2 fibroids, albeit in multiple procedures, for the management of severe menstrual symptoms, the risk of endometrial damage and adhesions may negate any fertility benefits. As such, for infertility, it may be prudent to remove such fibroids by laparoscopy, although it does increase the risks associated with a full thickness myometrial incision such as uterine rupture in the future pregnancy and labour.

Abdominal Myomectomy - Laparoscopic Versus Laparotomy

With improvements in hysteroscopic myomectomy techniques, the use of abdominal myomectomy to improve fecundity has narrowed to a small subgroup of infertile patients with fibroids.All fibroids FIGO L3 and above (and large L2 as outlined above) are best removed by laparoscopy or laparotomy. The improvement in reproductive outcomes appears to be similar by both the approaches.

NON SURGICAL TREATMENT OF FIBROIDS AND INFERTILITY

Medical treatment

Contemporary medical management of uterine fibroids exploits the estrogen- and progesterone-responsiveness of uterine fibroids; however, no pharmacological agent is curative of fibroids. Also, medical management, whilst useful in managing menstrual and pain symptoms, are contraceptive and therefore not applicable to the infertile women. Other medical treatments such as mefenamic and tranexamic acid can be safely prescribed.

Most commonly used agents have been GnRH analogues. Newer, novel therapies including aromatase inhibitors, mifepristone, selective estrogen receptor modulators, and selective progesterone receptor modulators have shown promise in symptom improvement and fibroid regression without the hypoestrogenic symptoms associated with GnRH analogues.

Ulipristal acetate

Ulipristal acetate (UPA), a selective progesterone receptor modulator is now approved and licensed for the medical treatment of uterine fibroids in many countries. UPA has been shown to improve menstrual symptoms and lead to regression in fibroid size.The regressive effects are maintained for 6 months, primarily because the compound increases apoptosis of leiomyoma cells.[3]This phenomenon has allowed for intermittent dosing, and UPA is now licensed accordingly.The maximum duration of therapy is 3 months, and the recommended interval between therapies has to be a minimum of two washout-menstrual cycles, which also allows for any endometrial changes, the so-called PAEC to revert to normal. UPA is marketed in strengths of up to 100 mg for emergency contraception; however, contraceptive effects of a daily 5 mg dose are unknown, and therefore, patients should be advised to use alternate contraception such as condoms during therapy in order to avoid any teratogenicity. LuyckX et al. reported the first series of 18 such pregnancies in 52 women participating from a single centre in Pearl II and Pearl III studies. Thirty-seven women were treated with one-off 3-month UPA therapy (Pearl II, Pearl III) and 15 with intermittent therapy lasting a total of 6 to 12 months (Pearl III extension). Of the 21 women who wished to conceive after completion of UPA therapy, 19 underwent myomectomy, and 2 did not. Seventy-one per cent (15/71) women conceived for a total of 18 times, 12 of which were spontaneous and a further 6 achieved with IVF.[4] The two women, who did not undergo myomectomy, had a total of three pregnancies between them, but only one live birth.[4]However, this data also highlights the high miscarriage rate in the presence of fibroids despite reduction in size (2/3 versus 4/15 conceptions in women who did not undergo myomectomy versus those who did) and therefore the superiority of myomectomy over reductive therapies.[4]

Radiological Interventions

The goal of this section is to review the important new techniques for uterus-sparing treatment of uterine fibroids and particularly their use in women with fibroids and infertility.Newer uterus-sparing treatments include laser ablation, laparoscopic and vaginal occlusion of uterine arteries, MRgFUS, and UAE. However, for many of these techniques data on their reproductive outcomes in patients trying to conceive are insufficient to make recommendations.

Uterine Artery Embolization

Uterine artery embolization was first described in 1995 by Ravina as an alternative radiological treatment option for women with large fibroids no longer desiring their fertility. MRI imaging shows a transient ischemia within the body of the uterus and the endometrium typically lasting for up to 72 hours after the uterine artery embolization (UAE) procedure. Also, the uterine and ovarian artery has been shown to anastomose on angiography, in at least one side in approximately 46 % of women. Therefore, inadvertent embolization of ovarian tissue may result in premature ovarian insufficiency and failure especially in older women or those with low baseline ovarian reserve. Reassuringly, the reported incidence of amenorrhea in the under 40 age group is less than 1 %. Mara et al. conducted an RCT evaluating UAE versus abdominal myomectomy in an infertile population.[5] The pregnancy rates were 50 and 78 % in the UAE and myomectomy arms, respectively. They recruited young patients below age 35 [mean age 32 (SD ±4.1) years] which may explain the high conception rates overall. Also, the latency period, i.e. time to conception was longer for UAE (mean= 18 months) compared with myomectomy (mean = 13 months). The reintervention rates were higher (19 out of 58) in the UAE arm, as has been observed in other studies.[6] Given the current evidence base, UAE is not a treatment of first choice for women with infertility or those desirous of future fertility. Instead, it is to be reserved for poor surgical candidates.

Magnetic Resonance-Guided Focused Ultrasound Surgery

Another alternative treatment modality which has demonstrated encouraging preliminary results is the use of magnetic resonance-guided focused ultrasound surgery (MRgFUS). This treatment involves the application of MRI-directed beams of ultrasound capable of heating an area of fibroid tissue to up to 70 °C and causing destruction through coagulative necrosis. Rabinovici et al. reviewed all pregnancies reported to the FDA MAUDE (manufacturer and user facility device experience) database following MRgFUS. In total, 54 pregnancies were reported in 51 women with a mean age at MRgFUS of 37.2 years and mean time to conception of 8 months.[7] The miscarriage rate was 28 %. The preliminary experience is encouraging, with a high rate of delivered and ongoing pregnancies.

The evidence regarding effect of fibroids on infertility and reproductive outcomes is weak and mostly inconclusive. In infertile women, appropriate

evaluation and classification of fibroids, particularly those involving or suspected to be involving the endometrial cavity is essential. Submucosal fibroids (FIGO L0-L2) should be treated hysteroscopically (or laparoscopic for large L2) to improve conception rates. The management of intramural fibroids should be individualized on a case to case basis, whereas subserosal fibroid are unlikely to have any major impact on fertility. Conservative treatment measures (Medical, UAE and MRgFUS) should not be routinely offered to women who wish to maintain or improve their fertility due to lack of data on their safety and effectiveness.

References

1. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril. 2009;91(4): 1215–23.
2. Camanni M, Bonino L, Delpiano EM, Ferrero B, Migliaretti G, Deltetto F. Hysteroscopic management of large symptomatic submucous uterine myomas. J Minim Invasive Gynecol. 2010;17: 59–65.
3. Croxtall JD. Ulipristal acetate: in uterine fibroids. Drugs. 2012;72(8):1075–85.
4. LuyckxM, Squifflet JL, Jadoul P, Votino R, DolmansMM, Donnez J. First series of 18 pregnancies after ulipristal acetate treatment for uterine fibroids. Fertil Steril. 2014;102(5):1404–9. doi:10.1016/j.fertnstert.2014.07.1253.
5. Mara M, Maskova J, Fucikova Z, Kuzel D, Belsan T, Sosna O. Midterm clinical and first reproductive results of a randomized controlled trial comparing uterine fibroid embolization and myomectomy. Cardiovasc Intervent Radiol. 2008;31:73–85.
6. Gupta JK, Sinha A, Lumsden MA, Hickey M. Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database Syst Rev. 2012;5:CD005073. doi:10.1002/14651858.CD005073. pub3.
7. Rabinovici J, David M, Fukunishi H, Morita Y, Gostout BS, Stewart EA, et al. Pregnancy outcome after magnetic resonanceguided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. Fertil Steril. 2010;93:199–209.

Intrauterine Adhesions

DR K U KUNJIMOIDEEN
Consultant, ARMC IVF Fertility Centre
Kozhikode, Kerala, India
Belhoul Hospital, Dubai, UAE
Secretary - IFS Kerala Chapter

INTRODUCTION

Intrauterine adhesions (IUAs) are bands of fibrous tissue that form in the endometrial cavity, often in response to a uterine procedure. Disease severity can range from thin strings of tissue to complete obliteration of the cavity. Clinical sequelae include infertility, recurrent pregnancy loss, menstrual abnormalities, and pain. Clinical challenges include primary prevention of adhesions and prevention of recurrent adhesions after surgical treatment.

DEFINITION AND TERMINOLOGY

IUAs, or intrauterine synechiae, is a condition in which scar tissue develops within the uterine cavity. Intrauterine adhesions that are accompanied by symptoms (eg, infertility, amenorrhea) are referred to as Asherman syndrome [1]. The degree of adhesion formation and the impact of the adhesions on the contour of uterine cavity vary greatly. Minimal disease is characterized by thin strands of tissue stretched across the uterine cavity while severe disease is characterized by complete obliteration of the cavity, with the anterior wall of the uterus densely adherent to the posterior wall.

ETIOLOGY AND RISK FACTORS

IUAs appear to result from trauma to the basalis layer of the endometrium. The basalis layer appears to be most susceptible to damage in the first four postpartum or postabortal weeks. Subsequent tissue healing on opposing surfaces of the uterus may eventually fuse to produce tissue bridges. These intrauterine adhesions range from flimsy adhesions composed of endometrial tissue to dense adhesions consisting entirely of connective tissue. The resulting adherence of the uterine walls may result in partial or complete obliteration of the uterine cavity. In addition, vascularization may be compromised due to endometrial damage and scarring. These changes account for the menstrual abnormalities, frequent dysmenorrhea, infertility, and recurrent pregnancy loss. Risk factors include intrauterine processes that have the potential to damage the basalis layer, including: Pregnancy – While it is impossible to separate the impact of pregnancy-related changes from the risk of an intrauterine procedure on the development of subsequent IUAs, pregnancy appears to be an independent risk factor distinct from intrauterine surgery. In addition, the duration of pregnancy and the timing of pregnancy relative to the procedure appear to impact the risk of IUA formation. Repeated curettage following pregnancy loss also increases the risk of developing adhesions, but again it is unclear how much of the risk is related to the gravid state versus repetitive intrauterine trauma. Possible explanationsfor uterine susceptibility to IUA formation following pregnancy include the low-estrogen state associated with the postpartum or postabortion time period, antagonistic effectsfrom elevated prolactin levels associated with breastfeeding, or post pregnancy physiologic changes that make the basalis layer more susceptible to injury. Intrauterine procedures like intrauterine manipulation, separate from pregnancy, is associated with the development of IUAs as demonstrated by the formation of adhesions after procedures such as myomectomy or curettage in nongravid uteri [2]. Some studies suggest that removal of multiple fibroids at the time of hysteroscopic myomectomy is associated with higher risk of IUAs than removal of one fibroid, while other studies report no differences in the risk of adhesions with a single or multiple hysteroscopic myomectomy. Inflammation or infection – In a study assessing chronic endometritis in women with known IUAs, 35 percent of women (29 of 82) had chronic endometritis confirmed by histology (3). However, it is not known if the chronic endometritis was the cause or the sequelae of the adhesions. The role of postpartum or postabortal infection in adhesion formation is
also unclear as data are limited. In contrast, genital tuberculosis is associated with IUAs, which are often severe, with complete obliteration of the uterine cavity. These patients typically present with amenorrhea and cyclic pelvic pain. The adhesions are believed to form secondary to chronic inflammation of the endometrium. Uterine compression sutures – Uterine compression sutures (eg, B-Lynch suture) used to treat severe postpartum hemorrhage have been associated with the development of IUAs. In four retrospective reviews, IUAs were diagnosed in 19 to 27 percent of women who received uterine compression sutures to treat postpartum hemorrhage (4).

CLINICAL PRESENTATION

The classic clinical presentation of IUAs is of an ovulatory woman who develops secondary amenorrhea or hypomenorrhea after an intrauterine procedure, particularly if the procedure was performed on a gravid uterus. Pregnancy-related intrauterine procedures occurring prior to symptom onset have been reported in 91 to 99.8 percent of women treated for Asherman syndrome [5]. Alternately, some women are identified as likely having IUAs by imaging studies ordered for the evaluation of infertility (eg, saline infusion sonohysterogram [SIS] or hysterosalpingogram [HSG]. Infertility – Infertility has been reported in 7 to 40 percent of women with IUAs. IUAs are one of the differential diagnoses for the etiology of female infertility, and may be discovered when a hysterosalpingogram or hysteroscopy is performed as part of the standard infertility evaluation. Possible mechanisms by which IUAs could contribute to infertility include blockage of sperm or injury/destruction of the endometrium that prevents implantation. Recurrent pregnancy loss – Recurrent pregnancy loss may occur in women with IUAs due to abnormalities of implantation in areas of denuded endometrium or insufficient vascularization. In one study of 85 women who underwent hysteroscopic lysis of IUAs, 13 percent had recurrent pregnancy loss (defined as ≥3 losses). Incidental finding – IUAs

may be found as an incidental finding in a woman who undergoes a pelvic ultrasound, saline infusion sonohysterogram, hysterosalpingogram, or hysteroscopy for another indication (eg, infertility, abnormal uterine bleeding). As asymptomatic women, do not routinely undergo hysteroscopy or pelvic imaging, the prevalence of asymptomatic IUAs is not known.

DIAGNOSTIC EVALUATION

The main components of the diagnostic evaluation for IUAs are the medical history and uterine cavity evaluation. The assessment begins with a history of menstrual symptoms and any pregnancies or intrauterine procedures that occurred prior to the onset of symptoms. Some patients may have undergone a prior pelvic ultrasound as part of their evaluation for infertility or menstrual dysfunction. In some cases, a pelvic ultrasound may demonstrate an unusually thin endometrial lining, in the peri or postovulatory phase. A pelvic ultrasound is not required for the diagnosis of IUAs. Imaging studies — SIS and hysterosalpingogram (HSG) have limited roles in the diagnosis of IUAs. While these imaging studies can detect adhesions, they do not provide complete information about the extent and appearance of adhesions or the condition of the endometrium compared with hysteroscopy.

The next steps are determined by the likelihood of adhesive disease:

- Women with a high suspicion of IUAs go directly to endometrial evaluation, typically with hysteroscopy. While hysteroscopy is the gold standard, a saline infusion sonohysterogram (SIS) can also be used to evaluate the uterine cavity (6).
- Women with a low risk of IUA ultimately often undergo hysteroscopy, but may have additional testing prior. As an example, for women with a primary complaint of oligomenorrhea or amenorrhea and suspicion of IUAs, we first perform SIS or office ultrasound to assess the endometrial thickness. A thin endometrial lining (2/3), the type of adhesion seen at the time of hysteroscopy (filmy, filmy and dense, dense), and the patient's menstrual pattern (normal, hypomenorrhea, amenorrhea are noted.

The European Society for Hysteroscopy system grades adhesions based on the operator's ability to disrupt them with the hysteroscope and visualize the tubal ostia as well as the amount of scarring of the uterine cavity. (G:gravida; P:para; SpAb:spontaneous abortion; VTB:induced abortion) (Reproduced from: The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Müllerian anomalies and intrauterine adhesions. Fertil Steril 1988; 49:944.) European Society for Hysteroscopy classification of intrauterine adhesions Grade Extent of intrauterine adhesions

I. Thin or filmy adhesions easily ruptured by hysteroscope sheath alone and Cornual areas normal.
II. Singular filmy adhesions connecting separate parts of the uterine cavity. Visualization of both tubal ostia possible. Cannot be ruptured by hysteroscope sheath.
IIa. Occluding adhesions only in the region of the internal cervical os.Upper uterine cavity normal.
III. Multiple firm adhesions connecting separate parts of the uterine cavity. Unilateral obliteration of ostial areas of the tubes.
IIIa. Extensive scarring of the uterine cavity wall with amenorrhea or hypomenorrhea.
IIIb. Combination of III and IIIa.
IV. Extensive firm adhesions with agglutination of uterine walls. Both tubal ostial areas occluded. Reproduced from: Deans R, Abbott J. Review of intrauterine adhesions. J Minim Invasive Gynecol 2010; 17:555.

TREATMENT AND PREVENTION

A joint review of studies by the AAGL and the European Society of Gynaecological Endoscopy (ESGE) reported that the risk of adhesion formation appears to be reduced with, Procedures confined to the endometrium compared with those involving the myometrium or opposing surfaces, procedures using cold loop lesion removal rather than electrocautery and procedures with less resection compared with greater resection (eg, polypectomy compared with resection of multiple fibroids)

Hysteroscopic Resection

The standard treatment of symptomatic intrauterine adhesions is lysis under direct hysteroscopic visualization. Blind dilation and curettage or blind cervical probing, common modes of treatment prior to the development of hysteroscopy, are no longer advised because they do not remove abnormal tissue, disease classification is not possible, and indiscriminate curettage may further damage the endometrium. The goal of surgery is to restore the size and shape of the uterine cavity, as well as endometrial function and fertility. Cervical dilation and hysteroscope insertion – Care must be taken during cervical dilation in women with severe occlusion of the uterine cavity because it is easy to create a false cervical passage and to perforate the uterus. Guidance with pelvic ultrasonography can help define the cervical canal and the junction between the cervical internal os and the intrauterine cavity. Ultrasonography can also be used to guide dissection. A small (5 mm) rigid hysteroscope can be used to pass through the cervical canal and into the uterine cavity under direct visualization to decrease the chance for creation of a false passage. We use a 0- or 12-degree hysteroscope for this dissection.

Excision of adhesions

The procedure is begun by placing the hysteroscope at the internal os and lysing adhesions with sharp dissection. Adhesive bands are identified through the hysteroscope, and clipped at the junction of the band to the endometrium in order to excise the adhesion. We prefer to use small, rigid scissors because scissors avoid the thermal tissue injury that occurs with electrosurgery. Careful dissection is continued until the entire uterine cavity is free of adhesions. The goal is restoration of normal anatomy. Alternatives to scissors include blunt adhesiolysis and bipolar electrosurgery, in which the adhesive bands are vaporized. With a completely obliterated cavity, dissection beginning in the midline and moving laterally under ultrasound guidance may be effective. Identification of the tubal ostia, either prior to or during the lysis procedure, can provide useful markers of the lateral and fundal cavity edges, and can be used to guide the degree of tissue removal. Aggressive dissection that might enter the myometrium should be avoided.

Adjunctive interventions

For cases that require more extensive dissection, such as when there is agglutination of the walls of the cavity, we suggest concurrent laparoscopy or ultrasound guidance to reduce the risk of uterine perforation. Alternatively, fluoroscopy can be used in severe cases to guide dissection. While there are no data reporting a lower risk of perforation or improved outcome with adjunctive procedures, the rationale is that the use of such approaches may lessen the impact of perforation should it occur. If perforation is suspected or confirmed when energy is being used for the dissection, then laparoscopy is necessary to exclude an inadvertent bowel injury. If perforation occurs using instruments without energy, expectant management is reasonable. If adhesions are so severe that the cavity cannot be entered with the hysteroscope, a laparotomy with hysterotomy is possible, but is rarely performed, and is reserved for severe cases in which no other treatment options are available or possible.

Prevention of Adhesion Reformation

The goal of post-lysis management is to reduce the risk of reformation of adhesions and promote regrowth of endometrium. However, optimal postoperative management is not known. As the optimal methods to prevent adhesion reformation are not known, the management is mostly based upon personal experience in addition to the available evidence (mainly observational studies) (8). One preferred approach is to give 2.5 mg of conjugated equine estrogens or 4 mg estradiol orally, twice daily, for 30 days. On the last 10 days of estrogen therapy we add 10 mg of oral medroxyprogesterone acetate or 2.5 mg of oral norethindrone acetate to the regimen to stimulate withdrawal bleeding. An intrauterine pediatric bladder catheter (ie, pediatric Foley bladder catheter), can be used in addition to estrogen therapy, to provide mechanical separation of the uterine walls during the healing phase.

Repeat hysteroscopy

Repeat hysteroscopy can assess for adhesion recurrence, and allow for repeat adhesion resection if reformation has occurred. Such second-look hysteroscopy is commonly performed up to three months after initial adhesiolysis, although the use of serial hysteroscopic procedures at shorter time intervals has also been described.

Therapies in development

Medications that improve endometrial vascular flow and stem cell therapy are potential treatments for adhesion prevention. However, data are very limited and these treatments are only offered as part of research protocols. While preliminary studies have suggested that endometrial treatment with platelet-rich plasma may reduce proinflammatory gene expression in endometrial cells and improve endometrial growth, data are insufficient to advise use of this therapy.

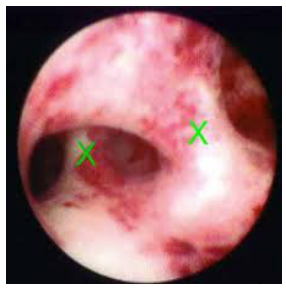
Recurrence

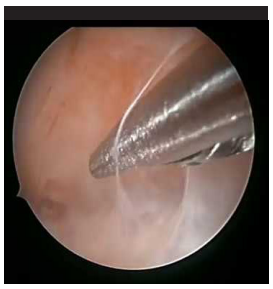
The recurrence rate following treatment is as high as 33 percent in women with mild to moderate IUAs and 66 percent in women with severe adhesions.

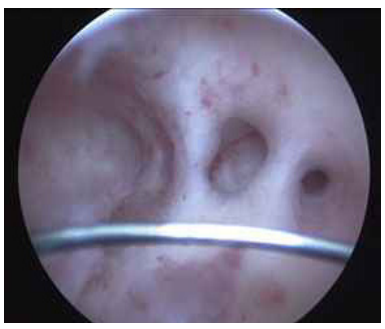
Obstetric outcomes

The likelihood of pregnancy following adhesiolysis appears to vary directly with the severity of disease. In a retrospective study of 357 women who underwent hysteroscopic adhesion resection

and were followed for a mean of 27±9 months, the pregnancy rates after adhesiolysis were 61 percent (mild disease), 53 percent (moderate disease), and 25 percent (severe disease) (9). Pregnancy complications can include intrauterine growth restriction, preterm delivery, and abnormal placentation (ie, accreta).







REFERENCES

1. Asherman JG. Traumatic intra-uterine adhesions. J Obstet Gynaecol Br Emp 1950; 57:892.
2. Mazzon I, Favilli A, Cocco P, et al. Does cold loop hysteroscopic myomectomy reduce intrauterine adhesions? A retrospective study. Fertil Steril 2014; 101:294.
3. Chen Y, Liu L, Luo Y, et al. Prevalence and Impact of Chronic Endometritis in Patients With Intrauterine Adhesions: A Prospective Cohort Study. J Minim Invasive Gynecol 2017; 24:74.
4. Rasheed SM, Amin MM, Abd Ellah AH, et al. Reproductive performance after conservative surgical treatment of postpartum hemorrhage. Int J Gynaecol Obstet 2014; 124:248.
5. Hanstede MM, van der Meij E, Goedemans L, Emanuel MH. Results of centralized Asherman surgery, 2003-2013. Fertil Steril 2015; 104:1561.
6. Seshadri S, El-Toukhy T, Douiri A, et al. Diagnostic accuracy of saline infusion sonography in the evaluation of uterine cavity abnormalities prior to assisted reproductive techniques: a systematic review and meta-analyses. Hum Reprod Update 2015; 21:262.
7. AAGL Elevating Gynecologic Surgery. AAGL Practice Report: Practice Guidelines on Intrauterine Adhesions Developed in Collaboration With the European Society of Gynaecological Endoscopy (ESGE). J Minim Invasive Gynecol 2017; 24:695.
8. Di Spiezio Sardo A, Calagna G, Scognamiglio M, et al. Prevention of intrauterine post-surgical adhesions in hysteroscopy. A systematic review. Eur J Obstet Gynecol Reprod Biol 2016; 203:182.
9. Chen L, Zhang H, Wang Q, et al. Reproductive Outcomes in Patients With Intrauterine Adhesions Following Hysteroscopic Adhesiolysis: Experience From the Largest Women's Hospital in China. J Minim Invasive Gynecol 2017; 24:299.

Female Genital Tuberculosis

DR NAMITA KOTIA

Director, Aastha Fertility Care

IVF Specialist&Gynaecologist, Obstetrician,

Heart & General Hospital, Jaipur

Secretary - IFS Rajasthan Chapter

Tuberculosis has resurged worldwide and become a major public health concern. A report of WHO shows that there are at present 20 million TB patients in the world of whom three quarter, that is 15 million live in developing countries(1). There are almost 9.4 million new cases a year. On global scale it has a devastating impact on developing nations. Over 95% of new tuberculosis cases and deaths occur in developing countries with India and China accounting for 40 % world's TB burden.Female genital tuberculosis [FGTB] usually remains silent and physical signs are not present definitely. Most cases of FGTB are found in premenopausal women, theoretically because an atrophic endometrium provides a poor milieu for Mycobacterial growth. Investigating for Infertility and Menstrual irregularity in premenopausal women unmasks the diagnosis of FGTB.The diagnosis itself remains a challenge as it is achieved most effectively through combination of high index of clinical suspicion and a combination of microbiological and histopathological tests.

INCIDENCE

The incidence of FGTB in India is 1-19% and 3-16% of infertile patients have FGTB(2). The incidence of FGTB is very high in women seeking ART being 24.5 %(3). It is found to be more common in younger age group [20-40 years].

ETIOPATHOGENESIS

The infecting agent is Mycobacterium Tuberculosis; occasionally Mycobacterium Bovis may cause infection especially in underdeveloped countries where pasteurization of milk is lacking. These are obligate aerobes with replicating cycle on the order of 17-23 hours and are characterized by their acid fast staining. FGTB is secondary to pulmonary TB [commonest] or extra pulmonary TB [GIT, Kidneys, Meninges, Skeletal system and Miliary TB.] through hematogenous and lymphatic route.

Table 1.
Frequency of tuberculosis in genital organs (4)

Organ	Frequency (%)
Fallopian tubes	90–100
Endometrium	50–60
Ovaries	20–30
Cervix	5–15
Vulva and vagina	1

(From Schaefer G: Female genital tuberculosis. Clin Obstet Gynecol 19:23, 1976

Once the genital tract is colonized, granulomas containing viable tubercle bacilli form within pelvic organs. After development of tubercular hypersensitivity, these generally become silent with inactivation and 1-10 years or more may pass before infection becomes reactivated or clinically manifest.

PATHOLOGY

When the bacilli infect, there is an initial reaction of neutrophillic inflammatory exudates and within 48 hours it is replaced by mononuclear cells.These mononuclear cells become primary sites for intracellular tubercle replication. Due to cellular immunity destruction of bacilli occurs with caseation necrosis. Later, reactivation of a focus of infection results in proliferative granulomatous lesions.

CLINICAL PRESENTATION

Symptoms related to genital tuberculosis (7)

Systemic
- Weight loss
- Fatigue
- Low-grade fever

Infertility
- Primary
- Secondary

Menstrual disturbances
- Amenorrhea
- Menorrhagia
- Metrorrhagia
- Oligomenorrhea

Abdominal swelling
Postcoital bleeding
Vaginal discharge
Dyspareunia

Physical signs in genital tuberculosis (7)

Normal
- Abdominal mass
- Pelvic mass
- Adnexal mass
- Abdominal tenderness
- Pelvic/adnexal tenderness
- Ascites
- Excessive vaginal discharge
- Ulcer in the vulva, vagina, and cervix
- Enlarged uterus with pyometra
- Fistula

DIAGNOSIS

Presentation is varied and a high index of clinical suspicion and the use of appropriate investigations is required to make diagnosis.Patients who should be investigated for Presumptive FGTB : A premenopausal woman presenting with infertility, menstrual problems, unexplained abdominal pain or pelvic mass. Rarely patients have systemic symptoms of fever, weight loss and night sweats. Ectopic pregnancy and cervical/ vaginal lesions are rare presentations.

The various modalities for diagnosis are enlisted in Table:

Table 2: Tests for diagnosis

TEST	PATIENTS	COMMENTS
CHEST RADIOGRAPH	All	All patients presenting with symptoms consistent with TB should have a chest X –ray to look for evidence of previous or active TB.
HIV	All	EPTB is associated with HIV infection. All patients should be offered integrated counseling and Testing.
PREGNANCY TEST	All Childbearing Age	To rule out pregnancy and to ensure safe testing.
PELVIC USG	All	Part of initial assessment of most patients. Presenting with gynecological symptoms.
HSG	Selected	May be done as part of infertility work up, but many women will have a normal HSG.
CT Pelvis / MRI Pelvis	Selected	To characterize lesions and plan surgical intervention in selected patients.
PET CT	Selected	Although not widely available, PET scans may give more information about presence of activity of Tubercular tubo-ovarian mass lesions.
ENDOMETRIAL ASPIRATE	Selected	Obtained for AFB staining and microscopy, culture and drug susceptibility testing. Sensitivity is low.
LAPAROSCOPY	Selected	Laparoscopy with biopsy of lesions is required when other noninvasive infertility investigations are inconclusive. Dual advantage of pelvic organ visualization and specimen. From otherwise inaccessible sites. Specimens should be subjected to staining and microscopy AFBs; culture and drug susceptibility testing and histopathology.

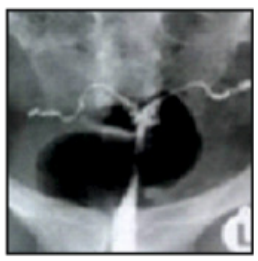
Chest radiograph: 10-15% of cases have abnormalities suggestive of prior pulmonary TB and/or signs of earlier pleurisy which may have been caused by TB (6).

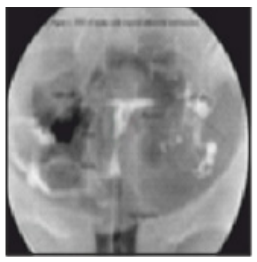
Montoux test: This is traditional method; a reaction greater than 15 mm is classified as positive. MT has less than 100% sensitivity and specificity (7).

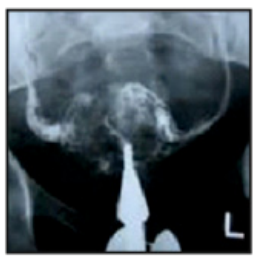
Menstrual blood: Since endometrial is involved in majority cases, bacteriologic examination menstrual blood with AFB and culture is recommended. Sensitivity is quite low; 10% were found positive when menstrual blood was collected within 12 hours of the onset of menses (4).

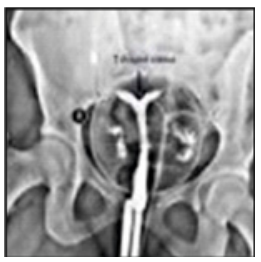
Endometrial culture: Endometrial tissue is obtained at the end of menstrual cycle or within 12 hours of onset of menstruation especially from cornual area. An AFB stain could be used initially followed by culture which takes 40 days or more for 75% of all positive culture to show growth. However, culture for TB was found only in 25% of cases of tubercular endometritis (8).

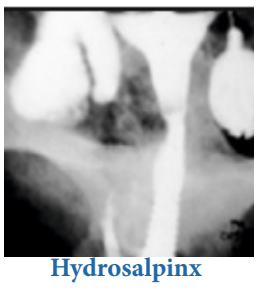
HSG: HSG is gold standard for evaluating internal architecture for genital tract. Uterine cavity is classically distorted, shriveled, there may be intrauterine adhesions/synechia and depending on severity of affection the cavity may be obliterated or T shaped. (9)Tubal involvement is depicted as irregular contours, out pouching, pipe stem appearance, hydrosalpinx and peritubal adhesions.

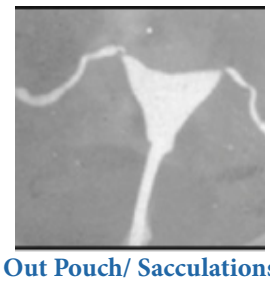

Shriveled Uterine Cavity

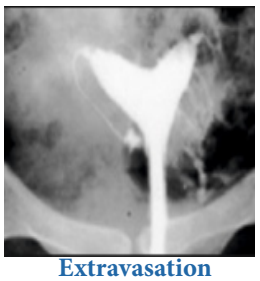

Asherman

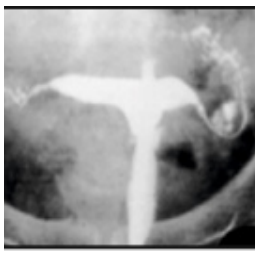

Obliteration ofCavity


T shapedcavity


Hydrosalpinx


Out Pouch/ Sacculations

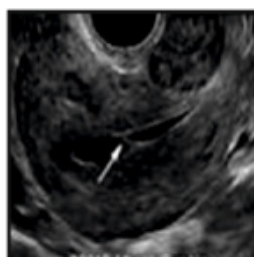

Extravasation

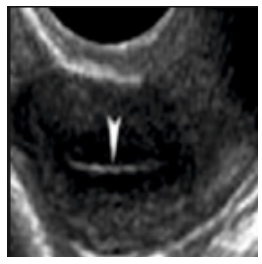

Rigid Pipe Like

Ultrasound (7)

(a) Endometrium

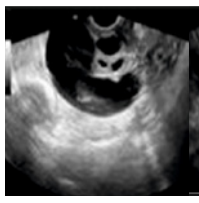
Endometrial tuberculosis on ultrasound appears as heterogeneous hyper echoic area representing foci of calcification or fibrosis, intrauterine synechia, distorted uterine cavity and thin /thickened endometrium.

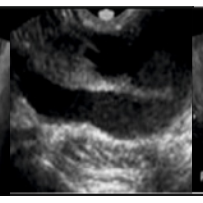

Synechia

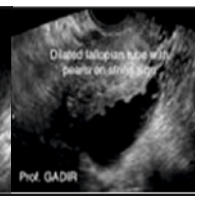

Thin Endometrium

(b) Fallopian Tubes

These may appear dilated, thickened, as hydrosalpinx [clear fluid] and occasionally as pyosalpinx [thick caseous material].

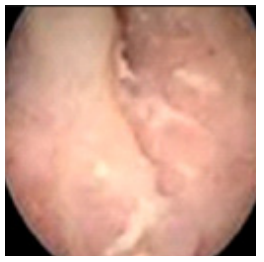

Hydrosalpinx

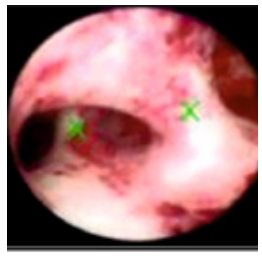

Pyosalpinx



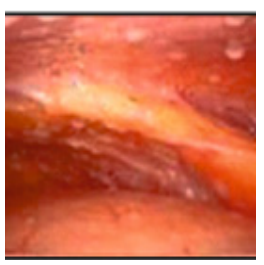
Dilated Thickened Tube

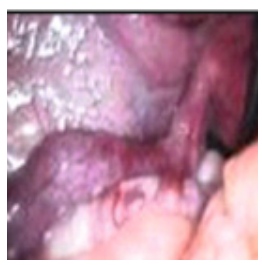
Hysteroscopy: Hysteroscopic evaluation of cavity in endometrial tuberculosis has varied appearances. Ideally hysteroscopy in a patient with suspected FGTB should preferably be done along with laparoscopy to avoid false passage formation. The cavity may appear as normal with bilateral normal Ostia [early stage TB], endometrium may appear pale looking or partially/completely obliterated by adhesions often involving ostia.(11)


Pale Looking Endometrium with Fibrosis


Intrauterine Synechia

Laparoscopy: Although laparoscopy is an invasive procedure but is advantageous as it aids in visual inspection of ovaries, tubes, peritoneal cavity and biopsy of tubercular lesions and specimens can be collected for AFB staining, culture and histopathology. In sub acute stage there may be congestion, edema and adhesions in pelvic organs. Sometime miliary tubercles as yellow, white, and opaque plaques can be seen on fallopian tubes and uterus. In chronic stage there may be nodular salpingitis; swollen, short tubes with agglutinated fimbriae. Unilateral / bilateral hydrosalpinx or pyosalpinx also depict chronic stage (12).


Peritoneal TB


Hydrosalpinx withB/L Tubal Block

Histopathological examination: For diagnosing FGTB caseating granulomas is required to be present in specimens which included epitheloid cell, giant cells, fibrosis and proliferation of lymphocytes associated with caseous necrosis. The ideal time for endometrial sampling is late secretory phase.

Bacteriological evaluation

(a) AFB Staining & Culture: Acid Fast staining [ZIEHL- NEELSON (ZN)] or Fluorescent [Auramine, Rhodamine] staining is generally used. For ZN staining to yield a positive result, a sample should contain 10000 – 1000000 bacilli /ml.Culture is more sensitive and requires 10 – 100 bacilli /ml of tissue / fluid sample for diagnostic yield.

(b) Culture methods: Solid cultures are usually performed on L J medium on Middle brook 7H10 medium. Liquid culture is performed using automated BACTEC mycobacterial growth indicator tube 960 (MGIT 960) based on modified Middle brook 7H9 Broth with oxygen sensitive fluorescent detection technology. Advantage of Liquid culture is its sensitivity and ability to perform phenotypic drug susceptibility tests and genotyping for molecular epidemiology. Liquid cultures require 9 – 10 days for positive results and 6 weeks for being considered negative while in L J medium cultures at least 4 – 8 weeks is required.

Molecular techniques

PCR is a rapid molecular method for identification of nucleic acid sequences specific to M tuberculosis. PCR assays can detect < 10 bacilli / ml with a testing time of only 8 – 12 hours, but due to its false positivity; correlation with clinical evidence, bacteriological culture, and histopathological and Laparoscopic findings is required.

Recent advances

WHO has endorsed GENEXPERT MTB / RIF assay with simultaneous resistance to rifampicin with results in less than two hours. However, further research is required for its role in FGTB (13).
Currently, there are no standard guidelines or algorithm for the diagnosis of FGTB, and extensive research is needed for early diagnosis and appropriateInterventions.

An algorithm which can aid the clinicians in the diagnosis of FGTB ***(Fig 1)***: (14)

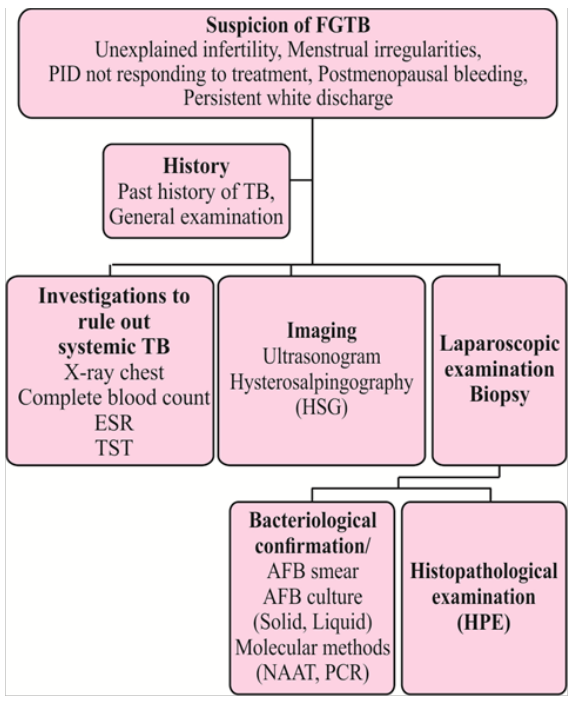


Fig 1: Diagnostic algorithm for female genital tuberculosis (FGTB)

PID, pelvic inflammatory disease; ESR, erythrocyte sedimentation rate; TST, tuberculin skin test; AFB, acid-fast bacilli; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction.

DIFFERENTIAL DIAGNOSIS (15)

Site of involvement	Differential diagnosis
Tuberculous salpingitis	Pelvic inflammatory disease
	Ectopic pregnancy
	Ovarian cyst
	Endometriosis
	Diverticulitis
Endometrial tuberculosis	Dysfunctional uterine bleeding
	Endometrial carcinoma
Ovarian tuberculosis	Ovarian malignancy
Cervical tuberculosis	Carcinoma of the cervix
Vulval tuberculosis	Elephantiasis vulva

TREATMENT

Aims of treatment:

1. To achieve TB cure
2. To prevent the long term sequelae
3. To restore normal anatomy if has been distorted

Drugs 2RHZE/4RH [2 months rifampicin, isoniazid, pyrazinamide, ethambutol / 4 months rifampicin, isoniazid]

Duration : Six months
Referral : Requires assessment by a gyne cologist to make the diagnosis and treat compli cations. Empirical ATT in women presenting with infertility alone should only be started following assessment by a specialist.
Follow up : Assess response to treatment at completion of 6months' ATT
Surgery : Surgery is not part of primary treatment in FGTB; however, it is sometimes needed for large, residual tubo-ovarian abscesses. Surgery in FGTB is associated with higher rates of Complications as there are a lot of adhesions as well as the possibility of infection recurrence. Tubal anatomy can sometimes be restored surgically in infertile women following ATT.

However, infertility may be an irreversible long-term consequence of FGTB. Giving repeated courses of ATT to women who remain infertile following completed ATT for FGTB is not necessary.

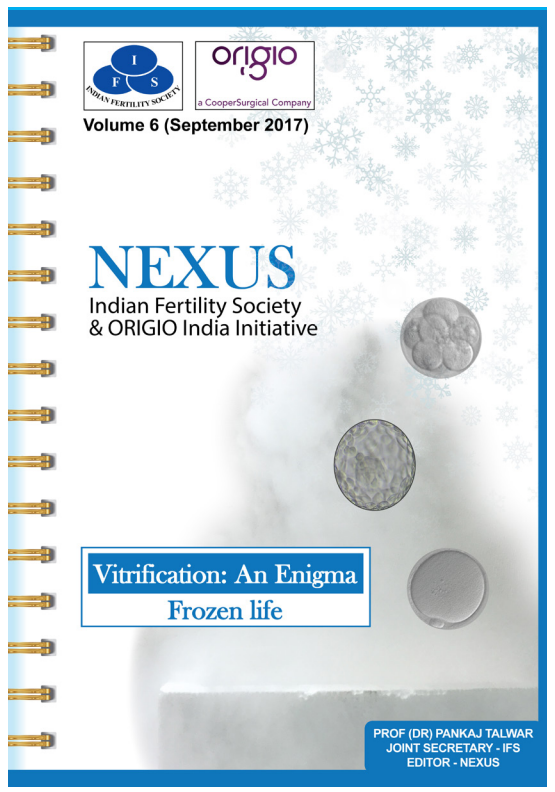
OUTCOME

Spontaneous conception is seen in 31 – 59 % patients treated with ATT. The outcome may be live birth, spontaneous abortion or ectopic pregnancy. If patient fails to conceive spontaneously ART is to be considered .

FGTB is major cause of infertility. Due to its asymptomatic nature diagnosis remains a challenge. However early diagnosis and treatment is vital to avoid complications and restore fertility.

REFERENCES

1. Rana T, Singh UB,Kulshreshta V, Kaushik A, Porwal C, Agarwal N, et al. Utility of reverse transcriptase PCR and DNA-PCR in the diagnosis of female genital tuberculosis. J Med Microbiol.2011; 60:486-491.
2. Sharma JB. Current diagnosis and management of female genital tuberculosis. J Obstet Gynaecol India 2015; 72:1761-8.
3. Singh N, Sumana G, Metal S. Genital tuberculosis in Indian Infertility patients.Int J Gynecology Obstet. 2007;97:135-8.
4. Schaefer G.Female genital tuberculosis. Clin Obstet Gynaecol.1976; 19:223-39.
5. Kumar S.Female genital tuberculosis.In: Sharma SK, Mohan A, editors, tuberculosis, 3rd edition, Delhi: Jaypee Brothers Medical Publisher Ltd: 2015, 311-24.
6. Hoppe LE, Kettle R, Eisenhut M, Abubakar I; Guideline Development Group. Tuberculosis—diagnosis, management, prevention, and control: Summary of updated NICE guidance BMJ 2016; 352: h6747.
7. American Thoracic Society: Diagnostic standards and classification of tuberculosis. Am Rev Respir Dis 142:725, 1990.
8. Alvarez S, McCabe WR: Extra pulmonary tuberculosis revisited: A review of experience at Boston City and other hospitals. Medicine 63:25, 1984.
9. Ahmadi F, Zafarani F, Shahrzad GS. Hysterosalpingographic appearances of female genital tract tuberculosis: Part II: Uterus. Int J Fertil Steril 2014; 8: 13-20.
10. Shah HU,Sannananja B, Baheti AD, Udare AS, Badhe PV. Hysterosalpingography and ultrasonography findings of female genital tuberculosis.Diagn Interv Radiol 2015; 21: 10-5.
11. Sharma JB, Roy KK, Pushparaj M, et al. Hysteroscopic findings in women with primary and secondary infertility due to genital tuberculosis. Int J Gynecology Obstet. 2009;104:49–52.
12. Baxi A, Neema H, Kaushal M, Sahu P, Baxi D. Genital tuberculosis in infertile women:Assessment of endometrial TB PCR results with laparoscopic and hysteroscopic features.J Obstet Gynecol India 2011; 61 : 301-6.
13. Raj A, Singh N, Mehta PK. Gene Xpert MTB/RIF assay: Anew hope for extrapulmonary tuberculosis. IOSR J Pharm2012; 2 : 83-9.
14. G. Angeline Grace, D. Bella Devaleenal & Mohan Natrajan: Genital Tuberculosis in females.Indian J Med Res 145, April 2017, pp 425-436.
15. Tripathy SN, Sapkal R. Tuberculosis manual for obstetricians& gynecologists. New Delhi: Jaypee Brothers MedicalPublisher (P) Ltd.; 2015.



Thin Endometrium in ART

DR KUMUD PASRICHA
Shivam Fertility & IVF Centre
Jalandhar
Secretary - IFS Punjab Chapter

Endometrium plays a vital role in the implantation of fertilized egg. It acts as a soil for the successful implantation, thus affecting pregnancy outcome. The endometrial thickness (ET) and Endometrial pattern (EP) before the day of ovulation is a predictor of the outcome of implantation. The endometrium changes throughout the menstrual cycle under hormonal influence. In the initial proliferative phase the endometrium is thin. It increases in thickness and reaches its peak (till LH Surge), under the influence of estradiol, which plays a major role in endometrial preparation for successful implantation. The endometrial pattern at this stage is triple layer/multilayer, exhibiting hypoechoic core surrounded by refringent external lines. After ovulation, under the influence of progesterone, the endometrium changes to a homogenous hyperechoic lining, suggestive of secretory phase (1).

Khalifa et al (2) described two patterns of endometrium observed at ovulation. Later, Mahajan and Sharma (3) graded EP on the basis of endometrial receptivity, with Grade A being most receptive with triple and multilayer pattern and Grade C being the non-receptive endometrium (homogenous). Grade B pattern is seen in the endometrium with intermediate receptivity, showing homogenous character near junctional zone with a well-defined central echogenicity.
Transvaginal ultrasound (TVS) is the best modality for the serial observation of the endometrial changes throughout the cycle (4). Earlier, 2D view only allowed measurement of ET and EP, but recently, with the advent of 3D and 4D USG, the endometrial volume, the uterine blood flow and the sub-endometrial flow can also be observed, thus aiding the prediction of outcome of ART.

Defining Thin Endometrium

A thin endometrium is defined as the threshold of the endometrial thickness below which the implantation and pregnancy rate is significantly low, other parameters being normal. Many authors recommend a cutoff of <6 mm for thin endometrium (4,5,6) below which biochemical pregnancies and spontaneous abortions have been reported.

How does thin endometrium affect ART?

In 2005, Zhang et al (7) studied 97 IVF-ET cycles and observed that increased ET was associated with higher pregnancy rates whereas thin endometrium reduced pregnancy rates even in young patients. The endometrial pattern on the day of HCG administration also predicts the outcome of pregnancy. Dickey et al (8) analyzed 200 IVF, GIFT and TET. They found that increasing maturity of EP was positively correlated with estradiol levels (r=6.20, p=0.05), number of mature eggs (r=0.13, p<0.05), and number of top quality embryos (r=0.40, p=0.001). Fecundity was increased when ET>9mm and a triple layer endometrium was present. The incidence of biochemical pregnancies was 2.5% when ET was 9-13 mm. This incidence increased to 27.8% when ET was <9mm or >13 mm and 67% when ET was <3 mm.

Factors Causing Thin Endometrium

What restricts the endometrium to grow? A thorough knowledge of various causative factors are needed, in order to evaluate and correct them, so as to get an optimal endometrium on the day of the ovulation trigger. Thin endometrium can be due to inflammatory, iatrogenic or idiopathic causes. Pelvic inflammatory disease and tuberculosis are infections that lead to destruction of the basal layer, which causes fibrosis of the endometrium. Repeated or vigorous curettage, myomectomy and polypectomy can also cause intra-uterine adhesions distorting the endometrial lining. Injudicious use of clomiphene citrate can also affect the lining. Sometimes, the uterine musculature and architecture is also distorted, which affects the growth of the endometrium. Before commencement of any modality of ART, these factors should be rectified to yield high results.

Managing the thin endometrium

The key to good results in ART is to have a healthy endometrium for successful implantation and pregnancy. There are various modalities available for increasing the endometrial thickness.

Estrogen Support

Exogenous estradiol can be administered either vaginally or orally, as a gel or tablet. Chen et al (9) studied the effect of extended administration of estrogen from Day 14 to 82. They concluded that mean endometrial thickness in a controlled ovarian stimulation cycle, increased from 6.7 mm to 8.6 mm after extended estrogen administration, with pregnancy rate of 38.5% vs 4.3% in the control group.

Sildenafil

Many observational studies have found that vaginal sildenafil improves endometrial lining in 70% women, when given for 10 days. In a recent comparative prospective study, Mangal and Mehirishi (10) found that sildenafil significantly increases the endometrial blood flow as compared to estradiol. Though the ET and EP were comparable in both groups, the pregnancy outcomes were significantly higher in the sildenafil group.

Tamoxifen

Tamoxifen, a selective estrogen receptor modulator, has long been known to cause endometrial thickening hyperplasia and cancer, when used continuously. This action of Tamoxifen, may be used for treating and preparing refractory endometrium. Chen & Chen (11) reported three cases of IVF in 2013 with thin endometrium. In all the three cases, the ET increased to 7.7 mm after 5 days of treatment with tamoxifen, resulting in successful implantation. This led them to conclude that tamoxifen can be the option to refractory endometrium not responding to extended estrogen administration.

Granulocyte Colony Stimulating Factor (G-CSF)

The level of G-CSF in serum and follicular fluid acts as a prophesier for the success of IVF. One possible explanation for the role of G-CSF in endometrial preparation is through its interaction with other cytokines and ovarian steroid hormones. It improves ovarian stimulation and implantation by improving endometrial receptivity.

Data on this, however, is conflicting. In a study by Kunicki et al (12), 37 women with thin endometrium (<7 mm), were given G-CSF infusion. The clinical pregnancy rate was 18.9%. In the group of women, who had conceived, endometrium expanded from 6.87 mm to 8.8 mm and in the other ET increased from 6.71 mm to 8.33 mm. They concluded that G-CSF infusion does improve ET after 72 hours. On the contrary, in another non-RCT study (15), 68 patients with thin ET were compared. 34 were infused with 300 µg/ml G-CSF intrauterine, on Day 12 of the IVF cycle. They found that ET and cycle cancellation rate (15.2%) in this group were comparable to the control group (15.2%). Hence, they concluded that G-CSF failed to demonstrate any improvement in ET.

Endometrial Scratching

Many studies have demonstrated the role of endometrial scratching on Day 8/ Day 11 of ART cycles. They found the implantation and pregnancy rates to be more than double after local endometrial injury (13). The possible mechanism suggested is the increase in endometrial receptivity after increased MIP-1B and TNF expression, consequent to the inflammation induced by the injury .

Hysteroscopy

The removal of scarred tissue and adhesiolysis by hysteroscopy can improve the endometrial lining and provide good results. Therefore, hysteroscopy should be considered in patients with thin endometrium, especially those with past relevant history.

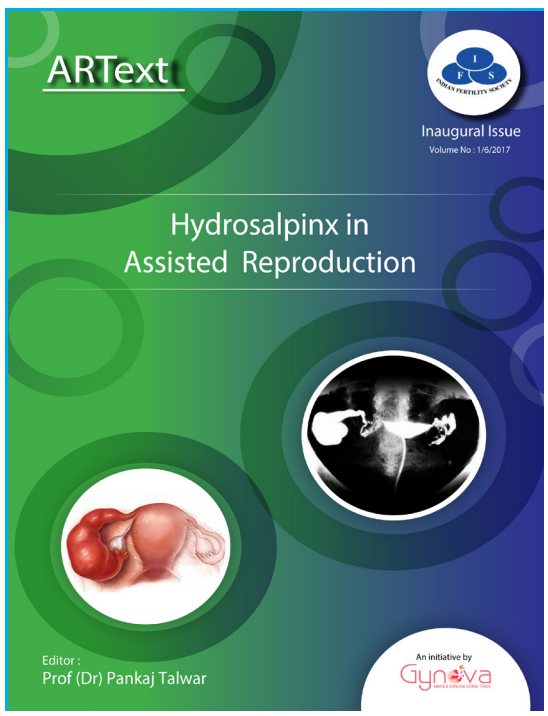
Thin refractory endometrium is a curse in ART. Even though, ET alone is not predictive of IVF outcome, it is an important and treatable problem. Thin endometrium should always be dealt with patience and actively. Considering patients' options and wishes, an honest trial of all feasible options should be offered to all such women, to achieve a successful pregnancy outcome.

References

1. Oliveira JB, Baruffi RL, Mauri AL, Petersen CG, Borges MC, Franco JG., Jr Endometrial ultrasonography as a predictor of pregnancy in an in-vitro fertilization programme after ovarian stimulation and gonadotrophin releasing hormone and gonadotrophins. Hum Reprod. 1997;12:2515–8.
2. Khalifa G, Brzyski RG, Oehninger S, Acosta A, Muasher SJ. Sonographic appearance of the endometrium: The predictive value for the outcome of in-vitro fertilization in stimulated cycles. Hum Reprod. 1992;7:677–80.
3. Mahajan N, Sharma S. The endometrium in assisted reproductive technology: How thin is thin? J Hum Reprod Sci. 2016;9(1):3-8.
4. Shapiro H, Cowell C, Casper RF. The use of vaginal ultrasound for monitoring endometrial

preparation in a donor oocyte program. Fertil Steril 1993;59:1055-8.

5. Coulam CB, Bustillo M, Soenksen DM, Britten S. Ultrasonographic predictors of implantation after assisted reproduction. Fertil Steril 1994;62:1004-10.
6. Gonen Y, Casper RF. Prediction of implantation by the sonographic appearance of the endometrium during controlled ovarian stimulation for in vitro fertilization (IVF). J In Vitro Fert Embryo Transf 1990;7:146-52.
7. Zhang X, Chen CH, Confino E, Barnes R, Milad M, Kazer RR. Increased endometrial thickness is associated with improved treatment outcome for selected patients undergoing in vitro fertilization-embryo transfer. Fertil Steril 2005;83:336-40.
8. Dickey RP, Olar TT, Curole DN, Taylor SN, Rye PH. Endometrial pattern and thickness associated with pregnancy outcome after assisted reproduction technologies. Hum Reprod 1992;7:418-21.
9. Chen MJ, Yang JH, Peng FH, Chen SU, Ho HN, Yang YS. Extended estrogen administration for women with thin endometrium in frozen-thawed in-vitro fertilization programs. J Assist Reprod Genet 2006;23:337-42.
10. Mangal S, Mehirishi S. To study and compare the effect of vaginal sildenafil and estradiol valerate on endometrial thickness, blood flow and pregnancy rates in infertile women undergoing intrauterine insemination. Int J Reprod Contracept Obstet Gynecol 2016;5:2274-7.
11. Chen X, Chen SI. Successful Pregnancy in Recurrent Thin Endometrium with new uses for an Old Drug. J IVF Reprod Med Genet 2013;1:110.
12. Kunicki M, Lukaszuk K, Woclawek-Potocka I, Liss J, Kulwikowska P, Szczyptanska J. Evaluation of granulocyte colony-stimulating factor effects on treatment-resistant thin endometrium in women undergoing in vitro fertilization. Biomed Res Int 2014;2014:913235.
13. Eftekhar M, Sayadi M, Arabjahvani F. Transvaginal perfusion of G-CSF for infertile women with thin endometrium in frozen ET program: A non-randomized clinical trial. Iranian Journal of Reproductive Medicine. 2014;12(10):661-666.



Endometrial Monitoring By Ultrasonography To Predict Outcome Of Fertility

DR MANOJ CHELLANI
Director Aayush Test Tube Baby Center
Raipur, Chattisgarh
Secretary - IFS Chattisgarh Chapter

There is no controversy regarding the importance of precise and specific endometrial maturational development in allowing implantation following assisted reproduction treatment.

Sonographically, the endometrium is one of the most dynamic structures in the body. Two anatomical parameters were suggested to evaluate uterine endometrium by ultrasound: **endometrial thickness** and **endometrial pattern**. Endometrial thickness is defined as the minimal distance between the echogenic interfaces of the myometrium and endometrium measured in the plane through the central longitudinal axis of the uterine body. Endometrial pattern (texture, reflectivity) is defined as the type of relative echogenicity of the endometrium and adjacent myometrium, as demonstrated on a longitudinal uterine ultrasonic section[1]. In principle, the central echogenic line represents the uterine cavity; the outer lines represent the basal layer of the endometrium or the interface between the endometrium and the myometrium. The relatively hypo-echogenic regions between the two outer lines and the central line may represent the functional layer of the endometrium[2] . Endometrial pattern, as demonstrated by high-resolution ultrasonography, varies during the cycle.[3,4,5]

Apart from anatomic parameters we can assess physiologic parameters in form of uterine blood flow. Colour Doppler signals are measured at the uterine arteries and their ascending branches located in the outer third of the myometrium.[6] The impedance of blood flow through the uterine arteries may be expressed as the pulsatility index (PI), and the resistance index (RI). The window of implantation in the human is quite wide. Endometrial thickness is maximal at around ovulation, but no standardization exists as to the exact timing of the ultrasonographic examination that best predicts pregnancy to occur.

In practice, one would need prognostic indicators that could be used, at the latest, on the day of human chorionic gonadotrophin (HCG) administration, allowing maximal time for necessary modifications to the stimulation protocol, oocyte retrieval scheduling or preparation for embryo cryopreservation if embryo transfer is to be postponed.

THE ENDOMETRIUM

From the first day of the menstrual cycle until the mid-cycle, the normal endometrium progressively thickens and develops sonographically detectable strata. This appearance can be described as layered, trilaminar or 5-line. Past the mid-cycle, the normal endometrium brightens and progressively thins. These sonographic endometrial patterns appear to be related to the changes in the glandular and vascular elements of the endometrium during the menstrual cycle. Fleischer et al determined that the endometrium is thickest during the secretory phase (3.6 +/- 1.4 mm), less thick during the proliferative phase (2.9 +/- 1.0 mm) and thinnest during menstruation. These values are for the half-thickness as measured from the endometrial canal to the endometrial-myometrial junction. Full thickness measurements ranged from 4 to 12 mm, with an average thickness of 7.5 mm. This endometrium will either slough if no pregnancy occurs or will undergo various changes in the event of a pregnancy.

In preparation for implantation, the endometrium undergoes transformations influenced by the ovarian hormones produced during the early secretory phase. These modifications include: an increase in the rate of blood flow, an increase in the number of cells populating the stroma and epithelium, an increase in uterine oxygen consumption, an increase in oxygen diffusion into the uterine lumen and a generalized edema.1The spiral arteries respond to the hormonal changes of the menstrual cycle and undergo transformations, as well. These responses include: proliferation of the endothelium, thickening of the wall and coiling. These vessels play an important role in implantation. The chances for a normal implantation may be reduced if the spiral arterioles are inadequately developed.

SONOGRAPHIC EVALUATION OF ENDOMETRIUM-

Based upon sonographic finding, Michael Applebaum described uterine Biophysical Profile ("UBP"). The findings are weighted according to the Uterine Scoring System for Reproduction ("USSR").

Ultrasound Technique Unique to the Uterine Biophysical Profile(UBP)

To perform the UBP, following guidelines are recommended:

1. To determine the presence of a 5-line appearance, information from both the transabdominal and transvaginal studies may be useful. For example, although a 5-line appearance may be noted transabdominally, it may not always be possible to see it endovaginally due to uterine position (and vice versa). In this case, a 5-line appearance is considered to be present and endometrial vascular penetration may be estimated when performing the endovaginal study.
2. Perform the Doppler study slowly. The flow of blood in the endometrium is of low velocity. It may take time for the ultrasound machine to register the presence of blood flow and create the image. If one sweeps through the endometrium too quickly, flow may not be seen. Additionally, endometrial blood flow has a mercurial personality -- it may appear as if it comes and goes. It may also appear in some

areas and not others. Do not observe hastily.
3. Endeavor to make the endometrium as specular a reflector as possible. Use the techniques of manual manipulation of the anatomy and probe pressure to achieve this.
4. Scan endovaginally both coronally and sagittally. There may be a difference in how well the blood flow is imaged.
5. When measuring the endometrium in the A-P dimension, try to obtain the value when no contraction affecting it is present. Contractions may alter this value. Also, when possible, obtain the measurement in a standard plane such as when both the endometrial and cervical canals appear continuous.

Endometrial Blood Flow

If one divides the endometrial and periendometrial areas into the following four Zones:

Zone 1 -- a 2 mm thick area surrounding the hyperechoic outer layer of the endometrium
Zone 2 -- the hyperechoic outer layer of the endometrium
Zone 3 -- the hypoechoic inner layer of the endometrium
Zone 4 -- the endometrial cavity

It is possible to see variations in the depth of vascular penetration before, during and after the mid-cycle. Most patients without diagnosed infertility (presumed normal) usually demonstrate flow into Zone 3 by the mid-cycle.

Doppler ultrasound has been used as a means to predict a negative outcome for a given IVF cycle. Pre-transfer, if failure could be predicted, the embryos could be frozen until a more favorable cycle occurs. This could prevent embryo wastage and subsequent patient disappointment. The PI is measured from the flow velocity waveforms as the systolic peak velocity minus end-diastolic velocity divided by the mean. It may be classified as low, medium and high in the ranges 0.00–1.99, 2.00–2.99 and ≥3.0 respectively (8). The RI is calculated as the ratio of peak systolic flow velocity minus end-diastolic velocity divided by peak systolic velocity, ranging from 0.0 to 1.0. Diastolic blood flow may be categorized as full or continuous and discontinuous, i.e. reduced or absent flow velocity(9). It is also possible to measure endometrial blood flow concentrating on endometrial vessels located within 10 mm of the lateral endometrial border(10). Sterzik et al concluded that, in patients who became pregnant after embryo transfer, the RI of the uterine arteries was significantly lower than those who did not get pregnant(11). Steer et al demonstrated that patients with a low uterine artery PI on the day of embryo transfer were more likely to conceive than those with a high PI. In this series, no one with a PI > 3.0 conceived. While using color Doppler technique, inadequate vascular penetration of endometrial blood flow (not within Zone 3) prior to transfer has been associated with an unfavorable outcome(12). Vascular penetration towards the endometrial canal differs among patients. Patients with uterine artery PIs of less than 3.0, have not revealed any successful pregnancies unless there is vascularity demonstrated either within Zone 3 or within Zones 3 and 4 prior to transfer. Successful pregnancies with demonstrable blood flow in Zone 4, suggesting the presence of an intracavitary mass, have been noted.

The Uterine Biophysical Profile

1. Endometrial thickness in greatest AP dimension of 7 mm or greater (full-thickness measurement).
2. A layered ("5 line") appearance to the endometrium.
3. Blood flow within Zone 3 using color Doppler technique.
4. Myometrial contractions causing a wave like motion of the endometrium.
5. Uterine artery blood flow, as measured by PI, less than 3.0
6. Homogeneous myometrial echogenicity
7. Myometrial blood flow seen on gray-scale examination (internal to the arcuate vessels)

The Uterine Scoring System for Reproduction ("USSR") comprises evaluation of the following parameters:

1. Endometrial thickness (full-thickness measured from the myometrial-endometrial junction to the endometrial- myometrial junction).
2. Endometrial layering (i.e., a 5-line appearance).
3. Myometrial contractions (seen as endometrial motion).
4. Myometrial echogenicity.
5. Uterine artery Doppler flow evaluation.
6. Endometrial blood flow.
7. Gray-scale myometrial blood flow.

Each parameter is scored as follows:

1. endometrial thickness
   a. < 7 mm = 0
   b. 7 - 9 mm = 2
   c. 10 - 14 mm = 3
   d. > 14 mm = 1
2. endometrial layering
   a. no layering = 0
   b. hazy 5-line appearance = 1
   c. distinct 5-line appearance = 3
3. myometrial contractions (seen as wave-like endometrial motion high-speed playback from videotape)
   a. < 3 contractions in 2 minutes (real-time) = 0
   b. > 3 contractions in 2 minutes (real-time) = 3
4. myometrial echogenicity
   a. coarse/inhomogeneous echogenicity= 1
   b. relativelyhomogeneous echogenicity =2
5. uterine artery Doppler flow evaluation
   a. PI > 3.0 = 0
   b. PI< 2.5 - 2.99 = 0
   c. PI < 2.2 - 2.49 = 1
   d. PI < 2.19 = 2
6. endometrial blood flow within Zone 3
   a. absent = 0
   b. present, but sparse = 2
   c. present multifocally = 5
7. myometrial blood flow internal to the arcuate vessels seen on gray-scale examination
   a. absent = 0
   b. present = 2

The values assume a technically adequate ultrasound examination with no abnormalities of uterine shape or development, no other gross uterine abnormalities (e.g., significant masses) and a normal ovarian cycle (e.g., without evidence of ovarian-uterine non - coordination). A male factor component to the infertility is not present.

In limited experience with this system, thus far, a "perfect score" of 20 has been associated with conception 100% of the time. Scores of 17 - 19 with conception 80% of the time, Scores of 14 - 16 have a 60% chance, while scores of 13 or less have resulted in no pregnancies. Absent endometrial flow, despite highest values for the other parameters, has always been associated with no conception. No doubt, other factors apart from sonographic signs of "uterine receptivity" are at work in determining conception. (7)

Anatomical ultrasonographic parameters predicting uterine receptivity are endometrial thickness and pattern. Measured on day 0, in natural cycles the mean endometrial thickness was found to be significantly thinner compared with cycles with ovarian stimulation (8.9 ± 8.0 versus 10.6 ± 2.5, P = 0.01; Ueno et al., 1991).

No study has addressed systematically the question of the relative efficiency of sonographic evaluation as a prognostic indicator for conception according to its exact day of performance. However, ultrasound evaluation may be performed efficiently prior to the day of embryo transfer. The first question to be addressed is whether the mean endometrial thickness in conceptional cycles is significantly greater than in non-conception cycles. Glissant et al. (1985) reported significantly thicker endometrium in conception cycles compared with non-conception cycle but he also stated that endometrial thickness as a single parameter had no predictive value on the occurrence of pregnancy[5]; however, several reports using abdominal sonography gave contradictory findings. At present, insufficient data exist describing a linear correlation between endometrial thickness and the probability of conception[13,14,15].

Another question is- Is there an ideal range for endometrial thickness? Based on the literature survey, interestingly, the ranges of mean endometrial thickness for conception and nonconception cycles in the reports are virtually the same, being 8.6–11.8 and 8.6–11.9 respectively. Third question is regarding any corelation between rate of biochemical pregnancies with endometrial thickness? There is no concensus on this matter in different studies.

Finally, is there a minimal endometrial thickness required to establish a clinical pregnancy following ART? After study of Gonen et al. (1991), endometrial thickness of 6 mm to establish a clinical pregnancy in natural cycle became widely accepted but for assisted reproduction treatment concerned, in various studies several authors have reported a minimal endometrial thickness below which no pregnancies are observed. These minimal endometrial thicknesses vary between 5 and 8 mm, measured during the late proliferative to early luteal phase.

Regarding endometrial pattern, however, iso-echogenic or intermediate patterns did not preclude the possibility of pregnancy[9,16,17], but predominantly the triple-line pattern along with good diastolic blood flow were found to be the only predictive markers of clinical and term pregnancies. Thus sonographic imaging also gained physiological dimension to add to the anatomical one. Good uterine perfusion, as shown by full diastolic blood flow with low resistance during the early and mid-secretory phases and expressed by a low RI, was correlated with conception following assisted reproduction treatment [11,17].

Comparing all groups, significantly (P < 0.001) more non-conception cycles had a PI >3.3 than conception cycles. The RI was found to be a less predictive parameter than diastolic uterine blood flow. Uterine artery impedance, measured by the mean PI of left and right uterine arteries, was shown to have a significant correlation with biochemical markers of uterine receptivity, including 24 kDa protein, uterine oestradiol receptor and endometrial histology dating (Steer et al., 1995). Using a PI upper limit of 3.0 or 3.3, the Doppler assessment of uterine blood flow had a high NPV and sensitivity (in the ranges 88–100 and 96–100% respectively) and a relatively higher range of PPV and specificity (44–56 and 13–35% respectively) compared with the other ultrasonic parameters.

Whereas most of the studies concentrated on the main external uterine arteries, recently Achiron et al. (1995) used Doppler flow measurement of the small endometrial vessels to assess endometrial perfusion. Hypo-oestrogenic premature ovarian failure patients had high impedance to blood flow, corrected to normal values by exogenous oestrogen administration[10].

CONFOUNDING FACTORS

The value of high-resolution ultrasonographic measurement of uterine thickness or echogenicity in predicting implantation following embryo transfer is controversial. Several confounding factors may contribute to this, including differences in techniques and/or criteria of assessment, different fertility agents used in the studies, different patient characteristics and a lack of calculation of actual PPV and NPV in some of the studies.

Differences in ultrasonographic examination techniques do exist. Even the decision about the specific endometrial plane in which to perform the measurement may influence the results. Differences exist between resolutions of the previously used abdominal and the currently used vaginal probes, and also between the various ultrasound machines on the market. Doppler blood flow results are quite susceptible to the performer's decision. More importantly, a lack of an agreed definition of the parameters leads to studies that use different criteria.

The specific fertility agents used may influence the measured ultrasonic parameters and therefore the study results.. Variable patient characteristics such as adnexal and possibly uterine disease, any uterine anomaly and age >40 years, could influence the sonographic results. Different patient selection criteria in the studies and possible differences in the fertility potential of the study and control groups could have a confounding influence on the analysis of the findings.

Sher et al. (1991)observed that patients frequently (96%) showed optimal endometrial grading during natural and ovarian stimulation cycles. Moreover, 55% of those having suboptimal grading during a natural cycle improved following ovarian stimulation[18].

The 'gold standard' and final proof of uterine receptivity is conception. However, implantation by itself also depends on embryo quality, and the differentiation between these two factors in each case is not always obvious.The endometrial sonographic parameters used to predict uterine receptivity still lack specificity. The reported low specificity in the various studies indicates that uterine receptivity is one among several different factors contributing to implantation. The importance of measuring endometrial thickness at around the time of embryo transfer is to ensure the presence of a minimal thickness to permit implantation. An evaluation of endometrial pattern, simplified to multilayered and non-multilayered, may serve to postpone or cancel those cycles in which poor endometrial development is demonstrated. Although the NPV is high, the PPV is still limited, along with a low specificity.

REFERENCES

1. Friedler S ,Schenker J G,Herman A ,Lewin A .The Role of ultrasonogrpahy in the evaluation of endometrial receptivity following assisted reproductive treatment:a critical review .Human reproduction update 1996,vol .2,No .4 pp.323-335.
2. Forrest, T.S., Elyaderani, M.K., Kuilenburg, M.I. et al. (1988) Cyclic endometrial changes: US assessment with histologic correlation. Radiology, 167, 233–237.
3. Fleischer, A.C., Pittaway, D.E., Beard, L.A. et al. (1984) Sonographic depiction of endometrial changes occurring with ovulation induction. J. Ultrasound Med., 3, 341–346.
4. Smith, B., Porter, R., Ahuja, K. and Craft, I. (1984) Ultrasonic assessment of endometrial changes in stimulated cycles in an in vitro fertilization and embryo transfer program. J. In Vitro Fertil. Embryo Transf., 1, 233–238.
5. Glissant, A., de Mouzon, J. and Frydman, R. (1985) Ultrasound study of the endometrium during in vitro fertilization cycles. Fertil. Steril., 44, 786–790.
6. Fleischer, A.C., Herbert, C.M., Hill, G.A. et al. (1991) Transvaginal sonography of the endometrium during induced cycles. J. Ultrasound Med., 10, 93–95.
7. Applebaum Michael . The Uterine Biophysical Profile (UBP).Endosonography in obstetrics and Gynaecology .Gautam Allahabadia (Ed) Rotunda Medical Technologies (P) Ltd Mumbai India 1997;343-52.
8. Steer, C.V., Campbell, S., Tan, S.L. et al. (1992) The use of transvaginal colour flow imaging after in vitro fertilization to identify optimum conditions before embryo transfer. Fertil. Steril., 57, 372–376.
9. Fleischer, A.C. (1991) Ultrasound imaging 2000: assessment of utero–ovarian blood flow with transvaginal color Doppler sonography; potential clinical applications in infertility. Fertil. Steril., 55, 648–691.
10. Achiron, R., Levran, D., Sivan, E. et al. (1995) Endometrial blood flow response to hormone replacement therapy in women with premature ovarian failure: a transvaginal Doppler study. Fertil. Steril., 63, 550–554.
11. Sterzik, K., Grab, D., Sasse, V. et al. (1989) Doppler sonographic findings and their correlation with implantation in an in vitro fertilization program. Fertil. Steril., 52, 825–828.
12. Steer, C.V., Campbell, S., Tan, S.L. et al. (1992) The use of transvaginal colour flow imaging after in vitro fertilization to identify optimum conditions before embryo transfer. Fertil. Steril., 57, 372–376.
13. Fleischer, A.C., Herbert, C.M., Sacks, G.A. et al. (1986) Sonography of the endometrium during conception and nonconception cycles of in vitro fertilization and embryo transfer. Fertil. Steril., 46, 442–447.
14. Rabinowitz, R., Laufer, N., Lewin, A. et al. (1986) The value of ultrasonographic endometrial measurement in the prediction of pregnancy following in-vitro fertilization. Fertil. Steril., 45, 824–828.
15. Welker, B.J., Gembruch, U., Diedrich, K., Al-Hasani, S. and Krebs, D. (1989) Transvaginal sonography of the endometrium during ovum pick up in stimulated cycles for in vitro fertilization. J. Ultrasound Med., 8, 549–553.
16. Dickey, R.P., Olar, T.T., Curole, D.N., Taylor, S.N. and Rye, P.H. (1992) Endometrial pattern and thickness associated with pregnancy outcome after assisted reproduction technologies. Hum. Reprod., 7, 418–421.
17. Serafini, P., Batzofin, J., Nelson, J. and Olive, D. (1994) Sonographic uterine predictors of pregnancy in women undergoing ovulation induction for assisted reproductive treatments. Fertil. Steril., 62, 815–822.
18. Sher, G., Herbert, C., Maassarani, G. and Jacobs, M.H. (1991) Assessment of the late proliferative phase endometrium by ultrasonography in patients undergoing in-vitro fertilization and embryo transfer (IVF/ET). Hum. Reprod., 6, 232–237.

Improving Endometrial receptivity

DR UMA SHRIVASTAVA
Executive Director
Infertility Centre Kathmandu, Nepal
Secretary - IFS Nepal chapter

INTRODUCTION

In the last two decades there has been a lot of progress in the area of reproductive medicine. In Assisted Reproductive Technology ovulation is well controlled by newer options. Fertilization has been facilitated by modified IVF techniques, ICSI, assisted hatching etc. But conception rate has not shown much differenceis the scenario of live birth. Prediction of conception not only depend on ovulation or fertilization. Most of these well fertilized best embryos fail to implant in the endometrium because Controlled Ovarian Hyperstimulation (COH) decreases endometrial receptivity and has a negative effect on implantation. One of the factors in COH is late follicular rise in progesterone which is associated with lower ongoing pregnancy rate (1). In addition, best embryos do not result in live birth due to several reasons. The failure of implantation has lead to great frustrations and there is a need to better evaluate both the endometrium & the embryo.

PROCESSES OF IMPLANTATION

Implantation of embryo in the endometrium is a coordinated function between endometrial status and the embryo itself. Implantation takes place through a series of process: apposition, adhesion and invasion.***(Fig 1)***

Apposition

Apposition is when the embryo comes closer to theendometrium. At this point, there seems to be a series of immunological reaction which allows release of mediators like chemokines and cytokines from the side of endometrium. In the meantime, the embryo also releases a glycoprotein L-selectin which may allow it to attach to the endometrial epithelium (1).

Adhesion

Adhesion or binding the embryo to the endometrium follows soon after apposition. At this stage the embryonic trophoblast and endometrium both secrete glycoproteinintegrins which allow adhesion. In the endometrium, different integrins are secreted; type $\alpha 1\beta 1$ is secreted soon after ovulation and remains till late luteal phase whereas integrin $\alpha v\beta 3$ is secreted during 19-20th day of the normal menstrual cycle. This integrin is supposed to open the implantation window. Inadequate secretion of this integrin is found in cases of inadequate luteal phase (2).

Invasion

Invasion is facilitated by firm attachment of trophoblast cells which transmigrate through

different layers of endometrium, epithelial layer, basement membrane layer containing matrices with collagen, inner layer with blood and lymphatic vessels. Here the trophoblast differentiates into cytotrophoblast and syncytiotrophoblastas shown in ***Fig.1*** which makes the embryo easy to cross talk to all endometrial components (3).

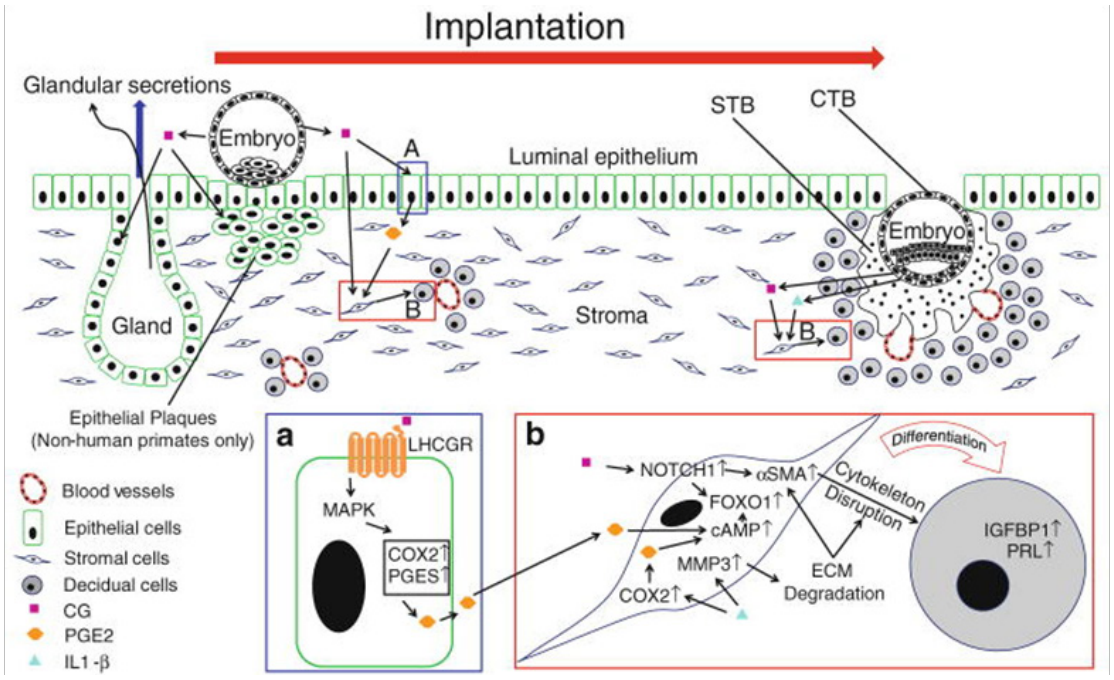


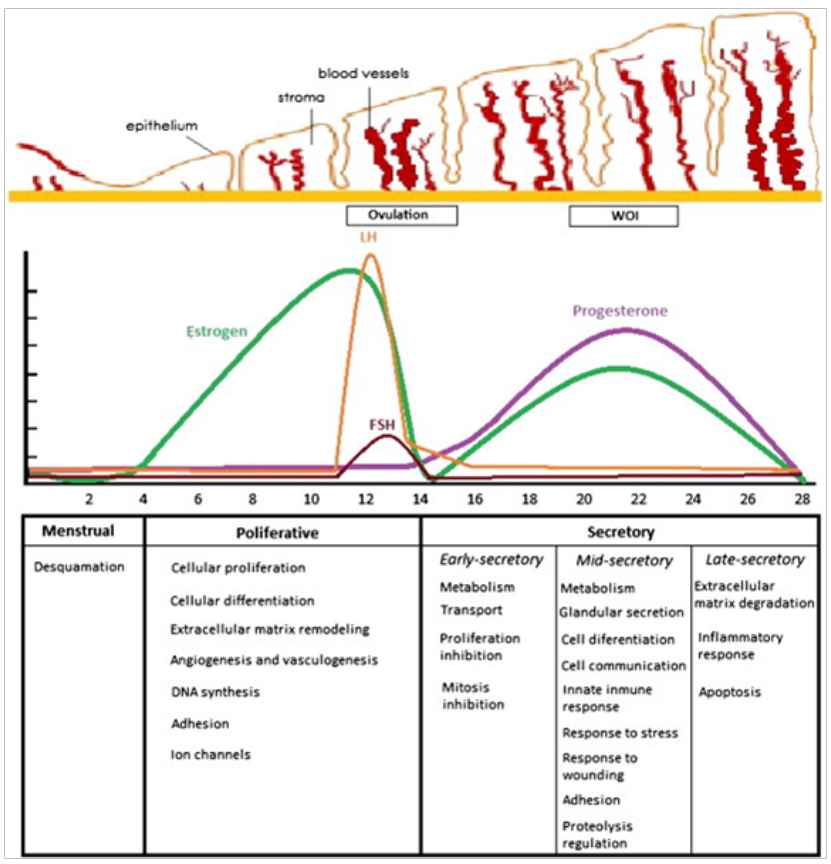
Fig.1 Endometrial responses to the embryonic signal (Adopted from Su et al. (4)

FAILURE OF IMPLANTATION

There are patients who have abnormal inefficient thin endometrium, overgrowth or hyperplastic endometrium or there is chronic endometritis. These cases do fail to implant. But there are patients who fail to implant even though they had best quality embryos with morphology score criteria. In addition, anempty endometrial cavity with normal development of trilaminar endometrial lining on TVS also fails to implant good embryos. These are cases of unexplained implantation failure. The so-called normal looking endometruim which fails to implant needs to be properly tracked for window of implantation.

WINDOW OF IMPLANTATION

The endometrium allows the embryo to implant during a short period which is its receptive period between 19-21 days of menstrual cycle in normally cycling women. This is the period what we call window of implantation (WOI) (5). The endometrial window of implantation should synchronize with embryonic window of implantation.The receptive type of endometrium allows the embryo to implant. At the same time, the embryo must be well developed to be able for implantation. Time of implantation defines the fate of embryo not only in nature but also in ART embryo. The endometrial window of implantation lies in the secretory phase of menstrual cycle which represents enlarged glands and tortuous arteries in the endometrium as shown in ***Fig 2.***



Menstrual	Poliferative	Secretory		
		Early-secretory	*Mid-secretory*	*Late-secretory*
Desquamation	Cellular proliferation	Metabolism	Metabolism	Extracellular matrix degradation
	Cellular differentiation	Transport	Glandular secretion	
	Extracellular matrix remodeling	Proliferation inhibition	Cell diferentiation	Inflammatory response
	Angiogenesis and vasculogenesis		Cell communication	
	DNA synthesis	Mitosis inhibition	Innate inmune response	Apoptosis
	Adhesion		Response to stress	
	Ion channels		Response to wounding	
			Adhesion	
			Proteolysis regulation	

Fig.2 Biological processes along the endometrial cycle in relation to menstrual cycle (Adopted from Ruiz-Alonso et al. (6))

ANALYSIS OF ENDOMETRIAL RECEPTIVITY

1. Serum Progesterone Assay

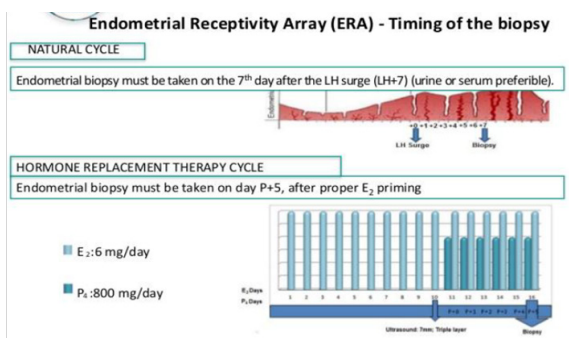
Progesterone, assayed in serum on the day of ET is proposed as less invasive new biomarker for embryo implantation that can adjust the moment of embryo transfer to improve the results. Measurement on the day of ET and 2 days after ET(> 9.2ng/ml) relates toreceptive status of endometrium. Progesterone is assayed in natural cycle and HRT cycle. However, it is not certain whether the timing of P exposure or serum P level is important for receptivity. But it is also evident that increased serum progesterone at the end of follicular phase reduces endometrial receptivity (7).

2. Endometrial Receptivity Assay (ERA)

The tests are carried out in patients who had repeated implantation failure (RIF). The aim of the test is to individualize treatment protocol fit for the individual and carry out personalized genetic tests. As shown in the ***Fig 3*** in natural cycle endometrial biopsy is taken during luteal phase on the 7th day after LH surge (LH+7)which is detected in serum or urine. In HRT cycle biopsy is taken on the 5th day of progesterone exposure (P+5) after proper E2 priming. ***(Fig 3&4)***

The biopsy tissue is sent for RNA sequencing with expression of 238genes which are supposed to be involved in endometrial receptivity. The genetic profile of the endometrial biopsy sample of the individual is compared to those of LH +7 of natural cycle and P+5 to the HRT cycle.

Fig 3 : ERA: Timing of biopsy



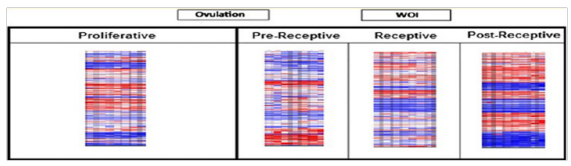


Fig.4: Endometrial Transcriptomics Profile (Adopted from Giemeno PD et al.(8))

The computational bioinformatic analysis of data of RNA sequencing differentiates& predicts the following type of endometrium according to their gene expression.

- Pre-receptive
- Receptive
- Post –receptive
- Non-receptive

Receptive Endometrium

The gene expression profile or transcriptomics studies show 238 genes signature for a normal receptive endometrium. .The receptive endometrium during this period possesses good metabolic, secretary & immunological activities necessary for implantation of embryo. Hence the embryo must be transferred at this phase because this is the window of implantation (WOI) of the individual. In this period there is favorable endometrium or embryo or there is synchrony between these two. The ERA, genetic profile defines

individual's personalized WOI which is used as best time for embryo transfer in artificial cycles. Endometrial factor is responsible in about 25% of cases of repeated implantation failure where the WOI is displaced in ERA. In the mean time ERA helps to identify other causes of infertility.

Non - receptive (NR) endometrium and Personalized embryo transfer

The gene expression profile does not correspond to normal receptive endometrium. There is poor endometrial receptivity where the dialogue between the embryo and endometrium is not possible i.e. there is embryo-endometrium asynchrony(9). Embryo should not be transferred at this phase. ERA tests in RIF cases have been found at non-receptive phase. Therefore personalized embryo transfer in such cases improves implantation and their reproductive outcome. Diagnostic technology was developed in 2009 to evaluate endometrial receptivity from molecular perspective.

Implantation failure becomes a tragic outcome for normally conceiving as well as infertile patients who undergo COH techniques. Proper identification of endometrial receptivity as window of endometrial implantation does help to recover more fertility. In recent years RIF is being seriously considered with better understanding of endometrial receptivity. Among other methods, ERA has been found one of the most reliable methods for the diagnosis of endometrial receptivity. It should be noted that even <6mm thin endometrium was found to be receptive & embryo transfer at this WOI has proved for successful pregnancy outcome. However, ERA is not easily accessible everywhere and therefore, newer approach of modulation of WOI may even provide better pregnancy outcome (10).

REFERENCES

1. Genbacev OD, Prakobphol A, Foulk RA, Krtolica AR, Ilic D, Singer MS, et al. Trophoblast L-selectin-mediated adhesion at the maternal-fetal interface. Science. 2003;299(5605):405-8.
2. Lessey BA. Adhesion molecules and implantation. Journal of reproductive immunology. 2002;55(1):101-12.
3. Simón C, Gimeno MaJ, Mercader A, O'Connor JE, RemohÍ J, Polan ML, et al. Embryonic Regulation of Integrins β3, α 4, and α1 in Human Endometrial Epithelial Cells in Vitro. The Journal of Clinical Endocrinology & Metabolism. 1997;82(8):2607-16.
4. Su R-W, Fazleabas AT. Implantation and Establishment of Pregnancy in Human and Nonhuman Primates. Regulation of Implantation and Establishment of Pregnancy in Mammals: Springer; 2015. p. 189-213.
5. Blesa D, Ruiz-Alonso M, Simón C, editors. Clinical management of endometrial receptivity. Seminars in reproductive medicine; 2014: Thieme Medical Publishers.
6. Ruiz-Alonso M, Blesa D, Simón C. The genomics of the human endometrium. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2012;1822(12):1931-42.
7. Labarta E, Martínez-Conejero J, Alamá P, Horcajadas J, Pellicer A, Simón C, et al. Endometrial receptivity is affected in women with high circulating progesterone levels at the end of the follicular phase: a functional genomics analysis. Human Reproduction. 2011;26(7):1813-25.
8. Díaz-Gimeno P, Ruíz-Alonso M, Blesa D, Simón C. Transcriptomics of the human endometrium. International Journal of Developmental Biology. 2014;58(2-3-4):127-37.
9. Haouzi D, Assou S, Mahmoud K, Tondeur S, Rème T, Hedon B, et al. Gene expression profile of human endometrial receptivity: comparison between natural and stimulated cycles for the same patients. Human reproduction. 2009;24(6):1436-45.
10. Mahajan N. Endometrial receptivity array: Clinical application. Journal of human reproductive sciences. 2015;8(3):121.

Recurrent Implantation Failure - How Far is the Uterus to blame?

DR ALOK SHARMA
MD, DHA, MICOG
Founder Secretary
IFS Himachal Pradesh Chapter

There is no controversy regarding the importance of precise and specific endometrial maturational development in allowing implantation following assisted reproduction treatment.

Sonographically, the endometrium is one of the most dynamic structures in the body. Two anatomical parameters were suggested to evaluate uterine endometrium by ultrasound: **endometrial thickness** and **endometrial pattern**. Endometrial thickness is defined as the minimal distance between the echogenic interfaces of the myometrium and endometrium measured in the plane through the central longitudinal axis of the uterine body. Endometrial pattern (texture, reflectivity) is defined as the type of relative echogenicity of the endometrium and adjacent myometrium, as demonstrated on a longitudinal uterine ultrasonic section[1]. In principle, the central echogenic line represents the uterine cavity; the outer lines represent the basal layer of the endometrium or the interface between the endometrium and the myometrium. The relatively hypo-echogenic regions between the two outer lines and the central line may represent the functional layer of the endometrium[2] . Endometrial pattern, as demonstrated by high-resolution ultrasonography, varies during the cycle.[3,4,5]

Apart from anatomic parameters we can assess physiologic parameters in form of uterine blood flow. Colour Doppler signals are measured at the uterine arteries and their ascending branches located in the outer third of the myometrium.[6] The impedance of blood flow through the uterine arteries may be expressed as the pulsatility index (PI), and the resistance index (RI). The window of implantation in the human is quite wide. Endometrial thickness is maximal at around ovulation, but no standardization exists as to the exact timing of the ultrasonographic examination that best predicts pregnancy to occur.

In practice, one would need prognostic indicators that could be used, at the latest, on the day of human chorionic gonadotrophin (HCG) administration, allowing maximal time for necessary modifications to the stimulation protocol, oocyte retrieval scheduling or preparation for embryo cryopreservation if embryo transfer is to be postponed.

INTRODUCTION

Implantation is a process whereby the embryo attaches itself to the luminal surface of the endometrium followed by migration via the luminal epithelium and invasion into the deep layer of the endometrium to become embedded into the deeper layer *(Fig. 1)*.

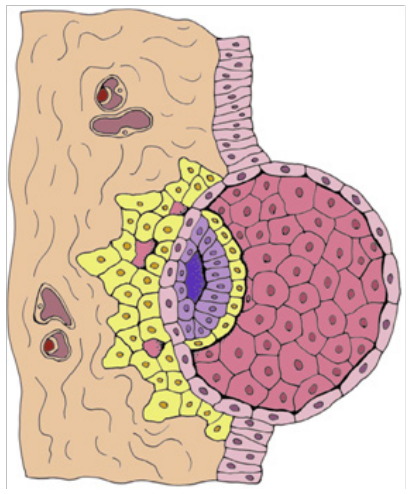


Figure 1 The initial stage of implantation, when the embryo is invading the epithelial layer of the endometrium to beembedded in the stroma compartment.

DEFINITION OF RECURRENT IMPLANTATION FAILURE

Recurrent implantation failure (RIF) is a clinical entity which refers to a situation when implantation has repeatedly failed to reach a stage recognizable by pelvic ultrasonography. There is as yet no universally accepted definition for RIF but after assessing all the causes of RIF, it can be defined as the failure to achieve a clinical pregnancy after transfer of at least 4 good-quality embryos in a minimum of three fresh or frozen cycles in a woman under the age of 40 years.[1,2,3]

CAUSES OF RECURRENT IMPLANTATION FAILURE

Gamete/embryo factors

Oocyte quality

Compromised oocyte quality as a cause of RIF is often suspected when there is a poor response to ovarian stimulation[4], with fewer numbers of oocytes retrieved, a high proportion of immature oocytes, a reduced fertilization rate and low embryo utilization rate. When the above features are associated with low antral follicle counts, high FSH and low anti-Mullerian hormone, it can be assumed that the underlying cause of RIF relates to poor oocyte quality.

Sperm quality

It is widely accepted that conventional semen analysis parameters do not accurately reflect sperm quality. Genetic tests are more likely to be useful as genome and epigenome integrity is essential for fertilization, normal embryo development and successful implantation. Several factors contribute to sperm DNA damage, including cigarette smoking, genital tract infection and previous chemotherapy or radiotherapy.[5]

Uterine factors

Congenital uterine anomalies : The septate uterus is the most common structural uterine anomaly.

Acquired intracavitary conditions : It includes submucous fibroids, endometrial polyps and intrauterine adhesions, may contribute to RIF.

Intrauterine adhesions: The presence of adhesions within the uterine cavity may interfere with successful implantation at an early stage by preventing the embryos from attaching to the luminal surface of the endometrium.

Adenomyosis: There is literature evidence available to suggest that adenomyosis has an adverse effect on female fertility.[6] Transvaginal ultrasonography is useful for the detection of adenomyosis but is operator dependent. The prevalence of adenomyosis in women with RIF is likely to be underestimated as it may not always be detected by transvaginal ultrasonography. Magnetic resonance imaging provides superior soft tissue resolution and is probably the most accurate noninvasive diagnostic technique available. The condition may appear in two forms, diffuse and focal, and the posterior uterine wall appears to be predominantly affected.

Hydrosalpinges: The adverse impact of hydrosalpinges on implantation may be attributed to a direct embryotoxic effect, a mechanical effect whereby the accumulated fluid may flush the embryo out of the uterus, as well as a negative effect on endometrial receptivity.

INVESTIGATIONS

Gamete and embryo factors

Ovarian function tests

Women with RIF should be offered ovarian reserve tests such as basal FSH, anti-Mullerian hormone and antral follicle counts to exclude any significant compromise of ovarian function associated with RIF, which may help in the counseling process.

Sperm DNA integrity testing

Several laboratory tests are available to measure sperm DNA fragmentation. Some clinics have already introduced sperm DNA integrity testing in the partners of women with RIF, which may well be premature. At present, sperm DNA integrity testing should only be offered to couples with RIF as part of a research programme.

Karyotyping

Although only a small proportion of couples with RIF have abnormal karyotype results, the rate is higher than that of the general population, suggestingan association between the two conditions. The test should be considered in couples with RIF.

Uterine factors

In women with RIF, thorough investigations must be carried out to exclude any uterine pathology contributing to the clinical problem.

Ultrasonography: It is a means to monitor follicle growth and endometrial development. It is often assumed that significant uterine pathology such as large intramural fibroids would have been detected during the course of IVF treatment. Transvaginal ultrasonography may also detect some cases of hydrosalpinges, especially if they are large and persistent. However, it is necessary to confirm whether careful evaluation of the uterine anatomy has ever been carried out by an experienced ultrasonographer, and if not, it ought to be arranged.

Sonohysterography: Sonohysterography (SHG) involves the use of contrast media, for example saline, along with transvaginal ultrasonography and is thought to improve the visualization of the uterine cavity. It has clear advantages over the use of HSG in that the use of radiation and iodine contrast is avoided and it is less invasive than hysteroscopy.

Hysteroscopy: Hysteroscopy is one of the most important investigations in women with RIF. It allows reliable visual assessment of the cervical canal and uterine cavity. It is considered to be thegold standard to diagnose intrauterine pathology and has minimal intraoperative and post-operative morbidity.

Combined laparoscopy and hysteroscopy: It allows for direct visualization of the internal and external contour of the uterus and enables the clinician to diagnose and treat concurrently.

MANAGEMENT

A multidisciplinary approach should be adopted in the management of a couple with RIF. It should involve not only an experienced fertility specialist but also a senior embryologist and, where appropriate, a reproductive surgeon or a counselor. Couples with RIF should be reviewed by an experienced fertility specialist as there are inevitably many questions to
be answered and important clinical decisions to be made. Appropriate counseling of the couple with RIF is of the utmost importance prior to proceeding with further treatment.

Lifestyle Changes

In addition to a review of investigations and treatment to date, clinicians should discuss and advise as to lifestyle changes which could improve the likelihood of treatment success.

Smoking

Women who smoke should be advised to stop as there is evidence that smoking is associated with an increased gonadotrophin requirement for ovarian stimulation, fewer oocytes retrieved, higher numbers of cancelled cycles, lower implantation rates and more cycles with failed fertilization in those undergoing IVF treatment.7Male partners of women with RIF should also be advised to abstain from smoking due to its adverse effect on sperm counts and motility, increase in abnormal sperm morphology and sperm DNA damage.

Body mass index

Underweight women (body mass index <19 kg/m2) should be encouraged to gain weight and obese women (body mass index >29 kg/m2) should be advised to lose weight prior to
further attempts at IVF treatment.

Alcohol consumption

Women with RIF should be advised to reduce consumption to one or two units once or twice a week when trying to become pregnant (NICE guideline, 2004) or abstain from alcohol altogether.[8]

Ovarian Stimulation Protocol

The ovarian response to gonadotrophin stimulation shouldbe reviewed. If the response is deemed satisfactory, it isnot necessary to change the stimulation protocol.In women with endometriosis and adenomyosis, the useof ultra-long protocol involving the administration of gonadotrophin-releasing hormone (GnRH) agonists for a fewmonths prior to IVF or ICSI may increase the pregnancy rate.[9]

Improving Embryo Quality and Selection

A carefulreview of recent investigations including age of thewoman, antral follicle count, basal FSH measurement, anti-Mullerian hormone concentration, number of folliclesproduced in response to stimulation, number of oocytesretrieved, the proportion of immature oocytes, fertilizationrate, the proportion of good-quality embryos and the totalnumber of good-quality embryos transferred should be noted.

Sperm DNA fragmentation

When suboptimal spermatozoa are considered to be a contributory cause of RIF, supported by an increased amount of sperm DNA fragmentation, several treatment options may be considered. First, medical treatment may be used to improve sperm quality. In particular, oral antioxidant treatment has been shown to reduce the incidence of sperm DNA fragmentation.10

Blastocyst transfer

Several studies have suggested that extending embryo cultureto day 5 or 6 in order to transfer the embryo at theblastocyst stage increases the implantation rate.[11] A recent Cochrane review by Blake et al. (2007), supportedthe rationale that blastocyst transfer improvesimplantation rates by enabling better selection of embryosand with better synchronicity between the embryo andendometrium.[12]

Assisted hatching

Hatching of the blastocyst plays an integral role in theimplantation process. Failure to hatch, due to intrinsic abnormalitiesin either the blastocyst or zona pellucida, is a possible
cause of implantation failure. Assisted hatching involves theartificial thinning or breaching of the zona pellucida and hasbeen proposed as one technique to improve implantationand pregnancy rates following IVF.[13]

Embryo Transfer

Embryo implantation has been found to be dependent on embryo quality, endometrial receptivity and transfer efficiency. In women with RIF, the details of previous embryo transfers should be reviewed, paying particular attention to any technical difficulties encountered. The transfer should be performed under ultrasound guidance.[14]

Hysteroscopy

Hysteroscopy improves the outcome of women with RIF. It may be performed as an outpatient procedure and small lesions may be removed at the same time.

Removal of Uterine pathology

Submucous Fibroids

The presence of a submucous fibroid in women with RIF,regardless of the size, should be removed as it was shownin the meta-analysis that removal of submucous fibroidsimproves clinical pregnancy rates.

Endometrial Polyps

Endometrial polyps in womenwith RIF ought to be removed. It has been shown that the
removal of endometrial polyps in women undergoing intrauterineinsemination resulted in doubling of the clinicalpregnancy rate.[15]

Uterine Septum

In women with RIF, uterine septae shouldbe removed, regardless of the size. It was found that small and large septae had similar adverseimpact, with significant increase in miscarriage rate inwomen undergoing IVF/ICSI treatment and that removal of these septae produced similar improvement in results.

Intrauterine Adhesions

Intrauterineadhesions would interfere with the implantation processand adversely affect the implantation rate and so, if presentin women with RIF, should be removed.

Intramural fibroids

Many clinicians would recommend removal of intramural fibroids if they are more than 4 cm in diameter. On the other hand, the couples should also understand that intramural fibroids may not

only cause implantation failure but also a number of other problems including miscarriage (both first and second trimester), red degeneration, preterm delivery, placental abruption, fetal growth restriction, malpresentation, difficulty with delivery and intrapartum and post-partum haemorrhage.

Adenomyosis

The role played by adenomyosis in reproductive failure is receiving increasing attention and is now recognized to be a cause of RIF.

Treating Thin endometrium

RIF may sometimes be associated with a thin endometrium (<7 mm) noted at the time of ultrasound examination on the day of HCG administration or embryo transfer. The observation suggests that the endometrium is not optimally responding to oestrogenic stimulation. There are several possible underlying causes. It may be congenital, associated with Turner's syndrome or a T-shape uterus.

Modified long protocol with exogenous oestrogen therapy

In the absence of any surgically correctable underlying pathology, there ought to be a strategy to improve endometrial growth by increasing the duration of oestrogenic priming prior to HCG trigger. The Royal Hallamshire Hospital employs a modified long protocol, which as yet has not been subjected to clinical trials. In essence, GnRH agonist is commenced in the mid-luteal phase of the cycle preceding IVF treatment. Two days after menstruation has started, usually a week after the initiation of GnRH therapy, high-dose oestrogen therapy in the form of oestradiol valerate 6–8 mg/day or oestradiol transdermal patch 400 lg/day is commenced. Endometrial thickness is monitored with serial ultrasonography after 7 days of oestrogen therapy and thereafter every 3 or 4 days until the endometrium has grown to more than 5 mm. At this stage, gonadotrophin may be commenced to stimulate the ovary to grow follicles, while the oestrogen therapy continues to ensure ongoing growth of the endometrium. The oestrogen therapy may stop on the day of HCG administration, when endogenous oestrogen concentration is often well over 5000 pmol/l.In women who fail to respond to the treatment outlined above or fail to achieve implantation again, the Hospital's policy is to repeat the treatment protocol in a further cycle, collect the oocytes, but not transfer any embryo. Luteal support should be started after oocyte retrieval as usual. An endometrial biopsy should then be obtained 7 days after oocyte retrieval for histological evaluation. If there is evidence of satisfactory secretory transformation, embryo transfer may proceed in a subsequent artificial cycle with high-dose oestrogen therapy. If, however, there is no evidence of secretory transformation, this suggests that theendometrium is unable to support implantation and the couple should be advised to consider surrogacy.

Sildenafil

Sildenafil citrate has also been proposed in the treatment of women with RIF associated with a thin endometrium. Sildenafil, a phosphodiesterase-5 inhibitor, augments the vasodilatory effects of nitric oxide. The hypothesis behind the use of sildenafil is that it increases endometrial blood flow, which then leads to an increase in endometrial function.

Luteal support with GnRHa

In a recent randomized, placebo–control study involving 120 women with thin (7 mm or less) endometrium, women who received GnRHa on day of oocyte recovery, on the day of embryo transfer and 3 days later appeared to have significantly higher oestradiol and progesterone concentrations, thicker endometrium and higher implantation and pregnancy rates than those who received placebo.[16]

Removal of hydrosalpinges

It is recommended that in women with hydrosalpinges. Fallopian tubes with minimal damage salpingostomy should be considered whereas tubes which are severely damaged (especially for those with intraluminal adhesions) ought to be removed (salpingectomy).

The drawback of this approach is the possible recurrence of hydrosalpinges after salpingostomy, which than necessitates a further procedure to remove the tube, further delaying the treatment and incurring extra cost.

Endometrial scratch

It was explored the possibility that local injury of the endometrium in the cycle preceding IVF treatment increases the success rate of implantation It is not exactly clear why the endometrial biopsies helped the implantation rate. Barash et al. (2003) speculated that the healing process following endometrial biopsy may release cytokines and growth factors which facilitate the process of implantation.17 However, it is not certain whether four endometrial biopsies are required or only one is necessary to produce the observed beneficial results.

Gamete donation and surrogacy

Couples with RIF need guidance on the appropriateness of proceeding with further IVF attempts. If implantation fails to occur despite repeated treatment attempts or if the prognosis of further IVF treatment is considered poor, alternative treatment options ought to be explored. If the likely source of the problem lies with the embryo, gamete donation should be advised. On the other hand, if the problem lies in the uterus, for example multiple small fibroids or Asherman's syndrome which has failed to respond to surgical treatment, surrogacy ought to be discussed.

REFERENCES

1. Das, M., Holzer, H.E., 2012. Recurrent implantation failure:gamete and embryo factors. Fertil. Steril. 97, 1021–1027.
2. Laufer, N., Simon, A., 2012. Recurrent implantation failure: current update and clinical approach to an ongoing challenge.Fertil. Steril. 97, 1019–1020.
3. Rotterdam ESHRE/ASRM–Sponsored PCOS Consensus Workshop Group, 2004. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS).
4. Ferraretti, A.P., La Marca, A., Fauser, B.C., Tarlatzis, B., Nargund, G., Gianaroli, L., 2011. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization:the Bologna criteria. Hum. Reprod. 26, 1616–1624.
5. Erenpreiss, J., Hlevicka, S., Zalkalns, J., Erenpreisa, J., 2002. Effect of leukocytospermia on sperm DNA integrity: a negative effect in abnormal semen samples. J. Androl. 23, 717–723.
6. Maheshwari, A., Gurunath, S., Fatima, F., Bhattacharya, S., 2012. Adenomyosis and subfertility: a systematic review of prevalence, diagnosis, treatment and fertility outcomes. Hum. Reprod. Update 18, 374–392.
7. Klonoff-Cohen, H., Natarajan, L., Marrs, R., Yee, B., 2001. Effects of female and male smoking on success rates of IVF and gamete intra-Fallopian transfer. Hum. Reprod. 16, 1382–1390.
8. National Institute for Health and Care Excellence, 2013. Fertility: assessment and treatment for people with fertility problems. Clinical Guidelines CG156.
9. Tremellen, K., Russell, P., 2011. Adenomyosis is a potential cause of recurrent implantation failure during IVF treatment. Aust. N. Z. J. Obstet. Gynaecol. 51, 280–283.
10. Barratt, C.L., Aitken, R.J., Bjorndahl, L., Carrell, D.T., de Boer, P., Kvist, U., Lewis, S.E., Perreault, S.D., Perry, M.J., Ramos, L., Robaire, B., Ward, S., Zini, A., 2010. Sperm DNA: organization, protection and vulnerability: from basic science to clinical applications – a position report. Hum. Reprod. 25, 824–838.
11. Machtinger, R., Dor, J., Margolin, M., Levron, J., Baum, M., Ferber, B., Shulman, A., Bider, D., Seidman, D.S., 2006. Sequential transfer of day 3 embryos and blastocysts after previous IVF failures despite adequate ovarian response. Reprod. Biomed. Online 13, 376–379.
12. Blake, D., Farquhar, C., Johnson, N., Proctor, M., 2007. Cleavage stage versus blastocyst stage embryo transfer in assisted conception. Cochrane Database Syst. Rev. CD002118.
13. American Society Reproductive Medicine, 2008a. The role of assisted hatching in in vitro fertilization: a review of the literature. Fertil. Steril. 90.
14. Brown, J., Buckingham, K., Abou-Setta, A.M., Buckett, W., 2010. Ultrasound versus 'clinical touch' for catheter guidance during embryo transfer in women. Cochrane Database Syst. Rev. 20, CD006107.
15. Bosteels, J., Weyers, S., Puttemans, P., Panayotidis, C., Van Herendael, B., Gomel, V., Mol, B.W., Mathieu, C., D'Hooghe, T., 2010. The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: a systematic review. Hum. Reprod. Update 16, 1–11.
16. Qublan, H., Amarin, Z., Al-Qudah, M., Diab, F., Nawasreh, M., Malkawi, S., Balawneh, M., 2008. Luteal phase support with GnRH-a improves implantation and pregnancy rates in IVF cycles with endometrium of < or = 7 mm on day of egg retrieval. Hum. Fertil. (Camb.) 11, 43–47.
17. Barash, A., Dekel, N., Fieldust, S., Segal, I., Schechtman, E., Granot, I., 2003. Local injury to the endometrium doubles the incidence of successful pregnancies in patients undergoing in vitro fertilisation. Fertil. Steril. 79, 1317–1322.

CHAPTER ACTIVITIES

DELHI

Infertility update Organized by Dr Surveen Ghumman under aegis of Indian Fertility Society, AOGD, FOGsd- held on 25th Oct 2017at hotel Park Inn by Radisson. Well attended by 82 delegates.

HARYANA CHAPTER

Lalita Memorial Hospital, Rewari hosted CME on 24th September, 2017 on "Challenges in Infertility" in association with IFS Haryana chapter and ROGS held at Rewari. Sessions were attended by over 73 enthusiastic participants with most informative discussion.

RAJASTHAN CHAPTER

Focus Group Discussion on Luteal Support and Current Practices of Infertility in India under AEGIS of IFS Rajasthan Chapter.

Attended by 60 IFS Members of Rajasthan on 2/09/2017

Symposium on 29/10/2017 on PCOS: IN UTERO TO MENOPAUSE, attended by 100 delegates Guest speaker Dr Shweta Mittal from Sir Gangaram Hospital Delhi.

CHANDIGARH CHAPTER

"Endometriosis Summit – SIFCON 2017" was organised on 10th September, 2017 by Dr Lavleen Kaur Sodhi (Organising chairperson), from 'DrSodhi's Health Care, Mohali'. It was co Chaired by DrSushmaSinha and Dr Shalini Gainder at Hotel JW Marriott as many as 290 delegates attended the conference.

KERALA CHAPTER

3rd Annual Conference of Kerala State Chapter of Indian Fertility Society , ARTCON 2017

ARTCON 2017 was held on 4th and 5th of November 2017 at Hotel Malabar residency, Kannur, Kerala. The Conference was inaugurated by Dr Sohani Verma, the president IFS as Chief Guest. 127 delegates attended the conference. Dr Pankaj Talwar, Joint Secretary IFS was the Guest of Honour. Dr Kunjimoideen, The secretary of the Chapter Presided over the meeting and Dr Venugopal, The Joint Secretary of the chapter felicitated the function.

Quiz competitions:

Three zonal level quiz competitions were held across the state and the winners participated in the state level competition held during the State chapter annual conference. Dr Venugopal, Dr Ashwath Kumar were the zonal level quiz masters. State level Quiz competition to select teams to represent Kerala chapter to Fertivision 2018-Quiz was held. Dr Kunjimoideen and Dr Shyjus were the quiz masters.

IUI Workshop:

Hands on IUI workshop for selected 30 gynecologists and 15 laboratory technicians were given on 10th September at Kozhikode.

Adolescent health awareness program by SIG on PCOS:

Adolescent health awareness program was conducted by the chapter at Govt Senior secondary School Calicut and 243 students attended the class.

PUNJAB CHAPTER

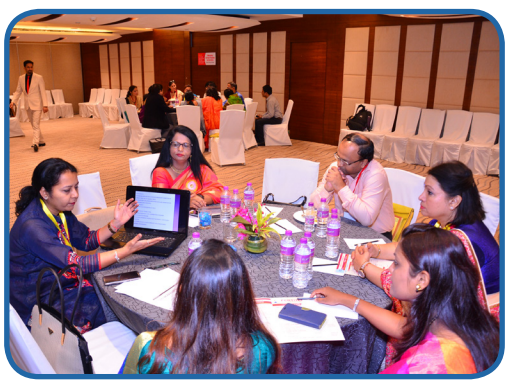
IFS Punjab Chapter had its board meeting on 10/11/2017 at hotel Ramada Jalandhar to plan annual confrence plus handing over the charge of IFS Punjab chapter by DrKumudPasricha. (Secretary IFS Punjab Chapter)

A clinical meeting on adolescent endocrinology & also the long term effects of the precoccious puberty was very well attended. More than 70 gynecologists from Punjab took part.

MAHARASHTRA CHAPTER

2017 Fertilty Infertitlity Management : Past–Present–Future 2nd & 3rd September, 2017 at Hyatt Pune, Organising Chairperson : Dr Bharati Dhorepatil, Organisisng Secretarty : Dr Kishore Pandit

The conference was very well appreciated and had a huge overwhelming response. The total number of delegates who attended the conference was 315.



CHATTISGARH CHAPTER

CME on Role of Micronutrients in Management of Infertility
IFS, organized by CG Chapter on 15th July 2017 at Hotel Vennington Court, Jail road, Raipur, CG. Dr. ManojChellani, Secretary, IFS, CG Chapter welcomed the speakers. Around 41 gynaecologists had attended the CME.

CME & Public Forum on Surrogacy & ART Bill: Current Scenario
Indian fertility society, Chhattisgarh Chapter and Raipur obstetrics and Gynaecology society had jointly organized a CME and Public forum on SURROGACY and ART BILL- Current Scenario on 16th August 2017 at Hotel Babylon Inn, Raipur.

13th Annual State Conference of AOGCG
Indian Fertility Society, Chhattisgarh Chapter in association with Raipur OBGY Society had organized 13th Annual state Conference of AOGCG-2017on the theme of High risk Pregnancy & Critical care in Obstetrics on 28th& 29th October 2017 at Hotel Babylon Inn, Jail road Raipur.

UP CHAPTER

An IUI Workshop was held on 12th August, 2017 at Lucknow under the aegis of IFS & Ajanta IVF. Attended by around over 40 delegates.

INDIAN FERTILITY SOCIETY

in collaboration with

AMITY UNIVERSITY

AMITY INSTITUTE OF MOLECULAR MEDICINE AND STEM CELL RESEARCH

LAUNCHES

DIPLOMA IN CLINICAL ART (ASSISTED REPRODUCTIVE TECHNOLOGY)

&

DIPLOMA IN CLINICAL EMBRYOLOGY

FIRST TIME EVER 1 YEAR DIPLOMA PROGRAMMES WITH UNIQUE ADVANTAGES

- Includes monthly teaching modules along with CME conducted in reputed IFS centers under eminent ART and reproductive medicine consultants
- The Clinical ART Fellowship includes hands-on training in clinical ART procedures, ultrasound and endoscopic surgeries
- Fellows can avail travel and academic grants
- Clinical Embryology includes intensive practical training in embryology lab procedures
- Completely merit based selection of candidates for a limited number of seats

EXPLORE EXCITING CAREER OPPORTUNITIES IN INDIA AND ABROAD

Career opportunities range from jobs in Fertility Clinics in India and abroad, opportunities in private healthcare organisations and in the field of infertility treatment, and research-centric roles like embryonic studies research in reputed universities and research in the reproductive sciences.

ELIGIBILITY & ENTRANCE EXAMINATION SYLLABUS

DIPLOMA IN CLINICAL ART

Eligibility: Postgraduate in OBGYN (MD/DNB). Registered with the MCI / State Medical Council. The candidate must be a life member of IFS.

Entrance Examination Syllabus: Clinical Reproductive Biology, Physiology, Anatomy, Endocrinology, Basic Embryology and Andrology. Clinical Genetics.

DIPLOMA IN CLINICAL EMBRYOLOGY

Eligibility: MBBS/Postgraduate in Medical Sciences or M.Sc./Ph.D in Life Sciences or Veterinary Sciences (Regular Course) from recognised institute in India.

Entrance Examination Syllabus: ICMR Guidelines, Basic Human Embryology, Human Cell culture, Genetics, TQM, Basic Semenology, Anatomy, Physiology & Pathalogy of Reproductive Biology.

Application Form is available online at www.indianfertilitysociety.org

Amity University, Sec-125, Noida (New Delhi NCR) | Tel: 98-160-26719, 98-105-66870 | www.amity.edu

IFS Secretariat: Akanksha IVF Centre, A 3/7, Janak Puri, New Delhi-58 | Tel. : 98-993-08083, 011-45682024
Email: indianfertilitysocietydelhi@gmail.com | Website: www.indianfertilitysociety.org

Global Standard Through R & D Excellence

Folisurge

Recombinant Follitropin ALFA

A Promise of Consistency

For Efficacy & Economy

Menotas

Menotropin 75/150 IU

Menotas HP

Menotropin 75/150 IU

INTAS

wish | Eva

Realizing the Dreams — Changing Lives Forever

For the use of Registered Medical Practitioner or a Hospital or a Laboratory only.

Design & Print by Core Creative: 9899960123