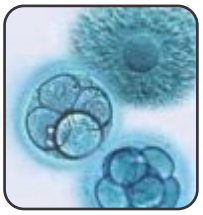
NOVEMBER - 2011

FOGSI FOCUS

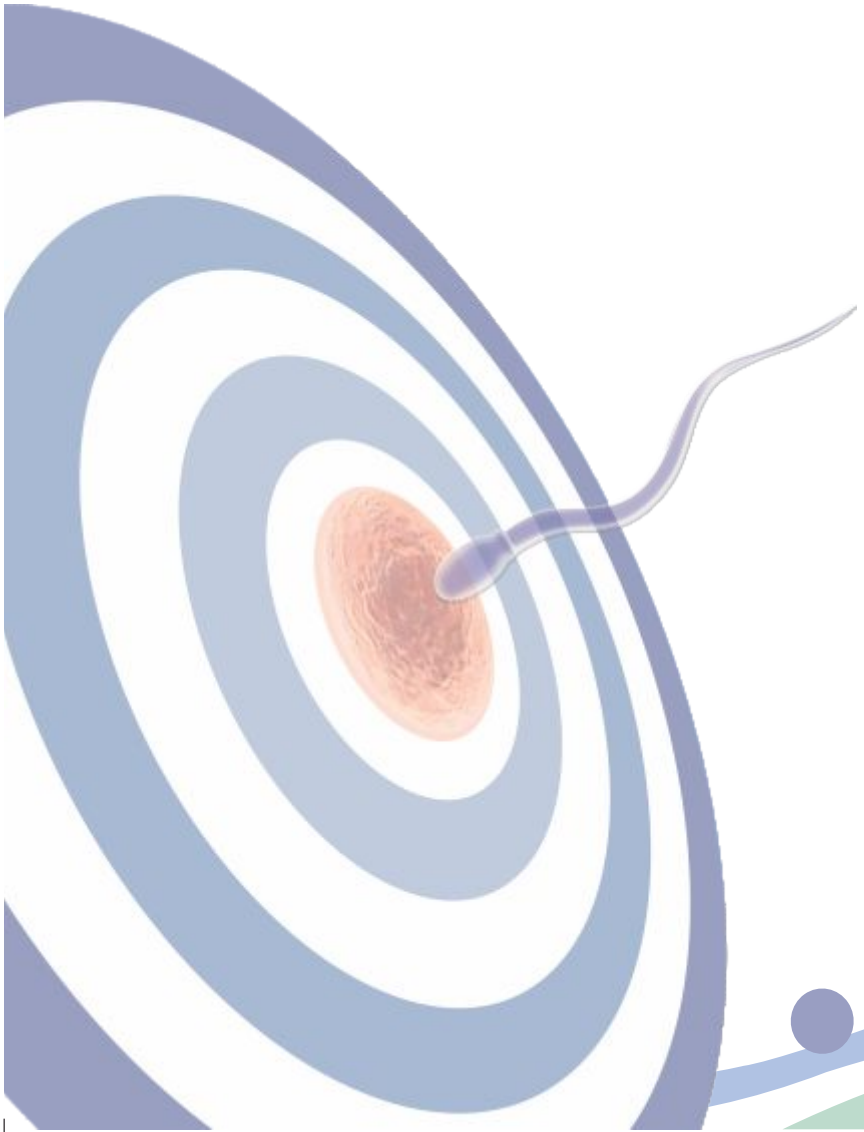
ADVANCED INFERTILITY MANAGEMENT



Editor
Dr. Nandita Palshetkar
1st Vice President, FOGSI

ADVANCED INFERTILITY MANAGEMENT

"Hope is a renewable option:
If you run out of it at the end of the day, you get to start over in the morning."



Editor
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FROM THE DESK OF THE FOGSI PRESIDENT

Dr. P. C. Mahapatra
Professor Obst. & Gyn.
S.C.B. Medical College, Cuttack
President - FOGSI 2011

During the last decade infertility has increased in great proportions in India.

With new reproductive and genetic technologies racing ahead, it is important to not only have basic background of facts and fundamental principles but also revisit and revise our perspectives of and treatments for infertility. Today, the treatments are geared towards both men and women confronting infertility issues.

The world of assisted reproduction is fascinating, and is one that also has a long history of evolution. For the practicing gynaecologist keeping up with the sheer number of advances is a challenge. Hence, this issue of the FOGSI FOCUS provides our gynaecologists with updated knowledge from experts in this field.

I was happy to know that this FOGSI FOCUS issue would be released in the 'Advanced Infertility Conference' in November, where various aspects Artificial Reproductive Techniques would be discussed, questions raised and decisions made.

The greatest wealth of a Professional is acquiring 'Skill' and it is true that it is in your moments of decision that your destiny is shaped.

This publication will constitute a valuable resource for specialists working in the multidisciplinary field of assisted reproduction.

I am sure that this book will be well appreciated by all members.

I congratulate Dr Nandita Palshetkar and the FOGSI Committee for this brilliant publication.

Dr. P. C. Mahapatra
President, FOGSI

FROM THE DESK OF THE FIRST VICE PRESIDENT, FOGSI

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Fertility problems have only dramatically increased making infertility a multifaceted condition with a myriad of causes. It is also no longer seen as a female- only issue, but a significant contribution comes from male factors as well.

As a result, we have to keep ourselves constantly updated on all perspectives of and treatments for infertility. Like any sub specialist, fertility specialists need to focus on additional advanced training and literature reviews on infertility. Advances in this field are providing new abilities for altering and influencing the beginnings of human life initiated outside the body, in the clinic, or in the laboratory. The well-established procedures of in- vitro-fertilization are being rapidly improved.

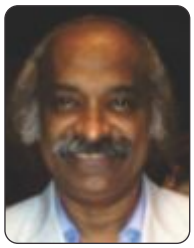
Hence, this issue of the FOGSI FOCUS highlights various recent topics on assisted reproduction. With contributions from well known experts in this field, this issue becomes a ready-reckoner in this field.

As a Vice President of FOGSI it is my vision to cultivate excellence through teaching and training. It is through such efforts from our Society that our members stand to benefit.

I thank all doctors who have contributed in making this issue an excellent guide in this subject.

Dr. Nandita Palshetkar
1st Vice President, FOGSI

LIST OF OFFICE BEARERS OF FOGSI FOR THE YEAR 2011-12



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FROM THE DESK OF THE FOGSI OFFICE BEARERS

Dear colleagues and friends,

The afternoon knows what the morning never suspected
... Swedish Proverb

For some time now each decade in our clinical practice has presented us with cutting edge research and advances in the field of Reproductive Medicine and Infertility that would have been unimaginable if we turned the clock back by just a few years. These developments are happening so rapidly that a clinician is often unable to keep up with them in real time.

FOGSI came into existence 60 years ago to address the academic and fellowship needs of its membership. Today as a specialist organization, it is noted for the high quality of its education programs and conferences where participants exchange information and discuss issues with leading experts from around the world.
As we welcome our colleagues from the different parts of the world and every corner of our country for the Advanced Infertility Management Conference being held between November 25 and 27, 2011 in Mumbai, we are happy to acknowledge the release of this FOGSI Focus periodical on Advanced Infertility Management. The Focus covers many important topics in the up to date management of infertility and will be of immense interest to any fertility clinician and endoscopy surgeon.

The publication in a very popular format developed by FOGSI and first presented under the presidency of Dr. Usha Krishna almost two decades ago is an advanced reference text written by a team of highly placed specialists in this field. We are sure that the readers will obtain a unique and invaluable opportunity to gather comprehensive information on advances in infertility from the contributions of these experts.
We would like to place on record our appreciation of the dedicated efforts of Dr Nandita Palshetkar, this issue's editor and First Vice President of FOGSI and want to take this opportunity to thank you, our Society member, for your time, commitment, and dedication to FOGSI and MOGS. As you know without you, our organizations would not exist and continue to grow!

Dr. P. K. Shah
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INDEX

1 INFERTILITY - AN OVERVIEW

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Calvin: I wish I could go to the moon
Calvin's Dad: I wish you could too
Calvin's Mom: Dear!
Mom and Dad drive me crazy. They don't understand me and I don't understand them.
It's hopeless! I'm related to people I don't relate to.
---- Calvin (A six year old precocious child from Bill Watterson's daily comic strip)

Since time immemorial, differences have existed between generations, but have never put off any people from desiring progeny. Universally, fertility and procreation have been revered & valued for their outcome, and for the fulfillment of life that they provide. And the emotions arising from the inability to procreate when desired, occupies a major part of the minds and lives of the people involved. It was once and still is in some communities, regarded as a disgrace, as a mark of divine displeasure, as grounds for divorce and even for compulsory suicide (on the part of the woman only!) The Egyptians, Greeks and earlier civilizations all had empirical treatments – love potions, amulets, prayers, sacrifices and the like [3].

Childlessness may result from recurrent abortions and stillbirth, but the commonest problem is a failure to conceive. It is this latter problem which is hence discussed here [2].

Definitions:

Infertility is defined as "The inability of a couple to establish pregnancy after one year of regular unprotected intercourse". This when the female partner is less than 35 years of age, but in cases when she is 35 years or more, the lower reference limit for time to pregnancy (TTP) is lowered to 6 months. The idea is that for women beyond age 35, every month counts and if made to wait another 6 months to prove the necessity of medical intervention, the problem could worsen.

Primary infertility is when no previous pregnancies have occurred, and secondary infertility is when a prior pregnancy, though not necessarily a live birth, has occurred. Secondary infertility is not the term used if there has been a change of partners (since it is *couples*, rather than individuals, who are infertile; in case of a change of partners, a new couple is created, with its own chances to be fertile or infertile). Provided there is not an absolute bar to conception on either side, the fertility of a marriage is the sum of the fertilities of the two partners.

With the advances in treatment over the last three decades, today there are very few couples who cannot potentially conceive. It should be noted that though we have herein continued to use the traditional word of "Infertility", the words infertility or sterility, imply an absolute state of inability to conceive, and so the preferred term would be "Subfertility" which would imply a relative state of lowered capacity to conceive.

Fecundability is the probability of achieving a pregnancy in a single menstrual cycle, whereas the probability of achieving a live birth in a single menstrual cycle is termed fecundity.

80% of couples will conceive within one year of unprotected intercourse, and approximately 86% will conceive within 2 years. Approximately 1 in 6 couples will have difficulty conceiving and may need medical help to identify and treat the possible causes of the problem.

Incidence:

About 10-15% of married couples in the reproductive age group remain childless [6]. This figure includes all age groups of the woman partner and also those couples using contraception of any kind. The incidence varies in different age groups and gets higher as the female partner ages. The age of the male partner does not make much difference, and factors affecting male fertility are less often age related. Nevertheless, not less than 8% of marriages, with the woman partner of a reasonable age and desirous of having children remain childless.

Key requirements for achievement of pregnancy

1. Regular ovulation
2. Normal ejaculate (semen volume, sperm numbers, motility and morphology)
3. Deposition of the semen in the vagina, close to the cervical external os
4. Survival of the sperm in the female genital tract
5. Patent and functionally normal fallopian tubes, with the ability to normally pickup the ovum at the time of ovulation
6. Fertilization i.e. fusion of the gametes in the fallopian tubal lumen
7. Transfer of the fertilized ovum into the uterine cavity
8. A normal receptive intrauterine environment, conducive to the movement of the sperm via it to the tubes, and favoring post-fertilization embryonic implantation

Causes:

There is always a cause for infertility and the frequency with which this is found depends on the thoroughness of the search. In many cases, there are several adverse factors operating at the same time, distributed between the partners [1].

The workup for detecting the cause should always include both partners. In any series of infertile marriages, the main etiological factor is found in the female partner about 50% of times. But 50% of the male partners can be shown by semen analysis to have some degree of subfertility. In around 10% of cases, the male partner is entirely responsible. Of every 100 men who marry one is absolutely sterile.

Causes in either sex :

Genetic, general factors like diabetes mellitus, thyroid disorders, adrenal disease, hypothalamic-pituitary factors and environmental factors and toxins.

Specific female causes :

These could affect either one or more than one of the organs contributing to fertility. So, evaluation should assess the ovaries (anovulation / oligoovulation - 30%), where diminished ovarian reserve, as also Polycystic Ovarian syndrome (PCOS) are key contributory factors, tubal disease (30%), peritoneal factors (4.8%), uterine and endometrial factors that could be hostile to the spermatozoa or to the newly fertilized ovum (3-5%), cervical factors (5.2%), vaginal hostility to spermatozoa, and associated factors, like toxins, endocrine disorders, and systemic hostility to spermatozoa or to the ova.

Specific male causes : [5] A failure to deposit spermatozoa in the vagina (as in cases of impotence, premature ejaculation, abnormalities of the penis such as hypospadias and phimosis and retrograde ejaculation into the bladder), Bilateral obstruction of the epididymis, the vas or the ejaculatory ducts, or due to errors in the seminal fluid (Sperm disorders are responsible in 30.6% of the cases).

Combined Infertility:

Both male and female contributory factors present. It may also be that each partner is independently fertile but the couple cannot conceive together without assistance.

Coital Errors:

Errors in the frequency and timing of coitus, sexual dysfunction such as erectile dysfunction, premature ejaculation, apareunia and dyspareunia (often causing unconsummated marriages), and the use of lubricants, which can have a contraceptive action.

Unexplained Infertility:

Infertility that is idiopathic, in the sense that its cause remains unknown even after an infertility workup happens in 13.4% of cases. In these cases abnormalities are likely to be present but not detected by current methods.

Approach to the issue:

When should infertility be investigated? [7]

i. Failure to achieve conception after 12 months of unprotected intercourse
ii. Women aged 35 years or more
iii. Women with anovulation documented
iv. When one of the partners is travelling often, and has long periods of absence
v. When one of the partners has undergone a reversal of sterilization procedure

It is prudent not to pursue an infertility evaluation in cases where the history reveals that the patient is not sexually-active, and if the couple does not meet the definition of an infertile couple.

Assessment:

A detailed evaluation of both partners is essential for a rational approach to treatment. Clinical workup can usually be accomplished in 1-2 cycles. Evaluation must be thorough, but individualized. Here the timing of the tests has to be planned such that the results are reliable, and at the same time so that the couple does not lose unnecessary time. It is important to not over test, and sometimes go ahead with the further line of testing even initially, e.g. proceed with laparoscopy if adhesive disease seems likely from the history and basic investigations. The most important factor in the evaluation of the infertile couple is the clinical history.

Ethics:

There are several ethical issues associated with infertility and its treatment. Each country has its own regulatory bodies responsible for the inspection and licensing of fertility treatment.

- An increase in multiple births due to ART- According to an ART surveillance and analysis in the United States [8], in order to minimize the adverse maternal and child health effects associated with multiple pregnancies, ongoing efforts to limit the number of embryos transferred in each ART procedure should be continued and strengthened.
- High-cost treatments are affordable by only some couples. Moreover, there is an ongoing debate over whether health insurance companies should be forced to cover infertility treatment.
- The legal status of the embryos fertilized in vitro and not transferred in not well defined. In September 2001, the National Bioethics Committee recommended "the creation of embryos solely for research purposes

should not be undertaken, but use of excess embryos for the purpose is permitted".

- The ethics of bypassing the natural selection to prevent transmission of genetic disorders from parent to child in fertility treatments.

Social and psychological impact:

Infertility may have profound psychological effects [4]. Marital discord often develops in infertile couples. What such couples need to be counseled about, to support their emotional & educational needs is that, infertility is a disease of couples, and not individuals. They should be guided as to where to go for information. Advances in assisted reproductive technologies, such as IVF, can offer hope to many couples, although barriers exist in terms of medical coverage and affordability. The adoption of a child is a matter on which individual outlooks differ, and so as a solution to the problem of infertility, it deserves a cautious approach by those concerned and should preferably never be advised by the medical consultant. The suggestion should come from the infertile couple themselves and only then its advantages and disadvantages discussed.

ART in India:

The social structure in most parts of India has led to the following concerns with respect to ART practice:

- Emphasis and pressure on having children (especially sons) because they are seen as the perpetuation of the self; if a man cannot have children, he is faced with the consequence of a complete genetic death
- Efforts to overcome infertility are undertaken with a greater amount of secrecy, the outcomes and attempts of which are often kept secret from the community and sometimes even the families
- Third party involvement is more widely (although secretly) accepted in India
- Concerns are focused on the outcome of a pregnancy (i.e. the means used to become pregnant, whether it's IVF, AID, or surrogacy, don't matter as long as the pregnancy has a successful outcome)
- Adoption is not an acceptable solution because it disrupts the parent-child bond
- The Indian Health Ministry has appointed the Indian Council for Medical Research (ICMR) to formulate guidelines for supervising Assisted Reproductive Clinics in India.

The evolution of Assisted Reproductive technologies (ART):

To understand science its necessary to know its history – Auguste Compte

1661 Concept of "*Omne vivum ex ovo*" i.e. everything living comes from the egg, was formed, by William Harvey.

1950 John Rock, the American scientist was the first to extract an intact fertilized egg.

1973 The Monash University team from Melbourne, Australia, reported the first pregnancy achieved through *in vitro* human fertilisation of a human oocyte in The Lancet, although it lasted only a few days and would today be called a biochemical pregnancy.

1977 Patrick Steptoe and Robert Edwards successfully carried out a pioneering conception which resulted in the birth of the world's first baby to be conceived by IVF, Louise Brown on 25 July 1978, in Oldham General Hospital, Greater Manchester, UK.

1979 Steptoe and Edwards were also responsible for the world's second baby conceived by IVF, Alastair MacDonald born on 14 January 1979 in Glasgow, UK.

1980 A team led by Ian Johnston and Alex Lopata were responsible for Australia's first baby conceived by IVF, Candice Reed born on 23 June 1980 in Melbourne.

1981 This was followed by a total of 14 pregnancies resulting in nine births in 1981 with the Monash University team. Also the first IVF baby was born in the USA led by the Jones and Jones team.

The subsequent use of stimulated cycles with clomiphene citrate and the use of human chorionic gonadotrophin (hCG) to control and time oocyte maturation, thus controlling the time of collection, then converted IVF from a research tool to a clinical treatment.

The Jones team at the Eastern Virginia Medical School further improved stimulated cycles by incorporating the use of a follicle-stimulating hormone (uHMG). This then became known as controlled ovarian hyperstimulation (COH). Another step forward was the use of gonadotrophin-releasing hormone agonists (GnRHA), thus decreasing the need for monitoring by preventing premature ovulation, and more recently gonadotrophin-releasing hormone antagonists (GnRH Ant), which have a similar function. The additional use of the oral contraceptive pill has allowed the scheduling of IVF cycles, which has made the treatment far more convenient for both staff and patients. The ability to freeze and subsequently thaw and transfer embryos has significantly improved the feasibility of IVF use.

1992 The next significant milestone in IVF was the development of the intracytoplasmic sperm injection (ICSI) of single sperms by André van Steirteghem in Brussels.

2002 One millionth IVF baby born (world-wide)

2006 Three millionth IVF baby born (world-wide)

2010 Robert Edwards was awarded the 2010 Nobel Prize in Physiology or Medicine "for the development of in vitro fertilization".

2011 Carl Wood (1929 – September 2011) of the Monash University, Melbourne, Australia, was dubbed "the father of IVF (in vitro fertilisation)" for having pioneered the use of frozen embryos.

In the US, ART 146,244 cycles started in 2009 resulted in 45,870 live births (deliveries of one or more living infants) and 60,190 infants.[8]

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2 EVALUATION OF AN INFERTILE COUPLE

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Introduction

Infertility is a common problem with one in every six couples experiencing difficulty in achieving conception at some stage in their reproductive lifespan. This is because one or both members of the couple could be subfertile or sterile. It is observed that the male partner is solely responsible in 40% and the female partner in another 40% of infertility cases. Both are responsible in the remaining 20% of cases. A thorough evaluation of the infertile couple is the most important step in managing such patients. Only once this is completed the various treatment options can be discussed realistically.

Evaluation of the female partner

History & Physical Examination

A detailed history is taken and a thorough physical examination is carried out at the couple's first visit. Several questions are asked with the aim of finding out any obvious cause of infertility and these probe all aspects of each partner's medical, sexual personal, social life and occupation. The World Health Organisation has formulated a set of standard questions which should be asked to all infertile couples[1,2].Like the history, physical examination is directed to find out any features pointing towards cause of infertility.

Routine investigations

A number of tests can be carried out to assess the functionality of the various reproductive organs. These include:

Tests for ovulation

- Basal body temperature: this test is based on the fact that rise in progesterone after ovulation increases the body temperature slightly (approx 0.5 C).
- Serial vaginal ultrasound scan in a spontaneous cycle helps tracking the follicular growth and judge the time of ovulation.
- LH surge detection using urinary LH test kits.
- Serum progesterone on Day 21 of cycle>4ng/ml indicates ovulation & >10ng/ml indicates adequate luteal phase.

Tests for Ovarian reserve

Various tests have been identified as markers for assessing ovarian reserve. These include:

- Baseline Serum FSH and LH: A day 2/3 FSH more than 10 mIU/ml indicates poor ovarian reserve. A LH/ FSH ratio of more than two indicates PCOS. Low LH, FSH, E2 indicates hypogonadotrophic hypogonadism.
- Basal Estradiol: Cycle day 3 Esatradiol less than 80 pg/ml is indicative of good ovarian reserve. ñUltrasound measurements: antral follicle count, ovarian volume & stromal blood flow: Day 2/ 3 AFC is one of the best predictors of response to ovarian stimulation. Decreased ovarian volume is indicative of ovarian aging and sometimes can be seen before rise in FSH.
- Serum Inhibin: Levels less than 45 pg/ml indicates poor response. It has also been observed that decrease in inhibin B may precede rise in FSH[3].
- Serum AMH (anti Mullerian hormone): AMH is a useful marker for predicting ovarian aging and the potential for successful IVF. Reduced baseline serum AMH indicates diminished ovarian reserve, associated with poor response to IVF. The normal values range from 0.7-3.5ng/ml.
- Dynamic Tests: These include clomiphene citrate challenge test and GnRH agonist test. There is a need for consensus on the performance of these tests and the definition of normality, if their use is to be continued. However, given the present level of evidence, these tests should be completely abandoned.

Other hormonal tests

- Serum Prolactin and Thyroid profile: Approximately 5% of women attending infertility clinic are diagnosed to have thyroid dysfunction[4]. Derangements in thyroid profile and prolactin can lead to anovulatory cycles, hence thyroid profile is an essential part of infertility workup.
- In case of patients with PCOS diagnosed by USG , or symptomatology or having feature of androgenisation fasting S.Insulin, fasting and post prandial blood sugars, DHEAS, Androstenedione and testosterone are also recommended.

Pelvic sonography

This helps in evaluating uterus, uterine cavity and adnexae. Ovarian volume, antral follicle count and presence or absence of PCO pattern should also be noted. Ultrasound today has revolutionised the management of infertility and is an indispensable tool especially in assisted reproductive methods.

Tests for tubal patency

Tests commonly used to check tubal patency include: HSG, HyCoSy, Laparoscopy.

Hysterosalpingogram (HSG): this is a time honoured test for tubal patency. It helps in evaluation of uterine cavity and to check the tubal patency. Uterine malformations, adhesions (Asherman's) or any alteration in the shape of the uterine cavity by fibroids etc can also be diagnosed. The test is usually performed in the 1st ten days of menstrual cycle once the bleeding stops. It is an inexpensive and reliable screening test. However it does not reveal any abnormalities in the pelvis like adhesions or endometriosis which may be contributing to infertility.

HyCoSy (Hysterosalpingo Contrast Sonography): It is an inexpensive, fast and well tolerated method of detecting tubal patency. The method has an added advantage that additional information on the uterine cavity, pelvic adhesions and fimbrial movement can be gathered.

Diagnostic laparoscopy and hysteroscopy is the gold standard for evaluating the uterus, patency of fallopian tubes and other pelvic structures, and may be required in certain cases to establish the exact diagnosis.

Evaluation of male partner:

A complete detailed history probing all aspects including medical, sexual, personal, social and occupational history should be taken. Besides the general physical examination a thorough examination of the genitalia should be carried out to rule out evident abnormalities like varicocele, hydrocele and inguinal hernia.

Semen analysis

This is the main investigation to evaluate male's fertility potential. It is important not only for the diagnosis of male infertility, but is also important for deciding upon treatment for the infertile couple.

The sample should be obtained by masturbation and ejaculated into a clean, wide-mouthed non toxic container made of glass or plastic, after a minimum of 2 days and a maximum of 7 days of abstinence. The specimen container should be kept at ambient temperature, between 20 °C and 37 °C, to avoid large changes in temperature that may affect the spermatozoa after they are ejaculated into it. Ideally, the collection must be done in the laboratory itself. However, if collected elsewhere the sample must reach the laboratory within one hour of collection. Any abnormal test result should be confirmed by repeating a semen analysis after few weeks or months to differentiate between a transient occurrence or a permanent finding.

The following table shows normal semen parameters as per WHO 5th edition.[5]

Appearance:	Homogeneous, Gray-opalescent
Odour:	Characteristic, not foul
Liquefaction:	Completes within 60 minutes at room temperature
Viscosity:	Leaves pipette as discrete droplets
Volume:	1.5ml or more
pH:	7.2 or more
Sperm concentration	15 million per ml or more
Total sperm count	39 million or more
Motility	32% or more forward progressive motility
Morphology	4% or more normal by strict criteria
Viality	58% or more viable
White blood cells	< 1 million per ml
Immunobead test	Few than 50% motile sperms with beads bound
MAR test	Few than 50% motile sperms with adherent particles

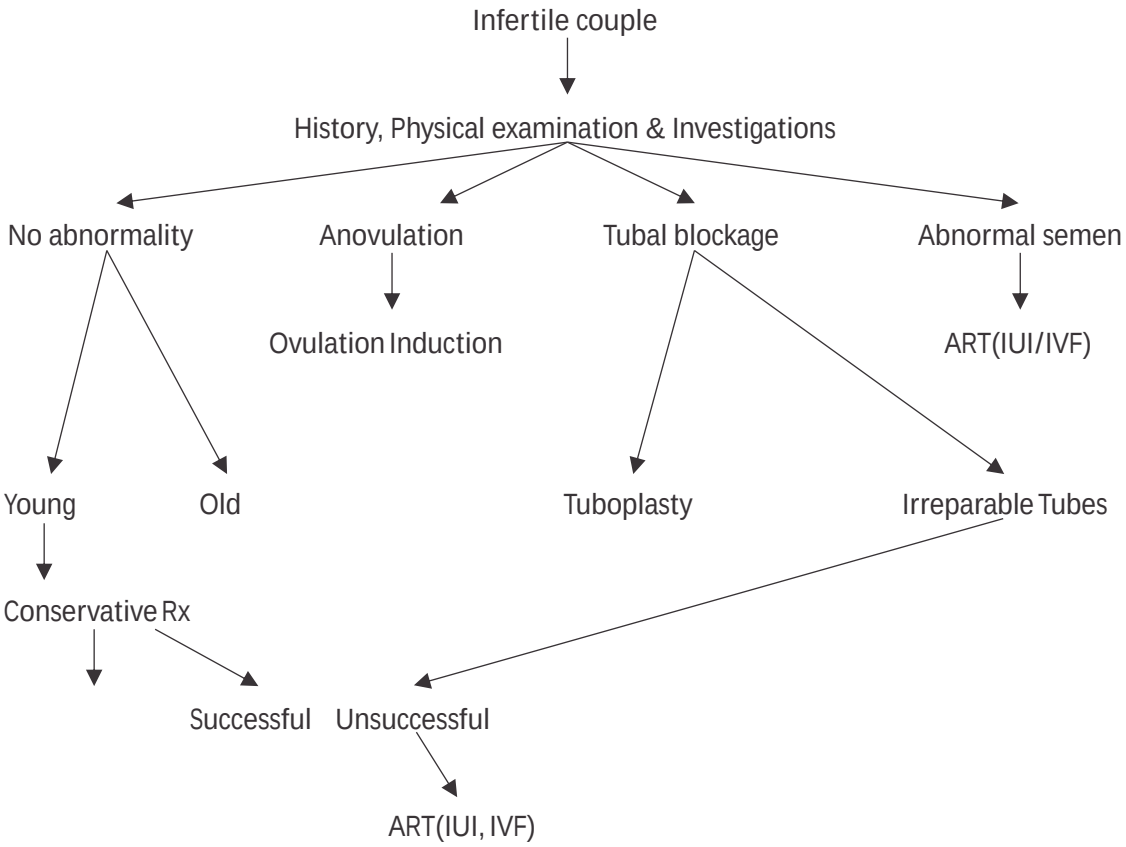
Additional investigations are indicated if any abnormality is detected while taking history, physical examination or initial semen analysis. These may include:

- Doppler ultrasound of scrotum for varicocele.
- Analysis of post orgasmic urine to rule out retrograde ejaculation

- Hormonal assays like Serum FSH, LH, Prolactin and Androgens in case of severe semen abnormality like severe oligospermia or azoospermia.
- Testicular biopsy in case of severe oligospermia or azoospermia
- Karyotyping to rule out abnormalities in the structure or number of sex chromosomes and autosomes such as Klinefelter's syndrome or microdeletions of Y chromosome.

Conclusion

Detailed evaluation of the infertile couple is the most crucial step in the management and helps in efficient decision making.



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3 TVS IN INFERTILITY

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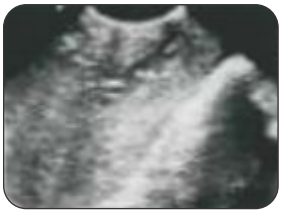
Transvaginal Sonography has an important role in the management of infertility *(Fig. 1).* Serial pelvic ultrasound pexaminations are useful in monitoring patients undergoing ovulation induction using ovulation-inducing drugs. In addition, the correct prediction of timing of ovulation is critical for infertility therapies such as intrauterine insemination, artificial or therapeutic insemination using donor sperm and the timing of intercourse during ovulation induction therapies.

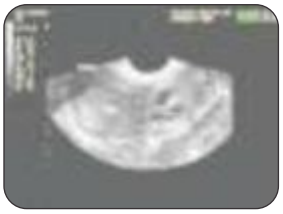
(A) Cervix: Cervix is evaluated forechoteture cervicitis, nabathian cysts, cervical mucus. It I s best seen in the AP view with the probe just away. TVS gives a good idea of the cervical factors of infertility.

(Fig. 2,3)

(Fig. 1 : Finger Tip Probe)



(Fig. 2 : Cervical Mucus)



(Fig. 3 : Nabothion Cysts)

(B) Uterus: Transvaginal ultrasound examination of the body of the uterus is done to observe detailed view of the myometrium and any anomalies.

Endometrium : The endometrial cavity should be visualizable as a separate entity within the uterus in virtually all menstruating patients. It is generally centrally located in the uterus. The cyclic histologic changes and changes in the thickening of the endometrium with hormonal stimulation can be imaged using transvaginal ultrasound during the different phases of the menstrual cycle.

Sakamoto described the characteristic sonographic image noted during the menstrual cycle in 1985. The proliferative endometrium is characterized by

(a) The presence of a well defined three line sign. *(Fig. 4)*

(b) Ahypoechogenicfunctional layer.

(c) A minimal or absent posterior accoustic enhancement.

The three line sign is formed by the central hyperechoic reflection representing the endometrial cavity and the additional hyperechoic reflection representing the thin developing layer of endometrium. There is also a surrounding hypoechoic halo.

Luteal phase endometrium is (a) hyperechoic, (b) posterior enhancement is present (c) three line sign and halo are absent. *(Fig. 5)*

Uterine Biophysical Profile : During the normal mid-cycle certain sonographic qualities of the uterus are noted viz.

(1) Endometrial thickness in greatest AP dimension of 7mm or greater (full thickness measurement).

(2) A Layered (5 line) appearance to the endometrium.

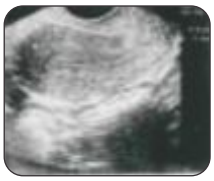
(3) Blood flow within zone 3 using color doppler technique. *(Fig. 6a, 6b)*

(4) Myometrial contractions causing a wave like motion of the endometrium.

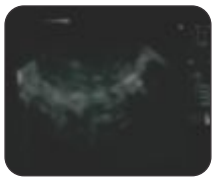
(5) Uterine artery blood flow as measured by PI, less than 3.0

(6) Homogeneous myometrial echogenicity.

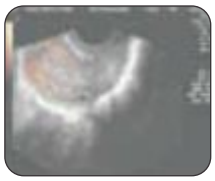
(7) Myometrial blood flow seen on gray scale examination (internal to the arcuate vessels).



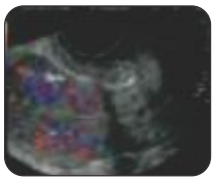
(Fig. 4 : Normal Cervix)



(Fig. 5 : Normal Uterus)



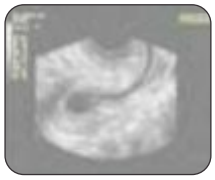
(Fig. 6a: Periovulatory endo)



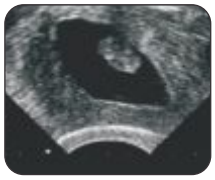
(Fig. 6b : Vascularity of Endometrium)

Uttering cavity Evaluation:

Transvaginal ultrasound with sonohysterography can very accurately delineate the cavity and pick up irregular endometrium, polyps, Asherman syndrome, submucous fibroids, double cavity, septum, unicomuate and T- shaped uterus. *(Fig. 7,8)*



(Fig. 7 : Saline Contrast)



(Fig. 8 : Polyp Fibroid)

Sonography

Sonohysterography or contrast sonohysterography (Hyscosy) is done by introducing a No.8 Foley's catheter or an infant feeding tube into the uterine cavity and injecting a sterile fluid media under ultrasound visualization (Normal Saline, hydrotubation fluid or commercially available echocontrast media - ECHOVIST). This offers a very accurate non-invasive method to evaluate cavity and should be routinely done after SSG and also in all infertile cases.

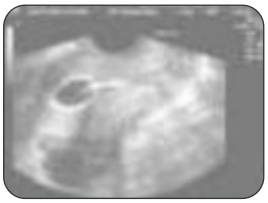
3D ultrasound and 3D reconstruction with echo contrast media is also a very accurate and good method for uterine cavity evaluation.

(C) Tubes

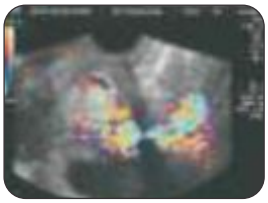
Fallopian tubes are isoechoic and cannot be normally seen on ultrasound unless pathological or fluid surrounds the tubes.

Sonosalpingography : also known as 'SION TEST' uses transvaginal sonography to confirm the tubal patency by visualizing the spill of fluid from the fimbriai end of fallopian tubes. This test is not a substitute for hysterosalpingography or Laparoscopy but is a noninvasive, cheap outdoor screening Procedure in infertility patients.

Method—No.8 Foley's calheter is put inside the uterus *(Fig. 9).* The bulb is inflated with 2 ml of distilled water. Prior to procedure the patient is asked to evacuate the bladder and base line Vaginal scan is performed. 20-60 ml of solution containing diploes, hylase and deamethasone is taken in 50 ml catheter tip syringe and pushed via Foley's catheter; spill is studied by TVS from the fimbriai end by observing a colorflow turbulence *(Fig. 10)*



(Fig. 9 : Foley's in Uterus)

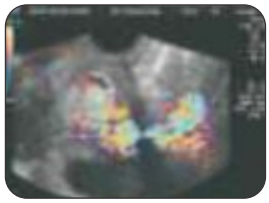


(Fig. 10 : Color Flow Turbulence)

(D) Ovary: TVS can accurately inform abentfollicular development, prediction of ovulation and confirmation of ovulation.

1. Follicular Development:

Developing follicles destined to ovulate increase in size 2 to 3 mm/day and reach a maximum diameter of 16to 33 mm before ovulation Selection of the dominant follicle is thought to occur by cycle days 5 to 7 but is not apparent sonographically until cycle days 8 to 12. Other antral follicles of the developing cohort will generally undergo atresia and will not exceed 14 mm in diameter *(Fig. 11).*



(Fig. 11 : Antral Follicle Cont)

2. Prediction of ovulation:

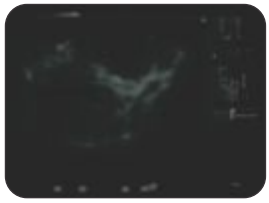
Potential signs of impending ovulation are:

(I) Presence of a dominant follicle (usually > 16-18 mm) and cumulus

(ii) Anechoic area, double contour, around the follicle (possible ovulation within 24 hours) *(Fig. 12)*

(iii) Separation and folding of the follicle lining (ovulation within 6-10 hours)

(iv) Thickened proliferative endometrium



(Fig. 12 : Double Contour)

3. Confirmation of ovulation:

(i) Disappearame of the follicle (91 % cases)

(ii) Decrease in follicle size (9% cases)

(iii) Fluid in cull de sac when not present in a previous scan

(iv) Development of intrafollicular echoes suggesting the formation of a hemorrhagic corpus luteum

Ovary in Anovulalory cycles

(1) Lack of any follicular development particularly in the hypogonadotropic hypogonadal patient *(Fig. 13)*

(2) Few nonovulatory (less than 11 mm) follicles, or

(3) Acyst or

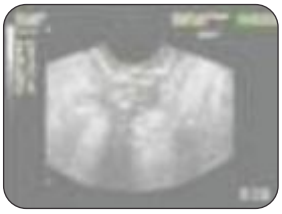
(4) PCOD -

(i) Enlarged overy (> 8 cms)

(ii) Multiple small cysts (0.2-0.6)

(iii) Anovulation (lack of follicular development)

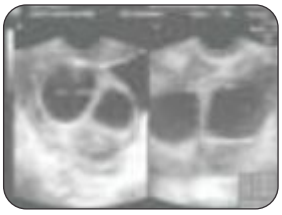
(iv) Resting or follicular endometrium



(Fig. 13 : Ovary Lacking Any Follicles)

Follicular Monitoring:

Monitoring of follicular growth by ultra sound is now an established practice in most fertility centres. Theability to visualise and monitor follicular growth was first postulated by Kratochavil etal (1972). Hackelor etal (1979) reported a good correlation between follicular diameter and plasma oestradiol levels in women in spontaneous menstrual cycles. The follicular diameters must be measured in the transverse and longitudinal planes to get the average diameter. Follicles may be seen in the ovaries as early as day 2 or 3 of the menstrual cycle, measuring 3-4 mm in size. The rate of follicular growth is between 1 and 2 mm per day (Hackeloer and Robinson 1978). Thus by day 12 the dominant follicle is around 12-16 mm in sizes Follicular rupture in normal cycle occurs when the mean follicular diameter is between 18 and 28 mm (Hackeloer 1979). In clomiphone stimulated cycles follicular ruptureoccurs between 18 and 24 mm (O^1 Herlihy 1980), whereas in HMG stimulated cycle it occurs between 15 and 20 mm (Ylostalo 1979) For timing of accurate ovulation, serial scanning is needed. Follicular collapse, disappearance of follicle, enlargement of follicle with appearance of internal echoes-indicate ovulation. *(Fig. 14)*



(Fig. 14 : Dominant Follicle)

Oocyte Retrieval:

After performing a preliminary scan to assess the number of follicles, position of both the ovaries, intervening bowel loops, adhesion, chocolate cysts etc., follicles in the ovary are tapped by a sterile disposable ovum pickup needle with attached silicon tubing and suction apparatus (set at 150 mmHg). At the end of one side, the needle is withdrawn and flushed with culture medium before proceeding to the ovary on the opposite side.

Colour Doppler in infertility

(i) Polycystic ovarian syndrome (PCOS) is a common cause of infertility and associated with a number of infertile patients.

Changes in ovarian circulation occur in intrinsic vessels. Low impedance flow is seen in early phase of cycle, as early as 3-5 days. *(Fig. 15)*

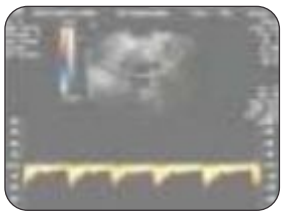
Uterine a shows high P.I. value Ovarian a shows R.I. of 0.66 + 0.13 in general cystic pattern type of PCOS and 0.5 O ± 0.05 in the peripheral cystic pattern type of PCOS. (ii) Endometrial blood flow study is well assessed by TV-CDS. It is important to assess the endometrial

receptively in various ART techniques.

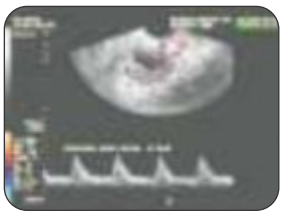
(iii) To assess quality of follicle and maturity of follicle and impending ovulation, by CDS of perifollicular flow,

(iv) To predict successful implantation in IVFby mean. Uterine A. P.I. If uterine A P.I. is > 3 than extremely low

chance of pregnancy is seen *(Fig. 16).*



(Fig. 15 : Blood Flow in PCO)



(Fig. 16 : R.I. of Ovarian a.)

Role of 3D USG

Three-dimensional ultrasonography is an exiting and rapidly developing field, providing images of the target organ in multiple tomographic sections. In particular, for the first time, the volume of the target organ can be accurately measured, regardless of its shape. 3 D sonography allows physicians to understand and appreciate the complex anatomy of the pelvis with ease.

Future modifications of 3D ultrasound in the field of infertility could include a combination with color doppler ultrasound to give an index of vascular changes, 3 D real time ultrasonography and direct quantitative computation of the volume of target. It is likely that 3 D ultrasound will be accepted in the future as the diagnostic gold standard for the female pelvis.

Fole of TVS in Interventional Procedures:

With the addition of intervention, today a specific pathological diagnosis is possible as now a needle can be guided into the lesion to take biopsies, fluid for cytology and to even treat simple cysts and localized pyogenic collections and even PCO puncture is being attempted.

The ability to diagnose conditions earlier and better than with transbdominal approach has put vaginosonography in an enviable position for interventional procedures to be carried out on the pelvic organs. Thus, the transvaginal transducer coupled with the biopsy guide, has become of late a crucial weapon in the armamentarium of the interventional ultraconologist. Whereas with Trans abdominal ultrasound, intervention is mainly a free - hand technique; with transvaginal ultrasound it becomes a guided procedure where in the operator can be confident that the needle will follow the path charted out by the software generated biopsy line on the monitor. Also, transvaginal ultrasound guided procedures have the advantage of easy accessibility to the pelvic organs in the needle path.

Conclusion:

Transvaginal sonography offers a very accurate, easy and reproducible method to evaluate the female pelvis and the female factors of infertility. Addition of color gives us more information about organ perfusion and addition of 3D has opened a new dimension to diagnosis of pelvic pathologies.

To practise infertility without Tvs is like walking in dark without a torch.

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4 HYSTEROSALPINGOGRAPHY IN INFERTILITY

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Introduction

Hysterosalpingography (HSG) refers to the radiographic evaluation of the uterine cavity and fallopian tubes after injection of a radio-opaque contrast medium through the cervical canal. It is the most common and the initial investigation for evaluating uterine cavity fallopian tube pathologies associated with infertility(1).The primary role of HSG is in the evaluation of the fallopian tubes. Ultrasonography is currently used for evaluation of the endometrium (i.e, abnormal uterine bleeding, and polyps) and pregnancy, whereas magnetic resonance imaging is used more in the evaluation of the uterine myometrium (i.e, uterine contour, myomas) and the ovaries(2).

Despite recent advances in various imaging modalities to assess the fallopian tubes such as a three-dimensional dynamic magnetic resonance hysterosalpingography (3D dMRHSG) and contrast enhanced hystero-salpingosonography, conventional HSG still remains the imaging modality of choice(1).

Preparation prior to procedure

No specific patient preparation is required for HSG. Because some patients may experience cramping during the examination, women are advised to take a non steroidal anti-inflammatory drug 1 hour prior to the procedure. Pre-operatively injection Atropine is given to prevent vasovagal attack as well as tubal spasm during the procedure. Alternatively Buscopan can be used to prevent tubal spasm.

Contraindications

Pregnancy and active pelvic infection.

Timing of the procedure

The examination should be scheduled during days 712 of a 28 day menstrual cycle (day1 being the first day of menstrual bleeding). The endometrium is thin during this proliferative phase, a fact that facilitates image interpretation and should also ensure that there is no pregnancy.

Procedure

The patient in the lithotomy position with a speculum and a bright lamp are used to visualize the cervical os which is then swabbed with Povidone iodine solution. Leech-Wilkinson cannula, the Rubens cannula, or a paediatric Foley catheter is selected and placed in the internal os. A 10 cc contrast filled syringe is attached to the cannula/catheter and the contrast is slowly injected under fluoroscopic control. Three films are taken, one as the contrast filled the uterine cavity, the second as it passed through the tube and spillage observed and a third delayed one, taken about 10 minutes later. A lateral film was taken when indicated (3).

Choice of Contrast media

Enormous efforts have taken place to develop safer contrast media while maintaining good diagnostic image quality. In 1985, these efforts led to the development of non-ionic low osmolar water soluble contrast media (1). Commonly used contrast media in India are urograffin & conray 280.

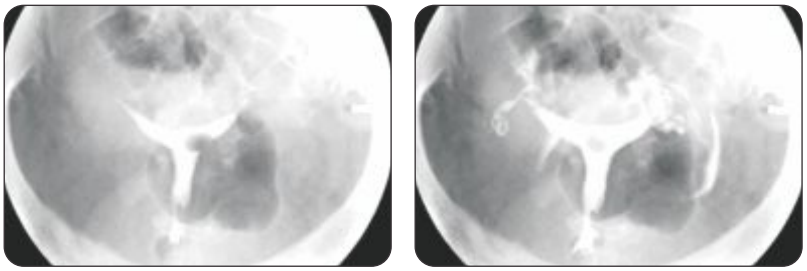
Complications of HSG

Bleeding, infection, pain & rarely, a vasovagal reaction. There is the potential for a reaction to the contrast material; however, such a reaction is very uncommon with the use of currently available low-osmolar nonionic contrast agents. There is also the potential for a systemic reaction to the contrast material if vascular intravasation occurs. . Finally, there is the potential for irradiation of an early, unsuspected pregnancy (2).

Technical artifacts

Air bubbles

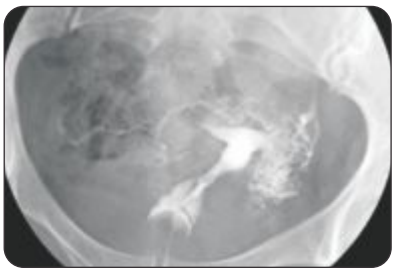
Air bubbles are often inadvertently introduced into the uterine cavity during hysterosalpingography. When multiple air bubbles are present, they can beeasily recognised. However, a single air bubble can be mistaken for other uterine pathologies, such as a polyp or a submucosal fibroid. An air bubble is seen as a mobile, spherical and well-defined filling defect. Its mobility and lack of persistence indicates its nature. It is possible to aspirate the air bubble and re-inject the contrast agent to show a normal uterine cavity. Alternatively, the air bubble can be expelled into the peritoneal cavity. Another indication of its true nature is that air bubbles move to the non-dependant part of the uterus when the patient turns.



Artifact due to air bubble. *(a) Hysterosalpingogram shows a well-defined filling defect in the left lateral aspect of the uterinecavity. (b) The filling defect is mobile and is now seen in the middle of the uterine cavity, compatible with an air bubble.*

Contrast intravasation

Contrast intravasation can occur via the venous or lymphatic routes. Predisposing factors include increased intrauterine pressure or recent uterine surgery. It can also be seen in a normal examination. It is seen radiographically as multiple thin lines, forming a reticular pattern and should not be mistaken for opacification of the fallopian tubes. In some cases, the ovarian veins may be opacified. While the contrast agent in the opacified fallopian tubes tend to persist, contrast in the veins and lymphatics tend to wash out once the injection stops.

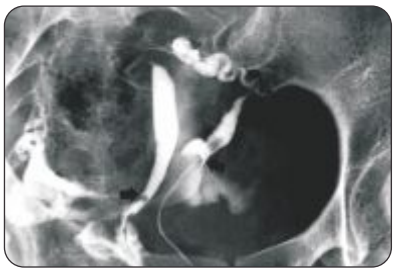


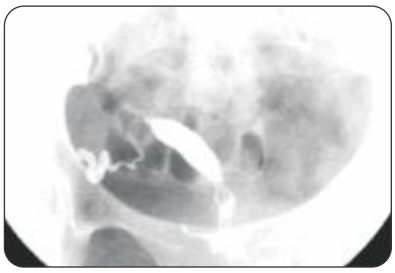
Artifact due to venous intravasation. Hysterosalpingogram shows multiple linear densities forming a reticular pattern adjacent to the outlined uterine cavity with opacification of the left ovarian vein, compatible with venous contrast intravasation.

Congenital uterine malformations

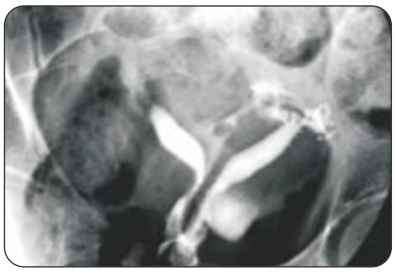
Mullerian ducts anomalies

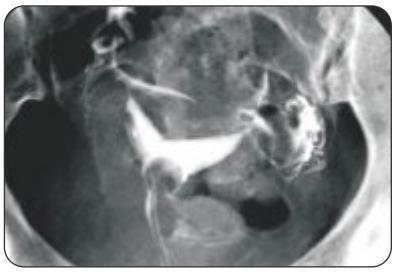
There is a spectrum of uterine anomalies related to defects of Mullerian duct fusion. These include uterus didelphys, unicornuate uterus , bicornuate uterus, septate uterus and arcuate uterus. The most common anomaly is the arcuate uterus, which has no impact on fertility. The arcuate uterus has a smooth convex fundal mucosal margin on the HSG and a smooth fundal serosal outline on USG or MRI. The presence of septate uterus and bicornuate uterus is inferred from the angle between the uterine horns. A wider or obtuse angle favours the diagnosis of a bicornuate uterus. However, they may appear similar on HSG and require correlation with USG or MRI, as accurate differentiation of these anomalies requires visualisation of the external contour of the uterus. MR imaging and recently, 3D USG, are the preferred modalities.





a.Didelphys uterus. Hysterosalpingogram shows two cervices (arrows) that were cannulated separately, and leading to their corresponding uterine cavities. b. Unicornuate uterus. Hysterosalpingogram showsopacification of a single left uterine horn. The other uterine horn was rudimentary and was only visualised on ultrasonography

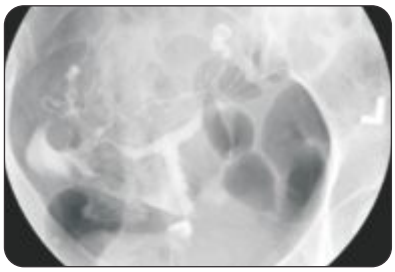




a.Hysterosalpingogram shows a deep cleft separating the two horns of the uterus. b.Hysterosalpingogram shows indentationof the uterine cavity outline in the fundal region, compatible with an arcuate uterus.

Infantile (T-shaped) uterus

Infantile uterus is seen as a T-shape uterine cavity on hysterosalpingography with a 1:1 ratio between the uterine body and cervix. This is in contrast with the normal adult uterus where the uterine body comprises 60%70% of the total uterine length. Infantile uterus is associated with maternal diethylstilbestrol exposure, oestrogen deficiency or prolonged intake of oral contraceptives by the patient.

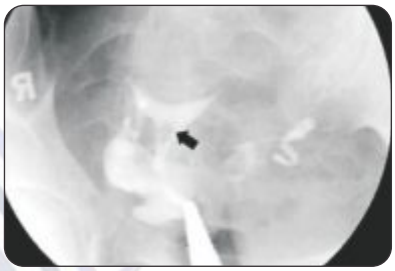


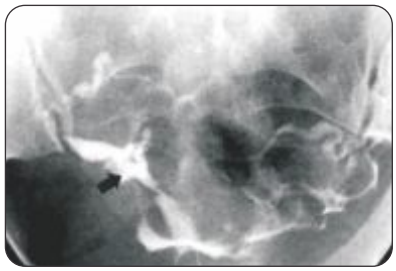
Hysterosalpingogram shows a T-shaped uterine cavity with a 1:1 ratio between the uterine body and cervix, compatible with an infantile uterus.

Other Uterine pathologies

Synechiae

Synechiae refers to adhesions within the uterine cavity from scarring. This can be a result of endometrial infection or from previous D&C. It is usually seen as a linear irregular filling defect in the opacified uterine cavity. It is important to recognise this filling defect during the early filling phase of the uterine cavity. Excessive amount of contrast agent within the uterine cavity may obscure this finding. The most severe form of adhesions is known as Asherman's syndrome which is associated with amenorrhoea and infertility.

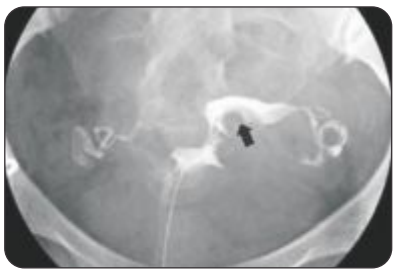




a.Hysterosalpingogram shows a linear filling defect (arrowed) in the uterine cavity, representing adhesions seen in synechia. b.Hysterosalpingogram shows a severe form of intrauterine adhesion with distortion of the uterine cavity (arrowed)

Submucosal leiomyoma

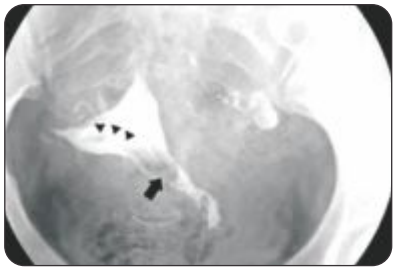
Leiomyomas are associated with habitual abortion, especially the submucosal type. Submucosal leiomyomas present as well-defined filling defects which distort the uterine cavity on hysterosalpingography. Small intramural or subserosal leiomyomas do not distort the endometrial cavity and are not visualised on HSG.



Hysterosalpingogram shows a distorted uterine cavity (arrowed) with loss of the normal triangular shape by multiple submucosal fibroids

Endometrial polyp

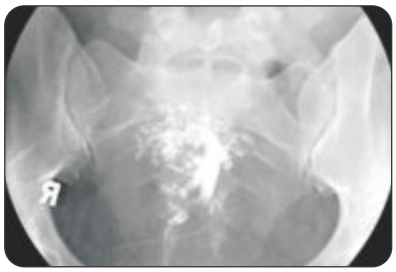
Endometrial polyp presents as a well-defined filling defect, sometimes with a visible stalk .This lesion is again better appreciated during the early filling phase of the procedure. Saline infusion hysterosonography or hysteroscopy is the modality of choice for characterisation of this lesion.



Hysterosalpingogram shows a well-defined filling defect in the lower uterine body (arrowed) with a stalk (arrowheads) arising from the right cornu, representing an endometrial polyp or fibroid.

Adenomyosis

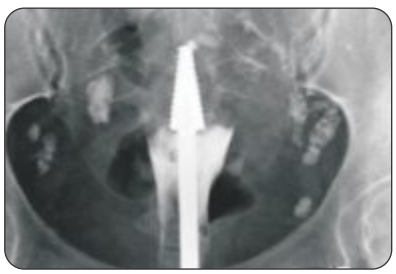
MR imaging is highly accurate for detection of adenomyosis. This condition is only occasionally recognised on HSG, if there is a connection between the ectopic endometrial glands and the endometrial cavity. It manifests as irregular branching out-pouchings that are continuous with the uterine cavity. Adenomyosis is associated with infertility.



Hysterosalpingogram shows adenomyosis with irregular branching outpouchings radiating from the uterine cavity, representing extension of the endometrial glands into the myometrium.

Endometrial tuberculosis

The appearance of endometrial tuberculosis on HSG is non-specific, and includes synechiae, distorted uterine cavity outline or contrast intravasation.

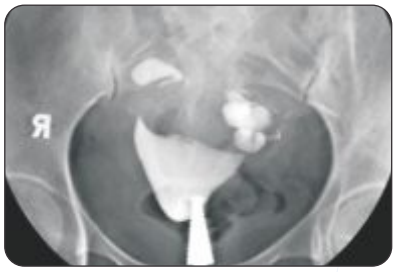


Hysterosalpingogram shows that the uterine cavity is severely scarred and obliterated by previous endometrial tuberculosis. All the contrast agent injected has refluxed into the vagina, with no filling of the uterine cavity. Multiple calcified densities in the pelvis represent calcified lymph nodes

Common pathological findings of fallopian tube

Tubal occlusion

Fallopian tube occlusion can occur secondary to inflammation or previous surgery. Radiographically, it manifests as non-opacification or abrupt cut-off of the fallopian tube with no free intra-peritoneal spillage. However, a common pitfall is non-opacification of the fallopian tube due to spasm. This entity may require administration of an antispasmodic or selective cannulation of the tube to distinguish it from a truly blocked tube.

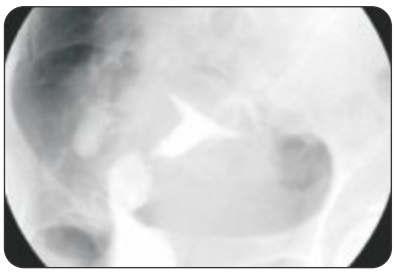


Hysterosalpingogram shows tubular convoluted structures on both sides of the uterus, representing bilateral hydrosalpinges. No intra-peritoneal spillage

of contrast is demonstrated

Hydrosalpinx

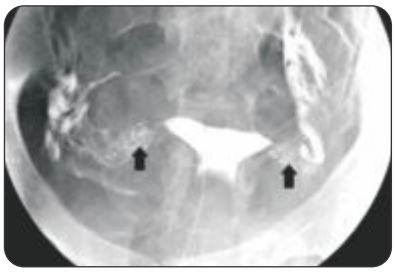
This is usually the sequelae of distal tubal occlusion leading to dilatation of the proximal segment. The hydrosalpinx is seen as a dilated, convoluted tubular structure on hysterosalpingography.



Hysterosalpingogram shows pooling of the contrast agent which had spilled from the right fallopian tube, secondary to peritubal adhesions. The contrast agent does not outline the peritoneal folds or the bowel loops.

Peritubal adhesion

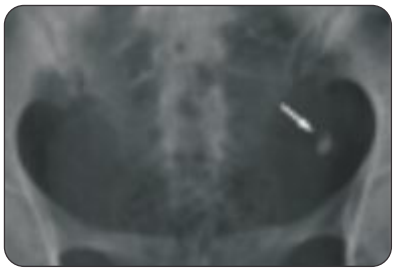
Peritubal adhesions occurs secondary to previous inflammation or surgery, similar to the causes of tubal occlusion. Adhesions around the fallopian tube results in loculation of contrast material that has spilled from the fallopian tubes. The spilled contrast material does not outline the peritoneal folds or bowel loops, as seen in normal cases.

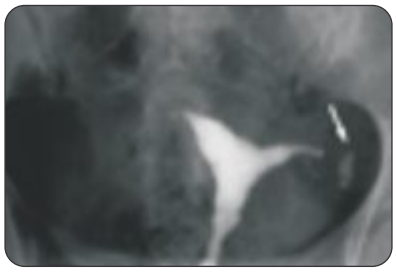


Hysterosalpingogram shows small outpouchings in the isthmic region (arrowed) of both fallopian tube.

Salpingitis isthmica nodosa

This entity is of unknown aetiology and is presumed to be post-inflammatory. It is associated with ectopic pregnancy and infertility. Corresponding radiological findings are small outpouchings or diverticula, mainly at the isthmic segment of the fallopian tube (4).



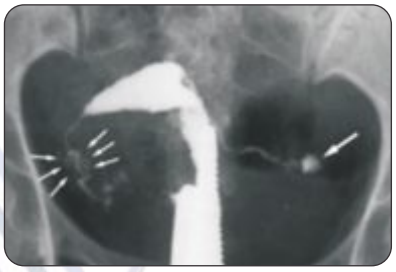


(a) Plain film of the pelvis frontal projection shows 10 x 6 mm calcific density (arrow) on the left side. (b) Hysterosalpingogram frontal projection shows isthmic obstruction of the left fallopian tube just proximal to the calcification. There is obstruction in the interstitial part of the tube on the right side. The endometrial cavity shows irregularity.

Tubal tuberculosis

Calcifications

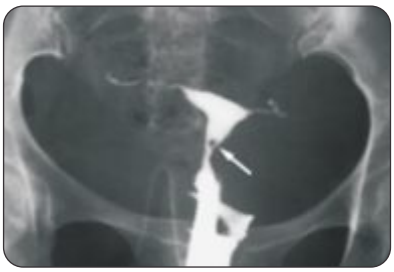
Plain films of the pelvis may show calcification of the fallopian tubes or ovaries. This calcification must be differentiated from calcified pelvic nodes, calcified uterine myomas, pelvic phleboliths and calcification in an ovarian dermoid (5). Tubal calcification can take the form of linear streaks, which lie in the course of the fallopian tube or appear as faint or dense tiny nodules.



Hysterosalpingogram frontal projection shows occlusion of bilateral tubes in the ampullary region with multiple diverticula bilaterally (small arrows). The thick arrow indicates terminal hydrosalpinx.

Tubal outline

Caseous ulceration of the mucosa of the tube produces an irregular contour of the lumen of the tubes. Diverticular cavities may surround the ampulla and give it a characteristic "tufted" appearance. Isthmic diverticula resembling those seen in Salphingitis isthmica nodosa may be seen (5). Blind ending sinus tract or occasionally fistula to adjacent bowel may form.



Hysterosalpingogram frontal projection shows isthmic obstruction of both fallopian tubes. The tubes appear rigid "pipe-stem" and are beaded. There is a lucent filling defect in the lower uterine segment suggestive of adhesion.

Tubal occlusion

Tubal occlusion is the most common HSG finding encountered in genital tuberculosis.Tubal occlusion in tuberculosis occurs most commonly in the region of isthmus and ampulla. Multiple constrictions along the course of fallopian tube can form because of scarring and give rise to "beaded" appearance to the tubes on HSG. Scarring also leads to a "rigid pipe stem" appearance of the tubes.

Hysterosalpingogram oblique projection shows ampullary obstruction of both the tubes (large arrows). There is dilatation of the ampullary region with prominent mucosal folds (small arrows) on the right side. The uterus is anteflexed.

Tubal Dilatation

Tuberculous hydrosalpinx is not uncommon in India (7), hydrosalpinx is usually moderate or slight with a club like appearance to the ampulla. Thickened mucosal folds in the dilated tubes are the commonly seen feature in tuberculosis.

Peritubal adhesion

Distal tubal disease usually appears secondary to peritubal adhesions. These adhesions disrupt the delicate anatomical relationship between the tube and the ovary, interfering with normal ovulation (7). The presence of a convoluted or corkscrew fallopian tube, peritubal halo, tubal fixation and loculated spillage of contrast material is suggestive of peritubal adhesions.

Although the various features described are not specific for genital tuberculosis, they are highly suggestive of it. The diagnostic criteria established by Klein et al (6) are very useful for this purpose:

- Calcified lymph nodes or smaller, irregular calcifications in the adnexal area.
- Obstruction of the fallopian tube in the zone of transition between the isthmus and the ampulla.
- Multiple constrictions along the course of the fallopian tube.
- Endometrial adhesion and or deformity or obliteration of the endometrial cavity, in the absence of curettage or surgical termination of pregnancy (5).

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5. Kodaman et al.Tubal factor infertility Current Opinion in Obstetrics and Gynecology 2004, 16:221229.