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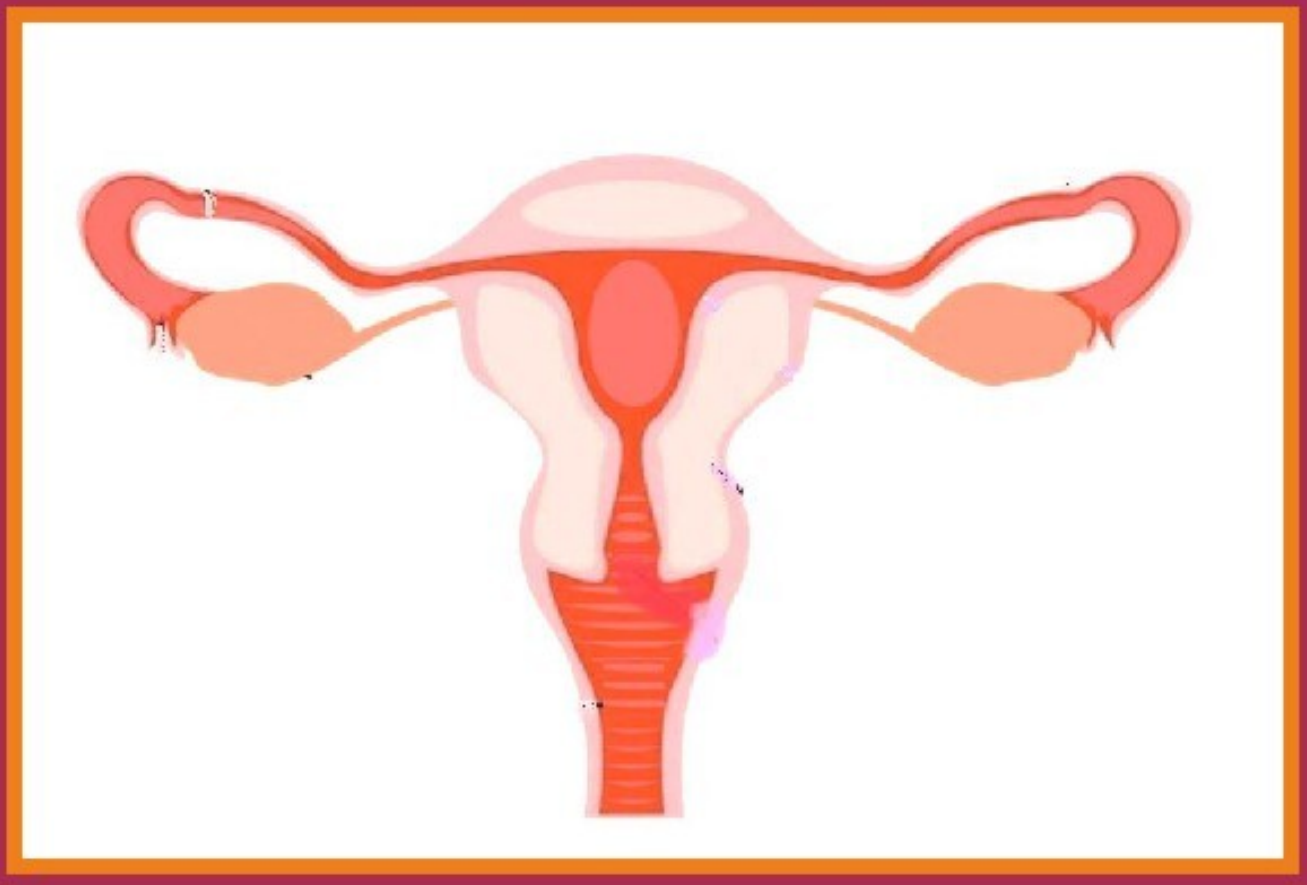
FEMALE INFERTILITY, CAUSES, RISK FACTORS, TREATMENT AND MANAGEMENT

STATE INSTITUTE OF HEALTH AND FAMILY WELFARE, UTTAR PRADESH

In Association with Department of Obstetrics & Gynaecology,
King George's Medical University, Lucknow

FEMALE INFERTILITY, CAUSES, RISK FACTORS, TREATMENT AND MANAGEMENT

CME MODULE



STATE INSTITUTE OF HEALTH AND FAMILY WELFARE, UTTAR PRADESH

In Association with Department of Obstetrics & Gynaecology, King George's Medical University, Lucknow

AKNOWLEDGEMENT

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MESSAGE

Shri Brijesh Pathak,
Hon'ble Deputy Chief Minister
Minister of Medical Health and
Family Welfare Department
Government of Uttar Pradesh

Continuing Medical Education (CME) enables medical professionals to enhance their knowledge base and provides an opportunity for knowledge creators to share their expertise with the broader medical community. CMEs facilitate collaboration among medical professionals, fostering valuable networking opportunities.

To address the sustainable development goals and alleviate the global burden of infertility diseases related to the male or female reproductive system, the Government of Uttar Pradesh is committed to enhancing its Healthcare Ecosystem through CME, incorporating technological advancements and medical breakthroughs.

Primary Health Centers (PHCs) and Community Health Centers (CHCs) serve as the initial point of contact with qualified doctors in the public health sector. By implementing systematic CME programs, these initiatives aim to update the proficiency of medical officers by imparting current knowledge and skills. This will significantly enhance patient care, instill patient confidence, and improve patient satisfaction.

In line with this objective, the State Institute of Health & Family Welfare, Uttar Pradesh (SIHFW), is actively developing CME modules that are crucial for our healthcare personnel. I anticipate that the Female Infertility, Causes, Risk Factors, Treatment and Management module will greatly contribute to the knowledge enhancement of medical officers in the Provincial Health & Medical Services in Uttar Pradesh. This will ultimately benefit both the medical officers and their patients.

I extend my best wishes to the SIHFW team in their continued development of CME modules, which will undoubtedly benefit the medical officers in the Provincial Health & Medical Services in Uttar Pradesh, and subsequently improve the well-being of their patients.

(Brijesh Pathak)


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Message

Shri Mayankeshwar Sharan Singh

Hon'ble State Minister
Medical Health and Family
Welfare Department
Government of Uttar Pradesh

I am proud of the fact that the State Institute of Health & Family Welfare, Uttar Pradesh (SIHFW) through this module on Continuing Medical Education (CME) on Female Infertility, Causes, Risk Factors, Treatment and Management for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, is addressing the need of knowledge upgradation in Female infertility diseases.

Since, advancements in medical science and research compels doctors to stay up to date current practices and trends. It is widely felt that CME programs are earnestly needed to impart recent knowledge and skills in systematic manner to update the existing proficiency of doctors.

By collating the relevant information in the field of women's infertility, covering all domains such as screening, detection, referrals, and treatment of patients, the module seeks to be a working document which can also be reviewed and updated periodically based on the experience of the implementation of the public health services.

In lieu of the above the State Institute of Health & Family Welfare (SIHFW), has developed module on Continuing Medical Education (CME) on Female Infertility, Causes, Risk Factors, Treatment and Management for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh. I hope that this module on CME is the first of many to come, that will aid our Medical Officers in knowledge up gradation on concurrent intervention practices.

I wish the director and the team at State Institute of Health and Family Welfare (SIHFW), Lucknow, Uttar Pradesh success in their endeavors of aiding an improved health service delivery system through such Continuing Medical Education on Female Infertility, Causes, Risk Factors, Treatment and Management.

(Mayankeshwar Sharan Singh)


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Message

Shri Partha Sarthi Sen Sharma

Principal Secretary
Department of Medical, Health
and Family Welfare
Government of Uttar Pradesh

Continuing Medical Education (CME) module serves as a mechanism through which medical professionals can remain updated on the rapidly evolving practices in the field of medicine. Given the post COVID era, it has become increasingly important for medical officers to keep pace with the emerging modes of treatment and management, which are developed in response to feedback from the medical community.

Medical officers at the primary level encounter numerous challenges in managing conditions such as Female's Infertility problem, and other emergencies related. Continuous knowledge and skill enhancement are required to effectively address these challenges. However, due to their responsibilities in managing healthcare centers and implementing government policies, medical officers have limited time to dedicate to learning.

Medical officers at the primary level face many challenges in managing women's infertility problems and other related emergencies. Continuous knowledge and skill enhancement is required to address these challenges effectively. However, due to their responsibilities of managing healthcare centers and implementing government policies, medical officers have limited time to devote to learning.

I would like to extend my congratulations to SIHFW and the other subject matter experts involved in the development of this comprehensive module. I hope that this CME module will shed light on the treatment of Female Infertility, Causes, Risk Factors, Treatment and Management and contribute to better healthcare outcomes.

(Partha Sarthi Sen Sharma)


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Message

Dr. Brijesh Rathor
Director General
Medical and Health Services
Uttar Pradesh

The effective treatment of Female Infertility, Causes, Risk Factors, Treatment and Management module plays a critical role in preserving lives and preventing severe health complications. Timely access to healthcare facilities equipped to handle women's health emergencies is instrumental in saving lives and minimizing physical impairments.

To address the needs of Medical Officers in the Provincial Health & Medical Services of Uttar Pradesh, the State Institute of Health & Family Welfare (SIHFW) has developed a comprehensive Continuing Medical Education (CME) program focused on Female's infertility problem. This program incorporates the latest advancements in the field and provides detailed guidance on essential management strategies for these conditions at the primary level. The aim is to facilitate early screening, detection, referrals, and treatment of female patients.

It is expected that Medical Officers in Uttar Pradesh, after completing this CME program, will be able to enhance their service delivery by effectively conducting screening, managing cases, making appropriate referrals, and providing treatment within their healthcare facilities. As a result, communities will benefit from improved access to healthcare services, increased women's patient satisfaction, and enhanced population health. This CME program not only enhances clinical and technical expertise but also strengthens the provision of healthcare services and bridges the gap between theory and practice in healthcare management.

With the development of this CME module on Female Infertility, Causes, Risk Factors, Treatment and Management for Medical Officers in Provincial Health and Medical Services in Uttar Pradesh, SIHFW will improve health services at PHC and CHC level. I extend my best wishes to the Director, Faculties and Research team at SIHFW and hope to see the publication of many more tailored CME modules in the future.

(Dr. Brijesh Rathor)


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MESSAGE

Dr. Shailesh Kumar Shrivastava

Director General Family Welfare,
Directorate of Family Welfare
Uttar Pradesh

Infertility is a common, yet often misunderstood, experience. Infertility is an important topic for family scientists because of its effects on families. its relevance to research in related areas, such as fertility trends and reproductive health and its implications for practitioners who work with individuals and couples experiencing infertility. In this module, we focus on common Female's infertility problem and treatment of infertility and highlight insights from recent research in this field.

This module on Continuing Medical Education (CME) on Female Infertility, Causes, Risk Factors, Treatment and Management for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh provides a coherent and research-based insight into the problem of female infertility, including its treatment. It has been designed and written for Medical Officers and healthcare professionals and takes government perspective in consideration, drawing upon and comparing ideas and developments from national and international healthcare practices.

I hope that after this CME, Medical Officers in Uttar Pradesh will be able to scale up the services delivery in provide optimal treatment in their health facilities, thus benefitting communities. In addition to improving clinical and technical area of expertise, this CME will lead to providing improved access to health services and enhancing female patient satisfaction and population health.

The director and team at State Institute of Health & Family Welfare, Uttar Pradesh and the team of experts of the field has done a commendable job by publishing this module on CME on Female Infertility, Causes, Risk Factors, Treatment and Management for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh. I hope the participants coming to attend their upcoming CME will take advantage of this initiative and make the most in their field with this handy module.

(Dr. Shailesh Kumar Shrivastava)


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MESSAGE

Dr. Narendra Agarwal
Director General (Training)
Medical Health and Family Welfare
Uttar Pradesh

It is very important to take complete care of the life and health of the woman suffering from the problem of female infertility. The reaching of an effected person to a centre which has facilities for management of women's health-related emergencies helps in saving lives and physical impairment.

This module on Continuing Medical Education (CME) on Female infertility problem for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh provides a coherent and research-based insight to Female Infertility, Causes, Risk Factors, Treatment and Management. It has been designed and written for Medical Officers and healthcare professionals and takes government perspective in consideration, drawing upon and comparing ideas and developments from national and international health care practices.

I hope that after this CME, Medical Officers in Uttar Pradesh will be able to scale up the services delivery in provide screening, management, referral and treatment in their health facilities, thus benefitting communities. In addition to improving clinical and technical area of expertise, this CME will lead to providing improved access to health services and enhancing patient satisfaction and female population health.

I would like to extend my congratulations to SIHFW and the subject matter experts involved in the development of this comprehensive module. I am optimistic that this CME module will shed light on the effective treatment and management of Female Infertility, Causes, Risk Factors.

(Dr. Narendra Agarwal)


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MESSAGE

Dr. Rajaganapathy. R
Director
State Institute of Health and Family Welfare
Uttar Pradesh

The primary objective of Continuing Medical Education (CME) is to ensure the perpetual learning and advancement of Medical Officers in order to deliver optimal medical care to their patients. The purpose of CME is to aid Medical Officers in augmenting their performance in terms of patient care and satisfaction.

Infertility is a medical condition that can cause psychological, physical, mental, spiritual, and medical harm to the patient. The unique characteristic of this medical condition is that it affects both the patient and the patient's partner as a couple. Although male infertility is an important part of any infertility discussion, this module will review the evaluation, management, and treatment of female infertility.

Within the healthcare domain, there has been a noteworthy endeavour to emphasize the significance of effectively treatment of women's infertility among Medical Officers in Provincial Health & Medical Services. It has been observed that a lack of systematic management has resulted in numerous fatalities. Hence, there is a requirement for a tailored CME program aimed at equipping Medical Officers in Uttar Pradesh with exposure to the latest advancement treatment in the field of infertility.

In order to accomplish this objective and enhance knowledge, the research and training faculty at State Institute of Health and Family Welfare (SIHFW), Uttar Pradesh, in collaboration with the help of Prof. Rekha Schan, her team, King George's Medical University (KGMU), LUCKNOW, have helped in formulation of this CME module. It is anticipated that this module will be widely disseminated, and feedback on its efficacy will be received in the upcoming months.

(Dr. Rajaganapathy. R)


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CHAPTER 1
ANATOMY OF FEMALE GENITAL TRACT

Author: Prof. Rekha Sachan

Introduction

- The female genital tract is divided into the external genitalia and the internal genitalia.
- The external genitalia consist of mons pubis, labia majora, labia minora, clitoris, vestibule, hymen, Bartholin's glands, external urethra meatus, and Skene's gland.
- The internal genital tract, including the female reproductive system, consists of the vagina, the uterus, the two fallopian tubes, and the two ovaries.

EXTERNAL GENITAL TRACT

The main function of the external genitalia is to protect the internal genital tract from infection, to act as sensory tissues during sexual intercourse. The vulva receives parasympathetic and sensory supply from two different innervation roots. The anterior part of the vulva nerve supply is by the ilioinguinal nerve (L1) and the genital branch of the genitofemoral nerve (L1,2). The posterior part of the vulva nerve supply is by the pudendal nerve (S2,3,4) and the posterior cutaneous nerve of the thigh. For the clitoris and vestibule, the parasympathetic innervation comes from the cavernous nerves a branch from the uterovaginal plexus.

MONS PUBIS

The mons pubis is a bed of fat covering the symphysis pubis underlying the skin. With the onset of puberty, pubic hair growth is initiated on both the mons pubis and the labia majora. This occurs at the around the second stage of the Tanner's staging of breast development with accompanying hair growth under the armpits.

LABIA MAJORA

The labia majora consist of two fleshy folds of skin, which extend from the mons pubis to the posterior commissure.

The outer skin of this very sensitive area is covered by hair, the inner surface is smooth, hairless and contain sweat and sebaceous glands that produce lubricant secretion

The Skene's gland is a para urethral gland which opens adjacent to the distal urethra. At times, the Skene's duct may be obstructed because the gland is infected causing skene's duct cyst. If the duct is infected it causes recurrent urinary tract infection and if the cyst is larger than 1 cm it causes dyspareunia.

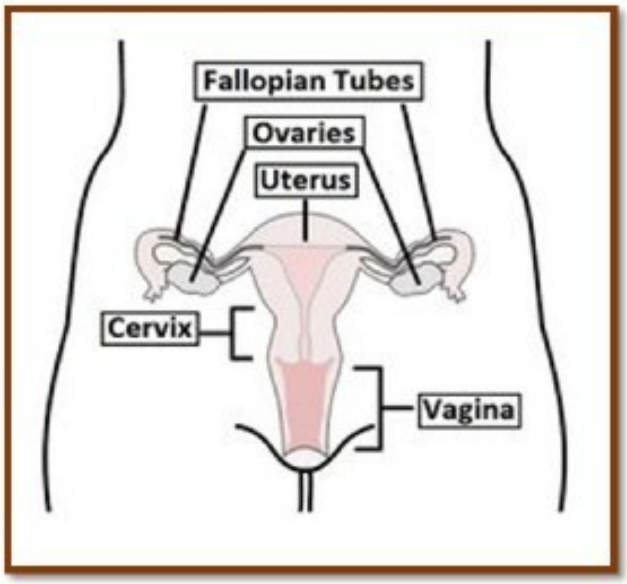

Figure 1: *Internal Female Reproductive Anatomy*

INTERNAL REPRODUCTVE SYSTEM

VAGINA

The vagina is a fibromuscular tube which extends from the vulva to the uterus in an oblique direction forming an angle of about 60° with the horizontal line, directed upwards and backwards. The size of the vagina ranges from 6-8 cm in length. Due to its obliquity, its posterior wall is larger than the anterior wall. It is more like the H shape than a round tunnel. Internally within the pelvic floor, it is located anterior to the rectum and posterior to the urethra and bladder.

Between the connection of the upper end of the vagina and the cervix, it forms two fornixes, the anterior fornix, and the posterior fornix. The vagina acts as a birth canal, the outlet for the menstrual blood flow and a cavity for sexual intercourse.

The cervix: The lowest part of the uterus connecting it to the vagina.

UTERUS

The uterus is a pear-shaped, hollow central landmark organ of the pelvic anatomy and internal genitalia. Its lower end is located at the level of the ischial spine, and supported by pelvic floor muscles and cervical ligaments. It is highly muscular and relatively mobile. The cavity lining is covered with endometrium which can be affected by a disease called endometriosis.

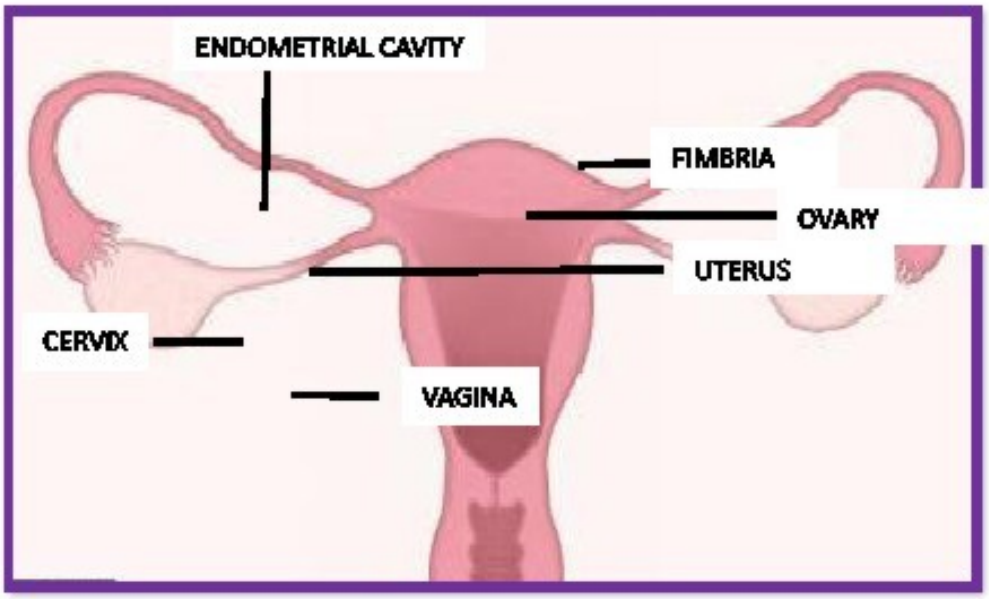

Figure 2: Female genital tract

During pregnancy, it reaches the epigastric area due to the fetus growth. During pregnancy the uterus is divided into:

- **The body:** The largest part of the uterus in which the unborn baby is growing.
- **The fundus** The tip of the uterus which extends all the way to the anterior stomach wall. In post-partum women the fundus can be palpated just below the navel. Physiologically, the fundal height should depress around one finger-width a day during puerperium until it can no longer be palpated.
- **Position of uterus** The uterus is located anatomically in anteversion & anteflexion position anterior to the rectum and posterior and superior to the bladder.

a) ***Anteversion*** - The angle between the axis of the cervix and the axis of the vagina making 90 angle, rotated forward.

b) ***Anteflexion*** The angle between the body of the uterus and the axis of the cervix, the body is bent forward.

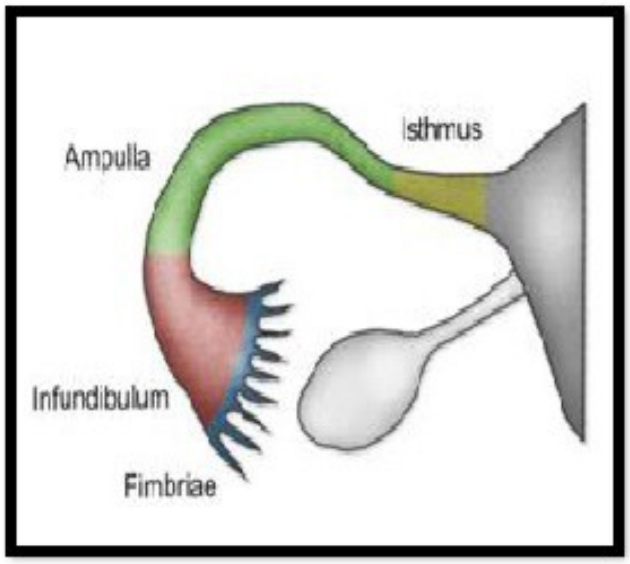

Figure 3: *Fallopian Tube*

FALLOPIAN TUBES

The Fallopian tubes are muscular J shape tubes presented on both sides of the uterus. They extend to penetrate into the abdominal cavity with a length of ~10 cm. Their main function is to transmit the ovum to the uterus. Fallopian tubes are divided into four sections:

- **Fimbriae:** Finger-like projections, entry point of the ovum into the fallopian tube when it is ejected from the ovary.
- **Infundibulum:** A funnel shaped opening to the tube, the fimbriae attaches to it.
- **Ampulla:** The widest section of the tube, this is where the fertilisation of the ovum with the sperm happens.
- **Isthmus:** The narrowest part of the fallopian tube which connects the tube with the uterine wall.

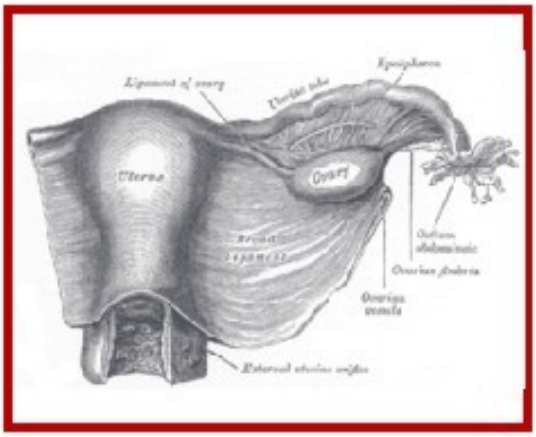

Figure 4: *Ovary*

The ovaries are two almond-shaped organs which main functions are the production of ova and sex hormones. They attach to the uterus by ovarian ligaments, and to the broad ligament via the mesovarium, which is a peritoneal ligament. For fertility purpose this is very important organ as it contains follicle. Growth of follicles and release of ovum is very important for pregnancy.

OVULATION

Ovulation refers to the release of an egg from an ovary. It usually happens around 12–16 days before the next period. Some women may feel pain in their lower abdomen at this time, and women's discharge may change in color and consistency. Tracking it can be an important part of fertility awareness. During ovulation, part of the ovary called the ovarian follicle discharges an egg. The egg is also known as an ovum, oocyte, or female gamete. It is only released on reaching maturity. The egg then travels down the fallopian tube, where it may encounter a sperm and become fertilized. Hypothalamus controls ovulation and the release of hormones during the menstrual cycle. The hypothalamus sends signals instructing the anterior lobe and pituitary gland to secrete luteinizing hormone and follicle-stimulating hormone (FSH). Pregnancy can occur anywhere from 5 days before ovulation to 1 day after. This is because sperm can live in the vagina for up to 5 days and an egg can live for about 24 hours after it is released.

Endometrium The physiological functions of the uterine endometrium (uterine lining) are preparation for implantation, maintenance of pregnancy, if implantation occurs, and menstruation in the absence of pregnancy. The endometrium plays a pivotal role in reproduction and continuation of species.

Menstruation is a steroid-regulated event, and there are alternatives for a progesterone-primed endometrium, i.e., pregnancy or menstruation. Progesterone withdrawal is the trigger for menstruation.
The menstruating endometrium is a physiological example of an injured or "wounded" surface that is required to rapidly repair each month.

The **endometrium** consists of two layers, the stratum basale and the stratum functional. The stratum functional cells proliferate under the influence of estrogen and desquamate at the time of menses.

The thickness of the endometrium varies throughout the menstrual cycle from 1 to 2 mm at the time of menses to 4 mm in the early proliferative (follicular) phase, to about 12 mm at ovulation, and maintaining 12 mm during an appropriate secretory (luteal) phase. Hyperplasia is defined as the abnormal proliferation of endometrial cells usually caused by estrogen unopposed by the action of progesterone. **The endometrium is a highly dynamic tissue and normally undergoes cyclic rounds starting with proliferation, followed by differentiation, degradation, and round up by regeneration.**

This phase prepares the endometrium for potential embryo implantation. After ovulation, which occurs around the midpoint of the menstrual cycle, progesterone becomes the dominant hormone. The endometrium enters the secretory phase, during which the glands further develop and secrete various substances that nourish the embryo. If fertilization and implantation occur, the embryo embeds itself into the richly prepared endometrial lining. Successful embryo implantation relies on the endometrium being receptive to the embryo's attachment. If implantation is successful, the endometrium continues to support the developing embryo by providing nutrients and a stable environment.

FERTILIZATION AND IMPLANTATION

Fertilization and implantation are the most critical events in the reproduction process. In this process, both egg and sperm are fused together to form a zygote. Later it gets implanted into the uterus and the development of an organism. **Fertilization in humans refers to the fusion of male and female gametes that facilitates the development of a new organism."**

Fertilization is the natural life process, which is carried out by the fusion of both male and female gametes, which results in the formation of a zygote. In humans, the process of fertilization takes place in the Fallopian tube.

During this process, semen comprising thousands of sperms are inseminated into the female vagina during coitus. The sperms move towards the uterus and reach the opening of the Fallopian tube. only a few sperms will succeed in reaching the opening of the Fallopian tube.

The secondary oocyte releases from the matured Graffian follicle of the ovary and enters into the Fallopian tube, where it is fertilized within 24 hours, after which it is released from the ovary.

Though surrounded by several sperms, the oocyte is fertilized by a single sperm. During meiosis-II, the sperm enters the secondary oocyte and completes the meiosis. After this, the secondary oocyte is known as the egg.

Both sperm and egg can show their vitality only to a limited period. Sperm is alive for 48-72 hours in a female reproductive system, whereas the egg can be fertilized for 24 hours before it is released.

STEPS OF FERTILIZATION IN HUMANS:

The fertilization process in humans takes place in several stages involving both the chemical and physical events. The different stages of fertilization in humans are mentioned below:

Acrosomal Reaction

The sperms incapacitation undergoes acrosomal reactions and release certain chemicals known as sperm lysins present in the acrosome.

Due to the acrosomal reactions, the plasma membrane of the secondary oocyte and the sperm are fused together so that the contents of the sperms can enter. When the plasma membrane of the sperm binds with that of the secondary oocyte, the plasma membrane of the oocyte depolarizes. This prevents polyspermy.

Calcium ions play a significant role in the acrosomal reaction. The main factors essential for acrosomal reactions are optimum pH, temperature and calcium and magnesium concentration.

Cortical Reaction

Soon after the fusion of the plasma membranes, the oocyte shows cortical reactions. Cortical granules found under the plasma membrane of the oocyte, which fuses with the plasma membrane and releases cortical enzymes between the zona pellucida and plasma membrane. The zona pellucida is hardened by the cortical enzymes that prevent polyspermy.

Sperm Entry

A projection known as the cone of reception is formed by the secondary oocyte at the point of sperm contact. This cone of reception receives the sperm.

Karyogamy

After the entry of the sperm, the suspended second meiotic division is completed by the secondary oocyte. This gives rise to a haploid ovum and a second polar body.

The head of the sperm containing the nucleus detaches from the entire sperm and is known as male pronucleus. The tail and the second polar body degenerates. The nucleus of the ovum is known as female pronuclei.

The male and female pronuclei fuse and their nuclear membranes degenerate. The fusion of the chromosomes of male and female gametes is called karyogamy. The ovum is now fertilized and is known as a zygote.

Activation of Eggs

The entry of sperm triggers the metabolism in the zygote. Consequently, protein synthesis and cellular respiration increase.

Implantation

Once fertilization happens, the cell starts to divide and multiply within 24 hours in the fallopian tube. This detached multi-celled structure is called a zygote. Later, after 3-4 days it travels to the uterus and now it as an embryo.

The embryo develops and undergoes various stages and gets attached to the endometrial layer of the uterus. This process of attachment is known as implantation.

Chapter 2

CLINICAL RELEVANCE OF REPRODUCTIVE TRACT ABNORMALLY IN FEMALE INFERTILITY


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CHAPTER 2

CLINICAL RELEVANCE OF REPRODUCTIVE TRACT ABNORMALLY IN FEMALE INFERTILITY

Author: Prof. Rekha Sachan

UTERINE ANOMALIES RESPONSIBLE FOR INFERTILITY

Uterine shape and health of the uterus, and even the lining of the uterus during a menstrual cycle can have a negative impact on fertility and even increasing the risk of a miscarriages.

Few studies suggest that up to 1 in 13 women have a uterine abnormality that affects fertility and health during pregnancy.

Uterine abnormalities affecting fertility listed below-

UTERINE POLYPS

A uterine polyp is an overgrowth of tissue of the uterine lining, which is known as the endometrium. These polyps can reduce the chances of successful pregnancy or increase the risk of miscarriage.

UTERINE FIBROID

Also referred to as myoma or leiomyoma, uterine fibroids are non-cancerous benign tumours of the uterine muscle. Many times these fibroids are small, and they may or may not affect fertility depending on their location in the uterus.

INTRAUTERINE ADHESION S

When trauma or infection affect the uterine lining, this can lead to scar tissue within the uterine cavity. This scar tissue can affect a woman's menstrual cycle. In some cases, infertility or miscarriage become more likely.

CONGENITAL UTERINE MALFORMATIONS

Females may have a malformed or poorly shaped uterus as a result of a genetic issue, this include-

T-shaped uterus,

Unicornuate and bicornuate uterus,

uterine septum.

About 1–2% of women are affected by POI, a phenotypically and etiologically heterogeneous condition characterized by primary or secondary amenorrhea, infertility, decreased estrogen production, elevated gonadotropins (follicle stimulating hormone and luteinizing hormone), and increased risk for osteoporosis and cardiovascular disease.

Functional disruption at the level of the hypothalamus or pituitary glands leads to hypogonadotropic hypogonadism, small ovaries, amenorrhea, and infertility.

INFERTILITY CAN ALSO RESULT FROM FERTILIZATION FAILURE -

Either due to oocyte maturation arrest and the inability to produce a haploid zygote

Due to a defective zona pellucida.

X CHROMOSOME ABNORMALITIES -

This abnormality can lead to recurrent fetal losses in 5–6% of women,

Deletions, Duplications, Inversions, Complex rearrangements, X-autosome translocations, and Single-gene sequence variants, carried by X chromosomes. In females, X chromosome abnormalities may result in early embryonic or fetal defects and death, particularly in male conceptuses.

Approximately 30% of X-linked genes are associated with a specific phenotype in humans, while pathogenic variants in a significant number of X-linked genes, such as *BCOR, EBP, FLNA, HCCS, IKBKG, MECP2, OFD1, OTC* and *REP1*, are presumed to be male-lethal.

Germline mosaicism This is another explanation of infertility and recurrent miscarriages of affected fetuses with X-linked or autosomal dominant lethal alterations. Maternal germline mosaicism for pathogenic variants has been reported for male-lethal genes, including *IKBKG*, *FLNA*, and *MECP2*, and is likely an under-recognized condition. Female fetuses can also be affected by male-lethal X-linked disorders in cases of skewed X chromosome inactivation.

Defects In Folliculogenesis It involves proliferation and differentiation of granulosa cells and maturation of the oocyte. This process includes a series of signaling events between the cells within the follicle. Although the granulosa and theca cells have long been implicated in ovarian function, animal studies have revealed a synergistic effect of GDF9 and BMP15 on granulosa cell differentiation, folliculogenesis, and ovulation.

Hypogonadotropic hypogonadism is a rare disorder characterized by the deficiency of gonadotropin-releasing hormone (GnRH) due to its impaired production, secretion, or function.

It often manifests as incomplete or absent puberty and infertility. GnRH acts via the GnRH receptor, which affects both synthesis and release of LH and FSH, which in turn, control gonadal maturation, which then feeds back via Inhibin and Activin to complete the hypothalamic–pituitary–gonadal axis.

A considerable proportion of patients affected by hypogonadotropic hypogonadism have genetic changes leading to an isolated or a syndromic condition with X-linked, autosomal recessive, and autosomal dominant inheritance. Hypogonadotropic hypogonadism is a genetically heterogeneous condition with both sporadic and familial cases and more than 25 causative genes identified to date. The most commonly affected genes are *ANOS1 (KAL1), SOX10, IL1*.


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Chapter 3

INFERTILITY WORKUP


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CHAPTER 3

INFERTILITY- WORKUP

Author: Prof. PushpaLata Sankhwar

INTRODUCTION

Infertility in a reproductive-age couple is defined as the inability to conceive after unprotected intercourse for ≥1 year.

When a female is greater than 35 years of age, an evaluation is recommended after 6 months of infertility or without successful pregnancy.
Earlier evaluation at any age is warranted with preexisting symptoms or medical conditions.

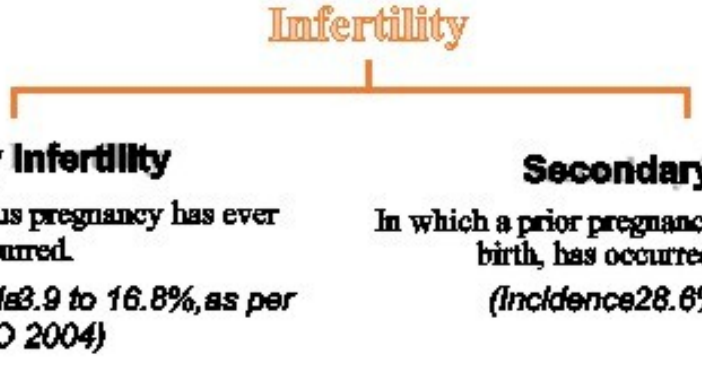
Fecundability is defined as the probability of pregnancy per cycle.

Fecundity is the probability of achieving a live birth per cycle.

Infertility can be classified into two groups-

a) Primary Infertility

b) Secondary Infertility



reproductive-age couples experience infertility. This prevalence is consistent in all developed countries, and there is evidence that it is historically stable. Infertility affects 8.8% of U.S. women aged 15 to 49 years and approximately 12.7% of reproductive-age women seek infertility treatment each year. 1, 2.

In India, the incidence of primary infertility varies from 3.9 to 16.8% and that of secondary infertility is 28.6%.

S.No.	Type	Prevalence
1.	Female factor infertility	40%-55%
2.	Male factor infertility	25%-40%
3.	Both factors infertility	10%-30%
4.	Unexplained infertility	25%

Source-Talley NJ et al: Essentials of internal medicine, ed 4, Chatswood, NSW, 2021 Elsevier Australia.

Table 1: *Prevalence of Types of Infertility*

CAUSES OF INFERTILITY-

The major causes of infertility include ovulatory dysfunction (20–40%), tubal and peritoneal pathology (30–40%), and male factors (30–40%); and the remainder is largely unexplained. Many couples suffer from multiple aetiologies.

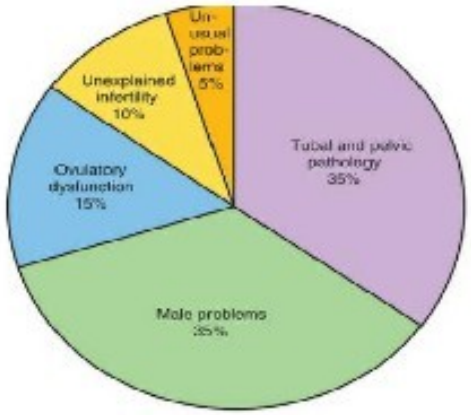


Figure 3.1: *Diagram showing the major etiological factors causing infertility*

PRELIMINARY EVALUATION OF THE INFERTILE COUPLE

Evaluation should be offered to all couples who have failed to conceive after a year or more of regular unprotected intercourse.

Earlier evaluation is justified in the presence of obvious risk factors, such as irregular or infrequent menses, history of pelvic infection, surgery or endometriosis, or having a male partner with known or suspected poor semen quality, and also is warranted after 6 months of unsuccessful effort for women over the age of 35 years. Any evaluation of infertility must begin with a careful history and physical examination.

HISTORY

- Duration of infertility and any prior treatment taken
- Coital frequency
- H/o sexual dysfunction (premature ejaculation)
- Menstrual history Including abnormal, irregular heavy menstrual bleeding-polyp, fibroid, decreased menstrual flow-Ashermann's syndrome, dysmenorrhea-endometriosis
- Previous Obstetric history
- History of contraceptive usage
- H/o of PPH in last pregnancy
- H/o ectopic pregnancy and treatment taken
- Medical and surgical history (H/o PID or STI)
- H/o medications and allergy
- H/o addiction (tobacco, alcohol)
- Family history (early menopause, birth defects)
- Endocrine dysfunction (thyroid, galactorrhea, hirsutism)
- Occupational history (glass industries, chimney workers)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Age,
- Weight and BMI
- Absence of secondary sex characters
- Thyroid enlargement
- Breast examination for any discharge, lump, surgery etc.

- Signs of androgen excess (virilization, hirsutism, acne)
- Abdominal tenderness, mass
- Abnormal pelvic examination: Enlarged uterus, adnexal masses, pelvic/abdominal tenderness, discharge per vaginum.

INVESTIGATIONS-

On 1st visit, after proper counseling of the couple, 1st line investigations should be advised. These include-

- CBC, Peripheral Blood Smear if sign of infection present.
- Urine analysis.
- Viral Markers (HIV, HBsAg, HCV) of both partners,
- Screening for Diabetes
- Complete transvaginal pelvic ultrasound to evaluate uterus, endometrial thickness, bilateral adnexa, Ovarian volume, AFC, POD
- LH, FSH, AMH, TSH, Prolactin on Day 2 of menses. (TSH and AMH can be done any day)
- Endometrial aspiration on day 21-22 of menses and its histopathological assessment to rule out any chronic endometritis or any other endometrial pathology.
- Husband Semen analysis after 3 days of abstinence.

On subsequent visit, the reports are analyzed and 2nd line investigations are done which include

- Tubal patency test by HSG or Sonosalpingography.
- If she is elderly or PCOS, Endometriosis or has secondary infertility, then specific investigations are done like Testosterone, Fasting insulin level, DHEA/DHEAS, APLA profile, and immunological assessment are advised.
- If the tubal patency test is OK and the fallopian tubes are patent then we opt for IUI procedures in natural or induced cycles.

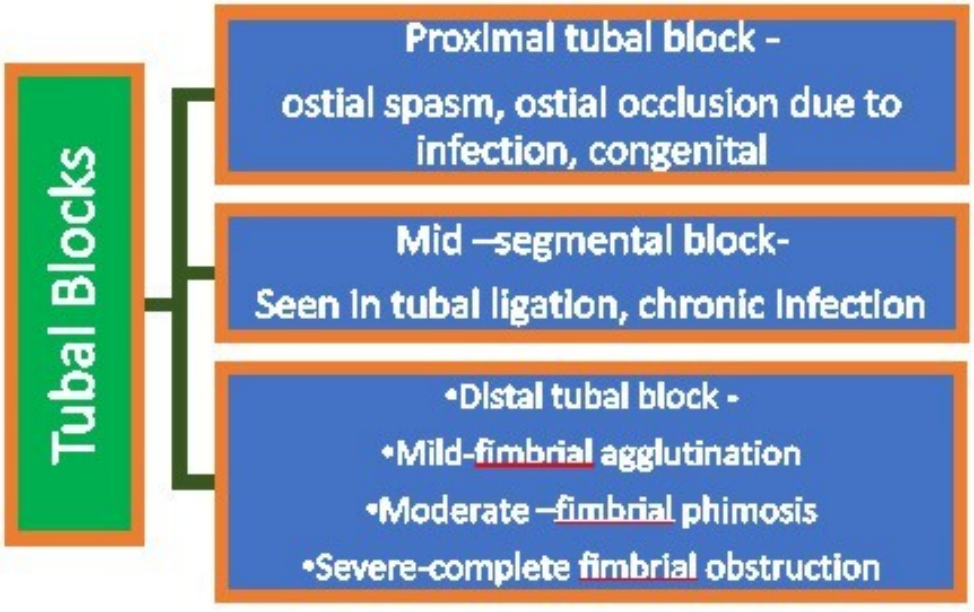
- If pregnancy doesn't occur in 3 to 6 cycles or the tubes are blocked bilaterally, then we opt for diagnostic laparoscopy and hysteroscopy which is considered the Gold standard test for infertility assessment.
- By these endoscopic procedures we assess and also treat the treatable causes of infertility then and there like adhesiolysis, cystectomy, tubal cannulation, polyp removal, guided biopsies and ovarian drilling procedures.

TUBAL FACTOR: TUBAL OCCLUSION AND ADNEXAL ADHESIONS

Tubal and peritoneal pathology is among the most common causes of infertility and tubal pathology accounts for 25–35% of female infertility.

A history of pelvic inflammatory disease (PID), septic abortion, ruptured appendix, tubal surgery, or ectopic pregnancy strongly suggests the possibility of tubal damage.

The mechanism responsible for tubal factor infertility obviously involves anatomic abnormalities that prevent the union of sperm and ovum.



METHODS FOR EVALUATION OF TUBAL PATENCY

1) HSG (Hysterosalpingography)

- Performed after menses and before ovulation (day 7-day 9 of LMP)
- Pretreatment with NSAIDs and inj Buscopan 30-60 min before the procedure

- Contrast used is water-soluble iodine-based urographin. Oil-based is avoided due to the risk of embolization.
- **Absolute contraindications** of HSG are Acute PID, acute TB, pregnancy, and allergy to contrast
- During the Procedure-3 **X ray films** are taken:

  1st film-scout film

  2nd film-documents uterine contour and tubal patency

  3rd film-post evaluation film to detect contrast loculation

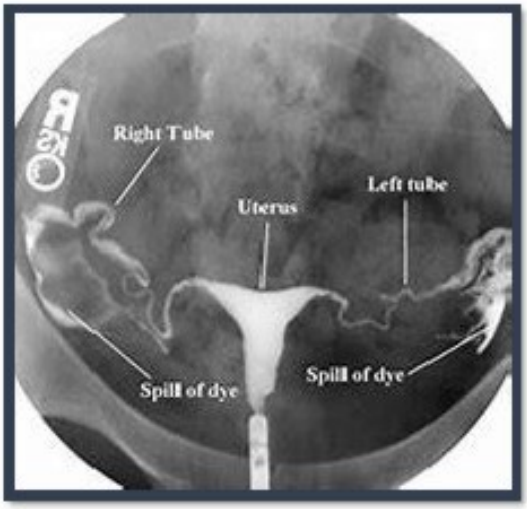


Figure 3.2- *Normal HSG*

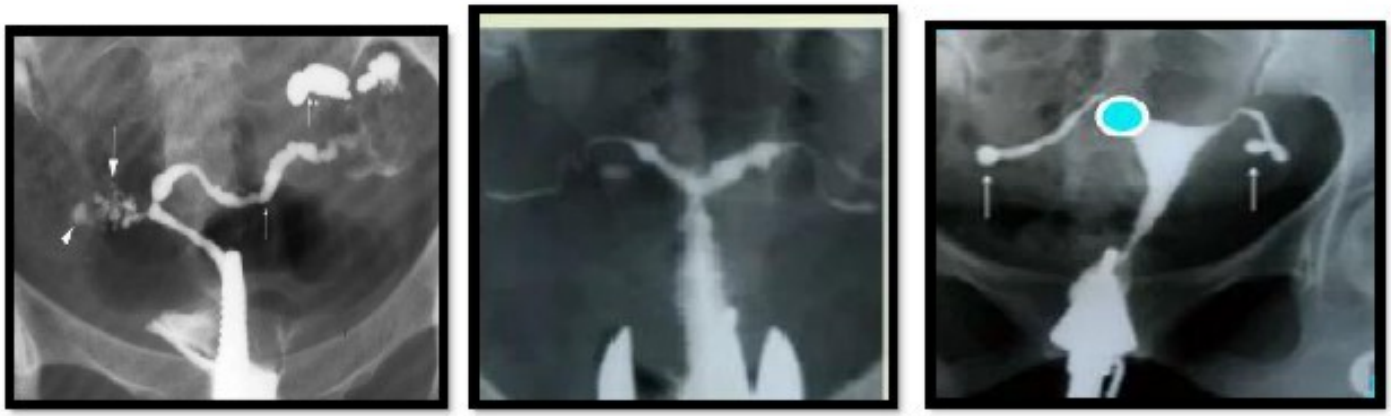


Figure 3.3 - *HSG in Tuberculosis- (i) Tobacco pouching, (ii) Lead pipe appearance, (iii) Golf club appearance*

2) Laparoscopy

- Gold standard for diagnosing tubal and peritoneal diseases.
- Performed under GA
- Direct visualization of uterus, anterior and posterior surface, cul de sac , ovaries, and fallopian tubes.
- **Chromopertubation**– Injection of methylene blue dye through a cannula attached to cervix or intrauterine permits evalnation of tubal patency
- Indigo carmine is preferred over methylene blue

Advantages –Direct visualization of pelvic organs

Concurrent treatment of peritubular and periovarian adhesion and subserosal uterine fibroid

Disadvantages are–

- Invasive procedure
- Site of block cannot be identified
- Anesthesia is required
- Expertise required
- Risk of bladder bowel injury is high

UTERINE FACTORS

Uterine pathology is diagnosed in more than 50% of infertile patients.

The Causes include- Endometrial polyps, Submucous myoma, Intrauterine synechiae, and Congenital uterine anomalies (uterine didelphus, septate uterus, bicornuate uterus).

Diagnostic imaging for uterine pathology –

- Hysterosalpingography
- Hysteroscopy
- TVS and saline sonohysterography

1) Hysterosalpingography

- Defines the size and shape of the uterine cavity and most uterine anomalies like (unicornuate uterus, septate uterus, bicornuate uterus, uterine diadelphous)
- Normal uterine cavity is symmetrical, triangular in shape, widest at the level of cornual orifices and smooth in its contour.
- Unicornuate uterus –is typically tubular deviates to the left and right and has one fallopian tube.

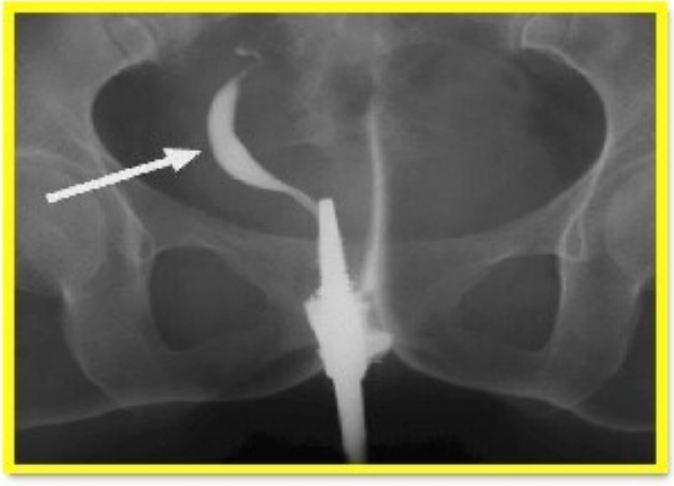


Figure 3.4 - *Unicornuate Uterus*

- Both septate and bicornuate uterus have common lower segment that divides into two horns to yield a Y shaped configuration with varying distance between the upper arms.

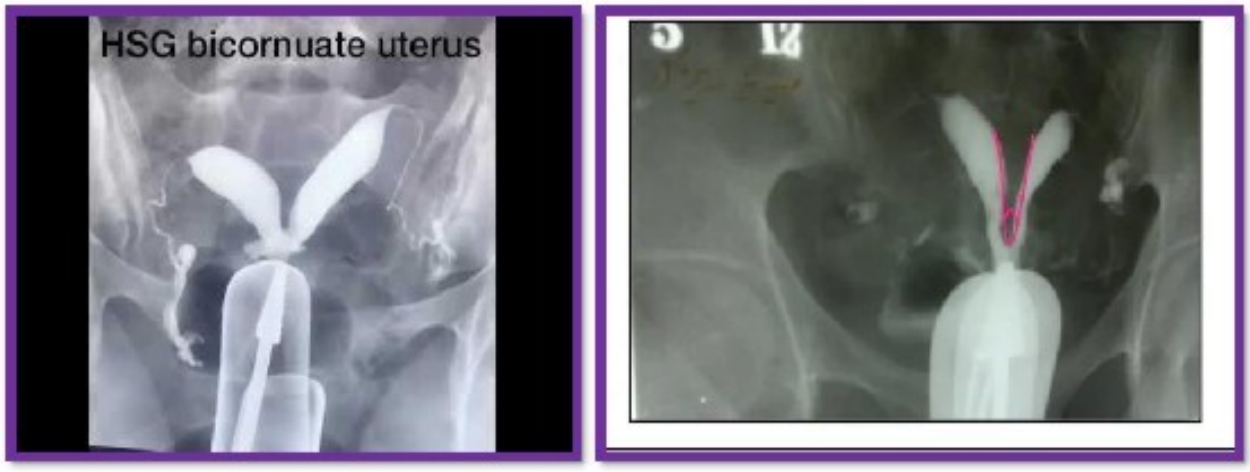


Figure 3.5-*Bicornuate Uterus and Septate Uterus*

- In uterus didelphus or complete septate uterus the two hemi-uterine must be imaged via their separate cervical openings found on opposite sides of two hemi-vaginas

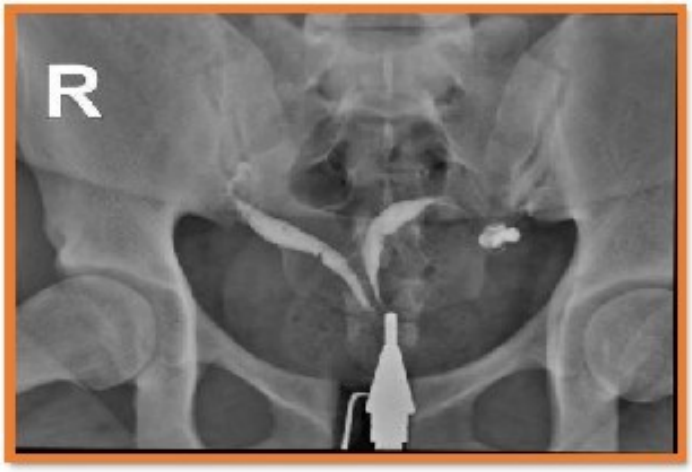


Figure 3.6- *Uterus Didelphus*

3) TVS and saline sonohysterography

Both 2D and 3D TVS are more sensitive than HSG

3D USG –successfully illustrates the endometrial cavity and map the location of fibroid.

Sonohysterography

- It involves the trans-cervical instillation of saline (3-5ml) via balloon catheter during the TVS to distend the uterine cavity and delineate the endometrium.
- SIS is performed during follicular phase of cycle and no anaesthesia is required.
- Endometrial polyp appears as hyperechogenic pedunculated lesions.
- Submucous fibroids have mixed echogenicity.
- Adhesion contain densely echogenic and cystic areas.

Advantages-

1. Ability to evaluate the adnexa, myometrium for fibroids And adenomyosis.
2. No anesthesia required
3. Office procedure

4. When combined with 3D USG it is good in assessing uterine contour and congenital anomalies such as septate uterus.

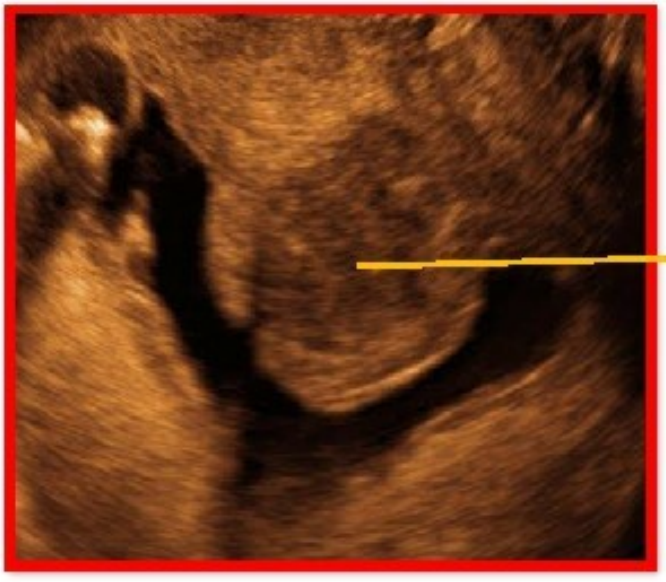


Figure 3.7- *Submucous Fibroid*

UNEXPLAINED INFERTILITY

Unexplained infertility is a diagnosis of exclusion, after systematic evaluation fails to identify a cause. The incidence of unexplained infertility ranges from 10% to as high as 30% among infertile populations.

Causes-

1) **LUFS** – Luteinized unruptured follicle syndrome

In this the graffian follicle fails to rupture and release it's oocyte, this problem seen in 25% female with unexplained infertility

Management-IVF is the only treatment

2) **Immunological**- Antisperm antibodies in cervical mucus

3) **Infection** – infection with chlamydia trachomatis, ureaplasma urealyticum, mycoplasma

Treatment –doxycycline 100 mg BD x 28 days

4) **Undiagnosed pelvic pathology**- adhesions, endometriosis

Management of unexplained infertility

- Timely intercourse is advised

- Laparoscopy can be considered to see for any pelvic pathology like adhesion, endometriosis.
- Super ovulation (controlled ovarian hyper stimulation) with IUI –baseline scan is performed on day 2 of menses to assess AFC and presence of ovarian cysts plus baseline estrogen and progesterone levels are done .
- Clomiphene 100mg/day x 5 days or gonadotropins 150-300 IU daily are used for ovulation induction. Trigger is given when at least 2 follicles of diameter ≥17-18mm and ET≥ 8mm.
- Antisperm antibodies in cervical mucus
  Test –post coital test(Sims huhner test).
  Done on day 13 of cycle (whenever LH surge is detected) or dominant follicle 18mm.
  Done after 2-12 hrs of act of intercourse and cervical mucus assessed under microscopy for cellularity, viscosity, mucus clarity, sperm motility

  ↓

  If all the sperms are degenerated, agglutinated, nonmotile or <10 motile sperms –suggestive of immunological infertility.

With proper evaluation and treatment, the majority of couples evaluated for infertility will achieve pregnancy. For those who fail treatments, ART with donor eggs and/or a gestational surrogate and adoption are realistic options.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Chapter 4

ASSESSMENT OF ETIOLOGICAL FACTORS OF INFERTILITY


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CHAPTER 4

ASSESSMENT OF ETIOLOGICAL FACTORS OF INFERTILITY

Author: Prof. PushpLata Sankhwar

FEMALE FACTORS CAUSING INFERTILITY:

various factors responsible for infertility are-

- ✓ Decrease ovarian reserve
- ✓ Ovulatory factors
- ✓ Tubal factors
- ✓ Uterine factors
- ✓ Others

OVULATORY FACTORS

Overall, disorders of ovulation account for approximately 30-40 %.

problems identified in infertile couples are ovulatory dysfunction it can be severe enough to prevent conception (**anovulation**), or only a contributing factor is **oligo-ovulation**. Menstrual history may be suggestive if oligomenorrhea, amenorrhea, or polymenorrhea are present.

Women with absent or infrequent ovulation should be tested- serum FSH, prolactin, and S.TSH testing should be performed.

Methods to document ovulation

1) **Basal body temperature-** Daily recording of oral or rectal temperature before the patient arises, eats or drinks
   Secretion of progesterone following ovulation- causes temperature increase of 0.5-1 degree from baseline temperature. Ovulation is assumed after 3 consecutive days of raised temperature

2) **Cervical mucus** –During fertile window cervical mucus is slippery and clear. The volume of cervical mucus peaks 2-3 days prior to ovulation

3) **Luteining hormone monitoring** – 2hrs following the peak of S.LH surge urinary LH can be detected .

ELISA kits are used having threshold of 35-50 milli IU/ml.

4) **Mid luteal serum progesterone** –Serum progesterone measurement should coincide with peak progesterone secretion in the midluteal phase (typically on days 21 to 23 of an ideal 28-day cycle or 7 days following the LH surge. A level of >3ng/ml(10nmol/l) confirms ovulation.

5) **Ultrasound monitoring**– Follicles reach a preovulatory diameter of 17-19mm in spontaneous cycles or 19 -25mm for clomiphene induced cycles.

Ovarian reserve tests are needed to predict fecundity and to gain prognostic information regarding success of stimulation.

Indications of testing ovarian reserve are

- Age>35 years
- Unexplained infertility
- Family h/o early menopause
- Previous ovarian surgery/chemo/radiotherapy, Smokers
- H/o poor response to gonadotropic therapy.

TESTS FOR OVARIAN RESERVE

1) Serum FSH and S.estradiol levels

- Done on Day 2-Day 4 of cycle
- S.FSH≥10IU/l is highly specific for poor response to stimulation (Senstivity-80 to100%, specifity-10to 30%)
- S. Estradiol levels alone are of no clinical significance
- If S.FSH is normal and S. estradiol levels (>60-80pg/ml) is a poor response predictor
- Abnormal S.FSH and S. Estradiol levels i.e if both is raised, it is suggestive of very poor response to stimulation.

2) Antral follicular counts (AFC)

- The antral follicles measuring 2-10 mm in both ovaries provides an indirect measure of ovarian reserve.
- Transvaginal ultrasonography is done on day 2-day-day 4 of menses

- AFC threshold value of <4 follicles – indicates high specificity for predicting poor response to ovarian stimulation and failure to conceive. (specificity-100%,sensitivity-9 to 73%)

3) Antimullerian hormone –

- Released from granulosa cells from preantral and small antral follicles
- Measured at any time in the menstrual cycle
- S.AMH values show direct relation to ovarian reserve (best test)
- Levels of AMH are gonadotropin independent and exhibit little variation within and between cycles.
- Decrease after use of OC pills and GnRH agonists.
- 0.2 to 0.7 ng/ml- poor response predictor (sensitivity 40 to 90%, specificity- 78 to 92%, NPV-100%)

Age (yrs)	Normal AMH value(ng/ml)
20-25	4.23
26-30	3.48
31-35	2.43
36-40	1.28
41-45	0.52

Sources : *J Hum Reprod Sci. 2021 Oct-Dec; 14(4): 372–379. Published online 2021 Dec 31. doi: 10.4103/jhrs.jhrs_65_21*

4) Ovarian volume

- Ovarian volume(ml)=length x width x depth x 0.52
- Normal ovarian volume -3 to 10 cc

- Volume <3 ml suggestive of poor response to ovarian stimulation (specificity 80-90%, sensitivity 11-80%)

5) **Others**

- Exogenous FSH stimulated estradiol/inhibin-B/AMH concentration/ Clomiphene challenge test
- Not used clinically

Chapter 5

TUBAL FACTORS IN INFERTILITY


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CHAPTER 5

TUBAL FACTORS IN INFERTILITY

Author: Dr. Vandana Solanki

INTRODUCTION

Tubal factor accounts for 25% to 35% of infertility. Noninfectious causes for tubal factor include tubal endometriosis, salpingitis isthmica nodosa, tubal polyps, tubal spasm, and intratubal mucous debris. The incidence of tubal infertility has been reported to be 8%, 19.5%, and 40% after one, two, and three episodes of PID, respectively. Live birth rates are negatively affected by the severity of a single episode of PID. C. trachomatis and Neisseria gonorrhoeae are common pathogens associated with PID and infertility. M. hominis and U. urealyticum have been implicated in PID but their contribution to infertility is less clear. Many patients with documented tubal damage have no history of PID and are presumed to have had subclinical chlamydial infections[2]. Female genital tuberculosis is an important cause of tubal blockage in India[3]. It may involve the proximal, distal, or the entire tube, and may be transient (obstruction) or permanent (occlusion).

PROXIMAL TUBAL OCCLUSION

Proximal tubal occlusion accounts for 10 to 25 % of tubal factor.

Causes- salpingitis ,SIN (salpingitis isthmica nodosa), intratubal endometriosis and amorphous plug.

DISTAL TUBAL OCCLUSION

Distal Tubal disease represents approximately 85% of all cases of tubal infertility. In addition to IVF, surgical interventions, such as salpingostomy and fimbrioplasty, are available for the treatment of distal tubal occlusion. Fimbrioplasty gives 60 % pregnancy rate compared to salpingostomy. Incidence of ectopic pregnancy also increases with the severity of tubal disease .

Following salpingostomy by laparoscopy, an intrauterine pregnancy rate of 44% has been reported in patients demonstrating normal mucosa.

ADHESIONS

Patients with adnexal adhesions that are extensive, thick, or vascular are less likely to benefit from surgery.

The limited evidence suggests that laparoscopic lysis of adhesions is first line of treatment for mild disease while patients with severe disease should instead undergo IVF.

TESTS FOR TUBAL PATENCY

Tubal patency tests are usually a part of initial testing for infertility. If there is no conception with 6 months of ovulation induction, then tubal patency testing is indicated. These tests are indicated for all cases of secondary infertility.

1. **Rubin`s Test (Tubal Insufflation Test)-** Now obsolete. Done in proliferative phase (between day 5 -10 of menstrual cycle). A Rubin`s cannula or Leech Wilkinson cannula (Fig. 1) is inserted in the cervix. Air or CO_2 is pushed under pressure and auscultation with stethoscope is performed in both iliac fossa. When air or CO_2 is pushed, it goes through uterus and fallopian tubes to the peritoneal cavity through fimbrial end and hissing sound of air can be heard if tubes are patent.
   Patient may complain of shoulder pain due to irritation of diaphragm by the pneumoperitonium.
   Contraindications- Pelvic infection.
   Disadvantages- It gives false result in 30 % cases due to tubal spasm (especially cornual).
   It is unable to locate the exact site of tubal blockage.

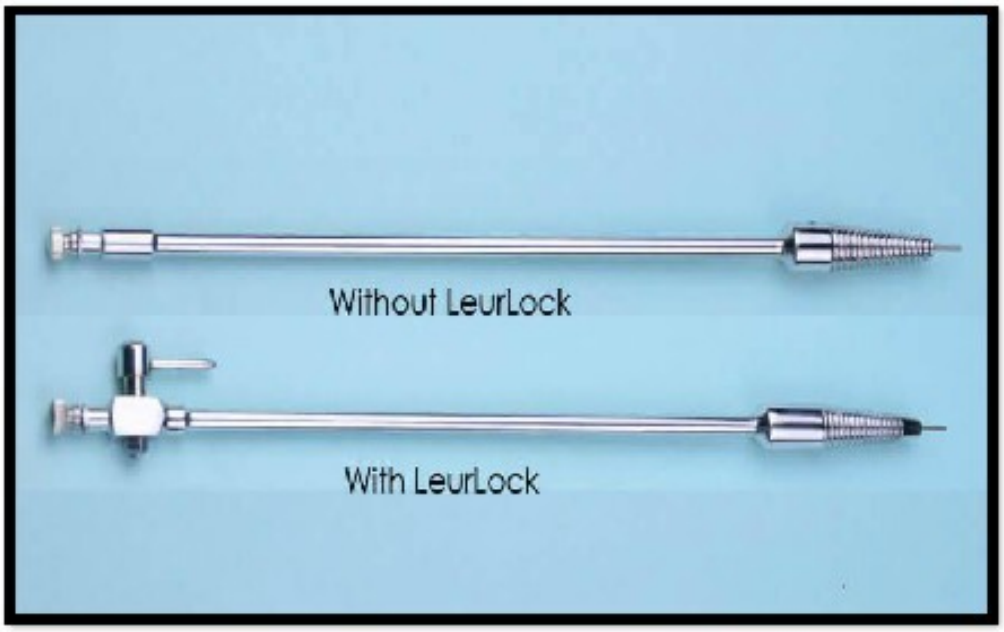


Figure 5.1: *Leech Wilkinson cannula / hysterosalpingography cannula*

2. **Hysterosalpingography** – It is most common method used for tubal patency test as it is time tested, inexpensive, simple and primary test for uterine and tubal evaluation. It can also diagnose uterine anomalies and synechiae in Asherman`s syndrome.
Generally performed between day 5 to 10 of a menstrual cycle. During this time , no clots are present in uterus to block Fallopian tubes or to give false impression of uterine anomaly and there is no risk of conception or ovulation.

Figure 5.2: *Hysterosalpingography*

Procedure –The labia majora, minora, and vagina are cleaned with antiseptic solution. Under all aspetic precaution vaginal examination is performed to determine size and anteversion of uterus. Posterior vaginal wall is retracted with Sim`s speculum. Anterior lip of cervix is held with Allis forceps or vulsellum. Sounding of uterus is done. Rubin`s cannula, Leech Wilkinson cannula or Foley`s catheter can be used to put contrast medium in uterine cavity.

In olden days oil –based contrast was used. However, they are not used in current practice due to risk of anaphylaxis, oil granuloma formation and risk of oil embolism if contrast goes in circulation.

In current practice water-based radiopaque contrast (urografin) is used.

Patient may be given drotaverine with mefenamic acid tablet before the procedure for pain relief and to relieve tubal spasm. A course of doxycycline 100 mg twice daily for 5 days is given. The procedure is done under direct fluoroscopic control usually in radiology department. The dye followed on fluoroscopic screen as it fills the uterine cavity, then tubal lumen and finally spillsout of tubal fimbriae into the pelvic cavity if tubes are patent.

Usually about 10-15 ml dye is adequate (capacity of uterus is 4-7 ml, of tubes is about 3 ml) to see the patency of tubes.

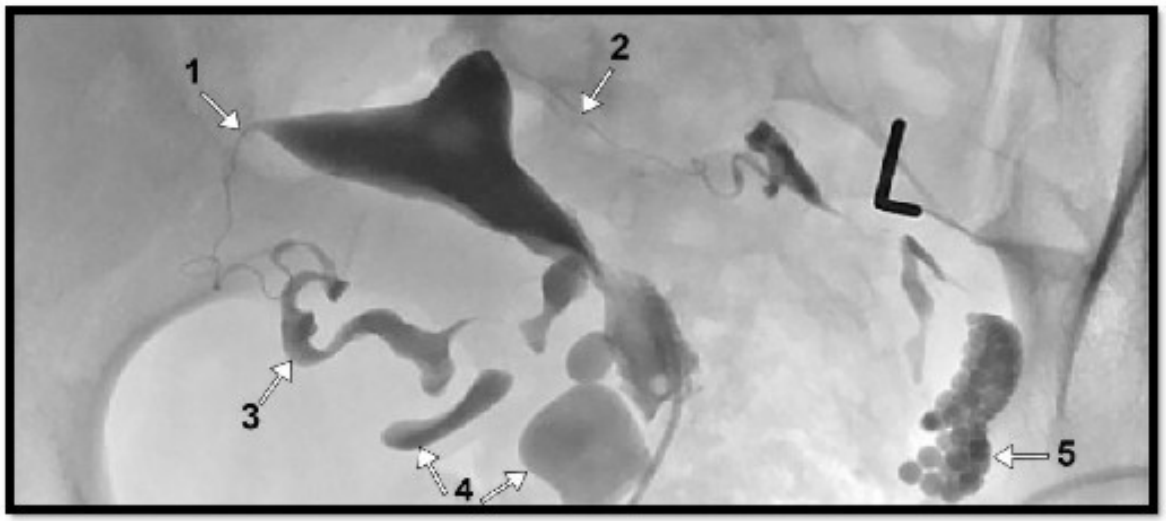


Figure 5.3: *Normal HSG image with OSCM in a 27-year-old woman with primary subfertility demonstrates contrast material opacifying the interstitial (1), isthmic (2), and ampullary (3) portions of the fallopian tubes. Free spill can have a varied appearance, noting the linear shape and a large globule on the right (4) and multiple small globules of contrast medium on the left (5). The right oblique positioning enables visualization of the entire left fallopian tube.*

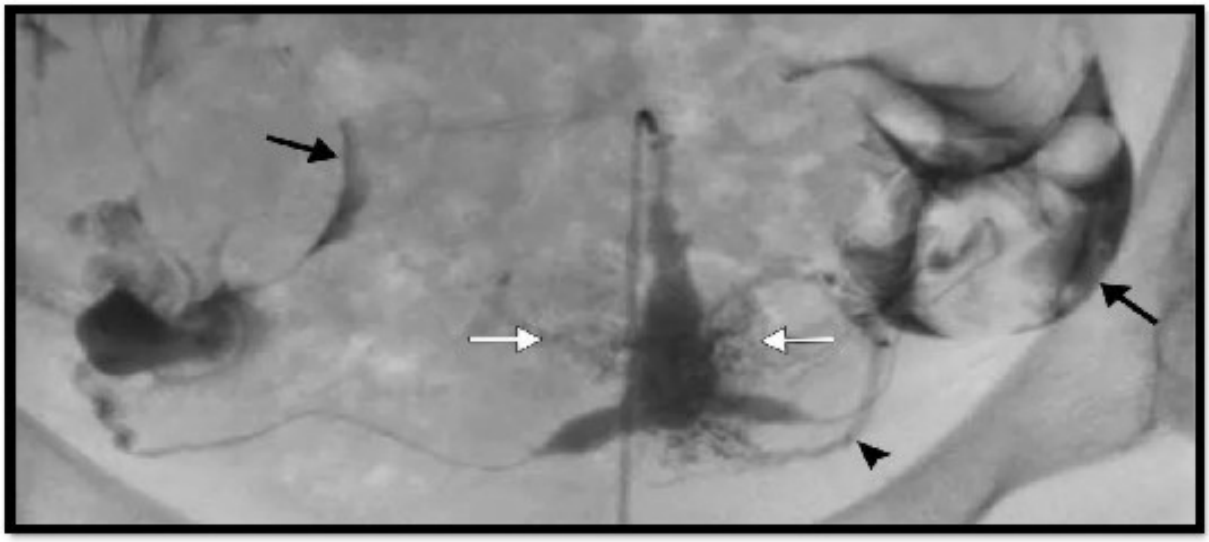


Figure 5.4. *Venous and lymphatic intravasation. HSG image with WSCM shows a retroflexed uterus and a fine lacelike network surrounding the uterine cavity (white arrows) with extension to the veins beyond the myometrium (arrowhead) due to the contrast material entering the veins and lymphatic vessels. Note the free spill from bilateral fallopian tubes (black arrows).*

Advantage of HSG-

1. Gives permanent record.
2. Shows the site of tubal blockage (cornual , mid tubal ,and fimbrial)
3. Shows other abnormalities of tubes like hydrosalpinx (tobacco – pouch appearance).

Complications-

1. Pain and collapse in some patients can be reduced by giving analgesics or antispasmodics before the procedure.
2. Allergic reactions in some patients.
3. Pelvic infections
4. Flare up of genital tuberculosis or genital infection (hence HSG should not be performed in suspected infection of tuberculosis).
5. It is avoided in iodine – sensitive patients.
6. Vasovagal attack

Success Rate –

Has been found to have 65% sensitivity and 83% specificity for diagnosis of tubal obstruction. False positive result (false impression of tubal obstruction when in reality tube is not blocked) may be obtained due to tubal contractions, especially cornual spasm , as the procedure is usually performed without anaesthesia.

3. Selective Salpingography

If tubal obstruction is observed at cornual end during HSG, a small guidewire can be used to cannulate the tube under fluoroscopic control and then the dye injected and X-ray films taken. It has the advantage of opening the tube also. But it is less commonly performed.

4. Sonosalpingography/Sonohysterography/Hysterosonography/Saline Infusion Sonography

Sonosalpingography is also called Sion test (named after Sion Hospital in Mumbai by G. Allahbadia and coauthors who popularized the technique).

Procedure-

Sonosalpingography is performed in follicular phase of cycle under ultrasonic control in which about 200 mL normal saline is infused into the uterine cavity

using a Foley's catheter with its inflated bulb (8-10 mL saline) lying above the internal os to prevent leakage of saline. Sonohysterosalpingography can detect endometrial defects better than HSG with sensitivity of 75% and specificity of 90%. It has a very high negative predictive value of 95% (much higher than HSG). It is particularly useful in determining whether a cavity defect is polyp or a pedunculated fibroid. It can also determine what portion of a submucous myoma lies within the cavity and is useful in planning of hysteroscopic resection of submucous myoma (if myoma is > 50% in cavity). Under ultrasonic guidance, it is possible to visualize the Fallopian tubes by following flow of saline in the uterus and out of tubes suggesting patency of tubes. However, it is less reliable for tubal patency testing than HSG. Presence of free fluid in pouch of Douglas is usually indicative of patent tubes.

Indications-

(i) To detect uterine anomalies especially in recurrent pregnancy losses and preterm labor
(ii) Before IVF treatment to see uterine cavity
(iii) In Asherman's syndrome (to see synechiae)
(iv) For testing tubal patency in infertility patients
(v) In abnormal uterine bleeding to detect endometrial polyps or leiomyoma

5. Hysterosalpingo-Contrast Sonography (HyCoSy)

Ultrasound contrast hysterosalpingography: In this technique X-ray radiation is not given. An ultrasound contrast medium like Echovist containing galactose microparticles is infused into the uterine cavity with Foley's catheter or a cannula and the flow of medium into uterine cavity, Fallopian tubes and peritoneal cavity is observed by ultrasound. Any pelvic pathology (myoma or cyst or adhesion) can be detected by ultrasound before injection of contrast. Hence it is a good alternative to HSG[13]. Use of 3D and 4D ultrasound can help in better detection of pelvic pathologies.

Disadvantages

(i) It is more difficult to perform (than HSG).
(ii) It needs trained gynaecologist and radiologist.
(iii) At one time only one tube is visualized.
(iv) It is less widely accepted.

6. Laparoscopy and Chromotubation (Dye testing)

Laparoscopy is the gold standard method for the accurate assessment of the condition of Fallopian tubes, uterus, ovaries and other pelvic structures. Chromotubation (dye test) is performed at the same time using a uterine cannula (Rubin's, Leech Wilkinson) or Foley's catheter and using methylene blue dye. Diluted indigocarmine can be used in patients of G6PD deficiency to avoid risk of methemoglobinemia.

Laparoscopy is performed under general anesthesia using a double puncture technique. Two ports are used with one large port at umbilicus for insertion of trocar, cannula and laparoscope while the second smaller port is for insertion of second instrument to lift Fallopian tubes or ovaries for better visualization of various pelvic structures. In case of patent tubes, methylene blue dye can be seen escaping through the fimbrial ends of the two Fallopian tubes. Video recording can be performed for keeping the record. Hysteroscopy (see later) can be combined with laparoscopy for better visualization of uterine cavity and its abnormalities (polyp, septum, myoma, etc.).

Indications

1. findings suggestive of tubal blockage on HSG
2. When endometriosis is suspected
3. When genital tuberculosis is suspected
4. It is also considered in patients who fail to conceive on clomiphene or gonadotropins.
5. patients with unexplained infertility.

Advantages

1. definite site of blockage can be seen.
2. Tubal pathology can be assessed more accurately. Thus conditions like peritubal adhesions can be diagnosed.
3. Tubal pathology can be assessed more accurately. Thus conditions like peritubal adhesions can be diagnosed.
4. Ovarian pathology can be detected (endometriosis, cyst, adhesions, PCOS), biopsy may be taken for confirmations of diagnosis.
5. Genital tuberculosis can be diagnosed more accurately (tubercles, caseous nodules, adhesions). Abdominal tuberculosis can also be detected.
6. Endometriosis can be diagnosed in ovaries, pouch of Douglas, uterosacral ligaments and peritoneum. 6. Surgical treatment can be performed in the same

sitting like ablation of endometriosis, removal of ovarian cyst, adhesiolysis, etc.

7. Tubal clipping or salpingostomy can be performed before IVF in hydrosalpinx cases.
8. Hysteroscopic surgeries like septal resection, adhesiolysis can be performed under laparoscopic control to avoid perforation of uterus.

Disadvantages

It is an invasive procedure, performed under general anaesthesia and needs expensive instruments and expert gynaecologist to perform the procedure. Hence it is not performed as the first test for patency of tubes but only when HSG is abnormal or there is evidence (clinical or ultrasonic) of tubal, ovarian or pelvic disease.

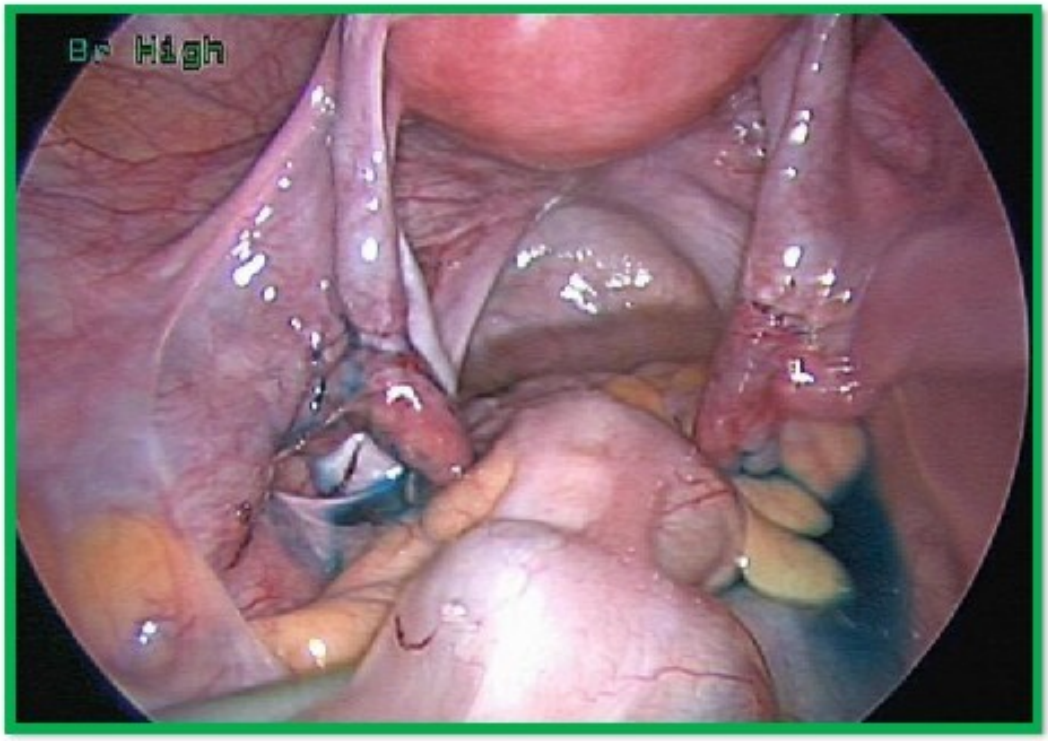


Figure 5.5: *Laparoscopic Chromopertubation –shows bilateral spillage of dye*

7. Hysteroscopy

Hysteroscopy is the endoscopic visualization of the endometrial cavity for detection of intrauterine abnormalities. Diagnostic hysteroscopy can be performed in minor operation theatre or office hysteroscopy without anaesthesia or with minimal analgesia. It is also performed to detect uterine anomalies (e.g.

septum, submucous myoma or Asherman's syndrome) and before IVF treatment (mock IVF). Simultaneous operative interventions can be done.

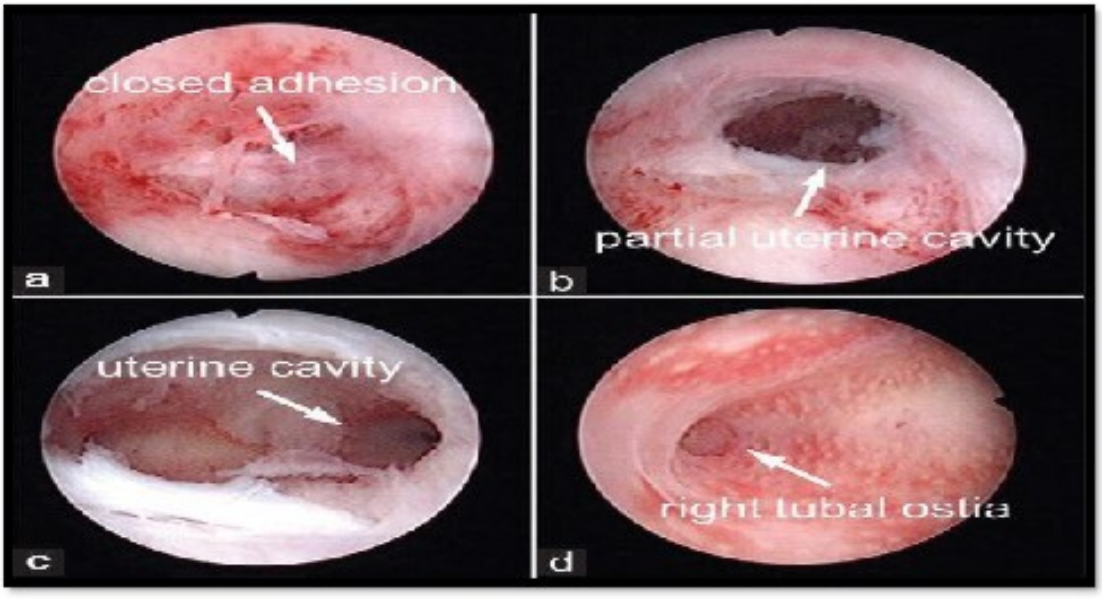


Figure 5.6: *Images showing dense adhesion with complete obstruction uterine cavity. The morphology of the uterine cavity was generally normal after blunt separating dense adhesion under abdominal ultrasonography. (a) Adhesion with complete obstruction in the low segment of the uterine cavity. (b) The uterine cavity after adhesion had been partially blunt separated. (c) The uterine cavity after the adhesion had been separated bluntly. (d) Visible normal right tubal ostia*

It is usually combined with laparoscopy under general anesthesia for better visualization while performing hysteroscopic surgeries like septal resection, resection of submucous myoma and hysteroscopic adhesiolysis in Asherman's syndrome. It is performed with a rigid hysteroscope using glycine or saline as medium.

Hysteroscopic, Cannulation and Falloposcopy

If cornual block of tubes is observed on laparoscopic and hysteroscopic evaluation, then hysteroscopic cannulation of tube and injection of dye can be tried. The dye comes out through fimbrial end if cannulation is successful.

Alternately falloposcope (flexible microendoscope) is inserted through interstitial part of tube under hysteroscopic guidance to see the interior of tube, any polyp or debris. The mucus plug or debris can be flushed out with cannulation or falloposcope. Small polyps can also be removed in the same sitting. If any synechiae are present, they can be broken with cannulation or by advancing

falloposcope tip in the Fallopian tube. Thus the patency of tube can be observed and obtained with this technique and tubal lumen can also be visualized.

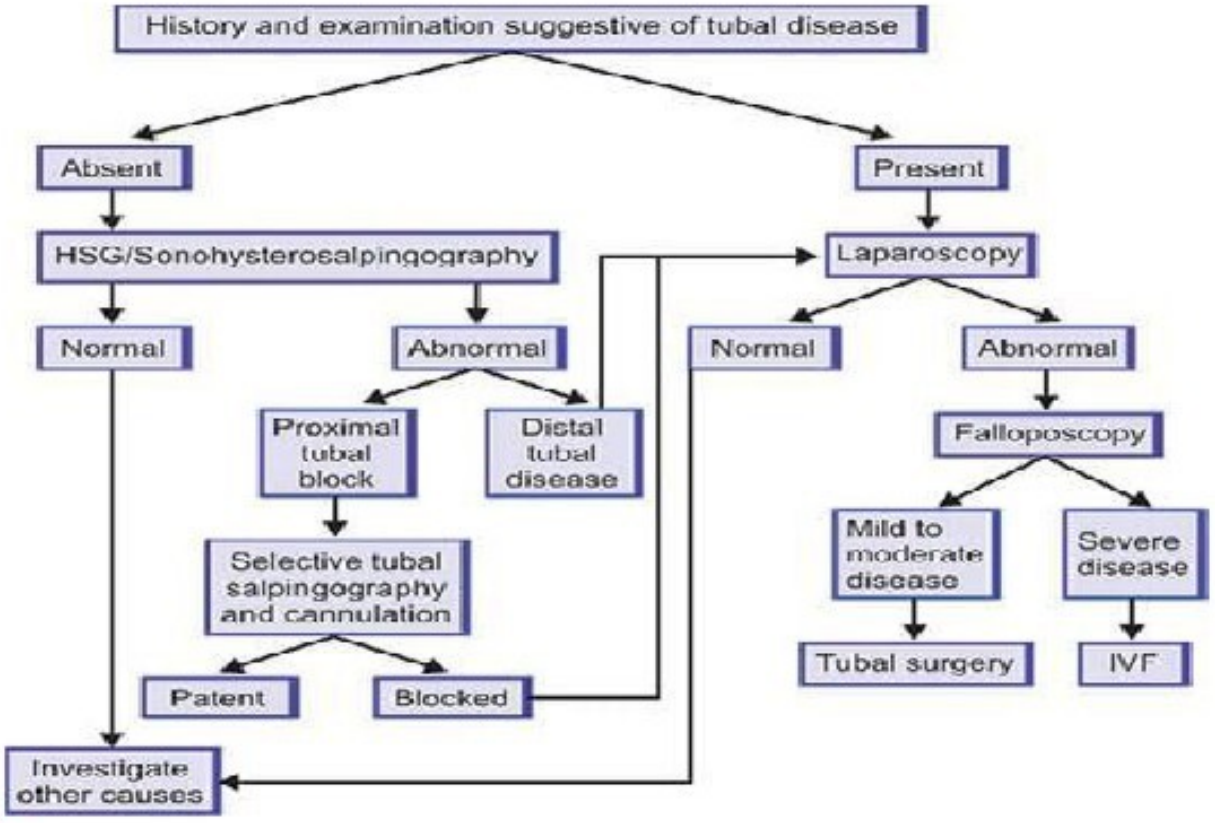
8.Combined Laparoscopy and Hysteroscopy

Combined laparoscopy and hysteroscopy has become a gold standard to evaluate the uterine, tubal and pelvic factor of infertility as well as to perform the needed surgery (septal resection, adhesiolysis, ablation of endometriosis) in the same sitting and thus has both diagnostic and therapeutic values[18].

Salpingoscopy

Salpingoscopy is performed through operating channel laparoscope by introducing a rigid fine endoscope through the fimbrial end of the Fallopian tube. It studies the mucosa of the Fallopian tube, any polyp, debris or adhesions in the tubes. A small biopsy can also be taken. It helps to decide whether tubal microsurgery or IVF will be more useful in the given case. However, due to easy availability of IVF, these techniques (falloposcopy and salpingoscopy) are rarely performed in current practice.

APPROACH TO TUBAL FACTOR



TREATMENT OF TUBAL FACTOR INFERTILITY

- **Proximal tubal Obstruction**-Comprises 10-25% of all tubal obstruction. The most common causes are mucus plugs, debris & spasm.
  Treatment options comprise of Cannulation, Catherisation, and Microsurgical segmental tubal resection and anastomosis are proven treatments for true proximal tubal obstruction
- **Distal tubal occlusion** - It accounts for 85% of all tubal infertility It occurs secondary to infection and endometriosis or prior abdominal surgery. Treatment options include Fimbriolysis, Fimbriplasty, and Neo-salpingostomy. In young women with mild distal block (fimbrial agglutination), laparoscopic surgery is an alternative to IVF but if the disease is severe(i.e. complete fimbrial block) IVF is the logical choice.

HYDROSALPINX

Collection of watery fluid in the uterine tube, occurring as the end stage of pyosalpinx is called as hydrosalpinx. However, hydrosalpinx is used for any distal tubal occlusion regardless of the cause, implying that a non-tubal infection such as an adjacent appendicitis can also cause hydrosalpinx. Furthermore, the end stage of a tubal infection has different appearances: the hydrosalpinx simplex is characterized by excessive distension and thinning of the wall of the uterine tube with the plicae being few and widely separated, while the hydrosalpinx follicularis describes a tube without any central cystic cavity with the lumen being broken up into compartments as the result of fusion of the tubal plicae.

The diagnosis of hydrosalpinx can be suspected and, in many cases, also confirmed by transvaginal ultrasound, if the tube is fluid filled. Ultrasound has the obvious advantage over hysterosalpingography of detecting the condition without the instillation of fluid, which carries a high risk of subsequent infection. Both methods, including instillation of contrast, can be used to diagnose a distally occluded tube without any fluid prior to instillation. Antibiotic prophylaxis is mandatory.

Laparoscopy is obviously the ultimate method for diagnosis of hydrosalpinx and associated pathology of pelvic adhesions. However, the method is highly invasive, and the opportunity should be taken to perform all diagnostic and therapeutic procedures at the same time.

Since 1994, there have been a large number of retrospective studies dedicated to the influence of hydrosalpinges on pregnancy results in IVF, most of them showing an impaired outcome. Patients with hydrosalpinges have been identified

as having significantly lower implantation and pregnancy rates than patients suffering from other types of tubal damage. There is a consistency in the results, showing a reduction by half in clinical pregnancy and delivery rates and a doubled rate of spontaneous abortion in women with hydrosalpinx. In addition, that cycles demonstrated a significantly reduced pregnancy rate [20]

INTERVENTIONS

According to the theory that the hydrosalpingeal fluid is embryotoxic and plays a causative role in impairing implantation and embryo development. Any intervention that blocks communication to the uterus and tubes would remove the leakage of the hydrosalpingeal fluid and can improve conception rates. Treatment with salpingectomy prior to IVF is the only surgical method that has been evaluated in a sufficiently large randomized controlled trial (RCT). Other suggested treatments for hydrosalpinx prior to IVF, such as tubal ligation, tubal clipping and transvaginal aspiration, may also be considered, but they need further evaluation in large prospective trials.

Chapter 6

OVUATION INDUCTION, FOLLICULAR MONITORING AND INTRAUTERINE INSEMINATION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CHAPTER 6

OVUATION INDUCTION, FOLLICULAR MONITORING AND INTRAUTERINE INSEMINATION

Author: Prof. Rekha Sachan

INTRODUCTION

After complete evaluation of the patients -

If no hormonal imbalance. No uterine abnormality, Endometrial lining is good, Fallopian tubes patent then if women age is less then she should be advised for Timed intercourse for three months if no conception then intrauterine insemination is the treatment of choice

If age is more ,30-35 years then patients should be considered for IUI since first cycle' for IUI first step to register the patients then call them from Day 2 of menses for basic trans vaginal sonography and continue in form of Follicular monitoring.

FOLLICULAR MONITORING

- Ovulation was initially monitored by conventional methods like BBT, mid luteal serum progesterone and urinary LH.
- Nowadays, USG is used for follicular monitoring for both natural and stimulated cycles.
- USG is the Vital component of IVF/IUI assessment and timing
- Employs a simple technique of assessing ovarian follicles growth on regular intervals, and documenting the pathway of ovulation.

Protocol

- Day 2 0r Day 4 scan called Baseline scan
- Serial follicular monitoring done

Why monitoring is important?

- To evaluate if the dose of drug used for ovulation induction being used is optimal

- To adjust the dose of the drug as some patients are hyper responsive and some are poor responder
- To find optimal time for ovulation induction
- To find optimal time for IUI
- To avoid excessive stimulation and prevent OHSS and multiple pregnancy

How to monitor?

- By ultrasound, color Doppler, power Doppler- to evaluate morphological growth of follicles
- By estradiol alone- indicates functional activity of follicles
- By both method
- TVS –accepted method at all infertility clinics

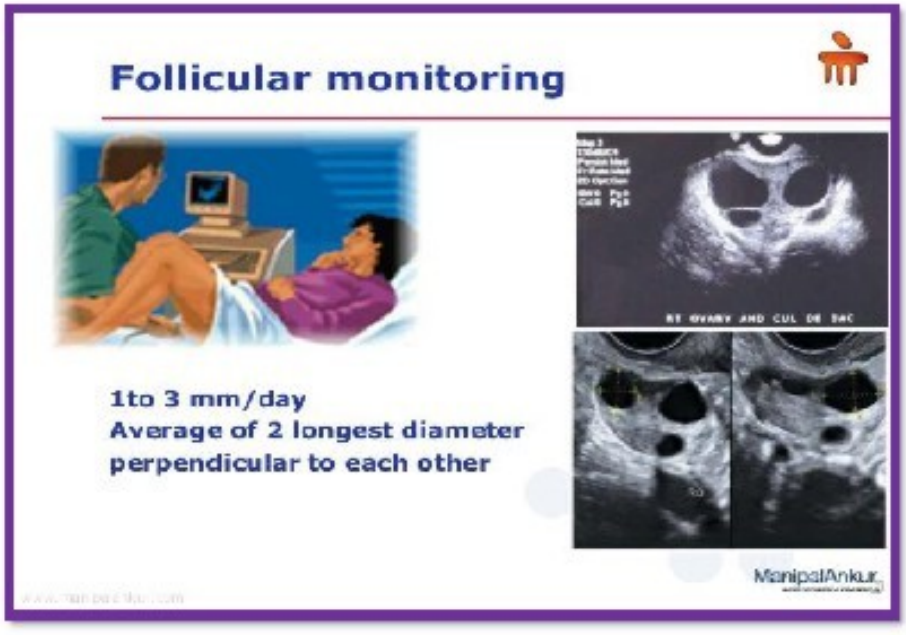

Figure 6.1: *Follicular Monitoring*

Pathophysiology

- Journey to ovulation begins during late luteal phase of prior menstrual cycle, when certain 2-5 mm sized healthy follicles form a population, from which dominant follicles is to be selected for next cycle This process is called 'recruitment'.

- Usual number of such follicles may be 3-11, which goes on decreasing with advancing age
- During Day 1-5 of the menstrual cycle, a second process of 'follicular selection' begins, when among all recruited follicles, certain growing follicles of size 5-10 mm are selected, while rest of the follicles regress or become atretic.
- This follicle starts growing at rate of 2-3 mm per day and reaches 17-27 mm size just prior to ovulation.
- During Day 5-7 of the menstrual cycle, a process of 'dominance' begins, when a certain follicle of 10 mm size takes the control and becomes dominant. This also suppresses the growth of the rest of the selected follicles, and in a way, is destined to ovulate.
- One important learning point in this regard is, "largest follicle on day 3 of the cycle, may or may not be a dominant follicle in the end. Process of dominance begins late, when suddenly a certain underdog follicle starts growing faster and suppresses others to become dominant".
- Almost nearing ovulation, rapid follicle growth takes place, and follicle starts protruding from the ovarian cortex, attains a crenated border, and it literally explodes to release the ovum, along with some antral fluid.

Ultrasound monitoring in induced cycles, and predicting success of IVF

- Most of the IVF studies are conducted after induction of ovaries with help of ovulation inducing agents like Clomiphene citrate. In such induced cycle, primary determinants of success are:
- ovarian volume
- antral follicle number
- ovarian stromal blood flow

Ovarian volume

- It is easy to measure,
- although not a good predictor of IVF outcome.
- a low ovarian volume does not always lead to anovulatory cycle.
- But, it's important to recognize a polycystic ovarian pattern and differentiate it from post-induction multicystic ovaries.

- Follicles arranged in the periphery forming a 'necklace sign', echogenic stroma, and more than 20 follicles of less than 9 mm size, signify a polycystic pattern in induced cycle.
- While, follicles in the center as well as the periphery, are seen in normal induced multicystic ovaries.

Antral follicle number

- **Antral follicle number** of less than three, usually signify possible failure of assisted reproductive therapy (ART).

Ovarian stromal blood flow

- This has been recommended as a good predictor of ART success. Increased peak systolic velocity (>10 cm/sec) is one of such parameters which has been advocated.

When to administer gonadotropins?

- Although, it's a matter of choice, based on experience of individual IVF specialists, there are certain parameters which may be considered.
- Minimal criteria suggested is a follicle size of at least 15 mm, and serum estradiol level of 0.49 nmol/L.
- Better prospects are at follicle size of 18 mm, and serum estradiol level of 0.91 nmol/L.
- Random hCG administration should be avoided, to prevent a risk of ovarian hyper stimulation syndrome (OHSS).

Significance

- Helps in prediction of impending ovulation and optimal timing for:
- Procedures like post coital testing,
- hCG administration,
- intercourse, donor or husband semen insemination
- egg collection
- If not ovulating can be treated with ovulation induction agents.

Advantages

- Diagnostic ultrasound can provide information that approximates a surgical assessment of reproductive anatomy without the expense and risks of a surgical procedure.
- Ultrasound can also be utilized repetitively
- throughout a single ovulatory cycle,
- providing dynamic information regarding ovarian function in a safe, convenient, noninvasive way
- when properly applied, cost-effective

Importance of D-3/4 scan

- Antral follicle count
- To rule out any cyst. (> 3 cm)
- Endometrial shedding
- Or any other pelvic pathology
- We expect normal sized ovaries with very small follicles
- (3—5 mm in diameter)
- Follicular size is measured by taking mean of 2 or 3 largest perpendicular diameters of each follicle.

Ultrasound follicular monitoring, trans vaginal ultrasound is the preferred mode,

- Serial USG follicular monitoring is started from
- day 7 or 8 of the cycle
- But in case of gonadotrophins we start scanning from 6th day of stimulation.

Assessing the follicular maturity

- The follicles normally grow at a rate of 2- 3 mm / day in a stimulated cycle.
- Definitive size of the follicle which confirms the maturity of oocytes is still controversial.

- A follicle measuring 18—20 mm has been found to contain a mature oocyte.

Correlation with serum estradiol levels

- Plasma estradiol levels correlates closely with the stage of development of the dominant follicle
- Serum estradiol levels >200 pg / ml on day 8 of stimulation indicates adequate dose of gonadotropins.

Ultrasound monitoring has totally replaced estradiol monitoring in most centers.

Predicting the risk of OHSS

If there are more than 4 follicles, larger than 16 mm or more than 8 follicles larger than 12 mm,it is best not to give hCG so as to prevent OHSS and high order multiple births.

In case of doubt do serum estradiol levels

Estradiol levels of > 1500 – 2000 pg/ml indicates risk of OHSS and is advisable to withhold hCG trigger.

OHSS (Ovarian hyper stimulation syndrome)–

- It is a complication of ovarian stimulation treatment for IVF.
- Rarely, may occur as a spontaneous event in pregnancy

OHSS syndrome consists of

- Weight gain
- Increase in abdominal circumference
- Ascites
- Pleural effusion
- Intravascular volume depletion with hemoconcentration
- Oliguria

Prevention

- Withholding hCG if there are predictive signs of OHSS
- Infusion of 5% albumin in 500 ml after oocyte retrieval

- Cabergoline 0.5 mg OD for 8 days started on day 1 of hCG administration

Treatment

- Colloids or Plasma expanders or 5% albumin in 500ml RL & Electrolyte correction
- Heparin and high thigh venous support stockings to prevent DVT
- Dopamine agonist to improve renal perfusion and preventing AKI

OVULATION INDUCTION

- Ovulation induction is a technique of inducing ovulation by administration of therapeutic agents namely ovulating agents.
- Discovery of above such agents has revolutionized treatment of infertility due to failure of ovulation.
- Ovulation induction has application in artificial reproductive techniques also.

FSH WINDOW

- It is the time required for selection of single follicle from a cohort of recruited follicles to develop into a dominant follicle under the influence of FSH.
- Ovulation induction prolongs FSH window & allows for more than a single follicle to be chosen as dominant follicle.

Pharmacodynamics and kinetics

- **Clomiphene Citrate** is a mixture of 3:2 two geometric isomers- euclomiphene and zuclomiphene.
- Euclomiphene is the active isomer with $t_{1/2}$ of 5 days.
- It is a selective estrogen receptor modulator i.e it selectively blocks cytoplasmic estrogen receptors in hypothalamus
- It tends to decrease cervical secretions and induce endometrial changes (reduced thickness, glands & blood flow)

Indications

- Anovulatory infertility

- Polycystic ovarian syndrome
- In vitro fertilization- Gamete intrafallopian transfer technique and assisted reproductive techniques
- To stimulate spermatogenesis

Contraindications

- Ovarian cyst, chronic liver disease, scotoma, negative progesterone challenge test

Regimen

- In women with amenorrhoea, it could be started on any day but in those with normal cycles, it should be started on 2nd day of the cycle for 5 day
- Serial ultrasound monitoring for follicular size from 10th day (normal being 1-2 mm/day)
- Dosage: 50 mg per day which can be increased by 50 mg each cycle to max. 150 mg
- Clomiphene therapy should not be administered for more than 6 consecutive cycles

Combination therapy

- When clomiphene Combined with hCG (5000 IU I/M) the ovulation rate is good and it compensate for luteal phase defect. It administered when dominant follicle reaches up to size of 20 mm.
- Metformin may be added in case of clomiphene resistance
- Clomiphene failure can be tackled by addition of tamoxifen 20 mg
- Addition of Dexamethasone in treatment of PCOS improves conception rate

Adverse effects

- Nausea, vomiting, headache, dizziness
- Hot flushes, sweating and osteoporosis due to estrogen deficiency
- Hair loss, weight gain
- Anti estrogenic effect on cervix and endometrium
- It causes corpus luteum phase defect hence abortion rate of 30%

- Ovarian hyperstimulation syndrome
- Multiple pregnancy

LETROZOLE

- It is a non steroidal aromatase inhibitor
- It has a half life of 45 hr and is eliminated via urine
- Mechanism: Inhibits aromatase and prevents conversion of androstenedione to estrone
- Dosage: 2.5 mg OD for 5 days
- Adverse effects: drowsiness and hepatic dysfunction
- Contraindication: Hepatic dysfunction

Advantages over clomiphene

- No anti estrogenic effect on cervix and endometrium
- Induces monofollicular stimulation, adequate LH surge and avoids multiple pregnancy
- Better fecundation
- No ovarian hyper stimulation syndrome (OHSS) hence suitable for PCOS patients

GONADOTROPINS

- FSH and β hCG are available as recombinant preparation which can be self-administered

Indications:

- Anovulatory infertility not responding to clomiphene
- Induction of multiple ovulation in ART
- Hypogonadotropic hypogonadism in males and females
- Cryptorchidism
- hCG is used in CLPD and early abortions

Adverse effects are OHSS, multiple pregnancy, local reaction at injection Site, fever, arthritis.

Intrauterine insemination is used most often in patients who have:

Donor sperm - This is sperm donated by someone who may be unknown to patients. It's an option if patient single, or partner doesn't have sperm or the quality of the sperm is too low to conceive.

Intrauterine insemination is most commonly used to achieve pregnancy in patients who need to use donor sperm to get pregnant. Donor sperm is obtained from certified labs and thawed before the IUI procedure.

Unexplained infertility - Often, IUI is done as a first line treatment for unexplained infertility. Before IUI ovulation induction should be done, so timely ovaries produce eggs and planned IUI to be done.

Infertility related to endometriosis - Fertility problems can happen when the lining of the uterus grows outside the uterine cavity, condition known as endometriosis. Often, the first treatment approach for this cause of infertility is to do ovulation induction and to obtain a good-quality egg along with doing IUI.

Mild male factor infertility- Another name for this is subfertility. Some couples have trouble getting pregnant because of semen, the fluid that contains sperm. A test, semen analysis should be advice to check the amount, size, shape or motility of sperm. IUI can overcome some of these issues. That's because preparing sperm for IUI helps separate higher quality sperm from those of lower quality.

Cervical factor infertility- Problems with the cervix can cause infertility. It provides the opening between the vagina and uterus. The cervix produces mucus around the time of ovulation. The mucus it helps sperm travel from the vagina to either fallopian tube, where the egg awaits. But if cervical mucus is too thick, it may impede the sperm's journey. The cervix itself also may prevent sperm from reaching the egg. Scarring, such as that caused by a biopsy or other procedures, can cause the cervix to thicken. IUI bypasses the cervix. It places sperm directly into the uterus and increases the number of sperm available to meet the egg.

Ovulatory factor infertility- IUI also may be done for people who have infertility caused by problems with ovulation. These issues include a lack of ovulation or a reduced number of eggs.

- **Semen allergy-** Rarely, an allergy to proteins in semen can cause a reaction. When the penis releases semen into the vagina, it causes a burning feeling and swelling where the semen touches the skin. A condom can protect you from the symptoms, but it also prevents pregnancy. IUI can allow for pregnancy and

prevent the painful symptoms of the allergy. That's because many of the proteins in semen are removed before the sperm is inserted.

Risks

Often, intrauterine insemination is a simple and safe procedure. The risk of it causing serious health problems is low. Risks include:

- **Infection.** There's a slight chance of infection after IUI.
- **Spotting.** During IUI, a thin tube called a catheter is placed through the vagina and into the uterus. Then sperm are injected through the tube. Sometimes, the process of placing the catheter causes a small amount of vaginal bleeding, called spotting. This doesn't usually have an effect on the chance of pregnancy.
- **Multiple pregnancy.** IUI itself isn't linked with a higher risk of becoming pregnant with twins, triplets or more babies. But when fertility medicines are used along with it, the chance of this happening goes up. A multiple pregnancy has higher risks than a single pregnancy does, including early labor and low birth weight.

How to Prepare

Intrauterine insemination involves some key steps before the actual procedure:

- **Watching for ovulation.** Because the timing of IUI is key, checking for signs that the body might ovulate is crucial. To do this, you might use an at-home urine ovulation predictor kit. It detects when your body produces a surge or release of luteinizing hormone (LH), which causes the ovary to release an egg. Or you might have a test done that makes images of your ovaries and egg growth, called transvaginal ultrasound. You also may be given a shot of human chorionic gonadotropin (HCG) or other medicines to make you ovulate one or more eggs at the right time.
- **Timing the procedure right.** Most IUIs are done a day or two after tests show signs of ovulation. Your doctor will likely have a plan spelled out for the timing of your procedure and what to expect.

Preparing the semen sample. Your partner provides a semen sample at the doctor's office. Or a vial of frozen donor sperm can be thawed and prepared. The sample is washed in a way that separates the highly active, healthy sperm from lower-quality sperm. Washing also removes elements that could cause reactions, such as serious cramps, if placed in the uterus. The likelihood of becoming pregnant rises by using a small, highly concentrated sample of healthy sperm.

What you can expect

The visit for intrauterine insemination often is done in a doctor's office or clinic. The IUI procedure itself takes just a few minutes once the semen sample is prepared. No medicines or pain relievers are needed. Your doctor or a specially trained nurse does the procedure.

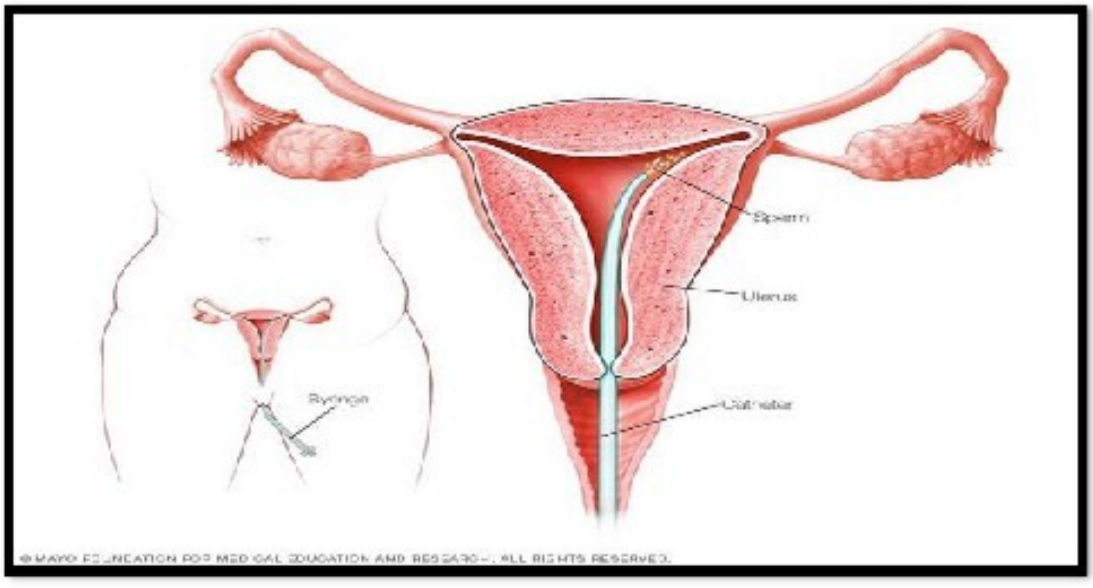

Figure 6.1: *Intrauterine Insemination (Enlarge image)*

INTRAUTERINE INSEMINATION

During the procedure

While lying on an exam table, you put your legs into stirrups. A plastic or metal-hinged tool called a speculum is used to spread open the walls of the vagina. During the procedure, the doctor or nurse:

- Attaches a vial that contains a sample of healthy sperm to the end of a long, thin, flexible tube called a catheter.
- Places the catheter into the vagina, through the cervix and into the uterus.
- Pushes the sperm sample through the tube into the uterus.
- Removes the catheter, followed by the speculum.

After the Procedure

After the sperm are placed in your uterus, you lie on your back for a brief time. Once the procedure is over, you can get dressed and go about your usual daily routine. You may have some light spotting for a day or two after the procedure.

Results

Wait two weeks before taking an at-home pregnancy test. Testing too soon could produce a result that is:

- **False-negative.** The test finds no sign of pregnancy when, in fact, you really are pregnant. You might get a false-negative result if pregnancy hormones aren't yet at levels that can be measured.
- **False-positive.** The test detects a sign of pregnancy when you really aren't pregnant. You might get a false-positive if you took fertility medicines such as HCG and the medicine is still in your system.

You may have a follow up visit about two weeks after your home pregnancy test results. At the appointment you may get a blood test, which is better at detecting pregnancy hormones after sperm fertilize an egg.

If you don't become pregnant, you might try IUI again before you move on to other fertility treatments. Often, the same therapy is used for 3 to 6 cycles of treatment to maximize chances of pregnancy.


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Chapter 7

THE ASSISTED REPRODUCTIVE TECHNOLOGY (REGULATION) BILL, 2021


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CHAPTER 7

THE ASSISTED REPRODUCTIVE TECHNOLOGY (REGULATION) BILL, 2021

Author: Dr. Vandana Solanki

In the current age of Assisted reproductive technology there is huge diversity in the management protocols. The ART bill aims at standardizing management protocols and care for the patients. The act provides uniform law and supervises assisted reproductive techniques provided taking into consideration safety and ethics.

The purpose of the bill is "for the regulation and supervision of the assisted reproductive technology clinics and the assisted reproductive technology banks, prevention of misuse, safe and ethical practice of assisted reproductive technology services for addressing the issues of reproductive health where assisted reproductive technology is required for becoming a parent or for freezing gametes, embryos, embryonic tissues for further use due to infertility, disease or social or medical concerns and for regulation and supervision of research and development and for matters connected therewith or incidental thereto."

The bill comprises of **6 chapters**

1) *Chapter 1* -Preliminary, comprises of definitions

2) *Chapter 2*-Authorities to regulate assisted reproductive technology

   A. The National and Surrogacy board

   B. State assisted reproductive technology board

   C. The National assisted reproductive technology and surrogacy registry and the appropriate assisted reproductive technology and surrogacy authority

3) *Chapter 3*-Procedures for Registration

4) *Chapter 4*-Duties of assisted reproductive technology clinic and assisted reproductive technology bank

5) *Chapter 5*-Offences and penalties

6) *Chapter 6*-Miscellaneous

CHAPTER 1

DEFINITIONS – Some important definitions are here below

(a) **"Assisted reproductive technology"** with its grammatical variations and cognate expressions, means all techniques that attempt to obtain a pregnancy by handling the sperm or the oocyte outside the human body and transferring the gamete or the embryo into the reproductive system of a woman;

(b) **"Assisted reproductive technology bank"** means an organization which shall be responsible for collection of gametes, storage of gametes and embryos and supply of gametes to the assisted reproductive technology clinics or their patients;

(c) **"assisted reproductive technology clinic"** means any premises equipped with requisite facilities and medical practitioners registered with the National Medical Commission for carrying out the procedures related to the assisted reproductive technology;

(d) **"Child"** means any individual born through the use of the assisted reproductive technology;

(e) **"Commissioning couple"** means an infertile married couple who approach an assisted reproductive technology clinic or assisted reproductive technology bank for obtaining the services authorized of the said clinic or bank;

(f) **"Embryo"** means a developing or developed organism after fertilization till the end of fifty-six days from the day of fertilization;

(g) **"Gamete"** means sperm and oocyte;

(h) **"Gamete donor"** means a person who provides sperm or oocyte with the objective of enabling an infertile couple or woman to have a child;

(i) **"Infertility"** means the inability to conceive after one year of unprotected coitus or other proven medical condition preventing a couple from conception;

(j) **"Patients"** means an individual or couple who comes to any registered assisted reproductive technology clinic for management of infertility;

(k) **"Sperm"** means the mature male gamete;

(l) **"woman"** means any woman above the age of **twenty-one** years who approaches an assisted reproductive technology clinic or assisted reproductive technology bank for obtaining the authorized services of the clinic or bank.

CHAPTER 2

AUTHORITIES TO REGULATE ASSISTED REPRODUCTIVE TECHNOLOGY

The National Board shall meet at least once in 6 months. The functions prescribed for the Board are as follows:

- To advise the Central Government and recommend changes regarding guidelines and administration of surrogacy and ART acts
- To evaluate and supervise the implementation of the various bodies under the Act
- To ensure that the standard procedures followed by the surrogacy clinics, ART clinics, and banks and to stipulate the minimum requirements for physical infrastructure, apparatus and personnel in the surrogacy clinics, ART clinics, and banks

To *supervise* the operation of State Board

- To supervise maintenance and proper functioning of the of the National Registry.

Members of National Assisted Reproductive Technology and Surrogacy Board.

The Chairperson: Minister in-charge of the Ministry of Health and Family Welfare

The Vice-Chairperson: Secretary to the Government of India in-charge of the Department dealing with the surrogacy matter

Three women Members of Parliament:

* Two shall be elected by the Lok Sabha
* One by the Rajya Sabha

Three members (not below the rank of Joint Secretary) of the Ministries of the Central Government regulating:

* Women and Child Development
* Legislative Department in the Ministry of Law and Justice
* Ministry of Home Affairs

Director General of Health Services of the Central Government expert Members to be appointed by the Central Government, two each from among:

* Medical geneticists or embryologists
* Gynecologists and obstetricians
* Social scientists
* Representatives of women welfare organizations
* Representatives from civil society working on women's health and child issues

Four Chairpersons of the State Boards to be nominated by the Central Government by rotation to represent the States and the Union territories:

* Two in alphabetical order
* Two in reverse alphabetical order

The Member-Secretary: An officer not below the rank of a Joint Secretary to the Central Government in-charge of Surrogacy Division in the Ministry of Health and Family Welfare

Term of office of each member will be **3 years**, and no member may be appointed for more than two terms

Members of State or Union Territory Assisted Reproductive Technology and Surrogacy Board.

The Chairperson: The Minister in-charge of Health and Family Welfare in the State

The Vice-Chairperson: The Secretary in-charge of the Department of Health and Family Welfare

Secretaries or Commissioners (or their nominees) in-charge of the Departments of:

* Women and Child Development
* Social Welfare
* Law and Justice
* Home Affairs

Director General of Health and Family Welfare of the State Government

Three women members of the State Legislative Assembly or

Union territory Legislative Council

Ten expert members to be appointed by the State Government, two each from among:

* Medical geneticists or embryologists
* Gynaecologists and obstetricians
* Social scientists
* Representatives of women welfare organizations
* Representatives from civil society working on women's health and child issues

The Member-Secretary: An officer not below the rank of Joint Secretary to the State Government in-charge of Family Welfare The term of office of each member will be 3 years, and no member may be appointed for more than two terms

The Board shall meet at least **once in 4 months.**

The **functions prescribed** for the board are as follows.

- To monitor, supervise and coordinate the authorities in the state and union territories and to enforce the implementation of the policies and guidelines of the Act

To **make recommendations** to the National Board

- To send reports of various activities taking place in the state/UT under the Act to the National Board and the Central Government

Appropriate authority: The Central and State Governments are given a period of 90 days to appoint an appropriate authority in each state and union territory which serves the purpose to enforce the Act.

The functions of the AA are as follows:

* To assign, suspend, or revoke registration of a ART clinic or bank
* To administer the implementation of the Act
* To investigate any violation and take necessary actions
* To recommend modifications in the present law taking into considerations the present changes in the technology and society

To manage the details of registration, cancellation and renewal of grants of ART clinics and banks

To maintain all details of certificates issued to commissioning couples/women

- AA will have the power to summon any person or search any place in case of an investigation

Members of the Appropriate Authority (AA) of State or Union Territory (UT).

The Chairperson: An officer of or above the rank of the Joint Secretary of the Health and Family Welfare Department of the State or UT

The Vice-chairperson: An officer of or above the rank of Joint Director of the Health and Family Welfare Department of the State or UT

* A woman representing women's organization
* An officer of Law Department of the State or the UT
* A registered medical practitioner

National Assisted Reproductive Technology and Surrogacy Registry

Functions of registry:

- To maintain a central database comprising details all, the ART clinics and banks of country, including the nature and types of services provided and the outcome of the services. It shall be regularly updated.
- It shall assist the national board in in forming new guidelines by providing the necessary database.

CHAPTER 3

PROCEDURES FOR REGISTRATION

Registration of Assisted Reproductive Technology Clinics and Banks

- Application for registration of ART clinic or bank should be made to the National Registry, within 60 days of establishment of National Registry.

Every application for registration shall be accompanied by an application fee of:

i) Rupees 1,00,000 for Level 1 ART Clinic

ii) Rupees 5,00,000 for Level 2 ART Clinic

iii) Rupees 1,00,000 for ART Bank

- In case an application is rejected, **no additional** fee is required for resubmission. But application fees will not be refunded.

The AA must grant a certificate of registration **within 90 days** (for surrogacy clinic) or 30 days (for ART clinics and banks) of receipt of application after proper enquiry.

Every application for renewal of registration shall be accompanied by an application fee of: -

Rupees 1, 00,000 for Level 1 ART Clinic Rupees 5, 00,000 for Level 2 ART Clinic Rupees 1, 00,000 for ART Bank

- Registry was made mandatory for all pre-existing ART clinics and banks or else they shall stop functioning after 6 months

New clinics and banks cannot start functioning unless they have applied and are registered.

- The record of all the registrations is maintained by the State Board.
- Registration is **valid only for a period of 5 years** for an ART clinic or bank

The appropriate authority has the power to cancel or suspend registration

CHAPTER 4

DUTIES OF ASSISTED REPRODUCTIVE TECHNOLOGY CLINIC AND ASSISTED REPRODUCTIVE TECHNOLOGY BANK

Duties of Assisted Reproductive Technology Clinics

- Counselling of the couple should be done regarding treatment options, procedures, cost, advantages, disadvantages, risk factors, complications and success rates.

The commissioning couple or woman have to be made aware of the rights of a child born through ART.

ART services can be given only to a **woman** between the ages **of 21 and 50 years**, and a **man** between the ages of **21 and 55 years**.

- ART clinics should provide a proper **discharge ticket** documenting the procedure performed
- All reproductive material should be used only after the **consent** of both the parties
- During one treatment cycle the gynecologist must **transfer 1-2 embryos in** the uterus of a woman.

Only in exceptional circumstances such as advanced maternal age, recurrent miscarriages, recurrent implantation failure (RIF), and such other circumstances, three embryos may be transferred.

Not more than three embryos may be transferred

Semen sample from two individuals should **never be mixed**

Embryos should not be split to increase the number of available embryos.

Preimplantation genetic testing **(PGT)** should only be used to evaluate human embryos heritable genetic diseases.

- PGT should **not be used to predetermine sex of the fetus** or to change the genetic constitution of the fetus.
- Gametes and embryos that are not used **cannot be donated.** The embryos that tested positive during PGT can be used for lab research only after consent by the couple.
- Cryopreservation of gametes **can be done or 10 years** but the duration can be extended to more than that by permission of national board

Ovarian stimulation of the woman must be appropriately performed and monitored in order to prevent ovarian hyperstimulation syndrome (OHSS).

Duties Specific for Assisted Reproductive Technology Banks

- To confirm testing of the donor for diseases such as human immunodeficiency virus (HIV), types 1 and 2, hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis (through Venereal Disease Research Laboratory (VDRL)

To screen gamete donors, to collect, screen, and store semen, and provide oocyte donors to the ART clinic

- The Act allows donation of gametes from **a known donor.**

* To obtain semen from **males** between **21 and 55 years** of age

To obtain oocytes from **females** between **23 and 35 years** of age

To ensure that sperm or oocyte of a single donor is not supplied to more than one commissioning couple.

Ensure that oocyte donor donates oocytes **only once** in her life

Retrieval of not more than **7 oocytes** from a donor during one cycle should be done

The gametes from a donor can be stored for a period of **10 years** after which they shall be allowed to perish. If the couple wishes to extend, then they must put an application 6 months before the term.

Unused gametes and embryos can be taken up for research purpose by consent from commissioning couple

The sale and transfer of gametes and embryos is strictly prohibited

* A donor must **surrender all parental rights** over the child or children born from his or her gamete.

* To maintain complete record of use of donor gametes

* To maintain proper record of all the donors and send it to the national registry.

The staff requirements given below will be mandatory for all ART Clinics/Banks.

Level 1 ART Clinic - minimum staff requirement

01 Gynaecologist with qualifications as specified below 01 Counsellor with qualifications as specified below

Level 2 ART Clinic - minimum staff requirement

Director

02 Gynecologist with qualifications as specified below

02 Embryologist with qualifications as specified below (One Senior and one Junior Embryologist)

01 Andrologist with qualifications as specified below 01 Anesthetist with qualifications as specified below 01 Counselor with qualifications as specified below

ART Bank - minimum staff requirement

01 Registered Medical Practioner trained in preparation and storage of semen sample

01 Counselor

Gynaecologist

The gynaecologist will be a medical post-graduate in gynaecology and obstetrics and should have record of preforming 50 oocyte retrievals under supervision of a trained ART specialist (Records of procedures to be maintained) OR with three years of training in a registered ART centre OR with super specialist DM /fellowship in reproductive medicine or experience of not less than 03 years in reproductive medicine.

Andrologist

The Andrologist in a clinic/ bank will be a urologist or a surgeon who has a post-graduate degree (MS General Surgery with training in Andrology that often takes on the task of treating male infertility along with some experience in the field of andrology or MCH/DNB Genitourinary surgery/Urology).

Senior embryologist

Post graduate in clinical embryology (on site) / PhD holder (onsite) in clinical Embryology post-graduate degree(onsite) from a recognized university with

additional one year of laboratory experiences of handling human Gametes and Embryos.

Junior embryologist

Graduate in Life sciences/ biotechnology/ reproductive biology/ veterinary science with three experiences in the relevant field OR Postgraduate in Life sciences/ biotechnology/ reproductive biology/ veterinary science.

Counsellor

A person who has at least a degree (preferably a post-graduate degree) in Social Sciences, Social work, Psychology, Life Sciences or Medicine, and a good knowledge of the various causes of infertility and its social and gender implications, and the possibilities offered by the various treatment modalities, should be considered as qualified to occupy this position. The person should have a working knowledge of the psychological stress that would be experienced by potential patients, and should be able to counsel them to assuage their fears and anxiety and not to have unreasonable expectations from ART. A member of the staff of an ART Clinic/Bank who is not engaged in any other full-time activity in the clinic can act as a counsellor.

Anaesthetist

Anaesthetist should have a MD/ DA in anaesthesia. The role of the anaesthetist in a surrogacy clinic is to provide adequate comfort and pain relief during oocyte retrieval and embryo transfer procedures.

Levels of ART clinics and banks.

Level 1 ART Clinics: Only intrauterine insemination (IUI) procedure may be carried out.

Can perform basic workup of infertility patients,

ovarian stimulation,

Follicular monitoring,

Semen preparation,

Freezing of husband's sperm.

Donor semen for IUI has to be obtained from ART bank

Level 2 ART clinics:

* Surgical retrieval of gametes: Oocyte pickup, TESA/PESA/TESE
* Handling the oocyte outside the human body: Oocyte washing
* Use of sperms for fertilization of oocytes: IVF/ICSI
* Transfer of embryo into the reproductive system of a woman
* Storage of gametes or embryos: Donor oocyte freezing, husband's sperm freezing for back up, social egg freezing, ovarian tissue freezing, oocyte freezing in cancer patients
* Research

ART banks

* Screening, collection, and registration of semen donors
* Cryopreservation of sperms
* Screening and registration of oocyte donors
* Maintenance of data of all donors, both for sperm and oocyte

CHAPTER 5

OFFENCES AND PENALTIES

For any advertisement regarding sex selection by ART clinic or bank punishment is imprisonment for 5- 10 years or a fine of 10- 25 lakhs.

Sale of gametes or embryos or gametes, import of embryos by a gynaecologist, registered medical practitioner or a geneticist is punishable by 5-10 lakhs. For further offences punishment can extend to imprisonment for 3-8 years and a fine of 10-20 lakhs.

All offences are cognizable and bailable.

Head of ART clinic or bank is held responsible for the offence unless proved otherwise.

CHAPTER 6

MISCELLANEOUS

The central government has the power to issue directions to the national board, national registry and appropriate authorities. State government has similar power over the state board. In case of any dispute, the judgement of the government holds superior. Boards have the power to search and seize records. The Act serves the purpose to complement the existing laws and can be amended.


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Chapter 8

OVARIAN STIMULATION PROTOCOLS IN IVF TREATMENT


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CHAPTER 8

OVARIAN STIMULATION PROTOCOLS IN IVF TREATMENT

Author: Prof. PushpaLata Sankhwar

The ideal ovarian stimulation regimen should have a low cancellation rate, minimize drug costs, risks, and side effects; and require limited monitoring. **The ultimate goal is to deliver a singleton pregnancy at term.**

Typical ovarian stimulation comprises 3 components:

1. Exogenous gonadotropins to stimulate follicular growth,
2. GnRH analogues to prevent spontaneous ovulation before oocyte retrieval,
3. LH activity for oocyte maturation.

There are various regimens described, ranging from no stimulation (natural cycles) to minimal stimulation and mild stimulation to aggressive stimulation protocols.

Here is the list of various protocols-

1. Natural cycle -no stimulation IVF
2. Minimal stimulation (mini-IVF)
3. Long Agonist protocol
4. Short agonist protocol
5. Ultra-short agonist protocol
6. Ultra-long protocol
7. Antagonist protocol
8. Random stimulation
9. Dual stimulation

Natural Cycle

In 1978 the first successful IVF procedure was performed without the use of drugs. In this protocol (natural cycle IVF), the first birth resulting from IVF is derived from a single oocyte collected in a natural ovulatory cycle, the spontaneous cycle is monitored and a single oocyte is retrieved before the midcycle LH surge occurs.

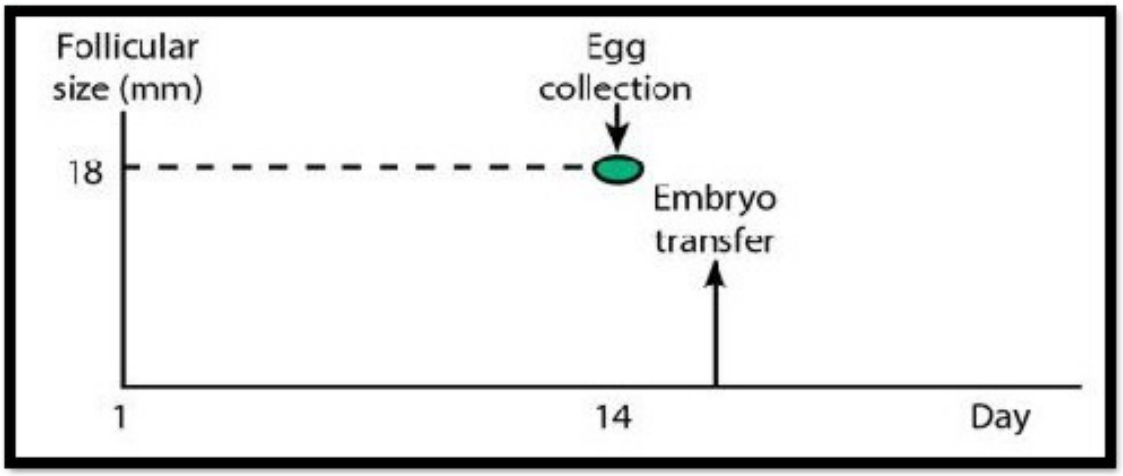

Figure 8.1: *Natural Cycle*

In the natural cycle, follicular dominance is achieved by the estradiol-induced negative feedback on the pituitary gland, causing a decline in FSH below threshold levels.

In IVF cycles, exogenous gonadotropins are used to achieve supra-threshold levels of gonadotropins during the phase of follicular recruitment to interfere with this process of dominant follicle selection and enable multiple follicular recruitment.

This procedure is simple, less expensive, less invasive and less stressful than other protocols, and does not cause ovarian hyper stimulation syndrome (OHSS) as no drugs are used. However, the pregnancy rates are low and cancellation rates are high.

CLOMIPHENE CITRATE

It was the first method of ovarian stimulation used in IVF but now has been completely replaced by more effective stimulation regimens.

Clomiphene (100 mg daily) from 5 days beginning on Day 3 of the cycle induces the development of two or more follicles in most normally ovulating women. The cycle cancellation rate is reduced as compared to the natural cycle, and the number of oocytes retrieved and pregnancy rates are greater. As in natural cycles, exogenous HCG is administered when the lead follicle matures and a GnRH agonist can be used to prevent premature LH surge.

A sequential treatment regimen where CC (100 mg daily) is given for 5 days and the addition of modest doses of exogenous gonadotropins (150-225 IU daily) on the last day of CC or the day after stimulates multi-follicular development.

Adding a GnRH agonist in the regimen can prevent premature LH surge but increases costs.

Apart from its common use as a stimulant, CC can prevent premature LH surges in IVF cycles. CC can be used continuously until the day of ovulation triggers and thereby reduces the cost, as GnRH analogues are not needed. A large retrospective case series of minimal ovarian stimulation with clomiphene reported premature ovulation rates of around 2.5% attesting to the effectiveness of clomiphene in preventing premature LH surges.

GnRH Agonist Down-Regulation Gonadotropin Stimulation

Long protocol: The long protocol has remained the standard ovarian stimulation regimen in IVF cycles until more patient-friendly protocols utilizing GnRH antagonists gained widespread acceptance.

Use of long acting GnRH agonists, like leuprolide and buserelin, prevents LH surge in a large majority of cycles, hence stimulation can continue till full oocyte maturity is reached. This leads to higher egg yield and pregnancy rates than with exogenous gonadotropins alone.

In the long protocol, a GnRH agonist is started during the mid-luteal phase of the previous cycle, i.e., on day 21. Usually, patients will commence menses within 7 days, and the gonadotropin treatment will start on day 2 of the menstrual cycle if pituitary down regulation is achieved. At this time, the levels of endogenous gonadotropins are at their lowest, and the flare effect will not affect follicular recruitment.

For Leuprolide acetate the usual treatment regimen begins with 0.1 mg subcutaneously daily for approx. 10 days or until onset of menses or gonadotropins stimulation, decreasing to 0.05 mg daily thereafter until the ovulation trigger. The typical starting dose of exogenous gonadotropins ranges between 150 and 300 IU of urinary FSH, recombinant FSH or urinary menotropins which is tailored according to the needs of individual women.

In women with unpredictable cycles, the onset of menses can be controlled by oral contraceptives (OCs), and the GnRH agonist is started 1 week before OCs are stopped.

After pituitary downregulation has been confirmed (serum E_2 <30-40 pg/ml, no follicles >10 mm in diameter), the gonadotropins are started in the dose of 150-300 IU of urinary FSH (uFSH) or urinary menotropins (hMG) daily. One can use either a 'step-up' or a 'step-down' approach, but the latter is generally preferred.

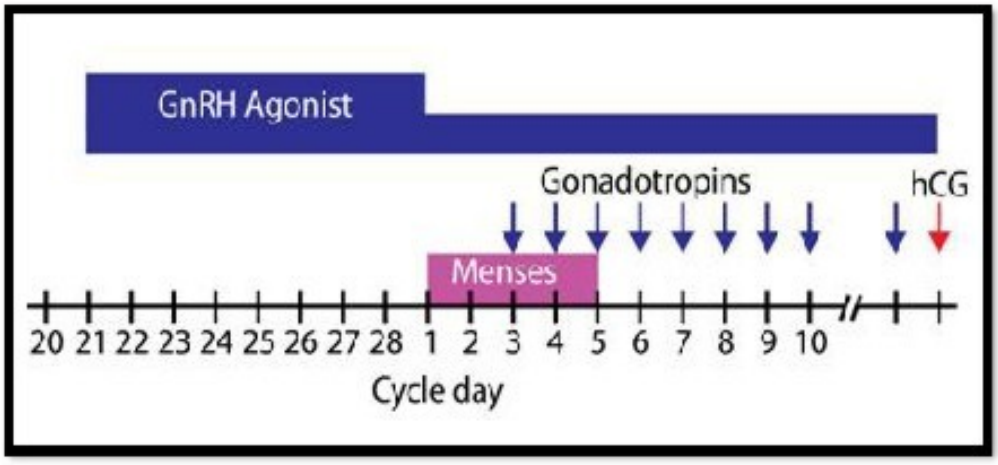

Figure 8.2: *GnRH Agonist*

It has been observed that women who develop ovarian cysts or require longer duration of GnRH agonists to achieve suppression of endogenous gonadotropins usually respond poorly to gonadotropin stimulation and are less likely to become pregnant.

SHORT OR FLARE PROTOCOL

This protocol makes use of the brief initial agonistic phase of response to a GnRH agonist as well as the suppression resulting from longer-term treatment. Here, leuprolide acetate is given in the dose of 1 mg/day on cycle days 2 to 4, and then reduced to 0.5 mg/day, and Gonadotropin stimulation is begun on day 3. Later adjustment in the dose of gonadotropin stimulation, if needed is based on response and indications for trigger are the same as in the long protocol.

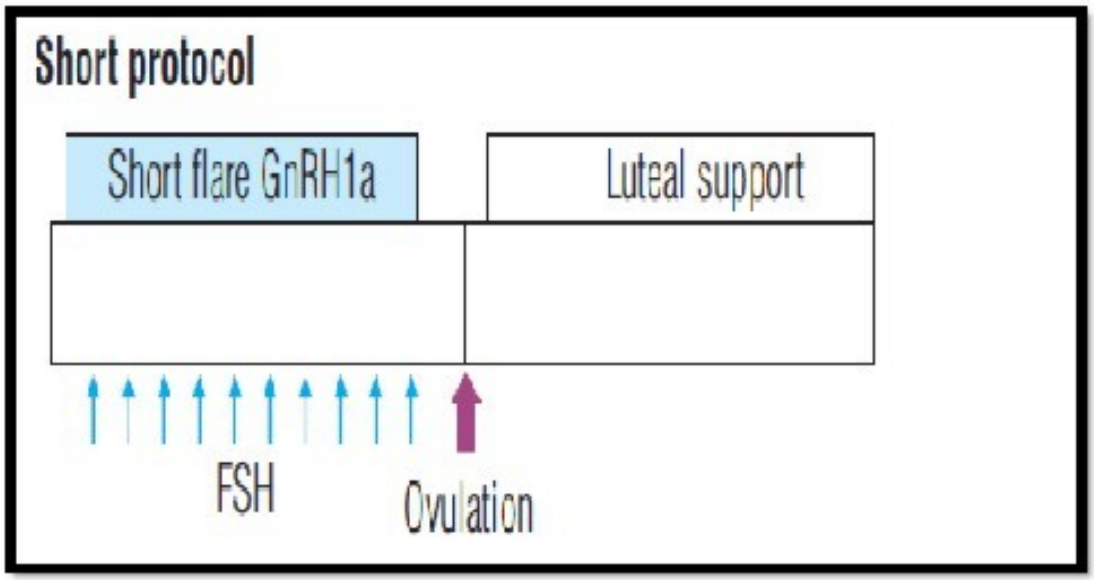

Figure 8.3: *Short or Flare Protocol*

The immediate stimulatory action of the GnRH agonist serves as the initial stimulus for follicular recruitment. Adequate follicular maturation is, on an average, reached in 12 days, which should allow enough time for sufficient pituitary desensitization to prevent any premature LH surges.

This protocol has been reported to improve the follicular response and lower the cycle cancellation rate in poor responders to the long protocol, but the pregnancy and live birth rates are low. Other disadvantages include decreased flexibility and significant increase in serum progesterone, which may affect oocyte quality, fertilization and pregnancy rates.

The "**OC microdose GnRH agonist flare** stimulation regimen is a variation of the standard short protocol involving 14-21 days of preliminary ovarian response with an OC (one pill daily), followed by microdose leuprolide treatment (40ug twice daily) beginning 3 days after discontinuation of OC treatment and high dose gonadotropin stimulation starting on day 3 of leuprolide therapy. The advantage over standard short protocol is because of lower doses of GnRH agonist serum progesterone and androgen concentration do not rise resulting in better oocyte quality and pregnancy rates.

ULTRASHORT PROTOCOL

The agonist is given for 3 days in the early follicular phase. On the second day of agonist administration, stimulation with gonadotropin is started. By this method, LH can be suppressed till the midcycle, and more oocytes can be retrieved with minimal risk of premature LH surge.

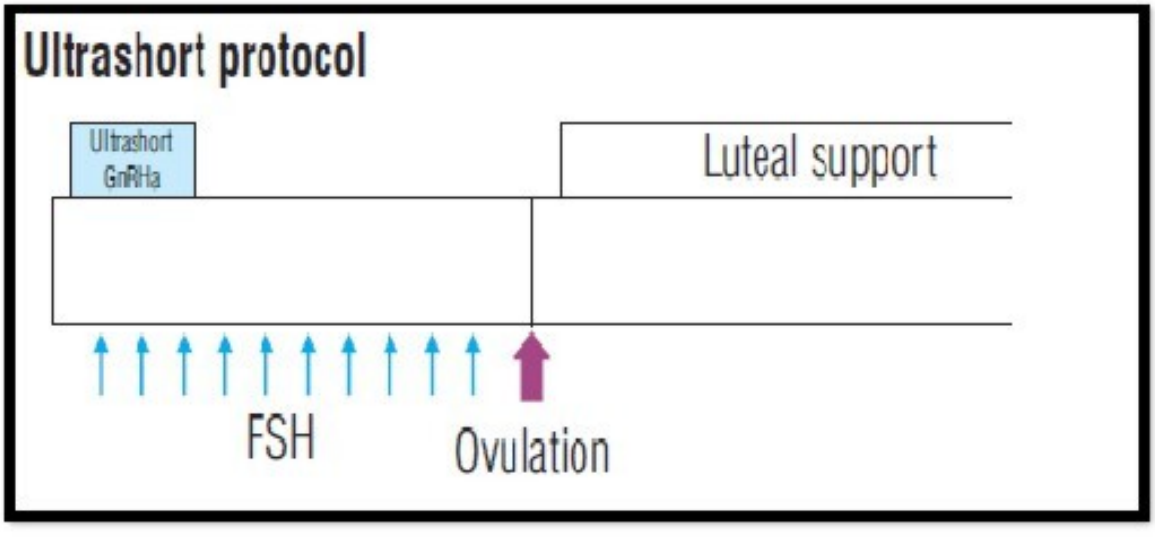

Figure 8.4: *Ultrashort Protocol*

ULTRALONG PROTOCOL

GnRH agonist is given for 3 months and then stimulation started. It is used for endometriosis patient.

Stop protocol Started in luteal phase 1week before the expected start of menses and stopped at the initiation of gonadotropin therapy. However, it is not popular due to erratic response.

GnRH ANTAGONIST GONADOTROPIN STIMULATION PROTOCOL

GnRH-antagonist protocols shorten the treatment period and reduce inconvenience for IVF patients. Unlike GnRH agonists, the antagonists block the GnRH receptors in a dose-dependent competitive manner and have no flare effect. Moreover, gonadotropin suppression occurs almost immediately.

The treatment protocol may be **fixed** and begin after 5-6 days of gonadotropin stimulation or tailored to the response of the individual (**flexible**), starting treatment when the lead follicle reaches approx..13-14 mm in diameter.

So far, only two GnRH antagonists are available for IVF use: cetrorelix and ganirelix. There are two approaches:

Single-dose protocol (French protocol): A single high dose (3 mg) of cetrorelix - not ganirelix as it is not available in depot formulation - is administered on day 8 or 9 of the stimulation cycle (Fig. 3). This is sufficient to prevent an LH surge for 96 hrs, although in slow responders a repeat injection may be needed.

Multiple-dose protocol (Lubeck Protocol): The antagonist (either cetrorelix or ganirelix) is given in small daily doses of 0.25 mg subcutaneously from the 6th or 7th day of gonadotropin stimulation, till and including the day of hCG administration. The Fixed (from Day 6) or flexible protocol can be used.

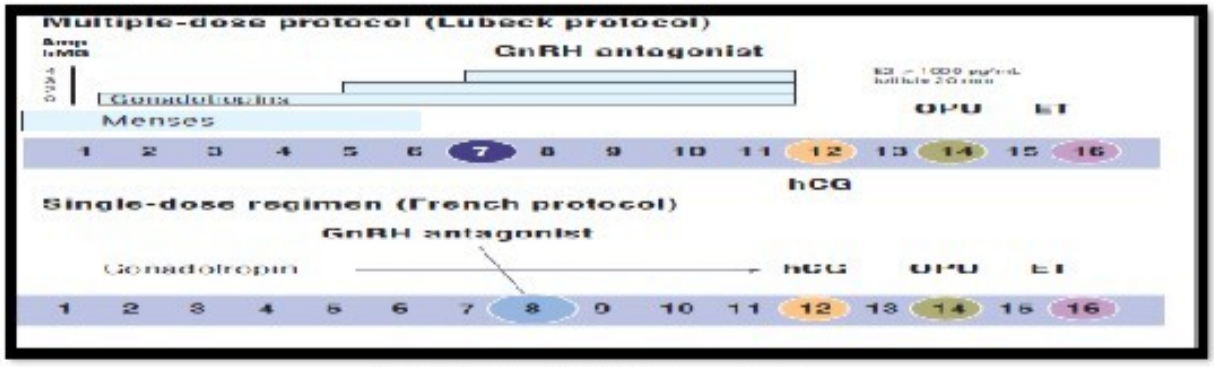

Figure 8.4: *Ultrashort Protocol*

GnRH agonist	GnRH antagonist
Fewer cycles cancelled	For prevention of premature LH surge
Eliminates LH surge	Immediately suppress GTs by blocking GnRH recep restricting treatment only to those days when LH surge likely to occur.
Controls basal LHsecretion	Mechanism of action dependent on equilibrium betwe endogenous GnRH and dose of applied antagonist.
Oocytes recover programmed	Lower GT consumption
Enhances intrafollicula growth and recovery better quality oocytes.	Lower risk of OHSS
Widens the window uterine implantation thu increasing pregnancy rates	Opportunity to give GnRH agonist for trigger
	Reduces the burden of treatment

A common variation of the antagonist stimulation regimen uses preliminary treatment with an OC to control menses, typically ending at least 5 days before the scheduled start, which may also help the synchronization of follicular cohort before stimulation begins. Another variation advocated for poor responders uses micronized estradiol (2 mg twice daily) beginning on day 21 of the preceding cycle to suppress the FSH during the late luteal phase, ending on the day before gonadotropin stimulation or continuing through the first 3 days of gonadotropin stimulation. The discontinuation of estradiol leads to rebound increase of endogenous FSH which synergize with exogenous gonadotropins to promote multifollicular development.

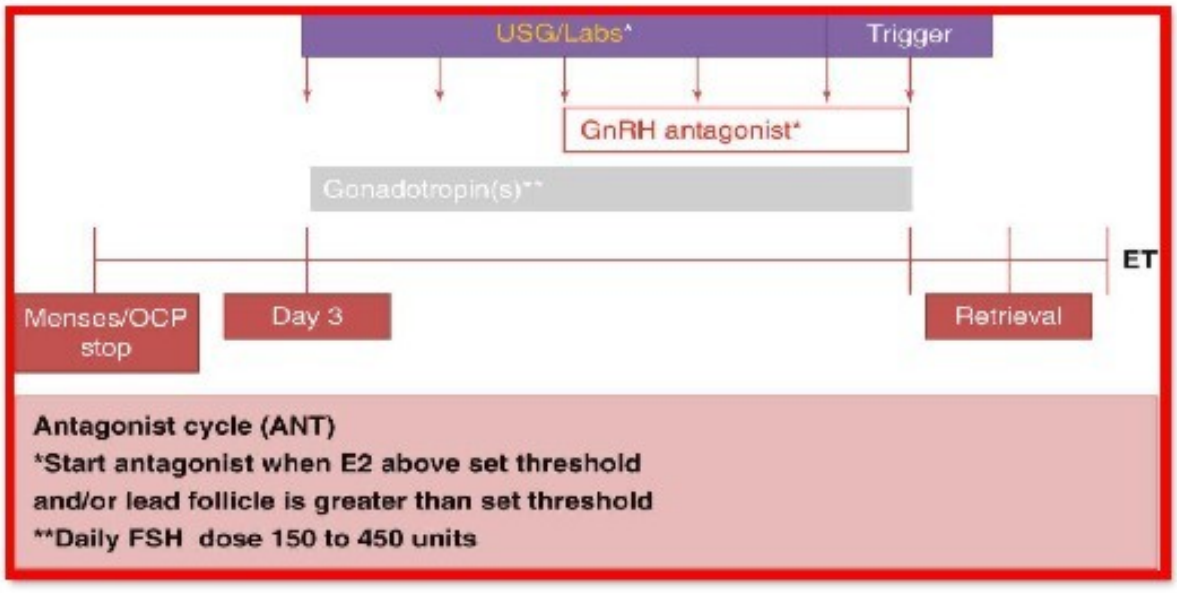

Figure 8.5: *GnRH Antagonist*

Advantages of GnRH agonist and antagonist

Protocol for PCOS Patients

Women with polycystic ovary syndrome (PCOS) are at high risk of developing ovarian hyperstimulation syndrome (OHSS) during ovarian stimulation. Use of GnRH antagonists in the general subfertile population is associated with lower incidence of OHSS than agonists and similar probability of live birth.

The antagonist protocol was found to have an edge over the agonist protocol due to

- Lower incidence of OHSS Grade II
- Shorter duration of stimulation (10 vs 12 days)
- Lesser total dose of gonadotrophin required (1575 vs 1850 IU)

Hence, GnRH antagonist might be the treatment of choice for patients with PCOS undergoing IVF.

CONCLUSION

The introduction of assisted reproductive technology (ART) techniques has enabled many infertile couples to have children of their own. Ovarian stimulation enhances the chances of success in ART procedures by increasing the number of eggs available for fertilization. Agents used for ovarian stimulation include clomiphene citrate, gonadotropins (FSH, LH, hCG, hMG) and GnRH agonists and antagonists.

Chapter 9

CRYOPRESERVATION


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CHAPTER 9

CRYOPRESERVATION

Author: Dr. Vandana Solanki

INTRODUCTION

Cryopreservation is the process by which biological material such as cells and tissues are preserved for an extended periods of time to maintain integrity of the tissue for future use.

It was first performed on animal semen to store sperm for artificial insemination. Lazaro Spallanzani was the first person to observe the effects of low temperature on human sperms in 1779.

Cryopreservation of sperms became possible only after discovery of cryoprotectants such as glycerol in 1949.

In 1953 Bunge and Sherman performed artificial insemination using cryopreserved semen which resulted in human birth.

CRYOPRESERVATION OF SPERMS

Indications of sperm cryopreservation

1) Obstructive azoospermia -Patients that undergo procedures such as MESA, TESA, PESA sperms are retrieved and are then preserved.
2) Nonobstructive azoospermia
3) Patients with cancer – Patients suffering from cancer and requiring chemotherapy can undergo cryo preservation for fertility preservation.

TYPES of CRYOPROTECTANTS –

1) Permeating cryoprotectants - Glycerol, dimethylsulfoxide
2) Non permeating cryoprotectants - Polyhydroxy ethyl starch, glycine, raffinose

For sperms glycerol is commonly used

Various methods of sperm freezing –

1) Vapour freezing method
2) Pellet method
3) Dry -shipper freezing method
4) Freezing in ethanol

SLOW FREEZING VERSUS VITRIFICATION

Slow freezing uses low level of cryoprotectants and the cooling rates are low. There is crystallization of extracellular water and the intracellular water is removed in a controlled manner hence preventing intracellular crystal formation

Vitrification uses high levels of cryoprotectants and involves very fast cooling (within seconds) which results in formation of glass like amorphous state.

CARRIER DEVICES FOR VITRIFICATION

Vitrification is usually carried out using carrier devices such as electron microscopy grid, open straw system, cryotop, cryoleaf , cryotip,, cryolock and hemi straw system

Figure 9.1: *CRYOLEAF*

Figure 9.2: *CRYOTOP DEVICE*

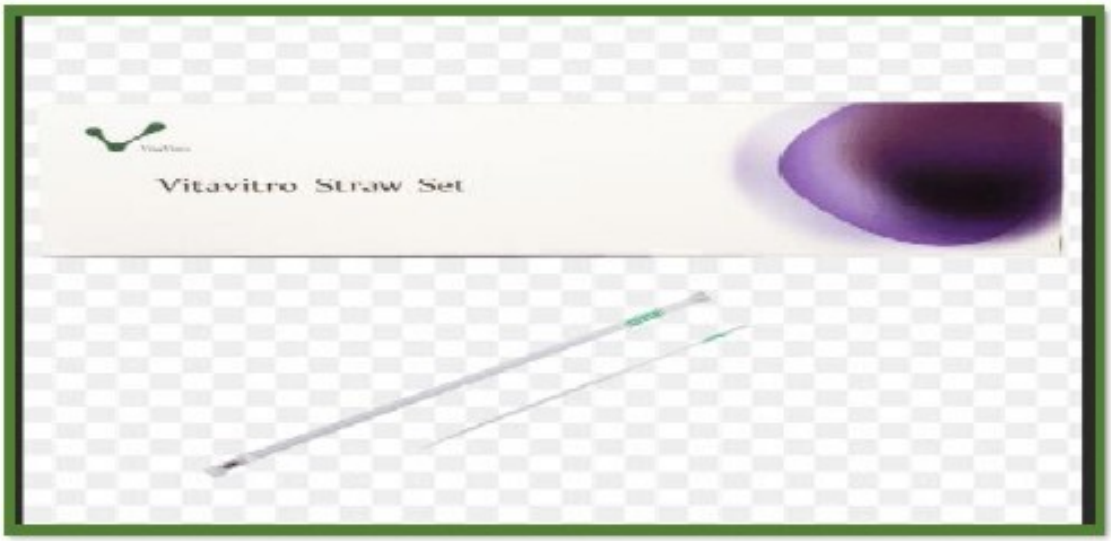

Figure 9.3: *OPEN PULLED STRAW*

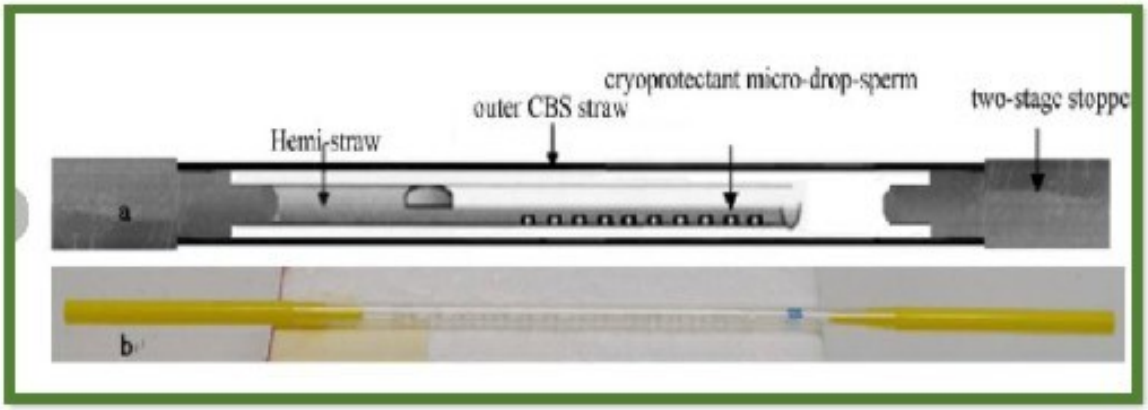

Figure 9.4: *HEMI PULLED STRAW*

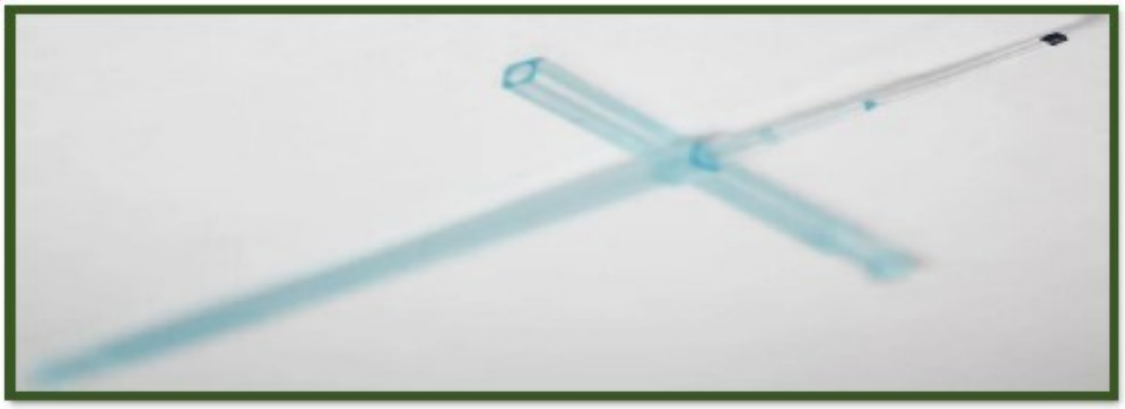

Figure 9.5: *CRYOLOCK*

CRYOPRESERVATION OF SPERMS

Semen is collected and allowed to liquefy for 30 minutes at 37 C. The cryoprotectant is added dropwise to unprocessed semen till a dilution of 1:1 is achieved. The mixture is allowed to equilibrate at room temperature for 10 minutes. Transfer the mixture to cryovials and then into cryocane and place in the refrigerator at 2-5 C for 90 minutes. Then the cryocane is placed over liquid nitrogen tank for storage at -196 C.

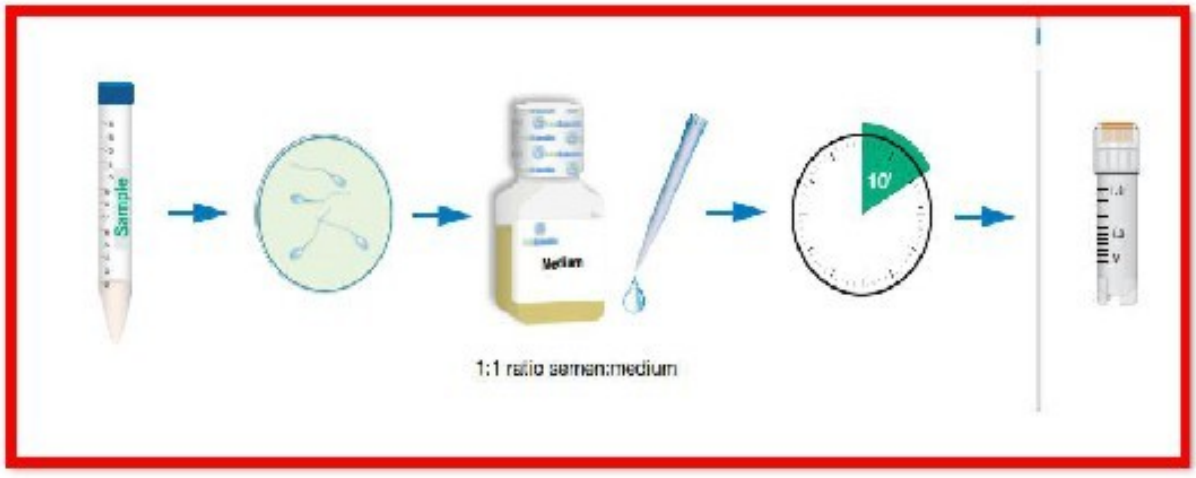

Figure 9.6: *Cryopreservation of Sperms*

THAWING OF SPERMS

Frozen specimens are removed from the storage tank and allow the cryovials to stand for 5 minutes at room temperature and then placed in a water bath at 37degree C for 10 minutes. Transfer the sperms to a sperm separation media and add 2 mL of sperm washing media and centrifuge for 15-20 minutes at 200-300

rpm. A pellet is formed at bottom of the vial. Remove the upper layers leaving behind 0.5 mL solution. Using a pipette remove the pellet and again centrifuge with 2 mL washing solution for 8-10 minutes at 200-300 rpm. Finally remove the Supernatant.

$$\text{Cryosurvival} = \frac{\text{\% of motility of post thawed specimen}}{\text{\% of motility of pre freeze specimen}}$$

INDICATIONS OF OOCYTE PRRSERVATION

1) Fertility preservation for women suffering from cancer
2) Donor eggs
3) Optimizing IVF cycles

OOCYTE VITRIFICATION

Oocytes are retrieved, evaluated and then the granulosa cells surrounding the eggs are removed. They are then passed from one medium to another by increasing the concentration of cryoprotectants. Once the oocytes shrink and do not rise up to the surface the oocytes are loaded on the carrier media and plunged into liquid nitrogen for 1 second. The carrier media is then sealed and kept in a container with liquid nitrogen.

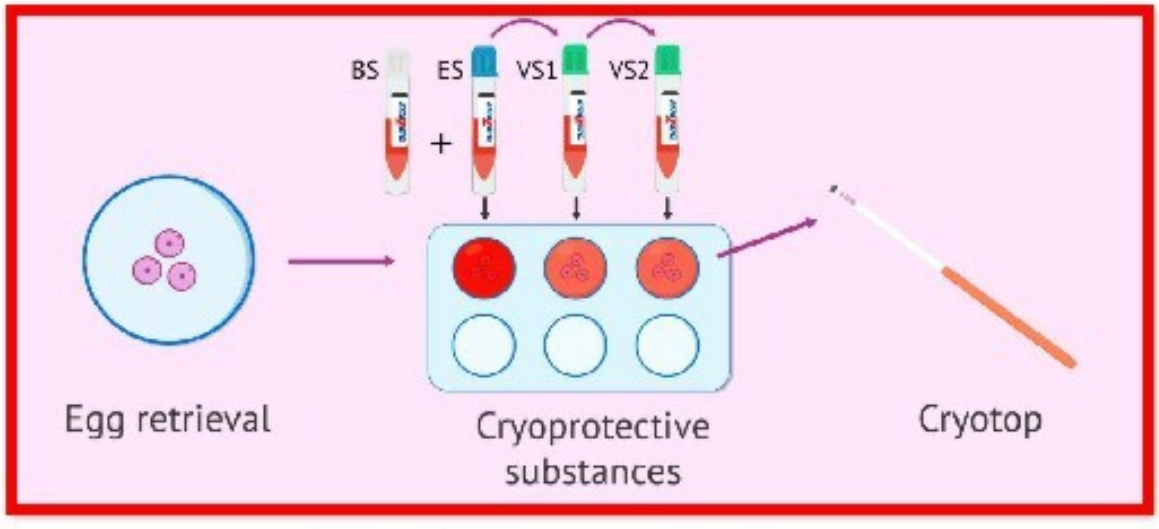

Figure 9.7: *Cryopreservation of Sperms*

BLASTOCYST VITRIFICATION

For blastocyst with Gardner grade 4 or higher there is risk of insufficient replacement of water with cryoprotectant. Hence they are put through a shrinkage solution to shrink the blastocyst. They are then passed through equilibrium solution for 15 minutes. They are then passed through a series of vitrification solution for at least 60-90 seconds. The embryos are then loaded on cryptop and plunged into liquid nitrogen for 1 second after which they stored in liquid nitrogen.

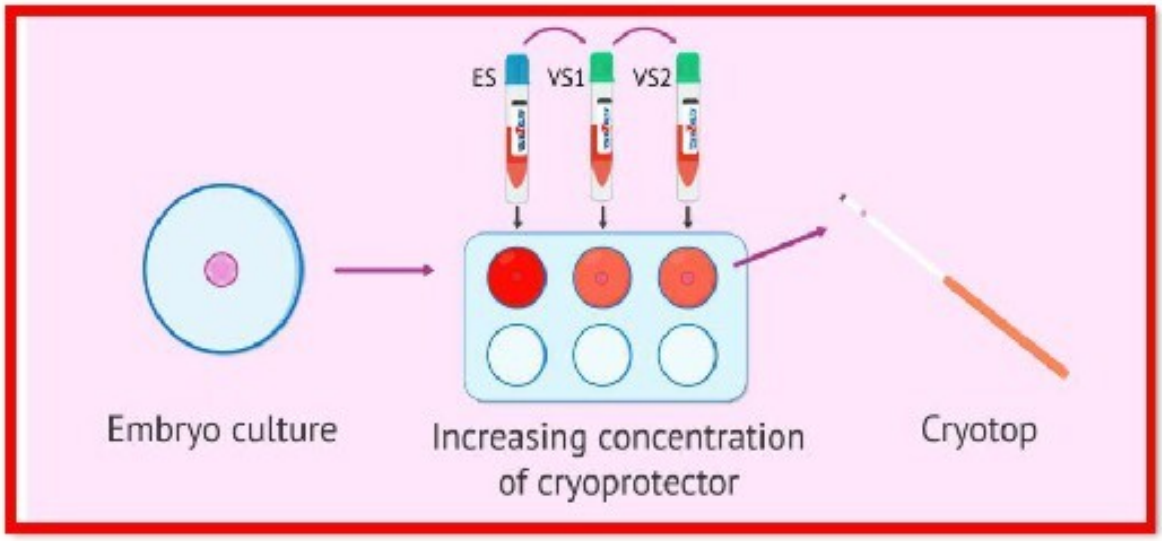

Figure 9.8: *Blastocyst Vitrification*

THAWING OF OOCYTES AND EMBRYOS

Prepare thawing solution by pre warming for 30 minutes in an incubator and 5 minutes in a water bath. Remove the crytop from the storage and remove its cover and transfer to thawing solution for 1 minute after which the embryo/ oocytes are transferred to diluent solution and are kept for 3 minutes. They are then transferred to washing solution and kept for 5 minute. Recovery culture is done to check viability.

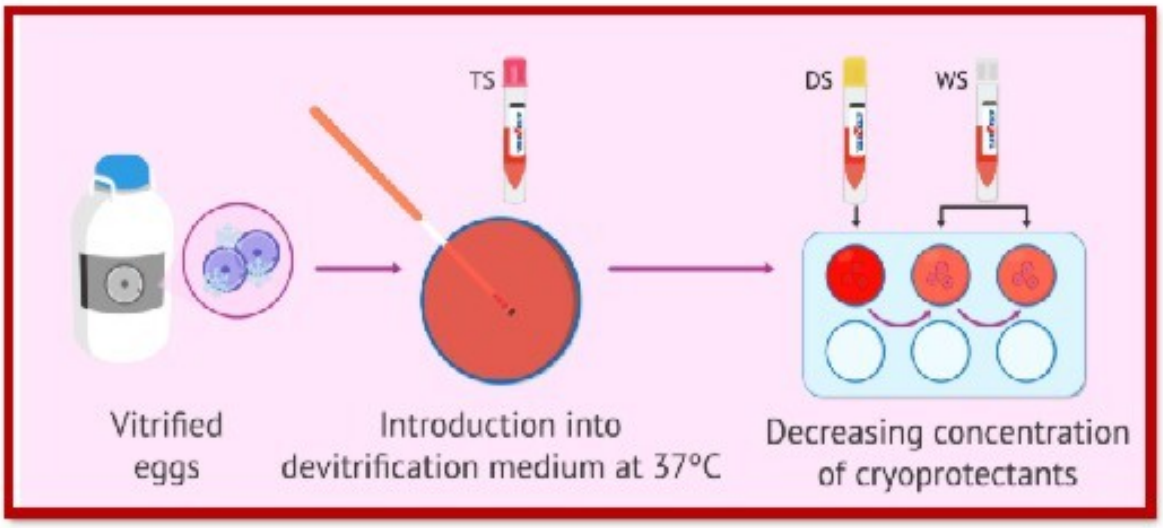

Figure 9.9: *Thawing of Oocytes and Embryos*


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Chapter 10

ROLE OF ENDOSCOPY IN INFERTILITY


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CHAPTER 10

ROLE OF ENDOSCOPY IN INFERTILITY

Author: Dr. Rekha Sachan

The introduction of endoscopy by Jacobaeus in 1910, there has been a change in the approach for the diagnosis and treatment of various diseases and female infertility. The advances in techniques of operative endoscopy, with high technology (such as endoscopes, video cameras) have made it possible to perform laparoscopically infertility-related procedures previously requiring laparotomy.

There are basically two types of gynecological endoscopy:

- Hysteroscopy.
- Laparoscopy.

Both of these can be diagnostic when the procedure only aims to diagnose a condition, or surgical or operative, where in addition to diagnosing, we can perform treatment simultaneously

The advantages of endoscopic surgery are

- Less aggressive technique, with less bleeding and complications.
- Shorter postoperative time and better recovery of the patient. Therefore, shorter hospitals stay and earlier return to work.
- Better treatment of problems related to reproductive aspects, since the visualization of uterus, ovaries, fallopian tubes, in closer and more direct view.
- Prevention of internal adhesion, with better results in subsequent ART treatments.
- Better aesthetic result from fewer scars, or even no scar in case of a Hysteroscopy.

In any case, the overall evaluation of the person or couple desiring pregnancy is critical to properly ascertain the indication of one technique or another, as well as the time to perform it and the necessary recovery time in order to safely and successfully perform an assisted reproduction treatment, or try for a spontaneous pregnancy. Diagnostic hysteroscopy, can be performed without general anesthesia, and it has proven **benefits in Implantation** when performed prior to embryo transferr.

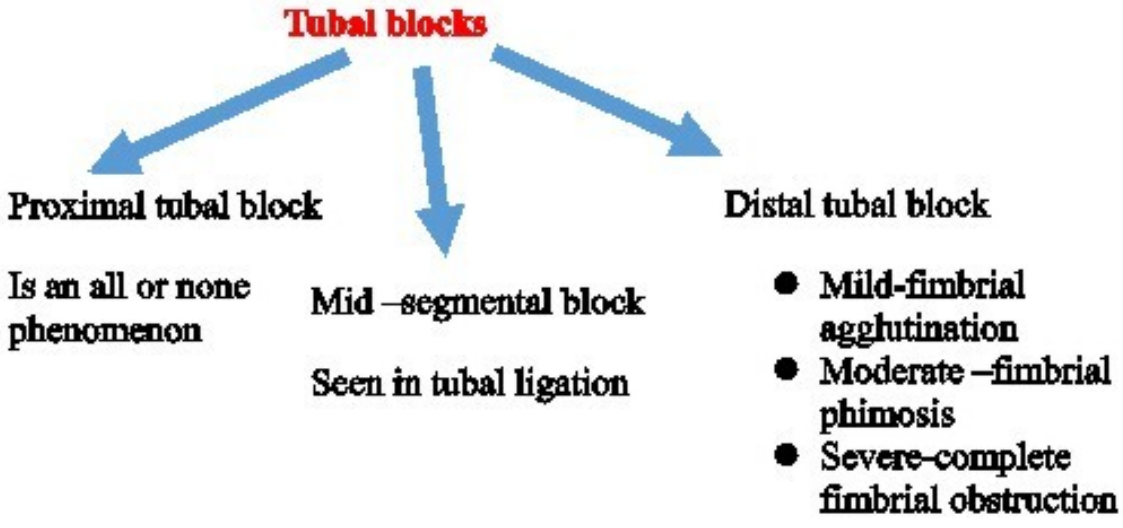
For tubal factor responsible for infertility better way to treat by laproscopic surgery

Tubal factors

Accounts for 25-35% of infertility

Causes-

- Tuberculosis
- PID (chlamydia, gonorrhea)
- Ectopic pregnancy
- Endometriosis
- Iatrogenic (tubal surgeries)



LAPAROSCOPY

Gold standard for diagnosing tubal and peritoneal diseases.

Laparoscopy usually Performed under GA

By laparoscopy - Direct visualisation of uterus, anterior and posterior cul de sac, ovaries and fallopian tubes

By Chromotubation permits evaluation of tubal patency –injection of blue dye through a cannula attached to cervix and it permits intrauterine evaluation of tubal patency, Indigocarmine is preffered over methylene blue dye.

Advantages of Laparoscopy –

1. Direct visualisation of pelvic organs
2. Concurrent treatment of peritubal and periovarian adhesions and subserosal uterine fibroid
3. It helps in evaluating endometriosis,
4. Treating endometriosis,adhesions or repairing tubes.

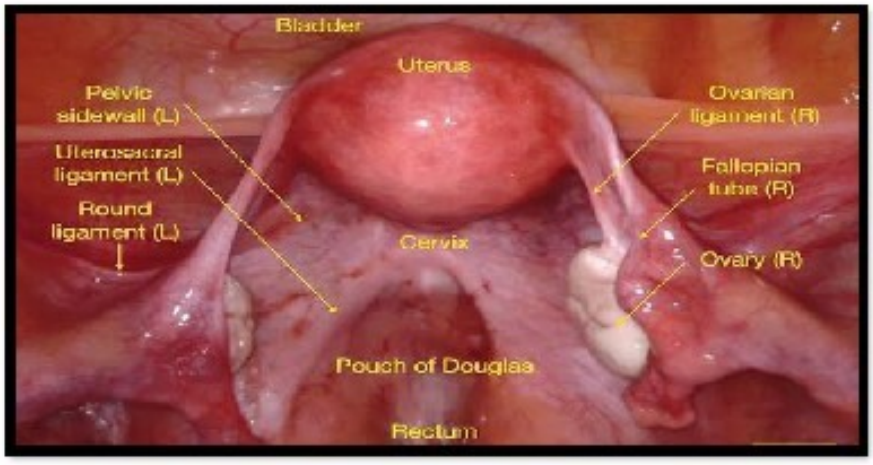
Disadvantages of Laparoscopy –

1. Invasive procedure
2. Site of block cannot be identified
3. Anesthesia is required
4. Expertise required
5. Risk of bladder bowel injury

Indications of Laparoscopy -

1) **Diagnostic Laparoscopy**
   - Infertility
   - Endometriosis
   - Adnexal mass evaluation
   - Pelvic pain (acute/chronic)

2) **Operative Laparoscopy**
   - Sterilization
   - Ectopic pregnancy
   - Ovarian cysts
   - Tubal recanalisation
   - Myomectomy
   - Hysterectomy



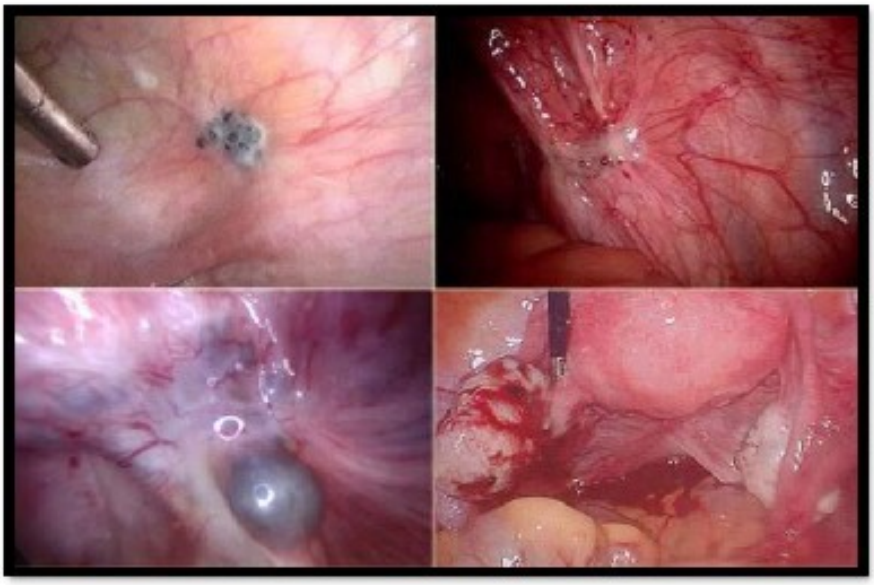


Figure 10.1: *Endometriotic deposits seen on laparoascopy*

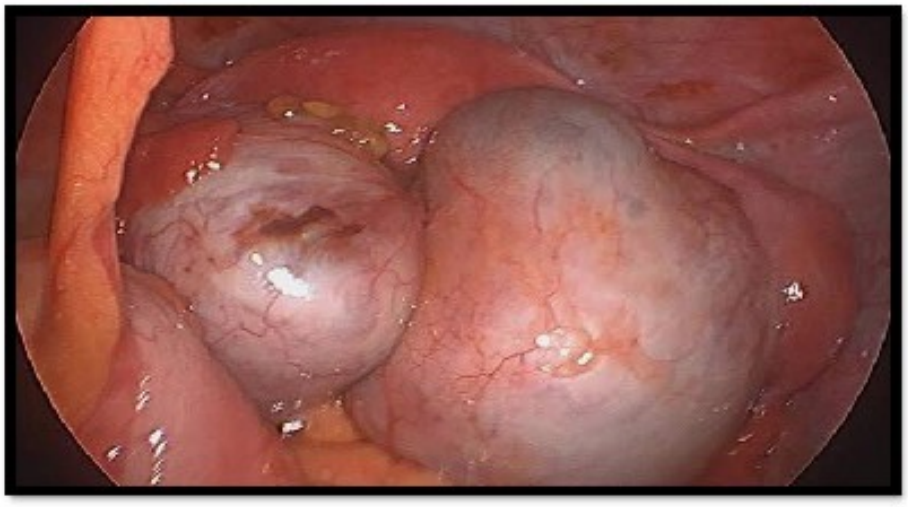


Figure 10.2:*Kissing ovariesseen on laparoscopy*

FOR ENDOMETRIAL FACTORS RESPONSIBLE FOR INFERTILITY BETTER WAY TO TREAT BY HYSTEROSCOPIC SURGERY

Hysteroscopy

Gold standard for both diagnosis and treatment of intrauterine pathology.

The procedure involves insertion of an endoscope through a cervical canal into the uterine cavity and instillation of distension media to facilitate visualization within the uterine cavity. This performed in early to mid-follicular phase.

Advantages

- This is office procedure
- It is diagnostic as well as therapeutic

Disadvantages

- Poor visualization in case of uterine bleeding
- Inability to evaluate structure outside the cavity
- Anaesthesia is required.

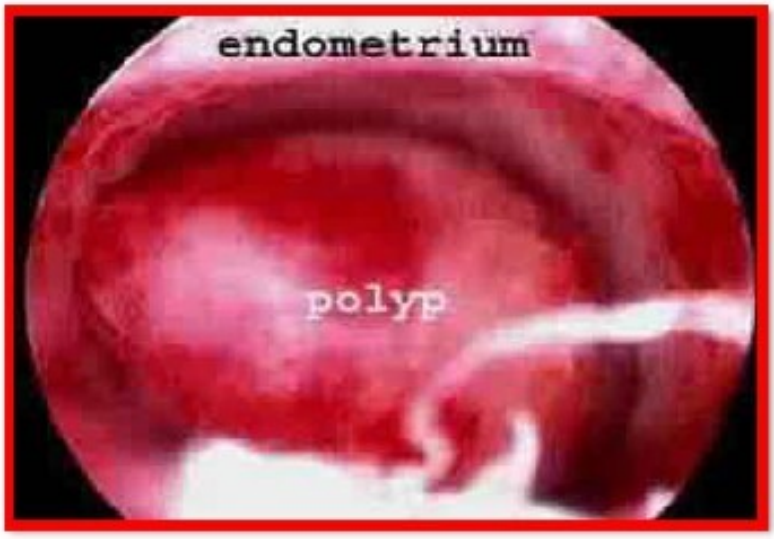


Figure 10.3*Endometrium*

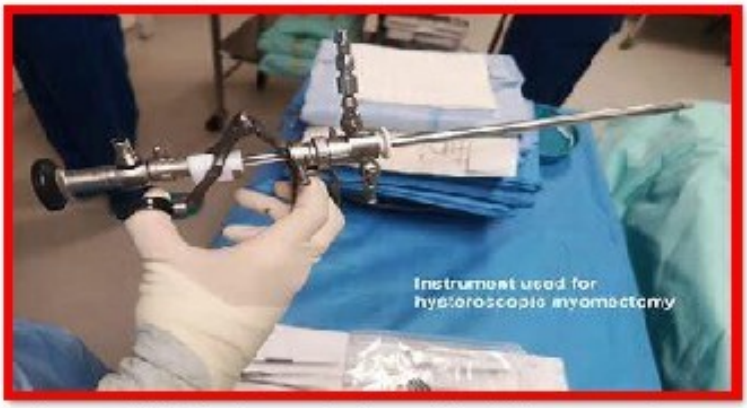


Figure 10.4*Instrumental used for hysteroscopic myomectomy*

Therapeutic uses of hysteroscopy

Congenital anomalies- Septate uterus –hysteroscopic metroplasty

- Polyp- hysteroscopic polypectomy
- Intrauterine synechiae

Hysteroscopic resection of synechiae plus estrogen therapy for 1 month plus intrauterine placement of pediatric foley catheter for 1-2 weeks.

Indications of hysteroscopy

1) **Diagnostic**
    - Intrauterine lesions like submucous myoma, polyp
    - Missing IUCD
    - Uterine anomalies
    - Intrauterine adhesions
    - Postmenopausal bleeding
    - To study Implantation failure.
    - Endometrial adenocarcinoma.
    - Endometrial polyps.
2) **Operative**
    - Septal resection
    - Tubal cannulation
    - Myomectomy
    - Sterilization
    - IUCD removal
    - Polypectomy
    - Adhesiolysis
    - Placement of intratubal devices (Essure)

Instrument

Hysteroscope: It includes-

- Telescope : eyepiece, barrel & objective lens.
- Angle options : 0,12,15, 25, 30 & 70 degree.
- O degree provides a panoramic view. angled one improve the view of ostia in an abnormally shaped uterine cavity.

Rigid hysteroscope

- in-patient and complex operating room procedures.
- 3-5mm in diameter
  more durable and provide superior image.

Flexible hysteroscope

- most commonly used for office hysteroscopy
- flexibility; tip deflection of 120-160 degree.
- irregularly shaped uterus & navigation around

intrauterine lesions.

Light source.

Halogen and xenon; xenon generator provides white light, which gives a superior color and intensity.

Camera Equipment

Diagnostic sheaths

- to deliver the distention media
- fit by means of a watertight seal lock
  4 to 5 mm in diameter, with a 1 mm clearance between the inner wall and the telescope, through which the distention media is transmitted.

Operative sheaths

- larger diameter - 7 to 10mm
  allows space for instillation of medium, for the telescope, and for the insertion of operating devices.

Resectoscope

Three basic electrodes: a ball, barrel, and a cutting loop.

- Accessory instruments
- alligator grasping forceps, biopsy forceps, and scissors, **Morcellator**
  Monopolar and bipolar electrodes

A new bipolar system named VersaPoint (saline may be used as distention media)

Distention media

Muscle of uterine walls requires a minimum pressure of 40 mm of Hg to distend the cavity.

Types of distention media

Gaseous liquid - high-viscosity and low-viscosity fluids

Carbon dioxide has specific quality.

- It is colorless gas
- It is ideal for office hysteroscopy.
- Can be given through insufflator
- it allows entry evaluation of the endocervical canal.

Disadvantages - Risk of gas embolism and no effective way to remove blood and debris with use of carbon dioxide.

High viscosity fluids -Dextran 70 (Hyscon)

Low viscosity fluids with electrolytes-

Normal saline and lactated ringer's solution commonly used because of easy availability and low cost and its miscibility with blood hence obscuring the vision ,side effect is pulmonary and cerebral edema

Low viscosity fluids without electrolytes-

- 1.5% glycine is the most commonly used medium.
- Other non-electrolyte media are - 5% glucose and sorbitol/mannitol.

Complications related to distention media:

- due to CO2 insufflation:
- Cardiac arrhythmias due to excessive absorption.
- Gas embolism.

due to fluid:

- Anaphylactic reaction
- Pulmonary edema
- Adult RDS

Chapter 10

DONOR IUI AND EGG DONATION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CHAPTER 11

DONOR IUI AND EGG DONATION

Author: Dr. Vandana Solanki

Intrauterine insemination with donor sperm (IUI with Donor sperm) is an assisted reproductive technology (ART) offered to couples with male infertility or risk of genetic disease transmission. The first successful human pregnancy from frozen sperm was reported in 1953 by Bunge and Sherman using dry ice for freezing. As cryopreservation of human semen results in a significant loss of spermatozoa motility and viability, only semen derived from a highly selected population of males is suitable for the purposes of insemination.

Now frozen semen is used exclusively for donor intrauterine insemination (IUIs) and it has proved to be highly effective in achieving pregnancy.

INDICATIONS OF DONOR IUI

- Azoospermia
- Moderate to severe male factor infertility and not able to afford ICSI.
- Some genetic disorder
- Single women
- HIV +VE Husband

DONOR CHARACTERISTICS

- Donors should be <40 years of age to minimize the potential risk of genetic abnormalities associated with aging.
- Anonymous (unknown), though occasionally a known donor might be used.
- Federal Food and Drug Administration (FDA) requires that all donor sperm must be quarantined for a minimum of 6 months prior to use.
- The donor is chosen by the doctor in charge of the sperm bank, so as to match the physical characteristics of the future father as closely as possible. The elements taken into account are the body size, hair colour, eyes and skin, as well as the blood type and Rhesus factor.
- The frozen semen is kept into quarantine to ensure that the donor is not a carrier of any disease transmittable through semen, such as the AIDS virus, hepatitis B and C, cytomegalovirus, etc.

SPERM BANK

- Detailed information about donor education, appearance, hobbies, and interest are kept in bank.
- The sperm donor will undergo an initial semen analysis to confirm that the sperm are of good enough quality to undergo freezing and thawing. If selected, the donor will produce further samples which are washed, concentrated, and frozen for at least 6 months.
- At this time the donor is retested for communicable diseases, and the sperm are then only available for release if all repeat testing is negative.

MODE OF INSEMINATION

After thawing the frozen sperm, the suspension is deposited in the cervix or the uterus with intrauterine insemination being preferred. It is performed by introducing a 0.2–0.5 ml sperm suspension, into the uterus with a small catheter, usually without ultrasound guidance. For frozen semen, IUI is better than intracervical insemination (ICI). In a recent Cochrane systematic review, Besselink et al reported a significantly higher pregnancy rate (OR= 3.37 95% CI 1.9-5.96) and live birth (OR=1.98 95% CI 1.02-3.86) after 6 cycles of frozen thawed donor IUI compared to ICI.

SUCCESS OF DONOR IUI

The success rate of donor insemination varies according to the patient's age as well as the presence of other factors influencing fertility (i.e. endometriosis or tubal disease).

In an appropriately selected population, the chance of pregnancy simply using donor insemination ranges from *8-15%*. The success rate may be higher if other medications are used to stimulate the ovaries.

Donor insemination does not increase the risk of birth defects.

EGG DONATION

Oocyte (egg) donation, is a significant advancement in the field of assisted reproductive technology (ART) that offers hope and opportunity to individuals and couples facing infertility challenges or genetic concern.

INDICATIONS OF EGG DONATION

Oocyte donor treatment is recommended in various situations where individuals or couples face certain fertility challenges or genetic concerns that make it difficult to conceive using their own eggs. Some common indications for oocyte donor treatment are as follows:

Diminished Ovarian Reserve: Women with diminished ovarian reserve, characterized by a reduced number or quality of eggs, may struggle to produce viable embryos using their own eggs. Oocyte donation provides a source of healthy eggs from a young donor with better ovarian reserve.

Advanced Maternal Age: The quantity and quality of a woman's eggs decline with age, which can cause higher risks of chromosomal abnormalities and infertility. Oocyte donor treatment offers a solution by using eggs from a younger donor to improve the chances of successful pregnancy.

Premature Ovarian Failure (POF): Before the age of 40, Egg donation can be an option for women with POF who want to experience pregnancy and childbirth.

Genetic Disorders: Couples or individuals with known genetic disorders that they do not want to pass on to their offspring may opt for egg donation to avoid transmitting those disorders to their children.

Repeated IVF Failures: Couples who have experienced numerous unsuccessful in vitro fertilization (IVF) cycles because poor embryo quality or other factors may consider using donor eggs to improve their chances of success.

Single Parent or Same-Sex Couples: Single individuals or same-sex couples where one partner lacks viable eggs might opt for oocyte donation to achieve parenthood.

Previous Oophorectomy: Women who have had their ovaries surgically removed due to conditions like ovarian cancer may not have functional eggs left. Egg donation can be a way for them to have a genetic connection with their child.

Women with Absent Ovaries: Women born without ovaries or those who have had both ovaries removed due to medical conditions can still experience pregnancy through egg donation.

The American Society for Reproductive Medicine recommends that egg donors be under the age of 34.

CRITERIA FOR AN EGG DONOR

The criteria for a woman to be an egg donor are stipulated in the Assisted Reproductive Technology (Regulation) Bill, 2021. It is important to know that egg donation in India is an anonymous process.

- The egg donor has to be a healthy woman between 23 and 35 years of age and should at least one child.

- An egg donor can only donate eggs once in her lifetime and no more than 7 eggs should be retrieved.
- An egg donor can only donate eggs once in her lifetime and no more than 7 eggs should be retrieved.
- An ART bank shall obtain all necessary information in respect of an oocyte donor, including the name, Aadhaar number, address, and any other details required.
- The gamete of a donor shall be stored for not more than ten years and at the end of such period such gametes shall be allowed to perish or be donated to a research organization registered under this Act for research purposes with the consent of the couple or individual.
- *Medical examination of donor*The donor shall be tested for the following communicable diseases, namely Human Immunodeficiency Virus (HIV) both type 1 and 2, Hepatitis B virus (HBV), Hepatitis C virus (HCV), Treponema pallidum (Syphilis) through VDRL
- A donor shall relinquish all parental rights over the child or children who may be born from her gamete.

Process of IVF with egg donor

IVF with egg donor process can broadly be divided into:

1. Recipient evaluation

A basic evaluation is done by the fertility specialist. The evaluation consists of tests to identify any abnormalities that could interfere with the procedure.

The tests include:

– Ultrasound examination to find abnormalities in the uterus

– Basic blood tests (Hormone profile, complete blood picture, etc.)

– Screenings such as Pap Smears and Mammograms

2. Donor selection

Donor will be selected from the egg donor profiles which will be shared with the recipient couple.
As mentioned, the donor will be anonymous. Physical attributes such as ethnicity, hair color, eye color, and other basic details such as education and

job will be shared with the recipient.

3. Syncing the donor and recipient's menstrual cycles

The recipient's and the egg donor's menstruation cycles are synchronized in an IVF with egg donation procedure. This is usually done using OCPs. Once a donor is picked the recipient women is put on a prescribed dose of estradiol tablets to sync their respective menstrual cycles to prepare the recipient women's uterus for embryo transfer from the second day of her period and the donor is given gonadotropin injections for ovarian stimulation.

4. The egg retrieval process from the donor

After ovarian stimulation, the ovarian follicles are triggered for oocyte maturation. It is important to know that the ovaries are triggered only after reaching an appropriate and desired follicle size. Following the maturation process, which typically takes 11–12 days, egg retrieval is done under general anesthesia along with trans vaginal ultrasound guidance. Once most of the follicles measure 18 to 22 mm on ultrasound, HCG is administered for triggering ovulation. The egg retrieval is scheduled 35 hours later.

5. After ovum pick up follow up:

Following the egg retrieval, the donor receives an injection with 100 mg of progesterone or progesterone pills and is scheduled for a follow up examination following ensuing menstruation. The recipient starts receiving progesterone injections on the day of the donor's egg retrieval and continues with such daily injections until the 12th week of pregnancy or evidence of a negative outcome (whichever occurs sooner). On the day of egg retrieval, the eggs are fertilized with the partner's sperm and an embryo transfer is performed 3 or 5 days' post egg retrieval. Two tests of beta HCG are performed two days apart on the 8th and 10th day post transfers of Day 5 embryos. Supplemental hormone therapy is continued throughout the first trimester.

6. Psychological Evaluation

The decision to proceed with donated oocytes is complex, and patients may benefit from psychological counseling to aid in this decision. The physician should offer psychological counseling to all couples and should require psychological consultation for couples in whom there appear to be factors that warrant further evaluation.

7. All potential recipient couples should be offered the option of cryopreserving and quarantining embryos derived from donor oocytes for 6 months, with

release after the donor has been retested. However, couples should be informed that embro crypreservation may significantly reduce implanation rates.

The recipient couple should be appropriately counseled in the event of seroconversion of the oocyte donor after cryopreservation of the embryos.

8. Record Keeping

It is necessary to maintain permanent records about each donor's initial selection process and subsequent follow-up evaluation. To the extent possible, clinical outcome should be recorded for each treatment cycle. A mechanism must exist to maintain these records as a future medical resource for any offspring produced.

9. Legal Issues/Consent

THE INFLUENCE OF AGE ON OUTCOME

While conventional IVF birth rates decline with increasing age of the mother, the birth rate in ovum donor recipients remains relatively constant in all age categories (50-60% per attempt). It is the age of the egg provider that influences outcome, regardless of the method of conception. Natural conception rates, conception following intrauterine insemination and conventional IVF conception rates all decline with advancing age of the woman. This is not the case in embryo recipients where the egg provider is of a younger age.

The miscarriage rate increases with the age of the egg donor rather than with advancing age of the recipient. Advancing age is associated with an increased incidence of miscarriage following natural conception, IUI and conventional IVF while the incidence of miscarriage remains constant regardless of the advancing age of the embryo recipient in egg donor cycles.

Chapter 12

FERTILITY PRESERVATION


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CHAPTER 12

FERTILITY PRESERVATION

Author: Profr. Rekha Sachan

Oncofertility is a term coined for fertility preservation in cancer patients. Improvement in cancer management and increasing survival rates has created a need for oncofertility. Current data suggest that for most tumors post treatment pregnancy does not increase the risk of cancer progression or obstetric or neonatal outcome. Unfortunately, fertility preservation services are rarely offered or even discussed with the patient before starting cancer therapy. The clinical impact of chemotherapeutic drugs on the ovary is variable ranging from no effect to complete ovarian atrophy. The degree of damage is dependent upon the type of the chemotherapeutic agent used, dose given, age of the patient and her baseline ovarian reserve. The prepubertal ovary is less susceptible to damage by chemotherapeutic agents while older women have a low ovarian reserve. Unlike chemotherapy, radiotherapy affects both the ovary and the uterus.

OVARIAN EFFECTS

Human oocyte is sensitive to radiation, with an estimated median lethal dose (LD50) of <2 Gy. Damage to the ovary by radiotherapy is dependent on the age of the patient and dose of the ovarian exposure. The effective sterilizing dose (ESD) is the dose of fractionated radiotherapy (Gy) at which POF occurs immediately after treatment in 97.5% of patients. ESD decreases with increasing age, being 20.3 Gy at birth, 18.4 Gy at 10 years, 16.5 Gy at 20 years, and 14.3 Gy at 30 years, with only 6 Gy being required to cause permanent ovarian failure in women over 40. The number of primordial follicles present at the time of treatment and the dose of radiation received by the ovaries determines the fertility "window." Ovarian failure has been reported in 90% of patients following total body irradiation (TBI) (10–15.75 Gy) and in 97% of females treated with total abdominal irradiation (20–30 Gy) during childhood.

UTERINE EFFECT

Uterine Exposure to radiation leads to reduced vascularity, damage to myometrium leading to fibrosis and hormone dependent endometrial insufficiency, which results in adverse reproductive outcomes subsequently.

The uterine volume is lower and endometrium atrophies completely if there is direct radiation. Increased rates of infertility, miscarriage, preterm labor, intra-uterine growth retardation and low birth weight have been reported, especially if conception occurs within a year of radiotherapy. An increase in perinatal mortality has been reported. patients receiving >45 Gy during adulthood and >25 Gy in childhood should be counseled to avoid attempting pregnancy. There is no clarity on the dose of radiation to the uterus, above which a pregnancy would not be sustainable. The first successful delivery after transplantation of cryopreserved ovarian cortical tissue and subsequent *in vitro* fertilization (IVF) has been reported in a patient of Ewing's sarcoma who had received sterilizing pelvic radiotherapy (54 Gy) and 40 weeks intensive high-dose chemotherapy for the treatment of Ewing's sarcoma 14 years earlierr.

FERTILITY -SPARING SURGERY

Ovarian transposition

Protects ovarian function by moving the ovaries out of the field of radiation. In cranio spinal irradiation, the ovaries are fixed as laterally as possible, away from the spine; for pelvic irradiation, they are moved outside the pelvis and anchored as high as possible above the pelvic brim either in the paracolic gutter or anterior abdominal wall. This requires mobilization of the ovary by cutting the utero-ovarian ligaments. Titanium clips are placed on the two opposite borders of the ovaries for radiological identification. Ovarian transposition does carry certain risks such as increased ovarian cyst formation, postoperative adhesions, chronic pelvic pain, migration of the ovaries back to their native position and POF, apart from the surgical risk. There is also the concern of metastatic disease in the ovaries though it exists in a minority of patients

Fertility Preservation Options Among Females are

- Embryo Freezing
- Egg Freezing
- Ovarian Tissue Freezing
- Radiation Shielding of Gonads
- Ovarian Transposition
- Radical Trachelectomy
- Ovarian Suppression
  - Harvesting eggs, in vitro fertilization, and freezing of embryos for later implantation
  - Harvesting and freezing of unfertilized eggs
  - Freezing of ovarian tissue and reimplantation after cancer treatment

- When radiation nessesary Use of shielding to reduce scatter radiation to the reproductive organs
- In cases of cancer cervix--Surgical repositioning of ovaries away from the radiation field
- In cases of cancer cervix- Surgical removal of the cervix with preservation of the uterus
- Gonadotropin-releasing hormone analogs or antagonists used to suppress ovaries


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Chapter 13

MANAGEMENT OF INFERTILITY IN SPECIAL SITUATIONS


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CHAPTER 13

MANAGEMENT OF INFERTILITY IN SPECIAL SITUATIONS

Author: Prof. Pushp Lata Sankhwar

INFERTILITY IN ADVANCED AGE-

As women ages, the genetic quality of their eggs and the efficiency with which their bodies reject genetically damaged embryos both declines leading to an increased risk of genetic problems in their offspring. This triad of declining fertility, declining hormone levels, and increasing risk for genetic problems is what most people mean when they say "biological clock." Male fertility and male sex hormones do decline with age. And the genetic quality of sperm does decline, leading to an increased risk of genetic problems in offsprings. Hence these features of aging have expanded the notion of "biological clock" to include both sexes. Also, the AMH level sharply decreases with age. The level below 1 warrants IVF/ICSI as chances of conception are low even with induced ovarian cycles and IUI. Ideal level of AMH for good outcome is between 1 to 3.5. Level below 0.5 are considered very low with poor outcome and with AMH less than 0.2, we expect negligible outcome.

WHEN TO SEE INFERTILITY SPECIALIST?

- If female is >35 years & unable to conceive after 6 months of unprotected intercourse.

All females have at birth - 2 million eggs which keep on declining like- At puberty - 400,000 eggs, at 40 years -40,000 to 50,000 and 45 years and beyond they reduce to around – 5000 eggs only.

So,

1. **In WOMEN > 35 YEARS**
   - ✓ Fertility rate per month - 10%
   - ✓ Miscarriage rate - 25%
   - ✓ Risk of Down's syndrome - 1 in 350
   - ✓ Genetic testing is recommended.
2. **WOMEN > 40 YEARS**
   - ✓ Sharp decline in achieving pregnancy. Fertility rate per month is 5%, Even with IVF success rate is 10%.90% of eggs are genetically abnormal on biopsy. Miscarriage rate is 33%

- ✓ Incidence of genetic abnormalities is 1 in 38 Oocyte donation success rate- is 80%. Risk of medical complications also increases like PIH, GDM, premature labor, placental abruption.

3. WOMEN > 45 YEARS

- ✓ Pregnancy is a difficult proportion < 1% chance of getting pregnant using their eggs as virtually all the remaining eggs are genetically abnormal
- ✓ Miscarriage rate-45%
- ✓ Incidence of genetic abnormality - 1/12
- ✓ Egg donation is the key.
- ✓ Higher risk of mortality.

(To exclude high BP, diabetes or heart disease before becoming pregnant.)

ENDOMETRIOSIS AND INFERTILITY

Endometriosis at all stages hurts fertility and causes subfertility. The incidences of endometriosis ranged from 21% to 48% in infertile women, while endometriosis was noted in only 1.3%–5% of fertile women undergoing tubal ligation. With minimal and mild endometriosis (Stage I and II) there are 10-15% chances of pregnancy per cycle ovarian stimulation and IUI.

Moderate (Stage III) and severe (Stage IV) require surgical intervention. Aggressive treatment of endometriomas is associated with a cumulative pregnancy rate of 60 % over 12 Months.

Indication of IVF/ICSI –

1. Failed Ovulation induction + IUI in Minimal – Mild Endometriosis
2. Failed Ovulation induction + IUI in Moderate – Severe Endometriosis in Women < 35 years
3. Moderate to Severe Endometriosis, and in Women > 35 years
4. Associated Male Factor
5. Associated Tubal Factor

SURGICAL TREATMENT is recommended before IVF/ICSI for stage 3 and 4 endometriosis.

Laparoscopic surgery is recommended for the large endometrioma > 4cm by-

- Aspiration Only
- Incision - Drainage & Vaporize Implants Lining The Cyst Wall
- Incision - Drainage & Excision Of Cyst Wall

Followed by MEDICAL TREATMENT-

- GnRH Agonist for 3 - 6 Months Improves the Outcome of Pregnancy and Reduces Miscarriages as GnRH Agonist Modulates NK Cells of Uterus and normalizes the Endometrial Aromatase expression.
- Immediately after medical treatment, IVF/ICSI is to be Done.
- Stimulation response for patients with endometriosis/endometriomas generally does not seem to be compromised, however, after the surgery, we do get a smaller number of follicles, though pregnancy rates are comparable. Individualized IVF protocols according to various stages of endometriomas.

Post - Surgical problems are due to-

- Decreased oocyte yield due to poor folliculogenesis
- Decreased ovarian reserve in post-surgical cases
- Technical Difficulty

(A) GENITAL TB AND INFERTILITY

Global Prevalence of Genital TB is about 8-10 million cases. Our 5 to 10% of the patients with infertility have Genital TB. Rising incidence is probably due to increasing prevalence of HIV infection. The most common initial symptom of GTB is infertility in 85% of cases. It leads to loss of normal tube anatomy and function due to chronic inflammation. It can also cause endometrial tissue destruction leading to hypomenorrhea and Ashermann's syndrome. GTB is Difficult to treat both surgically and medically. In the acute phase, the picture may resemble classical acute pelvic inflammatory disease (PID) with pelvic pain, fever, and vaginal discharge. Medical treatment is the mainstay of treatment. Treatment is similar to treatment of TB elsewhere in the body. The short-course chemotherapy regimens of 6-9 months are recommended internationally for all forms of extra-pulmonary TB. Genito urinary TB is classified as seriously ill extrapulmonary TB.

Surgery indication

Unresponsiveness of active disease despite adequate anti-TB chemotherapy

* Tubercular pyosalpinx
* Ovarian abscess
* Pyometra
* Persistent menorrhagia and/or chronic pelvic pain causing deteriorating health status

TREATMENT OF INFERTILITY-

The conception rate in genital tuberculosis is very poor. Also, the risk of ectopic is very high. The damage to the fallopian tubes is permanent.

Though tubal patency may have been restored, the tubes remain rigid and beaded in most. In the majority, menstrual symptoms return to normal.

The role of IVF in patients with genital TB is now being highlighted. Many recommend direct IVF without attempting tubal surgery. The success of in vitro fertilization depends on the extent of endometrial damage. The lesser the damage to the endometrium, the higher the chance of success. However, overall pregnancy rates per cycle in these patients are reported to be lower than those with tubal infertility due to nontuberculous pathology.

(B) INFERTILITY AND MALIGNANCY

Cancer treatments may compromise the fertility of children, adolescents, and young adults, and treatment-related infertility represents an important survivorship issue that should be addressed at diagnosis and in follow-up to ensure optimal decision-making, including consideration of pursuing fertility preservation. The risk of infertility varies substantially with patient and treatment factors. **Gonadal-sparing surgery is the goal of management of ovarian cysts and tumors in adolescent and young adult women.** Most ovarian tumors in girls and adolescents are benign. Malignant tumors are usually of germ-cell origin. For tumor marker-negative tumors, a fertility-sparing procedure can be performed.

Female survivors who have spontaneous menses, particularly if irregular, may still have decreased ovarian reserve and reproductive potential. Abnormalities of traditional laboratory markers such as follicle-stimulating hormone, estradiol, and inhibin-B levels are late markers of ovarian aging. Anti-Mullerian hormone (AMH) is more strongly correlated with antral follicle count and is an earlier predictor of decreased ovarian reserve. AMH is evaluable in both pre-and postmenarchal females and detects diminished ovarian reserve among female cancer survivors.

In the treatment of cervical cancer, the focus for women interested in future fertility has been on the prevention of anatomical changes that impair childbearing. The risk of infertility with hysterectomy is 100%, although successful pregnancies have occurred with oocyte retrieval and use of a surrogate. Fertility-sparing procedures, such as vaginal or abdominal radical trachelectomy in which the cervix and upper vagina are removed, are now options for highly selected patients. Pregnancy rates among women attempting to conceive range from 25% to 95%, with most estimates above 40%. Miscarriage rates range from

9% to 42% and rates of pregnancies with gestation beyond 37 weeks range from 14% to 55%. Improved pregnancy rates associated with vaginal radical trachelectomy vs laparotomic abdominal radical trachelectomy. Candidates for fertility-sparing procedures generally do not receive adjuvant radiation or chemotherapy.

Management of epithelial ovarian cancer also includes removal of critical reproductive organs. For highly selected women, depending on the extent and type of disease, fertility-sparing procedures with unilateral salpingo-oophorectomy and complete surgical staging may be performed. Pregnancy rates among women attempting to conceive after unilateral salpingo-oophorectomy for EOC have ranged from 27% to 53%.

Most ovarian germ cell tumors in adolescents and young adults are stage I and about 50% are cured with surgery. For women requiring further treatment, fertility preservation should be considered, given the effect of cisplatin on ovarian function remains unknown in this setting.

Infertility and Premature Ovarian Failure

It refers to a loss of normal function of ovaries before age 40.

*Affects 1% of women.

Depending on the cause, premature ovarian failure may develop as early as the teen years, or the problem may have been present from birth.

Causes

* Genetic disorders
* Autoimmune diseases
* Tuberculosis of the genital tract
* Smoking
* Radiation and/or chemotherapy
* Ovarian failure following hysterectomy
* Prolonged GRH (Gonadotrophin Releasing Hormone) therapy
* Enzyme defects
* Resistant ovary
* Induction of multiple ovulation in infertility

How to diagnose POI?

Elevated serum follicle-stimulating hormone (FSH) levels (>25 IU/L) on two separate occasions at least one month apart, with concomitant low estradiol (E2) levels (<50 pg/mL) and Amenorrhea for at least 4 months in women younger than 40 years of age are collectively required to establish a diagnosis of POI.

Management of POI-

1. According to ESHRE guidelines on the subject, there are no interventions that have proven to increase the chances of natural conception, while **egg donation is considered a reliable opportunity to achieve pregnancy** and the patient to be counseled for adoption as well.
2. It is generally accepted that a serum FSH level of > 40 mIU/mL is associated with sterility and that induction of ovulation in these patients is ineffective.
3. Many studies showed spontaneous ovulation in many POI patients treated with estrogens.
4. In these cases, up to 20% can conceive spontaneously.

(C) INFERTILITY DUE TO AZOOSPERMIA (MALE FACTOR)

Concept of DONOR IUI

Intrauterine insemination (IUI) is a procedure that treats infertility. IUI boosts the chances of pregnancy by placing specially prepared sperm directly in the uterus. When the procedure is performed using sperm from a man other than the patient's partner, it is termed therapeutic donor insemination (TDI). Therapeutic donor insemination (TDI) helps single women and women in same-sex relationships to have children.

Indications for Donar IUI

1. Therapeutic donor insemination (DI or TDI) is used for.

   a) Male infertility-Azoospermia / Blocked of ejaculatory duct/ testicular failure Oligospermia/sperm or seminal fluid abnormality;Erectile dysfunction/Undecided testes
   b) Genetic/Familial disorders ;
   c) The female is Rh-sensitized and the male partner is Rh-positive
   d) Single woman who desires a pregnancy but who lacks a male partner

2. Medical Reasons: which will cause permanent sterilization or genetic defect:

   a) Infections,
   b) STDs (Sexually transmitted diseases),
   c) Testicular or pelvic trauma , heat, irradiation,
   d) Radiotherapy, chemotherapy, drugs, tobacco, alcohol etc,
   e) Pre-Vasectomy Sperm Banking,

3. Military & Hazardous Occupation Fertility Preservation

Since the decision to have donor insemination involves emotionally laden areas such as sexuality, marriage, and the husband's self-image, the physician is justified in being concerned about the possibility of psychological sequelae. For the husband, of course, the situation is more difficult. He can take comfort in the thought that, by agreeing to donor insemination, he is giving his wife the supreme sign of his love and concern.

On the positive side, for the female, this is her opportunity to physically experience pregnancy, labor, and motherhood, and lay to rest any lingering doubts concerning her femininity. One would thus expect that on such a firm basis, a good marital relationship can continue. Several studies demonstrate that, with the proper selection of only strongly motivated couples who mutually arrive at the decision for TDI in full accord, there should be few serious psychological dangers.

(D) SURROGACY

Surrogacy is a method of reproduction whereby a woman (referred to as a surrogate) agrees to carry a pregnancy and give birth as a substitute for the contracted party/ies. Surrogacy may be Natural (traditional / Straight) or Gestational.

Methods of Surrogacy

- **Traditional surrogacy**: In traditional surrogacy, the surrogate mother is impregnated naturally or artificially, but the resulting child is genetically related to the surrogate mother. A traditional surrogate is the baby's biological mother since the child was conceived from the union of her egg and the father's sperm.
- **Gestational surrogacy**: In gestational surrogacy, the pregnancy results from the transfer of an embryo created by in-vitro fertilization (IVF), in a manner so the resulting child is genetically unrelated to the surrogate. Gestational surrogate mothers are also referred to as gestational carriers.
- **Commercial Surrogacy:** Implicates that the Surrogate Mother is rewarded a compensation fee for her involvement. This fee covers not only medical expenses but also miscellaneous expenses related to the pregnancy, including travel provisions, and a sum for her time and unselfish efforts.
- **Altruistic Surrogacy:** Conceals the Surrogate Mother in agreeing to become pregnant and deliver the baby for the Intended Parents without any rewarding financial compensation. Conversely, in this case, the Surrogate Mother can still be compensated for her pregnancy-related expenses. Throughout some places in the world, commercial surrogacy is illegal, and gestational surrogacy is prohibited in other places.

Issues Related with Surrogacy

* Attachment with the Gestational Mother
* Involvement with the Gestational Mother
* Identity of the Child
* Compensation
* Surrogate health issues
* Detachment of intended parents
* Social Issues

Many people favouring pro-life are strongly against the surrogacy method because they think it is against moral issues and degrading to a woman's body. However, some oppose the pro-life idea and think that as long as the situations are suitable and beneficial for both sides then it shall be fine. Everyone has different opinions about the surrogate mothering method because everyone is raised in different ways and backgrounds; so it is hard to judge someone's opinion based on what he or she believes.

Medical science allows motherhood to be divided into three categories: the genetic, the gestational, and the social mother. These "mothers" may be represented by as many as three different individuals. A gestational carrier becomes pregnant with the use of assisted reproductive technology and delivers a genetically unrelated child on behalf of someone else (ie, the intended parent[s]).

INDICATIONS

In countries that allow gestational carrier pregnancy, acceptable indications vary but generally include absent or non-functioning uterus, medical conditions that preclude safe pregnancy, and established inability to either conceive and/or carry a pregnancy. The indication should be documented in the patient's medical record.

- **Absent or non-functioning uterus** — The absence of a functional uterus may result from congenital or acquired abnormalities (e.g., Mayer-Rokitansky-Kuster-Hauser syndrome, hysterectomy for benign or malignant disease, Asherman syndrome). For women with absolute uterine factor infertility, an alternative to using a gestational carrier is uterus transplantation and is not universally available.

- **Maternal medical disease** — Gestational carriers may be used when the intended mother has an absolute medical contraindication to pregnancy or a medical condition that could threaten the health and life of the mother and/or fetus.

  For example:

  Women with poor cardiac or renal function may experience irreversible deterioration during pregnancy. Pregnancy in women with Eisenmenger syndrome is associated with maternal mortality of 30 to 50 percent

Women with medical conditions such as cancer or organ transplants may need treatment with drugs that cross the placenta or other interventions, such as radiation therapy, that can adversely affect the fetus. Cancers that express estrogen receptors may be stimulated during ovulation induction or pregnancy; thus, it may be desirable to avoid these processes in affected women.

- **Biologic inability to conceive or bear a child** — Women with recurrent pregnancy losses (RPL) or in vitro fertilization (IVF) implantation failures may consider the use of a gestational carrier. Women who decide to pursue this route should undergo a thorough evaluation as to the etiology of the RPL or failed IVF. If RPL or recurrent IVF failure is a result of aneuploidy, then one might consider a donor egg IVF cycle with or without a donor sperm before embarking on a gestational carrier approach to pregnancy.

Ethical considerations and resultant availability and legal issues-

Both ethical and practical considerations impact the decision to use a gestational carrier and the selection of the individual carrier. In response to the high expense associated with gestational carriers in some areas and restricted access in others, cross-border reproductive care, also referred to as medical tourism and use of gestational carriers from other countries have become more popular. In response, concerns have been raised about the potential social, economic, and racial exploitation of gestational carriers.

Some find the use of gestational carriers or surrogates reasonable "if it is an altruistic act by a woman to help a couple for which it is impossible or medically contraindicated to carry a pregnancy". Others object on moral or religious grounds. Additional controversies include the use of family members as gestational carriers, financial compensation, potential financial or emotional coercion, the obligations of clinicians, provision of consent for the new-born, and cross-border reproductive care. The recently introduced surrogacy law implemented in India in 2022 can handle the situation to a great extent.

ADOPTION

Adoption is a legal procedure in which the custody of an orphan child is given to a married couple or single woman who agrees to look after the child to the best of their potential.

Adoption is a gift to both parents and the orphan child who gets the love of parents and parents get the pleasure of having a child. The families may seek to adopt because of infertility, fetal loss, death of a child, desire for more children, or simply to provide a home to a child in need of a home. Paediatric healthcare

providers may provide preadoption counselling to prospective adoptive parents, evaluate children after adoption, and/or provide ongoing care to adoptees.

Confidentiality

Regulation of confidentiality in adoption seeks to balance the privacy and anonymity of biological parents with the "right-to-know" interest of the adopted child.
Statutes regarding confidentiality vary from state to state; information regarding the statutes in particular states is available through the Child Welfare Information Gateway.

Eligible Child to be Adopted as per the guidelines of the Central Government of India, any orphan, abandoned or surrendered child, declared legally free for adoption by the child welfare committee is eligible for adoption. A child is said to be an orphan when the child is without a legal parent or a guardian or the parents are not capable of taking care of the child anymore.

Conditions to be Fulfilled by an Adoptive Parent

* Medically fit and financially able to care for a child
* Must be at least 21 years old
* No legal upper age limit for parents
  - Adoption of the older children, age of the parents may be relaxed
  - Adopted child with special needs, the age limit may be relaxed
  - If the adoption is of a son, the adoptive father or mother by whom the adoption is made must not have a son living at the time of adoption.
  - If the adoption is of a daughter, the adoptive father or mother by whom the adoption is made must not have a daughter living at the time.

BARRIERS TO ADOPTION:

1. **Gender Bias** in Adoption: In India, it is stated that gender discrimination is eliminated but it still occurs in India. A woman is not given the same rights as men, a woman cannot adopt a child of her own free will till her husband is alive, even if the husband approves.
2. **Limited Availability:** Even if couples want to adopt a child there is not enough child available to adopt, according to CARINGS (Child Adoption Resource Information and Guidance System), there is only 1 child available for 10 parents.
3. **Time-Consuming process:** Adoption is a very stressful and time-consuming process, due to the heavy load of paperwork and background checks, it takes almost one month to one year for

adoption both national and international. The wait time is too long for adoption.

4. **Strict rules and regulations:** Domestic adoption is bound by strict rules and policies that affect the adoptive families. Due to these rules, many families fail to adopt a child which creates discouragement among the adopting families and the children too.

Adoption Scenario in India

In India, CARA is the state-approved agency that governs adoption in India, though some private adoptions are still active in private hospitals which are run through agents and unorganized sectors.

Adoption is the short-term word for happiness. It brings joy to both the child's and the parent's life by uniting them. With the changing times, domestic adoption has gained motion, and with the help of the Child Welfare Organization, the public is now aware of CARA. The government is also taking some initiatives to promote Adoption.


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Chapter 14

MALE INFERTILITY


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CHAPTER 14

MALE INFERTILITY

Author: Dr ML Patel

Evaluation of male infertility

- Failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse
- Both male and Female partners to be evaluated
- Female factors responsible -30%
- Male factors responsible -30%
- Combined male & female factors responsible- 40%

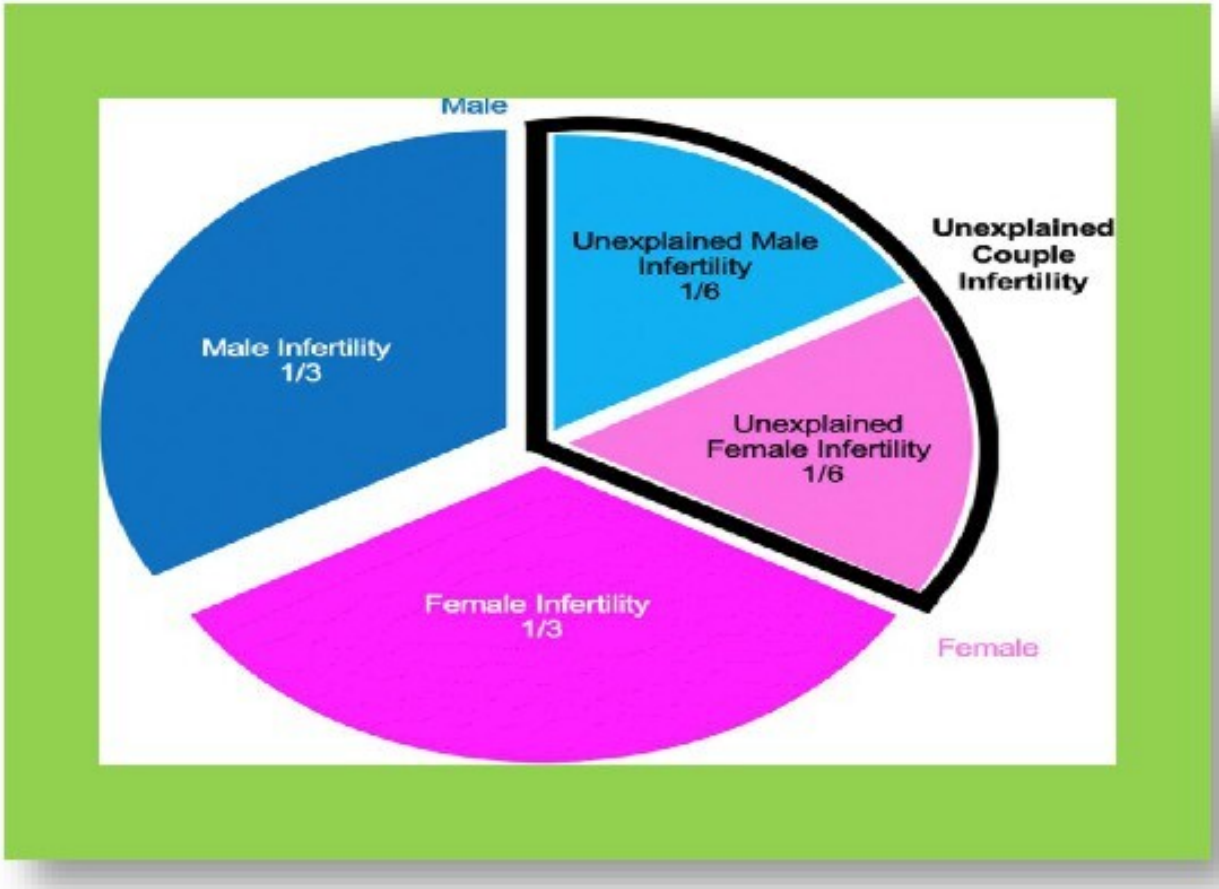

Figure 14.1: *Evaluation of Male Infertility*

Step by step evaluation plan

- Detailed history
- Examination
  - ✓ General examination
  - ✓ Genital organs local examination
- Investigation
- Semen analysis
  - ✓ Role of USG
  - ✓ Hormonal assessment
- Management Plan

History to be taken-

- Age
- Duration of Marriage
- H/O Alcohol & Smoking/Hukka
- Use of laptop/mobiles
- Use of energy drinks
- Type of exercises
- Trauma/Occupation
- Stress
- Erectile Dysfunction [ED] common as men get older
- Diabetes Mellitus & hypertension common in older males - affect fertility & ED
- Advanced paternal age increases de-novo intra & inter genic germline mutation, sperm aneuploidy, structural chromosomal aberration, DNA fragmentation, birth defects, genetically mediated conditions

Comorbidities-

- Hypertension, diabetes, TB
- Undescended testis, Hypospadias
- H/O treatment taken
- H/O surgery in genital organs
- H/O chemotherapy & radiotherapy
- H/O current medicines

Effects of Smoking on male fertility-

- Sperm structure and proteins
- Chromosomal damage
- Oxidative stress

- Semen parameters- concentration, viability, mobility, morphology
- Seminal plasma and sex gland function

Sexual History-

- Privacy & Confidentiality important
- Discuss with sensitivity & gain trust
- Male partner opens up with difficulty
- Infrequent coitus (staying in different cities due to work profile)
- Difficulty in vaginal penetration
- Painful intercourse
- Erectile dysfunction
- Premature ejaculation
- Retrograde ejaculation, painful ejaculation, hematospermia

Erectile Dysfunction [ED]-

- Persistent inability to attain & maintain erection for sexual performance
- Co-morbidities - Hypertension, DM, neurological problems
- Lifestyle - Smoking, alcohol, drug abuse
- Relationship problems
- Treatment - oral Phosphodiesterase – 5 inhibitors (PDE-5 inhibitor, sildenafil) if not contraindicated.

Premature Ejaculation [PE]- Avoidance of sexual intimacy

Premature ejaculation are of 2 types- primary and secondary

Causes of PE-

- Emotional/psychological factors
- Underlying ED
- Low serotonin/dopamine levels
- Extra sensitive penis
- Performance anxiety

Management- Behavioral therapy/counseling/medication –Dapoxetine, SSRI.

Retrograde ejaculation-

- Retrograde passage of semen into bladder
- H/O orgasm but no ejaculation (Aspermia)
- Post orgasm h/o of passage of cloudy urine
- Pharmacological. Neurological & anatomical causes

Can be treated with sympathomimetics and alkalinization of urine (2 hour Prior to urine collection and then sperms can be used for ART)

PHYSICAL EXAMINATION

General examination-

- Height & Weight, BMI
- **Obesity** – ass/w hyperinsulinemia and hyperglycemia
- Higher BMI - ↑ conversion of androgen to E_2 by adipose tissue by ↑ aromatase enzyme activity leading to subfertility
- Causes ED, ↓ sperm motility, ↑ OS, ↑ DNA fragmentation & ↓ testosterone
- T/E2 ratio < 10 (Abnormal)

Genital examination-

- Testis size (Normal testicular volume > 19 ml)
- Testicular consistency
- Sec sex character – body habitus, hair distribution, gynecomastia
- Presence and consistency of Vas Deferens
- Consistency of Epididymis
- Presence of varicocele
- Masses upon digital rectal examination

Semen Analysis-

- Most important component in initial clinical evaluation of male partner
- Semen parameters are highly variable biological measures and vary from ejaculate to ejaculate
- Parameters falling above / below the limits do not predict either fertility or infertility
- Important to counsel that multiple significant abnormalities in semen parameters increases their RR for infertility
- Therefore, at least 2 Semen Analysis obtained one month apart are important specially if first SA has abnormal parameters.

Semen sample collection and Storage-

- Should be collected near lab in proper container in a comfortable room with privacy connected with washroom
- If collected at home, should be brought within half an hour, kept in pocket or as near to body as possible.

Important differences in WHO 2010 (5th Ed) & 2020 (6th Ed) manual

Sr No	Parameters	WHO 2010 data	WHO 2020 data
1	Sperm concentration	15 mill/ml	16 mill/ml
2	Total motility	40%	42%
3	Progressive motility	32%	30%
4	Normal forms	4%	4%
5	Vitality	58%	54%
6	Volume	1.5 ml	1.4 ml
7	SDF	< 30%	

6th Ed WHO manual

Sr No	Parameters	Normal	Borderline	Pathological
1	Sperm concentration	≥ 20 mill/ml	10-20 mill/ml	< 10 mill/ml>
2	Progressive motility	≥ 50 %	35 – 49 %	< 35 %
3	Morphology	≥ 14 %	4 – 13 %	< 4 %
4	Sperm antibody binding	< 50 %	50 – 79 %	≥ 80 %

SEMEN VOLUME

Low semen volume-

- Result of collection problem
- Ejaculatory duct obstruction (EDO)
- Seminal vesicle hypoplasia
- Congenital bilateral absence of vas deferens (CABVD)

High semen volume-

- Active inflammation of accessory glands

Abnormalities in Sperm-

- **Azoospermia** - No sperm after centrifugation (3000 g for 15 min) in 2 samples
- **Cryptozoospermia** - < 1Mill/ml sperms in semen after centrifugation
- **Aspermia** - absence of ejaculate (semen) - RE
- **Oligospermia** - < 16 milliom/ml

Classification based on sperm count-

Polyspermia	Sperm count > 250 million/mL
Normospermia	Sperm count 15–250 million/mL
Mild oligospermia	Sperm count 10–15 million/mL
Moderate oligospermia	Sperm count 5–10 million/mL
Severe oligospermia	Sperm count < 5 million/mL
Azoospermia	No spermatozoa in the ejaculate

Hormonal evaluation-

- S. FSH
- S. Total Testosterone (<12 nmol/L is low)
- S. LH
- S. Prolactin

Things that lower the testosterone levels-

- Excessive exercise
- Poor diet
- Severe illness
- Sedentary lifestyle
- Alcoholism
- Stress

AZOOSPERMIA

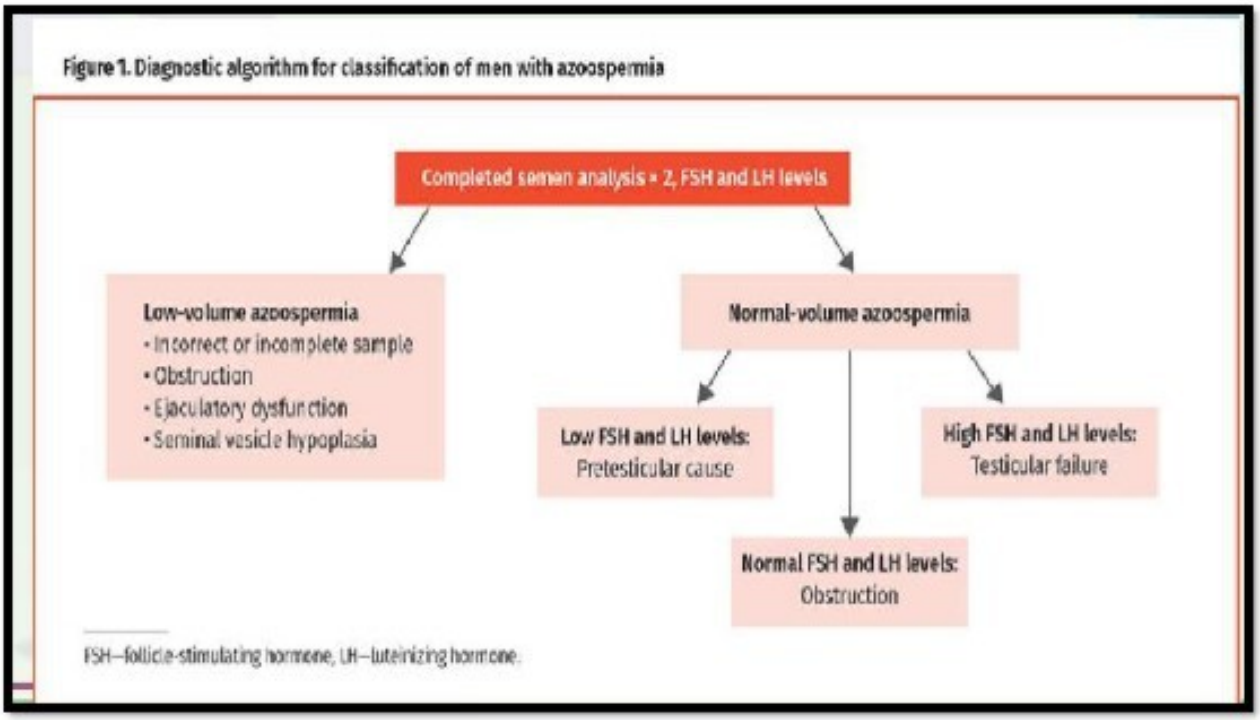

Figure 14.2: ***Azoospermia***

Obstructive azoospermia – Management

Vasal or Epididymal obstruction - microsurgical reconstruction
Ejaculatory duct obstruction (EDO) - trans urethral resection of ejaculatory duct (TURED)
Vasectomy - Re-anastomosis
Surgical sperm retrieval can be done from Testis or epididymis – TESA, PESA, TESE, Micro TESE – from testis always better

Non-Obstructive Azoospermia-

- Sperm retrieval & ART to have biological child
- If mature sperms cannot be obtained from testis- donor sperm or Adoption

Genetic Evaluation- karyotyping male partner

- Klinefelter syndrome (XXY)
- Y chromosome microdeletion
- CFTR gene mutation in congenital absence of bilateral vas deferens (CABVD)
- Sertoli cell only syndrome
- Maturation arrest (tubular sclerosis)

MANAGEMENT

1. **Oral medications-**
    - Multi vitamins, Selenium, Mg, Zn & other minerals
    - Coenzyme Q 10, L-carnitine
    - Vitamin C, Vitamin E
    - Melatonin
2. **Intrauterine insemination**
    - Increases healthy sperms at fertilization site with prepared washed motile sperms
    - Ovulatory/ Anovulatory cycles
    - At least one patent tube (preferably both)
    - Total motile sperm count > 10 million/ml
    - Sub-optimal Male factor
    - Unexplained infertility
3. **ART (IVF/ICSI)**
    - NOA – TESA & Micro TESE
    - Sertoli cell only syndrome
    - CBAVD
    - Y chromosome microdeletion with PGD
    - Klinefelter syndrome

CONCLUSION

- Be sensitive while evaluating male partner
- Proper history and examination
- Maintain privacy and confidentiality
- Semen analysis most important
- S. FSH and Testosterone indication limited
- Scrotal USG if indicated
- Genetic evaluation if indicated
- Individualized management by specialist


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Chapter 15

ADVANCED MANAGEMENT OF MALE INFERTILITY


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CHAPTER 15

ADVANCED MANAGEMENT OF MALE INFERTILITY

Author: Prof. B.P.Singh, Dr Abhishek Yadav

INTRODUCTION

Inability of a male to conceive a fertile female for at least a year after engaging in regular, unprotected sexual activity. Roughly 13 to 15 percent of couples worldwide experience infertility. Male factor infertility is solely responsible in about 30% of such cases. As male and female causes may co-exist in further 20% of cases, it is essential that both male and female partners are investigated for infertility and managed together.

Lifestyle and environmental differences may account for variation in the prevalence of infertility and in developing nations, there has been less epidemiological documentation of male infertility. Male infertility in India is a growing concern, reflecting broader global trends but with unique regional factors.

About one fourth of the men within infertile couples are not evaluated for male factor infertility. Secondary infertility cases should be evaluated in same way as men being evaluated for primary male factor infertility.

Early detection and management of male infertility can improve reproductive outcomes and prevent long-term psychological distress for affected couples. Goal is to identify and differentiate between reversible etiologic conditions, irreversible conditions amenable to ART using the male partner's sperm, irreversible conditions for which donor insemination or adoption is more advisable, and other pathologies or etiologies with implications for the patient and their family.

CAUSES

The causes and risk factors contributing to male infertility can be stratified as congenital, acquired, and idiopathic / environmental.

TABLE 1: Factors Contributing to Male Infertility	
Congenital / genetic factors	torchidism, hypospadias , Congenital absence of vas deferens truction of male genital tract l agenesis, Mullerian prostatic cysts microdeletions (AZF-a,b,c) ndrome (47, XXY) osaicism (46, XY/47, XXY), XX Male, XYY rome, Prader-Willi syndrome nal hyperplasia insensitivity syndrome
Acquired factors	• Varicocele • Testicular damage : Trauma,Torsion, Tumor, Mumps,Tuberculosis • Acquired hypogonadotrophic hypogonadism • Urogenital infections (epididymitis, prostatitis, prostatovesiculitis, genital tuberculosis, funiculitis, Gonorrhoea, mycoplasma) • Epidiymal cysts, spermatocele • Urogenital tract obstruction, ejaculatory duct obstruction • Exogenous factors (eg, chemotherapy, medications, radiation, heat) • Systemic diseases (live cirrhosis, renal failure) • Anti-sperm antibodies • Surgeries that can comprise vascularity of the testis • Sexual dysfunction (erectile or ejaculatory dysfunction) • Hormonal excess: Prolactinoma, excess androgen -adrenal tumor, anabolic steroids, excess oestrogens • Retrograde /anejaculation: TURP, /BNI, Alfa-Blockers
Idiopathic / Environmental risk factors	• Smoking, Tobacco, Alcohol, • Recreational drugs: marijuana • Obesity, Psychological stress • Advanced paternal age >40 yrs • Dietary factors- pesticides, heavy metals • Environmental or occupational exposure to gonadotoxin • Idiopathic

In half of the cases, the underlying etiology of male infertility is known to be due to hypospadias, cryptorchidism, testosterone deficiency, or underlying genetic causes such as Klinefelter's syndrome and cystic fibrosis.

About 20% cases, of male infertility are reversible and treatable conditions, including obstructive azoospermia, ejaculatory duct obstruction, prostatic midline cysts, vasectomy reversal, varicoceles, Hypospadias, sexual function disorders (Erectile dysfunction, Premature ejaculation, Retrograde ejaculation, anejaculation), gonadotropin deficiency, and reversible effects from prior testosterone exposure, gonadotoxins, and sperm autoimmunity.

Male infertility causes can also be classified as Pre-Testicular, Testicular, Post testicular:

Pre-testicular causes include hypogonadotropic hypogonadism, erectile dysfunction, coital disorders such as retrograde ejaculation, anejaculation, genetic factors, and or chromosomal abnormalities. **Testicular** disorders include testicular tumors, orchiectomy, primary testicular failure, cryptorchidism, and atrophic testes. Varicoceles are also associated with male infertility, most likely through impairment of testicular thermoregulation due to disruption of the pampiniform venous plexus heat regulation mechanism. Epididymal dysfunction can be caused by fetal intrauterine exposure to estrogens, various drugs and chemical toxins, epididymal cysts, spermatoceles with or without surgery, epididymitis, or may be idiopathic. **Post-testicular** etiologies include lesions of the seminal tract, inflammatory diseases, congenital absence of the vas deferens, post-vasectomy, erectile dysfunction, premature ejaculation, and the use of a condom or diaphragm. This category would also include bladder neck surgery, post-TURP surgery, retroperitoneal lymph node dissection, rectal surgery, multiple sclerosis, and alpha antagonist medications such as tamsulosin.

EVALUATION

A reproductive history and at least one semen analysis are recommended for an initial evaluation by the American Society for Reproductive Medicine (ASRM) and the European Association of Urology (EAU)[2,3], while the American Urological Association (AUA) suggests two semen analyses.[4] Referral to a reproductive specialist is advised for a comprehensive evaluation that includes a physical examination and gathering a complete medical history if the initial evaluation reveals abnormal results. More andrological tests and evaluations may be suggested in light of the findings.

TABLE 2: Detailed Medical History	
Infertility history	Duration of infertility Previous pregnancies and outcomes (primary/ secondary infertility) Partner's fertility history Previous fertility investigation and treatment
Sexual history	Libido Erectile dysfunction Ejaculatory dysfunction Type of lubricants Frequency and timing of coitus Sexually transmitted disease
Medical history	Cryptorchidism Timing of puberty, developmental reproductive history Breast enlargement, galactorrhea,early puberty (< 9 yrs) Anosmia History of testicular torsion, testicular trauma, tumor Diabetes Neurological conditions (spinal cord injury, multiple sclerosis) Infections (urinary infections, epididymitis or prostatitis, tuberculosis, mumps orchitis, recent febrile illness, STD -mycoplasma, gonorrhoea) Renal disease, liver failure, upper respiratory tract disease Cancer: testicular, prostate, others Sickle cell anemia
Surgical history	Orchidopexy Retroperitoneal or pelvic surgery Herniorrhaphy, hydrocele surgery Vasectomy Bladder neck or prostatic surgery
Gonadotoxin exposures	Medications (endocrine modulators, antihypertensives, antibiotics, antipsychotics) Environmental (pesticides, heavy metals) Chemotherapy or radiotherapy Lifestyle (obesity, tobacco, recreational drugs- cannabis, anabolic steroids)
Family history	Infertility Cystic fibrosis Androgen receptor deficiency

TABLE 3: Physical Examination	
General / Systemic Examination	Body habitus Hair distribution Breast Other secondary sexual characters Organ systems examination
External Genitalia / Groin	**Urethral meatus** – location & size, prepuce- phimosis **Penis**- size, deformity, plaque, lesion **Testis** – size (>15ml vol, >4cm size), consistency, sensation **Vas Deferens**– presence, thickening, nodularity **Epididymis** – size, induration, cyst, turgidity/ fullness Spermatocele Varicocele Any surgical scars, hydrocele

TABLE 4: Investigations	
General / Systemic Examination	• **First step in evaluation - conventional method** Two tests, at least 2 weeks apart 2-5 days abstinence Lab collection/home collection – sterile container/ condom Transport at room/body temperature in <1 hr Volume ≥ 1.4 ml Sperm concentration ≥ 16 million per ml Total sperm number ≥ 39 million per ejaculate Total motility ≥ 42% Progressive motility ≥ 30% Vitality ≥ 54% Sperm morphology ≥ 4% normal forms pH ≥ 7.2 (normal range 7.9 -8.1) Fructose (≥ 13 mol per ejaculate) Time to liquify: 5–25 min WBC < 1x 10^6 WBC / ml MAR test (antisperm antibody) <50% motile with bound Abs ▪ **Computer-aided sperm analysis (CASA):** Sperm fertility potential ▪ **Home-based sperm testing:** to screen for male infertility in at-risk populations
Hormonal studies	**Serum Testosterone** > 300 ng/ml **FSH** < 7.6 IU/L, marker of spermatogenesis **LH** Others if needed: Prolactin /Free Testosterone/ SHBG/ TSH

Radiology	**Scrotal USG:** if hydrocele, testicular volume, epididymis, vas deferentia, non-palpable/ sub-clinical varicocele, testicular blood flow and RI **Transrectal USG:** prostatic utricle cyst, seminal vesicle >2.5 cm / collapsed, Ejaculatory ducts **Abdominal USG/CT/MRI:** in absent vas – look for renal agenesis/ other GU abnormalities
Testicular FNAC / Biopsy/ FNA Mapping	**B/L testicular FNAC :** stages of spermatogenesis, mature spermatozoa, Sertoli cell only syndrome **B/L testicular Biopsy:** heterogeneous and unequal spermatogenesis, sperm cryo-preservation **B/L testicular Mapping FNAC:** 12-18 locations
Other tests	▪ Vasography: to define site of obstruction ▪ Uretho-Cystoscopy: prostatic midline cyst, veru montenum, EDO, stricture uretha ▪ Post Ejaculate Urine Analysis (PEU); for retrograde ejaculation if semen volume < 1 ml
Genetic testing	▪ Karyotyping: 47 XXY (Klinefelter's) ▪ Y chromosome microdeletion: AZF – c vs. a,b ▪ CFTR – in absent vas / idiopathic epididymal obstruction **Important in Azoospermia /severe oligospermia (5 mill /ml) and for counselling**
Specialized testing	▪ Sperm DNA fragmentation (SDF): in unexplained infertility with varioocele, environmental exposure, failed IVF/ ICSI ▪ Anti-Sperm Antibodies (ASA) ▪ Hyperviscosity testing ▪ Capacitation, Acrosomal Reaction, and Sperm Penetration Assays – if repeated IUI failures, in unexplained cases ▪ Hypoosmotic Swelling Test: distinguish between viable but non-motile sperm and dead sperm ▪ Sperm Vitality Staining: to differentiate between dead sperm and viable non-motile sperm. Identify necrospermia. ▪ Inhibin B level: High due to seminiferous tubular disorders or ductal obstruction - may lead to sperm self-destruction

TABLE 5: Treatment	
No treatment	▪ 23% of untreated infertile couples conceive after 2 years. ▪ Upto 33% conceive after 4 years. ▪ Men with severe oligozoospermia (<2 million sperm/mL), 7.6% of untreated patients produce a pregnancy in 2 years.
Lifestyle Changes	▪ Encourage Healthy lifestyle ▪ Reduce alcohol, smoking, avoid hot bath ▪ Stop illegal and recreational drug use (such as marijuana) ▪ Weigh reduction, regular exercise, stress reduction ▪ Avoid exposure to pesticides and heavy metals (such as lead, mercury, boron, and cadmium) ▪ Avoid potentially toxic artificial lubricants during sexual activity. ▪ Review prescription medications
Antibiotics	Treat any positive urine, urethral, semen culture
Supplements: Antioxidants/ Nutrients	Low Quality Evidence – for a possible increase in birth rate. Improve sperm motility, morphology, function and count. • Vit E, Vit C, Selenium, Zinc, Co-Q (300mg/day), L-Carnitine, N-acetyl cysteine, Lycopene, Folic acid/ B9 (0.5-1 mg) • L-carnitine – entry of fatty acids into sperm mitochondria • Folic acid - DNA methylation: less apoptosis Decreases oxidative stress and DNA fragmentation
Nonspecific Hormonal Manipulations	Most useful when testosterone is normal, and oestrogens are relatively higher - testosterone/estradiol (T/E) ratio <10: • **Non-steroidal Aromatase inhibitors:** improves semen parameters without much effect on pregnancy rates: anastrozole (1mg) or letrozole (2.5mg) thrice a week, can be combined with clomiphene citrate. • **Anti-oestrogen: clomiphene citrate:** 25mg/alternate day to 50 mg/day, less oestrogen feedback on FSH/LH so Increased gonadotropins increase spermatogenesis. Improves semen parameters over 3–6 months. Can be combined with tamoxifen for better outcomes. • **Oestrogen receptor antagonist:** Tamoxifen 10 mg BD. Also, might work in hypogonadotropic hypogonadism.

Specific Homonal manipulations	**Hyperprolactinemia:** Dopamine agonists **Secondary Hypogonadism:** HCG, hr-FSH, HMG, Pulsatile LH (in Kallman synd.)
Sexual dysfunctions	▪ **Retrograde ejaculation / ejaculatory failure:** Sympathomimetics – Despiramine , phenylephrine, pseudoephedrine Electro / Vibro Ejaculation: in SCI pts, probe in rectum ▪ **Premature ejaculation:** Behavioral psychotherapy (sex therapy), Drugs (Depoxetine, apomorphine)
Surgical procedures	▪ **Vasa deferens obstruction:** Vaso-vasostomy ▪ **Epididymal obstruction:** Microsurgical Vaso-Epididymal Anastomosis (VEA) ▪ **Ejaculatory Duct cyst:** Puncture, /deroofing/incision/resection
Sperm Extraction Techniques for Assisted Reproduction	▪ **Post Ejaculatory Urine (PEU):** in retrograde ejeculation ▪ **Electro-ejaculation :** in SCI , psychogenic anejeculation ▪ **Percutaneous Epididymal Sperm Aspiration (PESA):** In Epididymal Obstruction, ED
Indications of Cryopreservation of sperms	Following TESE At time of Testicular Biopsy while evaluation Men undergoing Chemo/Radiotherapy for cancer Electro-ejaculation in SCI, psychogenic anejaculation Medical conditions with risk of decreased semen quality
Assisted conceptions	• **Intra Uterine Insemination (IUI):** sperm into uterus • **In Vitro Fertilization (IVF):** embryos into uterine cavity • **Gamete Intra fallopian Transfer (GIFT):** Oocytes and sperms into fallopian tube via laparoscopy, Zygote Intra fallopian transfer (ZIFT), Tubal Embryo Transfer (TFT) • **Intra Cytoplasmic Sperm Injection (ICSI):** single spermatozoa injected directly into oocyte

The history, physical examination, hormonal studies, and imaging can help to differentiate between obstructive and nonconstructive azoospermia. It is worthwhile mentioning that semen volume, semen pH (alkaline vs acidic), and presence of fructose also aid in diagnosing azoospermia.

While ICSI has allowed many men with defective genes to father children, there is also the increased risk of transmission of various genetic defects to the progeny, and this should be carefully considered before proceeding. Therefore, genetic testing would typically be recommended for patients with severe oligozoospermia (<5 million sperm/mL) or azoospermia and consist of karyotype, CFTR, and Y chromosome testing for microdeletions (sometimes called AZF testing).

TABLE 6: Endocrine analysis for various conditions of hormonal imbalance in the hypothalamic-pituitary-testicular axis

Conditions	Follicle-Stimulating Hormone	Luteinizing Hormone	Testosterone	Prolactin
Normal spermatogenesis	Normal	Normal	Normal	Normal
Hypergonadotropic hypogonadism (primary testicular failure)	High	High	Low	Normal
Hypogonadotropic hypogonadism (secondary testicular failure)	Low	Low	Low	Normal
Abnormal spermatogenesis	High/normal	Normal	Normal/Low	Normal
Prolactin-secreting pituitary tumor	Normal/low	Normal/low	Low	High

Abnormalities in spermatogenesis are generally indicated by elevated FSH levels. Despite the pulsatile secretion of gonadotropin hormone, a single test might be considered adequate to evaluate the patient's endocrinological condition.

- Low testosterone with high FSH and LH suggests primary hypergonadotropic hypogonadism, which would affect both sperm production (FSH) and testosterone levels (LH). A karyotype should be done.
- Low testosterone with normal or low FSH and LH indicates secondary hypogonadism. Look out for serum prolactin.
- Normal testosterone and LH with a high FSH are suggestive of primary spermatogenic failure, especially if associated with azoospermia or severe oligozoospermia. (The normal LH indicates proper Leydig cell function, but the high FSH suggests damage to the seminiferous tubules.) Check testicle size and consider karyotyping as well as Y chromosome microdeletion testing.

A less severe form with mild oligozoospermia might indicate Sertoli cell dysfunction, causing reduced production of inhibin, which increases FSH.

- Normal levels of FSH, LH, and testosterone: Additional assessment is based on physical findings and semen analysis. A normal testicle size and azoospermia (no sperm in the ejaculate) would suggest obstructive azoospermia, which may be surgically treated. This may point to a CFTR gene mutation with or without clinical symptoms of cystic fibrosis if it is accompanied by bilaterally absent vas. It is important to find out if there is a family history of cystic fibrosis and to test both partners for CFTR gene mutations.
- High testosterone and LH but normal FSH: This would be consistent with partial androgen resistance.
- Cushing's disease can be confirmed by a 24-hour urine test for free cortisol, a dexamethasone suppression test, or by checking the midnight salivary cortisol concentration.

TABLE 7: Endocrine analysis for men with azoospermia

Etiology	Follicle-Stimulating Hormone	Luteinizing Hormone	Testosterone
Obstructive azoospermia	Normal	Normal	Normal
Nonobstructive azoospermia; pre-testicular	Low	Low	Low
Nonobstructive azoospermia; exogenous testosterone	Low	Low	High
Nonobstructive azoospermia; testicular	High (> 3 times)	High	Low

TABLE 8: Semen Analysis: Terminology
Aspermia: ▪ No semen ▪ Anejaculation or retrograde ejaculation
Asthenozoospermia: ▪ Decreased motility ▪ Pus cells, ASA, EDO, Varicocoele - oxidative ▪ Sperm structural defects, idiopathic ▪ Tt: Steroids/ IUI/ICSI
Teratozoospermia: ▪ Abnormal Structural morphology ▪ Globozoospermia – poor prognosis
Azoospermia: ▪ No sperms ▪ Accounts for about 10% to 15% of male factor infertility ▪ Obstructive: 40% cases – better prognosis ▪ Vol<1.5ml, acidic pH, Fructose –ve, SV/Ej Duct dilated Epididymis – full ▪ Non – obstructive: 60% testicular or pretesticular
Haemospermia (haematospermia): ▪ RBCs in Ejaculate ▪ Benign seminal vasculitis/Tumor/TB
Leukospermia (leukocytospermia, pyospermia): ▪ WBC > 1X106 /ml ▪ Infective ▪ Non-infective: toxins/varicocele/prostatitis/autoimmune
Oligoasthenoteratozoospermia

Nonpalpable varicoceles found only on scrotal ultrasound are generally not considered clinically significant, and varicocelectomy is not usually recommended to improve fertility by most experts or guidelines, but this is somewhat controversial.

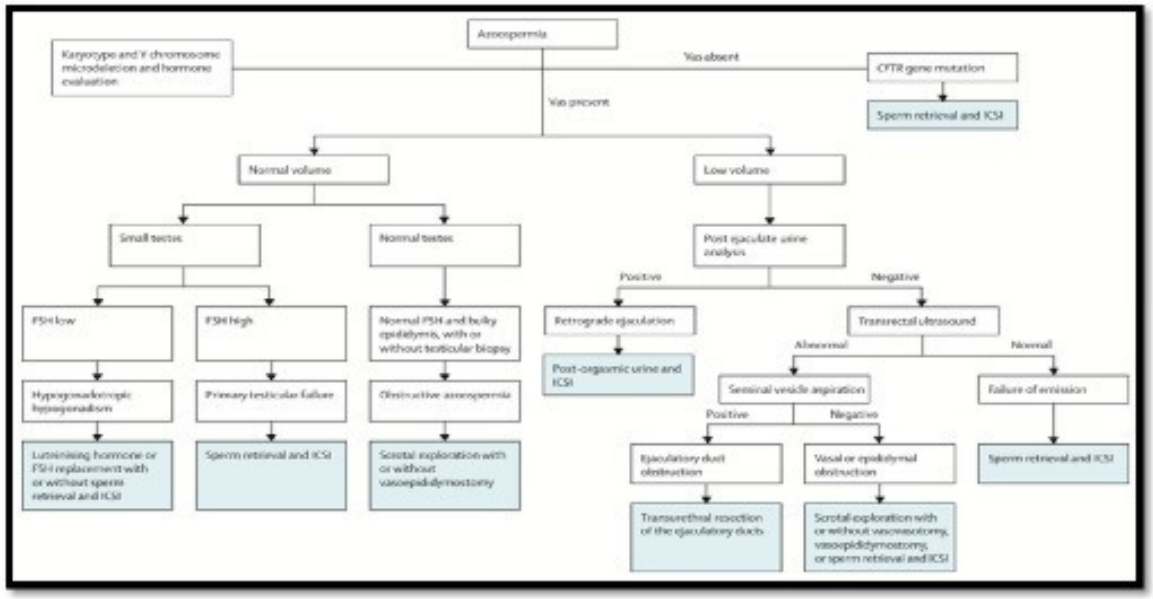
Routine use of scrotal ultrasound in male infertility is not recommended by American Urological Association (AUA) guidelines. However, some experts advise against it because it is cheap, painless, safe, and accurate in measuring the size of the testes. It also aids in the identification of pathology that is not otherwise clinically detectable, such as testicular cancers and small spermatoceles.

Despite being only 0.5 percent, the incidence of testicular cancer among infertile men is still 100 times higher than the risk in the general population.

In certain situations, a testicular biopsy may be necessary to rule out spermatogenic failure. When a man is suspected of having ductal obstruction, a testicular biopsy is usually carried out. These men typically present as azoospermic, with normal testes sizes and normal hormonal screening results. Vasography and the biopsy can be performed concurrently. When doing the biopsy, sperm and testicular tissue may also be extracted and frozen for ART; however, caution must be exercised to prevent sperm death by preservatives. Think about doing bilateral biopsies because there has been a documented disparity in testicular biopsy results between the two sides.

When semen volume is low (<1.5 mL), the pH is acidic, and in azoospermia when the vas is palpable and the serum testosterone is normal, it is suggestive of ejaculatory duct obstruction.

Transrectal ultrasound (TRUS) can identify ejaculatory duct obstruction where dilated ejaculatory ducts and seminal vesicles are seen.



ALGORITHM FOR AZOOSPERMIA

Varicocelectomy

Varicocele repairs are typically recommended for infertile men with abnormal semen parameters who have large, clinical grade 3 varicoceles. These varicoceles are easily detectable during a physical examination. Varicocele repair may also be considered for men experiencing symptoms related to the varicocele, regardless of infertility.

Most experts and guidelines suggest that men with infertility and small, non-palpable varicoceles (typically less than 3 mm in diameter) may not benefit from surgery, but this remains a topic of debate.

Overall, varicocelectomy is expected to ultimately improve semen parameters in at least 60% to 70% of patients with clinically significant varicoceles. A recent, comprehensive meta-analysis demonstrated that all significant standard sperm characteristics in infertile men with significant varicoceles improved after varicocele surgery.

Varicocele surgery is not recommended in men with extremely low sperm counts (severe oligozoospermia or azoospermia) or high FSH concentrations with bilateral small testes as these features suggest extensive testicular germ cell damage, making it unlikely they will see any improvement in their fertility potential.[6] It remains unclear if men with a clinically significant varicocele who have nonobstructive azoospermia would benefit from a surgical varicocele repair before ART.

A high resistive index and lower end-diastolic and peak systolic velocities would suggest decreased intratesticular vascular flow, which could prove to be more significant than clinical varicocele size alone. If these findings are confirmed, testicular volume determinations and ultrasonic measurements of intratesticular hemodynamics may ultimately be a better predictor of improved sperm parameters and fertility from varicocele surgery in infertile men than the simple determination of finding a clinically significant varicocele on physical examination.

When considering surgical options for subclinical varicoceles in adolescents, the decision-making process becomes much more intricate. The most effective approach is to thoroughly examine the most recent information, and openly discuss the advantages and disadvantages of surgery with both the patient and their family. This honest and comprehensive dialogue is essential in assisting men and their families in navigating these challenging decisions.

Even after successful surgery, some men will remain infertile due to their development of an exaggerated immune response to the sperm granulomas that form on the proximal side of a vasectomy. Men with increased FSH levels may require additional ART to achieve a pregnancy even after successful surgery.

Performing varicocele repairs and vasovasostomies simultaneously should be avoided as it may pose a risk of vascular compromise to the testicle, leading to atrophy. In selected cases, robotic-assisted vasovasostomy can be performed with comparable pregnancy rates of approximately 60%.

Intrauterine Insemination

This procedure involves collecting semen and sperm from the male partner or a donor and then placing it into the female uterus through artificial means. It is typically used when the postcoital test shows no sperm, or in cases of unexplained infertility or abnormal sperm parameters with some normal sperm present. This method helps to avoid potential allergic reactions from vaginal insemination and toxic cervical mucus. When used alone, the pregnancy success rate is only 4%, but when combined with female superovulation, the success rate can increase up to 17% per attempt. The overall success rate is around 12% per attempt, decreasing with each additional attempt. After 9 attempts, the pregnancy rates can increase by 40% to 50%.

For most cases of unexplained or mild male factor infertility, it is generally recommended to try 3 to 4 attempts before considering IVF. Women up to age 40 can expect reasonable pregnancy rates with this technique if their male partner has a total viable sperm count of at least 5 million. However, women aged 38 and 39 tend to have better results when their partner's total sperm count is over 5 million. On the other hand, for women over the age of 40, even higher total sperm counts of up to 10 million do not significantly improve the pregnancy rate, and IVF is typically recommended at that point.IUI techniques should not be used when the sperm are dead (as determined by a positive hypoosmotic swelling test or sperm vitality staining). Abnormal functional sperm tests (such as capacitation, acrosomal reaction, and sperm penetration assays) would suggest that IVF with ICSI should be used instead.

There are different methods to process semen in order to collect only high motility, normal morphology sperm. The semen is washed to remove dead cells, leaving behind healthy sperm which are then concentrated for insemination. In cases where the male has a low semen volume, multiple specimens can be combined and injected into the female partner's uterus at the optimal time. Successful intrauterine insemination requires a total motile sperm count of at least 1 million.

This count is calculated using the formula: Total Motile Sperm Count = Sperm Concentration (million/mL) x Sperm Motility (%) x Semen Volume (mL).

Although not as reliable as ICSI, IUI is much more affordable, making it a viable option when there is no female factor involved and the male's semen and sperm count/quality are satisfactory. It can be repeated without significant financial burden.

In Vitro Fertilization and Intracytoplasmic Sperm Injection

IVF is a fertility treatment option for couples who have not had success with IUI and ovarian stimulation, women over 40 years of age, or individuals with conditions that prevent the use of simpler methods like bilateral tubal disorders. During IVF, the female egg is fertilized outside of the body with around 100,000 sperm in a special medium. Whether the sperm used is from ejaculated semen or direct microdissection testicular sperm extraction (TESE) does not seem to impact miscarriage or live birth rates. At least 50,000 to 500,000 motile sperm are typically needed for IVF, or else ICSI may be required.

Direct microdissection TESE is the preferred method of sperm retrieval for ICSI.[6,14]Both fresh and cryopreserved sperm can be used.[6]Patients with retrograde ejaculation may require sympathomimetic medications, urinary alkalinization, urethral catheterization, induced ejaculation techniques, or TESE for sperm acquisition.[6] Sperm retrieval techniques for men with aspermia include induced ejaculation (sympathomimetic stimulation, vibratory effects, or electroejaculation), as well as surgical sperm extraction with TESE.[6] Usually, about 12 eggs are retrieved per cycle. After 2 days, the embryos from successfully fertilized eggs are at the 3 to 8-cell stage. 2 to 4 embryos are implanted into the female partner, and the remaining embryos are frozen. Pregnancy rates are normally reported at 10% to 45%.

ICSI, the most advanced assisted reproductive technology available, involves using a microscope and micropipette to inject a single sperm directly into an egg that has been surgically extracted from the female partner. The fertilized eggs are then implanted into the female partner's uterus. The fertilization rate of ICSI is around 60%, with an initial pregnancy rate of 20-30% per cycle.This rate can increase up to 45% after multiple cycles. About 30-40% of pregnancies resulting from IVF with ICSI result in multiple fetuses.

In general, IVF with ICSI is recommended for cases with severe male infertility that cannot be addressed through alternative methods, but where some viable sperm can still be extracted. It is also a viable option after other treatments have not been successful.

The only male conditions that would prevent the procedure are the absence of retrievable, viable sperm or necrospermia, which is thankfully rare.

BIBLIOGRAPHY

i) *Ummet Abur, Sezgin Gunes, in Epigenetics and Reproductive Health, 2021*

ii) *Source-Modified from https://www.livestrong.org/fertility. In Niederhuber JE: Abeloff's clinical oncology, ed 6, Philadelphia, 2020, Elsevier.*

iii) *Serafini P, Batzofin j. Diagnosis of female infertility .j Reprod Med 1989; 34:29-40.*

iv) *Tubal factor infertility, with special regard to chlamydial salpingitis. Mårdh PA. Curr Optn Infect Dis. 2004;17:49–52. [PubMed] [Google Scholar].*

v) *Genital tuberculosis in Indian infertility patients. Gupta N, Sharma JB, Mittal S, Singh N, Misra R, Kukreja M. https://doi.org/10.1016/j.ijgo.2006.12.018. Int J Gynaecol Obstet. 2007;97:135–138. [PubMed] [Google Scholar].*

vi) *Decherney AH. Anything you can do I can do better or differently :Fertil Steril 1987 ; 48:374-376.*

vii) *Thurmond AS, Rosch J . Nonsurgical fallopian tube recanalization for treatment of infertility . Radiology 1990;174:371-374.*

viii) *Dubuisson JB, Chapron C, Morice P. Laparoscopic salpingostomy :fertility results according to the tubal mucosal appearance .Hum.Reprd.,9,334-339.1994.*

ix) *American Society for Reproductive Medicine (2021) "Fertility evaluation of infertile women: a committee opinion," Fertility and sterility, 116(5), pp. 1255-1265.*

x) *Hysterosalpingography: MedlinePlus Medical Encyclopedia RadiologyInfo*

xi) *Dreyer, Kim; Rijswijk, Joukje van; Mijatovic, Velja; Goddijn, Mariëtte; Verhoeve, Harold R.; Rooij, Ilse A.J. van; Hoek, Annemieke; Bourdrez, Petra; Nap, Annemiek W. (2017-05-18). "Oil-Based or Water-Based Contrast for Hysterosalpingography in Infertile Women". New England Journal of Medicine. 376 (21): 2043–2052. doi:10.1056/nejmoa1612337*

xii) *Bendick A. J. (1947). "Present Status of Hysterosalpingography". Journal of the Mount Sinai Hospital, New York. 14 (3): 739–742. PMID 20265114.*

xiii) *Grigovich, Maria; Kacharla, Vidhi S.; Bharwani, Nishat; Hemingway, Anne; Mijatovic, Velja; Rodgers, Shuchi K. (October 2021). "Evaluating Fallopian Tube Patency: What the Radiologist Needs to Know". RadioGraphics. 41 (6): 1876–18961. doi:10.1148/rg.2021210033. ISSN 0271-5333. PMID 34597232. S2CID 238249552.*

xiv) *Gaglione R, Valentini AL, Pistilli E, Nuzzi NP. A comparison of hysteroscopy and hysterosalpingography. Int J Gynaecol Obstet 1996; 52(2): 151–3.*

xv) *Saunders RD, Shwayder JM, Nakajima ST. Current methods of tubal patency assessment. Fertil Steril 2011; 95(7): 2171–9*

xvi) *Chapron C, Querleu D, Bruhat MA et al. Surgical complications of diagnostic and operative gynaecological laparoscopy: A series of 29,966 cases. Hum Reprod 1998; 13(4): 867–72.*

xvii) *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;49:944–55. doi: 10.1016/S0015-0282(16)59942-7. [PubMed] [Google Scholar].*

xviii) *William D, Bradley S. Preoperative sonographic measurement of endometrial pattern predicts outcome of surgical repair in patients with severe Asherman's syndrome. Fertility and Sterility. 1995;2:410–413. dot: 10.1016/S0015-0282(16)57379-8.*

xix) *Falloposcopy: a microendoscopic technique for visual exploration of the human fallopian tube from the uterotubal ostium to the fimbria using a transvaginal approach. Kerin J, Daykhovsky L, Segalowitz J, et al. Fertil Steril. 1990;54:390–400. [PubMed] [Google Scholar].*

xx) *Guo Y, Xia EL, Xiao Y. Analysis of etiology and reproductive prognosis of laparoscopic diagnosis and treatment in 294 infertile women. China J Endosc. 2013;19(10):1115–7. Chinese.*

xxi) *Advances in the assessment of the uterus and fallopian tube function. . Watrelot A, Hamilton J, Grudzinskas JG. Best Pract Res Clin Obstet Gynaecol. 2003;17:187–209. [PubMed] [Google Scholar].*

xxii) *deWit W, Gowrising CJ, Kuik DJ et al. Only hydrosalpinges visible on ultrasound are associated with reduced implantation and pregnancy rates after invitro fertilization. Hum Reprod 1998; 13: 1696–701.*

xxiii) https://www.drishtiias.com/daily-news-analysis/assisted-reproductive-technology-regulation-bill-2021

xxiv) https://thc.nic.in/Central%20GovernmentalRules/AssistedReproductiveTechnology(Regulation)Rules2022,.pdf

xxv) *Speroff's Clinical Gynecologic Endocrinology and Infertility, Ninth edition*

xxvi) *Textbook of assisted reproductive techniques Volume 2: Fourth edition.*

xxvii) *The infertility manual by Kamini Rao, 4th Edition*

xxviii) Simplified Embryo Vitrification Protocols (irvinesci.com)

xxix) Vitrification and Thawing Media - Kitazato IVF (kitazato-ivf.com)

xxx) *Cardey-Lefort M, Ducrocq B, Uk A, Behal H, Barbotin AL, Robin G. Intrauterine insemination with donor sperm: only the number of motile spermatozoa inseminated influences both pregnancy and live-birth rates. Asian J Androl. 2022 May-Jun;24(3):287-293. doi: 10.4103/aja202149. PMID: 34596599; PMCID: PMC9226700.*

xxxi) *https://www.webmd.com/infertility-and-reproduction/default.htm*

xxxii) *https://www.drishtiias.com/daily-news-analysis/assisted-reproductive-technology-regulation-bill-2021*

xxxiii) *Krausz C. Male infertility: pathogenesis and clinical diagnosis.Best Pract Res Clin Endocrinol Metab 2011; 25: 271–85.*

xxxiv) *Salonia A, Bettocchi C, Carvalho J, et al. EAU guidelines on sexual and reproductive health. 2020. https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Sexual-and-Reproductive-Health-2020. pdf (accessed May 29, 2020).*

xxxv) *Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: a committee opinion. Fertil Steril 2015; 103: e18–25.*

xxxvi) *Jarow J, Sigman M, Kolettis PN, et al. The optimal evaluation of the infertile male: AUA Best Practice Statement. 2010. https://www.auanet.org/documents//education/clinical-guidance/Male- Infertility-d.pdf (accessed May 29, 2020).*

xxxvii) *Schlegel PN, Sigman M, Collura B, De Jonge CJ, Eisenberg ML, Lamb DJ, Mulhall JP, Niederberger C, Sandlow JI, Sokol RZ, Spandorfer SD, Tanrikut C, Treadwell JR, Oristaglio JT, Zini A. Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline Part I. J Urol. 2021 Jan;205(1):36-43. [PubMed: 33295257]*

xxxviii) *Schlegel PN, Sigman M, Collura B, De Jonge CJ, Eisenberg ML, Lamb DJ, Mulhall JP, Niederberger C, Sandlow JI, Sokol RZ, Spandorfer SD, Tanrikut C, Treadwell JR, Oristaglio JT, Zini A. Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline PART II. J Urol. 2021 Jan;205(1):44-51. [PubMed: 33295258]*

xxxix) *Carnarella R, Shah R, Hamoda TAA, Boitrelle F, Saleh R, Gul M, Rambhatla A, Kavoussi P, Toprak T, Harraz AM, Ko E, Çeker G, Durairajanayagam D, Alkahidi N, Kuroda S, Crafa A, Henkel R, Salvio G, Hazir B, Darbandi M, Bendayan M, Darbandi S, Falcone M, Garrido N, Kosgi R, Sawaid Katyal R, Karna K, Phuoc NHV, Birowo P, Colpi GM, de la Rosette J, Pinggera GM, Nguyen Q, Zini A, Zohdy W, Singh R, Saini P, Glina S, Lin H, Mostafa T, Rojas-Cruz C, Arafa M, Calogero AE, Dimitriadis F, Kothari P, Karthikeyan VS, Okada K, Chiba K, Kadioglu A, Altay B, Turunc T, Zilaitiene B, Gokalp F, Adamyan A, Katz D, Chung E, Mierzwa TC, Zylbersztejn DS, Paul GM, Sofikitis N, Sokolakis I, Malhotra V, Brodjonegoro SR, Adriansjah R, Tnjitmura A, Amano T, Balercia G, Ziouziou I, Deswanto IA, Martinez M, Park HJ, Bakarcioglu ME, Ceyhan E, Aydos K, Ramsay J, Minhas S, Al Hashimi M, Ghayda RA, Tadros N, Sindhwani P, Ho CCK, Rachman RI, Rodriguez Pena M, Motawi A, Ponnusamy AK, Dipankar S, Amir A, Binsaleh S, Serefoglu EC, Banthia R, Khalafalla*

K, Basukarno A, Bac NH, Singla K, Ambar RF, Makarounis K, Priyadarshi S, Duarsa GWK, Atmoko W, Jindal S, Arlanto E, Akhavizadegan H, El Bardisi H, Shoshany O, Busetto GM, Moussa M, Jamali M, Al-Marhoon MS, Ruzaev M, Farsi HMA, Mutambirwa S, Lee DS, Kulaksiz D, Cheng YS, Bouzoulta A, Sarikaya S, Kandil H, Tsampoukas G, Farkouh A, Bowa K, Savira M, Mogharabian N, Le TV, Harjanggi M, Anh DT, Long TQT, Soebadi MA, Hakim L, Tanic M, Ari UC, Parikh FR, Calik G, Kv V, Dorji G, Rezano A, Rajmil O, Tien DMB, Yuan Y, Lizarraga-Salas JF, Eze B, Ngoo KS, Lee J, Arslan U, Agarwal A., Global Andrology Forum. Does Varicocele Repair Improve Conventional Semen Parameters? A Meta-Analytic Study of Before-After Data. World J Mens Health. 2024 Jan;42(1):92-132. [PMC free article: PMC10782123] [PubMed: 37382284]

xl) Belker AM, Thomas AJ, Fuchs EF, Konnak JW, Sharlip ID. Results of 1,469 microsurgical vasectomy reversals by the Vasovasostomy Study Group. J Urol. 1991 Mar;145(3):505-11. [PubMed: 1997700]

xli) Farber NJ, Flannigan R, Srivastava A, Wang H, Goldstein M. Vasovasostomy: kinetics and predictors of patency.Fertil Steril. 2020 Apr;113(4):774-780.e3. [PubMed: 32228879]

xlii) Carson SA, Kallen AN. Diagnosis and Management of Infertility: A Review. JAMA. 2021 Jul 06;326(1):65-76.[PMC free article: PMC9302705] [PubMed: 34228062]

xliii) Kadour-Peero E, Steiner N, Frank R, Al Shatti M, Ruiter J, Dahan MH. Is controlled ovarian stimulation and insemination an effective treatment in older women with male partners with decreased total motile sperm counts? Arch Gynecol Obstet. 2022 Jan;305(1):261-266. [PubMed: 34223975]

xliv) Borges E. Total motile sperm count: a better way to rate the severity of male factor infertility? JBRA Assist Reprod. 2016 May 01;20(2):47-8. [PubMed: 27244760]

xlv) Kendall Rauchfuss LM, Kim T, Bleess JL, Ziegelmann MJ, Shenoy CC. Testicular sperm extraction vs. ejaculated sperm use for nonazoospermic male factor infertility. Fertil Steril. 2021 Oct;116(4):963-970. [PubMed: 34233843]

xlvi) Bernie AM, Mata DA, Ramasamy R, Schlegel PN. Comparison of microdissection testicular sperm extraction, conventional testicular sperm extraction, and testicular sperm aspiration for nonobstructive azoospermia: a systematic review and meta-analysis. Fertil Steril. 2015 Nov;104(5):1099-103.e1-3. [PubMed: 26263080]

xlvii) Zarinara A, Zeraati H, Kamali K, Mohammad K, Rahmati M, Akhondi MM. The Success Rate and Factors Affecting the Outcome of Assisted Reproductive Treatment in Subfertile Men. Iran J Public Health. 2020 Feb;49(2):332-340. [PMC free article: PMC7231713] [PubMed: 32461941]

xlviii) Zheng Z, Chen L, Yang T, Yu H, Wang H, Qin J. Multiple pregnancies achieved with IVF/ICSI and risk of specific congenital malformations: a meta-analysis of cohort studies. Reprod Biomed Online. 2018 Apr;36(4):472-482. [PubMed: 29609768]