AOGO FOCUS

Association of Obstetricians & Gynaecologists of Orissa

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SILVER JUBILEE YEAR ISSUE

Theme :
Disorders of Human Reproduction

Topic and Authors

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   Dr. Jagannath Pahi, Dr. Ompriya Pahi
2. Anatomical disorders of Reproduction -
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3. **Disorders of Sexuality in Clinical Practice**
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10. Overview of Current Management of Disorders of Human Reproduction
    Dr. Tushar Jyoti Kar, Dr. Sanjay Swain

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Please Complete the following checklist and attach to the manuscript :

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The Editorial Board, Silver Jubilee Year Issue, AOGO Focus

Dr. Sindhu Nandini Tripathy

Dr Maya Padhi

Dr Sanjay Swain

Dr Saumya Nanda

Dr Tushar Jyoti Kar

Dr Sasmita Swain

From Editor's Pen.....

Theme : Disorders of Human Reproduction

HARD TO CRACK

Dear Seniors, Colleagues and Fellow AOGOians,

To be elected/selected as editor not only for AOGO Focus, but for any professional association's mouth piece - literary/academic is the easiest among all posts of the executives. What I observed in my more than 30 years of experience as a hard core AOGO member, there is no single instance of repetition of editorship by default in consecutive years by a member's self-interest. Not because the editorship is too tuff a work for our learned members, but because of the difficult task of motivating and persuading our members to devote some time in front of the study table to prepare a descent write up for our AOGO Focus. This is equally true for both novice and veteran members as well as for the stalwarts of AOGO. The poor editor is handy capped to publish the AOGO Focus in schedule intervals without the assigned write ups on the editorial desk in time. He/she has to run from pillar to post, has multiple phones calls off and on and has to approach the learned authors at all first-hand opportunities - be it a social gathering or an academic meet. I also felt in some occasions that my contributors try to avoid me as if a cat comes across their way. Dates after dates rolled past several schedules, but waiting for the arrival of a standard write up will go on shifting dates after date as if a floating lotus seems within your reach in shallow water goes on floating away from one when you just going approaching it to pluck. Editor with great expectation goes on checking email on a regular basis every day, but alas in vain!

Definitely certain academicians are too punctual in submitting their write up at par with their promised time lines. But it cannot be published in time due to the delay in getting the write ups from other authors. Delay in publication becomes the moral responsibility of the editor and he now becomes answerable to the real punctual authors submitting their write ups in time. Attempting to explain the delay in publication, the poor editor neither can show the wound cropped in the forbidden locations nor can tell the fact.

Anyway, at the end of the day the editor is the happiest person when the published AOGO Focus is finally released on the dais. Feeling is just like a happy mother holding her new borne close to her heart just after a prolonged painful labour.

The 1st edition of AOGO Focus for the session: 2021-22 is on the theme "THE DISORDERS OF HUMAN REPRODUCTION". It's a decathlon with 10 basic subjects of discussion on human reproduction through the basic genetics, anatomy, endocrinology, etc to the overview of advanced management of reproductive disorders. The write ups are prepared by competent contributors from amongst our AOGO members. The true objective of AOGO Focus to excel academics within our members is well represented in this issue.

This special SILVER JUBILEE YEAR issue is dedicated to Late Prof. (Dr) D K Pattanayak (gracefully called by one and all of AOGO as DHIRA SIR), one of the towering personalities among the stalwarts of AOGO and FOGSI who left us recently on his eternal journey to abord.

My immense thanks to all the contributors for burning their night oil to prepare the high quality write ups with unconventional subject matter of this issue. There were some murmurs that the topic break ups are very hard to crack; but my dear authors proved that wrong by giving justice to one and every topic with very rational all round approach, defying all barriers on the way. Of course, our target readers are the best judges for comments on this issue of AOGO Focus.

I am also very much thankful to the FOUNDER EDITOR of AOGO Focus, Prof (Dr) Sindhu Nandini Tripathy for her constant encouragement to publish the issue as early as possible. In fact, she strolls down her memory lane for her brain child - THE AOGO FOCUS to draft an excellent write up on the evolution and march of AOGO focus till date to refreshen our memory. She also provided a copy of the MAIDEN EDITION of AOGO Focus published way back in September, 1997 from her treasure collection of galaxies of literary/academic publications. Thank you once again Mam' for all that you contributed for AOGO Focus from its inception. AOGO wishes you a long and cherished life to inspire us with your ever flowing love, affection and dedication for all the time to come.

On behalf of the entire editorial team, I thank Prof Tusar Jyoti Kar sitting President, AOGO, Prof Sasmita Swain, the able Honorary Secretary - cum - Treasurer, AOGO and all the office bearers of AOGO: 2021-22 for their confidence on me to bestow the responsibility of Editor, AOGO Focus.

I must thank my editorial board members - Prof (Dr) Maya Padhy and Dr Saumya Nanda; but for whom helping hands, the Focus may not be in this presentable form.

Last but not the least my thanks go to the targeted readers of this "Silver Jubilee Year Issue-2022" of AOGO FOCUS with the theme "Disorders of Human Reproduction" in anticipation of their appreciation with positive feedbacks to improve the forthcoming issues.

Wish all the learned members happy reading.

Long live AOGO & Long live FOGSI.

(Dr Sanjay Swain)
Editor
Email: sanjaybhaee@gmail.com

Jai Hind!

◆◆◆

From the pen of the founder Editor.....

" Let Noble Thoughts come to us from all sides."

It is my great pleasure and proud privilege to write few words in the forth coming publication of our dear AOGO FOCUS, after a gap of more than two years. The Pandemic affected all walks of our life along with our Academics and publications. Long Long ago, Lord Sri Ramchandra was King of Ayodhya, so also our Focus. Long time almost 25 years back , the first issue saw the light of the day on September 1997 with great enthusiasm and best wishes from one and all.

I personally feel and believe any organisation whether big or small should have a publication of its own to express its opinion, share the views of each other and chronicle the events of the Society. We all dream to do many great works. But a dream does not become a reality through magic. It takes sweat, resolution, vision and hard work . Many good things are launched with great pump and show. But what matters most is not the beginning but the continuing. I was worried about it when the first issue came out and still worried about its continuity when the pandemic came.

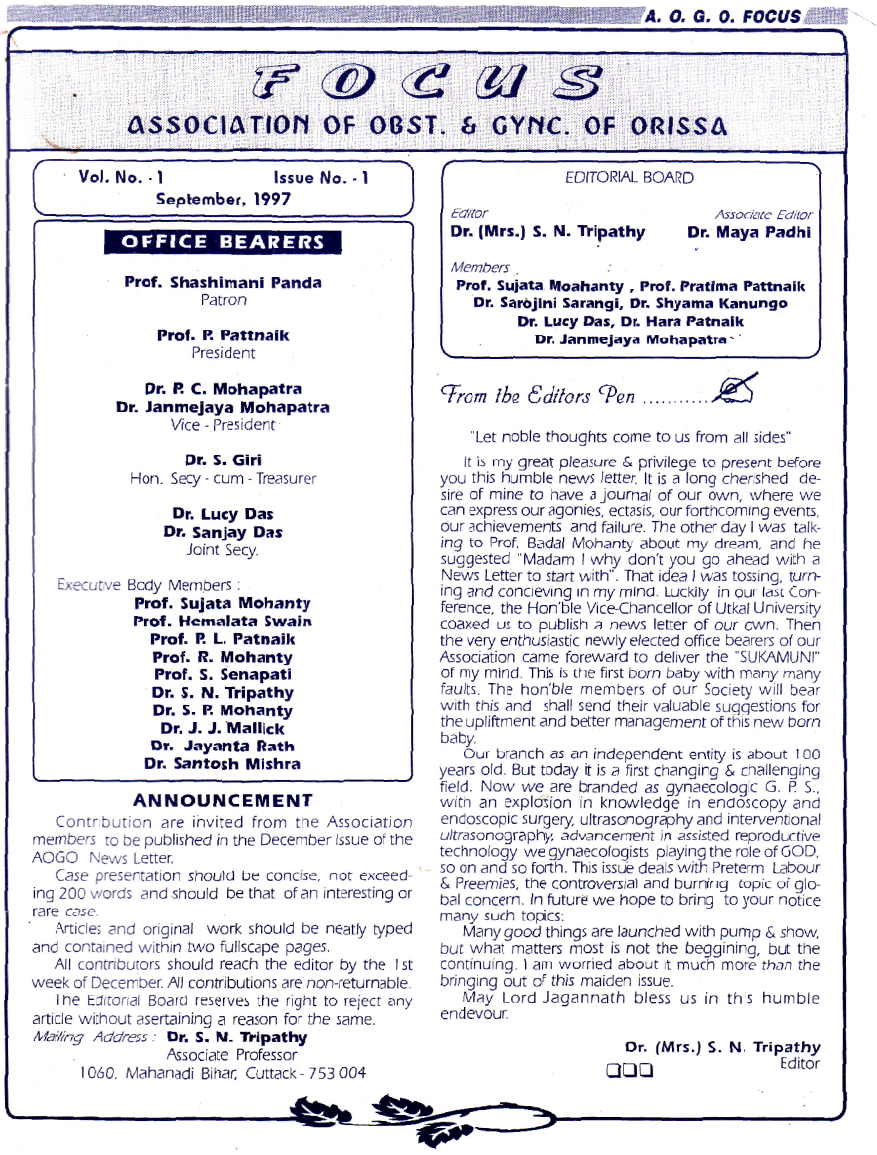
Four things are necessary for a publication. Finance, Good stewardship, contributions of up to date articles and a good publisher who deliver the publication in time. To start with I had everything a very good team, an efficient Associate Editor, along with a group of elite , enthusiastic editorial members. On those days there was no computer, No electronic transmission. To bridge the gap, Dr. Janmejoy Mohapatra, and Dr. Harprasad Pattnaik were there and the overall supervision of printing, finance was with Dr. P. C. Mahapatra and to deal with Babuni, Mr. Soumendra Mishra. Many of us do not know his real name, we just know him as Babuni, May it rain or snow we are sure that he will be with our Focus or Souvenir on the date of its release on the stage and from that time till date, he is printing our Focus and Souvenirs. Babuni, Keep it up. We are extremely grateful to you. Dr. Hara Pattnaik will carry the manuscripts to press, bring back the printed script, myself and Maya will correct it, again Hara will go to the press and deliver the same and like that the first issue was born, and it continued like that for many years. I am really really grateful to them, without their help, it would have been extinct long back. I am also very grateful to Maya for her dedication, sincerity and perseverance to bring out the Focus in time. I pay my humble gratitude to our senior professors and all other contributors for obliging us by an article whenever we asked for it. I am attaching here with the front page of our maiden copy, whatever we had decided at that time is followed up more or less till date, Research articles, A Burning topic of the time, and activities of the society. Pratima Madam was the President, she gave the message, minutes of 21 st Annual conference and executive body meeting was written by Maya, Birth Weight Patterns, is it important, An original research paper by me and Dr. Radha Tripathy. The Subject was Preterm labour, and articles were contributed by Prof. Sujata Mahanty, Dr. Renu Mahanty, and Premlata Pattnaik.

' A Job worth doing is worth doing it together and it means success'.

When I stepped down, I handed over the baton to Maya, 'The Old order change the making way for the new.' The Journey continued, each leaving their unique foot prints on the sands of time. New blood , new enthusiasm, and then the Pandemic. The whole world stopped what to speak of our Focus. We all are limping back to normal. The Society is now headed by two good Academicians Prof. Tushar Kar as president and Prof Sasmita Swain as secretary. and many enthusiastic members, so I hope no financial problem or lack of articles will be there. Under the expert stewardship of dear Dr. Sanjay Swain and his brilliant team, the journey for the Focus will be smooth .

May Lord Jagnnath bless us to continue the Focus as before.

Prof. (Mrs) S. N. Tripathy.
Founder Editor.



A. O. G. O. FOCUS

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Contribution are invited from the Association members to be published in the December issue of the AOGO News Letter.

Case presentation should be concise, not exceeding 200 words and should be that of an interesting or rare case.

Articles and original work should be neatly typed and contained within two fullscape pages.

All contributors should reach the editor by the 1st week of December. All contributions are non-returnable.

The Editorial Board reserves the right to reject any article without asertaining a reason for the same.

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From the Editors Pen .....

"Let noble thoughts come to us from all sides"

It is my great pleasure & privilege to present before you this humble news letter. It is a long cherished desire of mine to have a journal of our own, where we can express our agonies, ectasis, our forthcoming events, our achievements and failure. The other day I was talking to Prof. Badal Mohanty about my dream, and he suggested "Madam I why don't you go ahead with a News Letter to start with". That idea I was tossing, turning and concieving in my mind. Luckily in our last Conference, the Hon'ble Vice-Chancellor of Utkal University coaxed us to publish a news letter of our own. Then the very enthusiastic newly elected office bearers of our Association came foreward to deliver the "SUKAMUNI" of my mind. This is the first born baby with many many faults. The hon'ble members of our Society will bear with this and shall send their valuable suggestions for the upliftment and better management of this new born baby.

Our branch as an independent entity is about 100 years old. But today it is a first changing & challenging field. Now we are branded as gynaecologic G. P. S., with an explosion in knowledge in endoscopy and endoscopic surgery, ultrasonography and interventional ultrasonography, advancement in assisted reproductive technology we gynaecologists playing the role of GOD, so on and so forth. This issue deals with Preterm Labour & Preemies, the controversial and burning topic of global concern. In future we hope to bring to your notice many such topics.

Many good things are launched with pump & show, but what matters most is not the beggining, but the continuing. I am worried about it much more than the bringing out of this maiden issue.

May Lord Jagannath bless us in this humble endevour.

Dr. (Mrs.) S. N. Tripathy
Editor

This issue is dedicated to our beloved
Late Prof. Dr Dhirendra Kumar Pattanaik

Born on : 14th June, 1945 Departed on : 27th December, 2021

Association of Obstetricians & Gynaecologists of Odisha (AOGO), Cuttack pays homage to the departed soul of our beloved senior most member **Late Prof. (Dr.) Dhirendra Kumar Pattnaik** on his sad demise. He had an illestrious career as a Student, as a Teacher par excellence, a daring Surgeon and a stalwart of AOGO as well as FOGSI.
He was best known for his impartial and equivision personality. His smilling face and self-cofidence were source of inspiration to all those who were in his contact.
His services and involvement in AOGO & FOGSI activities will be ever remembered.

GENETIC DISORDERS OF HUMAN REPRODUCTION

Dr. Jagannath Pahi,
Dr. Ompriya Pahi,

INTRODUCTION

Disorders of reproduction are defined as pathologies that can affect reproductive function in humans and therefore cause conception failure [1]. The alteration of human reproductive function can be due to organic, congenital, functional, accidental, or genetic disorders.

Disorders of reproduction represent a significant social, emotional, medical, and economic burden for individuals and society. An estimated 10%-15% of couples suffer from infertility, with a female factor identified in 70% and a male factor in 50% (20% have both male and female factors). At least 3000 genes are known to play a role in fertility. Thus, a genetic factor may contribute to many-if not most-cases. Although many causes of infertility can now be determined in both men and women, most couples still receive a diagnosis of idiopathic infertility. A subset of these patients is likely to have an underlying genetic disorder that is either inherited (germline) or acquired (somatic). Although the most severe genetic reproductive disorders cause dysgenetic gonads or abnormal hormonal profiles, milder phenotypes are being recognized with increasing frequency.

Nonetheless, genetics are only one component to fertility, with hormonal, environmental, social, and other factors also playing a significant role. Confirmation of the clinical diagnosis through genetic evaluation (counselling and testing) can lead to more specific and targeted medical management.

The aim of this article is to highlight the conditions in which a genetic evaluation plays a role in improving the reproductive outcomes of infertile couples. In this article, we will try to squeeze in a crisp overview of different arrays of genetic disorders affecting reproduction.

PHYSIOLOGY OF REPRODUCTION

The hypothalamus releases GnRH which stimulate the pituitary to release gonadotrophins which in turn act on the gonads to facilitate gametogenesis (HPG axis). Genetic disorders can lead to anatomic or functional alterations causing reproductive failure.

Many genes have been identified that influence the development and function of the hypothalamic-pituitary-gonadal (HPG) axis.[2] These genes encode an array of transcription factors, matrix proteins, hormones, receptors, and enzymes that are expressed at multiple levels of the HPG axis, and regulate the complex developmental, paracrine, and endocrine interactions that are necessary for spermatogenesis and ovulation.

Figure 1 shows the genes involved in the HPG axis, mutations in which have been shown to cause hypogonadotrophic hypogonadism in humans.[2]

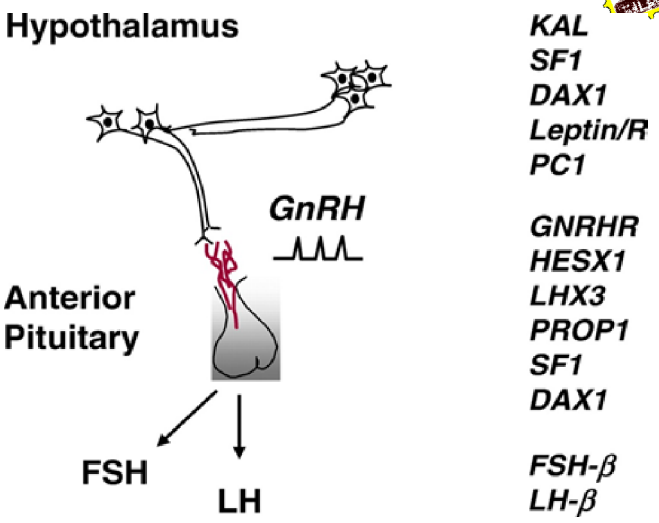

Figure 1. Overview of the hypothalamic-pituitary (gonadotrope) axis. Mutations in the genes listed in italics have been shown to cause HH in humans.

GONADAL DIFFERENTIATION AND GAMETOGENESIS

The development of a 46XY fetus into a fertile, phenotypic male is a dynamic process that requires: development of the bipotential gonad into a testis (testis determination); differentiation of the Leydig and Sertoli cells within the testis; androgen biosynthesis by the Leydig cells to virilize the external genitalia and support development of Wolffian structures (e.g. prostate); anti-Mullerian hormone [AMH (Mu?llerian-inhibiting substance)] production by Sertoli cells to regress Mu?llerian structures (e.g. uterus and upper vagina); testicular descent; and migration of germ cells into the developing gonad leading to spermatogenesis at the time of puberty. Single gene mutations affecting each of these processes have been described in patients with disorders of sexual development or infertility.

Figure 2 shows overview of the development and function of the gonad.[2] Mutations in the genes listed in italics have been reported in humans. Overexpression of the antitestis genes, DAX1 and WNT4, affect testis development in 46XY individuals, whereas overexpression or inappropriate expression of the testis genes, SRY and SOX9, affect ovarian development in individuals with a 46XX karyotype.

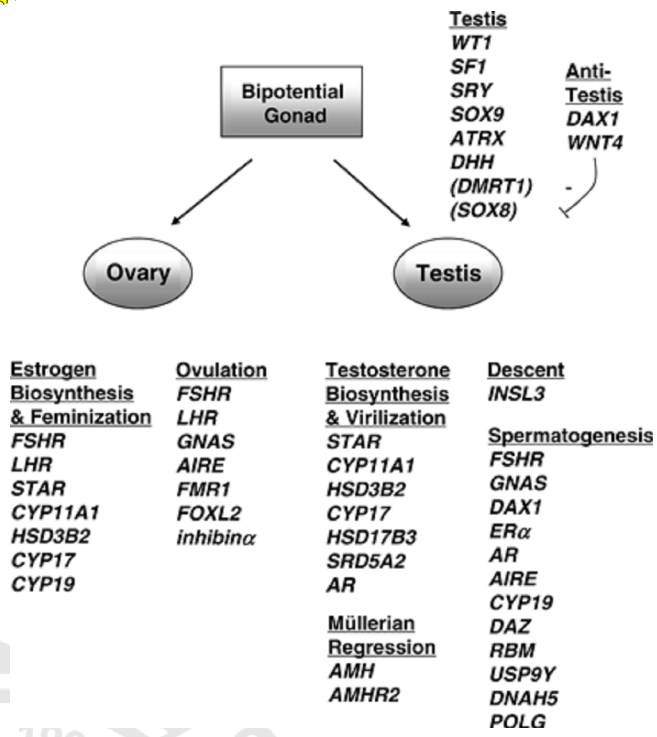

Figure 2. Overview of the development and function of the gonad.

TYPES OF GENETIC ALTERATIONS CAUSING INFERTILITY [3]

Sex chromosomes abnormalities such as Turner syndrome, Klinefelter syndrome, sex reversal (also called De la Chapelle syndrome for XX males), Jacob syndrome, triple X syndrome, and mixed gonadal dysgenesis.

Structural rearrangements such as microdeletions of chromosome Y involving AZF factor which is crucial for spermatogenesis, Y isochromosome: on the one hand, Ypisochromosome is implicated in male infertility since the AZF region is lost and the region of male determinism SRY is retained; on the other hand, Yqisochromosome is associated with female determinism with the presence of the AZF region [4]. Translocations between the Y chromosome and an X can lead to abnormal phenotypes causing sexual ambiguity or infertility [5].

Ring Y chromosome is characterized by a wide spectrum of phenotypes such as anomalies in genital organs, hypogonadism, oligospermia, or azoospermia [5].

Xqisochromosome often encountered in Turner's syndrome is characterized by amenorrhea, ovaries that function normally but are atypical (fibrous strips). Deletion of Xp can lead to gonadal dysgenesis, infertility, or amenorrhea depending on the breakpoint [6, 7].

A translocation between X and an autosome, when occurred in the POF1 and POF2 locus, results in ovarian disorders [8].

For autosomal chromosomes, structural abnormalities such as reciprocal translocations and Robertsonian translocations present an increased risk of miscarriages and male infertility due to the generation of imbalanced gametes [9, 10]. Regarding female infertility, these abnormalities lead to the production of unbalanced oocytes carrying structural abnormalities which can be the cause of failed fertilization or implantation and spontaneous miscarriages.

MALE GENETIC INFERTILITY [11]

Genetic factors have been found in all the etiological categories of male infertility (pre-testicular, testicular and post-testicular).[12] OMIM (Online Mendelian Inheritance in Man) reports more than 200 genetic conditions related to male infertility, ranging from the most common clinical presentations of infertility to the rarest complex syndromes in which signs and symptoms are beyond the reproductive problems [13]. In most cases, infertility is only one of the clinical signs of a complex syndrome; on the contrary, in some genetic conditions, infertility is the main phenotypic feature. Moreover, it is important to monitor these infertile patients over time because a greater morbidity and a lower life expectancy have been observed due to other systemic effects.

Genetic disorders in males can cause sperm abnormalities that result in infertility. These include Kleinfelter syndrome, the cystic fibrosis gene mutation affecting only males, Noonan syndrome and others.

These genetic disorders can stop production of sperm (azoospermia), result in poor motility of sperm (asthenozoospermia), or cause very poor-quality sperm (teratozoospermia). Genetic mutations can also result in the absence of the vas deferens that transports sperm.

Genetic disorders related to male infertility include whole chromosomal aberrations (structural or numerical), partial chromosomal aberrations (i.e., microdeletions of the Y chromosome) and monogenic diseases . In particular, abnormalities in sex chromosomes have a greater impact on spermatogenesis, while mutations affecting autosomes are more related, for example, to hypogonadism, teratospermia or asthenozoospermia and to familial forms of obstructive azoospermia.

We evaluate the man's sperm with a semen analysis. Guidelines recommend that all men with fewer than 5 million sperm per milliliter undergo genetic evaluation.[14,15]

There are several treatment options for male infertility, from lifestyle changes, micro-epididymal sperm aspiration to in vitro fertilization (IVF),ICSI(Intracytoplasmic sperm injection). Donor sperm may also be needed.

In the presence or high suspicion of a genetically based reproductive risk, the genetic test provides a more accurate diagnosis of infertility and provides the opportunity to inform the couple about the possible risk of transmission to the offspring.

Table 1. The chromosome aberrations related to testicular male infertility [16,17]

Indications for genetic test	Genetic condition	Frequency	Test	Chromosome/ genetic alterations	ART	Inheritance
Azoospermia/oligozoospermia; Sertoli cell syndrome type I and type II (presence of some tubules with normal spermatogenesis) and hypospermatogenesis diagnosis by histological evaluation	Microdeletion Y chromosome AZFc	1/2.500; (AZFc 60%, AZFb 15%, AZFb-c 22%, AZFa 3%); 13% of azoospermia cases; 3–7% of oligozoospermia cases	Molecular diagnosis by PCR of STS sequences	Interstitial deletion of AZFc Y region (recombination between palindromes b2 and b4); DAZ, BPY2, PRY2, CDY1	✓: testicular sperm retrieval + ICSI	Y linked
Azoospermia; spermatogenesis arrest by histological evaluation	Microdeletion Y chromosome AZFb			Interstitial deletion of AZFb Y region (deletions P5/proximal-P1); RBMY, CDY, HSFY, PRY		
Azoospermia	Microdeletion Y chromosome AZFb-c			Combined deletion AZFb + AZFc (P5/distal-P1 or P4/distal-P1)	✓: donor	NA
Azoospermia; Sertoli cell syndrome type I diagnosis by histological evaluation (i.e., complete absence of germ cells in seminiferous tubules)	Microdeletion Y chromosome AZFa			Deletion of AZFa Y (recombination between HERV15yq1 and HERV15yq2)		

Table 2. The chromosome aberrations related to pretesticular male infertility [16,17]

Indications for genetic test	Genetic condition	Frequency	Test	Chromosome / genetic alterations	ART	Inheritance
Hypergonadotropic hypogonadism, ↑FSH ↑LH ↓T, azoospermia, oligozoospermia; small testes, infertility, gynecomastia; neurocognitive deficits; metabolic syndrome, type 2 diabetes. Approximately 10% of these subjects have spermatozoa in the ejaculate, and in 30–50% of cases there is intratesticular spermatogenesis	**Klinefelter's syndrome**	1/660 newborns; > 5% in severe oligozoospermia ; 10% in azoospermia	Karyotype	47,XXY (85–90%) 46,XY/47,XXY mosaicism (6–7%) 46,XX/47,XXY or multiple X aneuploidy (3–8%)	✓ Testicular sperm retrieval + ICSI	De novo mutation
Short stature; gynecomastia, male external genitalia, small testes, cryptorchidism, hypospadias, infertility, ↑FSH ↑LH↓T; azoospermia/oligozoospermia	Nonsyndromic 46,XX Testicular Disorders of Sex Development **(De la Chapelle syndrome)**	1/20.000; 0,9% in azoospermia; 1–3% normospermia	FISH or CMA	SRY+ XX (80–90%)	✗ Testicular sperm retrieval; ✓ heterologous fertilization	AD
Penoscrotal hypospadias, cryptorchidism, infertility; ↑FSH ↑LH↓T; azoospermia/oligozoospermia				SRY− XX (< 10%)		Unknown
Short stature; small testes, infertility; ↑FSH ↑LH↓T; azoospermia/oligozoospermia			CMA or molecular diagnostic by PCR	CNV or rearrangements in SOX9, SOX3, RSPO1 and WNT4 (rare)		✓ AD for SOX9; AR for RSPO1 or WNT4
Tall stature, delayed development of speech, language or motor skills, autism spectrum disorder, hypotonia, motor tics, clinodactyly, scoliosis, attention deficit hyperactivity disorder; ↑FSH normal or ↓T; from normal to azoospermia; from 0.57 to 77.8% sperm mosaicism, a- or hyper diploidy	Double Y syndrome **(Jacobs syndrome)**	1/1.000; 0.4% in oligozoospermia	Cytogenetics tests	47,XYY; 46,XY/47,XYY mosaics	✓IVF or ICSI in case of oligospermic patients	Does not have a clear pattern of inheritance
Subfertility or uneventful andrological history; oligozoospermia	Balanced structural chromosome aberrations	5% of infertile men	FISH	t(SRY; X); der(13, 14); der(14, 21); der(14, 15)	✓	NA

Whole chromosomal aberrations

Sex chromosomes abnormalities accounting for approximately 4.2% of all whole chromosomal aberrations, are represented by sex chromosome aneuploidies in 84% of cases and by structural rearrangements of chromosome Y in the remaining 16% of cases. Klinefelter syndrome (karyotype 47, XXY) is the most frequent type of sex chromosome aneuploidy detected in infertile men [18,19]; the second most frequent gonosomal abnormality is Double Y syndrome or Jacobs syndrome, characterized by the presence of Y chromosome disomy [20,21]. In addition to reduced reproductive potential, carriers of chromosomal abnormalities have an increased risk of abortion or generate a child with an abnormal karyotype.

Partial chromosomal aberrations

Microdeletions in the long arm of the Y chromosome (Yq), named the AZF (Azoospermia Factor) region, have been found in 8-12% of azoospermic men and 3-7% of oligozoospermic men [22], resulting in the most common molecular genetic cause of male infertility [23]. The AZF region includes three groups of genes (AZFa, AZFb and AZFc) that are most responsible for spermatogenesis, so partial or complete deletions in this area may impair reproductive capacity. Indications for AZF deletion screening are based on sperm count (<?5?×?106 spermatozoa/ml) associated with primary testiculopathy, and ICSI is required to overcome infertility [24].

Male offspring will carry the same father's Yqmicrodeletions or even a worse one; therefore, genetic counselling is mandatory [25]. Parents should be aware of the risk of having a child affected by Turner's syndrome (45, X0) or other phenotypic anomalies associated with sex chromosome mosaicism [26].

The rearrangement of the AZFc zone is responsible for 60% of all Yqmicrodeletions [27]. The AZFc region (3.5 Mb) contains several copies of five repeats (b1, b2, b3, b4, and gr), whose similarity and large size predispose an individual to a relatively high incidence of de novo deletions via homologous recombination [28]. The most common is the loss of the whole b2/b4 region, which includes the DAZ family (Deleted in Azoospermia) and leads to spermatogenesis deterioration [28, 29]. More details about AZF are reported in Table 1

Single gene mutations [30]

Genetic causes related to pretesticular male infertility include Kallmann syndrome, Bardet-Biedl syndrome, X-linked adrenal hypoplasia congenital, Gordon Holmes syndrome, Hemochromatosis, Androgen insensitivity syndrome (AIS), 5-Alpha reductase deficiency (familial incomplete male pseudohermaphroditism, type 2)

Single gene mutations related to testicular male infertility are Prader-Willi syndrome, Noonan syndrome-1 (NS1), Denys-Drash syndrome, Aromatase deficiency, Russel-Silver syndrome, Bloom' s syndrome, Myotonic dystrophy 1, Fanconi anemia.

The genetic causes related to posttesticular male infertility include Congenital bilateral absence of the vas deferens (CBAVD) and Cystic fibrosis.

Currently, the main genetic tests routinely used for the diagnosis of male infertility are the karyotype, the study of chromosome Y microdeletions, and the analysis of the CFTR gene. It must also be considered that the role of de novo mutations should be further investigated, especially in light of what happens for Klinefelter syndrome and AZF deletions that occur almost exclusively de novo [22]. Therefore, to improve and personalize the entire diagnostic-therapeutic pathway of male infertility, targeted genetic tests should be performed in the presence of specific clinical pictures, always after appropriate genetic counselling: (1) for diagnostic purposes, (2) during clinical decision-making to establish the most appropriate ART strategy (for example, in the presence of deletions of the AZFa and AZFb regions, the possibility of sperm recovery using testicular biopsy is extremely low), and

(3) for prognostic purposes (to establish the risk of transmitting the pathology and plan a prenatal or preimplantation diagnostic procedures).

FEMALE GENETIC INFERTILITY [31]

Genetic abnormalities in women can cause ovulation disruption and infertility. These include Turners syndrome,fragile X syndrome, Kallmann syndrome and others. Gene disorders can also result in malformations of the reproductive system that make conception difficult or impossible. Women with a family history of problems conceiving due to endometriosis or premature menopause that can be caused by genetic issues may also have trouble conceiving.

In contrast to male infertility, little is known about the genetic bases of female infertility. Accordingly, fewer specific tests are routinely recommended to infertile females to investigate the presence of chromosomal disorders or single-gene defects related to their clinical phenotypes. Indeed, isolated infertility due to genetic causes is rare; more commonly, syndromic diseases contribute to female infertility. To date, genetic tests are mainly used for patients with POI, limited to chromosomal aberrations and FMR1 premutations.[32] Tables 3, 4 report the main chromosomal and genetic alterations that could interfere with healthy reproduction; for each of them, the main phenotypic presentations and the laboratory tests that are available are reported.

Table 3. The genetic causes related to ovarian female infertility

Indications for genetic test	Genetic disorder	Frequency	Genetic test	Chromosome/genetic alterations	ART	Inheritance
Short stature, skeletal abnormalities, kidney problems, webbed neck, lymphedema; ovarian hypofunction or premature ovarian failure, infertility	Turner (45,X) (other names monosomy X, TS)	1 in 2500	Karyotype	Monosomy X: 45,X0	✓- donor	Not inherited
Asymptomatic (only 10% of individuals with trisomy X are actually diagnosed); tall stature, epicanthal folds, hypotonia and clinodactyly; renal and genitourinary abnormalities; psychological problems	Trisomy X	1/1000	Karyotype	47XXX or mosaic	✓	NA
Irregular menstrual cycles, early menopause, premature ovarian failure, infertility	Fragile X-associated primary ovarian insufficiency (premature ovarian failure 1)	1 in 200 (4/6% of all cases of POI)	Molecular diagnosis of premutations in the FMR1 gene on chromosome Xq27.3	*FMR1 gene* (CGG segment is repeated 55 to 200 times)	✓- donor	X-linked

Normal general physical examination, absence of clinical findings involving other organ systems; typical female external genitalia, normally formed uterus and fallopian tubes, gonadal dysgenesis; skeletal abnormalities, campomelic dysplasia	Swyer syndrome (46,XY complete gonadal dysgenesis)	1 in 80,000	Molecular diagnosis	*SRY (15%); MAP3K1 (18%); DHH and NR5A1 (rare)*	ART	De novo; rare AD
Hypergonadotropic amenorrhea; lack of puberty; absence of secondary sexual features, decreased muscle mass, diminished libido, infertility	Kallmann	prevalence: 1/30,000; incidence: 1/8,000	Molecular diagnosis	*Type 1: ANOS1 Type 2 and 6: CHD7, FGFR1, HGF8 and SOX10 Type 3: FEZF1, PROK2, PROKR2*	✓	X-linked AD AR

Table 4. The genetic causes related to postovarian female infertility

Indications for genetic test	Genetic disorder	Frequency	Genetic test	Genetic alterations	ART	Inheritance
Underdeveloped or absent uterus and abnormalities of other reproductive organs; normal female external genitalia, breasts; hyperandrogenism; facial hirsutism; primary amenorrhea; infertility	Müllerian aplasia and hyperandrogenism (other names: Biason–Lauber syndrome, WNT4 deficiency)	Rare	Molecular diagnosis	WNT4 gene	NA	AD or de novo
Vagina and uterus to be underdeveloped or absent, although external genitalia are normal, primary amenorrhea	Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome (type 1)	1 in 4500	Molecular diagnosis	ESR1, OXTR, WNT9B	NA	AD
Underdeveloped or absent vagina and uterus, although external genitalia are normal; primary amenorrhea; unilateral renal agenesis; skeletal abnormalities; hearing loss or heart defects	Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome (type 2)					
Bone marrow failure, hypopigmentation, short stature, physical abnormalities, organ defects (gastrointestinal abnormalities; heart defects; eye abnormalities, malformed ears and hearing loss), and an increased risk of certain cancers; abnormal genitalia or malformations of the reproductive system and infertility	Fanconi anemia (Fanconi pancytopenia Fanconi panmyelopathy)	1 in 160,000 (more common among people of Ashkenazi Jewish descent, the Roma population of Spain, and black South Africans)	Molecular diagnosis	FANCA, FANCC and FANCG (90%)	NA	AR; AD (RAD51-related FA); X-linked (FANCB-related FA).

CONCLUSION

Healthy reproduction can be affected by unhealthy environmental and lifestyle factors, increasing paternal and/or maternal age, anatomical or genetic anomalies, systemic or neurological diseases, infections, trauma, and antibody development. As a consequence, infertility can be the result of nongenetic and genetic factors, and it is often multifactorial, polygenic or a combination of both. Presumably, hundreds of genes must interact in a precise manner during sex determination, gametogenesis, complex hormone actions/interactions, embryo implantation, and early development to generate healthy offspring. Indeed, known genetic causes of infertility include chromosomal aberrations, single gene variants and phenotypes with multifactorial inheritance. To date, specific genes and mutations have been confirmed to be associated with infertility phenotypes in males, females or both, and our knowledge regarding the molecular basis of infertility is continually growing.

Finally, it is important to translate advances in genetics into improved clinical management. In addition to genetic counselling, it may be possible to direct selected patients to various forms of assisted reproduction such as intracytoplasmic sperm injection for spermatogenic defects or in vitro fertilization for ovulatory dysfunction. Confirmation of a clinical diagnosis through genetic testing may lead to personalized medical management. Similar clinical symptoms may be the result of different genetic variations. Specifically, in more rare clinical situations, genetic evaluations (counseling and testing) can contribute to the specific identification of the disease or to the confirmation of a suspected diagnosis. The combination of the detailed clinical information provided and the identified genetic cause will allow the development of a personalized diagnostic-therapeutic strategy.

Progress resulting from the human genome project, along with advances in genomics and proteomics, will undoubtedly enhance the rate at which human reproductive mutations are found. Capitalizing on these scientific advances to improve patient care will be a major opportunity of the next decade.

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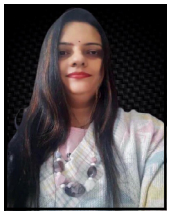
ANATOMICAL DISORDERS OF REPRODUCTION



Dr. Sanghamitra Dash

"Forget all the reasons it won't work and believe the one reason it will".

Before any formal evaluation begins, the major causes of infertility like basic components evaluation should be outlined for the couple which is specific for them. The major causes of infertility include tubal and peritoneal pathology (30-40%), ovulatory dysfunction (20-40%),male factors (30-40%) where as uterine pathology is a major causes for pregnancy losses and congenital anomalies of lower genital tract a major hinderance in menarche onset to consummation of marriage to predated pregnancy losses be it abortion or preterm labour causing high incidence of perinatal morbidity and mortality.

Key point: Human Reproductive Process.

- Sperm must be deposited at or near the cervix at or near the time of ovulation,ascend into the fallopian tubes,and have the capacity of fertilize the oocyte(male factor)
- Ovulation of a mature oocyte must occur,ideally on a regular and predictable basis(ovarian factor)
- The fallopian tubes must capture ovulated ova and effectively transport sperm and embryos (tubal factor)
- The uterus must be receptive to embryo implantation and capable of supporting subsequent normal growth and development (uterine factor)

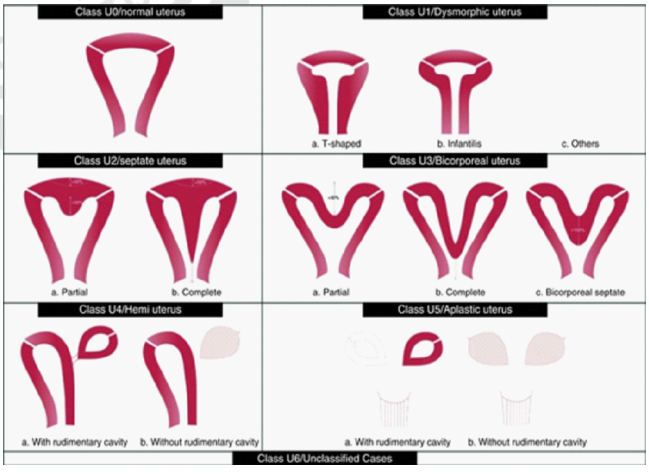
The human reproduction process is complex, but for purposes of evaluation it can be dissected into its most important and basic components. During evaluation of anatomical defects of reproduction both congenital and acquired abnormalities of genital tracts of both the partners play vital role.

Female factor defects:

Congenital defects of reproductive tract:

Uterine malformation:

- Congenital uterine malformations are a heterogenous group of disorder that may adversely affects reproductive potential. Sequence of genital development in accordance with Healey A 1 in (Table 2.1).
- The gold standard diagnostic modalities such as laparoscopy and hysteroscopy are invasive procedures and the most recent prevalence study by YY Chan2 is mentioned in (Table 2.2).



Schematic drawing of the ESHRE/ESGE classification system of uterine congenital anomalies from Ref. [8], dividing uterine anomalies in six classes.

Table 2.1 Time table of genital development.

Phase of genital development	Time(weeks of gestation)
Indifferent gonadal phase	4-6
Gonadal differentiation	7
Lateral fusion of both paramesonephric ducts	7-9
Vertical fusion occurs in the eighth week when the lower most fused paramesonephric ducts fuse with the ascending endoderm of the sinovaginal bulb.	8
Resorption of midline septum	20

Classification:

The basis of classifying uterine anomalies depending on Mullerian developmental process is proposed by Acien P3.

- The partial or total agenesis of one (unicornuate) or both Mullerian ducts(MRKH syndrome)
- Partial or total absence of fusion of both Mullerian ducts(bicornuate uterus and didelphys uterus)
- Partial or total absence of resorption of septum(partial or complete uterine septum)
- Lack of later development (T-SHAPED uterus and hypoplastic uterus)
- Segmental defects and combination of different anomalies.

Table 2.2.Incidence of congenital uterine anomaly.[2]
Unselected population-5.5%
Infertile women-8%
Miscarriage group-13.3%
Infertile women who also had a history of miscarriage-24.5%
Most common anomaly in an unselected group of women-arcuate uterus.
Most common anomaly in all of the high-risk groups-canalization defect.

ESHRE Classification:-

Main concepts are:

- Anatomy is the basis of classification.
- Anatomical variations resembling similar embryological developmental process are categorized to different classes.
- Classification into subclasses is based on clinically significant variations among different anomalies within a class.
- Vaginal and cervical abnormalities are mentioned separately in the present classification:

Reproductive complications associated with congenital uterine anomalies are recurrent first trimester and second trimestar loss,ectopic

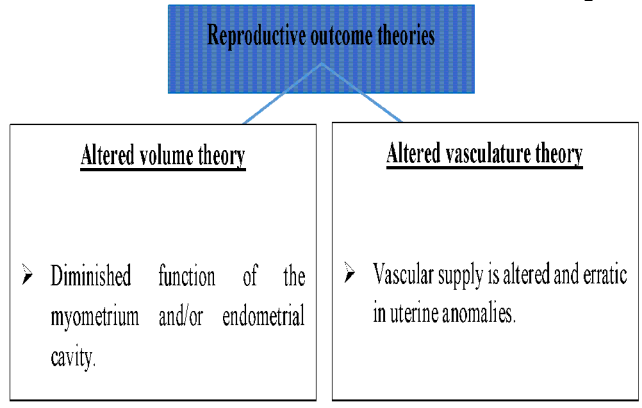


Table 2.3 Diagnostic work up in uterine anomalies5

Asymptomatic women	Symptomatic high risk population	Complex anomaly	Symptomatic adolescent
• Gynecological examination • 2D sonography	• Gynecological examination • 2D USG • 3D USG • HSG • HyCoSy,2D or 3D sonohysterography • Hysteroscopy and in cases of suspected adnexal pathology, laparoscopy.	• Abdominal and/or transrectal 3D USG • MRI • Hystero - laparoscopy with surgical correction in same setting.	• Gynecological examination • Abdominal and/or transrectal 2D and 3D US. • MRI as a first line diagnostic procedure. • Hysterolaparoscopy with surgical correction in same setting.

Table 2.4Conception rate in different uterine anomalies(Y Y CHAN)4

Table 2.4Conception rate in different uterine anomalies(Y Y CHAN)[4]

Anomaly	Infertility perspective in terms of conception rate in comparison with normal uterus as control [12] Risk ratio(95% CI)
Unicornuate uterus	0.74(0.39-1041)
Didelphys uterus	0.9(0.79-1.04)
Bicornuate uterus	0.86(0.61-1.21)
Septate uterus	0.86 p value <0.05 (0.77-0.96)
Arcuate uterus	1.03(0.94-1.12)

pregnancy,cervical incompetence,preterm labour,UGR,abnormal presentation,retained placenta. conception rate in different uterine anomalies is mentioned in (Table 2.4) as study by YY chan 4

Diagnosis accuracy of different procedures is

- 3D sonography-97.6%
- Sonohysterography-96.5%
- 2D sonography-86.6%
- Hysterosalpingography-86.9%
- CT scanning is no longer used.
- MRI is rarely used a s a primary screening

Total hysteroscopy gives a detailed and reliable information about vagina,cervix and uterine cavity.Combined hystero-laparoscopy is still the gold standard procedures.Management of congenital anomalies focus on improvement in reproductive outcome,pain management and treating endometriosis which is commonly associated.In mullerian agenesis,genetic offspring can be achived by in vitro fertilization with surrogate transfer.Uterine transplant is an option though.

In the unicornuate uterus, excision of the rudimentary horn is considered in presence of functional endometrium. Whereas didelphys uterus has a good prognosis in terms of pregnancy rate. although malpresentation and preterm labor are common. In the bicornuate uterus, a unification procedure can be considered in patients with a history of recurrent pregnancy loss and preterm labor. In the septate uterus, for hysteroscopic resection, the interstitial line should be taken as a guide to decide the extent of resection6. The benefits of metroplasty are controversial. For arcuate uterus surgical correction is not advised.

Congenital anomalies of cervix, vagina, and tube-Class 1 - anomalies of the genital tract include complete to partial agenesis and dysgenesis of the uterus, vagina, cervix, or all of these structures. Pelvic MRI aid in the diagnosis of vaginal atresia, McIndoe procedure is used. A neovaginal space is created between the bladder and the rectum, for placement of graft tissue full-thickness or split-thickness skin, bowel, labial flaps, buccal mucosa. The Davydov neovagina procedure utilizes the peritoneum.

Congenital absence of fallopian tubes is an extremely rare finding which is associated with the absence of kidney and ureter which reflects a defect in the mesonephric and homolateral paramesonephric duct.

Acquired Anatomical disorders:

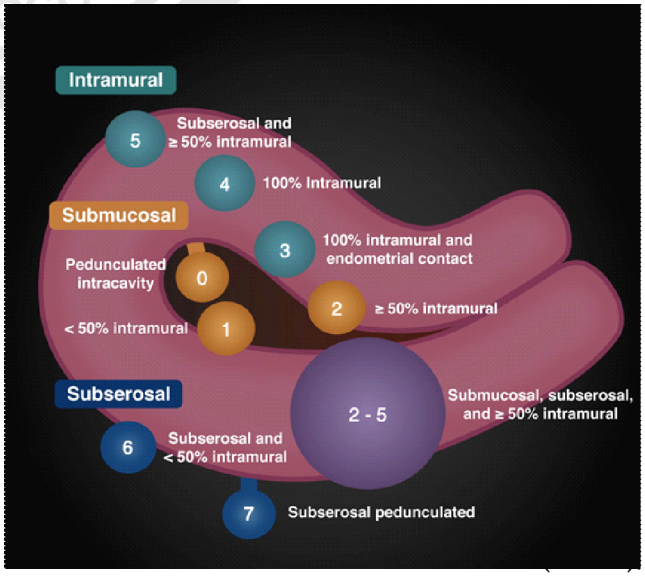
Myomas and Reproduction:

-The impact of intramural fibroid on infertility outcome and indication of myomectomy is still a dilemma. But submucosa myomas(0,1,2) have a definitive role in poor reproductive outcomes hence myomectomy is the rule.

-Between 2.7-12.6% of pregnant women seen suffer from leiomyoma and 71.4%. Myomas are seen to grow during the first and second trimesters, whereas 66% grow between the second and third trimesters. In 72% of women decrease in the size of fibroid after live birth has been observed.

-Myomas associated with pregnancy may show complications in 10-40% of cases.

Fibroids can cause an increased risk of miscarriage, preterm delivery, APH, EROM, abnormal presentation and increased chance of caesarean section.



intramural (3 - 5), and subserosal (6 - 7) layers of the uterus. Subtype '8' is not illustrated and denotes 'other' location e.g. cervical fibroid.

Simplified diagrams of the International Federation of Gynaecology and Obstetrics (FIGO) uterine leiomyoma classification.

Table 2.5 The presence of fibroids may probably affect fertility by following mechanism.

Altering the position of cervix	May decrease the chance of sperm entering the cervical canal	
Increase in the size or deformity of the uterine cavity	May hamper movement and transport of sperm	
Block the proximal end of tubes	Causes mechanical interference preventing the sperm oocyte adhesion and fertilization	
Changed tubo-ovarian relation	Interfere with ovum capture	
Altered uterine contractility	Might affect sperm or embryo movement or implantation	
Degeneration or venous dilatation above or adjacent a submucous fibroid	Interferes with implantation of embryo	
Impaired endometrial blood flow	Prevent endometrial development and implantation	
Endometrial inflammation or secretion of vasoactive substances	May alter endometrial receptivity	
Submucosal	0	Pedunculated intracavity
	1	<50% intramural
	2	≥50% intramural
	3	Contacts endometrium;100 % intramural
	4	intramural
	5	sub serosal ≥50% intramural
	6	sub serosal <50% intramural
	7	Subserosa Pedunculated
	8	Other(specifye.g.,cervical, parasitic)
Hybrid Leiomyomas	2-5	Submucosal and sub serosal

Table:2.6 Recommended treatment options for women with uterine fibroid tumors.

Patient characteristics	Treatment options
Asymptomatic women	Expectant management and follow up
Symptomatic women who desirous of future fertility	Non surgical treatment or myomectomy
Symptomatic women who do not desire future fertility but wish to preserve the uterus	Non surgical treatment or myomectomy
women who desire future fertility preservation and have had a pregnancy complicated by uterine fibroid tumors	myomectomy
Infertile women with distortion of uterine cavity	myomectomy
Women with severe symptoms who desire definitive treatment	myomectomy

Myoma and ART:

Myomas distorting the cavity carry a relative risk of 0.3 for pregnancy and 0.28 for implantation after ART when compared to infertile women without fibroids.

Intramural myomas have a less proneucleated effect with an odds ratio of 0.62 for implantation rate and 0.7 for delivery rate per transfer cycle.

There is a negligible impact of subserosal myoma on fertility with ART.

Investigations: USG,3D-USG (mapping), sono hysterography, HSG, office hysteroscopy.

Recommended treatment options : Medical Therapies: Include GnRH agonist, NSAIDs, Aromatase inhibitions, SPRMs(selective progestrone receptor modulations), PAS (progestrone receptor agonoists, OCP.

-Newer technologies include the management of Flostat vascular control system, uterine artery embolization, MAGNUS(magnetic resonance-guided focused ultrasound surgery).

Adenomyosis and Reproduction :

Benign penetration of endometrium into the myometrium is adenomyosis which exhibits no-neoplastic, ectopic, endometrial glands, and stroma surrounded by the hypertrophic and hyperplastic myometrium.

Effect on Reproduction:

- Impaired uterine contractility
- Altered endometrial function and receptivity
- Impaired implantation and decidualization.

Management includes medical therapy with GnRH agonist or surgical by adeno myomectomy and reconstruction of the uterus. Endometrial ablation and laparoscopic myometrial electrocoagulation are not advised for infertile patients.

Endometrial poly and reproduction :

Endometrial polyps are hyperplastic endometrial growth with a vascular center and a sessile or pedunculated shape extending into the uterine cavity.frequently seen in subfertile women. It may be related to mechanical interference with sperm transport, embryo implantation, or intrauterine inflammation, or altered production of endometrial receptivity factors.

Different diagnostic modalities like two-or three-dimensional TVs, saline infusion sonography, or hysteroscopy give a good detection rate and its removal under hysteroscopy guidance is done before planning pregnancy or ART procedures. However the available evidence suggests that polypectomy may improve reproductive performance in infertile women. Treatment must be individualized, depending on the size of a polyp, associated symptoms and circumstances leading to its discovery. 10,11

Synechiae and Reproduction :

Uterine synechia or adhesions are usually due to prior uterine surgery or intervention.TB endometrium and primarily curretge, though any uterine injury can cause scarring and adhesions. Asherman's syndrome as it is called is recognized as embryonic implantation and present as amenorrhea to hypomenorrhea.

The gold standard for diagnosis is by hysteroscopy and synechiolysis by hysteroscopy,fluoroscopy-guided gives good results.

Hysteroscopy can reveal a variety of findings. Central adhesion bands can appear as columns or bridges between the opposing walls of the cavity, dividing it into smaller irregular chambers of varying size and shape. Adhesion at the margins of the cavity often appears as half-drawn contains that may obscure one or both cornual orifices.10

Depending on their composition mucosal, fibromuscular, connective tissue, adhesions may or may not have a surface of the endometrium.

Tubo peritoneal anatomical defects:

Tubal factor:The tube is dynamic conduct and not a passive channel.Helps in sperm transport and Fertilization and embryo storage, nourishment, and transport it has a vital role. Cause of tubal damage:Inflammation e.g endometriosis.PID,genital TB, Submucous myoma at cornua,Torsion of the ovary and ectopic pregnancy,Cesarean section.RCOG recommendations for tubal assessment where there are no comorbidities e.g PID, previous ectopic pregnancy, or endometriosis, HSG is a reliable test, and where expensive is available Hycosy should be considered.

According to ESHRE guidelines-

If there is no consensus about pelvic or tubal health, it may be appropriate to perform three cycles of ovulation induction prior to checking tubal patency.History of abortion can increase the risk especially when it is infected.

Hydrosalpinx:

Hydrosalpinx can decrease the implantation and pregnancy rates to half in IVF, so it is better to do clipping or salpingectomy.

Endometriosis :

This is an estrogen-dependent inflammatory disorder in women of reproductive age group characterized by the presence of endometrial glands and/or stroma in sites other than the uterine cavity. Around 25-50% of infertile women may be affected by endometriosis and 30-50% of patients with endometriosis may suffer from infertility. Several mechanisms have been proposed to clarify the association between endometriosis and infertility:

- Distorted pelvic anatomy
- Altered peritoneal environment

- Altered systemic immune function
- Endocrine and ovulatory abnormalities
- Abnormal tubal function
- Abnormal fertilization and implantation
- Abnormal endometrial function

None of these mechanisms has been proved to cause decreased fecundity in women. These mechanisms are briefly discussed below.

Distorted Pelvic Anatomy

Major pelvic adhesions resulting from any disease can impair egg release from the ovary, block sperm entry into the distal fallopian tube, and inhibit ovum pickup. In animal models of endometriosis, pelvic adhesions appear to contribute to the observed decreased fecundity noted in animals with advanced endometriosis.

Altered Peritoneal Function

Many studies demonstrate that women with endometriosis have an increased volume of peritoneal fluid, increased macrophage concentration and function, and increased peritoneal fluid concentrations of prostaglandin, interleukin-l, tumor necrosis factor, and proteases. These alterations may impair oocyte, sperm, embryo, and fallopian tube function.

Altered Systemic Immune Function

IgG and IgA antibodies and lymphocytes may be increased in the endometrium of women with endometriosis. These abnormalities may alter endometrial receptivity to embryo implantation.

Endocrine and Ovulatory Abnormalities

Numerous endocrine and ovulatory disorders may be present in women with endometriosis, including the luteinized unruptured follicle syndrome, luteal phase dysfunction, abnormal follicular growth, and premature and multiple luteinizing hormone (LH) surges. In a monkey model, advanced endometriosis appeared to cause a decrease in fecundity, which was attributed partly to luteinized unruptured follicle syndrome and partly to luteal phase defects.

Abnormal Tubal Function

Peritoneal fluid from women with endometriosis reportedly contains an ovum capture inhibitor that prevents normal cumulus-fimbria interaction. Ovum capture inhibitor, a protein with a molecular mass of greater than 100,000 daltons, remains to be purified.

Abnormal Fertilization and Implantation

In women with endometriosis, it is not clear whether abnormal fertilization and implantation contribute to decreased fecundity. In a rabbit model of endometriosis, Hahn and colleagues reported that blastocysts failed to implant normally in rabbits with endometriosis. Lessey reported that some women with endometriosis lack endometrial ?v?3 integrin expression. They hypothesized that decreased endometrial integrin production in the mid-luteal phase causes infertility by impairing implantation. These observations support the concept that endometriosis may represent one component of a disease that is characterized by dysfunction in multiple components of the müllerian tract, including the cervix, endometrium, fallopian tubes, and peritoneum. The gold standard for diagnosis is laparoscopy.

Staging

Endometrial plaques, lesions, implants, endometriotic cyst, and /or adhesions are noted in the clockwise or anticlockwise direction and staging is done (Table 2.7)

Stage I	1-5	Minimal
Stage II	6-15	Mild
Stage III	16-40	Moderate
Stage IV	>40	Severe

Nezhat et al have divided endometriosis into three groups: Type I small cyst <2 cm on the ovarian surface with densely adherent cyst wall which is difficult to remove.

Type II begins as functional cysts which get invaded by endometrial glands and stroma, hence their cyst wall is easily removable.

Type III these are large cysts and their cyst walls are adherent at various sites adjacent to the area of superficial endometriosis.

Management of anatomical defects mainly by through surgical clearance with add-on therapy

with medical management and ART to improve reproductive outcome.7

THE AMERICAN FERTILITY SOCIETY
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____

Stage I (Minimal) · 1-5
Stage II (Mild) · 6-15
Stage III (Moderate) · 16-40
Stage IV (Severe) · >40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
Prognosis _____

	ENDOMETRIOSIS	<1cm	1-3cm	>3cm
PERITONEUM	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20

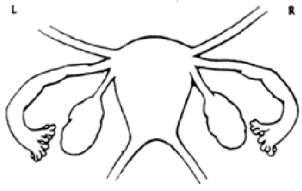
	POSTERIOR CULDESAC OBLITERATION	Partial	Complete
		4	40

	ADHESIONS	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
OVARY	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Additional Endometriosis: _____ Associated Pathology: _____

To Be Used with Normal Tubes and Ovaries

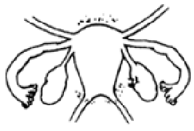


To Be Used with Abnormal Tubes and/or Ovaries

A

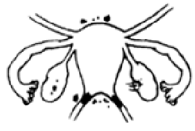
EXAMPLES & GUIDELINES

STAGE I (MINIMAL)



PERITONEUM
Superficial Endo – 1-3cm · 2
R. OVARY
Superficial Endo – <1cm · 1
Filmy Adhesions – <1/3 · 1
TOTAL POINTS 4

STAGE II (MILD)

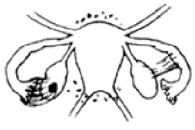


PERITONEUM
Deep Endo – >3cm · 6
R. OVARY
Superficial Endo – <1cm · 1
Filmy Adhesions – <1/3 · 1
L. OVARY
Superficial Endo – <1cm · 1
TOTAL POINTS 9

STAGE III (MODERATE)

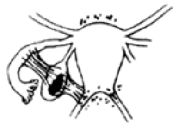
PERITONEUM
Deep Endo – >3cm · 6
CULDESAC
Partial Obliteration · 4
L. OVARY
Deep Endo – 1-3cm · 16
TOTAL POINTS 26

STAGE III (MODERATE)



PERITONEUM
Superficial Endo – >3cm · 3
R. TUBE
Filmy Adhesions – <1/3 · 1
R. OVARY
Filmy Adhesions – <1/3 · 1
L. TUBE
Dense Adhesions – <1/3 · 16*
L. OVARY
Deep Endo – <1cm · 4
Dense Adhesions – <1/3 · 4
TOTAL POINTS 29

STAGE IV (SEVERE)



PERITONEUM
Superficial Endo – >3cm · 3
L. OVARY
Deep Endo – 1-3cm · 32**
Dense Adhesions – <1/3 · 8**
L. TUBE
Dense Adhesions – <1/3 · 8**
TOTAL POINTS 51

*Point assignment changed to 16
**Point assignment doubled

STAGE IV (SEVERE)

PERITONEUM
Deep Endo – >3cm · 6
CULDESAC
Complete Obliteration · 40
R. OVARY
Deep Endo – 1-3cm · 16
Dense Adhesions – <1/3 · 4
L. TUBE
Dense Adhesions – >2/3 · 16
L. OVARY
Deep Endo – 1-3cm · 16
Dense Adhesions – >2/3 · 16
TOTAL POINTS 114

B

endometriosis. A. Scoring system and patient information. B. Examples of application of scoring system. (American Society for Reproductive Medicine: Revised American Society for Reproductive Medicine classification o Fig. 1. Revised American Fertility Society classification or f endometriosis: 1996. Fertil Steril 67,

ENDOMETRIOSIS FERTILITY INDEX (EFI)
SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score	Description		Left	Right
4	= Normal	Fallopian Tube		
3	= Mild Dysfunction			
2	= Moderate Dysfunction	Fimbria		
1	= Severe Dysfunction			
0	= Absent or Nonfunctional	Ovary		

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

Lowest Socre: Left + Right = LF Score

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	Description	Points	Factor	Description	Points
Age			LF Score		
	If age is ≤35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤3	2		If AFS Endometriosis Lesion Score is <16	1
	If years infertile is >3	0		If AFS Endometriosis Lesion Score is ≥16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score <71	1
	If there is no history of prior pregnancy	0		If AFS total score ≥71	0
Total Historical Factors			Total Surgical Factors		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS: Historical + Surgical = EFI Score

Anatomical defects in male partner causing infertility:

Azoospermia accounts for 1% among 10-15% of infertile men of which obstructive azoospermia accounts for 15-20%.

Congenital defects:

Congenital absence of Vas deferens: Common is cystic fibrosis, so genetic counseling has to be done before ART.

Undescended testis:

If corrected late or uncorrected also cause azoospermia.

Varicocele: The role of varicocelectomy in nonobstructive azoospermia is controversial. The anatomical urological association and the American Society of Reproductive Medicine recommend varicocele repair in palpable varicocele and at least are abnormal semen parameters.

Latrogenic: Genital trauma, prior pelvic or inguinal surgeries like hernia or hydrocele can be a cause of damage to vas causing obstruction.

Ductal obstruction:Normal ejaculate volume and azoospermia with normal testicular. Biopsy indicates ductal obstruction.

Transrectal ultrasound is helpful in the diagnosis. Vasography, Seminal vesiculography also aid in diagnosis.

Summary:

The treatment of infertility should be individualized. The evaluation should focus on the couple, regardless of past reproductive performance.

The four basic goals of management of infertility are to identify and correct specific causes of infertility when possible.

- To provide accurate information and
- to dispel the misinformation.
- To provide emotional support during a trying time.
- To guide couples failing to conceive with after forms of treatment to alternatives, including IVF, use of donor gametes, and adoption.

◆◆◆

DISORDERS OF SEXUALITY IN CLINICAL PRACTICE

Dr. Ranjit Kumar Nayak

Man survives earthquakes, experience the horrors of illness and all of the torture of the soul. But the most tormenting tragedy of all time is and will be, the tragedy of the bedroom.

--- Tolstoy

Sexual Health

Sexual health is a state of physical, mental, emotional, and social wellbeing in relation to sexuality and not merely the absence of disease dysfunction or infirmity - WHO.

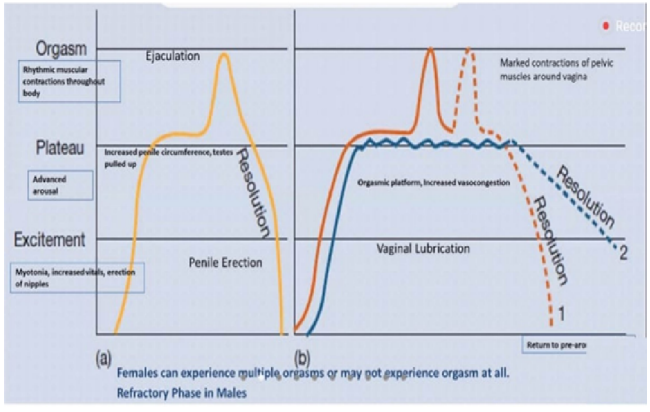
In India, the land of KAMASUTRA, Sexuality is considered as a taboo. Sexual dysfunction have been highly prevalent from the ancient times but have not been the topic of concern for many years.

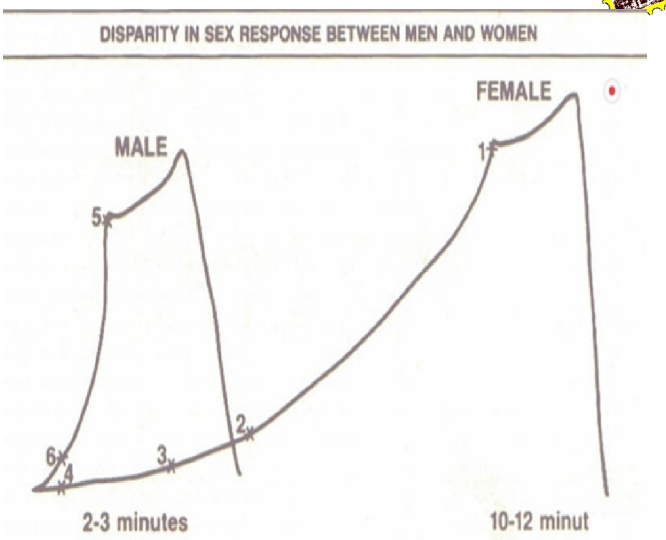
Female sexual Dysfunction (FSD) is very common, affecting nearly 1/3rd of all females. High incidence among patients attending infertility clinic and menopausal clinics. Most of the time it doesn't come to light. Women don't complain. Either they think it is normal or don't express because of shyness or embarrassment.

Sexuality has always been subject to the influence of social constructs. Negative messages about masturbation in girls and the view of women as passive recipients of men's sexual desire activity and inhibit their sexual interest. New views stress the importance of social factors as a cause of women's sexual avoidance or distress and deemphasizes the focus on hormonal and/or biological factors. Inadequate sex education, failure to meet cultural norms concerning sexual attractiveness or sexual response, fatigue due to family and work obligations or conflict between the sexual norms of culture of origin and those of the dominant culture may be at the heart of many sexual problems. Cross-cultural studies find markedly disparate rates of low desire depending on a woman's ethnic background and certain variables, such as sex guilt's and religiosity, mediate the association between a woman's culture and her level of sexual desire.

Sexual Response Cycle: The Sexual response cycle refers to the sequence of physical and emotional changes that occur as a person becomes sexually aroused and participates in sexually stimulating activates, including intercourse and masturbation.

The sexual response cycle constitutes 5 stages in both sexes, desire, excitement, plateau orgasm and resolution.





1. Desire phase

It consist of the motivational or appetitive aspects of sexual response. Includes sexual urges (drive), fantasies (motivation) and wishes

2. It has no specific physical changes

Refers to subjective feeling of sexual pleasure and accompanying physiological changes.

Here vaginal lubrication begins, Inner two-third of vagina expands, colour of vaginal wall becomes darker, Outer lips of vagina flatten and move back from the vaginal opening, Inner lips of vagina thicken, Clitoris enlarges, Cervix and uterus move upward,

Nipple become erect, breast size increases modestly, Sex flush appears, heart rate and blood pressure increases, general neuromuscular tension increases.

3. Plateau

Refers to heightened state of excitement attained with continued stimulation.

At this phase, vaginal Lubrication continues, orgasmic platform forms at outer 3rd of vagina, Testing of cervix, Inner two third of vagina lenthens and expands further, clitoris retracts, swelling of labia majora and minora with colour changes, Sex flush intensifies, Heart rate and blood pressure increases further, breathing becomes more shallow and rapid, voluntary contraction of rectal sphincter used by some women, further increase in neuromuscular tension

4. Orgasm

It is the peak of sexual pleasure, with rhythmic contraction of the genital musculature.

At this phase , Onset of powerful involuntary rhythmic contractions of genital musculature and uterus, Sex flush reaches maximum colour and spread. Involuntary contractions of rectal Sphincter, peak heart rate, blood pressure and respiratory rates, may be cramp like spasms of muscle groups in the face, hand and feet.

5. Resolution

It refers to a general sense of relaxation and wellbeing is experienced. After this phase

There in a refractory period in males, which may or may not be in females which are usually multiorgasmic or may be anorgasmic at times.

At this phase, Clitoris returns to normal position, orgasmic contractions disappear and relaxes, labria majora and minora returns to normal size and colour, vagina returns to normal size, uterus and cervix descend, breast, areola, nipple returns to normal size, Heart rate, blood pressure and respiratory rate return to baseline, general sense of relaxation and wellbeing.

Sexual Dysfunction

Sexual dysfunction are characterised by disturbances in the psychophysiological processes that involves the sexual response cycle or by pain associated with sexual intercourse.

DSM Classification of female Sexual Dysfunction.

DSM- IV - TR Classification
DSM- V - Classification

Hypoactive Sexual Desire Disorder (HSDD)

1. Female Sexual interest/arousal disorder.
2. Female Arousal Disorder
3. Female Orgasmic disorder
4. Dyspareunia
5. Genito-Pelvic Pain/Penetration disorder.
6. Vagisnismus
7. Sexual Aversion disorder
8. Sexual dysfunction due to a general medical condition

Hypoactive Sexual desire disorder is defined as a persistent or recurrent deficiency or absence of sexual fantasies or desire for sexual activity that causes marked distress or interpersonal difficulty not related to a medical or psychiatric condition or the use of a substance or medication lasting for a minimum of six months

Characterised by

- Reduced or absent spontaneous desire for sexual thoughts or fantasies.
- Reduced or absent responsive desire to erotic cues and stimulation.
- Inability to sustain desire or interest during sexual activity.

Etiopathogenesis :

Hormones :

Hormones may affect the responsivity of the sexual system and therefore should be considered in women with sexual dysfunction. Dopamine is the major neurotransmitter involved in sexual arousal. The most abundant and potent hormone before menopause is estradiol. A weak correlation between lower levels of estrogen and decreased sexual desire has been found. An adequate level of estrogen is important for maintaining vaginal lubrication and avoiding dyspareunia. Androgen levels peak when women are in their 20's and drop gradually with age, so that women in their 40's have approximately half the level of circulating total testosterone. Oral contraceptive pills, which increase the concentration of SHBG, there by lessening the bio available testosterone on sexual interest. Synthetic progestins have negative effects on sexual desire. Medical conditions affecting circulatory, endocrine, muscular skeletal and CNS, negatively impact the sexual function.

Relational aspects:

Sexual problems might be both the cause and result of unsatisfactory relationship. The women who lacks motivation for sexual contact as a result of her low emotional intimacy, trust or respect towards her partner is unfortunately a very common finding in the clinical scenario. A women's feeling for her partner are a major determinant of her sexual desire, above and beyond any hormonal contributors. Her partner's sexual dysfunction can also adversely affect her interest in sex.

Mood:

Mood instability, low self-esteem, and having an introverted personality style have been associated with decreased sexual interest and may all influence the responsibility of the sexual system. Depression significantly decreases sexual function.

Sociocultural influences:

Ethnicity and sociocultural norms concerning's sexual response, inadequate sex education, fatigue due to family and work obligations, failure to meet cultural norms, sex guilt and religiosity all adversely impact female sexual response.

Diagnosis:

Detailed history including onset, duration, behavioural adoption and avoidance, level of distress. Patient's medical history, reproductive history, comorbid condition psychiatric disorders like depression and anxiety. Targeted physical examination use of oral contraceptive drugs. Lab investigation like thyroid profile and prolactin, Sr. testosterones, lipid profile etc.

Treatment:

Because HSDD encompasses biological, psychological, social and contextual components a bio psychological approach is warranted.

Office based Counselling

PLISSIT Model.women are given permission (p) to discuss their problems and emotions and to explore solutions.Limited information (LI). Which includes basic sexual function education and (or) resources (Eg. Literature, Videos and erotica), Specific suggestion (SS) for addressing the problem in the form of directives and advice. Then intensive therapy (IT) e.g. Couple Therapy

Drugs:

Flibanserine - Is the only FDA approved drug for treatment of HSDD.

100mg once daily at bed time.

Estrogen - Desire disorders emerging from vulvo-vaginal atrophy can benefit from estrogen treatment. Local delivery is the preferred method of treatment. Can be given as tablets, pessaries/vagitories, cream or vaginal ring. Conjugated equire estrogens, estradial can be given. For women with a history of hormone- dependent cancer, management is decided in consultation with oncologist.

Transdermal testosterone patch (300 mcg/day).

Tibolone:

Its metabolites have estrogenic, progestogenic and andrgenic properties. Tibolone therapy has shown to increase sexual desire, frequency of arousability, sexual fantasies and vaginal lubrication.

DHEA:

Vaginal application of DHEA for post-menopausal vaginal atrophy significantly improves sexual desire/interest, sexual arousal, orgasm and pain. This may be especially beneficial for women in whom the use of estrogen is contra indicated.

Bupropion - 150 - 400 meg/day.

Intrnasal Bremelanotide.

Apomorphine.

Low dose sildenafil/tadalafil.

3. Psychological interventions:

Referral to Psychotherapist is often the next step.

Psychotherapy focuses primarily on the psychological and sociocultural factors contributing to distressing low desire.

Intervention include

- Cognitive Behaviour Therapy (CBT)
- Mindfulness training
- Couples Therapy
- Sensate Focus
- Involvement of Partner

Female Orgasmic Disorder (FOD)

Female orgasmic disorder (FOD) is defined as a persistent or recurrent delay in, or absence of, orgasm following a normal, sexual, excitement phase, causing marked distress or interpersonal difficulty, lasting at least for six months.

Risk Factors:

i. Psychosocial factors: Low educational level, religiosity, feeling guilty about sex, sexual inexperience, and negative attitude towards sex.

ii. Cognitive/Affective factors: Anxiety, depression, attentional focus on sexual cues clarity of emotional states and effective emotion regulation strategies, body image, and negative thinking styles.

iii. Relationship factors: Difficulties communicating in the sexual relationship, preffered sexual experiences and practices, dissatisfaction with partner, feelings of anger.

iv. History of childhood maltreatment (physical, psychological or sexual abuse),or adult experience of sexual abuse.

v. Medical Conditions: Diabetes, Vascular disease, multiple sclerosis, spinal cord injury, chronic pelvic infective conditions.

vi. Drugs: SSRIs, non-selective beta blochers, antipsychotics, chemotheropeatic agents, cardiovascular medications.

vii. Improper technique, lack of arousal, negative attitude, ignorance.

Treatment

- Counselling by PLISSIT approach
- CBT, Cognitive and behavioural psychothergpies should be utilised to address distressing cognitions, emotions and behaviours
- Directed masturbation.
- Sensate focus therapy.
- Mindfulness and yoga training
- Combination therapy like Directed masturbation, with sex education, anxiety reduction and CBT.
- Coital alignment training
- Mechanical aids/Vibrators
- Manual clitoral stimulation with partner

Drugs:

- Hormonal treatment for pre menopausal women (with low testerone and low estrogen).
- L- argine, panax ginseng, Ginkgobiloba, neutraceutical supplements.
- G-spot augmentation
- Laser vaginal rejuvenation
- PRP

Sexual Arousal Disorder:

Inability to complete sexual activity with adequate genital swelling- lubrication response that causes marked distress or interpersonal difficulty.

Types:

- Subjective sexual arousal disorder.
- Genital sexual arousal disorder.
- Combined genital and subjective arousal disorder

Factors that have negative influence on sexual arousal are fatigue, depression, disease, disability, drugs, progesterone, guilt, anxiety, stress.

Causes: Lack of lubrication, improper technique, relationship disturbance, Secondary to pain, negative attitude, menopause, trauma, infections.

Treatment:

- Sensate focus
- Cognitive Behaviour Therapy (CBT)
- Individual and Couple therapy
- Directed masturbation.
- Communication Skills.
- Eros clitoral therapy device.

Drugs:

- L-arginine gel/powder.
- Lubricants/ moisturises

- PDES inhibitors (tadalafal etc).

Genito Pelvic Pain Penetration disorder

Persistent or recurrent difficulties with one or more of the following are associated.

Vaginal penetration during intercourse, marked vulva vaginal or pelvic pain in anticipation of, during or as a result of vaginal penetration, marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration.

Two broad categories 1. Dyspareunia. 2. Vaginismus.

Dyspareunia: Recurrent or persistent genital pain associated with sexual intercourse that is not caused exclusively by lack of lubrication or by vaginismus and causes marked distress or interpersonal difficulty.

Types:

- Superficial.
- Vaginal.
- Deep Dyspareunia.

Causes of painful intercourse:

Pain can occur at the entry, after entry and during thrusting.

Entry Pain: Pain occurs during penetration if there is not enough of foreplay or proper stimulation of the body. Prior to penetration there will not be enough lubrication or genital discharge. Some men with erection or ejaculation problem may hurry for the penetration without foreplay. This causes pain during intercourse.

Drop in the estrogen level after delivery, during breastfeeding or after menopause causes decreased lubrication. Medications like antidepressants, sedatives, antihypertensive, and oral pills can affect desire and arousal and less lubrication causing pain. Genital injury, trauma, scars due to pelvic surgery post childbirth injuries can cause painful sex. Genital infections, Vulva vaginitis, dermatitis, septum in vagina can cause pain. Cancer vulva, vagina or uterus and its treatment leading to shortness and vaginal scaring can cause pain.

Deep Dyspareunia

Deep pain occurs in lower abdomen after deep penetration and thrusting, Conditions like endometriosis, pelvic infection, uterise retroversion/prolapse, fibroids, haemorrhoids, Cystitis, Surgical scars.

Psychological factors: like anxiety, depression, fear of pain, Pregnancy, infection can cause low desire and arousal and lubrication heading to dyspareunia, Disturbed relationship, and stress can cause tightening of pelvic floor muscles heading to pain. Initial pain during intercourse can cause fear of recurring pain, inability to relax causing more pain.

Management: Sex education, positive sex talk, sensate focus, progressive muscle relaxation prior to intercourse, Kegel's exercise with relaxation and biofeedback information about suitable positions is important.

Treatment of infections, itching, white discharge with appropriate antibiotics, Estrogen replacement in post menopause women, lubricants, moisturisers for vaginal application, surgery for tight hymen, Vaginal septum, PID endometriosis and post-operative adhesiors, scars, treatment of psychological issues, counselling for couple relationship issues.

Vaginismus:

Involuntary spasm of the pelvic muscles surrounding the outer third of vagina, especially the perineal muscles and levator ani muscles. This reflex contraction is triggered by imagined or anticipate attempts at penetration of the vagina or during the act of intromission or coitus.

Prevalence:

First described over 150 years ago, vaginismus in rarely taught in medical schools and residencies or discussed at medical meetings. Vaginismus affects 5 - 17 % of women & seen in clinical settings. Its true incidence is unknown, because many patients remain silent about this problem. Compared to other sexual disorders, especially of desire and orgasm, it appears to be one whose treatment has the greatest potential for success.

Types of vaginismus:

- Severe form of classical vaginismus makes penetration virtually impossible, cause a severe, burning pain, and leads to unconsummated marriage.
- Mild less pronounced degree of vaginismus, characterised by a stiffening of the vagina musculature, allowing penetration, yet accompanied by the same sort of pain.
- The condition may be primary (present from the first attempt of penetration) or secondary (following physical or psychological trauma, infection, menopausal charges or pelvic pathology).

Muscles involved in Vaginismus:

- Muscles of the outer 3rd of vagina. The pelvic muscles or the circumvaginal and perivaginal muscles Bulbo cavernosus, levator ani and pubo coccygius.

Etiology:

Psychological causes:

- Sexual molestation - A variety of childhood experiences have been implicated. Strict sexual or religious upbringing, waiting upto marriage for intercourse.
- Fear of first time sex (Pain, bleeding, tearing, ripping, penis too large, vagina too small, Sexually transmitted diseases, and fear of pregnancy).
- Fear of gynaecological Exmination - Undesirable penetration. While being restrained at a young age such as urinary cathetrisation, enemas, and stretching of vagina may set the stage for latter vaginismus.
- Misinformation, ignorance and guilt about sex 90% of this vaginismus patients showed a high degree of vaginismus patients showed a high degree of ignorance and misinformation regarding their sexuality.
- Lack of sex education.
- Negative views about sexuality in general and premarital sex in particular
- Women with vaginismus generally experience shame, disgust and dislike toward their genitalia.

Organic Pathology:

- Hymenial abnormalities, vaginal atrophy and adhesions, prolapsed uterus, Vulvar vestibulitis syndrome, endometriosis, infections, sexually transmitted disease.
- Any medical problem causing dyspareunia persists, the likely result in vaginismus.

Other Causes of Vaginismus:

- Religious Orthodoxy: High moral expectations instilled by mother or sexual guilt resulting from a strict, religious upbringing.
- Male partner's personality - The male can potentially cause or exacerbate vaginismus in the female partner by being under competent, over anxious or too forebearing.
- Male partner's sexual dysfunction - Increased incidence of erectile dysfunction and prematures ejaculation may be result of the vaginismus.
- The couples relationship - various types of difficulties in the couples relationship (Infidelity, conflict) may result in vaginismus.

Diagnosis and Evaluation:

History - Carefully constructed medicl and psychosexual history and the female sexual function index (FSFI) and sometimes the vaginal penetration cognition questionnaire (VPCQ) can be used.

It is classified 1st degree, 2nd degree, 3rd degree and 4th degree according to the severity.

Management:

Treatment is a team effort post treatment counselling is important regardless of the type of treatment utilized. Involve interplay of the physical and emotional aspects.

Dilator therapy:

Dilation program is helpful in overcoming the physical aspects of vaginismus as well as the psychological handicap of fear and anxiety of penetration. Progressively larger dilators help to stretch the vagina and allow the women to become comfortable with vaginal penetration.

- Patients are asked to keep daily logs of their dilation for about 1 month, then weekly logs.
- Finger penetration (Own finger, Partners finger) has been found to be helpful to initiate dilation.
- Isolated stretching of the introitus and incorporating dilators can be an effective form of treatment for vaginismus.
- Biofeedback alone or in combination with physical therapy and surface electromyography helps the patient understand how to lessen tension in the pelvic floor.

Sex Counselling:

Sex counselling helps the couple improve the communication skill, aid in overcoming compromised libido and can help with anxiety reduction and depression.

Psychothrapy:

Cognitive Behaviour Therapy (CBT) helps patients understand the thoughts and feelings that influence behaviour.

Botox for vaginismus treatment:

- Primary vaginismus with intravaginal Botox and progressive dilation under anaesthesia is studied for the more severe forms of vaginismus.
- Botulinum toxin A can be injected into one, a combination, or all of the three vaginal muscles responsible for vaginal spasm.
- A single injection is sufficient.

Kegel's relaxation exercise may be helpful.

Surgical treatment:

1. The Fenton's approach is to place a longitudinal incision, over the perineum at 6 0 clock position and suturing it horizontally, thus widening the introitus.
2. Recently Viswaprakash etal have described a surgical technique of Z palstyof the bulbospongiosus muscles, to dilate the introition.

Many experts feel that surgical approach is not useful at all since the condition is one of reflex spasm.

Male Sexual Dysfunction

Two major types of male sexual dysfunction encountered in clinical practice:

1. Erectile Dysfunction
2. Premature Ejaculation

Erectile Dysfunction:

Erectile dysfunction is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance for atleast a period of six months

Erectile dysfunction may affect psychosocial health and have a significant impact on the quality of life of patients and their partners.

Types:

1. Organic
2. Psychogenic
3. Mixed

Causes:

Psychosocial

- Performance anxiety
- Sexual attitudes and upbringing.
- Relationship disturbances
- Depression
- Psychiatric disorders

Neurological

- Spinal truma.
- Multiple Selerosis.
- Diabetic Neuropathy.
- Pelvic surgery (Prostatectomy)

Metabolic disorder

- Diabetes
- Hypertension
- Obesity
- Dyslipidemia
- Cigarette smoking

Endocrine

- Hypo/Hyper thyroidism
- Hypogonadism

Urological

- Peyronei's disease
- Pelvic trauma.

Diagnosis: General and sexual history, general physical examination, genitalia examination. Laboratory test, Plasma glucose, lipid profile, thyroid profile, Sr. testosterone.

Nocturnal penile tumescence and rigidity test, Intracavernosal injection test, penile Doppler, Psychiatric and Psychosocial assessment.

Treatment:

1. Oral pharmacotherapy:

Selective PDE5 inhibitors, work in the CGMP pathway to produce nitric oxide which mediates vascular and cavernosal dilation and erection.

Sildenafil - 50,100 mg used on demand 1 hr before intercourse.

Tdalafil - 5, 10, 20 mg used on demand 1 hrbefore intercourse, low dose tadafil can be used daily.

Varderafil- 5, 10, 20 mg used on demand patient can achieve satisfactory erection in 15 mins.

Avanafil - 100, 200 mg, used on demand 15-30 minutes before intercourse.

Choice of drugs depends on the frequency of intercourse, patient's personal experience and medical conditions.

These drugs absolutely contraindicated for patients on nitrates. Overall treatment goals should be individualised to restore sexual satisfaction for the patient and/or couple and improve quality of life based on the patient's expressed needs and desires.

2. Topical/ Intraurethral alprostadil :

Intraurethral insertion of a specific formulation of alprostadil 500mcg in a medicated pellet (MUSE). Erections sufficient for intercourse are achieved in 30-70 % of patients.

3. Shockwave therapy:

Useful for vasculogenic ED. Low intensity shockwave is given to penile shaft, which induces angiogenesis and neurogenesis and increases the flow into penile tissue and improvement in ED.

4. Psychosexual Counselling and therapy:

For patients with recognised psychological problems psychosexual therapy may be given either alone or with another theapeutic

approach in order to improve couple's sexual satisfaction and partner's sexual function. Different approaches include.

- Psychosexual education.
- Sexual skills training
- Marital therapy.
- Cognitive behaviour therapy. (CBT)

5. Vacuum erection device: (VED)

VED provides passive engorgement of corpora cavernosa, together with a constrictor ring placed at the base of the penis to retain blood within the penis. In term of erections satisfactory for intercourse, the efficiency in s 90% regardless of the cause of ED.

6. Intracavernosal Injection:

- Alprostadil 5 - 40 mcg injected into the corpora cavernosa, and erection occurs in 5 - 15 min and lasts as per the dose used.
- Papaverine
- Phentolamin.

Combination herapy as bimix (Papaveriu + phenotolamiu)

Trimix (Papaverine phentolamin + Al prostadil) can be tried in non-responders to monotherapy. For patients not responding to bimix or timix sildenafil can be added to them, result often good.

7. Hormonal therapy:

In thyroid disorder or hyperprolactinemia appropriate treatment should improve ED.

For testosterone deficiency, and testosterone replacement an endocrinologist should be consulted.

8. Penile Prosthesis:

When above modalities fail, then prosthesis implantation in indicated both semi rigid and inflatable penile prosthesis can be implanted according to the patient's desire.

Treatment:

Life style changes, Risk Factor Modification, Treat a Curable Cause of ED like Diabetes, Hypertension, Hypothrosism etc.

Premature Ejaculation:

Premature ejaculation is defined as a male sexual dysfunction characterised by ejaculation that always or nearly always occurs before or within about 1 minute of vaginal penetration, inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences such as distress, frustration and/or the avoidance of sexual intimacy.

PE is common, affecting upto 38% of men of all ages.

Types:

Lifelong PE:

- PE at all or nearly all intercourse attempts.
- With all or nearly all women.
- In majority of cases within 1 minute.
- Consistent during life.
- Reduced or absent control of ejaculation

Acquired:

- Early ejaculation occurring at some point of time.
- Normal ejaculation before onset of premature ejaculation.
- May be organic or psychogenic.

Natural Variable:

- Rapid ejaculation in consistent and irregular.

Premature like ejaculation dysfunction:

- Subjective perception of rapid ejaculation.
- IELT is normal or longer
- Reduced or absent control of ejaculation.

PE & ED

It is critical to differentiate PE from ED. Both are common conditions and may present in the

same patient. Many ED patients develop secondary PE, They ejaculated rapidly in order to achieve orgasm before loss of erectile rigidity. Treatment should start from ED followed by treatment of PE.

Treatment:

Behavioural/ Psychosexual therapy:

Stop - Start technique

Partner stimulates the penis until the patient feels urge to ejaculate. At this point he instructs his partner to stop, wait for the sensation to pass and then stimulation is resumed.

Squeeze technique (Masters & Johnson).

Partner applies manual pressure to base of the head of the penis just before ejaculation until the patient loses his urge. Then same procedure is repeated

Precoital masturbation partially desensitizes the penis and leads to a delay in ejaculation. It may be helpful for younger men suffering from PE.

Medical Treatment:

Dapoxetime - 30 - 60 mg on demand.

Tramadol - 50 mg 2 hr period to coitus on demand.

PDE5 inhibitors - can be tried but results controversial.

Severanu Secret Cream, extract of nine natural products, applied topically

Lidocaine - Prilocaine (EMLA) gel.

Applied 20 - 30 min prior to intercourse.

A condom is used to prevent diffusion of topical agent into vaginal wall causing numbness in the partner.

Lidocine - Prilocaine Spray.

Surgical Treatment:

Cryoneurolysis of Dorsal Penile nerve.

Selective penile dorsal neurectomy

Neuro modulation of dorsal nerves by pulsed radio frequency.

Selective resection (neurectomy) of branches of dorsal penile nerve.

"Penis is the Barometer of Men's Health"

Conclusion:

Sex and death are still the taboo in our society. Sex is not a matter of life and death but feelings about sexuality affects our self image, our zest of life, our relationship with others. Sex is an opportunity for expression of passion, affection, admiration, loyalty and other positive emotions. Affirmation of one's body and its function. Maintaining strong sense of identity, self-esteem and feeling valued as a person. Sex is a means of self-assertion, protection from anxiety, defiance of stereotypes of aging, pleasure of being touched, caressed, and romance, avenue for relationship , growth and experience.

Sexual health requires a positive and respectful approach to sexuality and sexual Srelationship , as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. Sexuality is an integral part of every individual from birth to death.

The origin of a child is a mother, a woman. She shows a man what sharing, caring, and loving is all about. This is the essence of a woman. Feminism needs to be adored, admired, trusted and respected. A woman always wishes love me till my heart stops. Mutual satisfaction is the benchmark which defines a conjugal life.

Break the silence, let's talk about sexuality. Love each other unconditionally, partners for life.

A Hero without Her is Zero.

SEX HAS NO EXPIRY DATE.

◆◆◆

ASEXUAL REPRODUCTION

Prof. Dr Sujata Swain

Humans are not particularly efficient at reproduction compared to many other mammals. The monthly chance of getting pregnant (fecundability) is about 25-30% for the first 3-6 months of trying. Approximately 85% of couples that will ultimately conceive spontaneously do so in the first 12 months.

Approximately 1 in 5 couples seek fertility advice from a doctor and over half of these couples require specialist assistance.

HUMAN REPRODUCTION

Sexual Reproduction

Asexual Reproduction

Medically Assisted Reproduction

Artificial Intrauterine Insemination

Assisted Reproductive Technology

SEXUAL REPRODUCTION

Forsexual reproduction & conception to occur, the man must ejaculate his semen, the fluid containing the sperm, into the woman's vagina around the time of ovulation, when her ovary releases an egg. Ovulation is a complex event controlled by the pituitary gland, which is located at the base of the brain. The pituitary gland releases follicle-stimulating hormone (FSH), which stimulates follicles in one of the ovaries to begin growing. The follicle produces the hormone estrogen and contains a maturing egg. When an egg is mature, the pituitary gland sends a surge of luteinizing hormone (LH) that causes the follicle to rupture and release (ovulate) a mature egg (Figure 1).

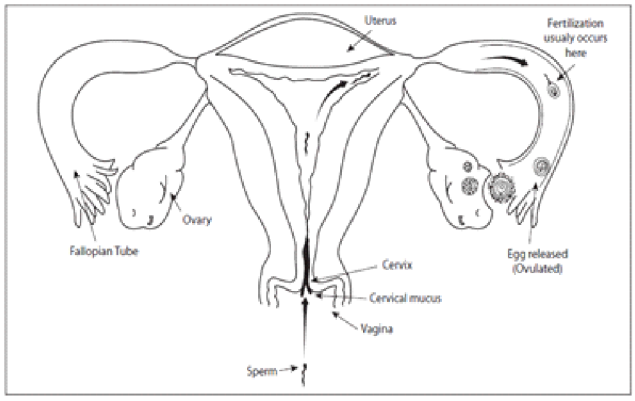
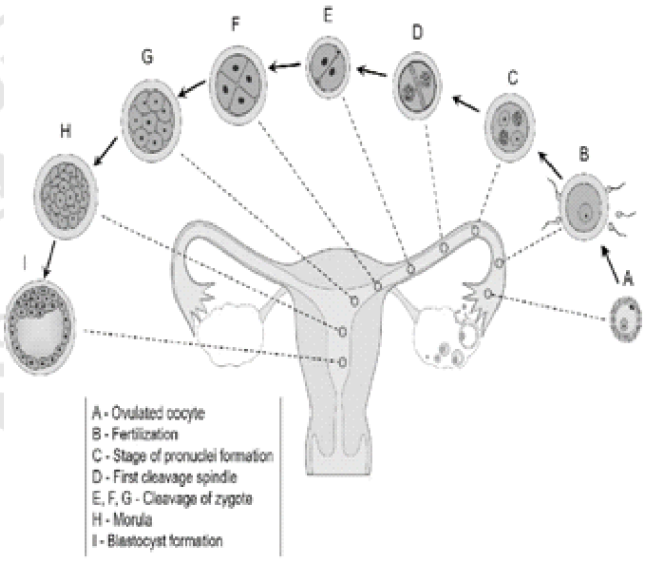


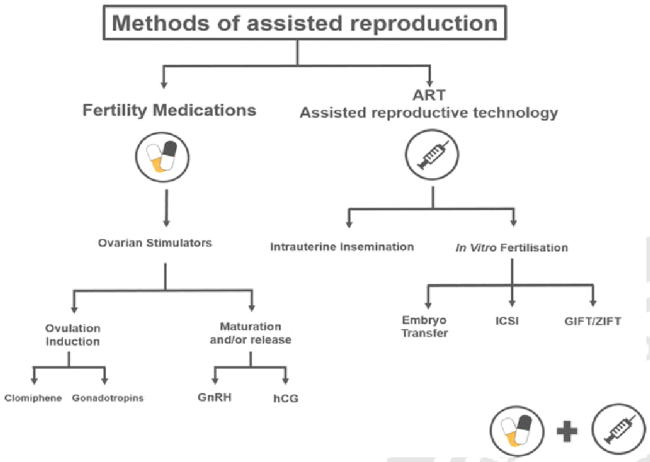
Figure 1. Solid arrows indicate path sperm must travel to reach the egg. The fertilized egg continues traveling through the fallopian tube to the uterus.



Following ovulation, the egg is picked up by one of the fallopian tubes. Since fertilization usually takes place inside the fallopian tube, the man's sperm must be capable of swimming through the vagina and cervical mucus, up the cervical canal into the uterus, and up into the fallopian tube, where it must penetrate the egg in order to fertilize it. The fertilized egg continues traveling to the uterus and implants in the uterine lining, where it continues to develop.

ASEXUAL REPRODUCTIONMEDICALLY ASSISTED REPRODUCTION

Fertility treatments are procedures and/or medication interventions used to initiate a pregnancy. The goal of assisted reproductive technology (ART) should be the provision of safe, efficient and affordable care to optimise the chance(s) of having singleton pregnancies and the delivery of healthy babies.



INTRA UTERINE INSEMINATION

Intrauterine insemination (IUI) is the therapeutic process of placing washed spermatozoa transcervically into the uterine cavity for the treatment of infertility. IUI theoretically allows a relatively higher number of motile spermatozoa to reach the oocyte . The rationale for washing sperm is to remove prostaglandins, infectious agents, and antigenic proteins as well as to remove immotile spermatozoa, leucocytes, and immature germ cells.

IUI is used to treat moderate male factor infertility and unexplained infertility. Another common use of IUI is to enhance the efficacy of treatment by ovulation induction for ovulatory disorders

The pregnancy rate of IUI is reported to 10-20% per patient, but the reported rates range from as low as 5% to as high as 70% . Based on the etiology of infertility, the highest rates were reported when IUI was used in patients with anovulation who were undergoing ovulation induction therapy at the time of the IUI treatment, male factor infertility, and unexplained infertility. In patients with endometriosis, the pregnancy rates were the lowest . The number of mature follicles (17?mm in diameter or more) is another prognostic factor in IUI success, where the presence of 3-4 mature follicles was associated with higher pregnancy rates and a lower incidence of high-order multiple pregnancies . Other prognostic factors included female age, infertility duration and amount of motile sperm.

The Use of IUI and Concurrent Ovarian Stimulation

It was found that live birth rate per couple was significantly higher when IUI was combined with ovarian hyperstimulation compared to IUI alone

The National Institute for Clinical Excellence (NICE) recommended, that when IUI is used to treat male factor infertility, ovarian stimulation should not be offered. For unexplained infertility, both IUI alone and IUI combined with ovarian hyperstimulation appear to be more effective than expectant management alone gonadotropins, in low-dose regimens (50-75 IU), were the most effective agents when ovarian stimulation was combined with IUI. Although less effective than gonadotropins, antiestrogens were more cost effective in IUI therapy. Neither a higher dosage (>75?IU gonadotropins) nor the addition of GnRH agonists was more effective. Conversely, the higher dosage and the GnRH agonists were associated with increased costs and risks of multiple gestations and of OHSS.

Semen Parameters and the Use of IUI

Total motile sperm of 30-50% before sperm preparation was found to be associated with positive IUI outcomes.IUI may be offered to couples with male factor infertility, in a low technology setting, if the total motile sperm count is more than 5 million per specimen.Short intervals from semen collection to sperm wash, from sperm wash to IUI, and from semen collection to IUI were associated with higher

pregnancy rates compared to semen collection at home with longer time intervals

Sperm Preparation Methods

Sperm wash, swim-up, and density gradient centrifugation are the most commonly used methods. Swim-up as a procedure is also associated with satisfactory IUI outcomes, comparable to density gradient centrifugation pregnancy rates.

Timing of IUI

Normal sperm is capable of fertilizing an oocyte in the female genital tract for about 5 days, and an oocyte is fertilizable for 12-24 hours after ovulation. Generally, in natural cycles, IUI can be performed 24 hours after the onset of LH surge as detected by urinary LH monitoring. In controlled ovarian stimulation cycles in which ovulation is triggered artificially, ovulation occurs 32-38 hours after human chorionic gonadotropin (HCG) injection . Use of urinary LH monitoring as a method of IUI timing was associated with higher pregnancy rates than the HCG administration method. LH monitoring for IUI timing is more practical, effective, and cost-effective when CC is used for ovarian stimulation

Number of Inseminations per Cycle

There is no evidence that double inseminations give rise to higher live birth rates in infertile couples compared to single inseminations. The NICE recommendation is for a single insemination when offering IUI as therapy.

Number of Insemination Cycles

The Cochrane reviewers concluded that most pregnancies occurred during the first 3 to 6 IUIs treatment cycles.

IUI may be considered as a good first-line treatment for couples with unexplained infertility, male factor infertility, and anovulation (IUI used concurrently with ovulation induction). In the clinical practice of IUI in a low-technology setting, combining oral clomiphene with IUI is as reasonable of an option as natural cycle IUI. For semen parameters, a motile sperm count above 1 million in the final specimen can serve as a cutoff point for offering IUI. Conventional sperm washing, density gradient centrifugation, or swim-up techniques can all be used for sperm preparation before IUI, with conventional sperm washing being the simplest. A single IUI per cycle should be performed, and the IUI can be performed approximately 24 hours after urinary LH surge is detected. Couples may be offered 3 to 6 IUI cycles to ensure sufficient opportunity to achieve pregnancy.

ASSISTED REPRODUCTIVE TECHNOLOGY

Assisted Reproductive Technologies are all treatments which include the handling of eggs and sperm and/or embryos. Some examples of ART are in vitro fertilization (IVF), gamete intrafallopian transfer (GIFT), pronuclear stage tubal transfer (PROST), tubal embryo transfer (TET), and zygote intrafallopian transfer (ZIFT). The Society for Assisted Reproductive Technology states that IVF-ET accounts for 99% of ART procedures.

In Vitro Fertilization (IVF)

IVF is a method of assisted reproduction in which a man's sperm and a woman's eggs are combined outside of the body in a laboratory dish. One or more fertilized eggs (embryos) may be transferred into the woman's uterus, where they may implant in the uterine lining and develop. Excess embryos may be cryopreserved (frozen) for future use. Initially, IVF was used to treat women with blocked, damaged, or absent fallopian tubes. Today, IVF is used to treat many causes of infertility, such as endometriosis and male factor, or when a couple's infertility is unexplained. The basic steps in an IVF treatment cycle are ovarian stimulation, eggretrieval, fertilization, embryo culture, and embryo transfer.

Ovarian Stimulation

During ovarian stimulation, also known as ovulation induction, medications or "fertility

drugs," are used to stimulate multiple eggs to grow in the ovaries rather than the single egg that normally develops each month (Table 1)

Table 1

Medications for Ovarian Stimulation

- human menopausal gonadotropin (hMG)
- follicle-stimulating hormone (FSH)
- luteinizing hormone (LH) (used in conjunction with FSH)
- human chorionic gonadotropin (hCG)
- clomiphene citrate
- letrozole

Medications to Prevent Premature Ovulation

- Gonadatropin-releasing hormone (GnRH) agonists
- GnRH antagonists

Clomiphene citrate and letrozole are administered orally while the other

medications listed are given by injection. These oral medications are less potent than injectable medications and are not as commonly used in ART cycles. There is no evidence that one injectable medication is superior to any other. Timing is crucial in an IVF cycle. The ovaries are evaluated during treatment with vaginal ultrasound examinations to monitor the development of ovarian follicles (Figure 2). Blood samples are drawn to measure the response to ovarian stimulation medications. Normally, estrogen levels increase as the follicles develop, and progesterone levels are low until after ovulation.

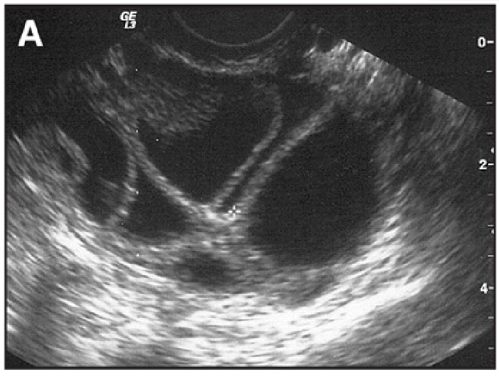


Figure 2. Ovarian follicles, stimulated by ovulation medications, visible on ultrasound. The dark, circular areas are the follicles.

Using ultrasound examinations and blood testing, the onecan determine when the follicles are ready for egg retrieval. Generally, 8 to 14 days of stimulation are required. When the follicles are ready, hCG or other medications are given. The hCG replaces the woman's natural LH surge and causes the final stage of egg maturation so the eggs are capable of being fertilized. The eggs are retrieved before ovulation occurs, usually 34 to 36 hours after the hCG injection is given.

Up to 20% of cycles may be cancelled prior to egg retrieval. IVF cycles may be cancelled for a variety of reasons, usually due to an inadequate number of follicles developing. Cancellation rates due to low response to the ovulation drugs increase with a woman's age, especially after age 35. When cycles are cancelled due to a poor response, alternate drug strategies may be helpful to promote a better response in a future attempt. Occasionally, a cycle may be cancelled to reduce the risk of ovarian hyperstimulation syndrome (OHSS). Treatment with a GnRH agonist or antagonist reduces the possibility of premature LH surges from the pituitary gland, and thereby reduces the risk of premature ovulation.

Egg Retrieval

Egg retrieval is usually accomplished by transvaginal ultrasound aspiration, a minor surgical procedure that can be performed in the physician's office or an outpatient center. Some form of pain medication is generally administered. An ultrasound probe is inserted into the vagina to identify the follicles, and a needle is guided through the vagina and into the follicles (Figure 3).

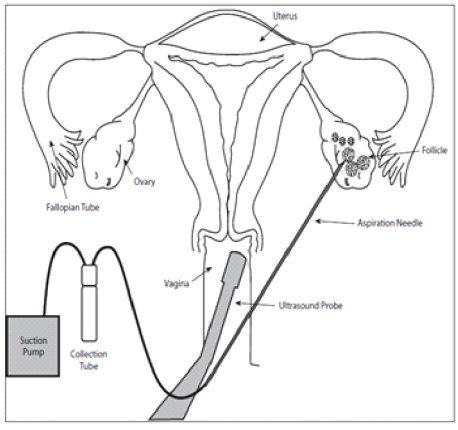


Figure 3. Egg retrieval is usually performed through the vagina with an ultrasound-guided needle.

The eggs are aspirated (removed) from the

follicles through the needle connected to a suction device. Removal of multiple eggs can usually be completed in less than 30 minutes. Some women experience cramping on the day of the retrieval, but this sensation usually subsides by the next day. Feelings of fullness and/or pressure may last for several weeks following the procedure because the ovaries remain enlarged. In some circumstances, one or both ovaries may not be accessible by transvaginal ultrasound.

Laparoscopy may then be used to retrieve the eggs using a small telescope placed in the umbilicus. For more information on laparoscopy, consult the ASRM patient information booklet titled, Laparoscopy and Hysteroscopy.

Fertilization and Embryo Culture

After the eggs are retrieved, they are examined in the laboratory for maturity and quality. Mature eggs (Figure 4) are placed in an IVF culture medium and transferred to an incubator to await fertilization by the sperm.

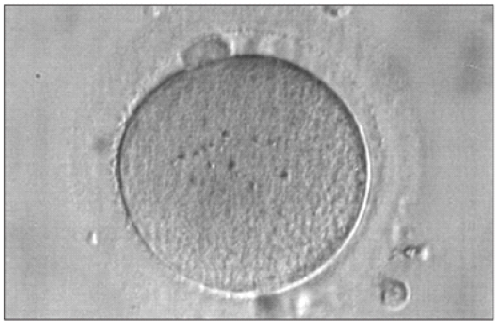


Figure 4. A mature, unfertilized egg.

Sperm is separated from semen usually obtained by masturbation or in a special condom used during intercourse. Alternatively, sperm may be obtained from the testicle, epididymis, or vas deferens from men whose semen is void of sperm either due to an obstruction or lack of production.

Fertilization may be accomplished by insemination, where motile sperm are placed together with the oocytes and incubated overnight or by intracytoplasmic sperm injection (ICSI), where a single sperm is directly injected into each mature egg (Figure 5). In the United States, ICSI is performed in approximately 60% of ART cycles. ICSI is usually performed when there is a likelihood of reduced fertilization (e.g., poor semen quality, history of failed fertilization in a prior IVF cycle). Overall, pregnancy and delivery rates with ICSI are similar to the rates seen with traditional IVF. Genetic counseling is advisable before ICSI if inherited abnormalities are identified that may be passed from father to son. For more information, see the ASRM fact sheet titled, Intracytoplasmic Sperm Injection.

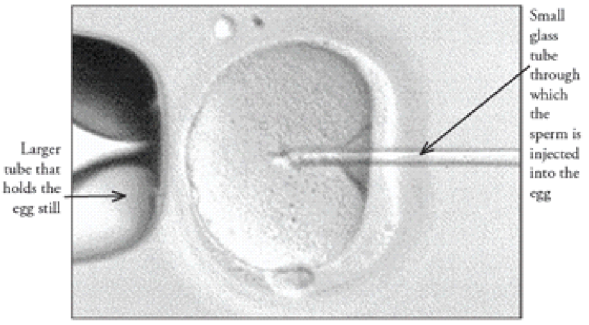


Figure 5. Intracytoplasmic sperm injection (ICSI), in which a sperm is injected directly into an egg to facilitate fertilization.

Visualization of two pronuclei the following day confirms fertilization of the egg. One pronucleus is derived from the egg and one from the sperm. Usually 65% to 75% of mature eggs will fertilize after insemination or ICSI. Lower rates may occur if the sperm and/or egg quality are poor. Occasionally, fertilization does not occur at all, even if ICSI was used. Two days after the egg retrieval, the fertilized egg has divided to become a 2- to 4-cell embryo (Figure 6).

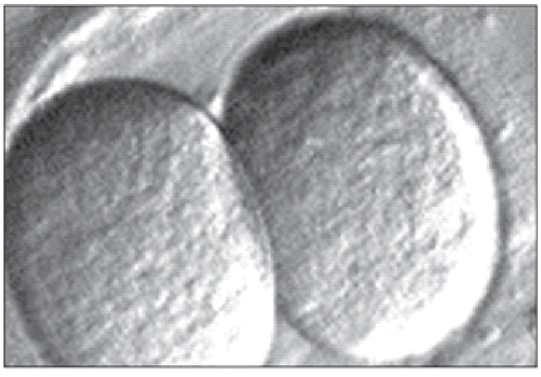


Figure 6. A fertilized egg has divided once and is now a 2-cell embryo.

By the third day, a normally developing embryo will contain approximately 6 to 10 cells. By the fifth day, a fluid cavity forms in the embryo, and the placenta and fetaltissues begin to separate. An embryo at this stage is called a blastocyst. Embryos may be transferred to the uterus at any time between one and six days after the egg retrieval. If successful development continues in the uterus, the embryo hatches from the surrounding zonapellucida and implants into the lining of the uterus approximately 6 to 10 days after the egg retrieval.

Assisted hatching (AH) is a micromanipulation procedure in which a hole is made in the zonapellucida just prior to embryo transfer to facilitate hatching of the embryo. Although AH has not been demonstrated definitively to improve live birth rates, AH may be used for older women or couples who have had unsuccessful prior IVF attempts.

Preimplantation genetic diagnosis (PGD) is performed at some centers to screen for inherited diseases. In PGD, one or two cells are removed from the developing embryo and tested for a specific genetic disease. Embryos that do not have the gene associated with the disease are selected for transfer to the uterus.

These procedures require specialized equipment and experience together with IVF. Some couples, especially those who are carriers of genetic diseases, consider embryo screening beneficial in reducing the risk of having an affected child. While PGD can reduce the likelihood of conceiving a pregnancy with an affected child, it cannot eliminate the risk. Confirmation with chorionic villus sampling (CVS), amniocentesis, or other testing is still necessary.

Embryo Transfer

The next step in the IVF process is the embryo transfer. No anesthesia is necessary, although some women may wish to have a mild sedative. The physician identifies the cervix using a vaginal speculum. One or more embryos suspended in a drop of culture medium are drawn into a transfer catheter (a long, thin sterile tube) with a syringe on one end. The physician gently guides the tip of the transfer catheter through the cervix and places the fluid containing the embryos into the uterine cavity. The procedure is usually painless, although some women experience mild cramping. The maximum number of embryos transferred is based on the patient's age and other individual patient and embryo characteristics. Since each embryo has a fair probability of implantation and development, the number of embryos to be transferred should be determined for each patient, taking into account the odds of achieving a pregnancy based on the number of embryos transferred weighed against the risk of multiple gestation..

Cryopreservation

Extra embryos remaining after the embryo transfer may be cryopreserved (frozen) for future transfer. Cryopreservation makes future ART cycles simpler, less expensive, and less invasive than the initial IVF cycle, since the woman does not require ovarian stimulation or egg retrieval. Once frozen, embryos may be stored for prolonged periods, and live births have been reported using embryos that have been frozen for almost 20 years. There are two methods used to cryopreserve embryos: conventional (slow) freezing and "vitrification" or fast freezing.

Donor Sperm, Eggs and Embryos

IVF may be performed with a couple's own eggs and sperm or with donor eggs and sperm, or both. A couple may choose to use a donor if there is a problem with their own sperm or eggs, or if they have a genetic disease that could be passed on to a child. Donors may be known or anonymous. In most cases, donor sperm is obtained from a sperm bank. Both sperm and egg donors undergo extensive medical and genetic screening, as well as testing for infectious diseases.

Donor sperm is frozen and quarantined for six months, the donor is re-tested for infectious diseases including the human immunodeficiency virus (HIV), and sperm are only released for use if all tests are negative. Donor sperm may be used for insemination or in an ART cycle. Unlike intrauterine

insemination (IUI) cycles, the use of frozen sperm in IVF cycles does not lower the chance of pregnancy.

Donor eggs are an option for women with a uterus who are unlikely or unable to conceive with their own eggs. Egg donors undergo much the same medical and genetic screening as sperm donors. The egg donor may be chosen by the infertile couple or the ART program. The egg donor must undergo ovarian stimulation and egg retrieval. During this time, the recipient (the woman who will receive the eggs after they are fertilized) receives hormonal medications to prepare her uterus for implantation. After the retrieval, the donor's eggs are fertilized by sperm from the recipient's partner and transferred to the recipient's uterus.

Some IVF programs allow couples to donate their unused frozen embryos to other infertile couples..

Surrogacy/Gestational Carrier

A pregnancy may be carried by the egg donor (traditional surrogate) or by another woman who has no genetic relationship to the baby (gestational carrier). If the embryo is to be carried by a surrogate, pregnancy may be achieved through insemination alone or through ART. The surrogate will be biologically related to the child. If the embryo is to be carried by a gestational carrier, the eggs are removed from the infertile woman, fertilized with her partner's sperm, and transferred into the gestational carrier's uterus. The gestational carrier will not be genetically related to the child. All parties benefit from psychological and legal counseling before pursuing surrogacy or a gestational carrier.

Risks of ART

The medical risks of ART depend on each specific step of the procedure. The following are some of the primary risks of ART procedures:

Ovarian stimulation carries a risk of hyperstimulation, where the ovaries become swollen and painful. Fluid may accumulate in the abdominal cavity and chest, and the woman may feel bloated, nauseated, and experience vomiting or lack of appetite. Up to 30% of women undergoing ovarian stimulation have a mild case of OHSS that can be managed with over-the-counter painkillers and a reduction in activity. In moderate OHSS, women develop or accumulate fluid within the abdominal cavity, and gastrointestinal symptoms may occur. These women are monitored closely, but generally do very well with simple outpatient management. The condition tends to resolve without intervention unless pregnancy occurs, in which case recovery may be delayed for several weeks. Up to 2% of women develop severe OHSS characterized by excessive weight gain, fluid accumulation in the abdomen and chest, electrolyte abnormalities, over-concentration of the blood, and, in rare cases, the development of blood clots, kidney failure, or death.

Although initial reports suggested that women who use fertility drugs have an increased risk for ovarian cancer, numerous recent studies support the conclusion that fertility drugs are not linked to ovarian cancer.

There are risks related to the egg retrieval procedure. Laparoscopy carries the risks of any surgery that requires anesthesia. Removing eggs through an aspirating needle entails a slight risk of bleeding, infection, and damage to the bowel, bladder, or a blood vessel..

The chance of multiple pregnancy is increased in all assisted reproductive technologies when more than one embryo is transferred. The risk of preterm delivery in multiple pregnancies is high, and babies may be born too early to survive. Premature babies require prolonged and intensive care and risk lifelong handicaps due to premature birth. Some couples may consider multifetal pregnancy reduction to decrease the risks due to multiple pregnancy, but this is likely to be a difficult decision.

Miscarriage occurs after ultrasound in nearly 15% of women younger than age 35, in 25% at age 40, and in 35% at age 42 following ART procedures. In addition, there is approximately a 5% chance of ectopic pregnancy with ART. It is not clear whether the risk of birth defects is

increased with IVF.

Assisted reproductive technologies involve significant physical, financial, and emotional commitments on the part of the couple. The treatments are involved and costly. Patients have high expectations, yet failure is common in any given cycle. Couples may feel frustrated, angry, isolated, and resentful. At times, frustration can lead to depression and feelings of low self-esteem, especially in the immediate period following a failed ART attempt.

Preparation for ART

Preliminary preparation for an ART procedure may be as important as the procedure itself. Testing for ovarian reserve may be recommended in order to predict how the ovaries will respond to fertility medication. The chance of success may be poor, for example, if tests demonstrate diminished ovarian reserve or fertility potential. Ovarian reserve may be determined by any of these methods: measuring FSH and estradiol levels on the second or third day of a menstrual cycle, measuring the level of AMH (antimüllerian hormone), performing a clomiphene citrate challenge test (CCCT), or counting the number of small follicles in the ovary (antral follicle count). An elevated FSH and/or estradiol level, a low antral follicle count, or a low AMH level is associated with reduced pregnancy rates, especially in women over the age of 35 years. However, age itself is the single most important factor in determining the chances for success with IVF.

Uterine cavity abnormalities such as fibroids, polyps, or a septum may need to be corrected before IVF or GIFT. A hydrosalpinx, a fluid-filled, blocked fallopian tube, reduces IVF success.

Semen is tested before ART. If semen abnormalities are identified, consultation with a specialist in male infertility should determine if there are correctable problems or underlying health concerns.

When sperm cannot be collected by masturbation, other forms of sperm retrieval are available. These procedures include penile vibratory stimulation (PVS) and electroejaculation (EEJ). During PVS, a strong vibrator is placed on the head of the penis to deliver stimulation resulting in ejaculation. During EEJ, electrical impulses from a probe placed in the rectum near the prostate often stimulate ejaculation. For men who are able to ejaculate, but who do not produce sperm in their semen, medical procedures are available to retrieve sperm from reproductive tissues. These procedures include microepididymal sperm aspiration (MESA), percutaneous epididymal sperm aspiration (PESA), or testicular sperm extraction (TESE). MESA can be performed to recover sperm after vasectomy or after failed vasectomy reversal, and in some men with absence of the vas deferens. TESE involves testicular biopsy and recovery of sperm directly from testicular tissue, and may be performed in an office setting with local anesthesia. Sperm obtained by these methods may be frozen, stored, and thawed for later ART.

When to End Treatment

Studies indicate that the chance for pregnancy in consecutive IVF cycles remains similar in up to four cycles. However, many other factors should be considered when determining the appropriate endpoint in therapy, including financial and psychological reserves. Members of the IVF team can help couples decide when to stop treatment and discuss other options such as egg and/or sperm donation or adoption, if appropriate.

Conclusions

The prevalence of MAR use around the world has been increased over the last years. With a noticeable surge of infertility/subfertility among women of childbearing age, these numbers are expected to remain on the rise. Fertility treatments are costly and the stakes are high. Best practice requires using the best available evidence to optimise outcomes, to improve live birth rates, and to reduce rates of multiple pregnancy, cycle cancellation, and ovarian hyperstimulation syndrome.

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ENDOCRINOLOGICAL DISORDERS OF REPRODUCTION

Dr. Saumya Nanda

The reproductive systems are vulnerable to disruption from various factors like disease, malnutrition and stress. Although the female axis is more sensitive to dysfunction, both male and female axes are susceptible.1

As the "master gland", the anterior pituitary controls the hormone secretion of the thyroid (thyroxine and triiodothyroxine), adrenal cortex (cortisol, dehydroepiandrosterone sulfate), and gonads (estradiol in females and testosterone in males).

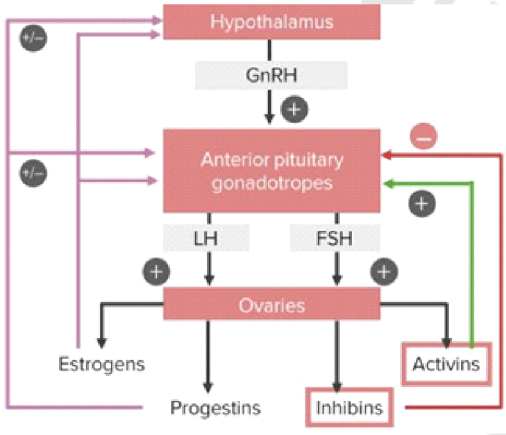

Fig-1

Neuroendocrine control of reproduction requires the pulsatile secretion of gonadotropin releasing hormone (GnRH) from hypothalamus released into the pituitary portal system to stimulate the synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the gonadotrophs. The gonadotrophins, in turn stimulate follicular development and secretion of gonadal steroids and peptides whose negative feedback effects on the hypothalamus and pituitary restrain gonadotropin secretion. At the mid-cycle, rising levels of estradiol are responsible for the positive feedback, which generates the preovulatory gonadotropin surge.

Disorders of reproductive endocrinology can occur from abnormal changes anywhere in the hypothalamus-pituitary-gonadal axis and can include a wide range of symptoms including infertility, hirsutism, virilization, oligomenorrhea and amenorrhea in women, and infertility and altered sexual function in men. 1

Gonadotropin deficiency

This may be primary (no pubertal development and primary amenorrhea/delayed puberty) or secondary (loss of previously present menses).

Congenital causes include defects in gonadotropin cell formation and function (such as the transcription factor Pit-1), or defects in GnRH secretion or its receptor, or controlling factors such as Kisspeptin-1.

Acquired gonadotropin deficiency may give primary and secondary amenorrhea, depending on time of onset (childhood vs. adulthood). In men, this presents as delayed puberty, or symptomatic loss of previously normal testosterone secretion. Organic causes involve any pathological process in the hypothalamic-pituitary axis. Hyperprolactinemia of any cause does suppress GnRH secretion.

Nonorganic causes affect the normal physiologic secretion of GnRH and are generally reversible. The most common nonorganic causes are marked disorders of nutrition, eating disorders, very excessive exercise, or combinations of weight loss,

exercise, and stress that have been shown to be additive. Eating disorders are often the underlying cause, especially in younger women.

Gonadotropin excess

Gonadotropin excess (largely laboratory finding) may be detected in either gender with gonadal failure.

Pituitary adenomas may rarely secrete biologically active gonadotropins that result in a clinical syndrome of gonadal hyperstimulation. There are rare reports of women presenting with menstrual changes, pelvic pain, ovarian cysts, and ascites resulting from excessive FSH secretion from a functioning pituitary adenoma.2

The most common subtype of non-functioning pituitary adenomas is of gonadotroph cell origin. Pathological examination of the tumour finds local production of fragments of alpha and betasubunits of FSH and LH.

Measurement of serum levels of alpha and beta subunits has been attempted to predict the pathological nature of such tumours, but have been poorly sensitive for this purpose. Because of the nonbiologically active production of these gonadotropin fragments, these tumours present with mass symptoms, mild hyperprolactinemia, or as an incidental finding but without sex steroid excess; there may be sex steroid deficiency due to mass effect upon the normal surrounding pituitary.

Ovarian insufficiency (sometimes called premature menopause) occurs when the ovaries either do not develop or are damaged and no longer function normally. Ovaries can be surgically removed, or damaged by the immune system, or from chemotherapy, or radiation treatments for certain types of cancer.

The premature loss of ovarian function (before the age of 40) can result in infertility and the loss of the beneficial effects of estrogen and progesterone, including benefits to bone and heart health, which are usually not lost until the natural age of menopause (approximately age 50). Symptoms of low estrogen can develop in many, but not all, women with ovarian dysfunction. These can include hot flashes, night sweats, poor sleep, and vaginal dryness. Although fertility cannot usually be restored in this setting, women have the option of utilizing in-vitro fertilization with egg donation to achieve pregnancy.

Pituitary Disorders that affect Reproduction Prolactinoma and Hyperprolactinemia

The combination of amenorrhea and galactorrhea in a young woman is a classic presentation of prolactinoma. Hyperprolactinoma has many etiologies. The mechanisms of reproductive dysfunction in hyperprolactinemia vary with etiology, but prolactin disrupts the pulses of GnRH and also directly reduces the production of LH and FSH. Cabergoline administered at 0.25 mg twice weekly is more potent and better tolerated than Bromocriptine . Surgery and radiotherapy is reserved primarily for rare tumours unresponsive to dopamine agonists and for patients intolerant to drugs.3

Table 1: Causes of Hyperprolactinemia

Cause	Characteristic features
Prolactinoma	Mass effects if macroadenoma
Acromegaly	Headaches, heavy perspiration, acral changes
Macroadenoma(not prolactin secreting)	Peripheral vision loss, anterior pituitary defects
Other infiltrative or hypothalamic diseases	Anterior pituitary defects
Drugs	Other side-effects of drugs
Pregnancy	Positive hCG, amenorrhoea
Renal failure	comorbidities
Chest wall stimulation	Variable Prolactin
Stress	
Primary hypothyroidism	

Acromegaly

It results from overproduction of GH and IGF-1 accompanied by acral bone and soft tissue growth. Majority of patients have GH-secreting pituitary tumour . Menstrual abnormalities are observed when mass effect impairs delivery of hypothalamic releasing factors to the anterior pituitary or when hyperprolactinemia occurs. Treatment includes somatostatin agonists such as Octreotide or Lanreotide given as monthly injections. Pegvisomant, a growth hormone receptor antagonist given by subcutaneous injection of 40 mg loading dose followed by 10-30 mg daily is successful in 60-65%. Pasireotidewhich binds to sst5 with higher affinity than octreotide, appears promising.

Adrenal Disorders

In women, the majority of testosterone is derived from adrenal derived precursors. Diseases that increase adrenal DHEAS production cause hyperandrogenemia in women which can impair fertility. Hypercortisolism can suppress gonadotropin production in women.Cushing Syndrome is categorized as iatrogenic or endogenous, is the most relevant form of hypercortisolism that impairs reproduction.

Table:2 Etiologies of Endogenous Cushing Syndrome

ACTH-Independent	**Adrenocortical adenoma**
	Adrenocortical carcinoma
	Macronodular hyperplasia
	Micronodular hyperplasia
ACTH-Dependent	**Corticotrope tumour (Cushing disease)**
	Corticotrope hyperplasia
	Ectopic ACTH syndrome
	Ectopic CRH syndrome

The most important scenario in which Cushing syndrome should be considered is in the young woman with oligomenorrhea and hirsutism mistaken for **polycystic ovarian syndrome.** Onset of hirsutism after 25 years, or specific signs of hypercortisolism such as easy bruising, thin skin, proximal muscle weakness and osteoporosis should prompt screening of Cushing syndrome.

Thyroid disorders

Thyroid autoimmunity (TAI) and/or thyroid dysfunction are prevalent in women of reproductive age and have independently been associated with adverse fertility and pregnancy outcomes, in the case of spontaneous conception or after assisted reproductive technology (ART). Thus, it seems reasonable to screen for thyrotropin (TSH) and thyroid peroxidase autoantibodies (TPO-abs) in infertile women attempting pregnancy. The importance of thyroid hormones has been highlighted ever since the discovery of TSH, its receptor as well as thyroid hormone receptors (TR-?1 and TR-?1) on ovarian surface epithelium and in oocytes of primordial, primary, and secondary follicles. Thyroid hormones seem to participate in the complex regulation of ovarian function.Thyroid hormones may also influence fertility aspects in an indirect manner, altering gonadotropin releasing hormone (GnRH) and prolactin secretion, sex hormone binding globulin (SHBG) levels and coagulation factors.4

Considering the importance of thyroid hormones, even mild thyroid failure has been proposed as one of the possible causes for adverse fertility and pregnancy outcomes.

The extent to which hyperthyroidism is related to fertility issues is not well established due to limited data in literature. However, in general, if not treated adequately, hyperthyroidism is associated with early pregnancy loss.

Thyrotoxicosis increases sex hormone binding globulin (SHBG) and estradiol (E2) serum levels compared to euthyroid women. The latter may result from an increase in SHBG or increased E2 and androgen production, combined with an increased conversion ratio to estrone and E2. In addition, LH secretion is increased in Graves' disease patients compared to euthyroid patients.Menstrual disturbances are common in hyperthyroid women. Early data suggest menstrual abnormalities in up to 65% compared to 17% in healthy controls.

Overt hypothyroidism is associated with an increased risk of fertility problems and unfavourable early and late pregnancy complications.

Hypothyroidism results in a number of hormonal changes. The rates of metabolic clearance of both androstenedione and estrone are decreased, whereas peripheral aromatization is increased. In addition, the plasma binding activity of SHBG is decreased. Consequently, plasma concentrations of both total testosterone and E2 are decreased and their unbound fraction increased. Hypothyroidism may also lead to a blunted LH response thereby stimulating TRH secretion and increasing serum prolactin levels. As prolactin impairs pulsatile secretion of gonadotrophin-releasing hormone (GnRH) this can lead to ovulatory dysfunction, including insufficiency of the corpus luteum with low progesterone secretion in the luteal phase of the cycle.

Therefore, clinical hypothyroidism leads to a number of ovulatory disturbances in women of fertile age. There may be changes in cycle length as well as in the volume of menstrual bleeding secondary to breakthrough bleeding following anovulation and/or disturbances in haemostatic factors associated with hypothyroidism.

The prevalence of menstrual abnormalities reported is 25%-60% in hypothyroid women compared to 10% in euthyroid women.

Thyroid autoimmunity and female infertility

TAI is the most frequent autoimmune disorder in women of childbearing age and increases the risk of thyroid dysfunction. The prevalence of TAI is generally estimated at around 10% and has been shown to be more common in women seeking counselling for infertility. A meta-analysis pooling 4 studies showed that the presence of thyroid antibodies in euthyroid patients is associated with unexplained subfertility (OR 1.5, 95% CI 1.1-2.0) .TAI has been linked to adverse pregnancy outcomes with an increased risk of miscarriage and preterm delivery in spontaneous pregnancy as well as in pregnancy after ART. 5

PCOS and Reproductive Health

PCOS is the most common cause of anovulatory infertility; ~ 90-95% of anovulatory women seeking treatment for infertility have PCOS. Women may learn they have PCOS only after seeking infertility treatment. Most women with PCOS have elevated levels of luteinizing hormone and reduced levels of follicle-stimulating hormone (FSH), coupled with elevated levels of androgens and insulin . These imbalances can manifest as oligomenorrhea or amenorrhea. Underproduction of estrogen and overproduction of androgens (testosterone, dehydroepiandrosterone, and androstenedione) by the ovaries can result in a number of additional clinical features, including tiny cysts on the surface of the ovaries (polycysts) and hair and skin symptoms. Women with PCOS who become pregnant are at higher risk than those without PCOS of developing gestational diabetes mellitus or suffering a first-trimester spontaneous abortion.6

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CANCER AND FERTILITY

Dr Bhagyalaxmi Nayak

Potential and actual infertility is one of the most distressing adverse consequences of successful cancer treatment in cancer survivors of all ages. Infertility can ensue from the cancer itself or the treatment there off. It affects the future quality of life of patients and leads to psychological distress, as well as being a predictor of stress in present and futurerelationships,and a factor in higher rates of divorce. Studies have demonstrated that patients fear rejection because of their impaired fertility status, and do not disclose their actual or suspected infertility to friends and/or new partners. Various studies demonstrate that not being given the opportunity to discuss reproductive concerns heightens psychological distress.

Oncofertility was a word coined by Dr. Teresa Woodruff in Michigan. This grew into a Consortium which got created in 2007 to address a significant health care need for cancer survivors. Over the last 14 years, this program has brought together a diverse multidisciplinary group of thought leaders that span several specialties of health care providers, etc. and community engagement groups, researchers, and learners passionate about improving the quality of life for cancer survivors. With scientific advances in ART technology there is a expanding option of fertility preservation in cancer patients.

Oncofertility refers to the medical field that bridges the specialties of oncology and reproductive endocrinology with the purpose of maximizing the reproductive potential of cancer patients and survivors. Cancer treatments, including chemotherapy, radiation, and surgery, may impair or destroy a person's ability to have children later in life. For women, these therapies can cause ovarian damage that can lead to genetically damage oocytes (eggs), ovarian failure, early menopause, or other reproductive problems. For men, treatments can similarly cause damage to the testes that interfere with sperm production and testosterone secretion. As cancer treatment is improving and survivorship increasing , fertility preservation options in women, men, and children has become an increasingly important issue. Fortunately, improvement in ART technology has maximized future fertility potential. The issue needs to be discussed with the patient and consultation with reproductive endocrinologists needs to be done as early as possible after the diagnosis of cancer, and optimally prior to chemotherapy or pelvic radiation. At the same time it is ideal to know the ethical issues surrounding the problem which varies from time to time.

Oncofertility also encompasses the endocrine health of the patient. . Thus, pubertal transitions in males and females, bone health, and menstrual health are all part of this discipline, enabling practitioners to work in interdisciplinary teams to solve problems in reproductive health. This emerging discipline will look after the essential considerations required for the assessement of reproductive risk and choice of fertility preservation options as well as considerations for developing oncofertility services for all but more specifically adolescents and young adults.

Fertility Preservation Options:

Shielding of the genital and pelvic region with a lead apron during radiation therapy to minimize the damaging effects of ionizing radiation on the ovaries and testes.

Ovarian Transposition to physically move the ovaries out of the pelvis through surgical techniques in cases where pelvic radiation is required in order to minimize the damaging effects of ionizing radiation on the ovaries.

Gonadotropin Agonist injections that will chemically down regulate the ovaries or testes and minimize their activity prior to receiving chemotherapy. The rationale is that ovaries and testes with minimal metabolic activity will experience less damaging effects from the chemotherapy. However, there is insufficient evidence to back this theory.

Oocyte cryopreservation in unmarried girls for future fertilization. Hormonal stimulation of the ovaries result in the maturation of multiple eggs that can be harvested by ultrasound guided aspiration and frozen for future use. This process may require 2-6 weeks to complete.

Embryo Banking in married women for future implantation. Hormonal stimulation of the ovaries result in the maturation of multiple eggs that can be harvested and fertilized to create embryos, which are then frozen for future use. This process may require 2-6 weeks to complete.

In Vitro Maturation (IVM) of oocytes, where multiple immature eggs are harvested by ultrasound guided aspiration without prior hormone stimulation. These eggs will then be matured in the laboratory either before or after freezing. The main advantage is the relatively short time period required to obtain immature eggs, which minimizes any delay before cancer treatment. It is quite a evolving method and not available at all facilities.

Sperm Banking to freeze sperm for future use. Multiple semen samples can be collected and frozen over a period of several days.

Testicular Sperm Aspiration or Extraction is a minor surgical procedure where sperm is retrieved directly from the epididymis or testes, which can then be frozen for future use. This is only required when no sperm can be produced through ejaculation.

Tissue banking where ovarian cortex or testicular tissue is surgically removed and frozen. This tissue can later be transplanted back into the body and hormonally stimulated to produce eggs and sperm with some success when the patient is ready to conceive. Scientists are currently developing methods to optimize this technique.

Donor Egg is recommended when the ovaries are permanently damaged by cancer treatment and no longer able to produce eggs. A known or anonymous egg donor is hormonally stimulated to mature multiple eggs that can be harvested and fertilized with sperm from the patient's male partner to form embryos. The embryos can then be transferred into the patient's own uterus to carry the pregnancy.

Donor Sperm is recommended when the testes are permanently damaged by cancer treatment and no longer able to produce sperm. The sperm from a known or anonymous donor is used to achieve a pregnancy with the patient's female partner.

Gestational Surrogate is required when cancer treatment damages the uterus and prevents a woman from carrying a pregnancy. Embryos created from a couple's eggs and sperm are transferred into the uterus of the gestational surrogate in order to carry the pregnancy.

Adoption is a legal transfer of all parental rights and responsibilities of a child from the biological parent.

Conclusion:

Patients suffering from cancer should be guided by their primary physician to access fertility services right from the begin. Oncofertlity is basically going to be a multidisciplinary team with Reproductive endocrinologists , oncologists, psychologist all working hand in hand to help the patient and family take the best decision at the right time.

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SURGICAL DISORDERS OF REPRODUCTION

Dr Manoranjan Mahapatra

INTRODUCTION

The chapter of surgical disorder of pregnancy is unfolding & getting more attention in recent time due to increase of 'scope for scopy' with advancement in both technique & technology related to the domain. Advancement in artificial reproduction is a setback to need for some of the procedures as primary necessity, particularly related to tubal factors & male factors.

What is fertility surgery?

There are many causes of infertility and some can be treated surgically to increase the chances for conception. Both men and women may need surgical infertility treatment. Some causes of infertility that require surgery are congenital and some may be acquired ,there by altering the anatomical or physiological status of reproductive system.Some causes of infertility in women that can be corrected by surgery include endometriosis, fibroids, polyps and other problems in the reproductive organs.For men, fertility surgery can treat varicocele or reverse a vasectomy.

When surgery is the option to manage infertility ,laparoscopy is the gold standard in comparison to laparotomy .Key hole surgery gives a chance to conceive earliest following faster recovery. Laparotomy ,having chance of gloves powder contamination, oozing from small bleeders ,exposure of surgical field with drying effect invites more morbidity & adhesion formation ,there by reducing the chance for fertility. Hence laparoscopy for peritoneal surgery & hysteroscopy for intrauterine causes is the standard mode of approach. Reproductive surgery can be divided into three categories:

1-primary conventional surgical treatment of infertility,

2-Surgery to enhance the pregnancy outcome of in vitro fertilization

3- surgery for fertility preservation .

DHL-DIAGNOSTIC HYSTERO LAPAROSCOPY :

DIAGNOSTIC LAPAROSCOPY- The role of diagnostic laparoscopy in the management of infertility is limited due to advancement of ultrasonography. However, it can be useful in the infertility evaluation of young women with a history of pelvic inflammatory disease, ectopic pregnancy, pelvic surgery, or chronic pelvic pain. Diagnostic laparoscopy can be avoided in older women and those with multiple infertility factors. These women are better served by IVF, instead of a surgical approach to treatment.

Chromopertubation - When laparoscopy is performed for diagnostic or therapeutic purposes in women with infertility, chromopertubation is often performed to assess tubal patency. Spillage of the dye from each tube is noted as a confirmation of tubal patency. If a repair procedure for tubal occlusion is performed, chromopertubation is repeated at the end of the procedure. Sono-

hysterosalpingography is another non-invasive alternative option.

DIAGNOSTIC HYSTEROSCOPY - Uterine cavity is assessed for presence of any adhesions, septum submucousmyoma, condition of tubal ostia ,endometrium status & status of cervical canal .Office hysteroscopy is a better option if isolated cavity assessment is performed.3D sonography,HSG are good gadgets for initial evaluation .Entry of air bubble or methylene blue dye into the tubal ostia suggests the absence of tubal occlusion.

DTHL-DIAGNOSTIC & THERAPEUTIC HYSTERO LAPAROSCOPY :

Concept of concurrent therapeutic along with diagnostic procedure is the demand of time for the aspiring couple. Better preoperative evaluation &counselling should be done prior to the procedure. Video recording of the procedure is necessary for documentation & providing the information to the patient as well as for the infertility specialist to deal in future.

A considerable benefit of many surgeries is that they can fix the cause of infertility at the time of the procedure, so in the future a woman can have multiple children if she desires. Some of the infertility conditions we most commonly treat by surgery are listed below.

Endometriosis

Ectopic endometrial tissue which flourishes in pelvis in the form of surface lesion to endometrioma. Deep infiltrating endometriosis is the biggest concern in recent time due to early onset of disease ,late marriage ,less no of child birth .Proper assessment of severity of lesion prior to surgery from symptoms of typical co menstrual dysmenorrhea , menorrhagia, Finding a fixed retroverted uterus with bluish discoloration of vagina, fixed pelvis with adnexal masses, presence of endometriotic cyst etc must be taken into account for assessment of severity.3D sonography ,MRI should be done to assess the severity & extent of Deep infiltrating endometriosis

The surgical principle for endometriosis should be aimed for conservative management with a principle of minimum intervention giving maximum outcome. Surgery may be done as upfront or a sandwich procedure following medical management with Gnrh analogue .Retroperitoneal dissection should be reserved for DIE & recurrent endometriosis. Oophorectomy should not be considered & minimum damage to the ovarian cortex to be done by avoiding thermal damage. Inj vasopressin in diluted form to the uterus & para salpinx area is a good option to achieve blood less surgery & smooth dissection .Guideline based practice is always helpful for such patients. First surgery is the best surgery, therefore optimum disease clearance should be achieved. 3D laparoscopy is a very good technological addition for better technical execution. Specimen should be retrieved either in an endobag or through POD, in order to avoid contamination to port site tissue thereby causing port endometriosis. Decision for surgery must be done as per the gadgets availability & surgical proficiency of operator.

OVARIAN CYST -

Proper clinical assessment, imaging with IOTA guideline-adnex model risk evaluation considering the biomarkers & other factors are necessary prior to surgery .For any doubtfull ovarian mass /cyst MIS to be done avoiding peritoneal spillage. Morcellation of any kind should not be done for any form of ovarian mass. ORADS -US 4,& 5 group of ovarian

masses should be dealt with laparotomy with frozen section back up. Early stage malignancy should be offered with fertility preserving surgery after proper counselling & consent .For advance & proved ovarian malignancy, proper oncologic surgical principle to be followed. Ovarian tissue, follicular or embryo preservation option must be explored prior to terminal surgery & adjuvant chemotherapy following conservative surgery.

FALLOPIAN TUBE BLOCKAGE -

Surgery depends on the location and extent of the blocked fallopian tubes. Here are the most common tubal procedures:

TUBAL ANASTOMOSIS - This surgery is used to reverse a tubal ligation or repair part of the fallopian tube that is damaged. Tubo tubal anastomosis to be done with fine sutures .Maintaining the Vascularity ,avoidance of lumen discrepancy, apposition of lumen are few of the surgical principle to be followed during tubal anastomosis.

SALPINGECTOMY - When a tube is damaged with destruction of cilia ,salpingectomy is a better option .Hydrosalpinx should be removed or clipped at it's medial end for better outcome of inevitable IVF .

SALPINGOSTOMY- This surgery also treats hydrosalpinx by creating an opening in part of the tube closest to the ovary. It is common that scar tissue will regrow after this surgery, which can re-block the tube. In modern infertility management salpingoscopy assessment should be done & documented for such desperately done procedure.

FIMBRIOPLASTY -This treatment option rebuilds the fringed ends of the fallopian tube that sweep the released egg into the fallopian tube .Minimal damage either physical or thermal should be done during the procedure.

PROXIMAL TUBAL CANNULATION (PTC)- For the uterine cornual blockage, hysteroscopiccanulation with or without guide wire is performed with laparoscopic concurrent guidance. For the non fibrotic blockage PTC is a rewarding procedure .A disposable catheter to be used to avoid post procedure salpingitis.

MYOMA OF UTERUS -

Site,size,number,type& symptoms must be considered before offering the treatment for myoma. Type 0,1& 2 are managed hysteroscopically. Other variants are better managed laparoscopic.

Myomectomy- decision of myomectomies to be made when myoma is symptomatic or cause for infertility. MIS is the method of choice but power morcellation to be judiciously decided after informed consent. In bag morcellation must be considered to avoid spillage of myomatous tissue to the peritoneal cavity there by chance of myomatosis .Hydrodissection with diluted vasopressin facilitates the myomectomy.Shoe lace technique of tying the uterine arteries prior to myomectomy is an alternative option.Barbed sutures are very good for better closure of myomectomy bed.

Myolysis -Deprivation of blood supply to the fibroid through heating, freezing or radiofrequency energy so the fibroid dies and shrinks.

Uterine artery embolization -Insertion of a catheter into the uterine artery and injection of embolising agents there by cut off the blood supply to the fibroids, killing or shrinking them.

Uterine polyps

Uterine polyps affect fertility by interfering with implantation of an embryo and they also

can cause miscarriage. Treatment for uterine polyps can be done convincingly under hysteroscopic guidance.

Pelvic adhesions-

Adhesions surrounding the ovary may impair the ability of an egg to reach the tube after ovulation. Adhesion of the tube can prevent the sperm from reaching the egg or an embryo from reaching the uterus. Adhesions are commonly a result of previous surgery or can accompany severe stages of endometriosis. Pelvic adhesions are most frequently removed using a laparoscopic procedure.

Polycystic ovary syndrome-

There are two surgical procedures used to treat PCOS.

Laparoscopic ovarian drilling (LOD) -A laser or electrocautery is used to make 4 -5 punctures in each ovary with short bust of energy thereby triggering the ovaries for ovulation.However due to availability of better ovulation inducing agents ,LOD is opted as a desparate procedure in modern infertility management.

Ovarian wedge resection -surgical way to remove part of the ovary. This procedure can cause scarring on the ovary there by damaging it, so this is rarely performed as a fertility option in modern days.

Egg retrieval

Egg retrieval is the process by which the eggs for an IVF procedure are removed from the ovarian follicles using a thin needle. The needle is gently inserted into the follicle, guided by ultrasound, and the egg is aspirated into the needle and removed from the ovary. Other than being used in IVF, the eggs gathered from this surgical procedure may be used for intracytoplasmic sperm injection (ICSI), conventional in vitro fertilization or cryopreservation.

Some of the congenital defects are often encountered which causes infertility / subfertility needing surgical intervention.Mullerian developmental anomaly leading to agenesis or spectrum of dysgenesis in the form of septateuterus, bicornuateuterus, unicornuate uterus etc can be corrected by different MIS procedure. Uterine transplantation is a reality which can satisfy many patients with MRKH syndrome, however a highly skilled & dedicated team effort followed by stringent follow up can leads to success. Unification operation for bicornuate uterus can very well be accomplished by laparoscopy. Better result is achieved with use of barbed sutures.Transcervical resection (TCRS) through hysteroscopy is a very rewarding procedure in well choosenpatients of septate uterus. Use of bipolar elements with normal saline distension medium minimises the complication in comparision to monopolar resectoscope. Cavity augmentation through hysterescopic lateral metroplasty is a very rewarding procedure for unicornuate uterus.
Some aquired defects like asherman's syndrome can very well be treated with hysteroscopicadhesiolysis followed by endometrial augmentation through high dose of estrogen. Hysteroscopicsubendometrial injection of autologous platelet rich plasma (PRP) using a Wallace needle through operating channel of hysteroscope is a very promising method in recent time bringing a ray of hopes to badly affected uterine adhesion with special mention to tuberculosis etiology.

Male fertility surgeries

Men may need surgery to correct structural deformity causing infertility. Types of surgeries

to improve or reverse infertility in men include a vasectomy reversal and a varicocelectomy.

Vasectomy reversal -A vasectomy reversal or vasovasostomy will reconnect the vas deferens, which was disconnected during the vasectomy. A small incision is made in the testicle to perform the procedure. The reconnected vas allows sperm to once again enter the seminal fluid.

Varicocelectomy - Varicocelectomy treats varicocele, which is an enlargement of the veins in the scrotum that disrupts a man's fertility due to thermal damage to immature spermatogonia. This surgery removes those enlarged veins to restore normal blood flow to the reproductive organs. Varicocele is not always treated, but surgery may be recommended if it is causing infertility.

Sperm retrieval

If the man's semen carries no sperm, there may be a structural problem preventing sperm from being released into the semen during ejaculation. Sperm retrieval techniques are done by using microsurgical epididymis sperm aspiration (MESA), percutaneous epididymal sperm aspiration (PESA) or testicular sperm extraction (TESE).

Similar to an egg retrieval in a woman, the sperm can then be used for IVF, ICSI, or cryopreservation

CONCLUSION - Disorder of reproductive system requiring surgery is an analytical based option for infertility management. Pre operative evaluation, necessity based decision for surgery, proper execution with preference to MIS, follow up guidance for further fertility management are critical components. A non biased decision should be taken from ART consultant &laparoscopist for the optimum result. A multi disciplinary approach is the key to success for such desperate couple.

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PSYCHOLOGICAL DISORDERS OF REPRODUCTION

Dr. Ajit Kumar Nayak
Dr. Pragyan Paramita Pradhan

Introduction

Psychiatric problems are a central or complicating factor for many patients who seek care on an outpatient basis. Psychiatric diagnoses are extremely common and account for considerable morbidity and mortality in the general population. However despite their prevalence, psychiatric disorders are often undiagnosed or misdiagnosed. 1-4 Clinical depression affects up to one-fourth of women during their lives, but probably more than half of those women are neither diagnosed nor treated. 5-8 Social stigmas attached to psychiatric diagnoses, patients, and practitioners, belief that individuals with psychiatric disorders are weak, unmotivated, manipulative, or defective, belief that psychiatric treatments are ineffective and unsupported by medical evidence are main barriers for people to seek help.

Psychological Disorders in Reproductive life

Mood, anxiety, and alcohol or substance use disorders are three families of psychiatric disorders commonly seen in women during their reproductive life and often are comorbid with reproductive disorders.9 Women also commonly have one or more comorbid psychiatric disorders, most commonly anxiety disorder and/or substance use disorder.

Mood disorders

The spectrum of mood disorders is divided into depressive disorders (major depressive disorder, dysthymic disorder and depressive disorder not otherwise specified); the bipolar disorders (bipolar I, bipolar II, cyclothymic disorder, and bipolar disorder not otherwise specified); and two etiologic disorders (mood disorder due to a general medical condition and substance-induced mood disorder).

Depression

Depression is the second leading cause of disability in women, and females are 1.5 times more likely to suffer from a major depressive episode than men (National Institute of Mental Health, 2010).10

Diagnosis: Self-report questionnaires are often used to identify individuals who require further psychiatric evaluation and gauge the frequency and intensity of depressive symptoms .By patient report, this questionnaire assesses the symptom severity required by DSM-IV criteria to diagnose major depressive disorder.

Anxiety Disorders

For women, the key transitions of menarche, pregnancy, and menopause may cause anxious feelings because of the perceived irreversible life changes that they may herald .11 Criteria established in the DSM-IV may provide guidelines to help distinguish anxiety disorder from normally expected worries.

Alcohol and Substance Disorders

Though previously more common in males than in female, alcohol and substance abuse are

increasing among females.Substance abuse leads to major complications, including intoxication and withdrawal.The most successful treatment for substance abuse disorders is a so-called 12-step program such as Alcoholics Anonymous. Most of the programs for the treatments of substance abuse were developed for men. Women are less responsive to the usual confrontational approach.Buprenorphine is a useful adjunct medication.

Eating Disorders

Eating disorders are classified by DSM-IV as anorexia nervosa (AN), bulimia nervosa (BN), and eating disorder not otherwise specified.

The core symptoms of both anorexia and bulimia are preoccupation with weight gain and excessive self-evaluation of weight and body shape. These disorders are 10 to 20 times more common in females than in males, particularly in those aged 15 to 24 years. 12 During adolescence, an estimated 4 percent of girls have some form of eating disorder, and approximately 0.3 percent suffers from anorexia nervosa. Anorexia usually begins early in adolescence and peaks at ages 17 to 18 years. Bulimia nervosa is more prevalent than anorexia but typically has a later onset. 13

Anorexia Nervosa

Anorexia Nervosa is divided into two subtypes: (1) a restricting type and (2) a bulimic type, which is distinct from bulimia nervosa. Symptoms begin in the form of unique eating habits that become more and more restrictive. Bulimic-type anorectics have been found to engage in two distinct behaviour patterns, those who binge and purge and those who solely purge. Individuals often present with dental problems, general nutritional deficiency, electrolyte abnormalities (hypokalemia and alkalosis), and decreased thyroid function. Electrocardiogram changes such as QT prolongation (bradycardia) and inversion or flattened T-wave.

Bulimia Nervosa

This disorder is identified by periods of uncontrolled eating of high-calorie foods (binges), followed by self-induced vomiting (purging). Moreover, bulimic women may often misuse laxatives or diuretics. Unlike anorexia, those with bulimia often recognize their maladaptive behaviours. Most bulimics have normal weights, although their weight may fluctuate. Thus, physical findings may be more subtle. One of the most characteristic signs is knuckle calluses found on the dorsum of the dominant hand.

These eating disorders often are accompanied by comorbid depression and anxiety symptoms. Rates of mood symptoms approximate 50 percent, and anxiety symptoms, 60 percent. 14 Simple phobia and obsessive-compulsive behaviors may also coexist. In many cases, patients with anorexia appear to have rigid, perfectionistic personalities and have low sexual interest. Patients with bulimia often display sexual conflicts, problems with intimacy, and impulsive suicidal tendencies. 15

Most may symptomatically improve with aging. However, complete recovery from anorexia nervosa is rare, and many continue to have distorted body perceptions and peculiar eating habits. Overall, the prognosis for bulimia is better than that for anorexia.

Management

Treatment of eating disorders involves a multidisciplinary approach. The American Psychiatric Association practice guidelines for eating disorders include: (1) nutritional rehabilitation, (2) psychosocial treatment that

includes individual and family therapies, and (3) pharmacotherapeutic treatment of concurrent psychiatric symptoms.15

Somatoform Disorders

Recurrent, multiple, often unexplained physical symptoms are hallmark features of somatoform disorders. These disorders are common, and their estimated prevalence in general clinical practice is 16 percent.16 symptoms cause significant distress and/or impairment in various domains of an affected individual's life.Moreover, one in four somatoform patients suffer from comorbid anxiety and depressive symptoms. Thus, a multidisciplinary approach is often required to effectively manage these women's symptoms.

SEXUAL DISORDERS

Psychiatric sexual dysfunction is characterized by painful intercourse or disturbances in desire, arousal, orgasm, or resolution that cause marked distress. Psychosocial risk factors for sexual dysfunction include comorbid psychologic disorders, negative emotions, maladaptive cognitions (such as inaccurate expectations), cultural factors, lack of education regarding sexual functioning, couple distress, and absent physical attraction.17 Psychiatric disorders such as depression and anxiety are frequently comorbid with sexual disorders.

Diagnosis of sexual disorders begins by judging if dysfunction is caused exclusively by a general medical condition, drug abuse, medication (e.g., antidepressants often disrupt sexual response), or toxin exposure. Subsequently, evaluation for a primary psychiatric disorder should follow.

Classification:

Hypoactive Sexual Desire Disorder

Persistently or recurrently deficient or absent sexual fantasies and desire for sexual activity, taking into account factors such as age and the context of the person's life.

Sexual Aversion Disorder

Persistent or recurrent extreme aversion to and avoidance of all genital sexual contact with a sexual partner.

Female Sexual Arousal Disorder

Persistent or recurrent inability to attain or maintain until completion of sexual activity an adequate lubrication-swelling response of sexual excitement Female.

Orgasmic Disorder

Persistent or recurrent delay in, or absence of, orgasm following a normal excitement phase taking into account factors such as age, sexual experience, and the adequacy of sexual stimulation she receives.

Dyspareunia

Recurrent or persistent genital pain associated with sexual intercourse (not caused exclusively by vaginismus or lack of lubrication)

Vaginismus

Recurrent or persistent involuntary spasm of the musculature of the lower third of the vagina that interferes with sexual intercourse.

Treatment of Sexual Dysfunction-

Multidisciplinary treatment is ideal for patients with sexual dysfunction. A team would typically include the referring physician, gynaecologist, psychologist, and a nurse-specialist. Psychological approaches usually include some combination of sexual education, communication enhancement, identification of emotional and cultural factors, cognitive-behavioral therapy, and couples therapy.

PREGNANCY AND POSTPARTUM PSYCHOLOGICAL DISORDERS

Although pregnancy was previously viewed as protective against depression, not only do some women experience the first onset of depression during this time, but this is also a period of vulnerability for relapse of psychiatric disorders.

For the most part, psychiatric disorders during pregnancy have a course and presentation similar to those same disorders in nonpregnant women. For this reason, there are no distinct diagnostic criteria for psychiatric disorders experienced during pregnancy and the puerperium.

Depression during Pregnancy

The prevalence of depression during pregnancy has been estimated to be highest (11 %) in the first trimester and to fall to 8.5 percent in the second and third trimesters. Studies specifically investigating depression during pregnancy have found associations with life stress, previous episodes of depression, poor social support (particularly from the partner), and maternal anxiety.18

Management

No antidepressant has been approved by the U.S. FDA during pregnancy. The FDA classifies most SSRIs as category C drugs. Two types of neonatal effects have been described following SSRIs. Serotonin syndrome is characterized by transient jitteriness, increased muscle tone, feeding or digestive disturbances, irritability, and respiratory distress. More seriously, persistent pulmonary hypertension in the newborn (PPHN) has also been associated with SSRI.19, 20

On balance, women who discontinue antidepressant medication during pregnancy relapse into depression significantly more frequently than women who maintain their pharmacologic treatment.

Depression in the Postpartum Period

Depression after childbirth has largely been divided into three categories: postpartum blues, postpartum depression, and postpartum psychosis. The strongest predictors of postpartum depression include prior history of depression or anxiety, family history of psychiatric illness, poor marital relationship, low levels of social support, and stressful life events in the previous 12 months.21, 22

Postpartum Blues

This transient state of heightened emotional reactivity can develop in up to 50 % of postpartum patients. Th e onset is 2 to 14 days after childbirth, and its duration is less than 2 weeks.23 Blues generally require no intervention. Rest and social support contribute significantly to remission. However, postpartum blues do constitute a significant risk factor for subsequent depression during the puerperium.

Postpartum Depression

According to the DSM-IV, postpartum depression refers to the diagnosis of major depressive disorder within 4 weeks after childbirth.Postpartum depression warrants careful assessment by a mental health professional, as treatment should be initiated immediately. SSRIs are usually first-line agents, although caution is necessary in breast-feeding mothers. In addition, a number of psychosocial interventions have demonstrated efficacy in treating postpartum depression. Of these, the most significant effects have been achieved with interpersonal therapy and cognitive behavioural therapy.

Postpartum Psychosis

This condition develops in less than 2 percent of new mothers, and its onset is generally within 2 weeks of childbirth. 23 The risk for this severe form of depression is increased for women who have had prior mood disorders. Particularly, prior postpartum psychosis increases by 30 to 50 percent a woman's risk with subsequent deliveries. Evaluation and antipsychotic pharmacologic treatment are

essential for these women. Hospitalization is often indicated until the safety of mother and infant is assured.

PSYCHIATRIC DISORDERS DURING MENOPAUSAL TRANSITION AND POST MENOPAUSAL PERIOD-

Menopausal transition has long been investigated as a vulnerable period for emergence of mood symptoms. Anxiety, irritable mood, and sleep problems are more likely to develop in perimenopausal and post menopausal women than in premenopausal women. 24, 25 Possible risks for depression and anxiety are a prior history of depression, severe premenstrual distress, hot flashes, and disrupted sleep, lower educational status, African-American ethnicity, unemployment, and major life stressors. 25Mood vulnerability during menopausal transition is believed to follow erratic physiologic fluctuations in reproductive hormones.

Treatment

The approach to treating mood symptoms involves both pharmacotherapy and psychotherapy. Recommended psychotropic medications are SSRIs and selective noradrenergicreuptake inhibitors (SNRIs). These agents are good options for women who do not wish to use hormone therapy. Additional benefits include alleviation of vasomotor symptoms and sleep disturbance.

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ROLE OF ONCO-BIOMARKERS IN DISORDERS OF HUMAN REPRODUCTION

Dr Jita Parija

A Biomarker is a characteristic , which is objectively measured and evaluated as an indicator of normal biologic process , pathogenic process or pharmacologic responses to therapeutic intervention (NIH- Working group). Biomarkers are classified into ;

1. Type 0 markers - Those which are a marker of natural history of disease and correlate longitudinally with known clinical indices .

2. Type 1 markers - Those that capture effects of a therapeutic intervention in accordance with it's mechanism of action .

Biomarkers may have utility at all points in management of cancer , namely as :

1. Predisposition Marker - To identify those with risk of developing cancer ; eg inherited mutation in BRCA1/2 and MMR genes .

2. Screening Markers - Used in early detection of Cancer eg , Prostate Specific Antigen in Prostate Cancer.

3. Diagnostic Marker - Used to define the type, stage and grade of tumor, eg. Immunohistochemical Assays of histopathological samples .

4. Prognostic Marker- Used to identify the likely disease course. It may direct therapy with low risk groups thereby avoiding therapy and on the contrary intensify therapy in the high risk group .

5. Predictive Marker - Used to identify those more (+ve predictive marker), or, less likely (- ve predictive marker); to benefit from treatment eg . ER , PR , HER 2 neu expression.

Biomarkers are also useful in drug development and used in many trials . A good biomarker should be objectively measured and should be reproducible , should be practical and costeffective, in order to be used in clinical practice. The biological state of a person can be determined by analyzing biomolecules such as DNA,RNA.Protein,Peptides . The diagnostic performance of a biomarker is expressed in sensitivity and specificity.

TUMOR MARKERS

They assume increasing role in all aspects of cancer care like diagnosis , screening and followup after treatment . There are more than 20 tumormarkers used in oncology .They are identified by genomic transcriptions and proteomic analysis and consist of DNA mutations / deletions ; increased / decreased mRNA or protein levels / protein modification. Secretory proteins are more useful because they can be detected in blood . The current detection limit of usable Tumormarker is 109 cells which is close to the clinical detection size of 1012 cells . A single biomarker may not be sufficient ; thus a combination of biomarkers will probably be required to increase sensitivity and specificity . Currently measurement of Circulating tumor cells , circulating tumor DNA , long non-coding RNA, circulating RNA, tumor derived exosome are potentialtumor markers and microbiome composition serves as a marker for efficacy of immune checkpoint inhibitors .

There are many biomarkers for organ specific cancers .When it comes to cancers of the female

reproductive tract; Biomarkers play an important role in diagnosing, screening, prognosticating and in the followup of Endomerial , Cervical and Ovarian cancers.

Biomarkers in Endometrial Cancer

A . Individual Genes

1. Oncogenes

Kras, HER2/neu, EGFR, PI3KCA & FGFR2 are the oncogenes which have proved to be biomarkers of Endometrial Carcinoma. These oncogenes are normally inactivated. Their activation causes cell division .

2. Tumor suppressor genes

PTEN, P53, P21 & CDKN2A/P16, are examples of timor-suppressor genes, which are considered as biomarkers of Endometrial cancer. The basic pathway for carcinogenesis is the P13K/AKT pathway,

2. Mismatch repair genes and micro satellite instability

These genes are important in maintaining genetic stability. Simple genomic repeat sequences are particularly vulnerable to replication errors. This phenomenon is referred to as MSI & results from accumulation of mutation during DNA replication & is associated with MMR gene mutation. MSI occur in 20-30% of cases of endometrial cancer

B. OTHER BIOMARKERS

These include Ki-7, BAX, BCl-2, ER & PR levels and DNA ploidly and aneuploidy.

Number of mitosis & Ki-67/ MIB-1 expression- Quantifies cell proliferation

Ki-67- Expression is raised in;

1. Serous Adenoma
2. High grade cancers
3. Invasive region in endometrial cancer.

Loss of BAX expression- It is an apoptosis promotor- is lost due to mutation in endometrial cancer

Enhanced expression of BCl2 an anti-apoptosis promoting gene in Endometrial hyperplasia & reduced expression in Endometrial cancer.

The treatment selection is based on the levels of the hormone receptor and this approach has improved has the treatment of endometrial and breast cancer. Difference in hormone targeted therapies in types-I & II endometrial cancer due to different ER signalling pathways are also of interest. Progesterones act through PR pathway and via the steroid receptors. PR is required for inhibition of endometrial proliferation caused by oestrogen and downregulates the activity of oestrogen, by preventing the transactivation of ER- Alpha.

Malignant transformation of tumor is the result of chromosomes instability.

Chromosomal aneiuploidy is found in:

1. 20-35% of endometrial cancer
2. In advanced cancers
3. In high grade non-endometroid cancer
4. When there is deep myometrial invasion.

Trials have been conducted to identify new biomarkers for comparing gene expression level in normal and cancer tissues.The techniques used were cDNA microarray & RT-q PCR technique.

Expression of biomarkers in Type1 & Type11 Endometrial carcinoma

Target	Function	Change	Type 1	Type 11
K-ras	Oncogene	Mutation	13-26	0-10
HER-2/neu	,,	Enhanced expression	Rare	18-80
PIK3 CA	,,	Mutation	26-36	26-36
FGFR2	,,	,,	12	12
PTEN	T-suppressor	,,	35-55	0-11
P 53	,,	,,	5-10	80-90
P16	Cancer-suppressor	,,	10	10-40
MLH 1	DNA Repair	Methylation	20-35	0-10
BCL2	T-suppressor	Mutation	65	67
BAX	Oncogene	,,	48	43
ER,PR	Transcription factor	Enhanced expression	70-73	19-24
B-Catenin	Oncogene	Mutation	28-35	0-5

The results showed that ER,PR, Kras & PTEN are mutated at high rates in Type1 cases.On the other hand P53, HER2/neu mutation were high in Type11 Endometrial cancer.A rare mutation, rather than the rate of mutation is more important factor associated with carcinogenesis .

Biomarkers as Prognostic Prediction in Endometrial carcinoma.

	Biomarkers
Consistent results in retrospective studies	DNA-ploidy, ER/PR, p53, K1-67, Bcl2
Inconsistent results in several studies	HER-2/neu, PTEN, P16, MSI, B-Catenin, K-ras
An association with Prognosis suggested in a few studies,	Angiogenesis factor, MVD, VEGF-A, VPI, VMI, GMP, E-Cadherin, PI3K Signal activation

Biomarkers For Prognosis of endometrial cancer

Many retrospective studies have proven the effect molecular markers on prognosis of endometrial carcinoma. The conclusions drawn are given below;

Aneiuploidy	Poor prognosis
Expression of steroid receptors	Good(high survival)
Overexpression of HER-2	Poor prognosis(Reduced survival rate)
Overexpression of p53	Poor prognosis
Loss of expression of p16	Poor prognosis
Loss of expression of PTEN	Poor prognosis
Mutation of PTEN	Controversial
Expression of Ki-67	High proliferative activity
Number of mitosis	Poor prognosis
Loss of expression of BCl-2	Poor prognosis

Role of Biomarkers in Treatment of Endometrial Cancer

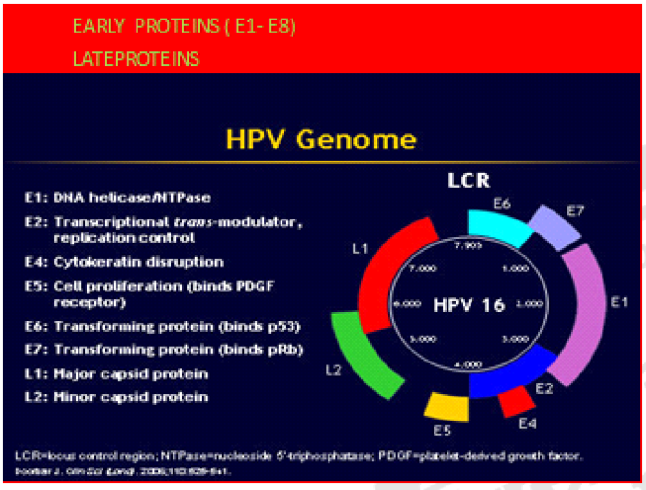
Drugs for molecular targeted treatment are being exposed for endometrial cancer. The potential therapeutic target includes aromatase, hormone receptors, EGFR tyrosine kinase, the VGFR family, PTEN as a downstream molecule in the P13K pathway & mTOR Abnormalities in the P13K pathway are common in endometrial cancer and the use of analogs of wortmannia, a P13K inhibitor, as drugs is being studied. A numbers go mTOR inhibitors, including temsirolimus, are being tested in phase 2 trials in the US. The efficacy & safety of Cetuximab, gefitimib, erlotimib, lapatinib & transzumab(EGFR-inhibitors) and aflibercept and bevacizumab(VGFR inhibitor) are undergoing phase-2 trials.

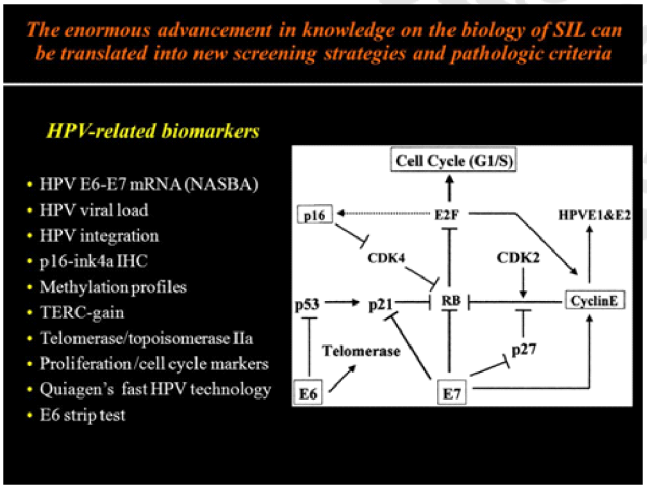
Individualization of treatment plays a significant role in cancer therapy. Some biomarkers e.g. CA19-9 & neuron-specific enolase(NSF) help in clinical diagnosis. Advances in molecular targeted therapy based on tumor markers will facilitate tailored treatment via tyrosine-kinase associated molecules and hormone receptors. Future studies are likely to focus on biomarkers for endometrial cancer and will aim to identify new therapeutic targets & optimize treatment based of biomarkers expression levels. Biomarkers like p53 & BCl2 have become indices for individualisation of treatment and prediction of prognosis. In endometrial cancer, an accurate method for predicting prognosis and risk of relapse for use in clinical practice may greatly contribute to areas such as application of fertility conserving treatment. Unfortunately in the present scenario biomarkers provide only limited information, therefore attempt has to be made to search for better biomarkers with greater sensitivity and specificity.

Biomarkers of Cervical Cancer

Help in monitoring the essential molecular events in histological and cytological specimens. Likely to improve the detection of lesion that have a high risk of progression in both primary screening and triage setting. Bio-markers are host protein and nucleic acid which are the products of HPV mediated alterations in the expression cell cyle .

A . Primary Biomarkers





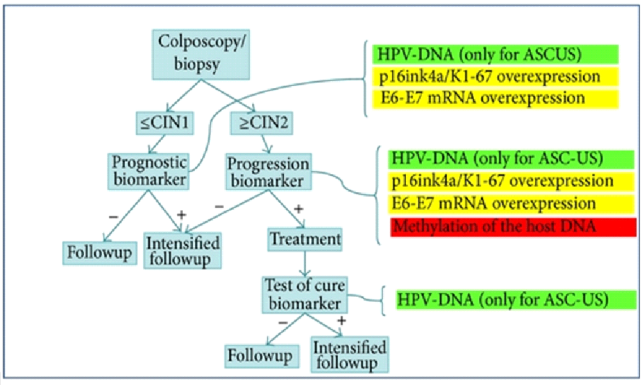
E 6 /E7 Mrna expression could predict the risk of cervical cancer better

o Role bio markers can change the perspective screen and treating progresive lsil or hsil to diagnose treat

o even the equivocal cases of lsil in papsmear and colposcopy , can be diagnosed and timely treated

o P16 +ve/+-ki 67 in lsil - treated by ablative procedures like , leep, cryotherapy, laser.

o help in early detection of progressive lesions , SPECIALLY CIN- I WITH P-16 +



Already recommended in principal guidelines
To be developed (phase I or II)
Applied in research settings (phase III) *FDA approved, not included in guidelines

B. SECONDARY BIOMARKERS

1. TUMOR SUPRESSOR GENE AND PROTONOCOGENES

p53 -dysregulated in progressive lesion and E6/ p53 integration is an early event which abrogates cell function.

o topoisomerase iia(TOP 2a)

o minchromosome maintenance 2(MCM2)

PRO EX TM

Mcm 5 and mcm 7 are potential bio markers CDC6 AND HPV oncoprotein over expression is increased in high grade dysplasia

1. p16ink 4 is overexpressed&it is the diagnostic and prognostic marker in agus lsil

2. IMMUNOSTAIN OF p16 INK4a with K i-67(cin tec plus), is recently used.

3. NOTCTH 1 FAMILY PEOTEINS HIGHLY EXPRESSED IN CIN III ONWARDS

4. R-b protein deregulation in poorly differentiated carcinoma

5. Telomerase activation is an early event in

cervical carcinogenesis mostly corelate with the grade of lesion,hr high risk 16, 18 and clinical staging. Upregulated htr and htert subunits of telomerase have also been in cervical cancer

6. Ki 67 is a nuclear protein that is expressed in all active phases of cell cycle and its expression is used to determine the cell proliferation status . In cervical intraepithelial neoplasia it is increased in the upper layers.

The e- cadherin a key molecule for cell adhesion. The decrease in expression can be corelated with aggressive behaviour and progression ofcancer.

2. GENETIC MARKER: DNAMETHYLATION

CDH 1- CALCIUM DEPENDENT CELL ADHESION PROTEIN.

CDKN2A(CYCLIN DEPENDENT KINASE INHIBITOR2A)INHIBITS CDK4 KINASE; REGULATION OF CELL CYCLE CONTROL IN G1

MGMT(METHYLGUANINE DNA METHYL TRANSFERASE) DNA REPAIR.

TERT (telomerasereverse transcriptase)- addition of short repeats to chromosomeor telomeres.

PAX.

o THE ABOVE GENES SHOW A LOW METHYLATION(,20%)IN NORMAL AND INCREASED LEVELS (CIN2, CIN 3 HSIL)AND IN INVASIVE CANCER.

3. CHROMOSOMAL ABNORMALITIES

o DELETION IN (2q, 3 p.4p,5q, 6q 11 q 13q,18 q)

o AMPLIFICATION(1q, 3q 5P,8Q)

o GAIN in 3q is most important. One gene within this region is TERC that could serve an effective triage for hpv positive who have ascus or lsil

4. Potential serum marker

Squamous cell carcinoma antigen is an is marker for early detection.It is a independent prognostic marker

o It correlates with the stage

o It is elevated 24-53% in stage ib or iia

o 75-90% in advanced stages ii b onwards.

5. CELL-PROLIFERATIVE MARKERS

Ki 67 is a nuclear protein,that thedetermines the cell proliferation status . In cervical intraepithelial neoplasia it is increased in the upper layers.

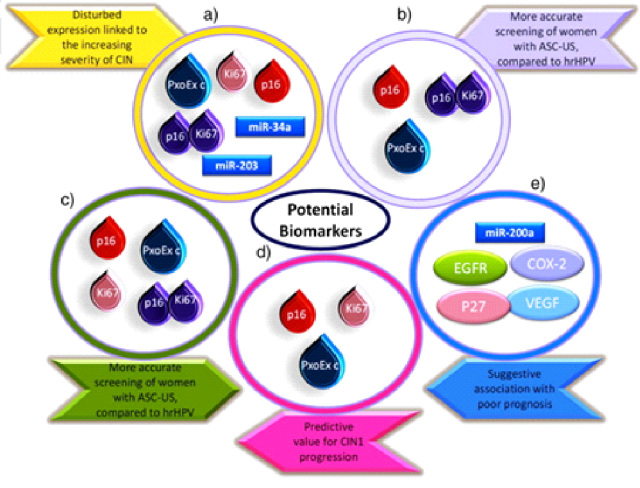
6. CELL ADHESION MATRIX PROTEIN

Cell adhesion matrix proteins cd44 - integral membrane protein in tumorogenesis. It is an epithelial stem cell marker used in novel approaches of diagnosis and treatment.

7. OTHER BIOMARKERS

o Ck 13 , mcm 5, cdc6, surviving, CEA and miRNA . mi-21 and mi r-126 are associated with cervical cancer

o they ueful in diagnosis and treatment of cervical cancer .



Prospective biomarkers will help to decide to reserve the treatment for women who are at a high risk of developing cancer rather than

treating HSil.

Biomarkers in Ovarian Cancer

1.Genetic Markers

2. Serum Tumor Markers .

Genetic markers of Epithelial Ovarian Tumor

- High grade serous : TP53, BRCA 1 & 2 , NFI , RBI CDK12 ,HRR genes.
- Low grade serous : BRAF , KRAS .NRAS , ERRB 2.
- Mucinous : KRAS , HER 2 Amplification.
- Clear cell : ARIDIA , PIK3CA, PTEN, CTNNB1, PPP2RI alpha.
- Endometroid : PIK3CA, PTEN, CTNNB1, PPP2RI alpha & MMRD.

Genetic markers of Non-Epithelial Ovarian Tumor (Sex Chord Stromal Tumors)

- Granulosa cell : FOX L2
- Sertoli-Leydig cell : DICER 1 .

Genetic markers of Non-Epithelial Ovarian Tumor (Germ cell Tumors)

Disgerminoma: KIT mutation, 12p amplification harbouring KRAS (80%).

Yolk Sac Tumor : PIK 3 CA /AKT1 mutation, 12p amplification harbouring KRAS (60%).

Mixed Germ Cell Tumor : 12p amplification harbouring KRAS (40%).

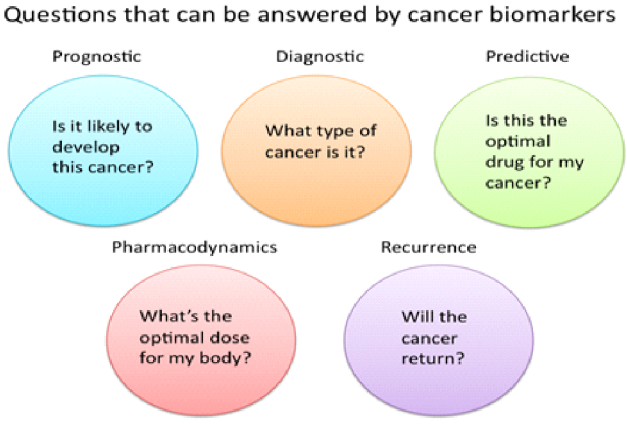
Genetic markers of Small Cell CancerOvary

SCCO - hypercalcaemic type : SMARC A mutation in 90% .

Serum Tumor Markers of Ovarian Cancer.

1. CA-125 : Serous , endometroid , clearcell
2. CEA : Mucinous
3. CA 19-9 :Mucinous
4. AFP : Yolk Sac Tumor
5. LDH : Disgerminoma
6. HCG :Nongestational Choriocarcinoma.
7. Inhibin A&B : Granulosa Cell Tumor

Thus Biomarkers play a very crucial role in the life of cancers of the female reproductive tract. Exclusively validated Biomarkers can be used in diagnosing, screening, tailoring treatment and follow-up of treated patients. They can be wisely used to predict the prognosis of the disease. In order to improve the development of biomarkers, Cancer Research UK ,has developed a road-mapfor it's proper use. NCRI, NCI and EORTC have created a working group to examine the risks and challenges of incorporating biomarkers into clinical trials. And finally;



Abbreviations used :

BRCA 1&2 -Breast Cancer Gene ,

MMRD - Mismatch Repair Deficiency ,

CA -125 - Cancer Antigen 125 ,

CEA - Carcinoembryonic Antigen ,

AFP - Alpha Fetoprotein, LDH - Lactate Dehydrogenase, HCG- Human Chorionic Gonadotrophin, EGFR - Epithelial growth factor receptor, VEGF-Vasculo-Endothelial Growth Factor, PCR-Polymerase Chain Reaction, SCCO- Small Cell Cancer of Ovary.

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OVERVIEW OF CURRENT MANAGEMENT OF DISORDERS OF HUMAN REPRODUCTION

Dr Sanjay Swain, Dr Tushar Jyoti Kar

Reproductive system disease is defined as any of the diseases and disorders that affect the human reproductive system. They include genetic or congenital abnormalities, abnormal hormone production by the ovaries or the testes or by other endocrine glands, such as the pituitary, thyroid, or adrenals, disorders of psychological origin, diseases due to infections, tumours and idiopathic disorders.

The academic contents of this silver jubilee year issue of AOGO Focus are (1) Genetic abnormalities, (2) Anatomical disorders, (3) Endocrinology disorders, (4) Surgical disorders, (5) Oncofertility, (6) Psychological disorders, (7) Disorders of Sexuality, (8) Asexual reproduction, (9) Role of Oncobiomarkers in management of disorders of human reproduction and (10) an Overview of current managements of Disorders of human reproduction. For detailed discussion of diseases and disorders affecting Human reproduction the respective chapters on the subject dealt in this issue may be referred. This one is to deal with some of the aspects of theme subjects not covered by the other contributors of this issue.

Genetic and congenital abnormalities:

In the male:

Congenital anomalies of the prostate gland and seminal vesicles are rare; they consist of absence, hypoplasia, or the presence of fluid- or semisolid-filled sacs, called cysts. Cysts of the prostatic utricle are often found in association with advanced stages of hypospadias and pseudohermaphroditism, a condition in which sex glands are present but bodily appearance is ambiguous as to sex; i.e., the secondary sexual characteristics are underdeveloped. Cysts may also cause urinary obstructive symptoms through local pressure on the bladder neck.

Severe anomalies of the penis are rare and are generally associated with urinary or other systemic defects that are incompatible with life. Anomalies are those of absence, transposition, torsion, and duplication of the penis. An abnormally large penis frequently is present in males with precocious puberty, dwarfism, an overactive pituitary, or adrenal tumours. A small penis is seen in infantilism and in underdevelopment of the genitals, or under secretion of the pituitary or pineal gland, and failure of development of the corpora cavernosa.

The only anomaly of the foreskin is congenital phimosis, characterized by a contracture of the foreskin, or prepuce, which prevents its retraction over the glans; the preputial opening may impede the flow of urine treated by circumcision.

There is a considerable variety of urethral anomalies. Stenosis of the external meatus is the most common, but congenital stricture of the urethra occasionally occurs at other points. Valves (or flaps) across the anterior or posterior part of the urethra may cause congenital urethral obstruction in males. Posterior urethral valves are more common than anterior valves and consist of deep folds of mucous membrane, often paper-thin and usually attached at one end to the verumontanum, a small prominence

in the back wall of the part of the urethra that is surrounded by the prostate gland. If too tight, the valves may obstruct the urethra and damage the kidneys.

Various defects are associated with incomplete closure of the urethra. One of the most common is hypospadias, in which the ventral side of the urethral canal is open for a distance at its outer end. Frequently the meatus is narrowed, and the penis also has a downward curvature beyond the meatus. The posterior part of the urethra is never involved; therefore, the muscle that closes the urethra functions normally, and urinary control exists. Although the condition occurs in both sexes, it is seen predominantly in the male. There is a high incidence of partial or complete failure of the testes to decent to scrotum resulting in cryptorchidism and of small external and internal genitalia. Epispadias, an opening in the dorsal side of the penis, is considerably less common than hypospadias. Dorsal curvature may also be present, but the disabling aspect is that the defect usually extends through the urinary sphincter and causes urinary incontinence. Other less common urethral anomalies include complete absence of the urethra, double urethra, urethra fistula , urethrorectal fistula and urethral diverticulum . Most of the above conditions are correctable by surgery.

Anorchidism (absence of one or both testes) is rare; it may be associated with the absence of various other structures of the spermatic tract. Generally, if one testis is absent, the other is found to be within the abdomen rather than in the scrotum. Congenitally small testes may be a primary disorder or may occur because of under activity of the pituitary. In both disorders, there is a lack of development of secondary sexual characteristics and some deficiency in libido and potency. Supernumerary testicles are extremely rare; when present, one or more of the supernumerary testicles usually shows some disorder such as torsion of the spermatic cord. Synorchidism, the fusion of the two testicles into one mass, may occur within the scrotum or in the abdomen. Cryptorchidism, the most common anomaly of the spermatic tract, is the failure of one or both of the testes to descend spontaneously into the scrotum; hormonal treatment may be useful in correcting the condition, but usually surgery is necessary for correction.

In the female:

The female external genitalia are less complex than those of the male but have anomalies that can at times severely interfere with the functioning of the female urogenital tract. The clitoris, an erectile structure that corresponds to the penis, except that it does not contain the urethra, may be absent but in other cases may be enlarged due to either a congenital or hormonal causes. Fusion of the labia minora as midline "sealing together" ;with usually a minute unfused area is left just below the clitoris, through which urine and menstrual fluid can flow. The chief difficulty with this anomaly is concerned with obstruction to the flow of urine and associated urinary tract infection. An imperforate hymen causes distension of the uterus and vagina with fluid other than blood before puberty and with blood after puberty (the two conditions are called hydrometrocolpos and hematocolpometra, respectively). The distended vagina compresses the urethra enough to interfere with urination and commonly may even cause complete retention of urine in the bladder and distension of the entire upper urinary tract. Fusion of the urethra and the hymen is characterized by a dense hymenal ring and a stenosed urethral opening. The consequent urinary obstruction commonly results in persistent urinary

infection. Most of the conditions are readily treated by surgery.

Anomalies of the vagina and uterus consist of complete absence, incomplete development, and duplication. The female urethra may have a congenitally narrow meatus; it may be distended; it may have an abnormal pouch, or diverticulum, in its wall; or it may open abnormally into the vagina. Hypospadias may occur in the female but is far less common than in the male. Epispadias is also present in the female. Reconstructive surgery is the only method of treatment. One of the rarest and most severe of the urogenital-tract anomalies, called urogenital cloaca, consists of congenital intercommunication between the rectum and the urinary bladder and vagina or between the rectum and the urethra and vagina.

Intersexuality:

Intersexuality (having both male and female characteristics) may be noticeable at birth or may become apparent after puberty. Intersexuality noticeable at birth may be classified as female or male pseudohermaphroditism or true hermaphroditism. Female pseudohermaphroditism, or female intersex, may be of adrenal or non-adrenal type. The adrenal type develops because of an inborn error in the metabolism of the adrenal hormone cortisol that leads to an increased secretion of corticotrophin (ACTH) and consequent excessive secretion of androgens. A newborn female with this condition is a chromosomal female and resembles a normal female, but an excess of male hormone has a masculinising effect on the external genitalia; the vagina tends to be connected to the urethra and the clitoris is enlarged, as are the labia (the labia majora are corresponding to the scrotum in the male). Effective treatment can be achieved by administration of adrenal hormones (e.g., cortisone, hydrocortisone), which suppress the pituitary so that its stimulus to adrenal production of androgenic hormones is minimized. The nonadrenal type of intersex is seen in infants whose mothers have been administered synthetic androgens or progestational compounds during pregnancy. Rarely, the condition is associated with the presence in the mother of a tumour of the ovary or adrenal gland. The newborn infant is a female with varying degrees of ambiguous genitalia; no treatment is necessary, and normal female development occurs at puberty.

Male pseudohermaphrodites are males with varying deficiencies of internal and external virilisation. Most commonly, the male intersex has a markedly hypospadiac penis, undescended testes, a cleft scrotum, and an enlarged prostatic utricle; a complete uterus and fallopian tubes may be found, with the vagina opening into the posterior wall of the urethra - pseudohermaphrodites without ovaries.

True hermaphrodites have recognizable ovarian and testicular tissue. A uterus is always present, but the internal genitalia otherwise vary greatly, often including both male and female structures. The external genitalia are usually ambiguous, and a sizable phallus is present; therefore, most of these children are raised as males. At puberty, over 80 percent of them develop enlarged breasts, and approximately half menstruate. Most hermaphrodites are chromatin positive-that is, they have, within and near the periphery of the nuclei of their cells, a substance, chromatin, that is normally found in the cells of females but not in those of males-and over half have a characteristically female set of chromosomes in their peripheral blood cells.

Surgical and hormonal therapy directed at

producing either a male or a female configuration of the body is based on the existing physical and psychological findings. Treatment also depends upon the age at which the diagnosis is made.

Klinefelter syndrome, Turner syndrome, and testicular feminization are intersexuality syndromes that become apparent prior to or after puberty. Klinefelter syndrome is a genetic disorder of males who have an extra sex chromosome (XXY) and subsequently are usually infertile, have small testes, and have enlarged breasts at the time of puberty (gynecomastia). Males with this syndrome have an increased risk of various autoimmune disorders such as diabetes mellitus and lupus.

Turner syndrome is a condition of females who, in the classic form, carry only a single X chromosome (XO). Characteristically, such persons are short, do not menstruate, and have a deficiency of estrogen; there is a distinctive cluster of congenital anomalies attached to this syndrome.

Testicular feminization, or androgen insensitivity syndrome, is caused by genetic mutations on the X chromosome that cause a male to be resistant to the action of androgens . Affected persons seem to be normally developed females but have a chromosomal sex that is that of the normal male. The gonads are well-developed testes, and evidence indicates that there is a normal production of testosterone, but there is cellular resistance to the action of this hormone, and therefore the affected person becomes female in appearance. Because these gonads are apt to form malignant tumours, they are usually removed surgically. Female sexual characteristics are then maintained by the administration of estrogenic hormones.

Functional genital disorders Affecting both male and female systems:

Delayed puberty:

The term delayed puberty may be a misnomer, because puberty delayed beyond age 19 is in fact a permanent failure of sexual development because of an abnormally low secretion by the pituitary gland of gonadotropic hormone, the hormone that stimulates growth and activity of the sex glands; this condition is called hypogonadotropic eunuchoidism. The term delayed puberty is usually applied to boys who develop more slowly than the average but who still eventually undergo full sexual development. Only in retrospect i.e., after the affected person reaches the age of 20 can one clearly differentiate these cases from the classic or incomplete forms of hypogonadotropic eunuchoidism. If there are social and psychological problems related to the sexual underdevelopment, therapy may consist of a course of chorionic gonadotropin, a hormone produced by the placenta and harvested from the urine of pregnant women. If puberty is merely delayed, it will usually progress normally after this treatment. If it fails to progress, the person does not have delayed puberty but rather has hypogonadotropic eunuchoidism.

Precocious puberty:

In healthy girls living in a temperate climate, the earliest sign of puberty (the Thelarche and Pubarche) has traditionally been considered to occur at a mean age of 10.6 years (standard deviation of 1.2 years). In boys, testicular growth is considered to begin at a mean age of 11.8, with a standard deviation of one year. True precocious puberty is a condition in which normal pituitary-gonadal function is activated at an abnormally early age. "Abnormally early" has traditionally been defined as younger than 9 years in boys and younger than

8 years in girls, though studies undertaken since the 1990s indicate that the normal onset of puberty may be occurring at a younger age in girls in developed countries and that therefore the age of precocious puberty for girls may actually be as low as 6 or 7. Pseudoprecocious puberty includes development of secondary sexual characteristics but not production of spermatozoa or ova; it may involve virilization in the female or feminization in the male.

The causes of true precocious puberty include brain lesions and hypothyroidism; the largest proportion of cases is of unknown cause. Precocious pseudopuberty in females may be caused by ovarian tumours or cysts, a tumour of the adrenal cortex and congenital adrenal hyperplasia. In males the causes include congenital adrenal hyperplasia, tumour of the adrenal cortex, tumour involving the Leydig cells of the testes, and teratoma (a tumour containing numerous types of tissue; here it includes adrenal-cortical tissue).

Infertility:

At least 10 percent of couples experience infertility, and deficiencies of sperm production in the male are the causal factor in about one-third of all cases. The common causes of male infertility are deficiencies in maturation of sperm; orchitis (often resulting from mumps), with destruction of the testes; obstruction of the passageways for sperm; abnormally low thyroid or high adrenal secretion; varicocele of the spermatic cord; or formation of antibodies to sperm by the male or the female. The most important step in the evaluation of male infertility is examination of the semen.

Infertility in the female is related to the faulty production of ova or to interferences in their union with spermatozoa. Disordered ovulation is responsible for approximately 25 percent of female infertility problems; anovulation and oligoovulation are among the most common disorders. Other common causes of infertility are blockages and scarring of the fallopian tubes, which can result from pelvic inflammatory disease (PID), uterine fibroids, or endometriosis. The sperm normally enter the uterus through the cervix and, from the uterus, move into a fallopian tube, where fertilization of an ovum takes place. During the few days prior to ovulation the glands within the cervix normally secrete thin, watery mucus that is beneficial to sperm survival and migration. Various factors, such as infection or estrogen deficiency, may decrease the quality of the mucus. Congenital anomalies of the reproductive organs may also cause infertility. Vaginal causes are usually uncommon, but obstruction may be due to an imperforated hymen or may be functional and arise from enlargement and contraction of the levator ani muscles supporting the pelvic organs, with openings for the anus, urethra and the vagina. Thyroid, pituitary, adrenal, or ovarian disease may interfere with ovulation - like the presence of large numbers of cysts in the ovaries - the condition previously called as Stein-Leventhal syndrome and currently it's known as Polycystic ovary disease (PCOD) or polycystic ovary syndrome(PCOS)). Finally, emotional factors may play a role in causing infertility. Treatment consists of the use of various hormones, surgical correction of tubal blockage, and psychotherapy.

Affecting the female system:

Abnormalities of menstrual function include painful menstruation, or dysmenorrhea; menorrhagia; irregular bleeding, or metrorrhagia; absence of menstruation, called amenorrhea; and dysfunctional/abnormal uterine bleeding. In addition, many women experience premenstrual syndrome. A few

women have transient abdominal discomfort at the time of ovulation (Mittelschmerz) because of slight bleeding from the follicle into the peritoneal cavity; oral contraceptives will remedy the condition by suppression of ovulation, or the discomfort can be treated with pain medications such as ibuprofen or naproxen (NSAID).

Cessation of periods at menopause has been established but before the normal the menopause the cessation of period is usually the result of some general illness, emotional stress, or mental disorder. It may also be due to disease of the endocrine system, not only of the pituitary gland but of other endocrine glands as well. Secondary amenorrhea results if the ovaries are removed or are irradiated but is unlikely to be caused by ovarian disease, as both ovaries would have to be damaged to stop all functions.

Affecting the male system:

Impotence :

Impotence is inability of the male to have satisfactory sexual intercourse and varies in form from the inability to gain an erection to weak erections, premature ejaculation, or loss of normal sensation with ejaculation. It may be caused by subnormal functioning of the testes, by arteriosclerosis of the arteries, by diabetes, by psychological factors, or by a disease of the nervous system. Certain medications prescribed for the treatment of peptic ulcer, hypertension, or psychiatric illness may adversely affect sexual ability. Therapy includes drug therapy (PDE-5 inhibitors such as Viagra), administration of hormones, or psychotherapy.

Priapism:

Priapism is prolonged penile erection that is painful and unassociated with sexual stimulation. The blood in the spaces of the corpora cavernosa becomes sludge like and may remain for hours or even days. About 25 percent of the cases are associated with leukaemia, sickle cell anemia, metastatic carcinoma, or diseases of the nervous system, but in the majority of cases it is idiopathic. There have been many forms of treatment, but drug therapy is effective in most cases. Regardless of treatment, impotence is common after an episode of priapism and even more common after repeated episodes of priapism.

Sexually transmitted diseases:

Sexually transmitted diseases (STDs), also called venereal diseases, are usually contracted during sexual intercourse with an infected partner. The principal disorders commonly transmitted in this manner include HIV & AIDS, syphilis, gonorrhea, chlamydia, and genital herpes.

Other infections affecting the reproductive system:

Puerperal infection:

A common cause of death during childbirth before the widespread use of modern sanitary practices and antibiotics, puerperal infections occur when bacteria, usually Streptococcus, invade wounds in the birth canal. The infection may cause abscess formation and can involve all of the genital organs and adjacent blood vessels, reproductive structures, and other abdominal tissues. Treatment consists of antibiotics, supportive therapy, and occasionally surgical drainage of abscesses.

Tuberculosis:

Primary tuberculosis of the reproductive system is rare and is usually brought from elsewhere in the body through the bloodstream. Nodular or pustular lesions on the penis or scrotum of men or the vulva of women, resembling the gumma (nodules) of tertiary syphilis, may appear one week after tubercular

infection. The nodules can become ulcerated, resembling the primary chancre of syphilis. Tubercular abscesses can also develop in most of the internal reproductive organs. Treatment consists of administration of anti-tuberculosis antibiotics. As the incidence of tuberculosis has declined in the developed countries, tuberculosis of the reproductive system has become exceedingly rare.

Inflammatory conditions:

Balanitis, or inflammation of the glans penis, and posthitis, or infection of the prepuce, result from the retention of secretions and bacteria beneath the foreskin and can be prevented with proper hygiene. Balanitis can also develop as a complication of certain sexually transmitted diseases. Acute prostatitis, inflammation of the prostate gland, may be caused by any of a variety of microorganisms, including those which cause sexually transmitted diseases; chronic prostatitis, the most common reproductive system infection in men older than 50, often follows the acute infection. Epididymitis can result in sterility. All of these are nonspecific infections that must be treated with antibiotics appropriate for the causative organisms.

In women, other infections of the reproductive system include bartholinitis, and vaginitis, generalized inflammation of the vagina caused by various yeasts, bacteria, or other irritants. Bacterial vaginosis, a type of bacterial infection, occurs as a result of changes in the balance of bacteria in the vagina. The most common symptoms of such ailments are vaginal discomfort, vaginal discharge, and itching and pain during urination or intercourse. Again, treatment of these conditions depends largely on the causative organism.

Structural changes of unknown causes:

In the female:

Endometriosis:

Endometriosis is a disease occurring only during a woman's menstrual life. This may occur in the uterus or elsewhere. The most common location of the implants of endometrial tissue are the ovaries; other areas and organs affected are the uterus, the ligaments supporting the pelvic organs, the rectovaginal septum , the sigmoid colon , the lower genital tract, and the peritoneum lining the pelvis. The condition may cause infertility. Treatment is with pain medications, hormone therapy, surgery, or a combination of these approaches.

In the male:

Benign prostatic hyperplasia:

Benign prostatic hyperplasia, an overgrowth of normal glandular and muscular elements of the prostate gland, arises in the immediate vicinity of the urethra and is the most frequent cause of urinary obstruction. The enlarged prostate usually causes symptoms after the age of 40. If undetected, the obstruction may cause bladder and kidney damage. The diagnosis is made by rectal examination or ultrasound, intravenous pyelogram (IVP), and cystoscopy. Treatment is by surgical removal of the excess tissue. The prognosis is good if detection is early and treatment occurs before the kidneys are damaged.

Tumours:

In the male:

Tumours of the external genitalia:

Tumours of the penis are almost all of epithelial origin and usually involve the prepuce or glans. Penile cancer is rarely found in men who have been circumcised during infancy. The growth arises on the glans or inner surfaces of the prepuce, and metastases occur through lymph

vessels that travel from the inguinal. The diagnosis is made by examination of a biopsy of the lesion. Treatment for small lesions consists of surgical removal of a part of the penis, chemotherapy, or radiation, while spread to inguinal nodes may be treated by removal of the node. The prognosis is good if the tumour is small and there has been no metastasis.

Tumours of the scrotal skin are rare; most are thought to arise from occupational exposure to various carcinogens, such as coal soot. Primary tumours of the epididymis are also uncommon, and most are benign.

Testicular cancer:

Testicular tumours are usually malignant; the peak incidence is between the ages of 15 and 35 years. This type of cancer accounts for about 1 percent of all malignant growths in men. The great majority of testicular tumours (greater than 90 percent) are of types that do not reproduce cells resembling those of the tissue of origin. The major route of metastases for these types of tumours is via the lymphatic system. The lymph nodes in the groin and the mediastinum are most commonly involved, but the lungs and liver are also frequent sites of tumour spread. The remaining 10 percent of the testicular tumours, which usually resemble the cells from which they arise, include the hormone-secreting tumours. In general, these tumours have been described in all age groups, are usually benign, and frequently arise in individuals with poorly developed or undescended testes (cryptorchidism).

The most common symptom first observed in all groups is painless enlargement of the testis. If, after careful examination, biopsy, or ultrasound, a tumour cannot be ruled out, the testicle may be removed for microscopic examination. Further treatment may consist of radiation or chemotherapy.

Prostate cancer:

Prostate cancer is rare before the age of 50 but increases in frequency every decade thereafter. It is the third most common cancer in males, second only to lung and stomach cancer. Like most tumours, prostate cancer has various causes, but it is thought to be influenced by the male sex hormone androgen. The progress of the cancer is so slow that, by the time it produces symptoms of urinary obstruction or sexual dysfunction, metastasis has occurred in many cases, most frequently to the spine, the pelvic bones, or the upper portions of the thigh bones. The diagnosis is made by rectal examination or transrectal ultrasound (TRUS). Tests that detect elevated levels of prostate-specific antigen (PSA) in the blood are also used to screen tumours of the prostate. If preliminary tests suggest prostate cancer, a biopsy is performed to confirm the diagnosis. If the tumour is discovered before it has extended beyond the prostate, the gland may be surgically removed. If spread has occurred, treatment may include radiation, hormone therapy, chemotherapy, or a combination of all of these approaches.

In the female:

Vulvar cancer:

Primary carcinoma of the vulva usually occurs in women over 50 and usually arises from the labia majora or labia minora. Most patients first notice a lump on the vulva or perineum; the diagnosis is made by examination of a specimen of tissues. Treatment consists of radiation, chemotherapy, or surgery.

Cervical cancer:

The causes of cervical cancer vary, but most cases are caused by complications associated with human papillomavirus (HPV) infection. The average age of occurrence for cancer of the cervix is age 45. Symptoms include vaginal bleeding or other discharge, pelvic pain, or dysparunia and post coital bleeding. The initial diagnosis is made by a PAP smear. The final diagnosis rests on histopathological examination of specimens of tissue from the cervix, obtained from a necked eye biopsy or colposcopy guided biopsy. Treatment is usually radiation, chemotherapy, or surgery, or combination of all, depending on the stage and size of the lesion. The prospect of five-year survival is quite high if the cancer has not spread beyond the cervix.

Uterine fibroids:

Uterine fibroids, also called uterine leiomyomata, are benign tumours that originate from the smooth muscle walls of the uterus and may be single but usually occur in clusters. They are most common in women of

African descent and in women who have not borne children, with highest incidence in women aged 30-45 years. New tumours rarely originate after menopause, and existing ones usually regress at that time but do not disappear. The symptoms are quite variable and depend largely on the location and size of the tumour; excessive menstrual bleeding is often caused by fibroids. The diagnosis is tentatively made by pelvic examination and confirmed by ultrasound or a by hysteroscopy. Small asymptomatic fibroids need not be treated; the larger ones may be treated by hormone therapy, by myomectomy, or by total or partial hysterectomy.

Uterine and ovarian cancer:

Cancer of endometrium is the most common cancer of the female genital tract. The risk factors of uterine cancer stem from an imbalance in which the levels of the hormone estrogen in the uterus are regularly higher than the levels of progesterone. The peak incidence is in the mid-50s, and there is also a strikingly high incidence in women who have not borne children. The chief symptom of the cancer is postmenopausal uterine bleeding or discharge. An endometrial tissue biopsy must be performed in order to diagnose uterine cancer. The treatment is primarily surgical but is often supplemented with chemotherapy, radiation, or hormone therapy. The survival rate from this disease is relatively good if the tumour is confined to the uterine body.

The treatment of ovarian cancer consists of surgery, radiation, chemotherapy, or a combination of all these approaches. The prognosis is variable and depends on the type of tumour as well as the extent of metastasis.

Conclusion:

This is not an exhaustive list the current management of disorders of human reproduction as the very subject is a dynamic issue and ever changing one from the very inception of mankind. One has to keep the mind and senses alert to update with upcoming developments in this field to keep him/her abreast with the most recent modalities of managements of the diseases of human reproduction to cater the best possible professional services.

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