UNIT 21 INFERTILITY

Structure

21.0 OBJECTIVES

After reading the unit, you will be able to:

- take a good history and investigate both partners;
- diagnose the factor/factors responsible for infertility;
- rectify these factors as far as possible by giving appropriate treatment possible at the first care level;
- counsel the patients and offer psychological support during their emotionally stressful period;
- inform the patients who have not responded to your treatment about the further treatments available; and
- refer the patients for advanced investigations and management to centres where assisted reproduction facility is available or refer them to social workers if they have opted for adoption.

21.1 INTRODUCTION

In this unit you will be informed about the factors responsible for infertility, the relevant history and investigations required for the assessment of these factors in both partners and the treatment which can be offered at the first care level. You will also be informed about

the other advanced techniques available at the specialized centres for assisted reproduction in couples where the initial treatment has not been successful.

While dealing with maternal and child health problems in a community, you will also have the responsibility of looking after the reproductive health during the interconceptional period. While you are striving to promote the idea of planned pregnancy, you have to help if there is any problem of conception when it is planned. **Infertility** is defined as failure to conceive after one year of unprotected coitus. However this period is not rigid and you should not turn away the young couple if they come for help before completion of one year. You must understand the psychological and emotional stress they are under. One out of every ten couples have some fertility problem. Recently there has been increase in the incidence of infertility. It could be because of increase in pelvic inflammatory disease following abortions, intrauterine contraceptive device, and also sexually transmitted diseases. It could also be due to delay in age of marriage and postponement of conception by oral pills thus passing the age of optimal fertility.

There have been great advances in the understanding of reproductive physiology and the technology which have enabled treatment for many infertility patients who previously had been declared untreatable. Reproductive medicine is now a vibrant and dynamic field.

The first visit of the couple is better utilized to explain the physiology of reproduction, take a detail history and do a complete physical examination.

21.2 ETIOLOGICAL FACTORS

Before you read any further, you must revise the anatomy and physiology of you read any further, you must revise the anatomy and physiology of reproductive system in both males and females so that you understand the problem which might be responsible for infertility.

You will recapitulate that the males must have normal spermatogenesis, an intact and patent vas deferens and the ability to deposit the sperms in the upper part of vagina. Male factors responsible for infertility could be either abnormal spermatogenesis or block of the vas or inability to have normal sex or any local infection.

The female must have a normal ovulation, a patent and normally functioning fallopian tube which picks up the ovum and propels it towards the uterus, normally developed endometrium which allows normal implantation of fertilized ovum and a normal cervical mucus which is receptive to sperms.

In females the problem could be:

Ovarian: Anovulation which may result from disturbance of hypothalamo-pituitary-ovarian axis and is also influenced by other systemic disorders specially thyroid and adrenal dysfunction, or due to ovarian pathology like polycystic disease of ovary, ovarian dysgenesis and male hormone producing tumours of ovary.

Tubal: Tubal blocks or kinks occur due to pelvic inflammatory disease (non-specific), tuberculosis or chlamydia or gonococcal infection. Kinks may also occur due to endometriosis, thus deranging the normal function of tubes.

Uterine: It may be fibromyoma uterus, adenomyosis, or Ashermanis syndrome. In Ashermanis syndrome the endometrium is destroyed either due to tubercular endometritis or after drastic curettage specially for incomplete abortion. Adhesions or synechia occur in the cavity.

Cervical: Either the cervical mucus may be hostile to the sperms making them immobile or the cervix may be stenosed or abnormally placed so that the sperms do not reach the uterine cavity.

Psychosexual: Normal sex may be inhibited thus preventing pregnancy.

Check Your Progress 1

1) Define infertility.

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2) What are the etiological factors of infertility?

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21.3 HISTORY AND EXAMINATION IN BOTH PARTNERS

21.3.1 History of Both Partners

A detailed history is taken at the first visit. It is preferable if you interview both partners together and also separately, so that each partner feels free to express and confide in you. The main aim of this interview is to try and assess the reasons for infertility. You should try and understand their emotional and psychological state, make them comfortable and encourage them to open up about their problem. The relationship built during this interview is extremely rewarding in persuing the costly time consuming and psychologically stressful investigations.

It is essential that you inquire about the duration of infertility, history of prior pregnancy if any and the investigations and treatment undertaken so far and whether they have any knowledge about the fertile period.

Infertility in males is not age related. Initially the husband's reaction may be negative and hostile. You must start with the inquiry about his occupation and medical or surgical conditions specially history of mumps, diabetes, hypertension or STDs, history of surgery for undescended testes, hernia, vericocoele or bladder problem or any other pelvic surgery. You should ask about the sexual history, potency, timing and frequency of intercourse, ejaculation and use of lubricants.

Inquire whether he is on any drugs like antihypertensives, nitroturantoin, sulphasalazine, cimetedine, anabolic steroids or chemotherapeutic agents or has had radiation.

Information of personal habits like alcohol or sauna bath is also important, it may affect spermatogenesis.

Infertile women usually have a feeling of guilt as they are the ones who are usually held responsible for not having a child by the society and the relatives. The age of the woman has bearing on childbearing. Reproductive capacity decreases with age specially after the age of 35 yrs.

It is not uncommon for rural women to seek treatment at a young age because they marry early and are under pressure to prove their fertility. You may use this opportunity to look for any adolescent problem and advise the couple to plan pregnancy at a later date.

You inquire about her menstrual history specially the duration, frequency and associated symptoms which may suggest ovulation like midcycle pain, discharge and spotting, premenstrual bloating of abdomen and breast pain, spasmodic dysmenorrhoea (refer Unit 19 of this block for details). Note down the date of last menstrual period.

Obstetric history: Ask about the outcome of previous pregnancy, whether she had febrile illness following it, specially if it was instrumental delivery or abortion. Whether she had any acute illness during pregnancy which could result in intrauterine death. Any history of diabetes or hypertension during pregnancy, or vaginal bleeding or post partum haemorrhage.

You must also take medical and surgical history of the woman.

— Medical history of thyroid disorders, diabetes, hypertension, tuberculosis, pelvic inflammatory disease, or sexually transmitted disease or any vaginal discharge.

— Surgical history of pelvic or abdominal procedures which might have led to pelvic inflammatory diseases or cervical abnormality.

— Psychosexual history or any marital problem.

21.3.2 Clinical Examination of Both Partners

Male Partner

A thorough examination is done to exclude stigmas of androgen deficiency and other endocrinopathies. Record height, weight and blood pressure. Look for gynaecomastia, anosmia or visual field disturbance.

Genital examination is very important and is not to be neglected. Note penile size, curvature, phimosis, location of urethral meatus as well as the size and consistancy of testes and epididymis.

Female Partner

Do general physical examination. Look for anaemia, lymphadenopathy, thyroid enlargement, abnormal or excessive hair distribution and B.P. Examine heart and lungs to rule out cardiac disease and pulmonary tuberculosis.

Breast examination is very important. You must examine her for nipple discharge. Galactorrhoea if present can be responsible for anovulation. Do abdominal examination to rule out any palpable lumps in the lower abdomen or enlargement of any viscera.

Pelvic examination is very important. Inspect vulva to note any enlargement of clitoris, infection of Bartholin glands or any discharge at the introitus. Look for the condition of hymen. It is intact if the couple has not had intercourse.

Next do a speculum examination. Make a note if there is any sign of cervicitis or vaginitis or if there is any cervical erosion or if cervix is placed just behind symphysis pubes. Note the nature of cervical mucus.

Do a bimanual examination. Feel for the tightness of introitus, the mobility of cervix and uterus, size of the uterus or any palpable adenexal masses or enlarged ovaries.

Last of all note if deep pelvic examination is painful, if so do a pelvirectal examination to feel for any nodules in the pouch of Dauglas.

Check Your Progress 2

1) What are the important points which you must ask in history in both males and females?

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2) What special feature you note on examination in females?

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21.4 INVESTIGATIONS

After taking the detailed history and doing the detail physical examination you have some idea as to the problems probably existing in the couple. In most couples there are certain basic investigations which you have to start with. Your effort should be to start with simple investigations preferably non-invasive to begin with. You must explain to the couple your plan of action and the reasons why each investigation is done. You must reassure them that though it may take time there is a lot which can be done to help them achieve pregnancy specially with the help of the new technology of assisted reproduction.

21.4.1 Male Assessment

First investigation done is semen examination which is simple and non-invasive and gives you a fair idea whether the male partner is at fault. How to do semen examination is described in your practical module.

Collection of Semen: A semen sample is collected by masturbation after abstinence for 3 to 5 days. The entire ejaculate is collected in a clean, wide mouthed glass bottle and delivered to the laboratory within 1 to 2 hours. You must provide a room with privacy near the laboratory. You must discourage the collection of the semen in condom and collection by coitus interruptus because the first portion of the semen contains the highest concentration of sperms.

Physical Examination of Semen: It is a gel-like coagulum after ejaculation which liquifies in 30 minutes. Viscosity is normal when semen can be poured drop by drop for examination and indicates the presence of a fibrinogen like substance from the seminal vesicles and liquifying enzymes from the prostate.

Volume: The volume is measured with a pipette to determine the complete sample of 2 to 5 ml. Persistently low volume suggests spillage, improper collection and obstruction of ejaculatory duct, seminal vesicles or retrograde ejaculation. In case of poor volume, soon after the masturbation semen specimen is centrifuged at 3000 rpm for 10 minutes and the residue is suspended in Ringer lactate solution and examined for motile sperms.

Sperm Count and Concentration: Sperms are counted under a microscope (x 400) using a standard hemocytometer. The number of sperms in a fixed volume is calculated by correcting for the dilution factor. Motile sperm concentration is a better index of fertility than absolute counts. It takes into consideration count and motility.

Oligospermia: Oligospermia is when the sperm concentration is less than 10 million per ml.

Azoospermia: Azoospermia is when two samples of semen show no sperms.

Sperm morphology: To assess morphology of the sperm a semen smear is made on a slide, dried and stained with Giemsa stain. The morphology of the head, midpiece and tail are observed. Abnormal form's and immature forms increase acutely with viral and bacterial infections or with certain drugs. Increase in abnormal forms is associated with reduced fertility.

Sperm motility: Sperm motility is expressed as percentage of sperms moving in 10 high power fields. The degree of motility is rated from 1+ to 4+ within 2 hours of collection of the specimen. At this stage the sperm should be progressively forward motile indicating grade 4+ motility. Necrospermia denotes no motility of sperm. However, they need not be dead sperms. Reduced motility with reduced counts and increased abnormal forms are often seen with varicocoele. Other causes of poor motility are seminal infection and auto-antibodies. Sperm agglutination — head to head, tail to tail and head to tail — suggests antisperm antibodies in serum and semen. Sperm motility can be studied objectively by using computerized image analysis. This method can study sperm velocity and linearity of sperm progression and amplitude of lateral head displacement. This studies the functional potential of sperm for in vitro fertilization in couples with unexplained infertility. The presence of fructose in the sample denotes that the sample is seminal fluid.

However, you must remember that stress, infection and environment may affect spermatogenesis transiently. Thus only when repeated samples show oligospermia, you should refer the person for sperm function and endocrinological evaluation to specialized centre.

Sperm function can be done by sperm penetration test and the endocrine evaluation is done by serum FSH, LH and Testosterone estimations. Hormonal assays are specially done in men who have a history of delayed puberty, decreased libido, impotency and abnormal semen analysis. Azoospermia in the presence of normal gonadotrophin is suggestive of obstruction in the vas with normal spermatogenesis. Fructose test in semen or Testicular biopsy can be diagnostic.

Normal Values of Semen

Volume: 2-5 ml.

Liquifaction : Complete in 30 minutes.

Count : 20-250 million/ml.

Motility : > 60%

Morphology normal: > 60%

Mixed antibody reaction negative.

21.4.2 Female Assessment

You start with the simpler tests:

Cervical Factor Assessment

In about 5 to 10% of women cervical factor may be responsible for infertility. Cervical mucus is a mixture of secretion produced by the secretory cells of the endocervix, endometrium, tubes and follicular fluid cellular debris from the epithelium of the uterus and cervix and leucocytes.

It is viscous, has elasticity (espinnbarkeiti) to draw into thread and ferning which is crystallization of salts in mucus and water in oestrogenic phase. Biochemically it is glycoprotein of mucin type, made up of peptide and oligosaccharide side chains.

The secretion of cervical mucus is regulated by estrogen and progesterone and, therefore, shows cyclic variations. Sperm penetrability and survival is influenced by cyclic variation of cervical mucus. Preovulatory mucus is most receptive to sperm penetration.

Cervical mucus score: Preovulatory cervical mucus is profuse, thin, clear, acellular and alkaline. Mucus provides energy to the sperm and the milieu for capacitation. The cervix also serves as a reservoir in the crypts. Thus sperms can reach the ova a few hours before and after ovulation. WHO has designed a scoring system to evaluate cervical mucus objectively. Five important Properties of cervical mucus are taken into account viz., the amount, spienbarkeit, ferning, consistency and cellularity. Each of these is scored from 0 to 3, with a maximum total score of 15. A score of 15 indicates good cervical mucus and less than 10 is considered favourable and less than 5 is hostile to the sperm. Semen

analysis and examination of cervical mucus must be done before planning post coital test and sperm cervical mucus contact test.

You can do some simple tests which would test the cervical mucus as well as the sperms.

- Post coital test is also known as Simsi Huhner test. It is an office procedure, it is simple and you can do it in the early stage of infertility investigation.

Significance of PCT

- It evaluates the interaction of the sperm and cervical mucus in vivo.
- It assesses cervical hostility due to infection or possible immunological cause.
- It also assesses coital technique or major sexual problems.

Timing: It is planned close to the day of ovulation as determined by cervical mucus change or basal body temperature. The couple is advised abstinence from sexual intercourse for 2 days prior to test. The test is then performed within 4 to 8 hours after intercourse.

Technique: An unlubricated speculum is inserted into the vagina. A sample of mucus is aspirated from the cervix with syringe and examined immediately under a microscope at 200x and 400x (high power magnification).

Interpretration 10 sperms with grade III motility per high power field is considered normal.

Causes of Abnormal Post Coital Test

The most common cause for abnormal post coital test is improper timing.

Increased viscosity of mucus which is seen in the luteal phase defect or when patient is being treated with clomiphene citrate.

The presence of anti-sperm antibodies.

Amputation or deep conization of the cervix.

Cervical stenosis.

Endocervicitis.

Poor coital technique.

Vaginismus or dysparunia.

Hypospadias, impotence, retrograde ejaculation.

Oligospermia, asthenozoospermia.

Semen Cervical Mucus Contact Test

A drop of cervical mucus with a drop of semen is mixed on a slide and observed after 30 minutes. If more than 25% of the cells show jerking and shaking movements, the test is positive for presence of local immunological antibodies.

Sperm Penetration Test

A drop of semen is placed adjacent to a drop of ovulatory mucus on a slide and a coverslip is applied. A negative test is indicated by complete failure of penetration or immobilization of penetrated sperm. However it is non-specific as immobilization can occur with infection.

Endometrial Factor

Endometrial sampling must be done in all cases specially so if the woman has oligomenorrhoea, hypomenorrhoea or amenorrhoea or if the woman has adenexal mass. It is important that you rule out tubercular endometritis as pelvic tuberculosis is common in

our country. It is present in about 8-9% of infertile women. In women who have amenorrhoea, if no tissue is obtained, then you can give estrogen for 3 months and then repeat the endometrial biopsy. In women who have regular menstrual cycles it should be done in premenstrual phase so as to obtain adequate tissue for histopathological examination. The endometrium must be sent for histopathological examination and if facilities exist you should send the endometrium for AFB culture — Histopathology and culture together increase the detection rate of tuberculosis.

If tissue examination shows tuberculosis than other investigations are abandoned for the time being.

Endometrial biopsy is also useful for assessing the ovarian function. The details are given in the para for ovarian function assessment.

Tubal Factor Assessment

The fallopian tube is a link between the ovary and the uterus. It helps in ovum pick up, sperm transport, fertilization and transfer of the embryo to the uterine cavity for nidation. If there is nothing in history to suggest that the tubes may be blocked, you should initially give the patient the benefit of the doubt and investigate other factors before testing the tubal patency.

The commonest cause of tubal obstruction is pelvic inflammatory disease. In our country tubercular salpingitis is an important cause of tubal block. Other agents responsible are chlamydia, trachomatis; N. Gonorrhoeae and non-specific bacterial infections. Post abortal sepsis, pelvic surgery and endometriosis may lead to adhesions and prevent ovum pick up and impair ovum transport.

The tubal factor as a cause of infertility is on the rise because of the increasing incidence of sexually transmitted diseases and endometriosis.

Tubal Patency Tests

A number of methods have been mentioned to assess tubal patency. Of these you can do Rubinis test or tubal insufflation test which is considered obsolete in modern gynaecology but it can be done at primary health care centre. If you have the X-ray facility you can do hysterosalpingography (HSG). If the patient requires further evaluation you can refer her for laparoscopy to specialized center because while doing diagnostic laparoscopy, chromotubation for patency of tubes can and corrective operative intervention like adhesiolysis can be done at the same sitting.

In an active work up of an infertile woman, tubal assessment is finally done by laproscopy.

Hysterosalpingography is a procedure done in the X-ray department. It is done in the proliferative phase of the cycle after ruling out any genital infection. Ten ml. of radio-opaque water soluble dye is injected through the cervical canal by means of a Leech Wilkinson Cannula. Fluoroscopic screening is done to see the dye passing through the uterine cavity, fallopian tubes and into the peritoneal cavity.

Advantages: It can be done under sedation with minimal discomfort. Permits visualization of the uterus. There is a record of the tubal defect and hence an objective tubal assessment.

Disadvantages: a) False positive results if tubal spasm occurs causing abstruction to the flow of dye beyond cornua. b) It does not give any information about peritubal adhesions. c) It does not permit ovarian assessment.

Laparoscopy

With the advent of endoscopy, the assessment of female infertility is considered incomplete without laparoscopy. The double puncture technique gives a complete view of the pelvic organs. The procedure is done in the secretory phase of the cycle so as to enable to see evidence of ovulation and is sometimes combined with hysteroscopy to visualise the uterine cavity and the endometrium.

Advantages are external surface and fimbrial end of the fallopian tube are assessed; it can identify tubal adhesions, their location, extent and type. Endometriotic deposits, pelvic tuberculosis and polycystic ovaries can be diagnosed. It differentiates true tubal blockage from a patent tube bound to the ovary, the prognosis being better in the latter situation.

Ovarian Factor Assessment

It is important for you to assess whether there is any ovarian dysfunction, you will have some idea of the ovarian dysfunction by her menstrual history. Regular 28 day cycle with spasmodic dysmenorrhoea and mid cycle pain or spotting suggests ovulatory cycle whereas irregular cycles with menorrhagia, oligomenorrhoea are usually anovulatory. For detail causes and work up refer to Unit 19 of this block.

However there are certain simple tests which you can carry out at the primary health care level.

Cervical mucus study which was discussed earlier in this unit is a good clinical indicator. A score of 15 with a drop in mid cycle indicates ovulation.

Basal Body Temperature (BBT) Chart

You should explain to the woman that she must keep the thermometer next to her bed. She can use ordinary thermometer. As soon as she wakes up she must put the thermometer under her tongue for at least 2 minutes without doing any other physical activity at all and note her temperature and record it on the temperature chart. She must be told that there should be regular hours of sleep and if she remains awake at night or has febrile illness she must make a note. With the estradiol surge there is a drop in basal temperature. With the increase in progesterone after ovulation there is increase in the basal body temperature by 0.5-1 (degree) F. Drop in temperature followed by sustained rise till before the menstruation indicates ovulation and good corpus luteum function.

Endometrial biopsy in the premenstrual phase (2-3 days before periods), can be sent for histopathological examination. This biopsy can also be dated by pathologists. If the progesterone output after ovulation is inadequate, then the development of endometrium may not be adequate for implantation to occur. If the lag is of more than 2 days e.g. the endometrium has the maturity on the 26th day of the cycle instead of 23rd day of the cycle, then this may be a possible cause of infertility. Unfortunately though the test is simple, it is invasive, and cannot be repeated a number of times to evaluate whether the women ovulates occasionally or always. You must do endometrial biopsy at least once, it would also help to diagnose tubercular endometritis.

Ultrasound facility if available is more acceptable method of monitoring the ovulation as it is absolutely non-invasive and reasonably reliable. Ultrasound examination of ovaries daily from 9th day onwards till the follicle ruptures will pinpoint day of ovulation so that in case any intervention is required you can do it on that day.

Hormone Assay

Serum progesterone or urinary pregnanediol estimation can be done in premenstrual phase to indicate ovu1ation but the tests are cumbersome and not cost effective so even the best of laboratories do not utilize these as a routine test for ovulation.

The hormone assays usually done in the specialized centres are serum FSH, LH, Prolactin Oestrogen to decide the hormonal therapy.

Uterine and Pelvic Factor Assessment

Endometriosis: With the rising age for planning pregnancy, endometriosic has emerged as a cause of infertility amongst the urban higher socio-economic group of women. An infertile patient with progressive dysmenorrhea may be suspected of having endometriosis. Anovulation, abnormal prolactin secretion, luteal phase defect, prostaglandins release in peritoneal cavity and peritubal adhesions are all likely causes of infertility in endometriosis.

Diagnosis is made on symptomatology and associated adnexal lumps and nodules in the pouch of Douglas. For confirmation of endometriosis and also to exclude any uterine factor for infertility you have to refer the patient for laparoscopy and hysteroscopy to the specialized centres.

Check Your Progress 3

1) What are the tests for ovulation which you can carry out at primary health care level?

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2) What are the advantages and disadvantages of hystero-salpingogram?

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3) How do you do post coital test?

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4) Describe the proper method of semen collection.

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5) Which cases would you refer for hysteroscopy?

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21.5 MANAGEMENT OF INFERTILE COUPLE

Management of an infertile couple will depend upon the etiological factors detected. Sometimes the patient conceives during investigation and at times even before the investigation are begun. May be it is a psychological effect, sympathetic approach and

reassurance perhaps relieves the tension and anxiety, which triggers normal ovulation and normal function of the reproductive track.

To begin with you have to do a thorough clinical examination, semen examination and perhaps get a BBT chart maintained for at least 1 cycle and a post coital test. In case you find any evidence of infection at this state you must treat the couple for bacterial both aerobic and anaerobic and chlamydia-infection. The usual treatment for chlamydia-infection is long acting Tetracycline (Doxycycline) 100 mg twice daily for 3 weeks along with B-complex tablets. For anaerobic infection you must prescribe Metrogyl/Flagyl 400 mg three times a day on full stomach for 7 days. Some patients conceive after this anti-inflammatory treatment.

If you have had no success so far you should do a premenstrual endometrial biopsy 2-3 days before periods in regular cycles and first day of period in irregular cycles. If you suspect uterine factor you can send her for hysteroscopy which can be done at the same sitting as endometrial biopsy. Hysteroscopy if performed will show if there is Ashermans syndrome, endometrial polyp, submucus fibromyoma, uterine septum or bicornuate uterus. It will also show the status of the tubal opening. You must treat any pathology detected at this stage. In case your centre cannot treat it, you refer the patient to concerned specialists.

21.5.1 Treatment of Male Factors

Men with Azoospermia due to block in the vas should be referred to surgeon for surgical correction. For men with oligospermia it is worthwhile to remove known environmental factors. You must advise them to stop heavy smoking and reduce high alcohol intake. Low sperm count and poor motility may also be due to professional stress in addition to other causes enlisted before. Hence you should counsel the patient that he must avoid professional stress if possible, he must refrain from use of tight underwears and frequent local cold baths. He is advised to take proper nutrition and you must prescribe vitamins. These things may help. If you detect any infection, use appropriate antibiotics, sometimes treatment of infection suffices and conception occurs.

If his spennatogenesis is defective and his FSH/LH are low you can give Gonadotrophin replacement. It improves the sperm count. If you find that oligospermia and asthenospermia is idiopathic you give clomiphene citrate 25 mg daily for 3 months. In some cases testosterone tablets (Nuvir) or testosterone injections can be helpful. In low counts or if semen analysis is normal, but PCT shows scanty sperms you can do artificial insemination of husband semen.

For vericocoele and testes lying in the groin, refer the patient to the surgeon. Tying off of vericocoeles by high ligation, surgical removal of hydrocoek and orchidopexy will be beneficial. In cases with immunological problem advise them to use condom for 6 months, that helps to reduce antibodies. If this does not help, it is treated by giving special steroid therapy. In case you can not help as in Testicular atrophy, you can suggest donor semen insemination in woman. It should only be done if both partners agree.

21.5.2 Treatment of Female Factors

Management of Ovarian dysfunction: Availability of clomiphene citrate, human gonadotrophins, GnRH analogue and bromocryptine have revolutionized therapy for patients with anovulatory cycles.

The menstrual history and investigation of the patient will indicate the likely hood of the following type of ovulatory disorders:

a) primary amenorrhoea

b) secondary amenorrhoea

c) periods after 1-4 months — Even if she is ovulating, ovulation is completely unpredictable or she may not be ovulating. If you detect any thyroid or adrenal disorders, treat that first before you attempt correction of hypothalamo-pituitary-ovarian axis to induce ovulation. If you find hyperprolactenemia then start the

patient on bromocryptine, that it self in most women will cause ovulation and you will not have to give other ovulation induction drugs.

In women with amenorrhoea who respond to progesterone challange test indicating good oestrogenic effect on endometrium and cervical mucus chomiphene is the drug of choice.

In women with hypogonadotrophic hypogonadism, polycystic ovarian syndrome and in whom there is no response to clomiphene citrate it is better to use Gonodotrophin therapy, but before administering gonadotrophin therapy you must make sure that the husband's semen is normal and tubes are patent. Except for the ovarian failure for which there is no treatment all the other causes of ovulation disorders are treatable.

Clomiphene citrate is a nonsteroidal agent. It has oestrogenic and antioestrogenic effect and is useful in women with hypothalamic pituitary dysfunction who have normal gonadotrophin and prolactin levels. The dose of clomiphene is individualized depending on the response. To begin you start with 50 mg every day for 5 days and start it on any day between 3rd to 5th day of cycle. Ovulation is monitered by B.B.T. chart, cervical mucus study and serial ultrasound preferably using a vaginal probe. If there is no ovulation dose is gradually increased up to a maximum of 250 mg daily for 5 days but not more than 6 cycles should be given. Most women respond to 50 to 100 mg dose. If you do not get ovulation with the maximum dosage of clomiphene citrate but follicle shows maturation, or if the leutal phase remains inadequate, you prescribe hCG 5000-10,000 units 1/M when the follicle size is about 2 cm. in addition to clomiphene. Ovulation occurs at 5 to 13 days after the last tablet of clomiphene in 80-90% of women but pregnancy results in only 40-50%. There is 6-8% chances of multiple pregnancy.

Side effects are breast pain and rarely visual symptoms. (Clomiphene citrate due to its antieostrogenic effect on the cervical mucus may make it thick and viscous so as to make it unfavourable for sperm motility. If you observe this give Lynorel 0.01 mg every day from 2nd to 14th day of cycle.) It may cause vasomotor flushes, pelvic discomfort, nausea. Rarely it may cause ovarian hyperstimulation syndrome.

Ganadotrophins

Either human menopausal gonadotrophin (pergonal) or pure FSH (Metrodin) is given by intramuscular injection starting with 75 International units. Ovarian stimulation is monitored by serial ultrasound and serum oestradiol. The dose is variable. You must adjust it depending on the response. When the follicle size reaches to about 20 mm, patient is given Intramuscular injection of hCG 5000 to 10,000 I.U. Ovulation occurs about 36 hours later. If the serum oestradiol is above 1000 n mol then withold hCG as it would increase the risk of ovarian hyperstimulation and do not give any further therapy in this cycle. You can commence the treatment again in next cycle. Pregnancy rate varies from 50-60%, majority of pregnancies occurring in 6 months. It is an expensive therapy and needs careful monitoring. It is better that you refer the patient if possible to specialized centre.

Complication

Ovarian hyperstimulation — the severity is dose related and the patients with PCOD are ,more prone to it. Multiple gestations may occur. Incidence of twins and triplets is increased with induction of ovulation by gonadotrophins as much as about 25%. This leads to increased incidence of abortions.

FSH

In polycystic disease pure FSH if given has better results than a combination of Clomiphene/LH as mentioned above. The reason being that there is already a reversal of LH/FSH ratio, which is about 2 to 3.

GnRH Therapy

It is a very expensive treatment. It stimulates the pituitary function, releases FSH & LH and induces follicle development. GnRH analogue is used to first down regulate the pituitary gland and reduce LH (specially in women with PCOD). This is followed by FSH

& hCG administration as mentioned above. This method is specially used in institutions practising assisted reproduction.

Corpus Luteal Deficiency

You can get some indication of this dysfunction through BBT chart which is abnormal or by dating of endometrium which is done by histopathologists. The endometrial development lags behind by 2 or more days. For example if the biopsy is taken on 23rd day of the ovulatory cycle and the histopathology shows development corresponding to 19th day then it signifies corpus luteal deficiency.

Duphoston 10 mg twice daily from day 16th to 25th of cycle or 2nd injection of HCG 3000 I U to 5000 I U can be given 4 days after the 1st injection of hCG, if that had been used for induction of ovulation or else. Inj. hCG 5000 I U can be given 3 days after ovulation.

Cervical Factor

Thick cervical mucus is treated by giving low dose oestrogen (Ethynyl oestadiol 10 hgm from day 2 to 14th of the cycle). Local infection is treated by systemic and local antibiotics. Any other cervical defect is overcome by intrauterine insemination.

If sperm antibodies are present in cervical mucus, you advise the couple abstinance for 6 months or administer cortico-steroids which sometimes help.

Endometriosis

You can carry out the medical treatment, but if she needs any surgical treatment you should refer the patient to special centres. Medical treatment includes danazole which is the drug of choice. Medication is started soon after periods 200-800 mg in divided doses for 6-9 months. If the patient has side effects due to danazol you can give her progestogen starting with 10 mg and increasing up to 30 mg daily in divided doses. Idea is to produce pseudo-menopause or pseudopregnancy which causes change in the endometriotic patches. Danazole causes pseudomenopause and progestogen causes pseudopregnancy.

Tubal Factor may be tubal adhesions, kinks or tubal block at different levels. For these adhesiolysis (preferably laparoscopic) and tuboplasty (micro surgery) is required. These are best done in centres where facility and expertize for laparoscopic surgery and microsurgery are available.

However the pregnancy rates after tuboplasty are not very encouraging, specially when done for diseased tubes, as it restores the anatomy but cannot restore the physiology which is disturbed due to destruction of endothelium.

Check Your Progress 4

1) What are the drugs used for an ovulatory infertility?

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3) What drug will you use for thick cervical mucus?

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21.5.3 Unexplained Infertility

At the end of the preliminary tests for evaluation of the male and female partners, you might have arrived at one or two causes of infertility. In selected cases you must refer the couple for more sophisticated and expensive tests which have been mentioned from time to time to confirm the endocrine or systemic immunological factors. In 10% of the couples there is no abnormality detected. There is normal ovulation, tubal patency, sperm cervical mucus interaction and sperm production. These can be termed as ‘normal infertile

couples' or 'Unexplained infertility'. On re-evaluation of female partners in these couples a discrepancy may be observed. Double puncture laparoscopy may reveal unsuspected endometriosis and abnexal adhesions. Detailed studies of ovulation may detect luteal phase deficiency. Intermittent infection or a small varicocoele difficult to detect might have been missed in the male partner.

If no etiological factor can be found, reassure the couple and advice them rest period of three to six months to gain respite from numerous visits and the stress of infertility work up. At the end of this the patient may be referred to an infertility centre for assisted reproduction procedures or for adoption.

Their infertility may be due to lack of sperm capacitation, tubal interaction with the gametes, impaired tubal motility and corpus luteum deficiency.

21.6 ASSISTED REPRODUCTIVE TECHNIQUES (ART)

21.6.1 In Vitro Fertilization and Embryo Transfer (IVF -ET)

Since 1973 when the first child was born as a result of IVF-ET, designed to by-pass blocked tubes, IVF-ET has been extended to end stage infertility in any couple. Over the last few years the initial invasive technique has been replaced by less invasive procedure with the help of ultrasound. There is marked improvement in fertilization rates with sperm preparations and micromanipulation, and in pregnancy rates with cryopreservation.

The current indications for ART are:

— tubal disease

— unexplained infertility

— treated endometriosis

— infertility due to male factor

— cervical hostility

— failed ovulation induction

— absent ovaries

The physician should be aware that the success of IVF-ET depends on the age of the woman. Thus after failure to conceive after adequate treatment of any infertility factor for 18 to 24 months, ART should be considered.

Those couples who are already under stress should be counselled before starting the therapy. They should be given information regarding the success rate so that they do not unduly raise their expectation. The high expectations popularized by the media may put unnecessary pressure on the patient and demand on the treatment.

IVF-ET consists of:

— controlled ovarian stimulation

— ova collection

— in vitro fertilization

— replacement of the embryos

There are a number of protocols for controlled ovarian stimulation and among those presently popular are long acting injectable GnRH analogue followed by HMG and then HCG 36 hours before egg aspiration. Eggs are fertilized in vitro and the four cell stage embryo is transferred to uterus. Pregnancy rates are up to 20-25% in some clinics, however take home baby rates are lower.

21.6.2 Other Procedures

Gamete Intrafallopian Transfer (GIFT)

This is an option when atleast one fallopian tube is patent. It consists of controlled ovarian stimulation, aspiration of oocytes and sperm which are injected into the fallopian tubes. As many as 4 to 10 oocytes are placed in the tube.

Pronuclear Stage Tubal Transfer (PROST)

Again, with one normal fallopian tube, the zygote in the pronuclear stage, after fertilization in vitro, is transferred to the tube.

Cryopreservation

Since only 3 to 4 embryos are transferred to the uterus, the excess embryos are cryopreserved for later use.

Oocyte donation

In line with donor semen, donor oocytes are now an option for use in women with premature ovarian failure and severe genetic defects. This requires close coordination of the menstrual cycles of the donor and the recipient.

Micromanipulation

This manipulation of single spermatozoa. It is used for assisting fertilization in male factor infertility. Sperm transfer in the perivitelline space or into the egg cytoplasm is tried when sperm function is very poor.

21.7 COUNSELLING

Counselling the infertile couple is an important component of the management.

At the first visit only you must tell them that the investigation and treatment of infertility may take a long time, even a couple of years. You should also inform them about the various aspects which need to be looked at, that the infertility investigation and management do not follow rigid line but are flexible and adaptable to their particular problem.

There are many instances where the pregnancy has resulted at some times while the investigations are still going on and before any definite treatment has been given.

You have to assure the couple that there are so many advanced assisted reproduction techniques now available and with their help, they are very likely to achieve pregnancy. They should be optimistic about the results and have patience.

21.7.1 Ethical Issues

In couple going in for assisted reproduction, you must inform the ethical issues involved in it. Both the partners must be made aware of the technique to be used and they should mutually agree for the same, especially if donor's semen or ova is used.

Situation in which ethical questions may arise

— Artificial insemination of donor’s semen.

— Donor’s ova is to be used in IVF-ET.

— If a surrogate mother is used.

— If more than two foetuses left may grow and reach maturity without associated maternal complications.

The medicolegal questions which may arise

In cases of AIDS, the husband may not accept the child and there could be psychological burden on him.

The wife may start having apprehensions, that husband may not accept the child.

The surrogate mother may refuse to give the child.

Rights and ownership may be questioned if both the parents die.

Property discretions may arise in cases of adopted child.

Selective infanticide in cases of implantation of multiple foetuses may create a guilt feeling.

21.7.2 Adoption

You must suggest the option of adoption in women who are having great difficulty in having baby or who know that pregnancy is impossible. They might find it an attractive alternative to assisted reproduction techniques which have either failed or too expensive for them to afford.

Sometime after the adoption of a baby after many years of infertility, the pregnancy occurs spontaneously. This usually happens in women with unexplained infertility. The adoption may release tension in couples who are over wrought about their infertility and removal of tension may increase their fertility.

If the couple opts for adoption, you must inform them about the social organizations who are involved in giving babies for adoption and give their addresses.

21.8 LET US SUM UP

In this unit you have learnt that in an infertile couple it is important to investigate and treat both partners. Both of them should be interviewed together at first visit and also individually. History of the type of profession in professional stress, smoking, alcohol diabetes, STD, mumps and operative procedure in males and menstrual disturbances, tuberculosis, STD or other vaginal infections, operative procedures on the lower abdomen and vagina and previous obstetric history in female is important. You must examine both for hypertension, diabetes, thyroid disorder and do a thorough genital examination to detect hydrocoele, undescended or atrophied testes or vericocoele in males and galactorrhoea, vaginal or cervical infection, tumors or anatomical defects in genitals organs in females. If you find any signs of any infection, that should be treated before starting the investigations. To begin with, you must start with the non-invasive investigations in both partners. Semen analysis in males; cervical mucus, BBT chart if possible in females. This should be followed by premenstrual endometrial sampling, tests for tubal patency. If further investigations are required you should refer them to specialized centers.

Simple ovulation induction by clomiphene can be done by you at PHC. You can monitor the ovulation by cervical mucus study, BBT chart and by USG, if facility is available. For Gn stimulation, it is better that you refer her to specialized centers of ART. If the patient comes back without any success then you have to give her moral support and advice her for adoption.

21.9 KEY WORDS

AFB : Acid fast bacielli

AID : Artificial Insemination of Donor

AIH : Artifical Insemination of Husband

ART	:	Assisted Reproductive Techniques
BBT	:	Basal Body Temperature
BP	:	Blood Pressure
FSH	:	Follicle stimulating hormone
GIFT	:	Gamete intrafallopian transfer
GnRH	:	Gonadotropin releasing hormone
HCG	:	Human Chorionic gonadotrophin
HMG	:	Human menopausal gonadotrophin
HSG	:	Hysterosalpingography
I U	:	International Units
IVF-ET	:	In vitro fertilization - embryo transfer
LH	:	Leutinizing hormone
ml	:	milliliters
PCOD	:	Poly Cystic Ovary Disease
PCT	:	Post Coital Test
PHC	:	Primary Health Centre
PROST	:	Pronuclear stage tubal transfer
rpm	:	Revolutions per minute
SIFT	:	Semen intrafallopian transfer
STD	:	Sexually transmitted disease
USG	:	Ultrasonography
WHO	:	World Health Organisation

21.10 ANSWERS TO CHECK YOUR PROGRESS

Check Your Progress 1

1) Inability to conceive after 1 year of unprotected coitus.

2) Male factor: Abnormal spermatogenesis, Block in Vas.

   Female factor: Anovulation or corpus luteum dysfunction. Disturbance of Hypothalamo-Pituitary ovarian axis Thyroid/Adrenal disorder. Ovarian factor, ovarian dysgenesis, PCOD Male hormone producing tumour.

   Tubal factor: Tubal block due to tubercular, chlamydia, bacterial infection. Tubal kinks due to infection, endometriosis

   Uterine factor: Asherman syndrome.

   Cervical factor: Cervical stenosis, infection of cervix and vagina.

Check Your Progress 2

1) In males — History of mumps, diabetes, STD, hypertension, surgery for undescended testes, vericocoele

— occupation

— drug

— sexual history

In females — History of galactorrhoea, tuberculosis, diabetes hypertension, pelvic inflammatory disease, STD, puerperal sepsis, post abortal sepsis. History suggestive of anovulatory cycle.

2) General examination: Including that for Thyroid disorder, hirsuitism, abnormal hair distribution, galactorrhoea.

Pelvic examination: Enlarged clitoris, Bartholinitis, abnormal discharge, signs of pelvic inflammation, adnexal masses and ovarian enlargement.

Check Your Progress 3

1) BBT Chart, Cervical mucus study, endometrial biopsy and ultrasonography if facility is available.

2) Advantages: No anaesthesia, permanent record, diagnosis of the site of block, any associated uterine anomaly.

Disadvantages: X-ray machine required, dye-reaction may occur, peritubal pathology, not diagnosed.

3) Post coital test done between 4-8 hrs. of coitus. Cervical mucus collected from the endocervix and tested for elasticity and viscosity. Spread on a slide and covered with coverslip, examined under high power. Abnormal forms, motility, of sperms and presence of pus cells noted.

4) Semen collected by masturbation after 3 days of abstinance in a container and soon give to laboratory. Condom collection not recommended.

5) Women suspected to have Ashermani's syndrome, endometrial polyp, submucus fibromyama.

Check Your Progress 4

1) Clomiphene Citrate, Gonadotrapin therapy (HCG)

2) Low dose of oestrogen

21.11 FURTHER READINGS

Bhargava, V.L., *Text Book of Gynaecology and Obstetrics*, Vol. I.

Howkins and Bourne, *Shaw's Text Book of Gynaecology*, The Pathology of Conception, 1995, 203-223.

Sperroff, L., Robert, R.G., Nathan. G.K., *Infertility*, 1994,809 - 946.

Tindall, V.R., "Infertility and Subfertility", *Jeffcoates Principles of Gynaecology*, 1994, 578-596.