بسم الله الرحمن الرحيم

"قالوا سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم"

صدق الله العظيم
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Chapter 1

Introduction

Infertility is a global health issue, affecting approximately 8-10% of couples worldwide. In some societies of Sub-Saharan Africa (known as the ‘infertility belt’) one-third of all couples are unable to conceive during their reproductive lives**.** ***(Kumar , 2007)***

Major causes of infertility include male factors, ovarian dysfunction, tubal disease, endometriosis, and uterine or cervical factors. A careful history and physical examination of each partner can suggest a single or multifactorial etiology and can direct further investigation. Options for the treatment of male factor infertility include gonadotropin therapy, intrauterine insemination, or in vitro fertilization. In certain cases, tubal disease may be treatable by surgical repair or by in vitro fertilization. Infertility attributed to endometriosis may be amenable to surgery, induction of ovulation with intrauterine insemination, or in vitro fertilization. Unexplained infertility may be managed with ovulation induction, intrauterine insemination, or both. ***(Jose-Miller et al., 2007)***

IVF has been the treatment of choice in severe tubal infertility. For most other indications, IVF is applied as a last resort therapy after the failure of other treatment modalities. ***(Eijkemans et al., 2006)***

Since 1978, assisted reproductive technology (ART) procedures have been used to overcome infertility. ART procedures include those infertility treatments in which both eggs and sperm are handled in the laboratory for the purpose of establishing a pregnancy (i.e., in vitro fertilization [IVF-ET] and related procedures). Since the birth of the first U.S. infant conceived with ART in 1981, use of these treatments has increased dramatically. Each year, both the number of medical centers providing ART services and the total number of procedures performed have increased notably. ***(MMWR Surveill Summ.*, *2007)***

In 2001, of all children born in Europe, 0.2–3.9% were born following assisted reproduction treatment (ART) ***(Fiddelers et al., 2007)***

IVF and embryo transfer has become an established and increasingly successful form of treatment for infertility. The last two decades have seen major advances in reproductive technologies, which along with improved data collection and documentation have increased public awareness of the availability and efficiency of assisted conception. The Human Fertilisation and Embryology Authority (HFEA) 9th Annual Report (2000). shows an improvement of live birth rate from ~14% in 1991–1992 to ~ 22% in 2000–2001 for IVF treatment in the UK.***(Thomas et al.*, *2006)***

Transferring the embryos into the uterine cavity is the last and most critical step in IVF. It is routinely done through the transcervical route and is associated with multiple potential negative factors. ***(Mansour ,2005)***

It is generally not a difficult task to insert the embryo transfer catheter and eject the embryos. If the procedure can be performed smoothly and easily, it is likely to result in a significantly better pregnancy outcome***.(Yang et al., 2007)***

Endometrial receptivity is a crucial fact in human reproduction. Endometrial assessment has been performed usually by endometrial biopsy**.** ***(Alcázar , 2006)***

Successful implantation requires a receptive endometrium, a normal and functional embryo at the blastocyst developmental stage and a synchronized dialogue between maternal and embryonic tissues. The process of implantation may be classified into three stages: apposition, adhesion and invasion during blastocyst apposition, trophoblast cells adhere to the receptive endometrial epithelium. The blastocyst will subsequently anchor to the endometrial basal lamina and stromal extracellular matrix (ECM). At this point, the achieved embryo–endometrial linkage can no longer be dislocated by uterine flushing. This is followed by the invasive blastocyst penetration through the luminal epithelium**.** ***(Achache and Revel, 2006*****)**

Chapter 2

Infertility

Infertility continues to be a highly prevalent condition; the proportion of couples seeking medical treatment for infertility is estimated at 4–17% ***(Shalender, 2007)***.

2.1 ***Definition:***

Fertility is the capacity to produce offspring, whereas fecundity is a woman's biological ability to reproduce based on the monthly probability of conception ***(Homan et al., 2007).***

Clinical infertility is defined as the inability to become pregnant after 12 months of unprotected intercourse. It has been estimated that approximately 15% of the population in industrially developed countries are affected ***(Homan et al., 2007).***

The question of subfertility must be raised after six cycles of unprotected intercourse without conception—regardless of age because most of the women <30 years of age should have conceived ***(Gnoth et al, 2005)***.

2.2 *Causes of infertility:*

Although infertility is often attributed to female causes, fertility is a two-person phenomenon. Successful conception depends on many complicated events, including satisfactory sexual and ejaculatory function, appropriate timing, and a complex set of interactions between the male and the female reproductive tracts. Male and female factors coexist in about one third of cases, while one third of cases are secondary to male factors only. Therefore, evaluation of both partners is critical, and the woman's gynecologic evaluation should proceed simultaneously with the man's ***(Shalender, 2007)***.

Table (1): Causes of infertility and its percentage.

CAUSE	%
Tubal or pelvic factors (blocked or damaged tubes because of pelvic adhesions or endometriosis)	35%
Male factors (abnormalities of sperm number, motility, morphology)	35%
Ovulatory dysfunction (infrequent or no ovulation)	15%
Unexplained	10%
Unusual (fibroids, polyps, uterine anomalies)	5%

(Meniru, 2001).

2.2.1 *Male causes*:

The primary problem resides exclusively in the male partner in 20% of infertile couples; in an additional 26%, problems reside in both the male and the female partner ***(Shalender, 2007).***

2.2.1.1 *Systematic causes:*

Diabetes and other diseases that affect the function of nerves in the body may cause impotence, retrograde ejaculation or no ejaculation at all.Any illness that cause high fever can depress production of spermatozoa for up to six months ***(Meniru, 2001).***

2.2.1.2 *Congenital abnormalities:*

Testicular: Genetic (Klinefelter's syndrome-Ychromosome microdeletions-immotile cilia syndrome), Congenital (Cryptorchidism).Posttesticular: Genetic (cystic fibrosis**) *(Yao and schust, 2002).***

2.2.1.3 *Aquired testicular damage:*

Testicular:Infective(orchitis),Antispermatogenic agents(heat –chemotherapy-Drugs-Irradiation) and Vascular(torsion-varicocele) ***(Yao and schust, 2002).***

2.2.1.4 *Varicocoele:*

The most common identifiable cause of male subfertility is a varicocele, a condition of palpably distended veins of the pampiniform plexus of the spermatic cord. The concept of

a subclinical varicocele arose from the observation in early reports that the detrimental effect of small varicoceles equaled that of larger varicoceles. Varicoceles are present in 10–30% of infertile men; their role in pathophysiology of infertility remains unclear However, more recent studies suggest that larger varicoceles have a greater impact on fertility ***(Shalender, 2007).***

2.2.1.5 *Male accessory gland infection:*

The accessory glands (seminal vesicles, prostate and cowper's glands) infection may affect the contribution of these glands in seminal fluid ***(Meniru, 2001).***

2.2.1.6 *Endocrine causes:*

Pretesticular azoospermia represents those conditions in which hypothalamic pituitary axis fail to stimulate spermatogenesis within the testis, congenital, aquired, and idiopathic etiologies of hypogonadotrophic hypogonadism are included in this category ***(Yao and schust, 2002)***.

2.2.1.7 *Obstructive azoospermia:*

Men with congenital absence of vas should be tested for cystic fibrosis transmembrane conductance regulator mutations. Obstruction should always be considered in men with azoospermia; however, FSH levels are typically normal in obstructive azoospermia ***(Shalender, 2007)***.

2.2.1.8 *Unexplained poor semen parameters:*

Yq microdeletions are the most prevalent cause of spermatogenic failure in men with azoospermia or severe

oligozoospermia. Infertile men with azoospermia or severe oligozoospermia should undergo karyotyping and testing for Yq microdeletions. In general, 15–20% of infertile men are azoopsermic, and 10% have sperm density below 1 million/ml. A specific cause of infertility is not determinable in 40–60% men. Most infertile men have idiopathic oligozoospermia ***(Shalender, 2007).***

2.2.1.9 *No demonstrable abnormality:*

Another common correctable cause of male subfertility is obstruction, which may occur after a vasectomy. Less common correctable causes inclquenude ejaculatory dysfunction, infection, medications, and hormonal deficiency when the sum of these correctable causes is calculated; it becomes apparent that more than one half of cases of male subfertility are potentially correctable ***(Shalender, 2007)***.

Table (2):Show the most common causes of male factor infertility and their distribution.

Male Factor Problem	Percentage
No Demonestrable cause(normale semen and sexual/ejaculatory function)	48.5
Idiopathic abnormale semen(no cause for abnormale semen parameters)	26.4
Varicocoele	12.3
Infectious factors	6.6
Immunological factors	3.1
Other aquired factors	2.6
Congenital factors	2.1
Sexual factors	1.7
Endocrine disturbances	0.6

Source: ***(Meniru, 2001).***

2.2.2 Female causes:

2.2.2.1 *Vaginal causes:*

An uncommon problem is vaginismus which is the condition in which there is involuntary contractions of the vaginal muscles to prevent insertion of the penis into the vagina ***(Meniru, 2001).***

2.2.2.2 *Cervical causes:*

Undeniably, the cervix and the cervical mucus participate in the reproductive process in several ways.Cervical mucous accepts or captures sperm from the ejaculate and the vagina, exclude all other seminal plasma constituents and filters out morphologically abnormal sperm, nurtures the sperm biochemically and serves as reservoir for sperm , therby prolonging their survival and the interval between the intercourse and ovulation that will allow conception. Mucous is aglycoprptein gel with solid and liquid phases and has amosic ultrastructure with interstitial channels between mucin strands that expand and contract in response to cyclic changes in the steroid hormone environment across the menstrual cycle to facilitate or inhibit the passage of sperm ***(Speroff and Fritz, 2005)***.

Cervical infertility (as defined by repeatedly abnormal post coital test (PCT) is a very clear-cut indication for carrying out intra-uterine insemination (IUI) combined with gonadotrophin ovarian stimulation ***(Balasch, 2000)***.

2.2.2.3 *Uterine causes:*

Fibroid:

The association of fibroid with infertility is unclear and controversial, In rare instance there may be fibroids blocking the point of entery of both fallopian tubes into the uterine cavity ***(Meniru, 2001).*** Leiomyomas have never been shown to be a direct cause of infertiliy ***(Yao and schust, 2002)***.

Endometritis:

Infertility may arise through the effect of toxins produced by bacteria and abnormal secretion from the infected endometrial gland ***(Meniru, 2001).***

Asherman's syndrome (intra-uterine adhesions):

The pathophysiologic mechanisms involved most likely relate to scanty or poorly vascularized and dysfunctional endometrium resulting from trauma.Any insult sever enough to remove or destroy endometriumcan cause adhesions ***(Speroff and Fritz, 2005)***.Implantation of the embryo is prevented in these patients because there is little or no endometrium left ***(Meniru, 2001).***

Uterine malformation:

Congenital uterine anomalies may be assossiated with infertility.with the exception of septate uterus, infertility assossiated with most congenital uterine anomalies is not amenable to surgical treatment ***(Yao and schust, 2002)***.

2.2.2.4 *Tubal causes:*

Tubal infertility is one of the major indications for in-vitro fertilization (IVF). ***(Allison, 2003).***

Risk factors for tubal disease are history of sexually transmitted disease, pelvic inflammatory disease, previous pelvic surgery (especially ruptured appendix or surgery for Crohn's disease or ulcerative colitis), previous use of intrauterine devices, or endometriosis. Appendectomy for a ruptured appendix is associated with a four-fold increased risk of tubal infertility ***(Allison, 2003).***

One episode of pelvic inflammatory disease gives a 13% risk of tubal infertility. Risk increases to 36% and 75% with second and third infections, respectively ***(Allison, 2003).***

2.2.2.5 *Ovulatory causes:*

Approximately 20–30% of the women seeking fertility treatment present with anovulation ***(Klemetti et al., 2007).***

Polycystic ovarian disease(PCOD):

The polycystic ovary syndrome is a common cause of infertility ***(Legro et al., 2007).***In 1935, Stein and Leventhal published a paper on their findings in seven women with amenorrhea, hirsutism, obesity, and a characteristic polycystic appearance to their ovaries one of the first descriptions of a complex phenotype today known as the polycystic ovary syndrome. Insight into the pathogenesis and treatment of the polycystic ovary syndrome has increased substantially in the decade since this topic was last addressed in this Journal. The condition is now well recognized as having a major effect throughout life on the reproductive, metabolic, and cardiovascular health of affected women ***(Ehrmann, 2007).***

The polycystic ovary syndrome affects 7 to 8% of women and may be the most common cause of female infertility.

Anovulation, early pregnancy loss, and later pregnancy complications have all been implicated in the low fecundity of women with this disorder. Obesity is also common in such women, and this condition alone appears to have an adverse effect on reproduction. The cause of the polycystic ovary syndrome is poorly understood, and both the diagnosis and treatment of the disorder are controversial. Women with this syndrome have hyperandrogenism, morphologic changes in the ovary (polycystic), inappropriate gonadotropin secretion (elevated levels of circulating luteinizing hormone), and insulin resistance with accompanying compensatory hyperinsulinemia ***(Legro et al., 2007)***.

Hypogonadotrophic hypogonadism:

Patients in this category have amenorrhoea and do not show withdrawal bleeding after treatment with progesterone. Because of the limited production of FSH and LH from the pituitary gland ***(Messinis, 2005)***.

Hyperprolactinemia:

Hyperprolactinemia can be assossiated with ovulatory factor infertility ***(Yao and schust, 2002)***.pituitary tumours are commom causes of Hyperprolactinemia ***(Meniru, 2001)***.

2.2.2.6 ***Endometriosis:***

Endometriosis could alter fertility by its known assossiation with elevation in a variety of cytokines,including tumour necrosing factor(TNF).these soluble mediators of inflammation may alter the peritoneal,intratubal or intrauterine environment and adversily affect fertilization,early embryo development, or implantation ***(Sallam et al., 2002).***

2.2.2.7 *unexplained:*

Unexplained infertility is a common diagnosis, made in up to 30% of infertile couples after the conventional diagnostic assessment. Negative diagnostic test results would be expected if female age were the single reason for delayed fecundity, or when a defect exists that cannot be found with currently available tests. Although diagnostic test results are normal, the prognosis for live birth is only slightly superior to that with other causes of infertility. The prognosis is worse when the duration of infertility exceeds three years and the female partner is >35 years of age. With less than two years duration of unexplained infertility the prognosis is good even without therapy, unless the female partner is >35 years of age *(**Collins, 2003)***.

2.2.3 Sexual and ejaculatory dysfunction:

Correctable or treatable causes of infertility, such as coital disorders, are present in only a small fraction, but it is important to recognize them because effective therapies are available ***(Shalender, 2007).***

2.2.3.1 *Infrequent sexual intercourse*:

Some couples may present with infertility because they don't have intercourse frequently enough to ensure that spermatozoa are present in the female genital tract around the time of ovulation ***(Meniru, 2001).***