1.1. Introduction to infertility

The medical definition of infertility is the failure to achieve a clinical pregnancy after twelve months or more of regular unprotected sexual intercourse (Zegers-Hochschild *et al.,* 2009). It is considered as one of the most important unappreciated health problems, particularly in developing countries (Ombelet *et al.,* 2008) and has been acknowledged as a public health issue by the World Health Organization (WHO) (Vayena *et al.,* 2002). It is estimated that there are 60–80 million infertile couples worldwide out of which 25–28% (15–20 million) are in India alone (Poongothai *et al.,* 2009). While in India, population control, and not infertility management is the public health priority, infertility is an issue of great importance to the couples who suffer from it. In a country like India, where womanhood is considered synonymous with motherhood, inability of a woman to bear a child can lead to tremendous psychosocial distress, not to mention the peer and family pressure associated with it.

The causes of infertility can be classified as (i) male factor (ii) female factor (iii) combined male and female factor and (iv) unexplained. Approximately 40% of infertility cases are due to female factor, 40% due to male factor, and 20% due to a combination of both. Male infertility conditions include semen parameter abnormalities, varicocele, congenital and acquired urogenital abnormalities, endocrine disturbances, genetic abnormalities, infections of the genital tract, blockage in the reproductive tract, immunological factors and exposure to drugs/toxins (WHO 2000). A normal reproductive tract conducive to the transport of spermatozoa and release of a good quality oocyte when the endometrium is receptive for implantation are the two pre-requisites necessary in the female partner for successful pregnancy. Disruption or asynchrony of one of these events leads to infertility in women.

1.1.1. Female infertility

Common causes leading to female factor infertility include ovulatory, tubal/tubo-peritoneal, ovarian pathologies, uterine causes, endometriosis, endocrinological, anatomical abnormalities and cervical pathologies. Table 1.1 summarizes the main etiological causes of female infertility. A quarter of all infertile cases, with no identifiable cause of infertility following thorough investigation of both the partners, are said to be suffering from idiopathic infertility.

Table 1.1: Main causes of female infertility

Ovulatory dysfunction/Anovulation	Polycystic ovarian syndrome (PCOS), hypogonadotrophic hypogonadism, oligo-ovulation due to obesity/stress or anorexia nervosa, hyperprolactinemia, ovarian failure, luteal phase defect, luteinized unruptured follicle, Kallman's syndrome
Tubal	Obstruction due to infection, mechanical compression, endometriosis
Uterine	Leiomyoma, endometrial polyp, Asherman's syndrome, Mullerian anomalies (bicornuate, didelphys etc)
Peritoneal/Pelvic	Peritoneal adhesions disturbing tubal motility, endometriosis
Cervical	Cervicitis or cervical stenosis following surgery
Immunological	Antibodies secretion into cervical mucus/ other sites that interfere with oocyte-sperm interaction

1.2. Causes of female infertility

Ovarian causes

Anovulatory infertility

Anovulation is a relatively common problem among infertile couples. An intact hypothalamo-pituitary-ovarian (HPO) axis is necessary for normal ovulation to occur. The four most frequent conditions are normogonadotropic, hypergonadotropic, hypogonadotropic and hyperprolactinemic anovulation. Normal FSH and estradiol (E2) are observed in ~ 80% (Rowe *et al*., 1993) of the anovulatory patients (WHO type II anovulation) as in case of PCOS women. Diminished levels of both gonadotropins and E2 leading to pituitary failure (WHO type I anovulation) is responsible in ~ 10% of the cases. In rest of the 10% of the women, persistently high FSH (>40 IU/L) and E2 levels (>80pg/dl) are observed (WHO type III anovulation) as seen in premature ovarian failure (POF). Hyperprolactinemic anovulation is due to macro or micro pituitary adenoma and pituitary function abnormalities.

Polycystic ovarian syndrome

PCOS is the major cause of anovulatory infertility associated with menstrual irregularities, hyperandrogenemia and insulin resistance. According to the Rotterdam criteria (2004), PCOS, after exclusion of the related disorders, is defined by any two of the three features: (i) oligo- or anovulation (ii) clinical and/or biochemical signs of hyperandrogenism and (iii) polycystic ovaries (Azziz, 2006). Hyperandrogenism and hyperinsulinemia appear to have an influence on the development of anovulation in women with PCOS, along with the possibility of an intrinsic abnormality of folliculogenesis (Franks *et al.,* 2008).

POF or early menopause

POF is the occurrence of early menopause or hypergonadotropic hypoestrogenic amenorrhoea and early depletion of ovarian reserve in women under the age of 40 years. POF occurs in approximately 1:1000 women before 30 years, 1:250 by 35 years and 1:100 by the age of 40 (Vilodre *et al*., 2007). POF is idiopathic in 74–90% of cases but can be familial (4–33%) or sporadic (Vujovi, 2009). Though the cause is often unknown, the condition is associated with genetic aberrations, autoimmune disease, iatrogenic after surgery around the ovaries, cytotoxic drugs, smoking, radiation or chemotherapy, enzymatic and metabolic.

Luteinized unruptured follicle (LUF)

LUF is a form of anovulation causing infertility and seen normally in about 10% of fertile women (Qublan *et al.,* 2006) and in 25% to 43% of infertile women (Wang *et al*., 2008). Despite LH surge, ovulatory follicle fails to rupture; however, luteal phase is not disrupted as the granulosa cells are luteinized with normal progesterone level. Though the exact cause is not known, unexplained infertility, endometriosis and pelvic adhesions and use of prostaglandin inhibitors have been attributed to LUF (Rizk, 2008).

Luteal phase defect (LPD)

It is suggested that defective luteal function or LPD may be a cause of infertility and early pregnancy loss. Owing to the fact that out-of phase endometrium in fertile women is often encountered, the earlier concept of histological dating of the endometrium showing maturation delay of more than two days for the diagnosis of LPD is no longer in use. Nowadays, LPD is diagnosed by a short luteal phase (<13 days) and/or inadequate secretion of progesterone (Rizk, 2008).

Tubal factor

The etiology of tubal damage can be intrinsic (ascending salpingitis, including salpingitis isthmica nodosa) or extrinsic (peritonitis, endometriosis, pelvic surgery). Regretted tubal ligation is the most common etiology of mid-tubal occlusion. Salpingitis may be due to chlamydia trachomatis, gonorrhea, mycobacterium tuberculosis and multibacterial infections. Evaluation of tubal infertility includes a hysterosalpingogram (HSG) and laparoscopic chromopertubation, with optional sonohysterography, salpingoscopy/falloposcopy (Sotrel *et al.,* 2009).

Uterine causes

Leiomyoma

The overall prevalence of fibroids among infertile women is between 20–50% (Levens *et al.,* 2008). These may cause infertility by interfering with the contour of the uterine cavity, blocking the fallopian tubes. Fibroids have been associated with implantation defects due to increased venous congestion and impaired uterine blood flow leading to histological alterations such as a reduction in the proportion of endometrial glands (Patterson-Keels *et al.,* 1994). Evidence also suggests that submucosal, intramural and subserosal fibroids interfere with fertility in decreasing order of importance (Somigliana *et al.,* 2007).

Uterine malformations

Müllerian anomalies, especially uterine anomalies, are associated with both normal and adverse reproductive outcomes (Rackow and Arici, 2007). Their mean prevalence amongst fertile women is ~4.3%, ~3.5% in infertile women and ~13% in women with recurrent pregnancy loss. Septate uterus (~35%) is the commonest uterine anomaly followed by bicornuate uterus (~25%) and arcuate uterus (~20%). Septate uterus may

have a role in the delayed natural conception of women with mainly secondary infertility (Grimbizis *et al.,* 2001).

Endometrium and Asherman's syndrome

Chronic endometritis is a subtle pathology causing infertility (Cicinelli *et al.,* 2009) and endometritis may result from latent genital tuberculosis. Infertility can arise due to the effect of toxins produced by *Mycobacterium tuberculosis* causing subsequent reduction in the sub-endometrial blood flow (Dam *et al.,* 2006). Uterine synechiae is also frequently associated with infertility. Most cases are associated with trauma to the gravid uterine cavity usually within 4 months of pregnancy and when the woman is in a hypoestrogenized state (Berman, 2008).

Pelvic causes

Pelvic adhesions

This condition is usually associated with up to 15% to 20% of all cases of infertility caused due to surgery or infection. Pelvic adhesions are thought to restrict the free movement of pelvic organs and affect the functioning of the ovaries and fallopian tubes resulting in infertility (González-Quintero and Cruz-Pachano, 2009).

Pelvic inflammatory disease (PID)

PID is one of the most common infections seen in reproductive-age women associated with infertility (Sweet, 2009). It is usually caused by multimicrobial agents, including *Neisseria gonorrhoeae, Chlamydial trachomatis, Mycobacterium tuberculosis*, *Mycoplasmal* and anaerobic bacteria (Haggerty and Ness, 2008). Permanent tubal alterations due to immuno-allergic reactions lead to fallopian tubes blockage and are one of the main causes of tubal sterility (Hoof, 2007; Judlin and Thiebaugeorges, 2009).

Endometriosis

It is estimated that about 20–25% of infertile women have endometriosis and infertility is secondary to anatomic causes in moderate or severe endometriosis (Glitz *et al.,* 2009). In women with minimal or mild endometriosis, the cause of infertility is not fully understood but is thought to involve hormonal, immunological, endometrial and uterine alterations (Cunha-Filho *et al.,* 2001; Giudice and Kao, 2004). Natural history of the disease varies from one individual to another. Inflammatory response to ectopic endometrial tissue, which appears to play an important role in disease progression, may also vary in each individual (Bukulmez, 2009).

Cervical causes

Cervical mucus should be adequate and thin in consistency to allow the penetration of the sperm to reach the site of fertilization. Antisperm antibodies against the partner's sperm are produced in women turning the cervical mucus inhospitable or hostile. Cervicitis due to infection of the cervix with common sexually transmitted diseases can cause cervical narrowing or stenosis.

Unexplained infertility

Unexplained infertility is defined as a condition when the results of the standard infertility evaluation procedure including semen analysis, assessment of ovulation, HSG, and, if indicated, tests for ovarian reserve and laparoscopy are found to be normal (ASRM, 2006). Almost 15% to 30% of the couples are diagnosed to be suffering from unexplained infertility (Quaas and Dokras, 2008). Various techniques used for the evaluation of women partners of infertile couples are discussed in the next section.

1.3. Evaluation of the female partner

Assessment of ovulation

Ovulatory dysfunction is present in ~ 40% of infertile women and in ~15% of infertile couples (ASRM, 2006) and can be due to PCOS, thyroid disease, hyperprolactinemia, and hypothalamic causes secondary to weight changes, as mentioned earlier. Eumenorrhea, defined as normal menstrual cycles by history, is considered to be strongly suggestive of ovulation. Serum progesterone level due to anovulation (< 3 ng/ml) is observed in only a very small number of eumenorrheic women (Malcolm and Cumming, 2003). Another method to exclude anovulation is the estimation of serum prolactin and thyroid hormone levels.

Ovulation assessment includes:

- Basal body temperature monitoring
- Luteinizing hormone surge detection
- Mid-luteal phase progesterone assay
- Ultrasonography of the ovaries and endometrium
- Detection of cervical mucus changes
- Endometrial biopsy for secretory endometrial development

Assessment of ovarian reserve

Day 3 serum FSH and E2 level, clomiphene citrate (CC) challenge test, and/or an ultrasonographic ovarian antral follicle count indicate ovarian reserve and may provide important prognostic information and help in appropriate treatment recommendations (ASRM, 2006). Antimullerian hormone is an emerging diagnostic marker of ovarian function as it is the earliest marker to change with age, with least intercycle and intracycle variability and can be assessed randomly during the cycle (Seifer and Maclaughlin, 2007).

Assessment of uterine factors

Assessment of tubal patency is a vital part of infertility evaluation. This may be achieved by HSG, laparoscopy, sonosalpingography and hystero-salpingo contrast sonography (HyCoSy). Tubal patency, internal contour of the uterine cavity and proximal and distal tubal obstruction can be assessed by HSG. In addition, uterine developmental anomalies, submucosal myomas, endometrial polyps, and intrauterine adhesions, with potential effects on fertility, can be detected (Rizk, 2008).

Tubal patency can be best assessed by laparoscopic dye pertubation (indigo carmine/methylene blue). Laparoscopy provides additional information such as visualization of the peritoneal cavity (pelvic adhesions, scarring and endometriosis), fallopian tubes, ovaries and peritubal adhesions. Specificity of diagnosis of tubal obstruction by HSG and laparoscopic chromotubation is estimated to be ~90% (Exacoustos *et al.,* 2003).

Sonosalpingography, an ultrasound guided non-invasive technique, is used to assess tubal patency and detect size and shape of the uterine cavity, polyps, submucous myomas, adnexal masses, uterine fibroids, adenomyomas, hydrosalpinges and synechiae. This technique, along with 3-D ultrasonography has diagnostic accuracy comparable to magnetic resonance imaging (MRI) for the diagnosis of uterine developmental anomalies (Rizk, 2008). HyCoSy is an ultrasound contrast technique where echo-enhancing agents are used for more consistent visualization of the fallopian tubes and delineation of the uterine cavity using ultrasonography (Strandell *et al.,* 2000).

Hysteroscopy allows direct observation of the uterine cavity, distortion of the endometrium or uterus and blockage at the tubal ostia. The cervix and endocervical canal can be visualized using a colpomicrohysteroscope. Ultrasonography is used to detect antral follicle count, LUF, follicular growth monitoring after stimulation, uterine fibroids, polycystic ovaries, endometrial polyps, ovarian cysts or tumors etc. In addition,

endometrial thickness and pulsatility and the resistivity indices indicating sub-endometrial blood flow is measured by Color Doppler (Zaidi *et al.,* 1995).

MRI provides a detailed view of anatomy in three dimensions, and has the ability to characterize tissues (Rizk, 2008). It is highly expensive and is indicated in the assessment of endocervical junction and diagnosis of adenomyomas.

Genetic assessment

Karyotyping is indicated in women with primary or secondary amenorrhea with elevated serum FSH, long-term unexplained infertility, and in recurrent spontaneous abortion.

1.4. Treatment of infertile women

Infertility treatment depends on the reproductive abnormalities in one or both the partners. Several medical, surgical and assisted reproductive techniques (ART) are available for treating these couples. Surgical treatment is warranted in women having severe endometriosis with chocolate cysts, submucosal fibroid, endometrial polyp, intrauterine adhesions etc. Micro-surgical tubal reconstruction for tubal infertility is suggested in case of normal male partner before in-vitro fertilization (IVF) is attempted. After the initial conservative or surgical line of management, treatment options for infertile couples include ovulation induction (OI) or ovarian stimulation (OS), intrauterine insemination (IUI) with or without OI and IVF followed by embryo transfer (ET) with or without intracytoplasmic sperm injection (ICSI).

The primary objective of OI is to restore normal physiology, i.e. selection of a single dominant follicle, followed by mono-ovulation (ESHRE Group, 2003). This single follicle is then fertilized by timed intercourse or artificial insemination (Hrometz and Gates, 2009). Development of 2–3 pre-ovulatory follicles and ovulation for subsequent fertilization in vivo is desired in case of ovarian hyperstimulation (Macklon, 2005).

Superovulation, along with timed intercourse or IUI, increases the chance of fertilization in women with ovulatory and unexplained infertility. In controlled ovarian hyperstimulation (COH), pituitary down regulation followed by stimulation of multiple follicles is achieved. COH is necessary in ART, such as IVF-ET and ICSI.

1.4.1. Ovulation induction/ovarian stimulation protocols

CC, an anti-estrogenic drug, is generally administered for OI. FSH is a conventional option in case of CC failure followed by other options such as aromatase inhibitors (AIs), insulin-sensitizers, laparoscopic ovarian electrocautery, dopamine agonists or their combinations. Multifollicular development enhances the risk of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS). Briefly, the methods used for OI are discussed below and the most commonly used drugs such as CC, letrozole and gonadotropins are discussed in detail.

Tamoxiphene is an anti-estrogen and has less anti-estrogenic effect on the endometrium and cervical mucus than CC (Annapurna *et al.,* 1997). Use of this drug for OI is limited as compared to CC, since data regarding pregnancy rates and outcome are limited (Steiner *et al.,* 2005).

Laparoscopic ovarian drilling (LOD) has replaced the classic wedge resection of the ovaries without much risk for multiple pregnancies and OHSS (Balen, 2001). LOD is reported to restore ovulation in ~90% and pregnancy in 69% of the women (Messinis, 2005). The pregnancy rates with LOD after 6–12 months are similar to those of 3–6 OI cycles with gonadotropins (Adamson and Baker, 2003). However, it is associated with the risk of periadnexal adhesions and diminution of the ovarian reserve.

Women with hyperprolactinemia are effectively treated with bromocriptine, a dopamine agonist that leads to ovulation in approximately 80% of these women (ACOG, 2002). However, cabergoline, another dopamine receptor agonist, is better tolerated and is as effective as bromocriptine (Balen, 2001).

It is reported that insulin-sensitizing agents, of which metformin is still most widely used, benefit PCOS women when combined with CC. Though studies have shown that metformin alone can restore ovulation in 25–95% of the women, data is not sufficient for its use as a first line therapy (Messinis, 2005).

Naltrexone, an opioid receptor antagonist, alone or in combination with an anti-estrogen induces ovulation in CC- resistant women (Roozenburg *et al.,* 1997). Naltrexone has limited support as a single ovulation inducing agent for PCOS although it is reported to augment OI regimens (Eyvazzadeh *et al.,* 2009).

1.4.1.1. Clomiphene citrate

CC is a triphenylethylene derivative and acts as a non-steroidal selective estrogen receptor modulator (SERM). It has a strong antiestrogenic and weak estrogenic activity and the agonist properties manifest only when the endogenous E2 levels are extremely low (ASRM, 2003). Since it acts as an anti-estrogen, induction of ovulation with CC requires an intact HPO axis and E2 level. The main mechanism of action of CC in OS is its antiestrogenic effect on the hypothalamus and the pituitary. Binding of CC to estrogen receptors in the hypothalamus creates pseudo low serum E2 levels leading to increased gonadotropin secretion through the estrogen negative feedback mechanism. This, in turn, produces a rise in the endogenous FSH level thereby stimulating follicular growth and ovulation (Casper, 2007).

CC is the first-line of treatment strategy in women with WHO type II anovulation and is cheap, safe and has few side-effects. It is also indicated in LPD and unexplained infertility for OI. CC is administered orally from day 3 to day 7 of the menstrual cycle starting from 50mg per day and can be increased up to 150mg per day. Following oral administration, CC reaches a peak concentration at 48 hrs and remains constant for the next 14 days. The discrepancy between ovulation and pregnancy rate (80% vs 40%) is partly due to its antiestrogenic effects on the uterus, cervix and vagina, resulting in a thin

endometrial lining and poor cervical mucus (Lambalk et al, 2005). CC fails in ~55% of women; either no ovulation occurs in 25% (CC resistant) of them or 40% fail to achieve pregnancy (CC failure) despite ovulation after the maximal dose of CC for 6 cycles (Eijkemans *et al.,* 2005). Miscarriage rate is reported to be similar to that in the normal population and multiple pregnancy rate (~6–8%), mainly twin pregnancies, is lower than gonadotropin regimens (Messinis, 2005). Women, who fail to ovulate with CC alone, may respond to CC when combined with insulin sensitizers, glucocorticoids, gonadotropin, ovarian drilling etc (ASRM, 2003).

1.4.1.2. Gonadotropins

FSH is a glycoprotein made up of two subunits, α and β, which binds to the specific FSH receptors on the granulosa cells and stimulates follicular growth in the ovaries. Gonadotropins synthesized from recombinant DNA technology were thought to improve the outcome significantly as batch to batch variation is minimal with this preparation as compared to the earlier urinary gonadotropin. However, no differences in the outcome have been found between the use of human menopausal gonadotropin (hMG) and either purified or rFSH (Messinis, 2005).

Gonadotropin therapy for OI is generally attempted in those patients who fail to respond to CC. Exogenous gonadotropins including FSH and hMG containing FSH/LH activity are the two preparations currently used in the treatment of infertility. FSH is used for OI or superovulation in patients undergoing IUI and COH/IVF protocols. Exogenous FSH necessary to induce follicle development is related to the dose required in previous stimulation, body mass index (BMI), age, antral follicle count and FSH threshold level, which varies widely amongst women (Devroey *et al.,* 2009). FSH threshold level should be reached gradually to prevent multifollicular development or excessive stimulation as done in low dose step-up protocol. An initial dose of 50-75 IU/day is continued for 14 days, and if required, the dose is increased by 37.5 IU/week up to a maximum of 225/IUday (Lambalk *et al.,* 2005) Intense monitoring of the follicular growth is necessary

by ultrasonography and serum E2 monitoring is necessary to prevent multifollicular development and hence, OHSS. An ovulation rate of 82%, pregnancy rate of ~40–45% and significantly high multiple birth rates have been reported with gonadotropins (Mulders *et al.,* 2003).

1.4.1.3. Letrozole

The rate limiting step in the synthesis of estrogen is the conversion of androgens to estrogen that is catalyzed by the enzyme aromatase, and this step is blocked by the AIs. This reduces the serum E2 level and stimulates secretion of endogenous FSH through the negative feedback mechanism on hypothalamic–pituitary system (Rizk, 2008). The resultant increase in gonadotropin secretion stimulates the growth of ovarian follicles. In addition, aromatase inhibition may increase the ovarian follicular sensitivity to FSH stimulation by temporary accumulation of intraovarian androgens (Casper, 2007). The two nonsteroidal third-generation AIs commercially available include anastrozole and letrozole. Letrozole is primarily used as an adjuvant treatment of early estrogen-receptor-positive breast cancer in postmenopausal women. It binds reversibly to the heme group of aromatase CYP19 (Casper and Mitwally, 2006).

Letrozole, has been recently used for OI in CC resistant anovulatory PCOS women or in women with inadequate endometrial thickness during CC treatment. Letrozole is administered orally from day 3 to day 7 of the menstrual cycle starting from 2.5mg per day and can be increased up to 7.5mg per day. After oral administration, it has a relatively short half life (~45hrs). A systematic review and meta-analysis indicates an ovulation rate of 50–75% and pregnancy rate of ~25% with the use of letrozole in assisted reproduction (Requena *et al.,* 2008). This drug is reported to have no adverse antiestrogenic effect on cervical mucus or endometrial thickness (El-Nashar *et al.,* 2006). The normal central feedback mechanisms remain intact in women treated with AIs, leading to monofollicular development. (Casper and Mitwally, 2006). Multiple gestation and miscarriage are substantially lesser with letrozole. Ovulation rate and pregnancy rate

have been observed to be more effective in letrozole as compared to anastrozole (Al-Omari *et al.*, 2004).

1.5. Assisted Reproductive Techniques

About 8% of the infertile couples need serious medical intervention involving the use of advanced ART procedures, such as IVF or ICSI. Such advanced treatment is expensive and not easily affordable to the majority of Indian population. Further, successful practice of ART requires considerable technical expertise and expensive infrastructure. Moreover, the success rate of any ART procedure is 30–40% under the best of circumstances.

1.5.1. IVF/ICSI

The chances of pregnancy in infertile couples have been increased considerably by IVF (Bing and Ouellette, 2009). Gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT) have been reported to be more effective than IVF, but are not frequently used techniques because tubal transfer of the gametes (or the embryo) requires a laparoscopic procedure. ICSI is another effective technique commonly used in couples with severe male factor infertility.

IVF has an average success rate of ~25–30% per cycle; variation depends on the patient profile, female age being the most significant one. Success rate is inversely proportional to the increasing number of cycles and duration of infertility. However, previous pregnancy and live birth increases the chances of pregnancy in the future attempts. Success rates in most of the infertile women are similar; however, women with multiple pelvic surgeries or history of severe endometriosis have 5% lower success rates. This may be attributed to poor response to OS (Adamson and Baker, 2003). Despite tremendous progress in the field of assisted reproduction over the years, the current success rate of ART remains quite unsatisfactory and is limited to 30–40% (Gerris *et al.,* 1999). Possible causes associated with poor ART success rate are being actively investigated worldwide (Swain and Pool, 2008).

1.5.2. IUI

IUI involves the placement of washed spermatozoa into the uterine cavity at around 36-40hrs of ovulation. Although IUI can be performed during spontaneous ovulation, it is routinely performed following administration of ovulation inducing agents (Quaas and Dokras, 2008). Though several reports exist on the use of IUI in natural cycles, increased live birth rate has been observed for IUI combined with OI (Verhulst *et al.,* 2006). A well timed single insemination per cycle is adequate and two inseminations may be appropriate in gonadotropin cycle. A maximum of six IUI cycles is recommended since no benefit is likely to occur on further IUI attempts (Crosignani *et al.,* 2005). IUI is indicated in mild male factor infertility and at least one million sperm cells should be available for better IUI outcome (ASRM, 2001). Other indications for IUI include unexplained infertility, cervical mucus hostility and ovulatory disturbances. The sperm preparation technique and type of catheter used for IUI does not seem to affect the success rate. The overall success of IUI varies, pregnancy rates ranging from 5–70% and with 9% mean pregnancy rate per IUI cycle (Rizk, 2008).

IUI following CC stimulation is the most commonly used protocol with an average pregnancy rate of 7% per cycle. Though an average of 12% pregnancy rate per cycle is observed in IUI cycles stimulated with FSH, it is associated with 13% miscarriage rates (ESHRE, 2009). IUI with or without OS is a common and affordable mode of treatment for appropriately selected infertile couples in the Indian clinical setting. It is well established that IUI treatment requires OS to achieve modest results and minimum risk. Further research is required on IUI treatment with mild stimulation for the development of less number of follicles (1–2) that might reduce the cost and chances of multiple gestation. Letrozole appears to be a promising drug associated with monofollicular development and not having any anti-estrogenic effect on the endometrium and cervical mucus. However, large, prospective, randomized, controlled trials are necessary to establish the advantages offered by letrozole in the treatment of infertility (Requena *et al.,* 2008).