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Institute of Reproductive Medicine

Current Views on Ovulation Induction

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INTRODUCTION

Ovulation induction is the process by which the development of ovarian follicles is stimulated by medication. Induction of ovulation is one of the commonly practiced therapeutic interventions to reverse anovulation or oligoovulation in the women who do not ovulate on their own regularly, the most common clinical situation being the polycystic ovary syndrome (PCOS). However, since the introduction of ART in the treatment of infertility, ovulation-inducing drugs are used even in ovulatory women with few modifications of protocol while using similar medications like those used in the treatment of anovulatory infertility. Currently, it is also recommended in women experiencing unexplained infertility or irregular menstrual cycles.

DEFINITION(S)

The purpose of using ovulation-inducing drugs include

a) Ovulation induction
b) Ovulation augmentation
c) Ovarian stimulation
d) Ovulation triggering

Ovulation induction involves inducing follicular development and rupture of follicles resulting in ovulation (release of mature oocyte) by medical treatment. This approach is indicated only in anovulatory women. Occasionally, induction is also performed by surgical intervention like laparoscopic ovarian drilling.

Ovulation augmentation is a mild form of stimulation offered to some infertile women. The most frequent situations are unexplained infertility and while inducing ovulation for IUI. The principal objective is to recruit one or two more follicles in the developing cohort for increasing the chance of pregnancy.

Ovarian stimulation is usually indicated in IVF treatment protocols. The purpose is to recruit larger cohort and synchronous development of several co-dominant follicles.

Ovulation triggering is indicated primarily in the down-regulated cycle the as in IVF. Even in the non-down regulated cycle like in IUI, ovulation triggering is performed for pre-fixing the exact time for intra-uterine insemination. The objective is to make the oocyte fertilizable (M-II oocyte) through the release of the first polar body. The 'trigger' (either hCG or GnRH-a) acts as a surrogate 'LH surge.'

In this chapter, indications, different drugs used, their merits and demerits, pharmacological action, and the protocols of administration will be discussed.

CLASSIFICATION OF ANOVULATION

In 1973, the WHO Scientific Group devised a classification of anovulatory women primarily based on the levels of gonadotropins and oestrogens. As per this classification, there are three groups of anovulatory women, as categorized below.

WHO Group-I: Hypogonadotropic hypogonadal anovulation (hypothalamic amenorrhea)

In this group, the primary defect is at the hypothalamic-pituitary (HP) level. The defect may be of two types, organic and functional. The more common variety is a functional defect which is also known as hypogonadotropic hypogonadism. One of the varieties is Kallman's syndrome which is not a functional defect but is a genetic disorder. Induction of ovulation in these cases is possible with gonadotropin (HMG, combination of FSH and LH) treatment. This type of anovulation is always associated with primary amenorrhoea. A brief description of this category of anovulatory infertility has been discussed at the end of this chapter.

WHO Group-II: Normogonadotropic normoestrogenic anovulation

This group is a mixture of varied hormonal dysfunctions that may primarily originate from diverse glandular and even extraglandular sources. Anovulation occurs despite the presence of an intact hypothalamic-pituitary-ovarian (HPO) axis. The absence of ovulation is due to the dis-coordinated functioning of

the three reproductive endocrine organs of the HPO axis. WHO-Group II represents the most common type of anovulatory infertility encountered in clinical practice. The most prevalent condition is known as polycystic ovary syndrome (PCOS), which itself is an amalgam of different pathophysiological mechanisms. These women require ovulation induction through different protocols.

WHO Group-III: Hypergonadotropic hypoestrogenic anovulation

In this class of anovulatory women, the fundamental defect is at the target organ level, i.e., in the ovary. Ovary may run out of eggs prematurely, which has been designated as the premature ovarian failure (POF) or primary ovarian insufficiency (POI). Medical treatment with oestrogen-progesterone suppression often may help but in general is unrewarding. The practical approach is in-vitro fertilization with donated eggs.

The current practice of ovulation induction is more or less in line with the therapeutic flow chart resulting from WHO classification. However, consequent upon broadening of our knowledge of the pathophysiology of anovulation and advent of newer therapeutic facilities, the validity of WHO classification has been questioned. It is argued that subdivision of anovulatory women into three groups according to gonadotropin and oestrogen levels without taking into account the diverse etiologies and complex pathogenesis has oversimplified the situation. Necessity for devising a modified classification that would encompass the diverse etiologies of anovulation and provide a guide to the currently evidence-based therapies has been raised.

In this submission, ovulation induction in WHO Group–II anovulatory women will be discussed at length followed by a brief description of WHO Group–I women. Management of WHO group-III women (POF or POI) will be addressed in a separate chapter.

THE BASIS OF INDUCTION OF OVULATION IN PCOS WOMEN

The primary defect in PCOS responsible for anovulation is hyperandrogenicity. According to Rotterdam definition (2003), a small sub-group of anovulatory women without the evidence of hyperandrogenism has been included under the category of PCOS. However, Androgen Excess Society (AES) task force on the phenotype of PCOS has mandated that PCOS should be first considered as a disorder of androgen excess or hyperandrogenism (2006). Based on this criterion, we still believe that phenotype of PCOS starts with hyperandrogenism followed by anovulation, morphological changes in the ovary, and other phenotypes of hyperandrogenicity like obesity, acne, hirsutism, etc.

Clinical associates of hyperandrogenemia in PCOS

a) Hyperprolactinemia: The patients with PCOS are often associated with hyperprolactinemia. Prolactin excess in PCO may be stress-induced. The stress of modern society stimulates adrenal cortex through ACTH production, and that may lead to hyperandrogenism through hyperactivity of adrenal cortex, specifically, the steroid-producing area zona reticulosa.
b) Hyperinsulinemia: It is now universally accepted that about 80% of PCOS women – lean or obese is associated with hyperinsulinemia (non-insulin dependent diabetes mellitus (NIDDM)). Excess insulin leads to excess androgen production in two ways – by stimulating excess LH secretion from the pituitary and by suppressing the production of SHBG and insulin-like growth factor-binding protein-1 (IGBP-1) at hepatic level.
c) Subclinical hypothyroidism: In this situation, sex hormone binding globulin (SHBG) is low. As testosterone largely remains bound to SHBG in subclinical hypothyroidism, the free testosterone level is elevated.

Insulin acts as co-gonadotropin. Insulin at pituitary level stimulates LH hyper-secretion leading to androgen excess. Insulin receptors have been found in the pituitary gland. Insulin also suppresses hepatic synthesis of SHBG and IGFBP-1 which results in increased free testosterone and IGF-1 levels. IGF-1 and insulin are chemically and structurally similar. Ovarian theca cells contain plenty of IGF-1 receptors. Excess insulin acting through IGF-1 receptors in the ovary leads to LH-mediated excess thecal androgen production.

A close association of PCOS with hyperinsulinemia is gradually being introduced as a new concept for the genesis of PCOS. According to this concept, the

primary endogenous abnormality in PCOS women may exist in the somatotropic axis related to growth hormone, insulin, IGF-1, etc., and gonadotropic axis defect concerned with FSH/LH and oestrogen production may be subsequently involved.

d) Hyperadrenalism: Some patients with PCOs are associated with borderline elevation of adrenal activity with mild to a moderately increased level of DHEAS. This should be differentiated from cases of congenital adrenal hyperplasia by the blood or urine levels of cortisol. Hyperadrenalism associated with PCO may also be stress-induced or genetic.

e) Hyperactive hypothalamic LH pulse generator: This newly proposed hypothesis suggests that an excess androgen production by the ovary (genetically determined) starts during intra-uterine life. This is because the LH pulse generator in the hypothalamus is hyperactive in high-risk fetuses who are genetically predisposed to develop PCOS in their childbearing period. This results in androgenic programming of the HP unit that favours excess LH secretion. Excess LH and androgen lead to preferential abdominal (central) obesity which is predisposed to insulin resistance and anovulation after puberty.

How does hyperandrogenism lead to anovulation?

Besides hyperandrogenicity and hyperinsulinemia, hyperoestrogenism is the next common endocrine disorder in PCOS women. Hyperoestrogenism may emanate from hyperandrogenism. This is one of the reasons why letrozole rather than clomiphene citrate has a preferential role for induction of ovulation in PCOS women. Before we understand the mechanism involved in the conversion of excess androgen to excess oestrogen (which is a more common associate of PCOS), it may be useful to have a basic idea of primary sequences of the endocrine pattern of a typical ovulatory cycle.

In the normal ovulatory cycle, oestrogen must 'decline' and also must 'rise' once. This does not happen in anovulatory women like PCOS or during pregnancy. In other words, there is no oestrogen fluctuation in anovulatory women. As a consequence, they have a 'static' level (more often elevated level) of oestrogen leading to a state of 'static' hyperoestrogenism. The state of hyperoestrogenism is routed through hyperandrogenicity.

In PCOS women, apart from hyperandrogenicity, in the majority, oestrogen level is also simultaneously elevated. The cut–off level of basal oestrogen in reproductive years has been arbitrarily fixed as normal (E2:30-60 pg/ml; normoestrogenic), low (E2: < 30 pg/ml; hypoestrogeneic), and high (E2: > 60 pg/ml; hyperoestrogenic). In normal ovulatory women, the oestrogen levels fluctuate during different phases of menstrual cycle, while in PCOS women, the oestrogen level remains static (whether normal or elevated) throughout the cycle. In the majority of PCOS women, the oestrogen level is persistently elevated. This may stem from aromatization of excess androgens to estrogens (E1, E2, and E3) by the adipocytes in the peripheral fat. Also the oestrogens are converted to catechol estrogens by the hypothalamus and pituitary that have an important role in the regulation of GnRH (the hypothalamus and pituitary are highly efficient in transforming E1 and E2 to catechol estrogens, the concentration of which are at least ten times higher than parent estrogens).

How does hyperoestrogenism lead to anovulation and characteristic morphology of polycystic ovaries?

The amplitude of the pulses of LH is significantly greater in anovulatory PCOS secondary to excessive and prolonged extraglandular production of estrogen from androstenedione. Hypothalamic receptors are blocked by static elevated oestrogens leading to the synthesis and release of elevated level of tonic (not pulsatile) GnRH. GnRH is preferentially a releasing hormone for LH than for FSH. As a result, static elevated LH level and normal or low static FSH level prevail in the circulation. Because LH level is static, there is no 'LH surge' to induce final maturation of the follicle and ovulation.

On the other hand, as a result of low or normal level of FSH (not absent) and elevated LH level, numerous follicles grow up to a certain level, remain stunted and incompetent. Elevated LH level leads to follicular atresia; and accumulation of stromal cells and connective tissue add to the bulk of the ovary. Besides, excess stimulation of theca cells results in androgenisation of the follicular microenvironment that may lead to oocyte atresia. The resultant effects are bulky and polycystic ovary, and anovulation.

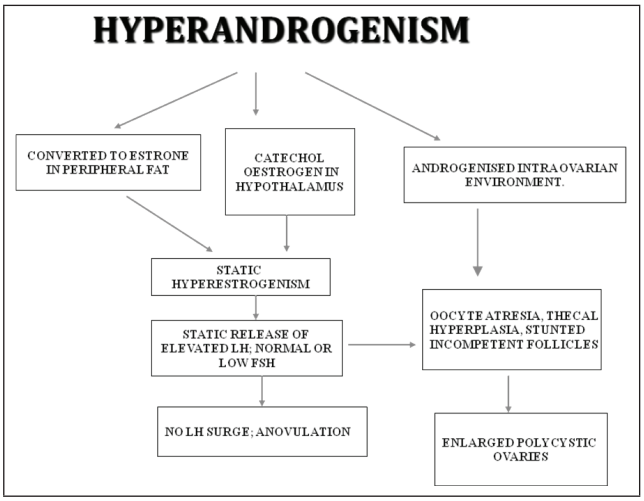


Diagram 1: Events leading to anovulation and polycystic bulky appearance of ovaries in PCOS due to hyperandrogeneism and 'static' (hyper) oestrogenism

Summarized events underlying anovulation in PCOS women

Two tropic hormones are involved; somatotropic and gonadotropic axis hormone. Hyperactivity of somatotropic axis releases excess growth hormone, insulin, and IGFs which perhaps is the primary defect in the pathogenesis of PCOS. The defect may be genetic. Erratic hyper-function of hypothalamic-pituitary–ovarian axis may be a secondary endocrine abnormality in PCOS women. The specific endocrine abnormalities include higher LH and androgen with low FSH and bioactive oestrogen levels. The follicular production of E2 may be low but the total oestrogen concentration remains constantly at a 'static' elevated level (not fluctuating) due to continuous peripheral conversion of androgen to E1, E2, and E3.

Management protocols broadly based on the unfavourable endocrine environments

Unfavourable endocrine environment	Ideal management protocol
Less FSH compared to LH	CC, CC-FSH or OC pill followed by CC-FSH
More oestrogen	Letrozole with or without FSH
More androgen	Dexamethasone-CC, Dexamethasone-CC-FSH
More insulin	CC-Metformin-FSH/HMG. Sometimes pretreatment with antiandrogens like spironolactone (aldactone, 50-200 mg for 2-3 months), metformin (1000 mg daily that indirectly lowers androgen)
Other adjunct, when necessary, with CC	L-thyroxin-CC, Bromocriptine-CC with or without gonadotropin

Take home message:

- For pharmacological manipulation of ovulation, four terminologies have been used: ovulation induction, ovulation augmentation, ovarian stimulation, and ovulation triggering
- Ovulation induction means inducing ovulation in anovulatory women; ovulation augmentation indicates production of more than one mature egg for better chance of fertilization and pregnancy, as in IUI; ovarian stimulation implies stimulation of multiple co-dominant follicular development as in IVF, and ovulation trigger involves induction of final maturity of an egg (to make it fertilizable)
- Commonest indication of ovulation induction is WHO group-II (PCOS) followed by WHO group-I (hypothalamic or hypothalamic pituitary defect) women
- Basic defect of anovulation in PCOS women is hyperandrogenecity (according to the definition by Androgen Excess Society), which is not entirely accepted by Rotterdam criteria
- The underlying causes of hyperandrogencity in women predisposed to PCOS are - hypothyroidism, hyperprolactinaemia, hyperinsulinaemia, hyperadrenalism, and hyperactive LH pulse generator in hypothalamus resulting in excess thecal androgen production
- Hyperandrogenism may lead to static hyperoestrogenism
- Static hyperoestrogenism is due to production of excess oestradiol (E2) in multiple follicles in ovary, conversion of testosterone to E1 in peripheral fat, and accumulation of E4 in the brain (hypothalamus) produced by aromatase from excess testosterone with the net effect as static elevated oestrogen
- As there is no oestrogen fluctuation, there are no LH surge and no ovulation
- Follicles are recruited every cycle, reach up to the semi-mature stage as FSH is not absent; but do not ovulate as there is no LH surge
- Semi-mature follicles are unable to reach maturity and become atretic leading to deposition of connective and fibrous tissue in the ovary every month
- Persistent accumulation of the atretic follicular remnants ultimately make ovaries polycystic and bulky – a typical appearance of PCOS

Anovulatory PCOS women may present with different clinical features and accordingly can be classified in three broad subgroups:

Group-A: These patients are

- Apparently normoestrogenic and normoandrogenic.
- Non hirsute, non obese, no history of genetic background or insulin resistance
- Only delayed menstrual cycles (35-45 days), no history of typical oligomenorrhea or secondary amenorrhooea
- On USG scan, the ovaries may be normal in size or enlarged but no thecal-stromal hyperplasia.

These cases are typical clomiphene responder

Group-B: The patients are

- Mildly androgenized with hirsutism, mild obesity, oligomenorrhea, and anovulation.
- Ovaries are enlarged, stromal hyperplasia, peripheral cysts may or may not be present These patients may still respond to CC but better option is to combine CC with metformin

Group-C: These patients are

- Typical obese and stocky subjects with family history of diabetes or PCOS
- Presents with oligomenorrhea or secondary amenorrhoea, and
- May have HAIR-AN syndrome, and ovaries are polycystic with stromal-thecal hyperplasia.

This group of patients are ideal candidates for

- Insulin sensitizing agent (ISA: metformin) with CC or gonadotropin
- ISA plus ovarian drilling
- Down regulation followed by gonadotropin plus ISA, but may also require follicular aspiration (to evade the risk of ovarian hyperstimulation)

These patients should be treated in the tertiary infertility center with meticulous monitoring.

About 30-40% of patients in group B and C may not respond to conventional CC, ISA or gonadotropin treatment. They may require adjunctive treatment. In these cases DHEAS, prolactin and baseline E2 are to be estimated. They may respond to dexamethasone, bromocriptine or aromatase inhibitors (letrozole) for adjunctive treatment see chapter on Role of Adjunct

CONVENTIONAL DRUGS USED FOR OVULATION INDUCTION

Clomiphene citrate (CC), commonly known by its brand names Clomid and Serophene, has been traditionally used as the first-line treatment in managing women with anovulatory infertility. When CC failed, gonadotropin was the alternate choice. In the last decade, letrozole, an aromatase inhibitor has emerged as alternative ovulation induction agent. Very recently, Government of India has approved the use of letrozole for ovulation induction. However, despite expansion of therapeutic armamentarium during the recent past, CC still remains the first choice in treating majority of anovulatory women.

Clomiphene citrate

Introduction of CC as ovulogen

The medication which is most commonly used to treat anovulation is CC. Clomiphene was first synthesized in 1956, introduced for trial in 1960, and approved for clinical use in the United States in 1967. It was first used to treat cases of oligomenorrhea but was expanded to include the treatment of anovulation when women undergoing treatment had higher than expected rates of pregnancy. Clomiphene is a non steroidal triphenylethylene derivative which acts as a selective oestrogen receptor modulator (SERM), having both oestrogen agonist and antagonist properties. However, clomiphene acts purely as an antagonist or anti-oestrogen; its weak oestrogenic actions are clinically apparent only when endogenous oestrogen levels are very low. The commercially available form of clomiphene is the dihydrogen citrate salt (clomiphene citrate). Clomiphene is a racemic mixture of two different stereoisomers, enclomiphene (62%; originally known as cis-clomiphene) and zuclomiphene (38%; originally known as trans-clomiphene). Enclomiphene is the more potent isomer and the one responsible for its ovulation-inducing action. Half life of enclomiphene is relatively short, so serum concentration rises and falls quickly during and after treatment. Zuclomiphene is cleared slowly; serum level remains detectable for weeks after single dose.

Mechanism of action of CC as ovulation inducing drug

Central action: The structural similarity to oestrogen allows clomiphene to compete with endogenous oestrogen for nuclear oestrogen receptors at sites throughout the reproductive system including hypothalamus. However, clomiphene binds to nuclear oestrogen receptors for a longer period of time and thereby reduces receptor concentrations by interfering with receptor recycling. In the hypothalamus oestrogen receptor depletion makes hypothalamus unaware of the presence of static elevated level of oestrogen. Hypothalamus perceives that circulating oestrogen levels are lower than actually they are in the circulation. This creates a negative oestrogen feed-back effect on hypothalamus which **triggers normal compensatory mechanism to alter the pattern of GnRH secretion and stimulate increased pituitary gonadotropin release. This in turn leads to normal follicular development.** At the pituitary level, clomiphene also might increase the sensitivity of gonadotroph cells to GnRH stimulation.

When used in ovulatory women, clomiphene citrate increases GnRH pulse frequency while in anovulatory women like PCOS, who have already an increased GnRH pulse frequency, clomiphene acts by increasing the pulse amplitude only. In successful treatment cycles with the increasing concentration of FSH, one or more follicles emerge and grow to maturity. The consequent rise of oestrogen which ultimately reaches a peak and thereafter plateau will trigger an LH surge and finally end in ovulation. In summary, clomiphene acts primarily by stimulating the normal endocrine mechanism which defines the hypothalamic pituitary ovarian feed-back axis (deranged in anovulatory PCOS patients).

Peripheral action: The adverse peripheral action of clomiphene consists of its antioestrogenic effect on endocervix, endometrium, and cervical mucous. However, these effects are not always present in all patients receiving clomiphene induction. It may be possible that the adverse effects of clomiphene are present in those patients who have a higher serum oestradiol level or in those individuals who are more sensitive to the effect of higher serum oestradiol level.

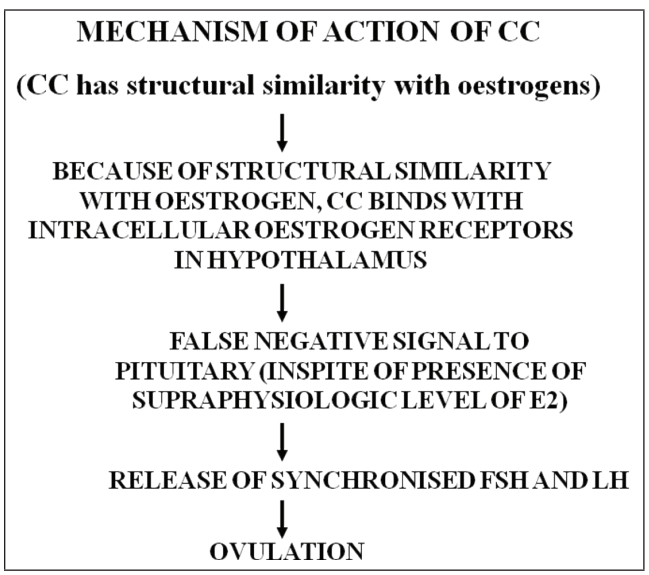
Adverse effects of CC-induced hyperoestrogenism

Deleterious effects of CC-induced hyperoestrogenism are observed on developing oocyte, embryos and blastocyst hatching. These ill effects are possibly due to abnormal chromosomal integrity and mitochondrial dysfunction. Hyperoestrogenism also leads to abnormal luteal phase due to defective corpus luteum function. Elevated E2 level impairs ductal (fallopian tube) environment and fluid resulting in impaired spermatozoal motility and embryo transport. The placental development in its early stages is also adversely affected by supra-physiological level of E2.

Deleterious effect on endometrium

Elevated level of E2 also leads to dyssynchrony of 'implantation window', abnormal expression of endometrial pinopodes, defective expression of endometrial oestrogen-progesterone receptors, abnormal endometrial blood flow and abnormal integrin expression. The net effect is 'defective' endometrial receptivity.

However, to what extent the failure to achieve pregnancy in spite of effective induction of ovulation is attributed to antioestrogenic action of clomiphene and adverse impact of supraphysiological level of oestrogen induced by clomiphene on ovum, embryo, placenta etc. remains a debatable issue.



Clomiphene citrate is a commonly used drug for ovulation induction – WHY?

CC is the most commonly used drug because it is (a) safe and simple, (b) orally effective, and (c) less ex-

pensive. CC has been used for nearly 50 years as an ovulation inducing drug. Ovulation occurs in 80% but pregnancy rate per cycle is only 20%. Higher dose (>150mg/day) and longer duration of clomiphene citrate therapy (>6 cycles) do not confer any clinical benefit. The probable cause of lower pregnancy rate with CC may be its possible anti-oestrogenic effect on the peripheral tissues, endocervix and endometrium. Additionally, as outlined in the preceding section, supraphysiological level of oestrogen, a consequence of clomiphene induction may have adverse impact on corpus luteum, ovum and embryos. Recently these peripheral adverse effects of CC have been contradicted. These adverse effects are more apparent with higher doses and after longer duration of treatment. Anti-oestrogenic effects of clomiphene induction are not usually eliminated with supplementation of exogenous oestrogen. The older regimes of treatment involving CC from d3 to d7 and ethinyl oestradiol (0.01mg) from d7 to d12 has now been abandoned.

CC resistance and CC failure

Patients who ovulate following CC induction but do not become pregnant or pregnancy ends in miscarriage are designated as CC failure cases. This may be due to supra-physiological level of E2 or poor endometrial receptivity. On the other hand, CC resistant patients are those who do not ovulate in spite of CC induction. The possible causes may be related to elevated insulin or LH, TSH or prolactin. The management of these cases consists of addition of adjuncts like metformin, bromocriptine, eltroxin, hCG etc. Even with these combinations improvement in results appears marginal.

In such cases (both CC resistance and failure), gonadotropin is the next choice. Undoubtedly this is more effective but expensive as well. The specific disadvantages associated with gonadotropin induction are:

- Higher cost of treatment
- Increased risk of multiple pregnancy
- Risk for ovarian hyperstimulation syndrome
- Requires close monitoring with ultrasound and hormonal assessment
- The inconvenience of parenteral administration

In addition, both CC and gonadotropin induction invariably induces various grades of hyperoestrogenism. Hyperoestrogenism adversely affects the developing oocyte, embryo competence, endometrial receptivity, corpus luteum function, tubal motility and developing placenta.

Aromatase inhibitor (letrozole)

Introduction of aromatase inhibitor (letrozole) as a drug for ovulation induction

The adverse impacts of supraphysiological level of oestradiol in response to clomiphene and gonadotropin induction stimulated the idea to introduce aromatase inhibitors as an alternative drug for induction of ovulation; and letrozole is a recent addition in that direction.

Special benefits of aromatase inhibitors (letrozole)

Transient anti-oestrogenic effect in hyperoestrogenic anovulatory women as in PCOS

- Short half-life
- No anti-oestrogenic effect on endometrium
- No abnormal LH surge or premature lutenization

Special characteristics of aromatase inhibitors on ovulation induction

Aromatase inhibitors have high intrinsic potential for total suppression of oestrogen (97% to 99% in doses of 1-5mg daily). The maximum suppression of E2 occurs between day5 and day7 followed by subsequent rise to trigger LH surge around day12 to day14. Rise of E2 is not supra-physiologic as with CC.

Mechanism of action of letrozole:

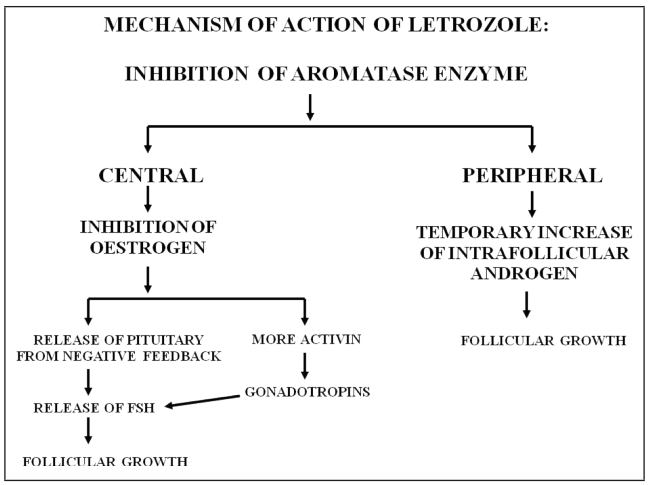
Central mechanism. Centrally letrozole inhibits negative feed-back effect of circulating oestrogen as well as locally produced oestrogen in the brain. Pituitary is now free to release gonadotropin for follicular growth and development. In addition, withdrawal of oestrogen increases the ovarian production of 'activins' that directly stimulates the pituitary 'gonadotroph' to produce more FSH.

Peripheral mechanism. In the follicles, letrozole increases follicular responsiveness to FSH stimulation. This is due to accumulation of intra-ovarian androgen. Androgens have been found to augment follicular gonadotropin receptor expression.

Reduced E_2 level following letrozole induction – is it incompatible?

Published reports indicate that mid-cycle E2 level per follicle following letrozole was half of that found with CC induction. Even then intra-follicular E2 levels are in the physiologic range. This is not incompatible with follicular growth. The rates of oocyte retrieval, fertilization, and embryo development are not inferior or may be superior to clomiphene stimulation cycle. This may be because oestradiol production at the time of ovulation is normal since letrozole is rapidly cleared from the circulation and the nature of aromatase enzyme inhibition is totally reversible.

The overall mechanism has been represented in the following diagram



Though both clomiphene and letrozole act by withdrawal of negative feed-back effect of oestrogen on hypothalamus how is it that CC produces hyperoestrogenism whereas letrozole does not. This is because letrozole directly suppresses circulating oestrogen, though temporarily, but clomiphene provides false negative signal of oestrogen suppression in the presence of elevated level of circulating oestrogen.

Clomiphene citrate vs. Letrozole: similarities and differences in the mechanism of action

Similarities: In anovulatory women with intact hypothalamic pituitary ovarian (HPO) axis, release of adequate pituitary FSH is inhibited by negative feed-back effect of 'static' elevated E2 on pituitary. Both CC and letrozole inhibit this inhibitory effect of E2 on pituitary. Hence pituitary is relieved of this inhibitory effect and thereby releases adequate amount of FSH for follicular development.

Differences: CC through its structural similarity with oestrogen binds to the hypothalamic receptors thus making the hypothalamus unaware to perceive the presence of elevated static oestrogen. This creates a 'false' negative signal, thereby withdrawing the negative impact of circulating level of static elevated E2. FSH:LH ratio is synchronized allowing LH surge to occur resulting in eventual follicular rupture and ovulation. Clomiphene therefore acts as an SERM.

By contrast, letrozole directly inhibits oestrogen production by inhibiting the enzyme, aromatase. Pituitary escapes from the negative impact of inhibitory effect of elevated E2. This allows adequate release of pituitary FSH which permits adequate follicular growth ultimately culminating in ovulation. Therefore, letrozole works as a selective oestrogen enzyme modulator (SEEM).

While peripheral action of letrozole (androgen accumulation) is beneficial for follicular growth, those of CC (anti-oestrogenic activity on endocervix and endometrium) are harmful for sperm migration and embryonic implantation. This is more marked in patients who are hypersensitive to clomiphene induction.

Literature confirms that letrozole has a definitive role in anovulatory women who have not responded to the clomiphene therapy. According to a large study from a research network supported by the National Institutes of Health, letrozole appears to be more effective in women with PCOS to achieve pregnancy. The ovulation rate, cumulative live birth rate, and live birth benefit in obese women were superior with letrozole to that with CC. Although it is probable that the overall benefits of letrozole surpass CC, many available data do not confirm this view. Therefore, the role of letrozole as an alternative to CC as first line therapy continues to be debated. There is need for large well-designed trials

Gonadotropins for ovulation induction

We have developed protocols for ovulation induction where gonadotropin is used in different small doses in all types of ovulation induction. PCOS is the commonest cause of anovulation and therefore initially we will outline the gonadotropin schedule in different grades of PCOS as we use them in clinical practice. Conventionally, we use

HMG because the cost is less and it is now more or less accepted that HMG and FSH are similar in respect of their effectivity. Routine folliculometry is performed when induction of ovulation is combined with IUI, or when hCG triggering for final oocyte maturation has been planned. In both these circumstance, instead of one, two ampoules of gonadotropins, one on d3 and one on d8 are administered.

Take Home Message:

- Clinically, PCOS patients can be categorized broadly into three groups. Group-A: – mild variety with minimal manifestation of clinical and biochemical hyperandrogenicity and ovarian changes; Group-B – moderate and Group-C - severe grades of clinical, biochemical manifestations and ovarian morphological changes
- The first group needs simple treatment with CC or letrozole with or without adjuncts like insulin sensitizing agents, eltroxin, bromocriptine etc. to improve pregnancy outcome. In our protocol, we always use low (1 or 2 ampoules) dose gonadotropin and luteal phase progesterone support
- The second group, invariably requires addition of ISA or other adjuncts including gonadotropin
- The third group should be treated in tertiary infertility centre and may require continuous gonadotropin with or without down-regulation finally ending in IVF
- Laparoscopic ovarian drilling is a rewarding alternate option in Group-C PCOS women
- In ovulation induction protocol, CC is the first choice because the treatment is safe, simple, and less expensive
- However, pregnancy rate is low (~20%) compared to ovulation rate which may be as high as 80%
- Failure to achieve pregnancy may be of two types: those who do not ovulate (CC failure, ~ 20%) and those who ovulate but fail to achieve pregnancy (CC resistant, ~ 80%)
- Failure to achieve pregnancy may be due to adverse consequences of CC induction including antioestrogenic effect of CC and supraphysiological level of oestrogen
- Gonadotropin, the next choice in CC failure cases is not only expensive and a complicated protocol but may be associated with complications like OHSS and multiple pregnancy
- The third generation aromatase inhibitor, letrozole which was introduced for the treatment of carcinoma of breast proved to be an effective replacement for CC failure cases
- Because of its use in carcinoma of breast, there was some concern for its use in ovulation induction and use of the drug for induction of ovulation was banned in India temporarily.
- However the restriction is now withdrawn and letrozole has now been approved for induction of ovulation
- Letrozole has already proved to be an effective alternative, if not superior to the conventional drug clomiphene, without the risk of teratogenic effect on the offspring
- Both CC and letrozole act by withdrawal of negative feedback effect of static elevated oestrogen and thereby allowing pulsatile release of FSH and LH which restore normal ovulatory function. This is the similarity of action for both CC and letrozole
- However, there is dissimilarity as well. While letrozole acts by direct and real suppression of circulating oestrogen though temporarily, but clomiphene through its weak oestrogenic component occupies hypothalamic nuclear reception and makes it unaware of presence of oestrogen in spite of its existence in supra-physiological level in the peripheral circulation. Through a false negative feed-back signal, hypothalamus releases normal levels of FSH and LH, and ovulatory function is restored
- Peripheral action of CC consists of adverse effect on cervical mucous and endometrial receptivity but peripheral action of letrozole induces accumulation of androgen in the follicular fluid which increases follicular sensitivity to gonadotropin
- Additionally inhibition of oestrogen in the brain leads to increased synthesis and release of activin which leads to increased secretion of gonadotropin
- The special benefits of letrozole are transient

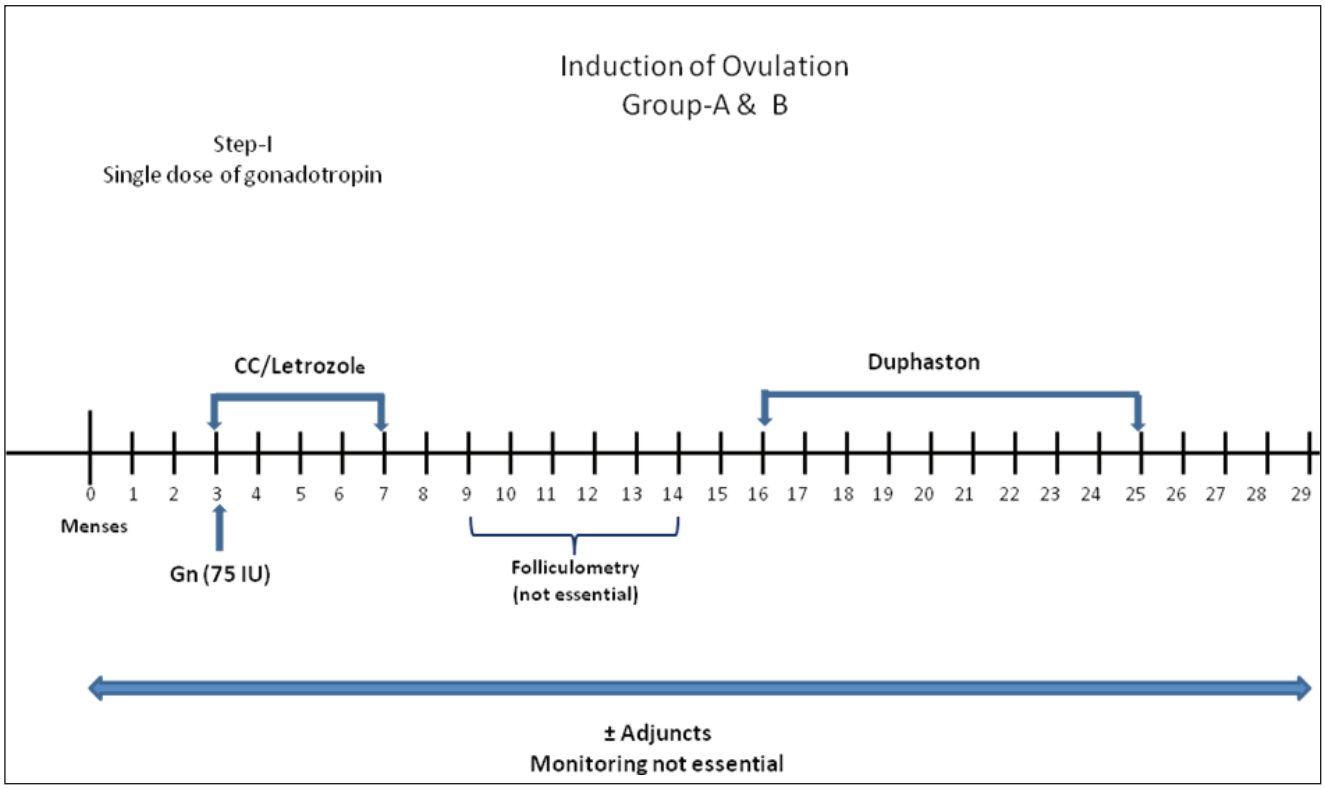


Diagram-I

antioestrogenic effect in hyperoestrogenic anovulatory PCOS, short half-life, no antioestrogenic effect on endometrium and no abnormal LH surge or premature luteinization

- Inspite of all these benefits in favour of letrozole, CC is still the first drug of choice for ovulation induction. Because this drug has been used for last 50 years without side effects where as letrozole induction has been practiced only for 20 years and its efficacy and safety are yet to be confirmed
- Low doses of gonadotropin have been used along with CC or letrozole to enhance outcome of induction but specific precautions are to be taken to avoid side effects of this drug like OHSS or multiple pregnancy
- In special situations, laparoscopic ovarian drilling may have a better positive role for ovulation induction – specially in Group-C PCOS patients

Ovulation Induction protocols (As practiced at IRM, Kolkata)

Indications of ovulation induction/augmentation (WHO group-2 anovulatory PCOS and unexplained infertility)

Before initiating ovulation induction protocol, other infertility factors are excluded. The commonest indications include a) Anovulatory PCOS women (WHO Group-II) and women with unexplained infertility, b) WHO group-I (hypogonadotropic hypogonadal women), though rare, they are also treated with induction of ovulation but in a modified protocol. A brief description of the protocol with our experience with these types of patients will follow at the end of this section, c) Women with unilateral tubal block may be associated with mild to moderate pelvic adhesion are also initially given the choice of ovulation induction (for augmentation) prior to shifting them to more expensive IVF treatment d) Lastly, oligozoospermic men (mild to moderate degree; 10-20 million/ml) but without asthenozoospermia, not responding to medical therapy are also treated with drugs for ovulation induction / augmentation followed by IUI. In all these groups other causes of infertility are excluded.

In the following paragraphs, the protocols used primarily for anovulatory PCOS women at IRM, Kolkata will be discussed, followed by use of similar protocols in women with unexplained infertility, unilateral tubal block and spouses of sub-fertile

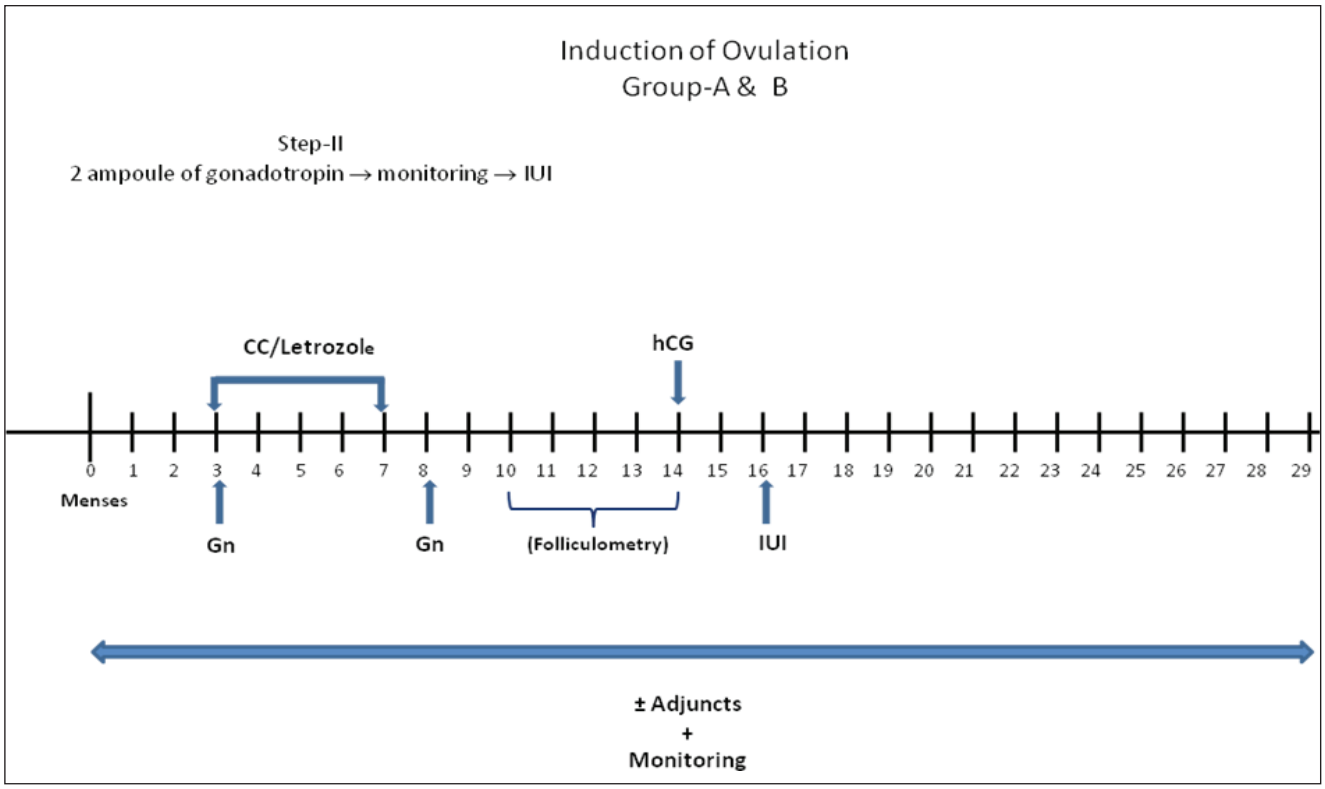


Diagram-II

oligospermic men (without asthenozoospermia) will be outlined. Finally, protocols used for WHO Group-I women (hypo-hypo group) with our recent experience in a specific group of women (Kallman's syndrome) will be presented.

Protocols for anovulatory PCOS women

As indicated earlier, protocol for induction of ovulation will differ in different groups of PCOS women. In general four protocols are used in three different groups of PCOS women.

Protocols for Group-A and Group-B: Stepwise these protocols are as described below.

Step-1 Protocol

CC (50 mg twice daily) or Letrozole (2.5 mg twice daily) from d3-d7

+

HMG/FSH (75 IU) 1 ampoule on d3

+

Intra-vaginal Dydrogesterone (10 mg twice daily) or Micronized natural progesterone (200 mg twice daily)

If there is no conception, subsequent menstrual cycle will start 5 to 10 days following last dose of luteal phase progesterone. The protocol is repeated for three consecutive cycles. In cases of failure to achieve pregnancy we move on to; (Diagram-I)

Step-2 protocol (Diagram-II)

Clomiphene (50 mg twice daily) or letrozole (2.5 mg twice daily) from d3 to d7

+

Injection gonadotropin (HMG/FSH 75 IU) on d3 and on d8

↓

USG scan for folliculometry from d10

↓

hCG trigger,- when lead follicle is 17-18 mm

↓

IUI/TI (Timed intercourse)

Step-2 protocol has been represented in diagram -II

Step-3 protocol

If these protocols fail, the subsequent step-3 protocol will include administration of higher doses of gonadotropins but in combination with CC or letrozole. There are two sub-groups in this protocol. The first sub-group: Gonadotropins are used in

'interrupted' schedule (alternate days) overlapping with clomiphene or letrozole or in second sub-group: in a sequential fashion, meaning that gonadotropin is started at the end of CC or letrozole schedule (d5 or d8). USG folliculometry starts on d10; hCG trigger is administered when lead follicle is about 17-18 mm. This is followed by IUI. These two protocols ('IIIa-interuppted' and 'IIIb - sequential') are represented in following diagrams III and IV.

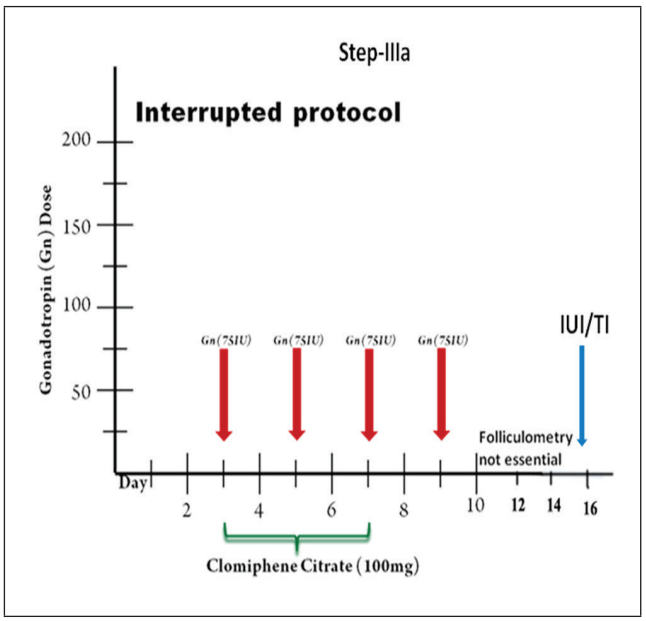


Diagram-III:- Interrupted protocol – along with clomiphene citrate (d3-d7) – gonadotrophin

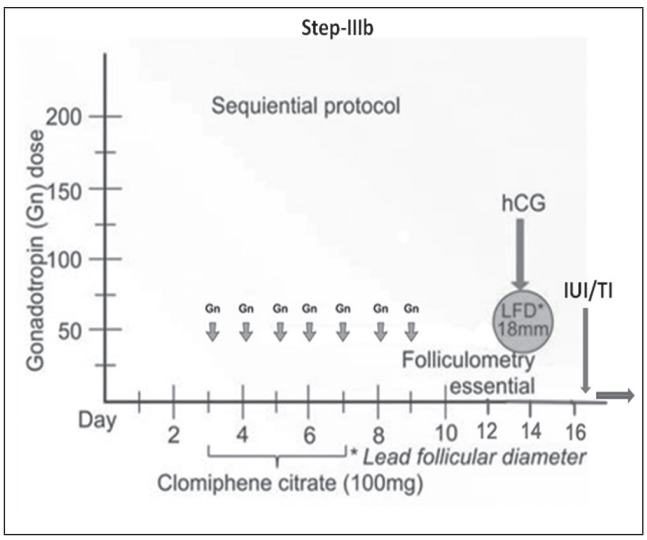


Diagram -IV:- Sequential protocols - Clomiphene citrate is administered (d3-d7) – gonadotrophin is started from d5 or d8 continued till LFD is

If this schedule also fails, the next move is to proceed to step-4 continuous gonadotropin therapy eliminating CC and letrozole.

Step-4 Protocol

This protocol is also followed in group-C PCOS women. In this schedule CC or letrozole is not used. Gonadotropin (HMG/FSH- 75-150 IU) is administered daily from d2 onward. Co-treatment with metformin may be necessary as most of these women are hyperinsulinemic. These cases require USG monitoring from d7/d8 onwards for adjustment of the dose of gonadotropin (either step-up or step-down) and GnRH–antagonist addition may be necessary to prevent pre-mature 'LH surge'.

In cases when too many follicles develop, the patients are to be shifted from IUI to IVF programme. The protocol is similar to those used in group–C PCOS women (see subsequent paragraph and diagram).

Group-C anovulatory women: These cases are grossly androgenised with evidences of hyperinsulinemia and they should be treated in tertiary infertility care units. Several options of treatment have been suggested: (a) pre-treatment with insulin sensitizing agents, lifestyle changes, (b) pre-treatment with OC pill, and (c) pre-treatment with ovarian drilling.

The objectives of all these treatments are to down-regulate LH, androgen, insulin and obesity to make her fit for ovulation induction followed by IUI or in-vitro fertilization. Following these pretreatments, the options are a) conventional IVF with either agonist or antagonist down regulation (preferably antagonist), b) Gonadotropin stimulation (150 IU) without down regulation daily from d2, USG folliculometry from d6/d7, and adjustment of dose of gonadotropin under antagonist down regulation control. When too many follicles develop, patients are shifted to IVF protocol for follicular aspiration and IVF for prevention of OHSS. If average or less numbers of follicles develop, IUI is performed. This is known as a protocol 'IUI converted to IVF' (Figure –VI).

Few areas of our protocol of induction of ovulation need further elaboration and clarification. Question-wise these areas are:

- Why one or two ampoules of gonadotropin are added in group-A and group-B PCOS women?
- Why folliculometry is not included with induction in group-A PCOS women?
- Why progesterone has been added in group-A and group-B PCOS women which are not monitored by USG folliculometry?

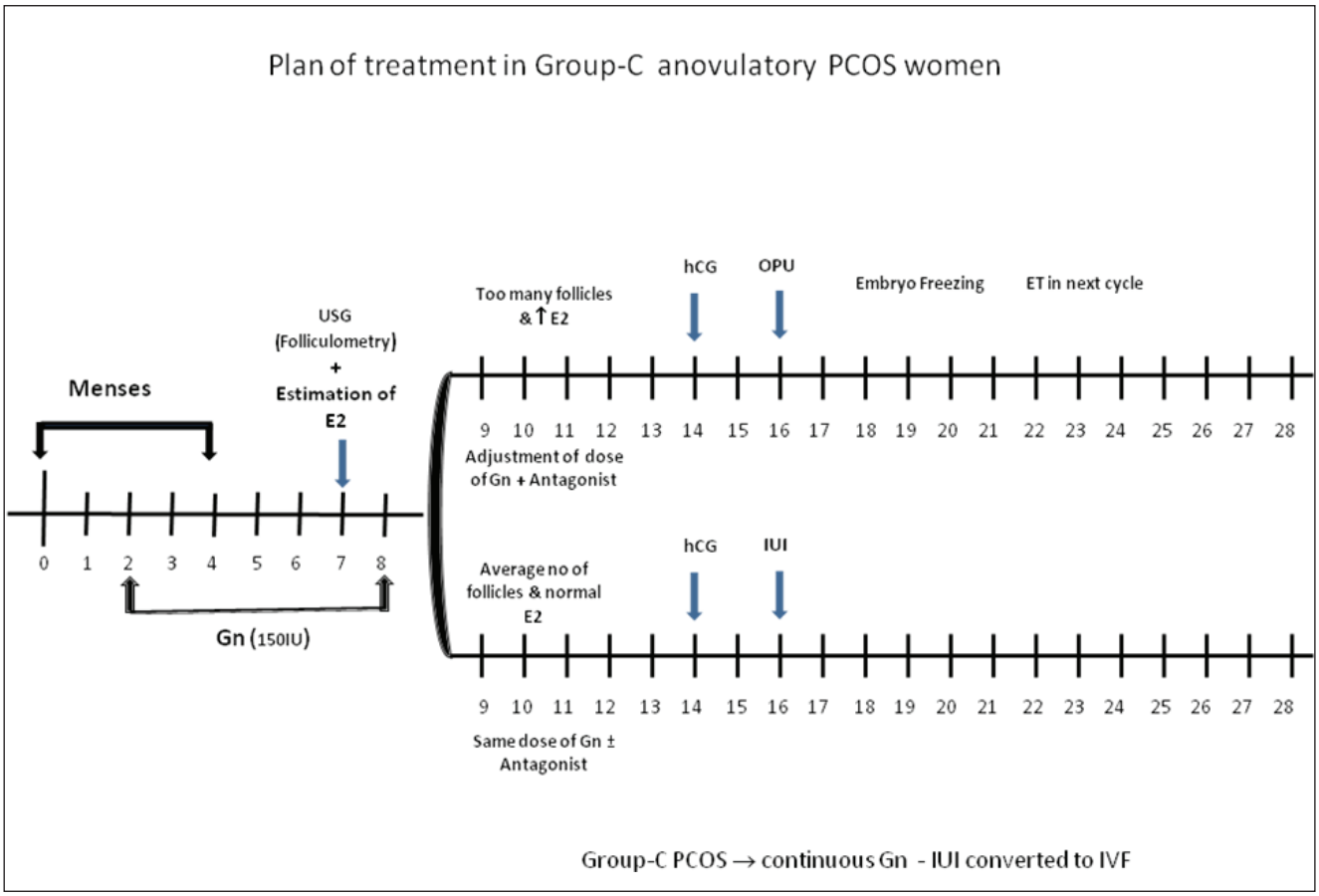


Diagram-V

- In continuous gonadotropin stimulation protocol, as used in some cases of group-B and group-C PCOS women, dose of 150 IU gonadotropin has been suggested. What is the risk of OHSS with this dose?
- Does addition of gonadotropin with CC and letrozole increase pregnancy rate compared to those with only CC induction? What is the evidence?
- Is addition of extra ampoule of gonadotropin with CC or letrozole effective in women with unexplained infertility as has been found with PCOS?
- What is the choice of gonadotropins; FSH or HMG?

The explanations are as follows:-

- In Group-A and majority of Group-B patients, CC or letrozole with one or two ampoule(s) of gonadotropin is used and routine folliculometry is not performed. The protocol is simple, less expensive and more convenient for the couple. The patients need not come to the clinic for folliculometry everyday.
- The objectives of adding gonadotropin to CC or letrozole are: one or two additional co-dominant follicle(s) are recruited through d3 gonadotropin before actual emergence of dominant follicle, which is scheduled by day5/day6. In addition, d8 gonadotropin administration will increase E2 level in late follicular phase which will have more positive feedback effect on hypothamus for release of an 'effective*' LH surge essential for production of 'mature**' (see footnote) oocyte. The benefits of this protocol have been supported by our study which has already been published (Table-1). Moreover, as the dose of gonadotropin administered is low, they do not require vigilant monitoring.
- Similar rewarding outcome with one or two ampoule(s) of gonadotropin, however, was not achieved in women with unexplained infertility. Therefore, women with unexplained infertility may require more than simple correction of possible subtle ovulatory defect.

- Luteal support is added for two reasons: a) luteal phase deficiency following CC therapy is not uncommon (anti-oestrogenic effect on endometrium), and b) in the absence of pregnancy, the onset of next period is uncertain (oligomenorrhoea is common in PCOS patients).
- For starting the next stimulation protocol, urine for pregnancy test and drugs for withdrawal bleeding will not be necessary with routine progesterone treatment in the luteal phase. However when induction with CC and HMG is followed by IUI – the protocol is modified
- Instead of one ampoule on day3 another ampoule is added on day8 and in these cases the cycle is monitored by serial ultrasound scanning for folliculometry.
- The gonadotropin choice between recombinant FSH vs. HMG will depend on the clinical features of hyperandrogenecity and hyperinsulinemia with biochemical evidence of abnormal LH rise (basal level >12mIU/ml). If these features are not present, as in group-A, and in some cases of group-B PCOs patients, there is no difference in pregnancy outcome following the use of either rFSH or HMG in group-C patients who usually have high basal level of LH (>12mIU/ml).
- Ovarian drilling is an alternative option for these gonadotropin hyper-responding women if facilities for IVF are not available.
- When continuous gonadotropin is used in a dose of 150 IU daily, as in some cases of Group-B and most of the cases in group-C, vigilant monitoring is essential, and if necessary, they are to shifted from IUI to IVF protocol.

Table-1: Comparison of pregnancy and miscarriage rate in PCOS patients who received only clomiphene and those who received one ampoule of gonadotropin with clomiphene

Outcome parameters	Group A	Group B	Relative rate ratio	P value
	CC+HMG protocol (n=460)	CC-protocol (n=451)	(95% CI)	
Pregnancy rate	22% (n=102)	9.3% (42)	2.38 (1.70, 3.32)	0.0001
Miscarriage rate	8.8% (9)	9.5% (4)	0.92 (0.30, 2.84)	0.99

***What is meant by 'effective' LH surge and 'mature oocyte'**

In this context, this is worth recapitulating that at the terminal stage of follicular development (d10-d11) each mature follicle should contribute to 75pg to 100pg of circulating E2. In stimulated cycle, if there are 3 or 4 co-dominant follicles, the 'peak' oestradiol level is expected to reach at 300-400 pg/ml, which will generate 'effective' LH surge.

There is another event during this period. Effective LH surge is generated when the level of LH reaches a range between 90-100 IU/L. Moreover, the dominant follicle(s) should remain exposed to this level of LH surge for a period ranging between 16 hrs and 24 hrs for the release of a 'mature' oocyte.

**'Mature' oocyte indicates release of first polar body of the occyte in the perivitelline space with gradual disappearance of germinal vesicle (GV). In IVF laboratory, maturity of the retrieved oocytes can be indentified under the microscope immediately after oocyte retrieval. But, in the ordinary induction of ovulation protocol, one has to depend on qualitative detection of urinary LH by 'LH Kit' that may be started on d10 simultaneous with ultrasound assessment of follicular development. LH surge followed by ovulation are confirmed by colour change on LH kit and ultrasonographic visualization of collapse of dominant follicle and appearance of fluid in POD. Currently urinary LH monitoring is not practiced; USG monitoring of developing follicle is the preferred choice. But precise assessment of maturity of the oocytes (for example first polar body in perivitelline and disappearance of GV in the ooplasm) which has been ovulated in that particular cycle cannot be assessed properly. This is one of the reasons underlying a discrepancy between the incidence of ovulation and actual occurrence of pregnancy following ovulation induction with or without IUI.

Laparoscopic ovarian drilling (LOD) for ovulation induction

LOD is not a medical treatment for ovulation induction, but rewarding alternative to gonadotropin in CC-resistant PCOS women. The suggested mechanisms of action of LOD include a reduction of androgens and inhibin levels following the destruction of ovarian follicles and a part of the

ovarian stroma that causes an increase of FSH, allows optimum delivery of the gonadotropins and post-surgical local growth factors, and restores ovulation function. A comprehensive review concluded that LOD leads to spontaneous restoration of fertility in 20–64% of CC-resistant PCOS women, while a meta-analysis reported a success in 44–50% of patients.

Tamoxifen (TMX) as an ovulogen

It is a nonsteroidal SERM, which closely resembles CC. Like CC, TMX occupies oestradiol-binding sites on the hypothalamic–pituitary axis and prevents the negative feedback effect of oestradiol, resulting in increased endogenous gonadotropin secretion. Direct action on ovary without involving hypothalamo-pituitary axis has also been suggested. Unlike clomiphene, tamoxifen acts as an agonist on the oestrogen receptors of the endometrium which is beneficial, especially for those suffering from an adverse response following the administration of CC. Published literature reported ovulation rate of 50–90% and pregnancy rate of 30-50% following TMX; and this is achieved with dose of 20–80 mg.

Women who had thin endometrium with CC (<7 mm) exhibited improved endometrial thickness when tamoxifen was used for ovulation induction in the subsequent cycle. (36, 37) Contrary to previous literature, a recent RCT conducted by Badawy et al showed a statistically significant lower ovulation rate following TMX compared to CC in PCOS women. According to this study CC is more successful than TMX in PCOS women.

Enclomiphene as an ovulogen

As already stated, CC is a mixture of enclomiphene and zuclomiphene. Enclomiphene is more potent isomer and is responsible for ovulation induction. Zuclomiphene, less active isomer gets accumulated for a longer time in the body and is detectable in the circulation even after 1 month of treatment. It has been suggested that the side effects of CC like thin endometrium and thickening of cervical mucus is due to this zuclomiphene. However, there is no evidence that enclomiphene, as compared to clomiphene, improves endometrial thickness and pregnancy rates.

Take home Message:

- Commonest indication of ovulation induction is WHO group-II anovulatory PCOS.
- Ovulation inducing drugs are also frequently used for ovulation augmentation, especially in unexplained infertility.
- Less common indications are women with unilateral tubal block and female partner of sub-fertile oligospermic husband
- WHO group-I (hypo-hypo) women are also rare indication of induction of ovulation.
- Other infertility factors are excluded before initiating protocols of ovulation induction in these women.
- Apart from WHO group-I women,- protocols of ovulation induction or augmentation are similar in all groups.
- In anovulatory PCOS women, stepwise four protocols are followed depending on patient characteristics (grouping of PCOS patients)
- Group-A and majority of group-B PCOS patients receive CC or letrozole (d3-d7) and additionally one ampoule of gonadotropin on d3 (protocol-1)
- They do not require USG monitoring for folliculometry
- Progesterone (either dydrogesterone or micronized vaginal progesterone) is added as routine from d16 to d25
- This protocol is used because the procedure is simple and less expensive
- If these protocols fail,- two ampoules of gonadotropin (75 IU each) are added one on d3 and one on d8 (protocol-2)
- This protocol requires folliculometry,- ovulation trigger with hCG,- usually followed by IUI or TI (Timed intercourse)
- When this protocol also fails to induce ovulation and pregnancy, the dose and duration of gonadotropin injection are increased but still in a restricted manner (to avoid OHSS and multiple pregnancies)
- CC or letrozole are combined as in protocol-1 and 2 to increase the effectivity of induction.
- Two different schedules of gonadotropin administration are followed: interrupted (d3, d5, d7 and d9) administration overlapping with CC or letrozole initiated from d2 or d3 (step-IIIa); and sequential administration of gonadotropin (75 IU) starting from d5 or d7 and continuing till the lead follicular diameter reaches 17 or 18 mm (step-IIIb).

- These protocols (IIIa and IIIb) end with ovulation trigger with hCG followed by IUI.
- In case these protocols also fail, the next step is continuous gonadotropin (150 IU) daily from d2 (step-IV) until the lead follicle(s) reaches 17-18 mm
- Ovulation trigger with hCG is given followed by IUI.
- The last protocol (step-IV) is also the conventional protocol in group-C PCOS women.
- This protocol is recommended in tertiary care unit because some of these women may be hyper-responsive and may require follicular aspiration and IVF.
- In group-C anovulatory PCOS women, pre-treatment with insulin sensitizing agent (metformin, inositol), life style changes, OC pill and or ovarian drilling will help.

OVULATION INDUCTION IN WHO GROUP-I WOMEN

WHO Group-I women also suffer from hypothalamic amenorrhoea. In this group clomiphene and related drugs are ineffective because an intact and functional hypothalamic pituitary ovarian (HPO) axis is essential for their pharmacological action.

Two groups of drugs are commonly effective:

a) Pulsatile gonadotropin releasing hormone
b) Exogenous gonadotropin containing both FSH and LH

Pulsatile GnRH is effective only in hypothamic anovulation and not useful when pituitary is also affected. In pituitary defect replacement with gonadotropin is the only choice.

Though currently GnRH is not used in clinical practice – a brief review of this hormone may be of interest for the readers.

Pulsatile GnRH

In the 1980s, exogenous pulsatile GnRH therapy was first used successfully to induce ovulation in WHO Group-I anovulatory women. The method was simple because its use does not require extensive and costly monitoring, and also it is associated with low risk of both multiple pregnancies and ovarian hyperstimulation. Moreover, GnRH therapy generates the physiological level of FSH and LH through internal feedback mechanism between pituitary and ovary that results in follicular growth and development similar to a regular menstrual cycle in response to 'turning on' of the system by GnRH. In principle, pulsatile GnRH therapy represents an artificial hypothalamus.

Indications of use

Functional hypothermic amenorrhoea and anovulation [diagnosed by the absence of menstrual bleeding following a progestin challenge test and exclusion of space occupying lesion (SOL) by imaging] is the most typical indication of induction of ovulation with GnRH. Less commonly, GnRH pump has also been used in women with polycystic ovaries (who require a lower dose of GnRH (2.5µg per bolus) to avoid OHSS) and also hyperprolactinaemic bromocriptine intolerant women. However, they are rare indications for GnRH pump induction of ovulation.

Methods and dose

As GnRH is absent, there is no cyclical function of HPO axis. Hence treatment with GnRH may be started any day, and this will lead to a subsequent release of sequential pulsatile levels of FSH, oestrodiol, LH and progesterone in the follicular, ovulatory, and luteal phases, ending in either pregnancy or menstruation (if pregnancy does not occur).

GnRH is administered constantly in a pulsatile fashion through a programmable and portable mini pump. GnRH is available in the crystalline form which can be reconstituted in aqueous diluents and remainS stable at room temperature for at least three weeks.

The pump is fixed to a belt (just like police man's belt) which has to be worn around the waist continuously round the clock requiring some special devices for bathing and sleeping.

Route of administration is either subcutaneous or intravenous. For intravenous administration, heparin in a concentration of 1000 U per ml is added to the solution. The intravenous route is favoured in most of the clinics. The needle is left in place and changed when there are signs of local

inflammation. Subcutaneous route is preferred in women who are at risk for bacterial endocarditis. The dose of subcutaneous administration is 20µg per bolus as against 5µg per bolus with intravenous administration.

The pulse frequency of the bolus administration has been empirically fixed at 90 – minute cycle throughout the treatment. The response is assessed by weekly estimation of serum oestradiol. The dose may be increased by 5 µg increment if the response is inadequate.

The time of ovulation is difficult to ascertain. Ovulation occurs 14 days after initiation of treatment, but the range extends from 10 days to 22 days. The exact date of ovulation can be determined by serial USG monitoring, but the couple can also use the urinary LH kits to detect the date of LH surge and try for pregnancy for 2 to 3 days beginning the day of colour change.

Luteal phase following ovulation has to be supported either by continuing GnRH pump or by administration of hCG (2000IU) IM twice a week for 2 weeks (injection beginning from the day of ovulation as determined by USG scan or LH kit). Most of the patients wish to discontinue the pump. Exogenous progesterone may also be used as an alternative to hCG following discontinuation of GnRH-a pump.

Side effects are minimal. But the problems are mainly related to the inconvenience of carrying the pump for 14 to 21 days continuously and also for acquiring the knowledge of the functioning of the pump during this period. For these reasons this treatment has not been trendy and practically abandoned in modern infertility treatment.

Pregnancy rate with GnRH-a pump is, however, quite satisfactory. Persistence of repeated cycle treatment may yield a cumulative pregnancy rate of approximately 80% after 6 cycles and 93% after 12 cycles. The abortion rate is 20%, and this is typical of all methodologies. If used in polycystic ovary syndrome, pituitary should be down-regulated with GnRH agonist protocol and the down-regulation protocol should be repeated every cycle before GnRH pump therapy is used for induction of ovulation. However, in POCS women cumulative pregnancy rate has been estimated as 60%. Obese patients are less likely to respond, and they have a higher incidence of abortion.

Even after saying so much about GnRH pump therapy and the associated advantages the procedure has not received much acceptance by the patients.

Exogenous gonadotropin replacement

Currently, this is the accepted form of treatment. These patients require gonadotropin induction in high doses for a prolonged period, and as both FSH and LH are deficient, they need either HMG or combination of rFSH and rLH induction. Prior priming with HRT makes the ovaries and uterus more sensitive to gonadotropin stimulation. Our protocol consists of:

Withdrawal bleeding with OC pills followed by sequential administration of conjugated oestrogen (Premarin – 0.625mg) 1 tab daily from d5 to d25 combined with progesterone (Allyloestrinol – Maintane 0.5mg) twice daily from d16 to d25 for 3-6 cycles followed by gonadotropin induction. This protocol of pre-treatment is expected to make the uterus and ovaries more sensitive to subsequent gonadotropin induction.

Usually, the minimum starting dose of HMG essential for efficient induction of ovulation is 225 IU daily, and the dose has to be adjusted subsequently depending on follicular response ascertained by ultrasound scan on d7/d8. The duration of stimulation may be as long as 15 to 20 days.

When rFSH and rLH are used, the ratio of starting dose is rFSH: rLH::3:1 which is reversed to 1:3 in the late follicular phase when the lead follicular diameter is reaching to 17mm to 18mm, and a triggering dose of hCG (10000IU) is administered. IUI or IVF follows. If one cycle fails, the starting dose of gonadotropin may have to be escalated in subsequent cycles.

Ovulation induction in a special class of hypo-hypo anovulatory group – Kallmann Syndrome: OUR Experience

One of the rare examples of hypogonadotropic hypogonadal anovulation is Kallmann syndrome (KS). Incidence is one per 50000 women. It is predominantly an x-linked recessive disorder caused by the mutation of the Kal-1 gene on Xp.22.3. Rarer kind of this syndrome includes an autosomal

dominant form. The patients with KS, apart from hypogonadotropic hypogonadism, may have other clinical features like anosmia, facial asymmetry, cleft palate, colour blindness, deafness and renal abnormalities. It is important to note that some women with KS have an isolated gonadotropin deficiency without any other phenotypic abnormalities and may present de-novo with infertility. It is often possible to stimulate ovulation with gonadotropin replacement therapy. Hypogonadism in these cases is due to GnRH deficiency which results from failure of embryonic migration of GnRH-producing neurons to the hypothalamic area because of genetic mutation.

These patients respond well to exogenous HMG and hCG protocol. We present here our own experience of achieving three pregnancies in patients with KS with brief review of the literature.

In patients with KS, approximately 120 pregnancies have been reported in the literature since 1990. Most commonly used protocol for ovulation induction in women with KS is HMG. We have published successful conception in a series of three KS patients with HMG induction. One patient achieved pregnancy with ovulation induction, second with fresh embryo transfer, and the third with frozen embryo transfer. Out of these three, two delivered at term, and both children were doing well at one year of follow up. Both these patients were diagnosed with KS during their pubertal years and were on cyclical hormone therapy since adolescence. Their ovaries responded satisfactorily to gonadotropins, and the uterus was well responsive to oestrogen therapy. The third patient was diagnosed with KS at 31 years of age, and HT was given only for six months for priming before starting ovulation induction. Since her uterine size was minimal (20x24x48mm), the growth of endometrial thickness was monitored with incremental doses of oestrogen. Endometrial thickness was only 5 mm in spite of high dose of oestrogen, and the guarded prognosis was explained to the couple. During ovarian stimulation with high dose gonadotropins, her endometrial thickness increased to 7.1 mm. She conceived after embryo transfer but unfortunately had a missed abortion. After managing these three cases, we extrapolated that it is essential to treat these women with hormone therapy from puberty onwards, not only to attain secondary sexual characteristics but also for satisfactory fertility outcome. In another case series, follicular response to gonadotropins was insufficient in patients not previously primed with hormone therapy in comparison to hormone-primed patients. Ovulation induction and conception can be achieved sooner and with less cost, if they are already primed.

Another case report of KS suggested that testosterone supplementation before ovarian stimulation dramatically improved follicular response to gonadotropins in patients who were previously resistant to gonadotropin stimulation. Similarly, LH-priming in hypogonadotrophic hypogonadism before ovarian stimulation with FSH may reduce the dose required for preovulatory follicular development. Although it may be challenging to attain fertility in KS with persistent efforts, results are not always disappointing.

Take home message:

- In WHO-I anovulatory women, induction with clomiphene or letrozole is not possible because these drugs require an intact hypothalamic-pituitary-ovarian axis for their pharmacological action
- Provided pituitary is normal, GnRH pump works as an artificial hypothalamus
- The pump induces physiological release of pulsatile gonadotropins (FSH & LH) from pituitary and oestrogen and progesterone from ovary – inducing mono-follicular ovulation
- Unlike treatment with gonadotropins, pulsatile GnRH pump avoids the risk of ovarian hyper stimulation and multiple pregnancies
- Continuous infusion of GnRH is carried out either via intra-venous or subcutaneous route through programmable and portable mini-pump
- Dose administered is 20µg/bolus (subcutaneous route) or 5µg/bolus (intravenous route) with a pulse frequency fixed arbitrarily at 90 minute cycle throughout the treatment
- Pump is continued even after ovulation but most women are reluctant to continue the pump after ovulation has occurred
- The dose is adjustable according to response. Ovulation is detected either through serial

folliculometry or with the help of urinary LH kit to fix up the timing of IUI or TI

- Luteal support either in the form of small doses of hCG or progesterone is essential
- Apart from hypothalamic anovulation, GnRH pump for ovulation induction has also been used (though rarely) in PCOS women not responding to CC or hyperprolactinaemic women intolerant to bromocriptine
- Satisfactory pregnancy rate of 80-90% has been reported following persistent GnRH pump therapy in hypothalamic anovulation and about 60% in PCOS women
- Inspite of all these advantages, the inconvenient methodology for the use have made GnRH pump an unpopular treatment and is rarely practiced currently
- Alternative treatment with exogenous gonadotropin (both rFSH and rLH or HMG) has become the treatment of choice
- However, to maintain the sensitivity of ovaries and uterus during reproductive years, it has been suggested that a prior priming of the uterus with sequential administration of oestrogen and progesterone is essential
- These steroid hormones not only stimulate growth and development of secondary sex characters but also help maintain ovaries and uterus sensitive to subsequent gonadotropin stimulation used for induction of ovulation
- Low dose androgen in the form of DHEAS has also been recommended for augmenting ovarian and uterine sensitivity to subsequent gonadotropin stimulation

Further reading

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Role of Tamoxifen in Women with Thin Endometrium (<7mm) after Clomiphene Use

Sunita Sharma, Gunja Bose, Ratnaboli Bhattacharya, B N Chakravarty

INTRODUCTION

Tamoxifen (TMX) closely resembles Clomiphene citrate (CC) both in structure and mode of action. It appears to have agonistic action on the endometrium.[1] TMX, primarily developed for use in the treatment of breast cancer, is a selective estrogen receptor modulator that closely resembles CC. Published literature reported ovulation rate of 50-90% and pregnancy rate of 30-50% following TMX.[2] Like CC, TMX occupies estradiol-binding sites on the hypothalamic– pituitary axis and prevent the negative feedback effect of estradiol, resulting in increased endogenous gonadotropin secretion.[3] Direct action on the ovary without involving hypothalamic-pituitary axis has also been suggested.[4] TMX unlike CC acts as an agonist on the endometrium and cervical mucus.[2] Simultaneously, its use for ovulation induction for short duration is also not associated with increased risk of ovarian and endometrial cancers.[5]

The increased estrogenic stimulation that has been observed with TMX action on the lower genital tract may be beneficial, especially for those suffering from an adverse response following the administration of CC. It was postulated that, by administration of TMX, it might be possible to mimic the action of CC for the stimulation of ovarian follicles and avoid the adverse effects of CC on the endometrium. All these make TMX a promising alternative to gonadotropins.

Intrauterine insemination (IUI) is commonly used for large group of subfertile patients.[6] It is cheaper, easy to perform, and more acceptable to the couple when compared to in-vitro fertilization (IVF)/intra-cytoplasmic sperm injection (ICSI).

Clomiphene citrate (CC) continues to be the most commonly used drug for ovarian stimulation in IUI cycles. Despite an ovulation rate of 50–75%, pregnancy rate per cycle is in 10%–20% of cases[7,8] due to anti-estrogenic effect of CC at the level of endometrium. Endometrial thinning has been observed in 15%–50% of women who used CC.[9,10]

In order to increase endometrial thickness (ET) various strategies have been tried to minimize the anti-estrogenic actions of CC but with limited success. Addition of systemic or vaginal estrogen along with CC treatment was reported to increase ET.[6,7] Low-dose aspirin[8] and sildenafil used intravaginally[9] may modulate uterine artery blood flow and hence improve ET. Other methods like starting CC earlier in the cycle,[10] use of letrozole[11] and delaying the hCG administration[12] has also been proposed. However, all these options to get better endometrial thickness are controversial.

Treatment with gonadotropins and IUI is found to be highly successful in patients who do not conceive after treatment with CC undergoing IUI. Gonadotropin use raises several concerns like expense, intensive monitoring, multiple pregnancy rate, which is equal to or higher than in IVF.[13]

A prospective study was conducted at our institute to compare the efficacy of low dose CC (50mg), TMX, and gonadotropins in women with thin endometrium (<7mm) following CC (100mg) in IUI cycle.

Materials and Methods:

This was a prospective study carried from December 2011 to June 2013. A total of 502 women between 25 to 38 years undergoing 932 IUI cycles were included for the following indications: male factor, anovulation, and unexplained infertility (Figure 1). All women had endometrial thickness (ET) less than 7mm after 100mg of CC in earlier cycle were recruited. Pelvic ultrasonography was performed and patients with any uterine or adnexal pathology were excluded from the study. All male partners who had total motile sperm count of less than 5×10^6/ ml were also excluded.

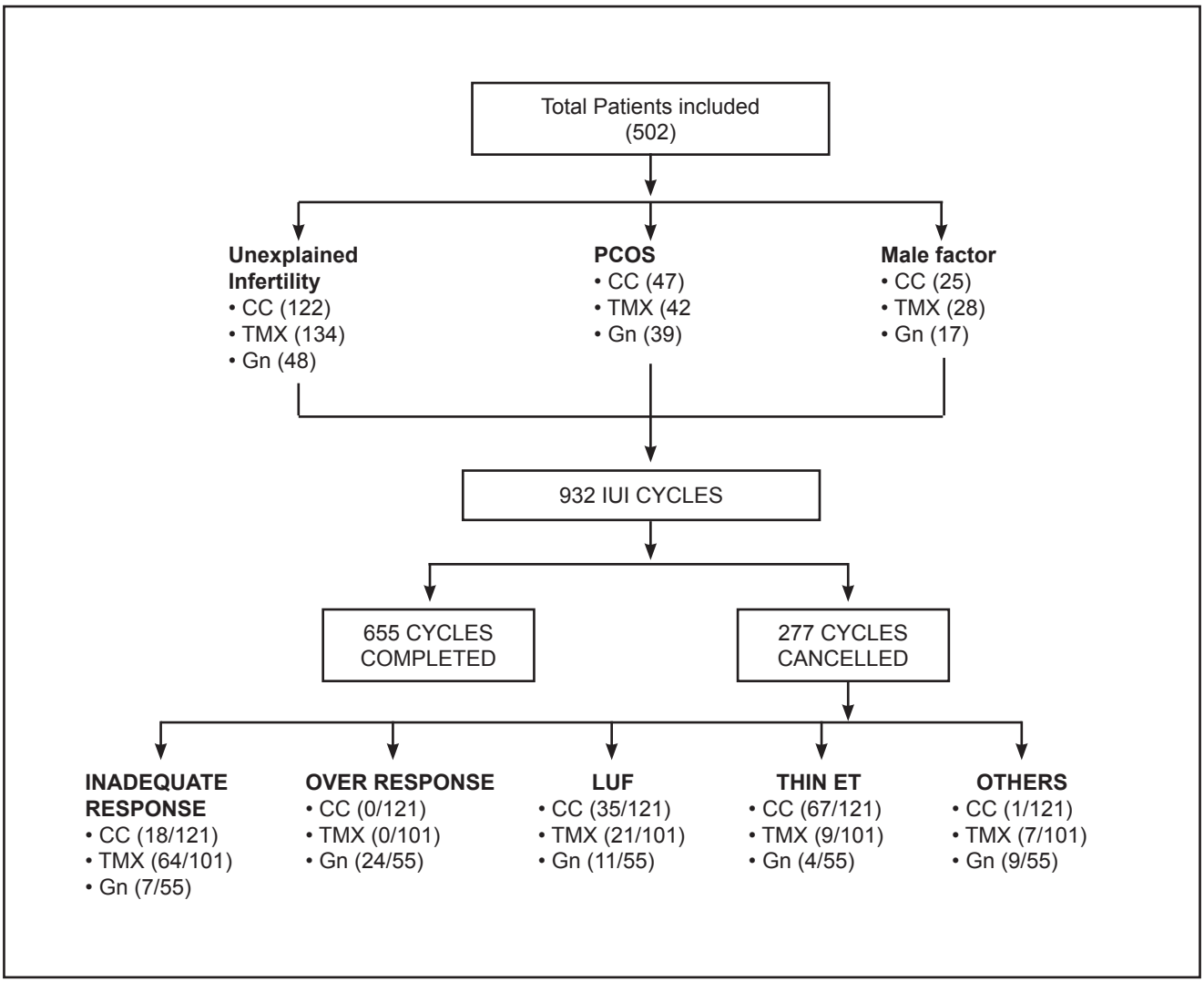

Figure 1: Flow chart depicting number of patients, etiology and performed IUI cycles

A hysterosalpingogram (HSG) was done to rule out tubal block and patients with at least one tube patent were only taken. Moderate to severe endometriosis patients were excluded from the study. Polycystic ovary syndrome (PCOS) was defined according to the modified Rotterdam revised ESHRE/ASRM criteria.[19] The diagnosis of unexplained infertility was done based on normal findings in semen analysis, mid-luteal serum progesterone and tubal patency seen by HSG or laparoscopy.

Total 502 women who had thin endometrium (<7mm) after CC (100mg) in IUI cycles were divided into three groups based on drug of ovarian stimulation. Two months gap was given prior to ovulation induction in all three groups. Group A included 182 patients who had 364 stimulation cycles, received CC 50mg /day from D3 - D7. Group B included 179 patients who had 342 stimulation cycles, received TMX 40mg /day from D3 - D7. Group C included 141 patients who underwent 226 cycles, received u-FSH 75 to 150IU starting from D3 till day of hCG.

Serial transvaginal sonography (TVS) was done from day 10 of the cycle for follicular monitoring. The measurement of the internal diameter of each visible follicle was performed in two planes and the average diameter was taken. In addition, the ET, was measured from the outer to outer edge of the endometrial–myometrial interfaces in the widest part of the endometrial cavity in the mid-sagittal plane. Urinary hCG (5000IU) was given when the leading follicle was ≥18mm and ET ≥ 7mm for ovulation trigger. In patients with ET <7mm ovulation trigger was postponed till ET reached ≥7mm. Women with persistent thin ET(< 7 mm) and/ follicle >24mm were also excluded from the study. Cycle was cancelled in 24 patients who had ≥4 follicles with ≥16

mm diameter. Our main outcome measures were to anayse ET, pregnancy rate and live birth rate.

RESULTS:

Total 277 cycles were cancelled out of 932 cycles. Most of the cancellations in TMX group was due to inadequate response or failure to achieve follicle of ≥16 mm. On the contrary, over response that led to the presence of too many mature follicles (>4 follicles ≥16 mm) was the main cause of cancellation in the gonadotropin group (43.63%). In low dose CC group thin endometrium and luteinised unruptured follicle were the major cause of IUI cancellation. On-demand failure to obtain a semen sample was another reasons for cancellation (Figure 1). In PCOS women response to TMX was inadequate in 55.2% of cycles which were cancelled (Table 1). The clinical profile including age, duration of infertility, BMI, baseline FSH, LH and E2 of patients belonging to Group A, B and C undergoing IUI are comparable. Different cycle parameters of the three groups are shown in Table 2. The ovulation rate was found to be comparable in all groups. Endometrium thickness was found to be significantly higher in both TMX and gonadotropin group than CC group. Follicle number in the TMX group was significantly low (p<0.001) compared to CC or gonadotropin group. However, size of the follicle was significantly higher in clomiphene group compared to other two groups on the day of hCG. TMX and gonadotropin group showed similar pregnancy rate (14.52% vs 14.89%) and live birth rate (12.2% vs. 12.7%). But, in low dose CC both pregnancy rate (p<0.002) and live birth rate (p<0.004) were statistically lower compared to TMX or Gn groups. There were three cases of twin pregnancy in gonadotropin group (Table 3).

Table 1: Inadequate response in PCOS women

	Total PCOS cycles (241)	Cycles cancelled in PCOS (76)	%
CC	91	16	16.4%
TMX	96	53	55.2%
Gn	54	7	12.9%

Note: CC: clomiphene citrate; TMX: tamoxifene; Gn: gonadotropin

Table 2: Inadequate response in PCOS women

	Clomiphene (Gr A)	Tamoxifene (Gr B)	Gonadotropin (Gr C)	P Value
Ovulation rate	66.75%	71.63%	78.6%	NS
Cancellation rate	33.51%	28.9%	24.3%	NS
No of follicles	2.2±0.58	1.3±0.49	2.3±0.49	AB-NS AC-p<0.001 BC-p<0.001
Size of follicles on the day of hCG	21.08±1.67	19.44±1.1	18.41±0.62	AB-p<0.001 AC-p<0.001 BC-p<0.001
ET	7.5±0.46	8.6±0.96	10.07±0.69	AB-p<0.001 AC-p<0.001 BC-p<0.001

Table 3: Pregnancy outcome

	lomiphene (Gr A)	Tamoxifene (Gr B)	Gonadotropin (Gr C)	P Value
Pregnancy rate (n)	4.94% (9)	14.52% (26)	14.89% (21)	AB- p<0.002 AC- NS BC-NS
Miscarriage rate (n)	1.64% (3)	2.2% (4)	2.1% (3)	AB-NS AC-NS BC-NS
Live birth rate (n)	3.2% (6)	12.2% (22)	12.7% (18)	AB- p<0.004 AC- p<0.004 BC-NS
Multiple pregnancy	1	NIL	3	AC-NS

DISCUSSION:

The present study showed the role of TMX in ovulation induction compared to gonadotropin and low dose CC in women with thin endometrium following CC. ET as a predictor of success for ART treatment is well established. Studies have shown that pregnancy and implantation rates for the patients with endometrial thickness >7 mm were significantly higher than those of patients who showed a thin endometrium.[2] Furthermore, ET <8 mm on the day of administration of hCG increases preclinical abortions.[22] Thin endometrium, the most common antiestrogenic side effect of CC treatment, has been seen in 15-50%. This unfavourable effect of CC increases with higher dose.[23] Hence, in our study we have included group A, in which the patients were stimulated with lower dose of CC (50mg) so that the antiestrogenic effect on endometrium will be low. Since thin endometrium is a risk factor for implantation failure, gonadotropin stimulation was used as the next line of management. Gonadotropin therapy, although effective, not only burdens the patient with stress and medical cost but can also cause multiple pregnancy and ovarian hyperstimulation

syndrome (OHSS). Therefore, preventing CC induced thinning of the endometrium by alternative methods like TMX appears promising.

Women who had thin endometrium with CC (<7 mm), exhibited improved endometrial thickness when TMX was used for stimulation in the subsequent cycle.[24,25] In line with the above findings, in our study, we also observed improved ET following TMX similar to the above studies.

The pregnancy rate and live birth rate in TMX group were found to be comparable to gonadotropin group, but significantly higher when compared to CC group (Table 3). Inadequate response leading to cancellation of cycles was significantly higher in PCOS women following TMX. It appears that TMX is not as effective as CC for ovulation induction in PCOS women. This is in contrast to the meta-analysis which concluded that there are no appreciable differences in ovulation or pregnancy rates after treatment with TMX or CC in anovulatory infertility.[26,27] Similar to our findings, a randomized controlled trial (RCT) by Badawy et al reported a significantly lower ovulation rate following TMX compared to CC in PCOS women, which concluded that CC is more successful than tamoxifen in PCOS women.[28]

It has been noted that leading follicle in CC group on the day of trigger was greater ($p<0.001$) compared to the other two groups. This is because many patients in the CC group had ET <7mm when the follicular size reached ≥18mm and hence hCG administration was delayed till endometrial thickness reached ≥7mm, which resulted in greater follicular diameter. The number of cancellations due to over response following gonadotropins was higher probably due to increase in dose of gonadotropin when inadequate response was noted. Though mechanism of action is similar in both CC and TMX, we noted significantly less number of follicles following induction with TMX.

We conclude, TMX appears to be a promising drug in patient with thin endometrium after CC stimulation by increasing live birth. It seems to be less effective in women with PCOS who earlier responded well with CC. Further RCTs are needed to confirm the findings.

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Management of Tubal Factor Infertility in the Era of ART

Ratnaboli Bhattacharya, Sunita Sharma, B N Chakravarty

The human fallopian tube is more than just a passive pipeline, it plays an active role in reproduction. The basic functions of the fallopian tubes were first described by Regnier de Graaf in 1660. It is responsible for the ovum pick-up, maintains sperm motility, furnishes the environment for fertilization, helps in the mechanical transport and physiological sustenance of gametes and early conceptus. Complex and coordinated neuromuscular activity, cilial action and endocrine secretions are needed for good tubal function

Causes of Tubal Infertility

- Salpingitis-PID, TB
- Endometriosis
- Previous tubal ectopic pregnancy
- Previous abdominopelvic surgery
- Previous complicated appendicitis

About 15% to 33% of female infertility is the result of tubal disease with more than half due to salpingitis. The etiologic agent for PID is most frequently Chlamydia trachomatis, followed by gonorrhea and mycobacterial infections. Tuberculosis of the fallopian tubes is quite common in developing countries. The incidence of genital tuberculosis in Indian women seeking ART was 24.5% overall but as high as 48.5% in tubal factor infertility. Genital TB generally occurs secondary to pulmonary (commonest) or extra pulmonary TB like gastro-intestinal tract, kidneys, skeletal system, meninges and miliary TB through hematogenous and lymphatic route. However, primary genital TB can rarely occur in women whose male partners have active genitourinary TB (e.g., tuberculosis epididymitis) by transmission through infected semen .Direct contiguous spread from nearby abdominal organs like intestines or abdominal lymph nodes can also cause genital TB. The fallopian tubes are involved in 90–100 % cases with congestion, military tubercles, hydrosalpinx, pyosalpinx and tubo-ovarian masses.

However 50% patients with documented tubal factor infertility have no identifiable risk factors.

Tubal patency tests

Hysterosalpingogram

HSG is usually performed between day 7-12 of menstrual cycle to ensure the absence of pregnancy and facilitate maximum uterine cavity visibility with a thin proliferative phase endometrium. It has a sensitivity of 53% and a specificity of 87%.[1]

The advantages are that it can show the position of tubal occlusion, peritubal adhesions, uterine cavity and U/L patency can be differentiated from B/L patency. It is relatively simple, cheap, widely available and requires less expertise.

Its disadvantages lie in the fact that it exposes the patient to radiation and carries a risk of PID (1-3%). HSG can give false positive results due to tubal spasm, debris or reporting errors in 12.5% cases and false patency in 11% like hydrosalpinx or dye intravasation. HSG is absolutely contraindicated in patients where there is a possibility of pregnancy and patients with a history of acute PID. The relative contraindications are history suggestive of PID, recent uterine instrumentation and iodine allergy.

The appearance in genital tuberculosis is typical. The findings are-Calcified lymph nodes/Small irregular calcification in adnexa, obstruction of fallopian tube in b/w isthmus & ampulla, beaded appearance, jagged tubal contour + small luminal defects, pipe stem configuration, Maltese cross appearance, golf club appearance, rossette type, leopard skin appearance of ampulla or tobacco pouch appearance.

Water-soluble medium is preferred due to superior image quality and safety whereas oil soluble medium can be associated with oil embolisation and granulomas but it confers a therapeutic benefit compared to water-soluble contrast medium.[2]

Saline infusion sonography (*Sonohysterography*)

SIS /IUI/Foley catheter is inserted through the cervical os and normal saline is infused slowly (5-10 ml) while the uterus is imaged with vaginal ultrasound. SIS has a sensitivity of 75%, Specificity of 83%, NPV of 95% and PPV of 40%.

Hysterosalpingo-contrast-sonogaphy (HyCoSy)

It is a transvaginal ultrasound technique where water-soluble contrast medium is injected into the uterine cavity using a 5F/7F catheter on an OPD basis. It has good statistical comparability and concordance with HSG with higher sensitivity and specificity and 76% concordance rate with laparoscopy + dye.[3]

Selective salpingography

Radiopaque dye is directly injected in the tubal ostium through a catheter introduced transcervically under fluoroscopic control.

Other procedures

Transvaginal hydrolaparoscopy (THL) is a process where rigid angled endoscope is introduced to see the Pouch of Douglas (POD), pelvic side-walls, adnexa and tubal patency after insufflation of the pelvis with fluid medium. In salpingoscopy, there is endoscopic visualisation of the endosalpinx of the tubal infundibulum and ampulla at laparoscopy and/or THL while Falloposcopy involves endoscopic visualisation of the whole endosalpinx at hysteroscopy. Fertiloscopy combines hysteroscopy, THL and salpingoscopy. However, these do not have any universally agreed and validated system to classify normal and abnormal findings. Therefore, there is a lack of prognostic ability with these procedures.

Laparoscopy and dye test

Laparoscopy with chromopertubation is the Gold standard test. It is indicated in abnormal HSG findings and women with history or symptoms of pelvic disease. Endometriosis and isolated proximal occlusion (10-20% of tubal factor infertility) can be directly visualised with laparoscopy.

Laparoscopy allows direct visualisation of fallopian tubes and pelvic cavity and mild/moderate endometriosis and peri-adnexal adhesions can be also be treated alongwith.[4] Sometimes it is not possible to determine the actual site of occlusion. Laparoscopy also involves higher medical costs and longer post-procedural pain and recovery.

HSG vs Laparoscopy

Both are invasive procedures, HSG being less than laparoscopy. HSG is not a reliable indicator of tubal occlusion- Obstructed tubes on HSG were confirmed by laparoscopy in only 38%. However, HSG is a reliable indicator of tubal patency- patent tubes were confirmed by laparoscopy in 94% cases. Tubal pathology detected at laparoscopy was found to have a stronger effect on future fertility than that detected at HSG. However, patients older than 35 years, or having dysmenorrhea, history of PID/ genital TB and patients with a pelvic lump should undergo a laparoscopy preferentially over HSG.

Should tubal patency tests be used routinely?

Initial investigations of an infertile couple include assessment of sperm (seminal fluid analysis), pelvic anatomy (TVS) and ovulation and ovarian reserve (follicular phase gonadotrophins). Invasive tubal testing is only offered to those who choose or need OI, IUI or natural conception. In low-risk women undergoing OI there is no need for routine use of a tubal patency test.

Treatment

Management of tubal infertility has undergone huge changes after the advent of operative laparoscopy and assisted reproductive technologies (ART). Several studies have shown that results of IVF are equivalent or better for tubal diseases as compared to surgery. With tubal surgery, the patient gets an option of attempting conception repeatedly and getting pregnant naturally more than once. However it carries with itself a number of surgical complications such as bleeding, infection, organ damage, anesthesia related complications, chances of ectopic pregnancy and post operative discomfort. IVF on the other hand is less invasive, has good per cycle success rate but is expensive and is associated with risks of ovarian hyperstimulation syndrome and multiple pregnancy.

Tubal surgery in properly selected cases can give good results while in poorly selected cases can have poor results. Thus the proper selection of patients is important for getting optimal results. The age of the patient, ovarian reserve, prior fertility, number of

children desired, site and extent of the tubal disease, presence of other infertility factors, experience of the surgeon, and success rates of the IVF program are the most important. IVF is the method of choice in older patients (age>35yrs) with moderate to severe tubal disease. In younger patients (age<35 years) with milder form of the disease, reconstructive tubal surgery can be attempted. In patients with severely diseased tubes, previous surgery failure, absent tubes, both cornual and fimbrial block, tubal defect complicated by other infertility factors like oligospermia, it is more prudent to attempt assisted reproductive techniques. On the other hand patients with small hydrosalpinx, limited flimsy adhesions, normal mucosa, normal/thin wall and partial occlusion are ideal candidates for tubal reconstructive surgery.

Success with Tubal Surgery

Several studies in the previous decade have demonstrated high pregnancy rates after tubal surgery. A case series on women who underwent surgery for distal tubal occlusion reported livebirth rates (LBR) of 20% to 30% . This study reported a 25% cumulative pregnancy rate at 12 months and 40% at 50 months. The study group included a heterogeneous group of women with proximal and distal tubal damage. Fertility outcome has been closely linked to severity of tubal damage. A retrospective cohort study on 192 women reported a LBR of 69%, 48% and 9% in women with grades I, II and III tubal damage.[5]

Hydrosalpinx

Hydrosalpinx is an end stage of distal tubal disease. Several studies have shown that hydrosalpinx has a bad effect on IVF success rates. The pregnancy, implantation, and delivery rates were 50% lower and that the spontaneous abortion rate was higher in the patients having hydrosalpinges . Embryos in these patients were found to have reduced viability.[6]

86% of hydrosalpinges visible by USG have severe mucosal damage. Suitability for reconstructive surgery in these patients is best assessed at laparoscopy with recourse to salpingoscopy where appropriate . Randomized clinical trials (RCTs) in women having IVF with hydrosalpinges, with or without prior laparoscopic salpingectomy, showed that salpingectomy increases the pregnancy rates and live birth rates to levels similar to those of women without hydrosalpinx . A Cochrane analysis concluded that laparoscopic salpingectomy or occlusion is a suitable option in IVF patients with communicating hydrosalpinges . Patients with a unilateral hydrosalpinx have also been found to have lower pregnancy rates with IVF . Unilateral salpingectomy in these women resulted in a significant improvement in IVF pregnancy rates .

It has been proposed to establish cut off values for the size of hydrosalpinx to decide when to intervene before IVF. But size of hydrosalpinx on TVS may vary during a cycle. Two indices have been established -

1) Detection on USG - Pregnancy rates were lower (15%) in patients with visible hydrosalpinges c.f patients in whom hydrosalpinges were not visible (31%).
2) Bilateral affection - B/L disease had lower pregnancy rates (12% vs 24%) and lower implantation rates (5% vs 11%) than U/L disease. Thus, total amount of fluid in hydrosalpinx is negetively correlated to the chance of achieving a pregnancy.

Diseased tubes with a retention of >50% normal mucosa have the best prognosis following reconstructive surgery. Hydrosalpinx can be treated with various methods like Salpingectomy, Tubal occlusion by laparoscopy or hysteroscopy, Salpingostomy or Transvaginal aspiration. Proximal tubal occlusion for hydrosalpinges is done hysteroscopically with Essure coil inserts, but data on IVF success rates are limited. The trailing coils within the endometrial cavity may act as an intrauterine contraceptive device, interfering with embryo implantation during IVF. A new device for hysteroscopic proximal tubal occlusion, Adiana, uses radiofrequency to stimulate interstitial scarring followed by insertion of a small silicone elastomer matrix.[7,8]

IVF

IVF is the treatment of choice in moderate to severe tubal disease. Distal tubal occlusion with hydrosalpinx>1.5 cm in diameter, when there is both distal and proximal tubal disease and if there is no pregnancy within 12 months of tubal surgery are ideal for IVF.

Success with IVF

IVF in tubal factor infertility offers a 30% LBR per cycle.[9]

The advances in IVF has also diminished the role of tubal surgery. Financial constraints lead many women and clinicians to continue to favour surgery. Tubal surgery may also be more desirable for couples who object to IVF for religious, moral or emotional reasons. Despite being expensive and invasive, IVF is the preferred choice in older women with severe tubal damage. With reported livebirth rate per IVF cycle in most centres as high as 30%,[9] and the uncertainties around the outcome of tubal surgery, there may be a preference to IVF which contributes to poor recruitment for surgical RCTs. Furthermore, women with tubal damage find the spontaneous pregnancy rate unacceptably low (12-month cumulative PR of 2.4%), and consequently, expectant management is an unattractive option for them .

Tubal Sterilisation

Surgical reversal of tubal sterilisation has been found to be as successful as IVF. Good prognostic factors of tubal reversal surgery include female age<35 years and residual tubal length > 4 cm. Open microsurgery is the method of choice. However recent studies have showed laparoscopic reanastomosis maybe associated with comparable success rates.

Tubal surgery in the era of ART

Several studies have shown that results of IVF are equivalent or better for tubal diseases as compared to surgery. However there is a lack of adequate trials comparing pregnancy rates achieved with tubal surgery compared to those with IVF, since IVF success per cycle cannot be compared with tubal surgery success, which is per patient. Combined pregnancy rate from single IVF cycle is higher than the cumulative pregnancy rates of tubal surgery-taking advantage of the frozen embryos. In addition, waiting for at least 1 year to realize the success of the surgical procedure wastes precious time and reduces the chance of IVF conception subsequently. Women who conceive following reconstructive surgery are also at an increased risk of ectopic pregnancy (8-23%) in comparison to IVF (3-5%).

Data from our institute, IRM has revealed that the pregnancy rate in tubal factor infertility patients after IVF is 34.89% and the miscarriage rate is 18.02%. The rate of ectopic pregnancy in these patients is 3%.The livebirth rate was found to be 21.57%. On the other hand, pregnancy rates in these patients after tubal cannulation surgery is 1.14% and after hydrotubation along with ovulation induction is 5.38%.

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Work Statement of Patients for the Month from October to December 2017

Total No of Gynaecological & Obstetric Cases attended		**802**
No of Gynaegological Cases	637	
No of Obstetric Cases	165	
Gynaegological Cases		
Infertility		**584**
Primary	428	
Secondary	156	
Other Gynaecological Cases		23
History of Recurrent Spont Miscarriage (> 3)		19
History of Unexplained Spont Miscarriage (<3)		9
History of Recurrent Pregnancy Loss		2
Categorization of Infertility/ Gynaecologocial Cases		
Female Factor	242	(41.44%)
Male Factor	227	(38.87%)
Unexplained	86	(14.73%)
Combined Factor	29	(4.96%)
Total No of IVF & IUI Cycles		**543**
IVF Fresh Cycle		119
ET Done	65	
ET not done	54	
Cryo Cycle		51
IUI		**373**
Obstetric Cases		
Pregnancy folowing		
Medical treatment (Induction Ovulation)		45
Surgical Treatment		8
During investigation		44
Intrauterine Insemination		33
IVF-ET including FET Cycle		35
Pregnancy Loss		**0**
Elective Termination		
Spont. Termination		
RSM (> 3)	0	
USM (<3)	0	
RPL	0	
Other type of Pregnancy Loss	**0**	
Viable Deilvery		**61**
CS	61	
Normal	0	
Sucessful Delivery after		
IVF	26	
IUI	3	
OI	9	
Hydrotubation	0	
Spont	8	
During investigtion	15	
Baby outcome		
Alive		68
Singleton	53	
Male	23	
Female	30	
Twins		8 (16 pairs)
Male	7	
Female	8	
Neonatal Death		0
Still Born		0
Gynaecological Surgery		53
Laparoscopy + Hysteroscopy		33
Hysteroscopy		10
Mcdonald		2
EUA		2
T- Insersion		1
Cystectomy		1
Polypectomy		1
OHSS		2
Hysterectomy		1

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