A COMPARATIVE STUDY OF EFFICACY OF OVULATION INDUCTION DRUGS ALONE VERSUS OVULATION INDUCTION DRUGS AND GONADOTROPINS IN INFERTILITY

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IN

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MAY 2022

BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled **"A COMPARATIVE STUDY OF EFFICACY OF OVULATION INDUCTION DRUGS ALONE VERSUS OVULATION INDUCTION DRUGS AND GONADOTROPINS IN INFERTILITY"** is the bonafide work performed by **DR.S.S ISWARIYA LAKSHMI**, Post Graduate in the Department of Obstetrics and Gynaecology, Institute of Obstetrics and Gynaecology, Govt. Hospital for Women and Children, Madras Medical College, Chennai, towards partial fulfilment of the requirements of The Tamil Nadu Govt. Dr. M.G.R Medical University for the award of M.S Degree in Obstetrics and Gynaecology.

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DECLARATION

I, **DR.S.S ISWARIYA LAKSHMI,** solemnly declare that the dissertation titled, **A COMPARATIVE STUDY OF EFFICACY OF OVULATION INDUCTION DRUGS ALONE VERSUS OVULATION INDUCTION DRUGS AND GONADOTROPINS IN INFERTILITY"** has been done by me. I declare that this bonafide work or part of this work was not submitted by me for any award, degree, diploma to any other university either in India or abroad.

This is submitted to The Tamil Nadu Govt. Dr. MGR medical University, Chennai in partial fulfillment of the rules and regulations for the award of M.S Degree (Obstetrics and Gynaecology) held in May 2022.

Place:

Date:

DR. S.S ISWARIYA LAKSHMI

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Dissertation is not just a document or just research paper. It is an evidence of endless effort, hard work and motivation. It paves way to open the path of research stream which is going to help me in the translation of best evidence in to practice. It is not me, indeed it is a masterpiece of teamwork with bubbling spirit in every word of my thesis. I am here to acknowledge my team.

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DR. S.S ISWARIYA LAKSHMI

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INTRODUCTION

Infertility is defined as one year of regular unprotected intercourse without conception [(1)]. The term **subfertility** is used to describe women or couples who may not be sterile but exhibit decreased reproductive efficacy. Approximately 85-90%of healthy young couples conceive within one year, most within six months [(2)].Infertility therefore affects approximately 10-15% of couples and represents an important part of clinical practice. Cycle **fecundability** is the probability that a cycle will result in pregnancy and **fecundity** is the probability that a cycle will results in a live birth.

Fertility in women peaks between the ages of 20 and 24, decreases relatively little until the age 30-32 approximately, and then declines progressively. Miscarriage rates in natural conception cycles are generally low before age 30 and rise with age, only slightly for ages 30-34, but to a greater extent for ages 35-39 and ages 40 and older[(3)].

In humans, the number of oocytes peaks around the 20th week of gestation when approximately 6-7million oocytes arrested at the first meiotic prophase are found in the ovarian cortex. Afterward, regulated

apoptosis starts an irreversible decline in the germ cell population. The number of oocytes declines to 1-2million at birth and to 300000 – 400000 by puberty. Over the next 35-40 years of reproductive life, only about 400 oocytes will ovulate, the rest being lost through atresia. By age 40, the number of follicles shrinks to approximately 25000, and at menopause, there remains less than 1000 follicles.

The major causes of infertility includes

- Ovulatory dysfunction (20-40%)
- Tubal and peritoneal pathology (30-40%)
- Male factors (30-40%)
- Unexplained infertility (10%)

PHYSIOLOGICAL BASIS OF OVULATION

Ovulation is a physiological process defined as the release of ovum as a consequence of rupture of the dominant follicle of the ovary into theperitoneal cavity.The initial recruitment and growth of primordial follicles are not under the control of any hormone.After a certain stage(2-5mm in size) the growth and differentiation of primordial follicles are under the control of follicle stimulating hormone.Unless the follicles are

rescued by FSH at this stage,theyundergo atresia.During the early follicle development,the oocyte enlarge and thegranulosa cells proliferate to form a preantralfollicle.Over 3-6 months,the follicle develops FSH receptor in the granulosa cells and LH receptors in the theca cells[4].

At this stage, antral follicles depend on FSH for further development. Just before mensus, falling estrogen levels results in withdrawal of negative feedback centrally leading to increased gonadotropins levels. FSH stimulates granulosa cell proliferation and differentiation, with the development of more FSH receptors and the production of aromatase. LH stimulates androstenedione production by theca cells that diffuses into the granulosa cell providing substrate for estrogenproduction. This step is catalysed by the aromatase enzyme, which is induced by FSH. The so called two-cell, two-gonadotropin theorey[5] postulated that FSH concentrations must exceed a certain level(FSH) threshold before follicular development will proceed.

The duration of this period in which the threshold is exceeded(the FSH window) is limited in the normal cycle by a gradual decrease in FSH, occurring in the early mid follicular phase as a response to negative feedback rising estrogen levels produced by the larger follicles. Smaller follicles with fewer FSH receptors are no longer stimulated by FSH

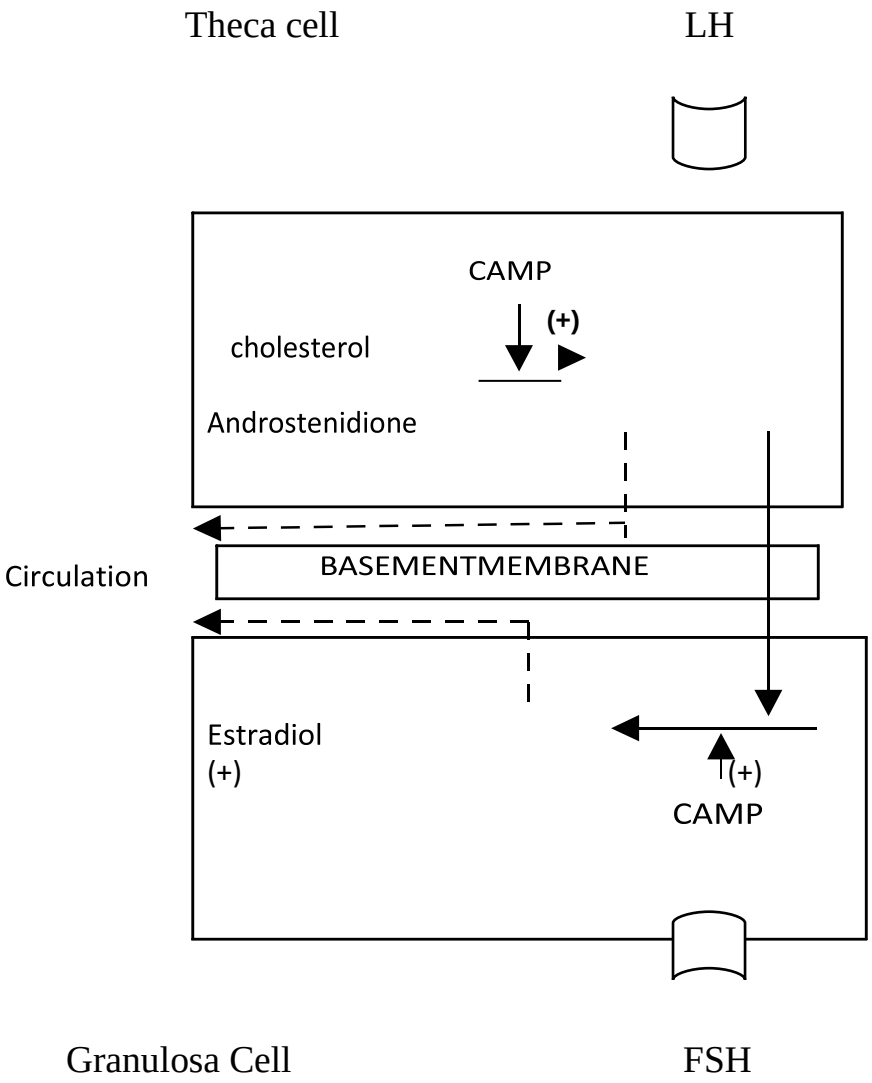
below the FSH threshold and there-by undergo atresia. Therefore, generally only one follicle reaches the stage of ovulation with each cycle, despite the presence of hundreds of primordial follicles, the number of which depending on a woman's age.FSH induces LH receptors in large antral follicles which are above one cm in diameter[6].Rapidly increasing levels of estradiol produced by the mature preovulatory follicle precede the midcycle FSH and LH surge that will initiate ovulation. Depending upon the circulating level of estradiol the time of LH surge is determined. The alteration in steroidogenic pathway results in progesterone as the primary steroid hormone produced after leutinization. The corpus luteum retains the ability to secrete progesterone.T he presence of multiple follicular growth suggests the presence of some estrogen in the luteal phase by growing follicles which will undergo atresia.

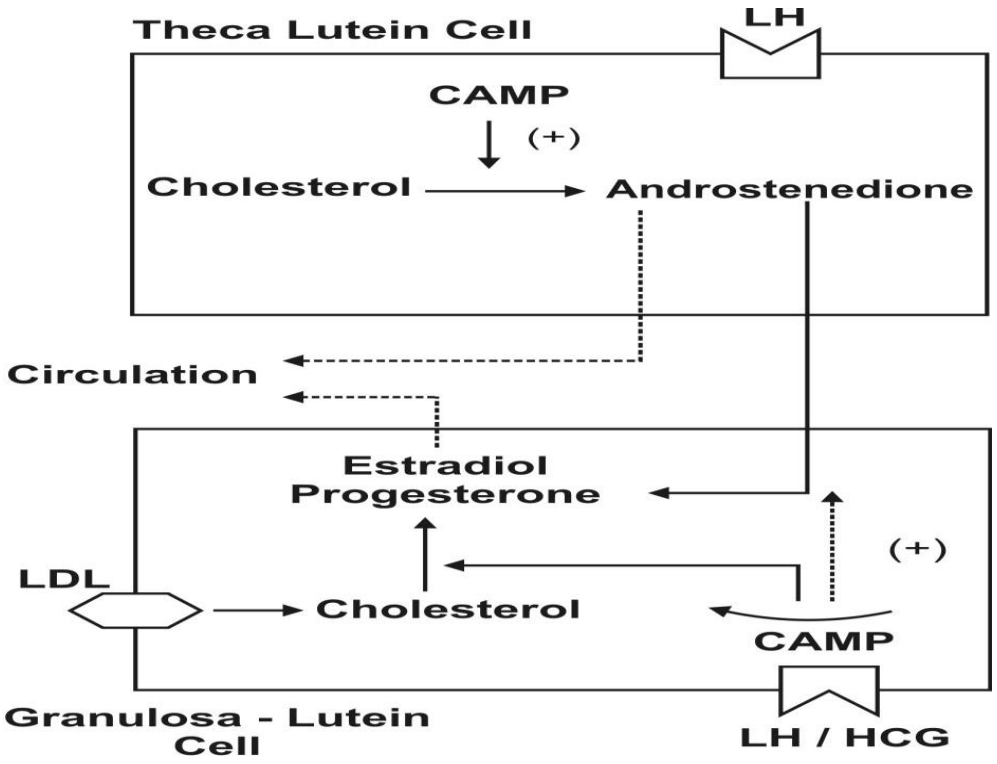
The corpus luteum undergoes regression with a fall in progesterone and estrogen followed by the onset of menses.FSH level rise with withdrawal of estrogen negative feedback and the next cohort of follicles begins to develop.

In summary, normal follicular development culminates in ovulation of a mature oocyte, followed by the development of a corpus luteum producing adequate amount of progesterone. This sequence of events is

orchestrated by the interaction of local ovarian factors and endocrine factors from the pituitary and hypothalamus. The presence of subtle abnormalities despite the occurrence of ovulation may be responsible for unexplained infertility.

TWO CELL TWO GONADOTROPIN THEORY





LUTEAL PHASE

AIM OF THE STUDY

To study about the comparative efficacy of ovulation induction drugs alone (Letrozole/Clomiphene citrate) versus ovulation induction drugs and gonadotropins (HMG) in ovulation induction in infertility in Institute of Obstetrics and Gynaecology and Government Hospital for Women and Children, Egmore and Institute of Social Obstetrics and Gynaecology and Government Kasturba Gandhi Hospital for Women and Children, Triplicane**.**

OBJECTIVES OF THE STUDY

Apart from comparing the efficacy of ovulation induction drugs alone versus ovulation induction drugs and gonadotropins in infertility, Objectives includes

1. To analyse the distribution of age in study participants.
2. To analyse the medical comorbidities such as diabetes mellitus, hypertension, hypothyroid, APLA in both the groups.
3. To compare the number and size of dominant follicle after ovulation induction drugs and gonadotropins in both the groups.
4. To compare the number of monofollicular development in both the groups.
5. To compare the endometrial thickness in both the groups.
6. To compare the Ovulation rate achieved in both the groups.
7. To compare the pregnancy rate achieved in both the groups.

REVIEW OF LITERATURE

OVULATION INDUCTION

Ovulatory disorders can be identified in 18-25% of infertile women [7].When an ovulation is the only infertility factor, the prognosis for pregnancy generally is quite good because modern ovulation induction strategies are highly effective. When a specific cause for an ovulation can be identified, treatment often restores normal cycle fecundity.

Ovulation induction refers to the therapeutic restoration of the release of one egg per cycle in the women who either has not been ovulating regularly or has not been ovulating at all. Although it is usually acceptable for OI to result in the release of two eggs, one should avoid the ovulation of more than two eggs in an effort to minimize the risk of OHSS and multiple gestations.

Once ovulation has been documented for a particular treatment. Patients should be mentally prepared to continue with that regimen for at least 3 cycles. Because for most treatment the pregnancy rate occurring per therapeutic cycle is the same for each of the first three cycles.

It is mandatory to exclude the male factor infertility by means of semen analysis and bilateral tubal patency by HSG.

DIAGNOSIS OF ANOVULATION

Ovulatory cycles typically are associated with a classic “biphasic” Basal body temperature. Basal body temperature recordings having no sustained interval of temperature elevation preceding the onset of menses strongly suggest an ovulation.

A progesterone concentration less than 3ng/ml implies anovulation, except when drawn immediately after ovulation or just before the onset of menses, when lower levels naturally might be expected. Ovulation is confirmed by an estimation of mid luteal plasma progesterone level and at least the minimum plasma concentration of 6.5ng/ml indicate ovulation. Ovulation occurs 10-12hrs after LH peak or 36 hrs after the initial rise in mid cycle LH.

The evidence of ovulation has been predicted by secretory activity in the gland during the premenstrual phase or at the onset of menstruation by endometrial biopsy. But it is not accurate.

At the time of ovulation mucus is thin and profuse with great elasticity and withstand stretching up to 10cm – Spinnbarkeit or thread test.

Other simple tests of ovulation include monitoring urinary LH excretion. Can be diagnosed by home urine LH kits that are designed to detect a high LH value at the time of LH surge.

CLASSIFICATION OF OVULATORY DISORDERS

Group 1: Hypogonadotropic Hypogonadal anovulation

5-10% of ovulatory women fall in this category.

Low or Low-normal serum FSH concentrations and low serum estradiol levels, due to absent or abnormal hypothalamic gonadotropin releasing hormone secretion or pituitary insensitivity to GnRH.

The following are the causes of hypogonadotropic hypogonadal anovulation:

- ✓ Hypothalamic amenorrhoea relating to physical, nutritional or emotional stress
- ✓ Weight loss
- ✓ Excessive exercise

- ✓ Anorexia nervosa
- ✓ Kallmann's syndrome
- ✓ Sheehan's syndrome

Group-2: Normogonadotropic Normoestrogenic Anovulation

This group is the largest,75-85% of anovulatory women falls in this category.

Normal serum FSH and estradiol levels and normal or elevated LH concentrations [8]. The following are the causes of normogonadotropic normoestrogenic anovulation:

- ✓ PCOS
- ✓ Congenital adrenal hyperplasia
- ✓ Androgen producing ovarian tumours
- ✓ Adrenal tumours.

Group – 3: Hypergonadotropic anovulation.

10-20% of anovulatory women falls in this category.

Elevated serum FSH and low AMH concentrations are found.

The following are the causes of hypergonadotropic anovulation :

- ✓ Ovarian failure
- ✓ Premature ovarian insuffiency
- ✓ Turner’s syndrome
- ✓ Pure gonadal dysgenesis
- ✓ Swyer syndrome
- ✓ Autoimmune disorders
- ✓ Radiotherapy/Chemotherapy
- ✓ Infections

GROUP 4 : Congenital or acquired genital tract disorders eg: Imperforate hymen ,MRKH syndrome, Asherman’s syndrome.

GROUP5: Hyperprolactinemia with Space occupying lesion (Eg) Pituitary adenoma.

GROUP6: Hyperprolactinemia without Space Occupying Lesion

(Eg) Hypothyroidism,drug induced.

GROUP7: Amenorrhea with an Space Occupying Lesion with normal or low Prolactin(Eg) Craniopharyngioma.

POLYCYSTIC OVARIAN SYNDROME

It is a complex disorder with heterogenous clinical and endocrine factors. Incidence in the reproductive age group is around 20-22%. Polycystic ovaries have its origin during adolescence and is thought to be associated with increased weight gain during puberty.

Clinical features:

- ✓ Asymptomatic (20%)
- ✓ Infertility (20-50%)
- ✓ Obesity (40%)
- ✓ Hyperandrogenism(66%)
- ✓ Menstrual irregularity (70%)
- ✓ Polycystic appearing ovaries

Biochemical/Endocrine abnormalities

- ✓ Raised LH
- ✓ Raised LH : FSH ratio

- ✓ Raised androgen – Testosterone and androstenedione
- ✓ Raised circulating estrogen
- ✓ Raised fasting insulin
- ✓ Raised fasting glucose
- ✓ Raised prolactin
- ✓ Decrease in SHBG
- ✓ Raised testosterone : SHBG ratio

Rotterdam criteria

1) Oligo/ chronic anovulation
2) Clinical / Biochemical evidence of hyperandrogenism
3) USG evidence of polycystic ovaries exclude other causes of hyperandrogenism**.**

OVULATION INDUCTIONDRUGS

1) SERMS - Clomiphene Citrate
2) Aromatase inhibitors - Letrozole

ADJUNCTS

1) Insulin sensitizers
2) Gonadotropins - Menotropins and recombinant gonadotropins.
3) GnRH - Pulsatile GnRH

   GnRH agonist

   - With HMG alone
   - With FSH/HMG
4) Dopamine Agonists
5) Dexamethasone
6) Pretreatment with OCPs

PHARMACOLOGY OF DRUGS

CLOMIPHENE CITRATE

Clomiphene citrate was synthesized in 1956, introduced for clinical trials in 1960, and approved for clinical use in the united states in 1967[9,10]. In early clinical trials,

60-80% of anovulatory women treated with clomiphene achieved ovulation and half of those who ovulated also conceived[9,10,11].

Clomiphene is a nonsteroidal triphenylethylene derivative that acts as a selective estrogen receptor modulator (SERM), having both estrogen agonist and antagonist properties[12].

CC is an orally administered nonsteroidal ovulatory stimulant designated chemically as

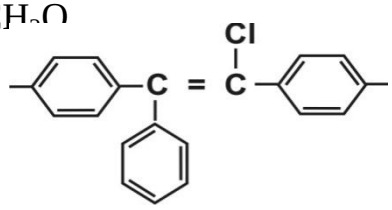
Molecular formula : 2 –(4 –(2 – Chloro -1, 2- diphenylethinylphenoxy) – N – N – diethyl Ethan amine

C28 H28 C1NO **.** C8 H8 O7

Molecular weight - 598.10

Structure

$C_2H_5N\ CH_2\ CH_2O$ $C_6H_8O_7$



However, in almost all clinical circumstances, clomiphene acts purely as an antagonist or antiestrogen; its weak estrogenic actions are clinically apparent only when endogenous estrogen levels are very low. Clomiphene is cleared through the liver and excreted in the stool.

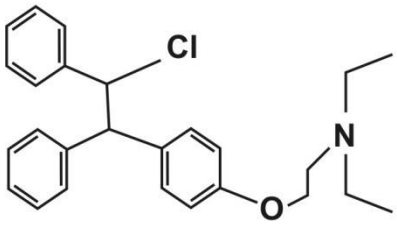
Clomiphene is a racemic mixture of two different stereoisomers, **enclomiphene**(62%, originally known as cis-clomiphene) and **zuclomiphene** (38%,originally known as trans – clomiphene)[13].

Enclomiphene is the more potent isomer and responsible for its ovulation – inducing actions. The half life of enclomiphene is relatively short, so serum concentrations rise and fall quickly during and after treatment.

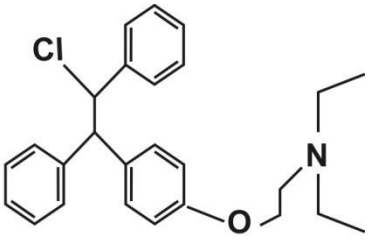
Zuclomiphene is cleared much more slowly; serum levels remain detectable for weeks after a single dose.

Zuclomiphene is mildly estrogenic as well as antiestrogenic and Enclomiphene is entirely antiestrogenic.

Zuclomiphene is approximately 5 times as potent as enclomiphene in inducing ovulation.



ZUCLOMIPHENE



ENCLOMIPHENE

MECHANISM OF ACTION OF CLOMIPHENE CITRATE

- CCis Structurally similar to estrogen hence itcompetes with endogenous estrogen for nuclear estrogen receptors at sites throughout the reproductive system. However, unlike estrogen, clomiphene binds to nuclear estrogen receptors for an extended interval of time and thereby depletes receptor concenterations by interfering with receptor recycling.

- At the hypothalamic level, CC depletes estrogen receptor thereby preventing accurate interpretation of circulating estrogen levels; circulating estrogen levels are perceived as lower than they truly are.

- CC reduces negative estrogen feedback which triggers normal compensatorymechanisms that alter the pattern of GnRH secretion and stimulate increased pituitary gonadotropin release,which,in turn, drives ovarian follicular development.

- In the pituitary, clomiphene also may increase the sensitivity of gonadotrophsto GnRH stimulation.

- When administered to already ovulatory women, Clomiphene increases GnRH pulse frequency[14].

- In anovulatory women wih PCOS who already exhibit an increased GnRH pulse frequency, clomiphene increases only pulse amplitude[15].

- Serum levels of both FSH and LH rise during Clomiphene treatment and fall again soon after the completion of typical 5 day course of therapy .

- In successfully treated cycles, one or more follicles emerge and reach the maximum maturity. In parallel, serum estrogen level rises progressively, ultimately triggering an LH surge and ovulation.

ANTI ESTROGENIC EFFECTS OF CLOMIPHENE CITRATE

- The endometrium is one of the most important target of antiestrogenic effect of CC.

- Endometrial thickness < 5-6mm is associated with failure to conceive.

- Deleterious effect on endometrium is demonstrated by reduction in glandular density and increase in vacuolated cells.

PHARMACOKINETICS

CC is excreted principally through intestine 5 days after oral administration. 51% has been excreted. However some CC continues to be excreted for atleast 6 weeks. (Mikkelson et al., 1986).

Peak plasma concenterations of zuclomiphene occurs 6 hrs after administration of 50 mg

A steady state of 25% reached at 48 hrs remains constant for the next 14 days.

Single dose studies showed that Zuclomiphene (cis) has a longer half life than enclomiphene (trans). Detectable level persisted for longer than a month.

INDICATION AND DOSAGE

- Anovulatory infertility; PCOS
- Unexplained infertility
- Amenorrhea – galactorrhea syndrome
- Psychogenic amenorrhea
- Post OCP amenorrhea
- Certain cases of secondary amenorrhea of undetermined etiology.

DOSAGE

Clomiphene is administered orally,typically beginning on the third to fifth day after the onset of a spontaneous or progestin induced menses.Treatment usually starts with a single 50mg tablet daily for 5 days

(D3-D7). A baseline TVS performed on D1 to D3 to exclude ovarian cyst.

Treatment usually starts with single 50mg tablet for 5 days(D3-D7) and, if necessary, increases by 50mg increments in subsequent cycles until ovulation is achieved. Most women who respond to CC will respond to either 50mg (52%) or 100mg (22%).

US FDA recommends maximum dose of 100mg/day. Considerable clinical experience with CC indicates that a dosage upto 250mg/day is safe[16].

If ovulation does not occur after 3 cycles of therapy, further treatment of CC not recommended and the patient should be reevaluated.

ADVERSE EFFECTS

- Ovarian enlargement -13.6%
- Vasomotor flushes - 10.4%
- Abdominal pain/discomfort - 5.5%
- Nausea/vomiting - 2.2%
- Breast discomfort - 2.1%

- Visual symptoms ((blurred or double vision,scotomata,light sensitivity) - 1.5%

- Headache - 1.3%
- AUB - 1.3%
- Most serious complication of CC therapy – OHSS (Ovarian Hyperstimulation Syndrome)

CONTRAINDICATIONS

- Hypersensitivity
- Pregnancy
- AUB of undetermined origin
- Ovarian cyst
- Uncontrolled adrenal or thyroid dysfunction or presence of intracranial lesion such as pituitary tumours.

CLOMIPHENE DRAW BACKS

- Discrepancy between ovulatory and pregnancy rates
- Poor endometrium 30%(peripheral antiestrogenic effect)
- Thickness<6mm
- Decreased endometrial glandular density
- Decreased uterine blood flow

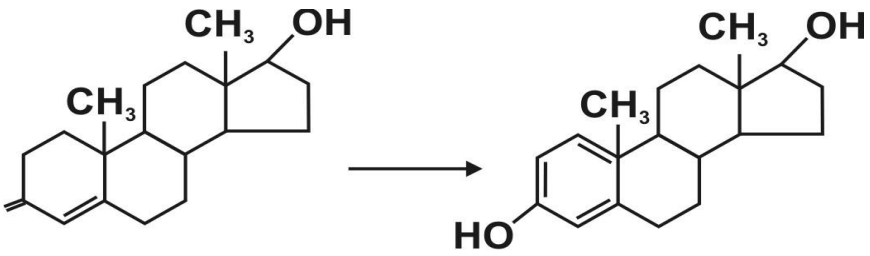
- Extended FSH window – multifollicular ovulation
- Clomiphene resistance (20-25% fail to ovulate)

AROMATASE INHIBITORS

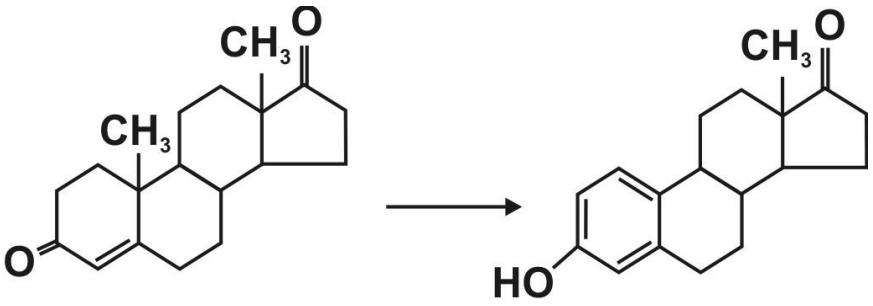
Aromatase inhibitors,which were used primarily in the treatment of postmenopausal breast cancer, emerged as a new class of ovulation inducing agents. Letrozole is now considered the first line therapy for ovulation induction in women with PCOS[18] ,as it provides significantly higher live birth rates compared to clomiphene[19].

Aromatase is a microsomal cytochrome P450 hemoprotein containing enzyme (the product of CYP 19 gene) and catalyses the rate limiting step in the production of estrogen. Aromatase activity is also present in ovaries, brain, and adipose tissue, muscle, liver, breast tissue .

AROMATASE CONVERTS TESTOSTERONE TO ESTRADIOL



AROMATASE CONVERTS ANDROSTENEDIONE TO ESTRONE



LETROZOLE

It is a third generation aromatase inhibitors. Highly selective and highly potent inhibitor of aromatase in vitro, in vivo in animals and in humans.

Anastrozole and letrozole are triazole (antifungal) derivatives that act as potent,competitive, nonsteroidal inhibitors of

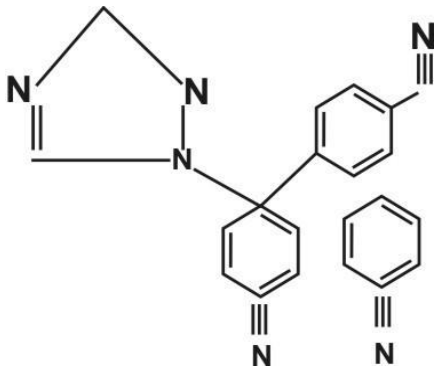
aromatase[20,21], the enzyme that catalyzes the rate – limiting step in estrogen production.

They block estrogen production both in the periphery and in the brain, resulting in a compensatory increase in pituitary gonadotropin secretion that stimulates ovarian follicular development.

Molecular formula : $C_{17}H_{11}N_5$

Molecular weight : 285.30

MOLECULAR STRUCTURE



4-4'-(1H-1, 2, 4 - Triazol - 1 - yl methylene) diabenzonitrite ;

4-(C_4 - cyanophenyl) - (1,2,4 - Triazol - 1 - yl methyl)

MECHANISM OF ACTION

- Blocks estrogen negative feed back, without depletion of ER.

- Both circulating estrogen and locally produced estrogen in the brain exert negative feedback on gonadotropin release.

- Inhibition of aromatization which blocks estrogen production from all sources.

- Release HP axis from estrogenic negative feedback which causes increase in gonadotropin secretion which in turn increases growth of follicles.
- Central feedback mechanisms remains intact. Suppression of FSH and atresia of smaller growing follicles occurs causing monoovulation.

In PCOS – Aromatase inhibitors do not antagonize the estrogen receptors in the brain and the initiation of follicle growth accompanied by increasing concentrations of both estradiol and inhibin results in a normal negative feed back loop that limits FSH response, thereby avoiding the risk of high multiple ovulation and OHSS.

PERIPHERAL MECHANISM OF ACTION

- Increased follicular sensitivity to FSH.

- Temporary accumulation of intraovarian androgen – amplifies FSH effects – stimulates IGF–1 synergize with FSH ~~p~~promotefolliculogenesis.

CHANGES IN THE ENDOMETRIUM

- Upregulation of ERs in the endometrium leading to rapid endometrial growth.

- Increased endometrial sensitivity to estrogen resulting in more rapid proliferation of endometrial epithelium and stroma and improved flood flow to the uterus.

INDICATIONS

- Regarded as the drug of choice for ovulation induction in anovulatory infertile women wih PCOS.

- The drug has also been tested in ovulatory women with unexplained infertility.

- As an adjuvant in conjunction with exogenous FSH or other medications to improve the outcome of OI.

- Induction of ovulation in CC failures

- Along with FSH for super ovulation for IUI or IVF (50% reduction in dose of FSH required)

DOSAGE

- Optimal dosage 2.5 – 5 mg from D3 – D7

- If 2.5 mg/day fails to induce ovulation,the dosage can be increased by 2.5mg increments upto a maximum of 7.5mg/day for 5 days.

PHARMACOKINETICS

- Letrozole is rapidly and completely absorbed (99.9% bioavailability).

- Extensively distributed to tissues.

- Large volume of distribution at steady state (1.87 lt/kg) range (1.47 – 3.24) and 60% bound to plasma proteins, mainly to albumin 55%.

- Half life ofLetrozole – 42 hrs.

- Area under cure (AUC) is greater in patients with breast cancer due to reduced metabolic clearance. Metabolized to a pharmacologically inactive carbinol metabolite (4,4' – methanol bisbenzo – nitrite) and excreted by kidneys. Of the radiolabel recovered in urine, 75% was the glucoronide of carbinol metabolite, 9% - 2 unidentified metabolites & 6% - unchanged letrozole.

DRUG INTERACTIONS

Co-administration of Letrozole and Tamoxifen 20 mg resulted in reduction of plasma levels of letrozole by 38% [(22)].

ADVERSE EFFECTS

- Most common side effect of letrozoleare headaches and cramps.
- Fatigue(20%)
- Dizziness(12%)
- Hot flushes(20.3%) less common with letrozole compared with clomiphene(33%)

- Nausea, vomiting, weight gain, tiredness, dizziness, Joint pain, unusual sweating at night.
- Moderate decrease in lymphocyte counts
- Transient depression
- Thrombocytopenia
- Allergic reaction – rare
- Less common - Constipation
- Vaginal dryness
- Swelling
- Troubled sleep

CONTRAINDICATIONS

- In pregnancy
- Embryotoxic and fetotoxic
- Increased resorption
- Increased post implantation loss
- Decreased number of live fetuses
- Congenial anomalies like absence and

  Shortening of renal papilla, Dilation of ureter, edema and incomplete ossification of frontal skull and metatarsals.

ADVANTAGES

- Mono follicular ovulation & decreased multiple pregnancy, OHSS & less monitoring
- Good Endometrium
- Convenience of administration & low cost
- Reduction in amount of FSH used for superovulation
- Good safety margin because of short half – life.

GONADOTROPINS

Gonadotropins: Historical Overview

In 1927, Aschheim and Zondek discovered a substance in the urine of pregnant women with the same action as the gonadotropic factor in the anterior pituitary. They called this substance as gonadotropin or "prolan." Furthermore, they believed that there were two distinct hormones, prolan A and prolan B. They subsequently used their findingsto develop the pregnancy test that carried their names.

In 1930, Zondek reported that gonadotropins were also present in the urine of postmenopausal women, and in the same year, Cole and Hart found gonadotropins in the serum of pregnant mares. This hormone,

pregnant mare serum gonadotropin, was found to have a potent gonadotropic effect in animals. However, it was only in
1937 that Cartland and Nelson were able to produce a purified extract of this hormone .

In 1947, Piero Donini, a chemist at the Pharmaceutical Institute, Serono, in Rome tried to purify hMG from postmenopausal urine. This purification method was based on a method used by Katzman et al., published in 1943 . The first urine extract of gonadotropin contained LH and FSH and was named Pergonal, inspired by the Italian words “per gonadi” (for the gonads). The approval to sell Pergonal was first granted by the Italian authorities in 1950.

It was not until 1948, as a result of the work of Stewart, Sano, and Montgomery,that gonadotropins in the urine of pregnant women were shown to originate from the chorionic villi of the placenta, rather than the pituitary. It was subsequently designated as “chorionic gonadotropin”.

After years of experiment, it gradually became apparent that the pituitary factor was needed for the production of mature follicles, and that chorionic gonadotropin could induce ovulation only when mature follicles were present. Within years, it became apparent that the use of

gonadotropin extracts from non-primate sources was of limited clinical value owing to the development of antibodies that neutralized their therapeutic effect.

Only in 1961, with Pergonal treatment, the first pregnancy was achieved in a patient with secondary amenorrhea, which resulted with the birth (in 1962 in Israel) of the first normal baby girl.

Urinary FSH (Metrodin) and highly purified FSH became available with the development of new technologies using specific monoclonal antibodies to bind the FSH and LH molecules in the HMG material in such a way that unknown urinary proteins could be removed. Metrodin has a specific activity of 100–200 IU of FSH/mg of protein, whereas Metrodin-HP highly purified has an activity of approximately 9000 IU/mg of protein.

- Gonadotropins are glycoproteins with an approximate molecular weight of 30,000daltons. They consist of approximately 20% carbohydrates.

- They are heterodimers composed of two subunits, a hormone non-specific alpha subunit and a hormone specific beta subunit provides specificity for receptor interactions.

- These subunits are heavely modified by glycosylation.

- Exogenous gonadotropins have been used to induce ovulation in gonadotropin deficient women and those who fail to respond to other.

- They are highly effective but also very costly and associated with OHSS and multiple pregnancy.

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GONADOTROPINS PREPARATIONS

- The exogenous gonadotropins available were **human menopausal gonadotropins** (HMG,Menotropins), an extract prepared from the urine of postmenopausal women containing equivalent amounts (75IU) of FSH and LH per ampoule or vial and requiring intramuscular injections.

- More purified urinary FSH preparations (urofollitropin) were developed by removing LH from urinary extracts using immunoaffinity columns containing polyclonal anti HCG antibodies[23].

- Two Recombinant FSH preparations currently available are marketed as follitropinalfa and follitropin beta. They are both structurally identical to native FSH and contain 1 alpha and 1 beta glycoprotein chain, but the posttranslational glycosylation process and purification procedures for the two are different.

- Most recently, follitropin delta, the first recombinant FSH protein that is expressed in a human cell line, has been available for use in assisted reproductive technologies.

- A recombinant form of human LH having physicochemical, immunologic, and biologic activities comparable to those of human pituitary LH also is available,supplied in vials with syringes designed to deliver 75IU.

- Combined use of recombinant LH and FSH or HMG helps to promote follicular development in women with hypogonadotropic hypogonadism who have a profound LH deficiency.

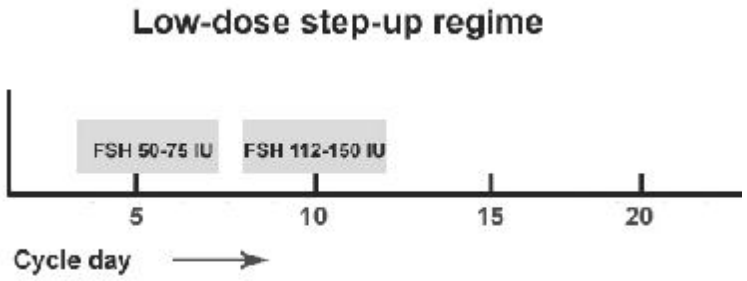
INDICATIONS OF GONADOTROPINS

- Women with hypogonadotropic hypogonadism
- Oral antiestrogen resistant anovulation
- Unexplained infertility

DIFFERENT REGIMENS FOR GONADOTROPIN THERAPY

Fixed dose regimen - A constant daily dose of 75-150 IU of gonadotropin is started from Day 2 or Day 3. Monitoring USG and E2 levels guide as to till when the injections are continued.

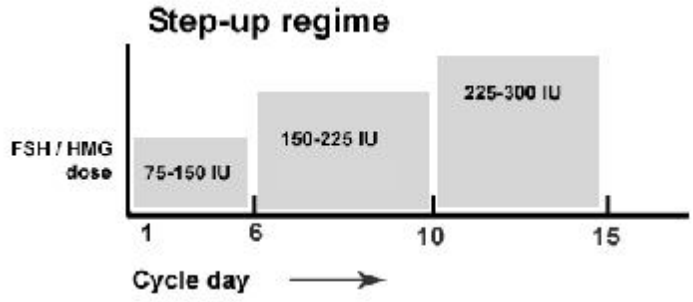
Chronic low – dose step – up regime – The principal behind this regimen is to find the "threshold" level of FSH which leads to the development of a single preovulatory follicle. The key feature of this regimen is the low starting dose (37.5-75 units/day) of drug, and a stepwise increase in subsequent doses, if necessary with aim of achieving the development of a single dominant follicle rather than the development of many large follicles, so as to avoid the complications of OHSS and multiple pregnancy. Serum E2 levels are measured and USG is performed on Day 7. If serum E2> 200pg/ml or follicle size is above 10mm, the same dose is continued. Otherwise, if the parameters are less than the above prescribed, the daily dose is increased by an increment of 37.5 units every week, till the serum E2 levels rises adequately[24].



Individually adjusted regimens, as guided by the TVS follicular scan and serum E2 Levels.

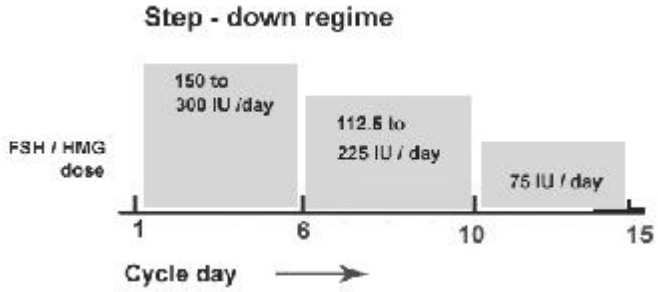
a) In both women with hypogonadotropic hypogonadism and those with oral antiestrogen resistant anovulation, initial attempts to induce ovulation generally should begin with a low daily dose(75

IU daily) in a **"STEP UP"** treatment regimen designed to define the effective threshold of response. After 4-7 days of stimulation, a serum estradiol level, with or without TVS, provides the first measure of response. Thereafter, the dose of gonadotropin may be maintained or increased, as indicated[25].



b) The alternative "**STEP DOWN**" treatment regimen is designed more closely approximate the pattern of serum FSH concenterations observed in spontaneous ovulatory cycles. Treatment begins with a higher dose (150-225 IU daily) and decreases gradually thereafter in an effort to promote continued development of only the more sensitive dominant follicle while withdrawing support from the less sensitive smaller follicles in the cohort. Considering that many anovulatory women are quite sensitive to low doses of exogenous gonadotropin stimulation, the step down method generally is best applied

However the two approaches can be effectively combined, first gradually increasing the dose of gonadotropins until a response is observed and then decreasing the dose once a dominant follicle has emerged[26].



Combined therapy with other drugs

Clomiphene citrate with gonadotropins– CC 100mg is administered from day 2 to day 6 and Inj HMG/FSH 75/150 units is given on day 6 and day 8. Transvaginal ultrasonography is done from day 8 onwards and in case the follicle growh or number is inadequate, additional FSH/HMG injections are administered[27].

DOSAGE

- HMG 75IU or 150IU on Day 7 and 9 given.

RISKS OF GONADOTROPIN TREATMENT

- Multiple pregnancy
- Multifetal pregnancy reduction
- OHSS

OHSS

OHSS is an iatrogenic complication of ovulation induction with exogenous gonadotropins. The disorder also can be observed occasionally in clomiphene induced cycles. However,to date, OHSS is not reported following ovulation induction with letrozole alone. To the contrary, one study including women at high risk of OHSS following ovarian stimulation for IVF reports decreased risk of OHSS when letrozole is given during the luteal phase.

RISK FACTORS

- Young age
- Low body weight
- High ovarian reserve
- PCOS
- Previous episodes of hyperstimulation

- Risk increases with serum estradiol levels and the number of developing ovarian follicles and when supplemental doses of HCG are administered after ovulation for luteal phase support.

MILD ILLNESS

- Characterized by mild nausea and vomiting
- Lower abdominal discomfort
- Diarrhea
- Abdominal distension
- Ovarian enlargement
- Only oral analgesics and counselling to alert affected women to the signs and symptoms of progressive illness are required.

SERIOUS ILLNESS

- Uncommon but not rare
- Incidence 1%
- Characteristics features – severe pain, rapid weight gain,tense ascites, hemodynamic instability,respiratory difficulty, progressive oliguria and laboratory abnormalities
- Hypotension,oliguria,dyspnea
- Hemoconcenteration, reduced peripheral perfusion and inactivity increases the risk of thromboembolism.

- Renal failure, ARDS(Acute respiratory distress syndrome),hemorrhage from ovarian rupture, and thromboembolic phenomena are potential life threatening complications of OHSS.

IUI

The first paper entitled intrauterine insemination (IUI) was published in 1962 (Cohen, 1962). Since then IUI has evolved through innovations such as sperm preparation, monitoring for pre-ovulatory timing and induction of ovulation with human chorionic gonadotrophin (HCG).

IUI also has been combined with ovarian stimulation using clomiphene citrate (CC) or gonadotrophins. Despite the fact that it has not been classified as an assisted reproductive technique (ART), it is widely used, often as an empirical treatment, for a broad range of profertility indications[(28)].

Rationale

The rationale of IUI treatment is to increase the rate of conception inthe couple by increasing the chance that maximum number of healthysperm reaches the site of fertilization. In couples with abnormalmucus, the rationale might be to bypass a possible cervical

factor.The post-coital test is not, however, a recommended routine in most countries.

Contraindications

IUI is contraindicated in women with cervical atresia, cervicitis, endometritisor bilateral tubal obstruction and in most cases of amenorrhea or severe oligospermia.

Indications

IUI with or without ovarian stimulation is considered to be indicated

for a broad range of diagnostic conditions.

- The most obvious diagnosis is male infertility, especially where donor sperm is required (Bensdorpet al., 2007).

- IUI is indicated for all categories of unexplained infertility and for couples with minimal and mild endometriosis.

- IUI in stimulated cycles may be considered while waiting for IVF, or when in women with patent tubes IVF is not affordable. In most of these indications, IUI or stimulated ovary/IUI is an empiric

treatment since it is likely that the majority of infertility involves factors that are untreatable[29].

IUI procedures and insemination Methods

Semen preparation

Prior to IUI, it is necessary to remove seminal plasma to avoid prostaglandin induced uterine contractions. Insemination with unprocessed semen is also associated with pelvic infection. Removal of the seminal plasma can be achieved by relatively simple procedures. The most frequently used methods involve centrifuging spermatozoa through culture medium or density gradients followed by re-suspension in suitable culture media. A systematic review of sperm preparation techniques concluded that there were in sufficient randomized studies to choose the best method. For normal semen samples, it is still unclear whether there is any advantage in isolating the most motile spermatozoa prior to insemination or whether similar results can be obtained using the whole population of spermatozoa in the sample[30].

Quality of the specimen

There is no consensus on a lower limit of semen quality at which one would advocate ICSI rather than IUI. Authors define their lower limits differently, as sperm concentration per millilitre or as the total

number of motile spermatozoa in the semen sample or as total number of motile spermatozoa in the sample for insemination. It has been reported that pregnancy rates are lower if the semen sample contains10 million sperm in total.

Mode of insemination

The sperm suspension can be deposited in the cervix, the uterus, the peritoneum or the Fallopian tube. IUI is by far the most common method. It is performed by introducing a 0.2–0.5 ml sperm suspension into the uterus with a small catheter, usually without imaging guidance.

With Fallopian tube sperm perfusion (FSP), the inseminate is4 ml, so that with this large volume of fluid the inseminate may fill not only the uterine cavity and Fallopian tubes, but also some of the volume may even end up inside the peritoneal cavity. For frozen semen, IUI is better than intracervical insemination(ICI): the likelihood of live birth after six insemination cycles is 2-foldhigher (OR: 1.98; 95% CI: 1.02–3.86) (Besselinket al., 2008). In two trials among patients with unexplained infertility, results with Fallopian tube Sperm perfusion were better than with IUI.

Timing of insemination

Insemination can be done at various time points around ovulation and can be done once or several times. In the majority of the published studies, the insemination is done 32–36 h following HCG administration[31].

It is assumed that the timing of insemination relative to ovulation is critical for an optimal success rate, so it is rather surprising that few studies were designed to find the optimal time for insemination. A systematic review found no difference in the pregnancy rate per couple with two inseminations compared with one (Cantineau et al., 2003).

Ovarian reserve and its assessment

The term ovarian reserve refers to the size and quality of the remaining ovarian follicular pool and the ability of the ovaries to respond to exogenous gonadotropin stimulation.

There are two intentions for ovarian reserve testing

- ✓ To predict fecundity

- ✓ To gain prognostic information regarding the likelihood of successful response to ovarian stimulation in women undergoing infertility
  treatment.

Ovarian reserve tests include both biochemical and ultrasonographic measures of the size and the quality of the ovarian follicular pool.

Biochemical tests include basal measurements such as FSH, Estradiol, inhibin B and antimullerian hormone(AMH)

Ultrasonographic measures of ovarian reserve include the antral follicular count (AFC) and ovarian volume.

Basal FSH and Estradiol Concenterations

Serum FSH concenteration was one of the earliest and commonly used tests of ovarian reserve. Since an isolated increase in FSH levels is one of the earliest indications of reproductive women in ageing, it was obvious choice for identifying women with diminished ovarian reserve. As a marker of ovarian reserve, serum FSH concenteration is best obtained during the early follicular phase (cycle days 2-4)

With current assays (using International Reference Preparation 78/549), FSH levels greater than 10 IU/L (10-20 IU/L) have high specificity for predicting poor response to stimulation, but their sensitivity for identifying such women is generally low(10-30%) and decreases with the threshold value[32].

The basal serum estradiol concenterations, by itself, has little value as an ovarian reserve test,[33,34,35] but can provide additional information that helps in the interpretation of the basal FSH level.

An early elevation in serum estradiol reflects advanced follicular development and early selection of a dominant follicle and will suppress FSH concenterations, thereby possibly making an otherwise obviously high FSH level indicating Diminished ovarian reserve.

When the basal FSH is normal and the estradiol concenteration is elevated

(>60 – 80 pg/ml), the likelihood of poor response to stimulation is increased and the chance of pregnancy is decreased . When both FSH and estradiol are elevated, ovarian response to stimulation is likely to be very poor.

Due to their low diagnostic performance, basal FSH and estradiol measurements are being increasingly replaced with serum AMH and AFC in daily practice.

Antimullerian hormone

Antimullerian hormone is produced by the granulosa cells of preantral and small antral follicles, beginning when primordial follicles start developing into primary follicles and ending when early antral follicles reach a diameter of 2-6mm[36,37].

Small antral follicles are likely the primary source of antimullerian hormone because they contain large number of granulosa cells and a more developed vasculature .

AMH is a very promising screening test for diminished ovarian reserve but is likely to be more useful in a general IVF population or in women at high risk for diminished ovarian reserve than in women at low risk for diminished ovarian reserve. Low threshold values have good specificity for poor response to ovarian stimulation, but not for predicting pregnancy.

Antral Follicle Count

Reproductive-aged women have an estimated 20-150 growing follicles in the ovaries at any one time, although only those large enough to be imaged >2mm can be visualized by transvaginal ultrasonography. Antral follicles are FSH sensitive and can progress to more advanced stages of development when stimulated with exogenous FSH.

Histologic studies have revealed that the number of small antral follicle in the ovaries is proportional to the number of primordial follicles remaining[38]. Therefore, as the supply of primordial follicles decreases, the number of visible small antral follicles also declines.

The antral follicle count – The total number of antral follicles measuring 2-10mm in both ovaries thus provides an indirect but useful measure of ovarian reserve[39,40].

AFC correlates with onset of the menopausal transition, indicating that it relates to the number of follicles remaining. Some, perhaps as much as half, of the antral follicles that can be imaged are probably in the process of atresia, but there is no way other than observing their response to FSH stimulation to distinguish them from viable growing follicles.

However, AFC correlates well with oocyte yield in IVF cycles, suggesting that gonadotropin stimulation can still rescue follicles that may be in the early stages of atresia. Several studies have observed a relationship between the AFC and response to ovarian stimulation in IVF cycles.

A Low AFC has high specificity for predicting poor response to ovarian stimulation and treatment failure, making it a useful test, but low sensitivity limits its overall clinical utility.

MATERIALS AND METHODS

STUDY DESIGN

A Prospective study

PERIOD OF STUDY

2020 September – 2021 September

PLACE OF STUDY

Department of fertility research centre, IOG, Egmore and ISO-KGH,Triplicane.

SAMPLE SIZE

200 women were included in the study as per inclusion criteria after obtaining informed consent from each participant who had attended fertility research centre at Institute of Obstetrics and Gynaecology and Government Hospital for Women and Children, Egmore and Institute of Social Obstetrics and Government Kasturba Gandhi Hospital for Women and Children,Triplicane from September 2020 to September 2021.

INCLUSION CRITERIA

- Inferility lasting for one year or more with regular unprotected intercourse.
- Age 21-35 years
- Bilateral Patent fallopian tubes
- Normal pelvic USG
- No recent treatment for OI[within 6 monhs]
- Normal Semen analysis
- No history of treatment by exogenous gonadotropins.
- Willingness for written informed consent

EXCLUSION CRITERIA

1. Age > 35 years
2. Immunological causes of infertility
3. Hyperprolactinemia.
4. Poor patient compliance
5. Women with uterine, B/L Adnexal pathology egfibroid,ovarian cyst.
6. Those with previous history of any surgeries related to genital tract as per history were excluded
7. Premature ovarian failure

8. Ovarian tumours
9. Those with impaired hepatic / renal function
10. Coital errors
11. Lack of willingness.

The participants in this study were subjected to clinical, radiological and biochemical evaluation.

Clinical Evaluation

HISTORY

- **Age** (21 – 35 yrs): An association between age of the woman and reduced fertility has been well documented[40]. The decline in fecundability begins in early thirties, accelerates during late thirties and early forties. Oocyte related decline in fertility is due to decreased ovarian reserve [41].
- **Menstrual History :** Menstrual history including cycle length and characteristics and onset and severity of dysmenorrheal. In our study women with oligomenorrhea were included in the study after progesterone withdrawal bleed.
- Obstetric history including gravidity, parity, pregnancy outcomes, and associated complications.

- Coital frequency and sexual dysfunction
- Duration of infertility and results of any previous evaluation and treatment.
- Symptoms of thyroid disease,pelvic or abdominal pain, galactorrhea, hirsutism or dyspareunia.

CLINICAL EXAMINATION

The patients enrolled in our study were subjected to clinical examination which included the following

Weight and BMI was calculated.

BMI = weight in kg. / Height in m^2

It is a reliable indicator, Inexpensive and easy to perform.

Clinical evidence of acne, hirsutism, acanthosis nigricans(PCOS), hyperthyroidism and hypothyroidism were looked for in all patients enrolled in our study.

INVESTIGATIONS

Hysterosalpingography

HSG accurately defines the size and shape of the uterine cavity, provides clear images of most uterine development anomalies (unicornuate, septate, bicornuate and didelphys) and with exceptions, also identifies

submucous myomas and intrauterine adhesions that can have important reproductive implications.

HSG is best scheduled on the 8th to 9th day of menstrual cycle to minimize the risk of infection, to avoid interference from intrauterine blood and clot, and to prevent any possibility that the procedure might be performed after conception.

HSG may reveal bilateral tubal patency (60-75%) or unilateral (15-25%) or bilateral (15-25%) tubal occlusion[42,43]. Compared to laparoscopy

(the gold standard method) as a test of tubal patency, HSG has an overall sensitivity of 94% and sensitivity of 92%.Thus,if HSG shows patent tubes,tubal blockage is highly unlikely. The clinical implications are that when HSG reveals obstruction ,there is still a relatively high probability (approximately 60%) that the tube is open, but when HSG demonstrates patency,there is little chance the tube is actually occluded(approximately 5%).

Ultrasonography

For all patients antral follicle count measured. Evidence of fibroid & ovarian cyst / adnexal masses ruled out

Semen Analysis

Normal Reference Values :

Volume	1.5 – 5.0 mL
pH	>7.2
Viscosity	<3 (scale 0 – 4)
Sperm concenteration	> 20 million/mL
Total sperm number	>40 million/ejaculate
Percent motility	>50%
Forward progression	>2 (scale 0 – 4)
Normal morphology	>50% normal
Round cells	<5 million/mL
Sperm agglutination	2 (scale 0-3)

BIOCHEMICALINVESTIGATIONS

Complete blood count, random blood sugar, renal function test and liver function test were done in all patients. Any abnormality in any one of these investigations, those patients were excluded from this study

METHODOLOGY

200 patients were included in the study, of which 100 patients were given ovulation induction drugs alone and they are considered as group 1, of which 50 patients were given CC and other 50 patients were given letrozole.

Clomiphene citrate 100 mg/day from day 3 to day 7 of menstrual cycle.

Letrozole 2.5mg twice daily from day 3 to day 7 of menstrual cycle.

Other 100 patients were given ovulation induction drugs and gonadotropins and they are considered as group 2, of which 50 patients were given CC and Gonadotropins and other 50 patients were letrozole and gonadotropins.

Human menopausal gonadotropins 75/150 IU given on day 7 and day 9.

Both the groups of patients, were subjected to transvaginal ultrasonography to

- ✓ Monitor the number of follicles
- ✓ Assess the maximum diameter of the largest follicle
- ✓ To measure Endometrial thickness from D11 onwards.
- ✓ To assess for ovulation - Collapsed follicle and free fluid noted.

When the follicle reached a diameter of >=18mm,HCG (5000IU/10,000 IU) was given as a single intramuscular injection to trigger ovulation. Patients were advised intercourse 24–36 hours after HCG injection.

UPT was done as soon as the patients missed their periods. Pregnancy was defined by the presence of an intrauterine gestational sac with the presence of fetal heart rate on ultrasound.

RESULTS AND ANALYSIS

The mean age of the participants is 28.12 years (S.D=3.03 years).

The mean weight of the participants is 64.1 kg (S.D=9.3).

The mean BMI of the participants is 26.2 (S.D=3.9).

Out of 200 patients, 59% (n=118) had primary infertility and 41% (n=82) had secondary infertility.

Out of 200 patients, 60% (n=120) had irregular cycles and 40% (n=80) had regular cycles.

Around 44.5% (n=89) were hypothyroid while 1.5% (n=3) were diabetics and 1% (n=2) were APLA positive. Around 24.5% (n=29) had polycystic ovarian syndrome.

The mean number of years since marriage was 4.77 years (S.D=2) in our study

Letrozole+ gonadotropins had higher mean endometrial thickness and larger mean size of dominant follicle. The treatment used had a

statistically significant impact on the size of dominant follicle ($p<0.05$) and endometrial thickness ($p<0.005$).

Letrozole plus gonadotropins had higher mean endometrial thickness and larger mean size of dominant follicle, followed by Letrozole alone, Clomiphene plus gonadotropins and Clomiphene alone.

Monofollicular development were higher in letrozole plus gonadotropin combinations than the other group.

Multifollicular development were higher in Clomiphene plus gonadotropins combination than the other group ($p<0.0001$).

Ovulation rate were higher in letrozole plus gonadotropin combinations than the other group.

Out of 36 participants who were positive for UPT, majority of them were in the treatment arm of Letrozole plus gonadotropins (n=14), followed by Clomiphene plus gonadotropins (n=9), Letrozole alone (n=8) and then Clomiphene alone (n=5). This is not statistically significant ($p=0.130$).

Age distribution of the participants

The mean age of the participants is 28.12 years (S.D=3.03 years).

	Age (years)
Mean	28.125
Median	28.000
Std. Deviation	3.0374
Minimum	22.0
Maximum	35.0

Table 1: Age distribution of the participants

Figure 1: Age distribution of the participants represented in bar diagram

Weight distribution of the participants

The mean weight of the participants is 64.1 kg (S.D=9.3).

	Weight (kg)
Mean	64.10
Median	62.00
Std. Deviation	9.343
Minimum	42
Maximum	90

Table 3: Weight distribution of the participants

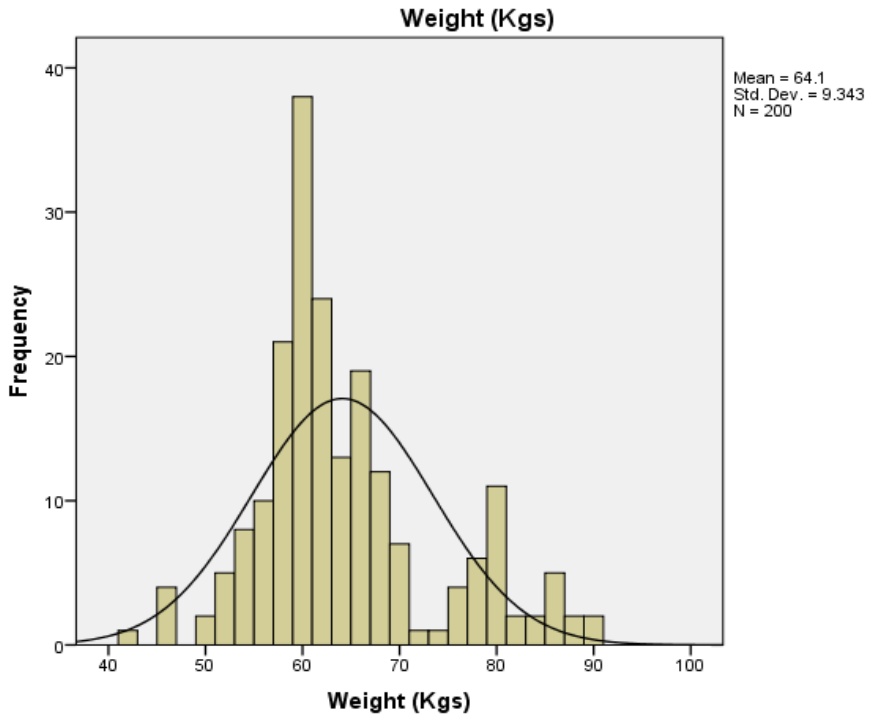


Figure 3: Weight distribution of the participants represented in bar diagram

BMI distribution of the participants

The mean BMI of the participants is 26.2 (S.D=3.9).

	BMI
Mean	26.2593
Median	25.2500
Std. Deviation	3.94412
Minimum	17.10
Maximum	39.20

Table 4: BMI distribution of the participants

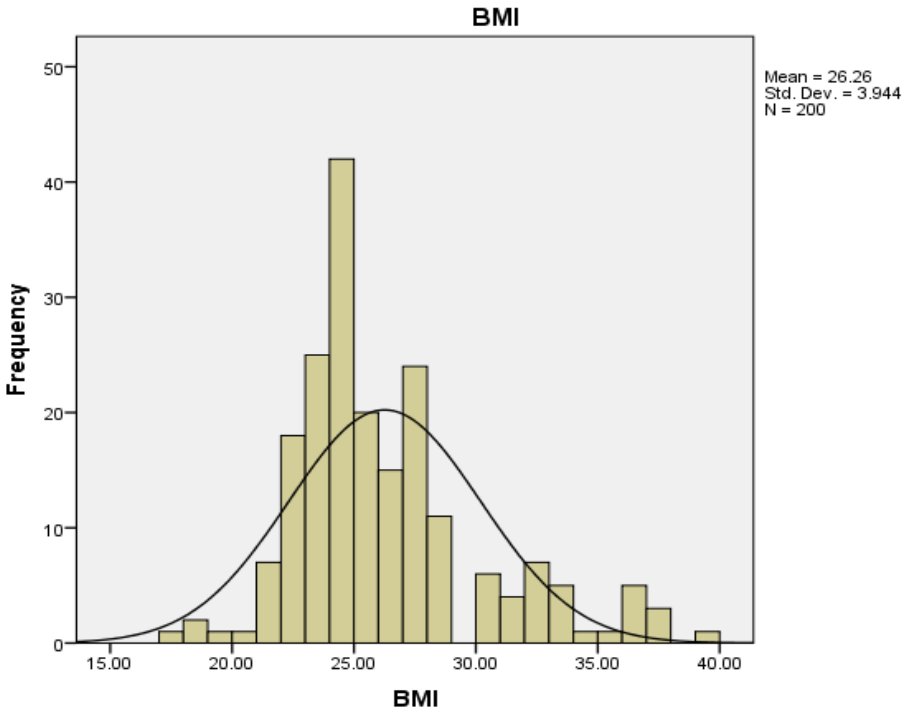


Figure 4: BMI distribution of the participants represented in bar diagram

Category	Age (Yrs) Mean ± SD	BMI Mean ± SD	Married since(yrs) Mean ± SD
Group 1	27.870 ± 2.8733	26.3140 ± 3.89338	4.53 ± 1.834
Group 2	28.380 ± 3.1870	26.2046 ± 4.01308	5.00 ± 2.118
Total	28.125 ± 3.0374	26.2593 ± 3.94412	4.77 ± 1.990

Group 1= Letrozole and Clomiphene Citrate, Group 2= Letrozole + Gonadotropin & Clomiphene Citrate + Gonadotropin, BMI = Body Mass Index

Incidence of infertility

Out of 200 patients, 59% (n=118) had primary infertility and 41% (n=82) had secondary infertility

Infertility	Frequency	Percent
Primary	118	59.0
Secondary	82	41.0
Total	200	100.0

Table 5: Incidence of infertility

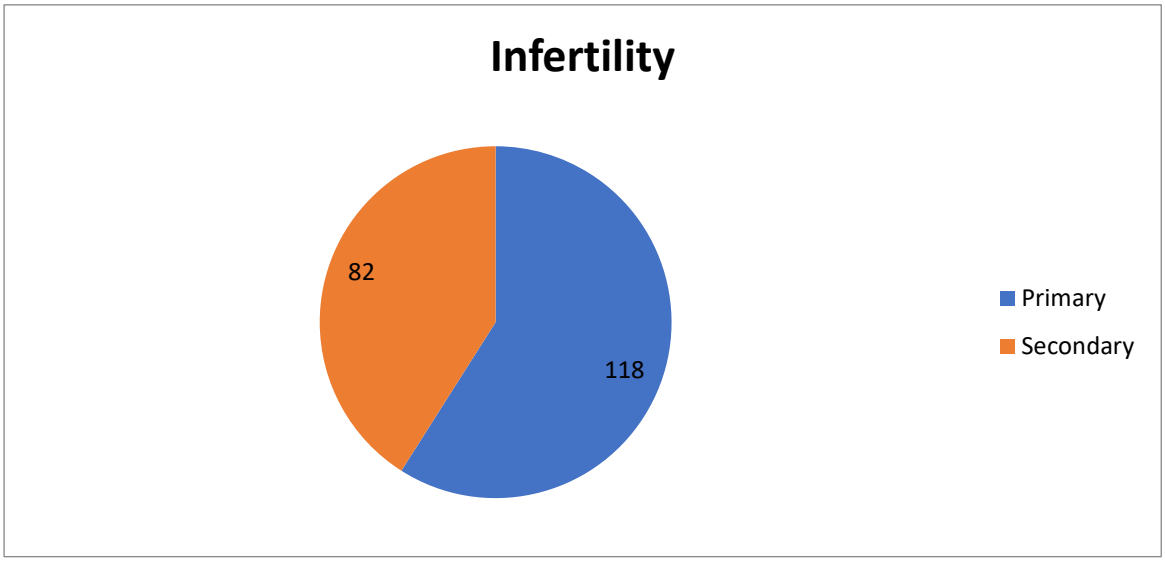


Figure 5: Incidence of infertility represented in pie chart

Characteristics of menstrual cycles

Out of 200 patients, 60% (n=120) had irregular cycles and 40% (n=80) had regular cycles.

Menstrual cycle	Frequency	Percent
Irregular	120	60
Regular	80	40
Total	200	100.0

Table 6: Characteristics of menstrual cycles

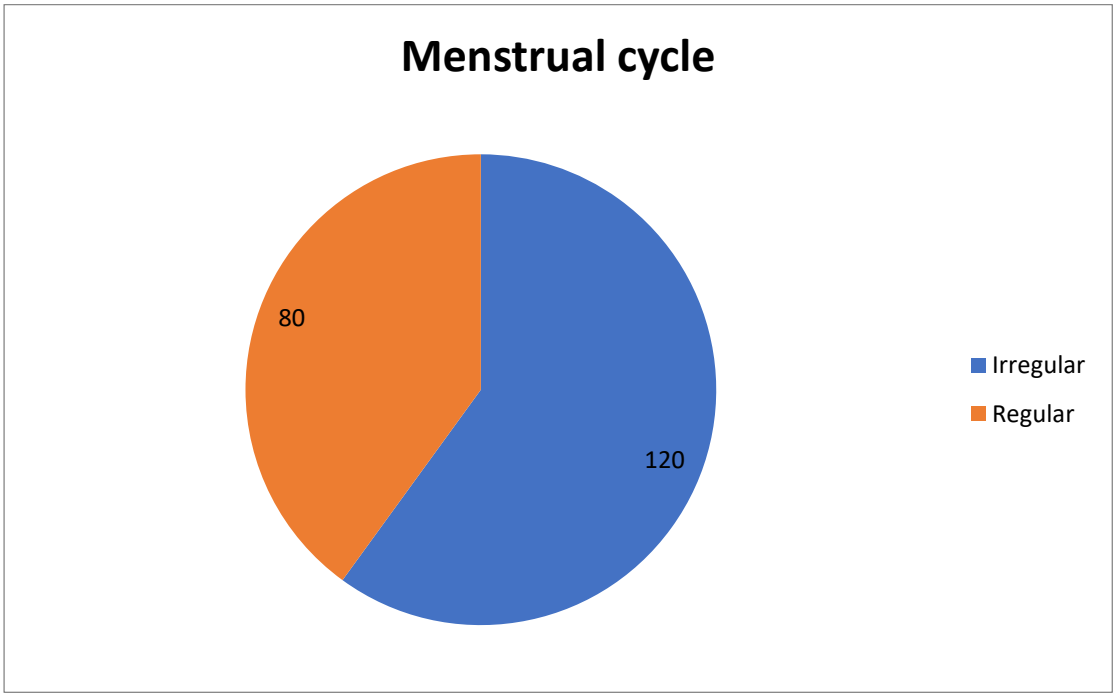


Figure 6: Characteristics of menstrual cycles represented in pie chart

Comorbidities

Around 44.5% (n=89) were hypothyroid while 1.5% (n=3) were diabetics and 1% (n=2) were APLA positive.

Comorbidity	Frequency	Percent
APLA positive	2	1.0
Diabetes Mellitus	3	1.5
Hypothyroid	89	44.5
No comorbidities	106	53.0
Total	200	100.0

Table 7: Comorbidities

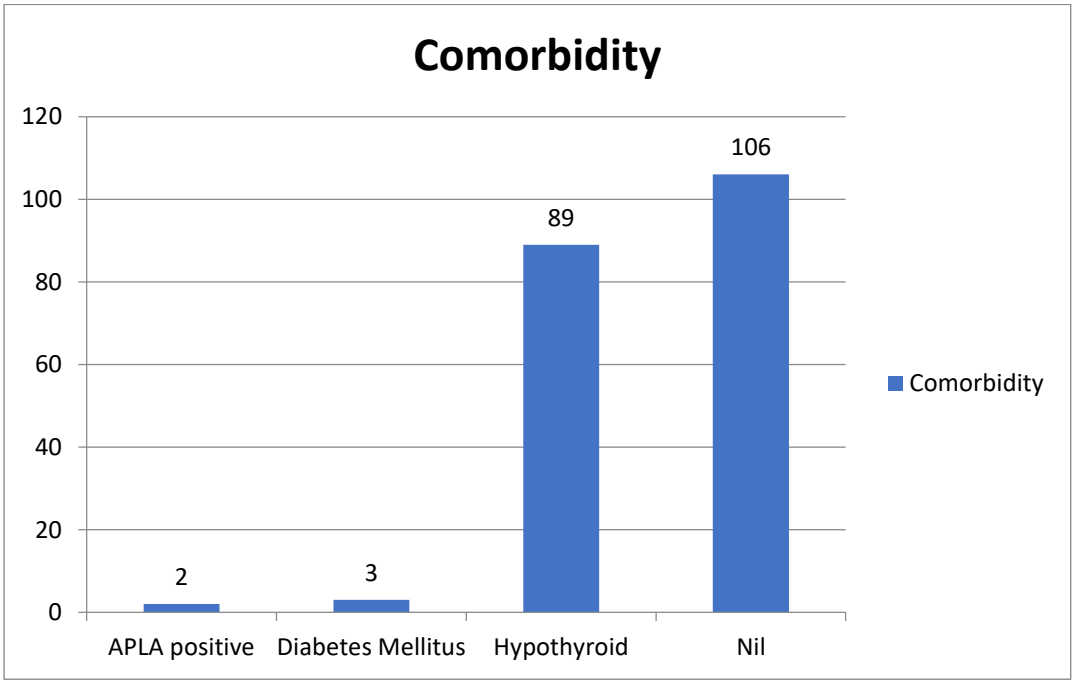


Figure 7: Comorbidities

INCIDENCE OF PCOS IN BOTH THE GROUPS

Poly Cystic Ovarian Syndrome	**Category**		**Total N (%)**
	Group 1 N (%)	**Group 2 N (%)**	
No	70 (70)	81(81)	151 (75.5)
Yes	30 (30)	19 (19)	49 (24.5)
Total	100 (100)	100 (100)	200 (100)
Pearson Chi-Square: Value = 3.271 , p =.071 (ns)			

*****p<0.01 - *p<0.05 (alpha Value) - statistically significant, ns- not significant, Group 1= Letrozole and Clomiphene Citrate, Group 2= Letrozole + Gonadotropin & Clomiphene Citrate + Gonadotropin,**

Table 8: Incidence of Poly Cystic Ovarian Syndrome

Around 24.5% (n=49) had poly cystic ovarian syndrome.

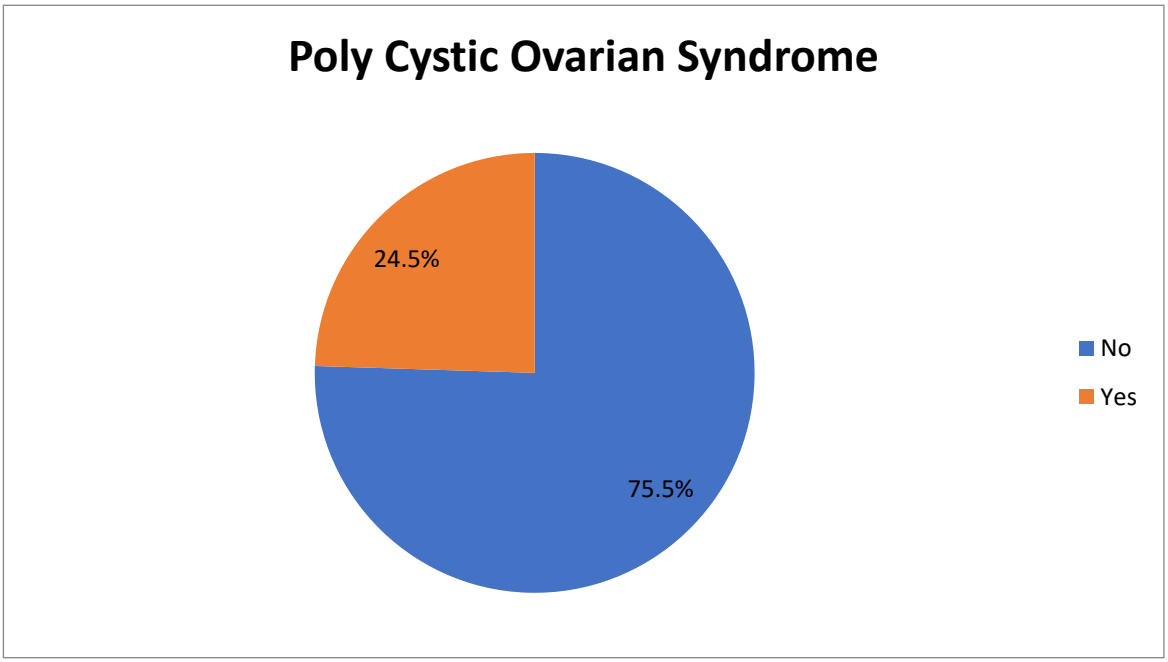


Figure 8: Incidence of Polycystic Ovarian Syndrome in pie chart representation

Number of years since marriage

The mean number of years since marriage was 4.77 years (S.D=2)

Mean	4.77
Median	4.00
Std. Deviation	1.990
Minimum	1
Maximum	12

Table 9: Number of years since marriage

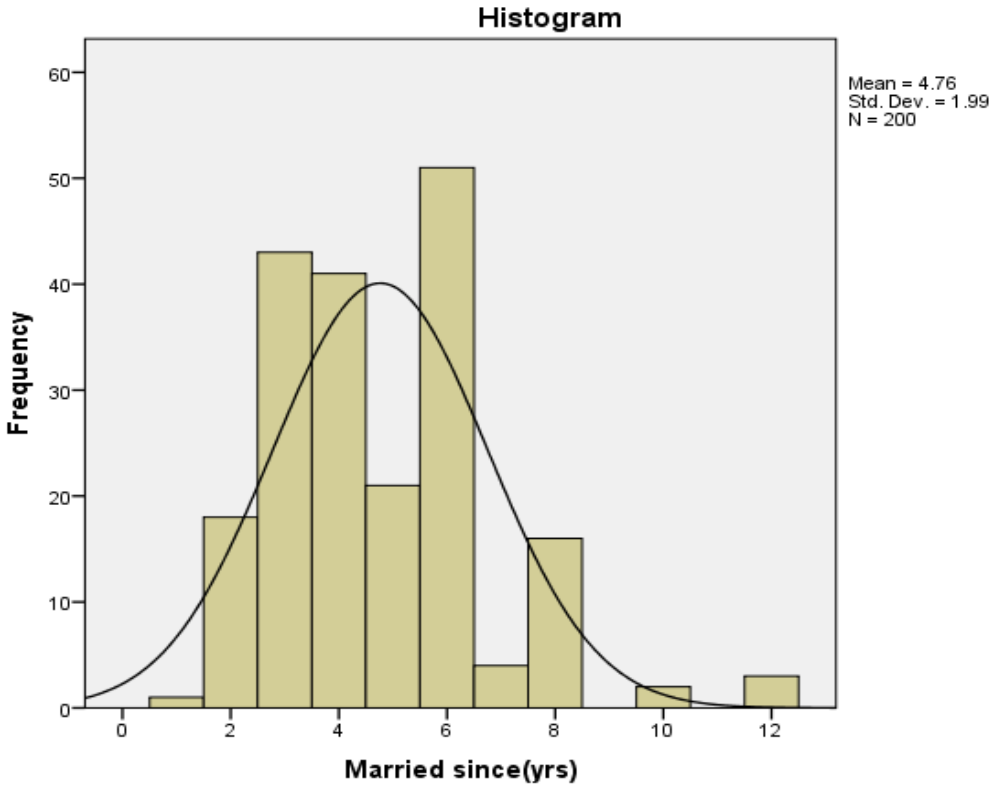


Figure 9: Number of years since marriage in bar diagram representation

Cross tabulation and chi-square analysis between treatment used and number of dominant follicles

The multifolliculogenesis were higher in Clomiphene plus gonadotropins combination than other groups (p<0.0001).

Number of dominant follicles	Categories				Total N (%)
	Clomiphene+Gonadotropins N (%)	Letrozole+Gonadotropins N (%)	Clomiphene alone N (%)	Letrozole alone N (%)	
0	8 (16)	7 (14)	14 (28)	15 (30)	44 (22)
1	13 (26)	35 (70)	14 (28)	26 (52)	88 (44)
2	19 (38)	8 (16)	12 (24)	9 (18)	48 (24)
3	10 (20)	0	10 (20)	0	20 (10)
Total	50 (100)	50 (100)	50 (100)	50 (100)	200 (100)
Pearson Chi-Square: Value = 45.721 , p =.000 * **					

*****p<0.01 - *p<0.05 (alpha Value) - statistically significant, ns- not significant**

Table 10: Cross tabulation and chi-square analysis between treatment used and number of dominant follicle

Cross tabulation and chi-square analysis between treatment used and method of conception

Method of conception	Categories				Total N (%)
	Clomiphene+ Gonadotropins N (%)	Letrozole+Gonadotropins N (%)	Clomiphene alone N (%)	Letrozole alone N (%)	
Natural	06 (66.6)	09 (64.3)	3 (60)	4 (50)	17 (47.2)
IUI	03 (33.4)	05 (35.7)	2 (40)	4 (50)	19 (52.8)
Total	09 (100)	14 (100)	05 (100)	08 (100)	36 (100)
Pearson Chi-Square: Value = 2.236, p =.524(ns)					

*****p<0.01 - *p<0.05 (alpha Value) - statistically significant, ns- not significant, IUI- IntraUtrine Insemination**

There was no difference in the method of conception across different treatment choices.

Table 11: Cross tabulation and chi-square analysis between treatment used and method of conception

Cross tabulation and chi-square analysis between treatment used and incidence of pregnancy

Out of 36 participants who turned positive on UPT, majority of them were in the treatment arm of Letrozole plus gonadotropins (n=14), followed by Clomiphene plus gonadotropins (n=09), Letrozole alone (n=08) and then Clomiphene alone (n=05). This is not statistically significant (p<0.005)

Incidence of pregnancy	Categories				Total N (%)
	Clomiphene+ Gonadotropins N (%)	Letrozole+ Gonadotropins N (%)	Clomiphene alone N (%)	Letrozole alone N (%)	
No growth of dominant follicle	8 (16)	7 (14)	14 (28)	15 (30)	44 (22)
Positive	09 (18)	14 (28)	05 (10)	08 (24)	36 (18)
Negative	33 (66)	29 (58)	31 (62)	27 (56)	120 (60)
Total	50 (100)	50 (100)	50 (100)	50 (100)	200 (100)
Pearson Chi-Square: Value = 9.879, p =.130(ns)					

. ***p<0.01 - *p<0.05 (alpha Value) - statistically significant, ns- not significant

Table 12: Cross tabulation and chi-square analysis between treatment used and incidence of pregnancy

Cross tabulation and chi-square analysis between ovulation induction drug used and number of dominant follicles

The multifolliculogenesis were higher in Clomiphene group than Letrozole group (p<0.0001).

Number of dominant follicles	Ovulation Induction Drug		Total N (%)
	Clomiphene Citrate N (%)	Letrozole alone N (%)	
0	22 (22)	22 (22)	44 (22)
1	27 (27)	61 (61)	88 (44)
2	31 (31)	17 (17)	48 (24)
3	20 (20)	0	20 (10)
Total	100 (100)	100 (100)	200 (100)
Pearson Chi-Square: Value = 37.220, p =.000* **			

*****p<0.01 - *p<0.05 (alpha Value) - statistically significant, ns- not significant**

Table 13: Cross tabulation and chi-square analysis between ovulation induction drug used and number of dominant follicles

Cross tabulation and chi-square analysis between ovulation induction drug used and method of conception

There was no difference in the method of conception across different treatment choices.

Method of conception	**Ovulation Induction Drug**		**Total N (%)**
	Clomiphene Citrate N (%)	**Letrozole alone N (%)**	
Natural	09 (64.2)	13 (59)	22 (61)
IUI	05 (35.8)	09 (41.6)	14 (39)
Total	14 (100)	22 (100)	36 (100)
Pearson Chi-Square: Value = .097, p =.755 (ns)			

*****p<0.01 - *p<0.05 (alpha Value) - statistically significant, ns- not significant**

Table 14: Cross tabulation and chi-square analysis between ovulation induction drug used and method of conception

Cross tabulation and chi-square analysis between ovulation induction drug used and incidence of pregnancy

Out of 36 subjects who became positive for UPT, majority of them were in the treatment arm of Letrozole (n=22). Clomiphene had 14 subjects with UPT positive. However, this was not statistically significant (p>0.05).

Urine Pregnancy Test	**Ovulation Induction Drug**		**Total N (%)**
	Clomiphene Citrate N (%)	**Letrozole alone N (%)**	
No growth of dominant follicle	22 (22)	22 (22)	44 (22)
Positive	14 (14)	22 (22)	36 (18)
Negative	64 (64)	56 (56)	120 (60)
Total	100 (100)	100 (100)	200 (100)
Pearson Chi-Square: Value = 2,311, p =.315 (ns)			

*****p<0.01 - *p<0.05 (alpha Value) - statistically significant, ns- not significant**

Table 15: Cross tabulation and chi-square analysis between ovulation induction drug used and incidence of pregnancy

Comparison of means of size of dominant follicle and endometrial thickness between ovulation inductions drugs used by unpaired Student –t- test

The treatment used had a statistically significant impact ($p<0.005$) on the size of dominant follicle and endometrial thickness. Letrozole had higher mean endometrial thickness and larger mean size of dominant follicle.

Changes in Follicular size and Endometrial thickness	**Ovulation induction drugs**		**t-value**	**P Value**
	Clomiphene (N= 100) Mean ± SD	**Letrozole (N= 100) Mean ± SD**		
Size of dominant follicle	17.54 ± 5.447	19.20 ± 4.870	2.3267	**0.02***
Endometrial thickness(mm)	7.471 ± .8924	8.533 ± 1.4007	6.3967	**0.000****

*****p<0.01 - *p<0.05 (alpha Value) - statistically significant, ns- not significant**

Table 16: Comparison of means of size of dominant follicle and endometrial thickness between ovulation induction drugs used by unpaired Student –t- test

Comparison of means of size of dominant follicle and endometrial thickness between treatments given by one way ANOVA

The treatment used had a statistically significant impact on the size of dominant follicle ($p<0.05$) and endometrial thickness ($p<0.005$). Letrozole plus gonadotropins had higher mean endometrial thickness and larger mean size of dominant follicle, followed by Letrozole alone, Clomiphene plus gonadotropins and Clomiphene alone.

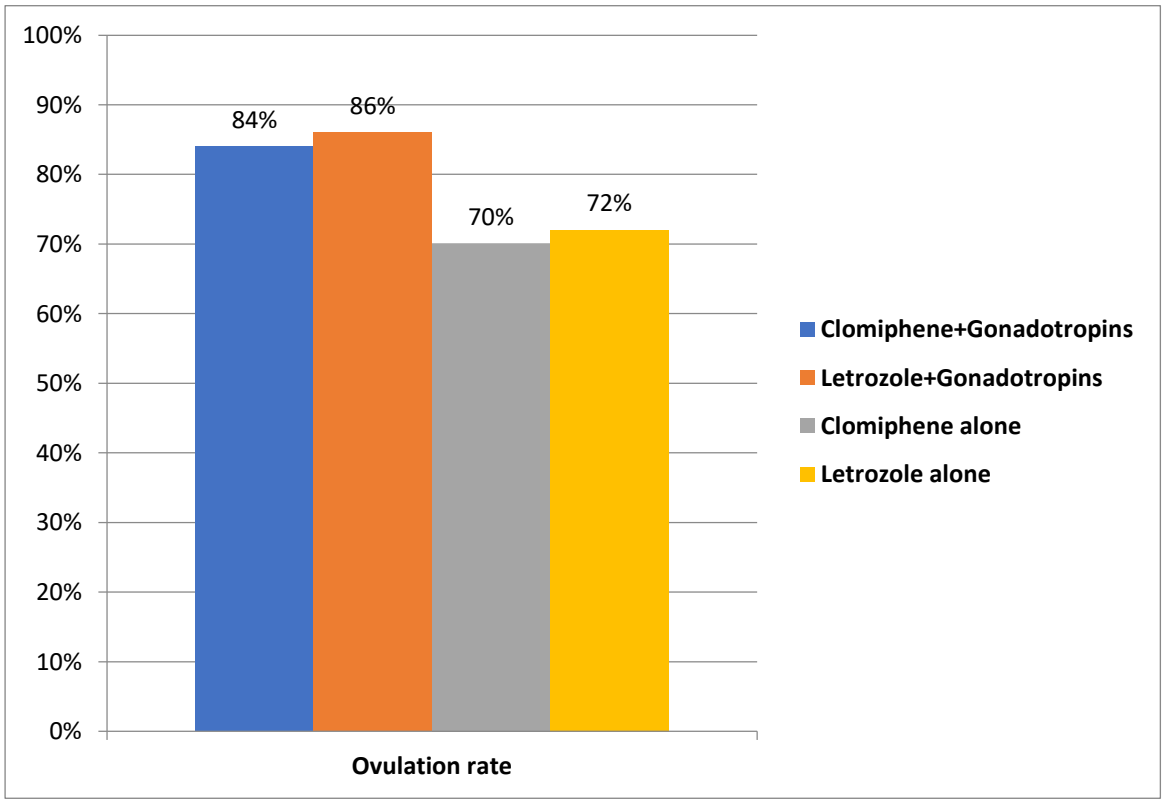
Changes in Follicular size and Endometrial thickness	**Categories**				**F Value**	**Sig**
	Clomiphene+ Gonadotropins (N= 50) Mean ± SD	**Letrozole+ Gonadotropins (N= 50) Mean ± SD**	**Clomiphene (N= 50) Mean ± SD**	**Letrozole (N= 50) Mean ± SD**		
Size of dominant follicle	19.92 ± 4.802	20.28 ± 4.486	17.96 ± 5.911	18.12 ± 5.041	2.783	**.042**
Endometrial thickness(mm)	7.630 ± .7421	8.702 ± 1.1757	7.312 ± 1.003	8.364 ± 1.58	15.078	**.000**

*****p<0.01 - *p<0.05 (alpha Value) - statistically significant, ns- not significant**

Table 17: Comparison of means of size of dominant follicle and endometrial thickness between treatments given by one way ANOVA

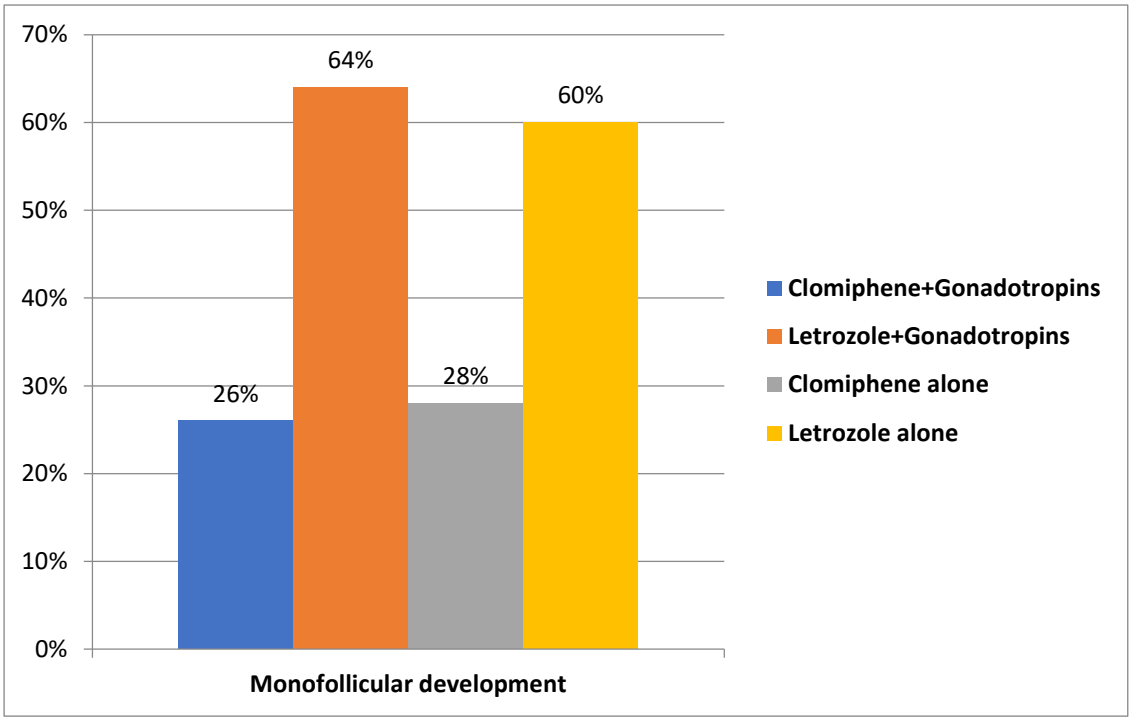
OVULATION RATE

	Categories			
	Clomiphene+Gonadotropins	**Letrozole+Gonadotropins**	**Clomiphene alone**	**Letrozole alone**
Ovulation rate (%)	84%	86%	70%	72%



MONOFOLLICULAR DEVELOPMENT

	Categories			
	Clomiphene+Gonadotropins	Letrozole+Gonadotropins	Clomiphene alone	Letrozole alone
Monofollicular development	26%	64%	28%	60%



SUMMARY

In the patients recruited in this study,

1) The mean age in Group 1 is 27.8 years and in group 2 is 28.3 years.

2) The mean duration of infertility in group 1 is 4.53 years and in group 2 is 5 years.

3) In letrozole and gonadotropin group, the ovulation rate was 86% and in letrozole 72%

   In Clomiphene citrate and gonadotropin group, the ovulation rate was 84% and in clomiphene 70%

4) In letrozole and gonadotropin group, 64% of cases developed single dominant follicle and 24% of cases developed two dominant follicle.In letrozole group, 60% of cases developed single dominant follicle and 24% of cases developed two dominant follicle.

5) In clomiphene and gonadotropin group, 26% of cases developed single dominant follicle and 44% of cases developed two dominant follicle.In clomiphene group, 28% of cases developed single dominant follicle and 20% of cases developed two dominant follicle.

6) The mean diameter of largest follicle in letrozole and gonadotropin group is 20.28mm and in letrozole group is 18.12mm

   The mean diameter of largest follicle in Clomiphene citrate and gonadotropin group is 19.92mm and in clomiphene group is 17.96mm

7) The mean endometrial thickness in Letrozole and gonadotropin is 8.7mm and in letrozole is 8.3mm

   The mean endometrial thickness in Clomiphene and gonadotropin is 7.6mm and in clomiphene citrate is 7.3mm.

8) Clinical pregnancy rate overall in our study is 18%

DISCUSSION

The current study revealed the comparative efficacy of ovulation induction drugs alone versus ovulation induction drugs and gonadotropins in infertility for a sample size of 200 participants from September 2020 to September 2021 at fertility research centre, Institute of Obstetrics and Gynaecology and Government Hospital for Women and Children,Egmore and Institute of Social Obstetrics and Government Kasturba Gandhi Hospital for Women and Children, Triplicane. It also revealed various factors like mean age, mean duration of infertility, number and size of dominant follicle, endometrial thickness, ovulation rate, pregnancy rate in both the groups.The patients enrolled in both the groups had no complications pertaining to Letrozole,Clomiphene Citrate, gonadotropins during our period of study.

Number of dominant follicle

In the present study, the monofollicular development were higher in Letrozole plus gonadotropin group. This is comparable to Mousa NS, Casper RF et al., also concluded that, one mature follicle ended in higher

pregnancy and live birth rate with combined use of letrozole and gonadotropin , also reduces the risk of OHSS also.

The current study is also comparable with Xi et al., 2015 a prospective study showed that rate of monofollicular development was significantly higher in letrozole plus gonadotropin group.

The current study is also comparable with Biljan et al., showing that letrozole was an effective alternative to CC in view of monoovulation.

BASIR et al., in his study concluded that L is an effective alternative to CC in OI in view of monoovulation.

Size of dominant follicle and Endometrial thickness

Letrozole plus gonadotropins had higher mean endometrial thickness and larger mean size of dominant follicle, followed by letrozole alone, clomiphene plus gonadotropins and clomiphene.

In our study, Letrozole plus gonadotropins had mean Endometrial thickness of 8.7, followed by letrozole 8.3mm, followed by clomiphene

plus gonadotropins 7.6mm, followed by clomiphene 7.3mm. This is comparable to BADAWY et al., 2007 studied 438 infertile women, concluded that Endometrial thickness was better in L group than CC group. (9.2 vs 8.1mm).

The mean endometrial thickness in (7.6mm/7.3mm) in CC group indicates the adverse effects CC on the endometrial growth that is thought to be due to depletion of the endometrial receptors.

The current study is also comparable with Yun et al., Concluded that ET at the day of HCG administration was significantly higher in letrozole gonadotropin group than the CC gonadotropin group.

The current study is also comparable with Sohravand et al., in his study concluded that Endometrial thickness was higher with L than CC group.

In our study, mean diameter of dominant follicle was greater in letrozole plus gonadotropins group(20.28), followed by clomiphene+gonadotropins(19.92), followed by letrozole(18.12), by clomiphene(17.96). This study is comparable with Healy et al., found that mean diameter of dominant follicle was greater in letrozole plus

gonadotropin group and also concluded that dose of gonadotropin were also less when combined with letrozole.

Multifollicular development

The current shows that multifollicular development is common with clomiphene plus gonadotropin group followed by CC, letrozole group. This is comparable with Malhotra et al., concluded that letrozole plus gonadotropin group is least associated with superovulation or multifollicular development and also concluded that letrozole plus gonadotropins should be preferred as the first line for superovulation in unexplained infertility

Pregnancy rate

Out of 36 subjects who became positive on UPT, majority were in the treatment arm of Letrozole plus gonadotropins, followed by clomiphene plus gonadotropins, letrozole alone and then clomiphene alone. This is comparable to Verhust SM, Hughes E, Cohlen BJ, reported that exogenous gonadotropins with letrozole or CC increase pregnancy rates and live birth rates compared to natural cycle or other ovulation induction drugs

The current study is also comparable with Arya S, Kuesic – Lavsic S, Jose J et al., concluded that use of letrozole with gonadotropins, a similar and acceptable ET at the day of HCG administration and a good pregnancy rate.

CONCLUSION

Letrozole and gonadotropins are more effective in inducing ovulation than letrozole alone in terms of monofollicularovulation ;Similarly, Clomiphene and gonadotropins are more effective in inducing ovulation than Clomiphene alone. Adequate endometrial thickness is achieved with Letrozole and HMG when compared with Letrozole alone. Same way sufficient endometrial thickness is achieved with clomiphene and HMG when compared with Clomiphene alone. When compared letrozole and CC group, sufficient endometrial thickness and monofollicular ovulation is achieved with letrozole group.

Pregnancy rate achieved in letrozole and gonadotropins group is relatively more compared to letrozole alone. Similarly, pregnancy rate achieved in clomiphene and gonadotropin group is relatively more compared to clomiphene alone. The mean diameter of dominant follicle is larger in letrozole and gonadotropin group compared to letrozole alone. Similarly, mean diameter of dominant follicle is larger in clomiphene and gonadotropin group compared to clomiphene alone. No case of OHSS has been reported in the study. Use of ovulation induction drugs along with gonadotropins reduces the dosage of gonadotropins given and also reduces the incidence of OHSS and multiple pregnancy.

Hence concluding that letrozole plus gonadotropin group were effective in inducing ovulation, development of adequate ET, develops adequate mean diameter of dominant follicle, monofollicular ovulation. It also reduces the OHSS and multiple pregnancy. It is the preferred treatment modality for superovulation in unexplained infertility.

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PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **"A COMPARATIVE STUDY OF EFFICACY OF OVULATION INDUCTION DRUGS ALONE VERSUS OVULATION INDUCTION DRUGS AND GONADOTROPINS IN INFERTILIY**" **of the candidate** DR.S.S ISWARIYA LAKSHMI, REG. NO 221916864., **for the award of M.S in the branch of** OBSTETRICS AND GYNAECOLOGY**. I personally** verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and the result shows Five percentage of plagiarism in the dissertation (D123723928)

Signature and Seal of the Guide

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PROFORMA

- Name:
- Age:
- Occupation:
- Outpatient number:
- Type of infertility:
- Menstrual History:
- Marital History:
- Sexual/coital history:
- Obstetric History:
- Past obstetric history:
- Past History:
- Medical : Diabetes, Hypertension, Renal disease, Cardiac illness,Asthma, Epilepsy
- Previous surgical history: yes/no
- Family history:
- H/O congenital anomalies, H/O twins
- H/O Diabetes mellitus, hypertension, tuberculosis, asthma, epilepsy.
- Personal history
- General examination:
- Weight:
- Height:
- BMI:
- Systemic examination:
- Cardio vascular system
- Respiratory system

- Per abdomen
- Per vaginal examination
- Local examination
- External genitalia
- Complete blood count
- Renal function test
- Liver function test
- USG – Fibroid, ovarian cyst
- Hysterosalpingogram – For Tubal patency
- Recent treatment for OI within 6 months – Yes/No
- Semen analysis

ABBREVIATIONS

Ht	-	Height
Wt	-	Weight
BMI	-	Body Mass Index
PCOS	-	Polycystic ovarian syndrome
HSG	-	Hysterosalphingography
TVS	-	Transvaginal ultrasonography
OI	-	Ovulation Induction
L	-	Letrozole
CC	-	Clomiphene citrate
HCG	-	Human Chorionic Gonadotropin
HMG	-	Human Menopausal Gonadotropin
OHSS	-	Ovarian hyperstimulation syndrome
AMH	-	Anti mullerian hormone
AFC	-	Antral follicle count
ER	-	Estrogen receptors
ET	-	Endometrial Thickness
SHBG	-	Sex hormone binding globulin
SERM	-	Selective estrogen receptor modulator
IVF	-	Invitrofertilisation
Group 1	-	Ovulation induction drugs alone
Group 2	-	Ovulation induction drugs and gonadotropins

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013/RR-16
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.S.S.ISWARIYA LAKSHMI,
Post Graduate – MS (Obstetrics and Gynaecology),
Madras Medical College,
Chennai - 600003.

Dear Dr. S.S.ISWARIYA LAKSHMI,

The Institutional Ethics Committee has considered your request and approved your study titled **"A COMPARATIVE STUDY OF EFFICACY OF OVULATION INDUCTION DRUGS ALONE VERSUS OVULATION INDUCTION DRUGS AND GONADOTROPINS IN INFERTILITY – A PROSPECTIVE STUDY"-NO.13082020.** The following members of Ethics Committee were present in the meeting held on **04.08.2020** conducted at Madras Medical College, Chennai 3.

1. Prof.P.V.Jayashankar	:Chairperson
2. Prof.N.Gopalakrishnan,MD.,DM., FRCP, Director, Inst.of Nephrology,MMC,Ch	: Member Secretary
3. Prof. K.M.Sudha, Prof. Inst. of Pharmacology,MMC,Ch-3	: Member
4. Prof. Alagarsamy Jamila ,MD, Inst. of Patholoy, MMC, Ch-3	: Member
5. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai	: Member
6. Prof.S.Lakshmi, Prof. of Paediatrics ICH Chennai	:Member
7. Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist
8. Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
9. Thiru K.Ranjith, Ch- 91	: Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

03/09/2020

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003.

PATIENT CONSENT FORM:

Patient may check**( )**these boxes:

( )I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask questions and all my questions and doubts have been answered to my complete satisfaction.

( )I understand that my participation in the study is voluntary and that I am free to withdraw at anytime without giving reason, without my legal rights being affected.

( )I understand that sponsor of the clinical study, others working on the sponsor's behalf, the Ethics committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that maybe conducted in relation to it, even if I withdraw from the study I agree to this access.

( ) However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

Study title:" **A Comparative study of efficacy of ovulation induction drugs alone versus ovulation induction drugs and gonadotropins in infertility – A Prospective study**."

Study Centre: MMC,Chennai

Patient's Name:

Patient's Age:

InPatient Number:

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately in form the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms.

I hereby consent to participate in this study.

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests and to undergo treatment.

Signature/Thumb impression of the patient

Patient's Name and Address:

Signature of Investigator

(Dr.S.S Iswariya Lakshmi)

INFORMATION SHEET

TITLE: A Comparative study of efficacy of ovulation induction drugs alone versus ovulation induction drugs and gonadotropins in infertility – A Prospective study.

Name of the investigator : Dr. S.S Iswariya lakshmi

Name of the Participant:

Purpose of research: To compare the efficacy of ovulation induction drugs alone versus ovulation induction drugs and gonadotropins in infertility.

Study design: Prospective study

Study population: The study would include 21-35 years aged women attending FRC OPD.

Possible risks: No risks to the patient.

Confidentiality of the information obtained from you: The privacy of the patients in the research will be maintained throughout the study.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Can you decide to stop participating in the study?

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time.

How will your decision to not participate in the study affect you?

Your decision will not result in any loss of benefits to which you are otherwise entitled.

Signature of Investigator Signature of the participant

Date:

Place:

அனுமதியுடனான ஒப்புதல் படிவம்:

-இந்த ஆய்விற்கான செயல்முறையின் நோக்கத்தை நான் புரிந்துள்ளேன் என்பதை உறுதிப்படுத்துகிறேன். எனக்கு கேள்விகளை கேட்க வாய்ப்பு உள்ளது. என்னுடைய எல்லா கேள்விகளும் சந்தேகங்களும் என் முழு திருப்திக்கு பதில் அளித்துள்ளன.

-ஆய்வில் எனது பங்கேற்பு தன்னார்வமாக இருப்பதையும், என் சட்ட உரிமைகள் பாதிக்கப்படாமல், காரணத்தைத் தெரிவிக்காமல் எப்போது வேண்டுமானாலும் விலக்கிக்கொள்ளலாம் என்பதையும் நான் புரிந்து கொள்கிறேன்.

-ஆய்வில் இருந்து நான் விலகி வந்தாலும் கூட, ஆராய்ச்சிக்கு பொருந்தக்கூடிய என் உடல்நல ஆவணங்களைப் பார்க்க என் நெறிமுறைக் குழு மற்றும் ஒழுங்குமுறை அதிகாரிகளுக்கு எனது அனுமதி தேவையில்லை என்பதை நான் புரிந்து கொள்கிறேன். இந்த அணுகலை நான் ஏற்கிறேன்.

-இருப்பினும், சட்டத்தின் கீழ் தேவைப்பட்டாலன்றி, மூன்றாம் தரப்பினருக்கு வெளியிடப்பட்ட அல்லது வெளியிட்ட எந்த தகவலிலும் என் அடையாளத்தை வெளிப்படுத்த முடியாது என்பதை நான் புரிந்து கொள்கிறேன். இந்த ஆய்விலிருந்து எழும் எந்தவொரு தரவு அல்லது முடிவுகளின் பயன்பாட்டைக் கட்டுப்படுத்துவதை நான் ஏற்றுக்கொள்கிறேன்.

-மேலே உள்ள படிப்பில் கலந்து கொள்ளவும், ஆய்வின் போது கொடுக்கப்பட்ட அறிவுறுத்தல்களுக்கு இணங்கவும், ஆய்வுக் குழுவோடு ஒத்துழைக்கவும், என் உடல்நலம் அல்லது நலம் அல்லது எந்தவொரு எதிர்பாராத அல்லது அசாதாரண அறிகுறிகளிலும் நான் பாதிக்கப்படுகையில் உடனடியாக ஆய்வு ஊழியர்களுக்கு
நான் இதனுடன் முழுமையான மருத்துவ பரிசோதனை மற்றும் நோயறிதல் சோதனைகள் இரத்தம், உயிர்வேதியியல், கதிரியக்க சோதனைகள் உட்பட சிகிச்சைக்கு உட்படுத்த அனுமதிக்கிறேன்.

ஆய்வு தலைப்பு: அண்டவிடுப்பின் தூண்டல் மருந்துகள் மற்றும் அண்டவிடுப்பின் தூண்டல் மருந்துகள் மற்றும் கருவுறாமை உள்ள கோனாடோட்ரோபின்கள் ஆகியவற்றின் ஒப்பீடு.
ஆய்வு மையம்: எம்.எம்.சி, சென்னை
பங்கேற்பாளரின் பெயர்:
பங்கேற்பாளரின் வயது:
நோயாளி எண்:

நோயாளியின் கையொப்பம்

நோயாளியின் பெயர் மற்றும் முகவரி: ஆராய்ச்சியாளரின் கையொப்sபம்:

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Master Chart – Key		
Row headings	Key	
Sl No	Sl No	
A	Age (Yrs)	
B	Height (Cms)	
C	Weight (Kgs)	
D	BMI	
E	Infertility	1-Primary 2- Secondary
F	Menstrual cycle	1-Regular 2- Irregular
G	Married since(yrs)	
H	Comorbids	0-Nil 1-Hypertension 2-DM 3A-Hypothyroid 3B - Hyperthyroid 4-APLA positive
I	PCOS	Y- Yes N-No
J	Ovulation induction drugs	1 – Clomiphene citrate 2 - Letrozole
K	Gonadotropins	Y- Yes N-No
L	No of dominant follicles	
M	Size of dominant follicle	
N	Endometrial thickness(mm)	
O	Method	0- No growth of dominant follicle 1-Natural 2-IUI
P	UPT	0- No growth of dominant follicle 1-Positive 2-Negative

SLNO	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	26	155	80	33.3	1	2	6	3A	Y	2	N	1	22	8	1	1
2	28	151	86	37.7	1	2	6	0	Y	2	Y	1	20	9	2	2
3	30	154	84	35.4	1	2	4	3A	Y	2	N	2	20	10	2	1
4	32	149	64	28.8	2	2	10	0	N	1	Y	2	18	8	2	2
5	28	158	62	24.8	1	1	5	0	N	1	Y	2	18	8.2	2	2
6	24	161	80	30.9	1	2	4	3A	Y	2	Y	1	22	8.5	1	2
7	25	155	56	23.3	1	1	6	0	N	1	N	1	18	8	1	1
8	35	154	87	36.6	2	2	12	0	N	1	Y	3	20	7.2	1	2
9	27	156	64	26.5	2	1	8	0	N	2	N	1	24	8.8	2	1
10	30	156	62	25.5	1	1	2	0	N	1	N	2	22	7.1	2	2
11	33	148	86	39.2	2	2	8	3A	N	2	Y	1	22	8.6	2	2
12	35	162	45	17.1	1	2	8	0	N	1	Y	2	18	8	2	2
13	30	150	46	20.4	2	2	5	3A	N	2	Y	1	24	8.6	1	2
14	29	148	52	23.7	1	1	3	3A	N	1	N	2	22	7.9	1	1
15	33	151	59	25.8	2	1	8	3A	N	2	Y	1	22	8.8	2	2
16	27	165	75	26.6	1	1	3	3A	Y	2	N	1	18	8.8	2	1
17	26	158	90	36.1	1	2	4	4	Y	1	N	0	8	6	0	0
18	27	142	51	25.3	1	1	2	3A	N	1	N	2	22	7.4	2	2
19	25	146	69	32.4	1	2	4	0	Y	2	N	1	14	8.8	1	2
20	24	156	45	18.5	1	2	2	0	N	1	Y	2	22	7.9	2	2
21	26	156	68	27.9	1	1	4	0	Y	2	Y	1	18	9	2	2
22	33	153	65	27.8	2	1	10	2	Y	2	N	1	20	10	2	2
23	30	155	76	31.6	2	2	8	0	Y	2	Y	0	10	6	0	0
24	28	154	65	27.4	2	2	6	3A	N	1	N	2	22	7.8	1	1
25	28	164	77	28.6	1	2	4	3A	N	1	Y	3	20	7.7	2	2
26	27	145	60	28.5	1	2	3	0	N	1	N	2	22	7.6	1	2
27	26	156	68	27.9	1	2	3	0	N	2	Y	1	23	9	2	2
28	24	151	42	31	1	2	2	0	N	1	N	0	8	6	0	0
29	30	153	65	27.8	2	1	6	3A	N	1	Y	2	24	7.5	2	2
30	33	156	68	27.9	2	1	5	3A	N	1	N	1	18	7.4	1	2
31	28	151	59	25.8	1	1	2	0	N	2	N	1	22	9	2	2
32	26	164	77	28.6	1	2	2	0	N	1	Y	3	18	7.9	2	2
33	28	156	68	27.9	1	1	3	0	N	2	Y	2	24	10	2	2
34	26	164	77	28.6	1	2	3	0	N	2	N	2	22	10	2	2
35	28	150	68	30.2	1	2	4	0	Y	2	Y	2	24	9	2	2
36	30	156	75	30.8	2	2	8	3A	N	1	Y	3	18	7.8	2	2
37	33	148	52	23.7	2	1	6	2	Y	2	N	1	22	8	2	2
38	32	158	55	22	2	1	6	3A	N	1	N	0	10	6	0	0
39	26	156	53	21.7	1	1	2	4	Y	2	N	2	22	8.7	1	2
40	25	158	56	22.4	1	1	3	3A	N	1	Y	2	18	8	2	2
41	24	154	54	22.7	1	1	4	3A	Y	2	Y	1	26	8.8	1	2
42	24	156	58	23.8	1	2	3	0	N	1	N	0	8	5	0	0
43	26	158	56	22.4	1	2	4	0	N	1	Y	3	18	8.1	2	2
44	28	158	58	23.2	1	1	5	0	N	1	N	0	8	5	0	0
45	29	156	83	34.1	2	2	5	3A	Y	2	Y	2	22	9	1	2
46	30	154	52	21.9	2	1	6	3A	N	1	Y	3	18	8	2	2
47	26	156	60	24.6	1	1	3	0	N	1	N	1	18	7.6	1	2

48	25	158	82	32.8	1	2	4	3A	Y	2	N	2	20	9	2	2
49	28	155	54	22.4	1	2	3	0	N	2	Y	2	18	10	2	2
50	26	156	56	23.01	1	2	3	3A	N	1	Y	2	20	7.5	2	2
51	29	158	78	31.2	2	2	6	0	Y	2	N	1	22	10	2	2
52	26	160	74	28.9	1	2	2	3A	N	2	Y	2	22	10	1	2
53	28	158	75	30	2	2	6	0	Y	2	N	0	12	5	0	0
54	26	158	68	27.2	1	2	2	3A	N	1	N	0	12	6	0	0
55	26	160	62	24.2	1	1	3	3A	N	2	N	1	24	11	1	1
56	28	158	65	26	1	2	4	0	N	1	Y	3	22	7.6	2	2
57	30	159	62	24.5	2	1	6	3A	N	2	Y	1	18	11	1	1
58	32	158	60	24	2	1	5	0	N	2	N	1	18	10	2	2
59	33	156	55	22.6	2	2	6	0	N	1	N	0	8	6	0	0
60	35	158	62	24.8	2	1	5	0	N	1	Y	3	22	7.4	2	2
61	26	158	58	23.2	1	2	3	0	N	2	N	1	18	8.9	1	2
62	24	156	60	24.6	1	1	2	0	N	1	N	1	20	7.6	2	2
63	34	154	50	21	1	1	3	3A	N	2	N	1	22	8.6	1	2
64	24	158	54	21.6	1	1	4	3A	N	2	Y	1	24	7.9	2	2
65	25	156	62	25.4	1	1	5	3A	N	1	Y	2	22	7.8	2	2
66	26	158	66	26.4	1	1	4	0	N	1	N	1	22	7.5	2	2
67	28	160	50	19.5	2	1	6	3A	N	2	Y	1	18	8.9	1	1
68	27	156	54	22.1	1	1	5	3A	N	1	Y	3	18	7.9	1	2
69	26	156	52	21.3	1	1	4	0	N	2	N	2	20	8.8	2	2
70	30	158	54	21.6	1	2	3	0	N	1	N	2	25	8	2	2
71	31	156	58	23.8	1	1	2	0	N	2	N	0	10	6	0	0
72	27	158	60	24	1	1	2	0	N	1	Y	3	24	7.6	1	2
73	28	158	62	24.8	1	1	3	0	N	2	Y	1	18	8.9	1	1
74	32	158	60	24	1	1	4	3A	N	2	N	0	12	6	0	0
75	34	160	58	22.6	2	1	6	2	N	1	N	0	13	6	0	0
76	32	158	58	23.2	2	1	5	3A	N	1	Y	2	18	8	1	2
77	33	160	60	23.4	2	1	7	3A	N	2	Y	2	22	9	1	1
78	30	158	60	24	2	1	6	0	N	1	N	2	22	8.5	2	2
79	32	158	60	24	2	1	5	3A	N	2	Y	1	18	10	2	1
80	29	154	59	24.8	2	2	6	0	N	1	Y	0	10	6	0	0
81	28	158	60	24	1	2	4	3A	N	1	Y	0	12	5	0	0
82	27	160	58	22.6	1	2	3	0	Y	2	N	2	24	8.9	1	2
83	25	158	60	24	1	2	2	3A	Y	2	Y	1	18	9	1	2
84	24	159	58	22.9	1	1	3	0	N	1	N	1	22	8.7	2	1
85	26	158	64	25.6	1	1	4	0	N	1	Y	0	10	8.7	0	0
86	27	155	80	33.3	1	2	4	0	N	1	N	2	18	8.9	2	2
87	28	151	86	37.7	1	2	3	0	N	2	N	1	22	8	1	1
88	25	154	58	24.5	1	1	5	3A	N	1	Y	2	24	8.6	1	2
89	27	149	64	28.8	1	1	3	3A	N	2	Y	1	26	9	1	2
90	28	158	62	24.8	1	1	3	3A	N	1	N	0	8	6	0	0
91	26	161	80	30.9	1	2	3	0	N	1	Y	0	9	6	0	0
92	28	154	86	36.2	1	2	4	3A	Y	2	Y	1	25	10	2	1
93	29	156	65	26.7	2	1	5	0	Y	2	N	1	18	9	1	2
94	30	158	64	25.6	2	1	6	0	N	1	Y	2	26	8.5	1	1
95	32	156	62	24.2	2	1	6	3A	N	1	N	0	10	6	0	0
96	28	149	56	25.2	2	1	8	0	N	1	N	2	18	8.6	2	1

97	26	152	60	25.9	1	1	4	3A	Y	2	N	2	20	9	1	2
98	28	160	58	22.6	1	1	3	0	N	2	Y	1	22	9	1	2
99	29	158	62	24.8	1	1	4	3A	Y	2	N	0	11	6	0	0
100	28	158	57	22.8	1	2	5	3A	N	2	Y	2	24	9	2	2
101	27	158	60	24	1	2	3	3A	Y	2	Y	1	26	8.9	2	1
102	28	160	58	22.6	1	1	4	0	N	1	N	0	10	6	0	0
103	30	158	60	24	2	1	6	3A	Y	2	N	1	18	8.6	1	1
104	32	156	82	33.6	2	2	6	0	N	1	Y	2	22	8.4	1	2
105	28	158	68	27.2	1	1	4	3A	Y	2	N	2	26	8.5	1	2
106	29	158	64	25.6	1	1	4	0	N	1	N	1	24	7.6	2	2
107	28	154	59	24.8	2	1	6	0	N	1	Y	0	12	6	0	0
108	29	158	62	24.8	1	1	4	0	N	1	N	3	22	8	2	2
109	28	156	64	26.2	1	2	4	3A	N	1	Y	0	12	6	0	0
110	26	157	66	26.7	1	1	4	3A	N	1	N	2	18	8.1	2	2
111	30	158	64	25.6	2	1	5	0	N	2	Y	1	20	8.6	1	1
112	31	158	54	21.6	2	1	6	3A	Y	2	Y	1	18	8.6	2	1
113	32	149	54	24.3	2	1	7	0	N	1	Y	2	22	8	1	2
114	33	152	56	24.2	2	1	8	0	Y	2	N	1	24	8.9	2	2
115	34	158	69	27.6	2	2	7	0	Y	2	Y	0	14	6	0	0
116	35	159	62	24.5	2	1	7	0	Y	2	N	0	12	6	0	0
117	28	158	60	23.1	1	1	3	0	N	1	N	2	26	8.6	1	2
118	24	154	66	27.8	1	2	4	0	N	1	Y	0	12	7.9	0	0
119	25	156	59	24.2	1	1	3	0	Y	2	Y	1	24	9	2	1
120	27	158	58	23.2	1	1	4	0	Y	2	N	0	14	6	0	0
121	28	156	59	24.2	2	1	6	3A	N	1	N	1	26	7.6	1	2
122	26	158	62	24.8	1	1	3	3A	N	1	Y	2	28	7.5	1	2
123	24	158	60	24	1	1	4	0	Y	2	N	2	24	7.7	2	2
124	24	156	58	23.8	1	2	3	3A	Y	2	N	0	12	10	0	0
125	25	158	64	25.6	1	2	3	0	Y	2	Y	1	22	10	1	1
126	25	155	80	33.3	2	2	6	3A	Y	2	N	0	14	5	0	0
127	24	151	86	37.7	1	2	3	0	N	1	N	0	9	6	0	0
128	26	154	58	24.5	2	1	6	3A	N	1	Y	0	10	6	0	0
129	28	149	64	28.8	1	2	3	0	N	2	N	1	18	9	2	2
130	27	158	62	24.8	1	1	4	3A	N	1	N	2	24	8	1	2
131	26	161	80	30.9	1	2	3	0	N	1	Y	1	24	8.2	2	1
132	28	155	56	23.3	1	1	2	3A	N	2	Y	0	10	7	0	0
133	29	156	58	23.8	2	1	6	0	N	1	N	1	22	8.3	1	2
134	26	162	59	22.4	1	1	2	3A	N	2	Y	1	24	9	2	2
135	25	158	58	23.2	1	1	3	0	N	1	Y	2	26	8	1	2
136	26	159	60	23.7	1	1	4	0	N	2	Y	1	22	10	1	2
137	28	157	59	23.9	2	1	6	0	N	1	N	3	18	7.9	1	2
138	26	159	59	23.3	1	1	3	3A	N	2	N	1	18	12	2	2
139	28	158	62	24.8	2	1	8	0	N	1	Y	1	20	7.9	1	2
140	25	156	68	27.9	1	2	3	3A	N	2	Y	1	18	10	1	1
141	32	159	62	24.5	2	1	8	0	N	1	N	0	10	6	0	0
142	23	158	59	23.6	1	1	4	3A	N	2	N	0	9	7	0	0
143	23	159	62	24.5	1	1	3	0	N	1	Y	2	22	7.9	1	2
144	24	160	80	31.25	2	1	6	3A	N	2	Y	0	10	6	0	0
145	23	158	60	24	1	1	4	3A	N	1	Y	1	20	8	1	2
146	29	158	59	23.6	2	2	6	0	N	2	Y	0	10	6	0	0

147	26	154	60	25.2	1	2	4	0	N	1	N	1	18	8.1	1	2
148	23	158	65	26	1	1	3	3A	N	2	N	1	18	10	1	2
149	22	150	60	26.6	1	2	3	0	N	1	N	3	22	7.5	1	2
150	26	154	62	26.1	2	2	6	0	N	2	Y	1	18	7.6	1	2
151	27	154	65	27.4	2	2	8	3A	N	1	Y	2	24	7.9	1	2
152	28	155	66	27.4	2	1	6	0	N	2	N	0	12	8.6	0	0
153	29	153	65	27.8	2	2	6	3A	N	1	N	3	22	7	1	2
154	28	156	68	27.9	2	2	4	0	N	2	Y	1	22	8.7	1	2
155	26	156	45	18.5	1	1	2	3A	N	1	N	3	22	7.8	1	2
156	26	158	90	36.1	1	2	3	0	N	2	N	0	14	7	0	0
157	28	148	56	25	2	1	6	3A	N	1	Y	1	18	7.6	1	2
158	28	154	87	36.6	2	2	6	3A	N	2	N	0	10	6	0	0
159	26	149	64	28.8	1	2	3	0	N	2	Y	1	20	7.4	1	1
160	26	155	80	33.3	1	2	2	0	N	1	Y	1	22	7.6	1	2
161	24	156	62	25.4	1	1	3	3A	N	2	N	1	24	9	1	1
162	25	158	64	25.6	1	1	4	0	N	2	Y	0	10	6	0	0
163	28	156	66	27.1	2	2	5	0	N	1	N	1	22	7.6	1	2
164	30	156	60	24.6	2	1	6	3A	N	1	Y	1	24	7.8	1	2
165	32	154	59	24.8	2	1	12	0	Y	2	N	0	8	6	0	0
166	29	159	62	24.5	2	2	6	3A	N	1	Y	1	22	7.4	1	2
167	35	158	80	32	2	2	8	0	N	2	Y	0	24	9	0	0
168	29	160	69	26.9	2	2	6	0	Y	2	N	1	18	10	1	2
169	28	156	80	32.8	1	2	5	0	N	1	N	0	8	6	0	0
170	26	158	62	24.8	1	2	6	3A	N	1	N	3	25	7.8	1	2
171	34	156	78	32	2	2	6	0	N	1	Y	1	26	7.6	2	1
172	22	159	69	27.2	1	2	4	3A	Y	2	N	1	22	9	1	2
173	27	162	68	25.9	1	2	4	0	N	2	N	0	12	6	0	0
174	26	160	69	26.9	2	1	6	3A	N	1	N	1	24	8	1	2
175	28	158	68	27.2	2	1	6	0	N	2	Y	1	26	8.7	1	2
176	29	160	59	23	1	1	5	3A	N	1	Y	2	27	8	2	1
177	30	159	72	28.4	2	2	5	0	N	2	Y	1	26	8.9	1	2
178	27	158	64	25.6	2	2	6	3A	N	1	N	3	22	8.2	1	2
179	31	159	69	27.2	2	2	6	3A	N	1	Y	1	24	8	1	1
180	32	158	70	28	2	1	5	3A	N	2	Y	1	18	8.8	1	2
181	35	160	58	22.6	2	2	8	0	Y	2	Y	1	18	7.9	1	2
182	33	159	62	24.5	1	1	4	0	N	1	Y	1	20	7.8	1	1
183	32	160	58	22.6	1	2	3	3A	Y	2	N	1	22	8.6	1	2
184	29	158	59	23.6	1	1	2	0	N	1	N	3	20	8	1	2
185	28	154	65	27.4	2	2	6	0	N	1	Y	1	22	7.8	1	1
186	27	159	66	26.1	2	2	6	3A	N	2	Y	1	20	10	1	2
187	29	156	62	25.4	2	1	6	3A	N	1	N	1	22	7.6	1	2
188	32	154	65	27.4	2	2	6	0	N	2	N	0	10	7	0	0
189	26	158	59	23.6	1	1	5	3A	Y	1	N	3	22	7.5	1	2
190	34	154	65	27.4	2	2	1	3A	N	2	Y	2	18	10	1	2
191	29	160	58	22.6	1	2	8	3A	Y	1	Y	1	22	7.6	1	1
192	34	159	62	24.5	2	1	8	3A	Y	2	Y	1	24	8	1	1
193	26	156	80	32.8	2	2	6	0	N	2	N	1	26	9	1	2
194	23	156	78	32	1	1	4	0	Y	1	Y	2	24	7.8	1	2
195	28	158	59	23.6	1	2	8	0	N	2	Y	1	22	9	1	2
196	35	160	58	22.6	1	1	12	3A	Y	1	Y	1	24	7.9	1	1

197	25	152	60	25.9	1	1	3	0	N	2	N	1	22	10	1	2
198	28	155	66	27.4	2	2	6	3A	N	1	N	1	18	7.8	1	2
199	30	160	67	26.1	2	2	6	0	Y	1	N	3	18	8	1	2
200	32	156	65	26.7	2	1	6	3A	Y	2	N	1	20	9	1	2