



## Protocols for Ovulation Induction

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## Introduction

Anovulation is a relatively common cause of infertility, accounting for about 25% of all cases. Ovulatory disorders may be either due to hypothalamic-pituitary ovarian axis dysfunction or other endocrine diseases. Anovulation has been classified by the World Health Organization (WHO) based on the circulating concentrations of gonadotropin and oestrogen into three categories:

1. Hypothalamic Pituitary failure / Hypogonadotrophic hypogonadism (WHO group I)
2. Hypothalamic Pituitary dysfunction / Normogonadotrophic anovulation (WHO group II) e.g. PCOS
3. Premature ovarian failure / Hypergonadotrophic hypogonadism (WHO group III)

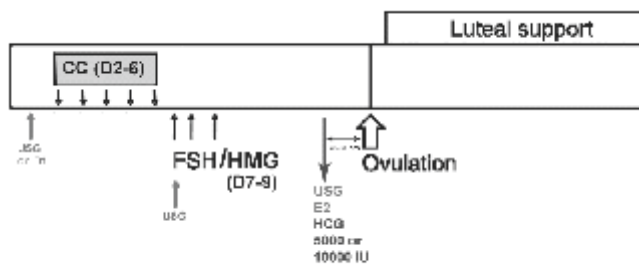
In anovulatory women, the purpose of treatment is ovulation induction (OI) i.e. the development of at least one follicle, whereas in other causes of infertility, ovarian stimulation is used to increase the number of follicles—an approach known as superovulation or controlled ovarian hyperstimulation.

## Agents / methods used and the related protocols

The commonest protocol used in our IVF Unit at Lilavati hospital is as follows:

- 5 days of Clomiphene Citrate (100 mg) from day 2 to 6 of the cycle.
- Injection FSH / HMG 75 or 150 IU on day 7, 8 and 9.

Injection HCG for triggering ovulation, when the leading follicle is 18 -20 mm, and if serum E2 is not more than 1500 to 2000 pg/ml.



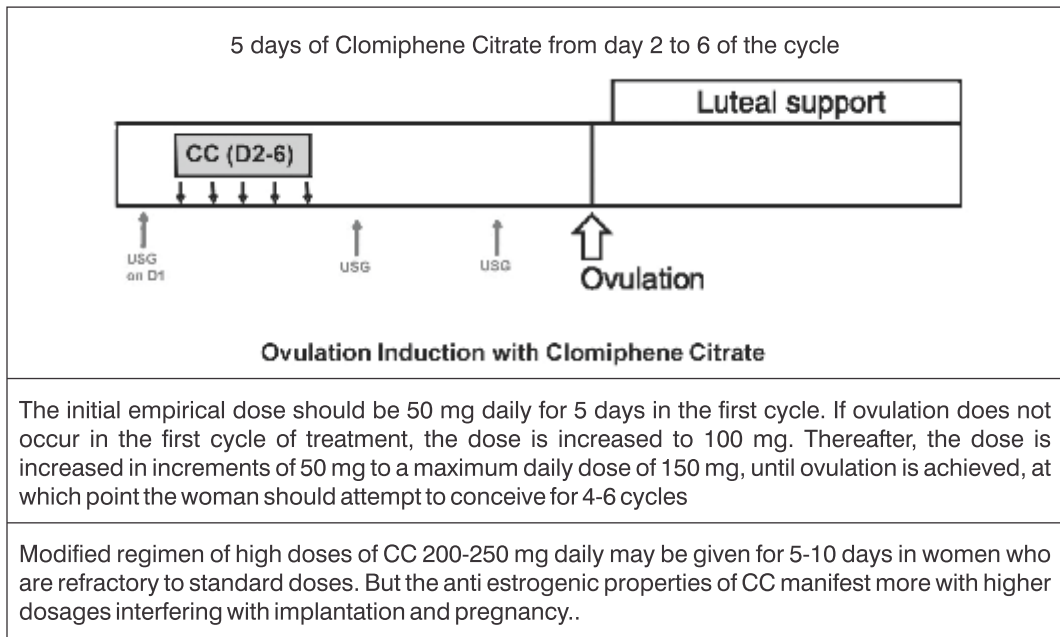
Ovulation Induction with Clomiphene Citrate + FSH + hCG

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### Anti-oestrogens :

The commonest used oral agent is Clomiphene Citrate (CC) a non-selective estrogen receptor modulator. It induces gonadotrophin release by occupying the oestrogen receptors in the hypothalamus, thereby interfering with the normal feedback mechanisms, increasing gonadotrophins and so stimulating the ovary to produce more follicles. The disadvantage is that they could produce peripheral antiestrogenic effects. Women with WHO Group II ovulation disorders (hypothalamic pituitary dysfunction) such as polycystic ovary syndrome should be offered treatment with clomifene citrate as the first line of treatment for up to 12 months because it is likely to induce ovulation. It has been reported to induce ovulation in 70-80% such cases with pregnancy rates varying from 30-50%. In combination with IUI, it has been successfully used in ovulating patients also.

Considering its hypothalamic site of action, it is not surprising that clomiphene is typically ineffective in women with hypogonadotrophic hypogonadism (WHO group I) (Speroff and Fritz, 2005)



### Gonadotrophins

Injectable Gonadotropins are more effective than oral agents but are expensive and associated with higher risk for ovarian hyperstimulation syndrome and multiple gestations.

*The principles of use are as follows:*

- FSH is necessary in the early phase of the cycle to recruit and select the follicles.
- Both FSH and LH are necessary for growth and maturation of the follicles.
- The daily increase in the follicular diameter in the active phase is by 1.5 to 2 mm/day.
- Serum Estradiol levels should be about 200-300 pg/ml per growing follicle of 16 mm or more.

*Indications for Gonadotrophins in OI:*

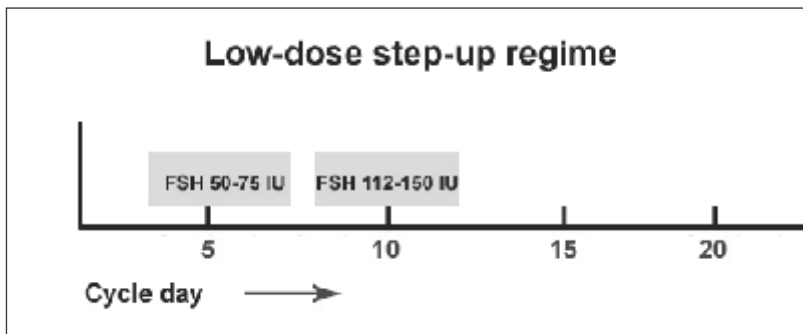
1. *Substitution therapy:* HMG is used in cases of WHO group I anovulatory disorders (hypothalamopituitary insufficiency).

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2. *Addition or assistance therapy*: In clomiphene failures and clomiphene resistance, as happens in certain cases of hypothalamopituitary dysfunction with or without associated hyperandrogenism (PCOS).

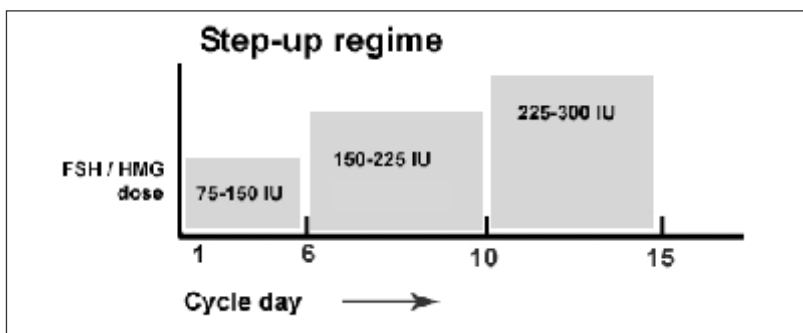
*Choice of Gonadotrophins*: **Human menopausal gonadotrophin (HMG), urinary follicle-stimulating hormone (uFSH) and recombinant follicle-stimulating hormone (rFSH)** are equally effective in achieving pregnancy.

#### **Different regimes for gonadotrophin therapy**

1. Fixed dose regime: a constant daily dose of 75-150 IU of gonadotropins is started from day-2 or day-3. Monitoring USG and E2 levels guide as to till when the injections are continued.
2. Chronic low-dose step-up regime: The principle behind this regimen is to find the “threshold “level of FSH which will lead 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 the 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 is > 200 pg/ml or follicle size is above 10 mm, the same dose is continued. Otherwise, if the parameters are less than the above described, the daily dose is increased by an increment of 37.5 units every week, till the serum E2 level rises adequately.

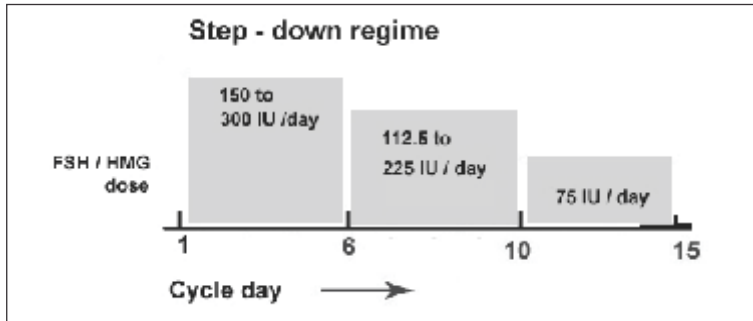


3. Individually adjusted regimes, as guided by the TVS follicular scan and Serum E2 levels.
  - a. Step-up protocol



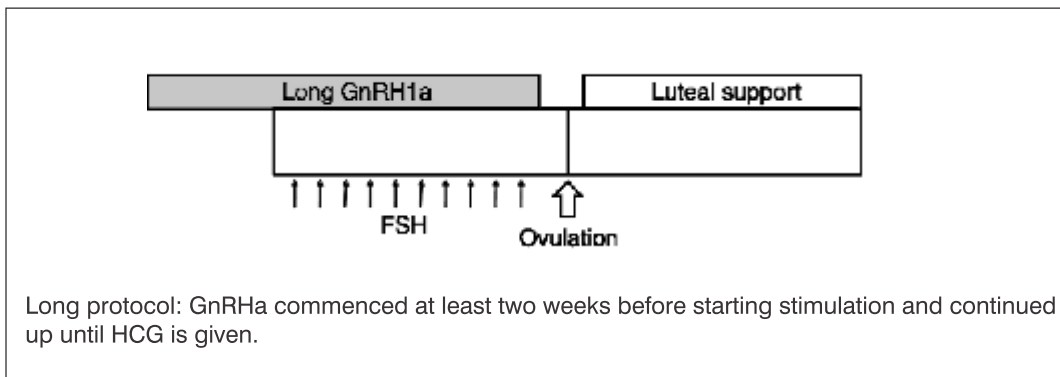
b. Step-down protocol:

le of  $> 10$  mm is observed on TVS. After this the dose is decreased in decedentsin two steps. The last dose is then continued till the day of the HCG injection.

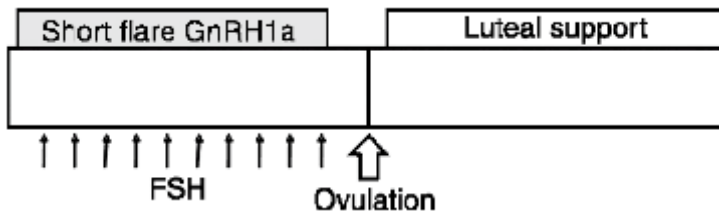


4. Combined therapy with other drugs

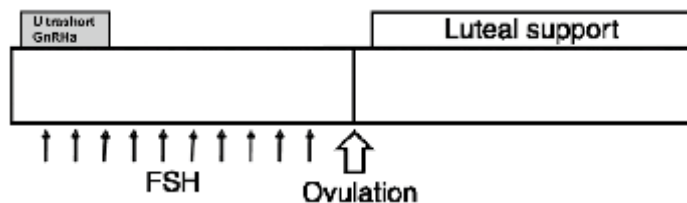
- **Clomiphene citrate with gonadotrophins:** CC 100 mg is administered from day 2 to day 6 and Inj.FSH/HMG 75/150 units is given on day 6 & day 8. Transvaginal sonography is done from day-8 onwards and in case the follicle growth or number is inadequate, additional FSH/HMG injections are administered.
- **GnRH agonists in combination with gonadotrophins:** In almost 15-20 % of cycles, which have been stimulated with gonadotrophins or CC, the exaggerated oestradiol level due to the multifollicular development often provokes higher LH levels during the follicular phase or an untimely LH hormone surge, which leads to cycle cancellation. Therefore, in order to avoid interference from endogenous gonadotrophin secretion, a combination of gonadotrophins and GnRH agonists has been used for pituitary downregulation prior to ovarian stimulation. However, they are not widely used in ovulation induction therapy for ovulatory disorders. The three different protocols are the long, short and ultrashort protocols, of which the most popular one is the long protocol.



*Gonadotrophin-releasing hormone (GnRH) antagonists:* The antagonist OI protocols are simpler and have better patient compliance. GnRH antagonists act by competitive inhibition of GnRH receptors, which results in rapid decline in FSH/LH levels thus preventing premature LH surge.



Short protocol: GnRHa commenced at the same time as starting stimulation and continued up until the day of hCG administration.



Ultrashort protocol: stimulation is commenced one to two days after starting GnRHa (which is given only for three days).

For IUI cycle stimulation, in cases of 2 or more failed IUI cycles with CC+ Gonadotrophins, we prefer to add the antagonist (daily dose) from the day the leading follicle is  $\geq 14$  mm up to and including the day of the hCG trigger injection.

For IVF cycle stimulation, the drug can be given in a single dose (French protocol) or daily dose (Lubeck protocol) regimen.

French: Gonadotrophins are started as usual and a single dose (3 mg) of antagonist is given on day 6 or when the serum E2 level is 250 pg/ml and the follicular size is 14 mm, whichever is earlier.

Lubeck: Gonadotrophins are started as usual and the antagonist is started when the follicle reaches a size of 14 mm, or from from 6th day of stimulation onwards in a dose of 0.25mg / day till the day of HCG injection.

In our unit we prefer to use the flexible antagonist protocol.

*Human chorionic Gonadotrophin (hCG)*: Useful as an 'ovulation trigger' in women manifesting an absent or inadequate midcycle LH surge. In such cases, exogenous hCG 5,000/10,000 IU is given as a single dose, when TVS shows that the dominant follicle has reached 18-20 mm in diameter.

#### ADJUNCTS TO OVULATION INDUCTION THERAPY

- **Metformin**: In anovulatory women with PCOS who have not responded to clomifene citrate and who have a body mass index of more than 25. This therapy has been seen to increase ovulation and pregnancy rates.
- Dopamine agonists such as **bromocriptine and cabergoline**: In cases of ovulatory disorders due to hyperprolactinaemia.

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- **Dexamethasone / Oral contraceptives:** In WHO group II, with high DHEA-S levels, OI with CC/ gonadotrophins along with Dexamethasone or pretreatment with oral contraceptives, may give better results.
  - **Ovarian drilling:** One time procedure to induce ovulation in -
    - CC resistant pCOS women, specially in lean women.
    - Patients with hyper secretion of LH.
    - High levels of androstenidione.
    - Patient requiring laproscopic assesment of pelvis.
    - Previous over response to COH for IVF.
  - Ovarian drilling is a technique whereby several surface lessions on the ovary,are created using monopolar coagulating current of 40W power, needle is activated for 2-3 sec at each point never done in hilar region, and not more than 4 puntures per ovary. At complision of procedure the ovarian surface is washed with cristalised surface.
  - It has ovulation rates of 70% and pregnancy rate of 55%-65%, which are similer to gonardotropin therapy.
  - Ovarian drilling compared to gonardotropin administration has fewer side effects, simpler to manage and has positive impact on the endocrine milieiu.
  - **Weight loss:** Regular and structured exercise helps decrease insulin resistance to a certain extent. 5% reduction in body weight helps ovulation induction (ASRM guideline 2008)

## MONITORING THE OVULATION INDUCTION CYCLE

**Serial Transvaginal ultrasound:** A baseline USG is done on day-2 to assess the ovaries and look for the antral follicle count and to rule out any cysts. Also the uterus with the endometrial lining is assessed. Serial USG is then done from day 9 onwards every alternate day till the leading follicle reaches a size of 18 mm or more, when the injection for triggering ovulation is administered.

TVS is preferred as it provides a direct and more accurate assessment of follicular development. Both the number as well as the size can be studied.

The follicles normally grow at the rate of 2 -3mm a day once the leading follicle reaches 10-12 mm size.

**Serial serum estradiol E<sub>2</sub> levels:** Plasma E<sub>2</sub> levels correlate closely with the stage of development of the dominant follicle. A value of more than 200 pg/ml indicates adequate dose of gonadotrophins.

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