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COH in PCOS women

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Treatment strategies and goals

In anovulatory women, the purpose of treatment in ovulation induction is the development of atleast one follicle, whereas in other causes of infertility, ovarian stimulation is used to increase the number of follicles, known as super ovulation or controlled ovarian hyperstimulation.

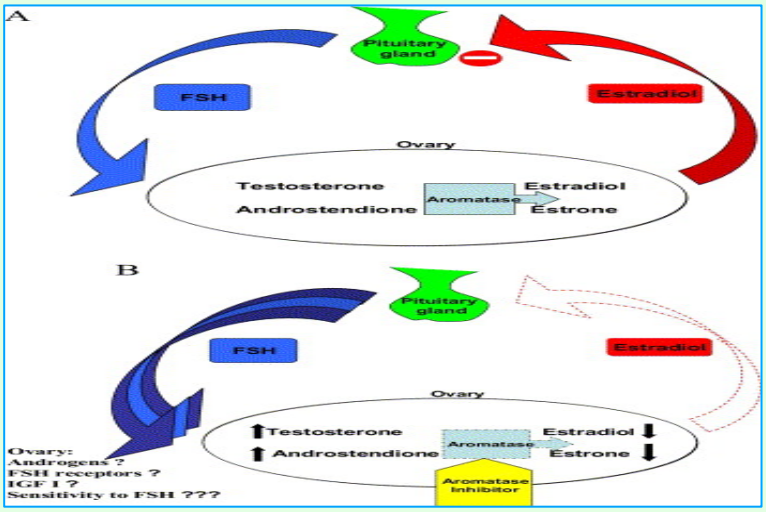
1. Aromatase inhibitors (AI)

Aromatase Inhibitors such as anastrozole and letrozole have been used for ovulation inductions. They prevent aromatization and this prevents androgens from being converted to estrogen. This causes a low estrogenic state. And therefore, acts on HPO axis and pitutary. This causes compensatory increase in the pulsatile GnRH secretion and thereby causes follicular growth.

Therapy regimen and efficacy

Letrozole doses can be started from 2.5mg/day to 7.5mg/day. Anastrozole is given as 1mg daily. Extended Regimens (10 days) and single dose regimens (20mg on Day 3), have also been used with studies suggesting positive results. Letrozole can be combined with planned relations or IUI. In anovulatory women, AI have shown almost a 60% ovulation rate with pregnancy rates varying from 12-40%. [1]

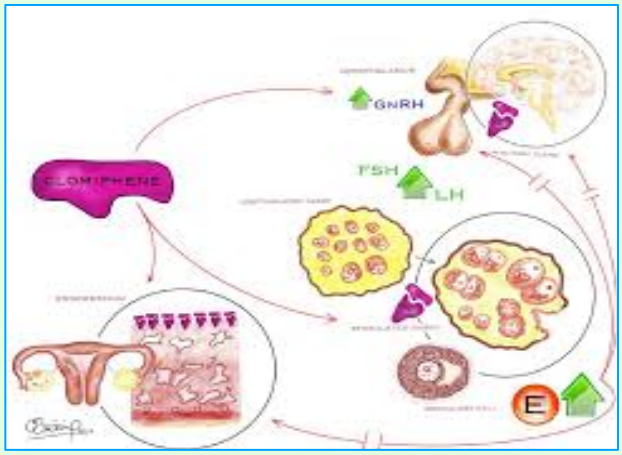
Fig 1 – Aromatase inhibitors- Mechanism of Action



2. CLOMIPHENE

A selective estrogen-receptor modulator that antagonizes the negative feedback of estrogen at the hypothalamus with a conséquent i ncrease in ovarian stimulation by endogenous gonadotropin, has been the preferred ovulogen for PCOS until recently. AI are now currently the first line of treatment in PCOS patients as Clomiphene has many drawbacks. It has an overall lower efficacy than AI with relatively higher multiple pregnancy rate along with higher incidence of clomiphene resistant cases.[2]

Fig 2 Clomiphene- Mechanism of Action



3. Adjuvant Regimens

These have traditionally been described in textbooks of reproductive endocrinology (especially glucocorticoids and bromocriptine) and are mentioned here for completeness; their utility is restricted in day-to-day practice.

A) Clomiphene and glucocorticoids

With normal and elevated levels of DHEA in CC resistant patients, addition of dexamethasone (0.5-2mg) or prednisalone (5mg) has shown increase in ovulation and pregnancy rates. The mechanism of action is not clearly know but there is a hypothesis that suggest the androgen suppression has direct effects on the oocyte and indirect effects on cytokines and intrafollicular growth factors.[3]

B) Clomiphene and human chorionic gonadotropin

HCG injection may benefit as surrogate LH surge to trigger ovulation in patients where CC is used especially in cases of unexplained infertility or co-existing male factor

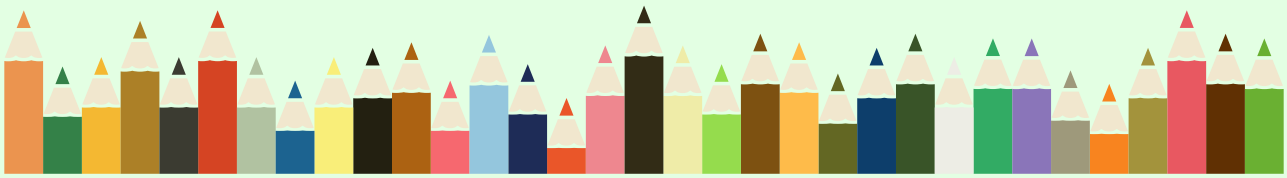
C) Clomiphene and metformin

Metformin should be considered in combination with CC in patients who are CC resistant. Metformin is usually given in a dose of 1500-2000mg/day. The starting dose of 500mg/day should be given after which the dose should be increased to the require dose. A liver function test should always be carried out prior to starting metformin.

A meta-analysis has suggested that metformin may improve success in weight management. Otherwise, the role of metformin in ovulation induction is controversial. Interestingly, metformin may have a role as pretreatment before standard assisted reproduction techniques. A recent RCT demonstrated improved pregnancy rates after 3–9 months of metformin before assisted reproduction techniques. 4

4. Exogenous GONADOTROPINS

The major boon of recombinant gonadotropins is that they provide a more consistent supply, there is barely any variation in the activity of the molecule and the biggest advantage is that there in antigenic urinary protein present. WHO group 2 patients who do not respond to oral ovulogens should be subjected to exogenous FSH and LH. Exogenous gonadotropins should be used as 2nd line of treatment for ovulation induction.[5] Super ovulation is often the goal of using gonadotropins in this population attempting to optimize cycle fecundity.



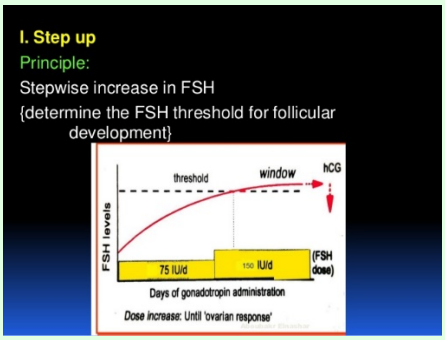
Prerequisites

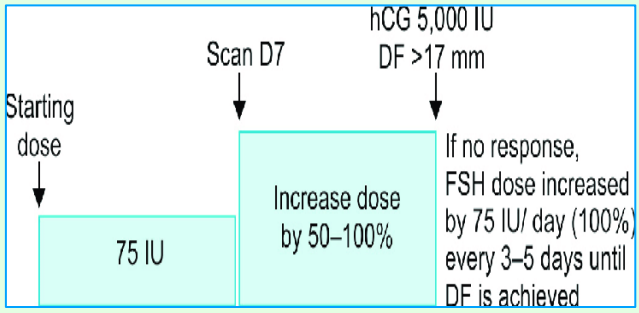
1. Extensive counselling is essential.
2. The couple must understand the expected expenditure and time that needs to be committed for monitoring the effects of the medicine.
3. Serum estradiol levels as well as follicular number and growth must be monitored to prevent OHSS.

a) The **'step-up'** protocol :

It is aimed at crossing the FSH threshold and reduce the risk of complications. The drawback of this protocol is that increases the duration of the cycle and can result in multifollicular growth.

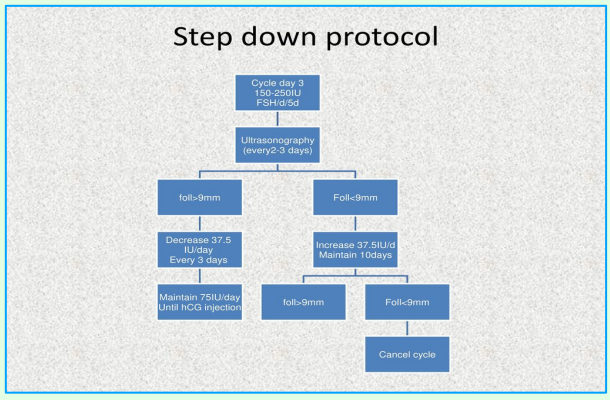
Fig 3 : Step Up Protocol:





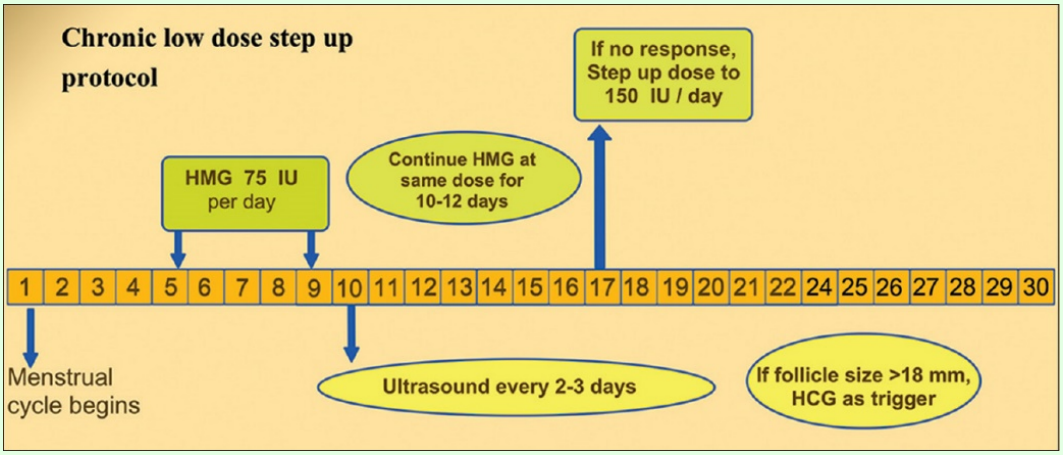
b) The '**step-down'** Protocol: This is where FSH is started at a higher dose so that the dominant follicle develops faster. Once the dominant follicle is established, the FSH levels can be reduced slowly to ensure monofollicular growth.[6]

Fig: Step Down protocol:



c) The '**low dose or chronic low dose step up' Protocol:**
This regimen may be considered in the first cycle to gauge a response for an individual patient. Eventually the other cycles can be done depending on the response in the first cycle.

Fig: **chronic low dose step up' Protocol:**



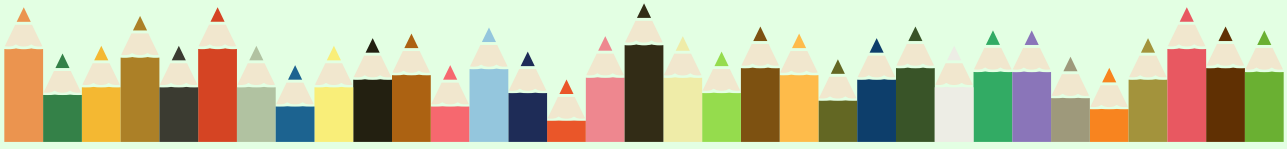
4. Controlled Ovarian Stimulation

GnRH agonists and antagonists

Among the various GnRH agonist protocols, namely ultrashort, short and long, the long GnRH agonist protocol has been used as the gold standard in IVF since its discovery in the 1980s. GnRH antagonists have recently offered an alternative approach in IVF treatment.

The long GnRH agonist protocol involves administration of 0.1 mg GnRH agonist (e.g., triptorelin/leuprolide) starting on preceding cycle-day 21 followed by administration of gonadotropin at 150-225 international units (IU) daily starting on cycle-day 2. The hCG trigger injection is given when follicles are 16 to 18 millimeters (mm) in size.

For the GnRH antagonist protocol, administration of gonadotropin is initiated after monitoring of patients' follicles sizes on cycle-day 2/3. Approximately after the 6th day of gonadotropin injection or when follicular size reaches more than or equal to 14 mm, subcutaneous administration of the GnRH antagonist (eg. Cetrorelix 0.25 mg/d) begins.



Conclusions:

Although clomiphene citrate as a treatment modality has existed for more than 50 years, an increased awareness of the effect of obesity and different PCOS phenotypes has emerged. Accordingly, ovulation induction in women suffering from oligo- and anovulation seeking fertility treatment has to be individualised according to weight, treatment efficacy and patient compliance, with the aim of achieving monofollicular growth, mono-ovulation and subsequently the birth of a singleton baby.

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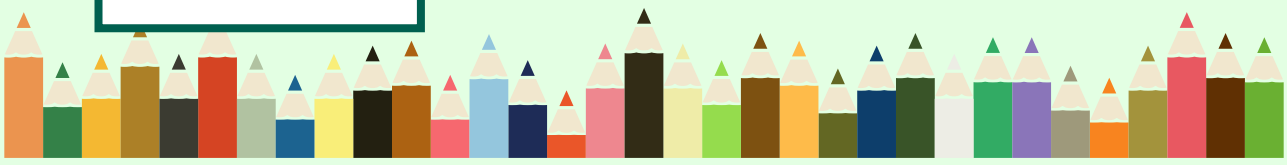


PCOS: Leading Cause of Female Infertility
heart disease
early menopause
headaches
fatigue
infertility
WEIGHT GAIN
acne
unwanted hair growth
moodiness
thinning head hair
pelvic pain
sleep difficulties