INDIAN FERTILITY SOCIETY

15th August, 2018

Special Independence Day edition

GONADOTROPINS IN ART

INDIAN FERTILITY SOCIETY

CERTIFIED MASTER COURSES
by Indian Fertility Society

These days it has been seen that due to paucity of time many practicing clinicians and embryologist are not able to attend long duration courses though they are really interested and in need of enhancing their existing skills. IFS has been getting repeated requests for short duration, very precise and specific training modules for the same from already practicing infertility specialists and embryologists.
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2. Advanced Andrology : DFI, PRP, Microfluidics — 30.9.18, Sunday
3. Cryobiology : Semen , oocyte , embryo , ovarian cortex banking — 1.10.18, Monday
4. Embryo culture, media and lab ware: Basics concepts , hands on laboratory procedures — 2.10.18, Tuesday
5. QA & QC in ART centre — 3.10.18, Wednesday
6. Ovulation induction, gonadotropins and cycle monitoring — 4.10.18, Thursday

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GONADOTROPINS IN ART

Dr M Gouri Devi
President - IFS

With great pride and honor, I write this message for the Eighth E-bulletin of IFS-ARTexT.ARText is our initiative to disseminate scientific and ethical (subject-related) knowledge, and to constantly update everyone with new researches and developments across the world. Through this endeavor, we aim to discuss and simplify the various complexities in clinical ART.

In the current issue, we will be discussing "Gonadotropins in ART". Gonadotropins have become the mainstay of clinical ART practice, and improving success rates of ART has a lot to do with mastering the art of gonadotropin use. So here, we elaborate on the roleand use of gonadotropins in clinical practice.

I am sure that you would benefit from this academic initiative of publication wing of IFS. Indian Fertility society feels proud and congratulates the editors for this bulletin.

Prof (Dr) Pankaj Talwar
Secretary General - IFS
Chief Editor - NEXUS & ARText

I am so happy to write these few lines for this **special Independence Day** bulletin on gonadotropins and stimulation protocols.

Controlled ovarian stimulation is a vital part of infertility treatment. A clear assessment of this treatment is difficult to accrue without practical experience, as each patient behaves differently. Individualization in ovarian stimulation is fast progressing and it is important to understand the basics and intricacies of the burning issue.

It is not only imperative to offer the most effective treatment, but an understanding into the finances of these hormonal preparations would also help the infertility specialist in giving the most cost effective treatment. The pharmacogenetics of ovarian stimulation is a fast progressing concept and is highlighted aptly in this E- bulletin. Fine-tuning of the ovarian stimulation protocol's can be executed with the available battery of hormonal preparations and adjuvant therapies. It is now clear that the "one-size-fits-all" approach may no longer subsist.

The availability of new markers of ovarian reserve, the improvement in methodology for their measurement, and the huge amount of clinical data have supported the view that individualization in IVF protocols is the way forward. Additionally, latest developments in this sphere may bring forth novel alternatives involving more bioactive gonadotropin agents with minimal side effects and increased efficiency.

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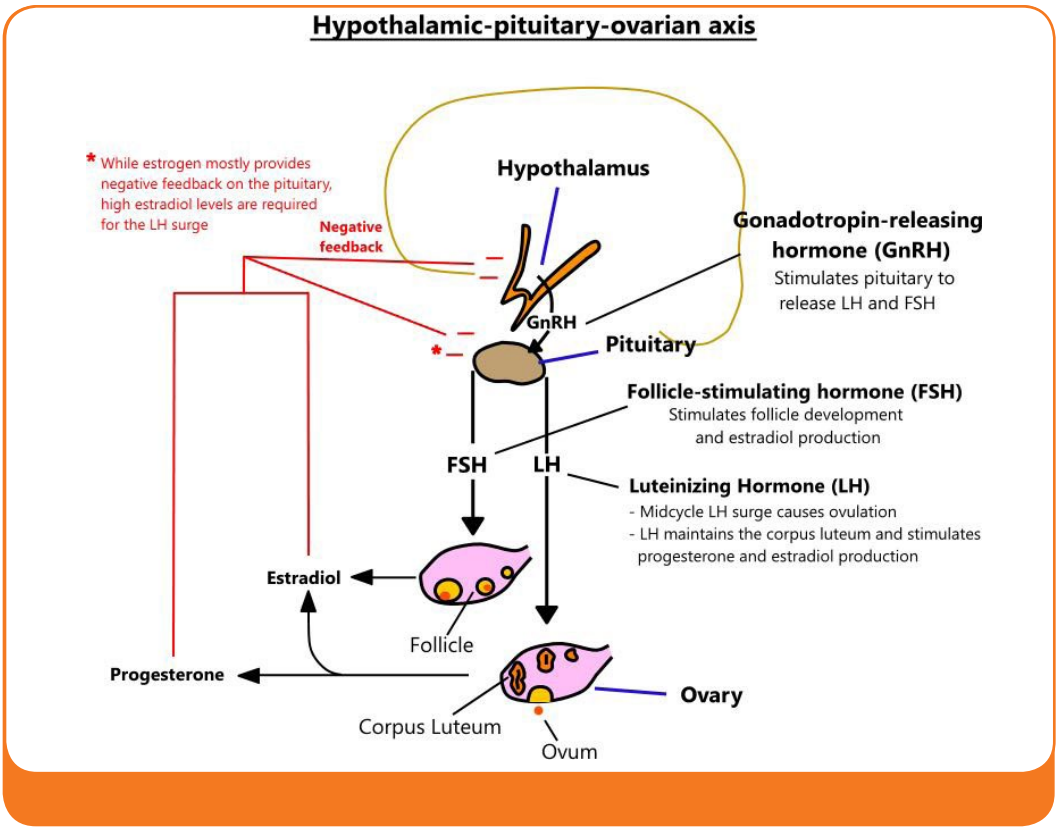
Gonadotropins were once used to induce ovulation in anovulatory women only (usually those with hypopituitary-hypogonadotrophic amenorrhea). Over the last few decades, use of gonadotropin therapy found a more widespread use in the treatment of infertility, as gonadotropins became the standard procedure for ovarian stimulation in assisted reproductive technologies (ART). Gonadotropin preparations available have also evolved from relatively crude urinary extracts to highly purified urinary extracts to the recombinant preparations. They are used for treating all types of infertility, and have been used in various doses and regimens.

One can use gonadotropins in clinical practice only after a thorough understanding of the hypothalamic pituitary ovarian axis.



This is a comprehensive review on "Gonadotropins in ART", where we have discussed all aspects of gonadotropin use (from history of evolution of different types of gonadotropins, to their clinical use, dosage, regimens, etc). We hope this will help you gain a better understanding of the topic. Enjoy reading.

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PART - 1
Gonadotropins in ART

1. INTRODUCTION

Fertility is essential for survival of any species. The inability to procreate is considered as a denial of basic rights and leads to disappointment and grief. In an attempt to make hypogonadotropic amenorrhoeic women ovulate, the Chinese were the first to isolate sex and pituitary hormones from human urine as early as the second century BC. The crystals they obtained were called **'autumn mineral',** coined by the prince of Haua-Nan before 125 BC. These were used to treat a several ailments relating to the sex organs, including hypogonadism, impotence and sexual debility, and even to stimulate growth of the beard. Over the years, use of gonadotropin therapy became an essential part of infertility treatment. Gonadotropin preparations available have also evolved from relatively crude urinary extracts to highly purified urinary extracts to the recombinant preparations.
(Needham J 1983)

2. HISTORICAL PERSPECTIVES

i. INTRODUCTION OF GONADOTROPIC PRINCIPLE

In the western world, the 'gonadotrophic principle' was discovered in 1926, when Smith showed that daily implants of fresh anterior pituitary gland tissue from mice, cats, rabbits and guinea pigs into immature male and female mice induced precocious sexual maturity, enlargement of the ovaries and superovulation. In 1927, **Zondek** postulated that the pituitary secretes two gonad-stimulating hormones, **'Prolan A' and 'Prolan B'.** In 1930, Zondek showed the presence of gonadotropins in the blood and urine of postmenopausal women. He postulated that Prolan A stimulated follicular growth and secretion of '**foliculin', and Prolan B** induced ovulation, corpus luteum formation and the secretion of lutein and foliculin. Thus, by 1930, Zondek had described the pituitary–gonadal relation as known to us today (equating Prolan A and B to FSH and LH, and foliculin and lutein to estrogen and progesterone).
(Smith PE 1926, Smith PE et al 1927, Zondek B 1929, Zondek B 1930, Fevold SL et al 1931)

ii. DISCOVERY OF HUMAN CHORIONIC GONADOTROPIN

In 1927 **Ascheim and Zondek** discovered a gonad-stimulating substance in the blood and urine of pregnant women, which produced follicular maturation, luteinization and hemorrhage in the ovaries of female mice. Organon made this extract commercially available in 1931, under the name **'Pregnon',** later changed to **'Pregnyl'**. Purified urinary preparations of hCG (prepared from urine of pregnant women collected during the first half of pregnancy, when hCG titers are highest) became available in 1940. The potency of these preparations ranged from 6000 to 8500 IU/mg. This gonadotropin was called **"chorionic gonadotropin"**, as it was shown to originate from the chorionic villi of the placenta. After many experiments, the **'two-step protocol'** concept was introduced in 1941. This stated that the pituitary gonadotropins were needed to stimulate follicular growth and development, and that chorionic gonadotropin could induce ovulation only when mature follicles were present.
(Ascheim S et al 1927, Gurin S et al 1940)

iii. INTRODUCTION OF HOG, SHEEP AND PREGNANT MARE SERUM GONADOTROPINS

From 1930 till early 1960s, gonadotropins derived from pig and sheep pituitary gland extracts and later, pregnant mare serum, were used for ovarian stimulation. Their use began to decline after discovery of a new phenomenon, the **'antihormones'** (i.e. formation of antibodies to animal gonadotropins, which decreased ovarian responsiveness in humans). Recognizing that antibody production could neutralize both exogenous and endogenous gonadotropins, efforts were made to extract and purify gonadotropins from human sources.
(Zondek B et al 1942)

iv. HUMAN PITUITARY GONADOTROPIN

Between 1958 and 1988, **human pituitary gonadotropin (hPG)** preparations were successfully used for ovulation induction throughout the world. However, hPG was withdrawn from the market following reports of cases of fatal priondisease (transmissible spongiform encephalopathy), iatrogenic Creutzfeld–Jakob disease (CJD) identified in Australia, France and the UK. This brought another era in the history of gonadotropin use to an end.
(Gemzell CA et al 1958, Buxton CL et al 1961, Cochius JI et al 1990)

v. HUMAN MENOPAUSAL GONADOTROPIN

In 1947, a chemist at the Pharmaceutical Institute, Serono, Rome, Piero Donini, tried to extract hMG from postmenopausal urine. The first urine extract of hMG contained a mixture of follicle stimulating hormone (FSH) and luteinizing hormone (LH) (about 5%), along with miscellaneous urinary proteins (95%), and was named **Pergonal**. Pergonal was approved for clinical use by Italian authorities in 1950. Thereafter, human menopausal gonadotropin (hMG) became the gonadotropin preparation of choice. Initially, it was used to induce ovulation in women with hypogonadotropic anovulatory infertility. One ampoule of hMG contained approximately 75 IU of FSH and 75 IU of LH as measured by standard bioassays. In 1961, the **first pregnancy with Pergonal** treatment was achieved in a patient with secondary amenorrhea, resulting in the birth of the first normal baby girl in **Israel** in 1962.

Soon after, **Cook et al** demonstrated that hMG preparations also contain up to five different FSH **isohormones** and up to nine LH species. These may cause discrepancies in patients' responses when using various lots of the same preparation. The major active agent, FSH, accounts for <5% of the total protein content in extracted urinary gonadotropin products. Some of the proteins found in hMG preparations include tumor necrosis factor binding protein I, transferrin, urokinase, Tamm-Horsfall glycoprotein, epidermal growth factor, and immunoglobulin-related proteins. These non-gonadotropin proteins are also responsible for local side effects such as pain and allergic reactions.

Hence, manufacturers attempted to produce **highly purified (HP) hMG.** HP hMG contains less LH and more hCG (which has a longer half-life than LH) than traditional hMG. However, even in HP-hMG products, several co-purified proteins have been identified. Also, human prion peptides have been detected in hMG and HP-hMG.

(Donini P et al 1949, Lunenfeld B et al 1973, Cook AS et al 1988, Giudice E et al 1994, Al-Inany HG et al 2009, Van Dorsselaer A et al 2011)

vi. PURIFIED URINARY FOLLICLE-STIMULATING HORMONE

The next step in the evolution of gonadotropins was the application of an immunocolumn with polyclonal anti-LH antibodies to remove LH from hMG, resulting in urine-derived FSH (u-FSH) containing mainly FSH activity together with co-extracted urinary proteins. The final product **(Metrodin)** contained 150 IU of FSH and 1 IU of LH per mg of protein and had a specific activity of 100–200 IU of FSH/mg of protein. This pure FSH preparation, apart from being a more purified product, also benefitted the concept that ovulation induction in patients with elevated endogenous serum LH levels could be performed without further exogenous LH administration.

Further refinement of the process in the late 1980s (using highly specific monoclonal antibodies to selectively bind the FSH molecules) led to the development of highly purified u-FSH **(Metrodin-HP)**, containing approximately 9000 IU FSH activity/mg protein, less than 0.1 IU of LH activity and < 1% urinary proteins. The purity also increased from 1–2% to 95%. Enhanced purity implied that the total amount of injected protein is very small, making the HP urinary FSH preparation suitable for subcutaneous administration.

(Eshkol A et al 1967, Loumaye E et al 1995)

3. DRAWBACKS OF URINARY GONADOTROPIN PREPARATIONS

Initially, there were **four urine-collection centers, one each in The Netherlands, Spain, Israel and Italy**. Overall, 600 women participated in these collection centers, and each woman was well known by the collectors. Since hMG was used to induce ovulation in women with anovulatory infertility only, the amount of urine produced by these women over a period of 1 year was sufficient for treating hypopituitary-hypogonadotrophic amenorrheic women (WHO grade I) worldwide at that time. With the pioneering work of **Howard and Georgeanna Jones**, use of hMG became the standard procedure for ovarian stimulation in assisted reproductive technologies (ART). As a result, there was a 100-fold increase in the volume of urine required to satisfy the worldwide need. These urine donors were recruited from countries in Europe, Korea, China, India and South America. Since individual collections could no longer be done.
The urine extraction process had various shortcomings:

(1) Lack of regulatory control;

(2) Impossible to trace donor source;
(3) Quality cannot be checked during transportation;
(4) Urine sources cannot be validated;
(5) Decontamination may denature proteins;
(6) Cross-contamination cannot be avoided;
(7) Poor quality control;
(8) Limited source.

In addition, a further cause for concern was the potential risk of transmission of '**emergent viruses**' including transmissible spongiform encephalopathies (prion diseases), human immunodeficiency virus (HIV), hemorrhagic viruses such as Ebola, transfusion-related hepatitis C-like viruses and, most recently, the **corona -virus** causing sudden acute respiratory syndrome (SARS).

(Jones HW et al 1982, Garcia GE et al 1983)

4. RECOMBINANT HUMAN GONADOTROPINS (FSH, LH AND CHORIONIC GONADOTROPIN)

Following the isolation of the gene encoding the β subunit of FSH in 1983, production of pure FSH using recombinant technology became possible. This involves introduction of genes encoding the α and β FSH subunits into the genome of a Chinese hamster ovary (CHO) cell line which then synthesizes and secretes a glycosylated bioactive dimeric FSH.
Benefits of recombinant FSH preparations are:

1. Absence of urinary protein
2. More consistent supply
3. Less batch-to-batch variation in biological activity

The world's first recombinant human FSH (r-hFSH) preparation was **follitropin alfa**, produced in 1988 and approved for clinical use in 1995 (GONAL-f®; Serono International SA, Geneva, Switzerland). A second r-hFSH (**follitropin beta**, Puregon®/Follistim®; Organon International, NJ, USA) was approved in 1996. Follitropin alfa and follitropin beta are similar in terms of immune-potency, in vitro biopotency and internal carbohydrate complexity, but **follitropin alfa contains a higher proportion of acidic glycoforms.**

The genes for the other gonadotropins have also been transfected into mammalian cell lines. r-hLH and r-hCG are now commercially available (r-hLH as Luveris, Merck Serono International, Switzerland; r-hCG as Ovidrel/Ovitrelle, Merck Serono International; and r-hFSH and r-hLH in a 2:1 ratio, Pergoveris, Merck Serono International).

(Horsman G et al 2000, Shoham Z and Howles CM 2012)

The FbM (Filled by Mass) concept

Doses of gonadotropin preparations have traditionally been expressed in international units (IU), representing activity measured in an in vivo bioassay. The bioassay used traditionally is the **Steelman–Pohley bioassay**, first developed in the 1950s. However, the assay has a number of limitations: it is time consuming, cumbersome, uses large numbers of rats, and is limited in its precision.

Recent advances in manufacturing processes have allowed recombinant gonadotropins to be quantified reliably by protein content (mass in mcg) rather than by biologic activity i.e FbM. This reflects a constant relationship between mass and biological activity and enables high batch to- batch consistency.

The safety and efficacy of GONAL-f FbM was confirmed in a large multicenter observational study carried out in UK in 1427 ART patients. In another study, **Balasch** and colleagues retrospectively compared the outcomes of 125 ART cycles using follitropin alfa FbM and 125 cycles using follitropin alfa FbIU. The duration of stimulation was significantly shorter and embryo quality and implantation rates (28.6% vs. 18.6%, p=0.008) were significantly higher in the FbM

group. Another multicenter, double-blind, randomized study demonstrated that the improved manufacturing process for the FbM over the FbIU preparation was associated with an improvement in the consistency of ovarian response ($p < 0.039$) and significantly improved between-batch consistency in the clinical pregnancy rate ($p < 0.001$).

(Steelman SL et al 1953, Bassett RM et al 2005, Lass A et al 2004, Balasch J et al 2004, Hugues JN et al 2003)

5. INDICATIONS AND CONTRA-INDICATIONS OF GONADOTROPINS IN CLINICAL PRACTICE

In women, gonadotropins are indicated for the treatment of infertility in the following clinical situations:

- Anovulation (hypogonadotropic hypogonadism, where a combination of FSH and LH stimulation is required.
- Anovulatory polycystic ovarian disease in women who have been unresponsive to treatment with clomiphene citrate.
- Controlled ovarian stimulation to induce the development of multiple follicles in medically assisted reproduction programs (eg, IVF/embryo transfer [ET], gamete intrafallopian transfer [GIFT], and intracytoplasmic sperm injection [ICSI]).

In men, gonadotropins are indicated for the treatment of deficient spermatogenesis caused by hypogonadotrophic hypogonadism.

Contraindications include tumors of the ovaries, breast, uterus, testis, pituitary, and hypothalamus; undiagnosed vaginal bleeding; hypersensitivity; primary ovarian failure; primary testicular failure; ovarian cysts or enlarged ovaries not related to PCOD; malformations of the sexual organs incompatible with pregnancy; and fibroid tumors of the uterus incompatible with pregnancy.

6. ROLE OF FSH IN FOLLICULAR DEVELOPMENT

FSH stimulates

- proliferation of granulosa cells, leading to follicular growth,
- aromatization of androgens (from the theca cells) into estrone and estradiol, and
- the appearance of LH receptors on the granulosa cell membrane

Follicular development at the beginning of each cycle occurs only when serum FSH concentrations exceed a specific threshold (the threshold concept). This FSH threshold is highly variable among individuals. In the presence of normal endogenous levels of LH, the number of follicles that mature to ovulation is determined primarily by the length of time that serum FSH remains above this threshold. Timing of FSH administration also helps to determine the number of follicles that mature. In normogonadotropic women, FSH alone is adequate for normal follicular growth and maturation.

(Cedrin-Durnerin I et al 2006, Kolibianakis EM et al 2006)

7. ROLE OF LH SUPPLEMENTATION

The **"two cell–two gonadotropin" model** proposed that both FSH and LH are required for optimal follicular maturation and estradiol synthesis. The '**LH window' concept** states that in the absence of a threshold level of serum LH, estradiol production will be insufficient for follicular development and endometrial proliferation. However, exposure of the developing follicle to excessive LH results in follicular atresia.

Thus, LH supplementation is needed along with FSH for healthy follicular development and oocyte maturation in patients with hypogonadotrophic hypogonadism (WHO type I anovulatory infertility), which is associated with low endogenous levels of LH (due to deficiency of endogenous gonadotropins). However, excessive doses of LH can hamper follicular growth in these cases as well. In an initial LH dose-finding study, women with hypogonadotropic hypogonadism, treated with 150 IU/day r-hFSH plus 225 IU/day r-hLH, developed significantly fewer follicles

compared with patients randomized to receive 75 IU LH.
As stated previously, LH supplementation has no benefit in normal responders undergoing COS. Several meta-analyses of studies comparing outcomes in women receiving supplementary r-hLH with those receiving r-hFSH alone showed no differences in outcomes between treatment groups. However, evidence suggests that **LH has benefits in women** aged above 35 years, and in poor responders. Addition of r-hLH to r-hFSH in women who required high doses of r-hFSH in previous cycles showed significant improvement in fertilization and clinical pregnancy rates.

(Kobayashi M et al 1990, Balasch J et al 2002, Shoham Z 2002, European Recombinant Human LH Study Group 1998, Kolibianakis EM et al 2007, Mochtar MH et al 2007, Howles CM 2011, Lisi F et al 2001)

8. USE OF HCG IN ART

Human chorionic gonadotropin (hCG) is used by all ovarian stimulation programs for the final triggering of ovulation due to inconsistency of the spontaneous LH surge in COS, and its inefficacy in patients receiving GnRH agonists. When preovulatory follicles of appropriate size are present, administration of hCG is followed by granulosa cell luteinization, a switch from estradiol to progesterone synthesis, resumption of meiosis and oocyte maturation, and subsequent follicular rupture 36–40 hours later. hCG is used as a surrogate LH surge because of the degree of homology between the two hormones. Both LH and hCG have the same natural function, i.e to induce luteinization and support lutein cells. Plasma metabolic clearance rate of hCG is slower than that of LH. hCG does not inhibit the subsequent spontaneous LH surge by the intact pituitary. By the 10th day after administration, <10% of the originally administered hCG is measurable.

Typical criteria for the administration of hCG to induce final follicular maturation in ART is the presence of at least one follicle of diameter ≥ 18 mm with at least two other follicles ≥ 16 mm and acceptable E2 concentration (approximately 150 pg/ml per mature follicle).

Another issue requiring clarification is the minimal effective dose of hCG to trigger oocyte maturation and ovulation. No differences in oocyte recovery have been noted when comparing doses of 5000 and 10,000 IU. However, a significantly lower number of oocytes were aspirated when a dose of 2000 IU was used.

With the development of recombinant technology, **r-hCG 250 mcg was found to be at least as effective as 6500 IU of u-hCG** with the benefit of improved local tolerance. The use of a higher dose of r-hCG (500 mcg) resulted in higher oocyte yield but also a three-fold increase of OHSS.

(le Cotonnec JY et al 1998, Nader S et al 1992, Demoulin A et al 1991, Abdalla HI et al 1987, The European Recombinant Human Chorionic Gonadotrophin Study Group 2000, Ludwig M et al 2003)

9. r-hFSH Versus hMG

r-hFSH and hMG are the most frequently used gonadotropins for COS for IVF/ICSI.

Numerous RCTs and meta-analyses have shown that all commercially available gonadotropins have similar efficacy and safety profiles. There is little difference between r-hFSH and hMG in outcomes, in terms of:

- Days of stimulation
- Gonadotropin dose
- Number of oocytes retrieved
- Final estradiol and progesterone levels
- Cancellation rates
- Pregnancy/live birth rate per woman

A **Cochrane systematic review** (2003) showed no difference in ongoing pregnancy/live birth rate per woman in IVF/ICSI cycles using rFSH or HP-hMG (). In 2005, a meta-analysis by **Al-Inany** showed no significant differences between hMG and r-hFSH in terms of ongoing pregnancy/live birth rate, clinical pregnancy, miscarriage, multiple pregnancy, or moderate/severe OHSS. In 2008, another meta-analyses including 12 trials involving 1453 hMG cycles and 1484

r-hFSH cycles showed a significantly higher live birth rate with hMG versus r-hFSH (OR = 1.2, p = 0.04) and similar rates of OHSS in each group (OR = 1.21; p = 0.39).

In another RCT, 127 normogonadotropic infertile women ≥ 35 years old undergoing IVF/ICSI cycle using long agonist protocol, received ovarian stimulation with HP-hMG or with r-FSH. More leading follicles (≥ 18 mm) and oocytes were obtained in the r-FSH group. The proportion of top-quality embryos and live birth rate per started cycle showed slight improvement with HP-hMG. This established non-inferiority of HP-hMG as compared to r-FSH. However, the cost of r-FSH was greater than that of other protocols.

(van Wely M et al 2011, van Wely M et al 2003, Al-Inany H et al 2005, Al-Inany HG et al 2008, Ye H et al 2012)

10. PHARMACOLOGY OF GONADOTROPINS

Natural (pituitary) gonadotropins are present in several isoforms (**called isohormones**). Isohormones can be separated on the basis of differences in electric charge (each one has a different isoelectric point), related to differences in the sialic acid content of carbohydrate components. More acidic isohormones have relatively low receptor-binding affinity and low intrinsic bioactivity with a long plasma half-life, whereas more basic isohormones have higher receptor-binding affinity and higher intrinsic bioactivity, with a short plasma half-life. Pituitary FSH and rFSH (esp. follitropin beta) have a higher proportion of basic isohormones than uFSH. Hence, rFSH displays higher intrinsic bioactivity compared with similar doses of uFSH. Repeated daily administration leads to steady state after 4 doses, and at steady state, circulating immunoreactive FSH concentrations are 1.5 to 2.5 times higher than after a single dose. Pharmacokinetic variables measured after IM and SC routes of administration are highly similar, although small differences in Cmin levels after multiple-dose administration might account for a greater pharmacodynamic response after SC than after IM administration.

(Ulloa-Aguirre A et al 1992, Stanton PG et al 1992)

11. SAFETY PROFILE OF GONADOTROPINS

The effects of gonadotropins on pregnancy, fetal development, delivery and its effects on infants do not differ from the outcomes reported in general population. Data on 1160 babies born after induction of ovulation with gonadotropins revealed that major and minor malformations were found in 63 infants (overall incidence of 54.3/1000 with major malformations 21.6/1000; minor malformations 32.7/1000). **This rate of malformation is not significantly different from that of the general population.**

(Shoham Z et al 1991)

12. USE OF PEN DELIVERY DEVICES

For successful use in clinical practice, consistent dosing and acceptability to the patient is as important as efficacy and consistency. **Pen injectors** have been developed for r-hFSH (follitropin alfa FbM and follitropin beta) to improve the accuracy and compliance of self-injection. Patients prefer a pen injector because it is easier to use, more convenient, and less painful than a conventional syringe. With the pen, rFSH may be self-administered or administered by a partner. The follitropin beta pen is a multiuse, adapted insulin pen that delivers 50–450 IU r-hFSH per injection from a separate cartridge. **Cartridges** that contain a cumulative deliverable dose of 300 IU, 600 IU, or 900 IU of follitropin beta solution are available; the recommended starting daily dose of follitropin beta is 50 to 250 IU, depending on the indication. The pen allows dose adjustment in increments of 25 IU. Prefilled cartridges used with the follitropin beta pen prevent loss of medicine caused by filling or changing needles, or removing excess air from the syringe.

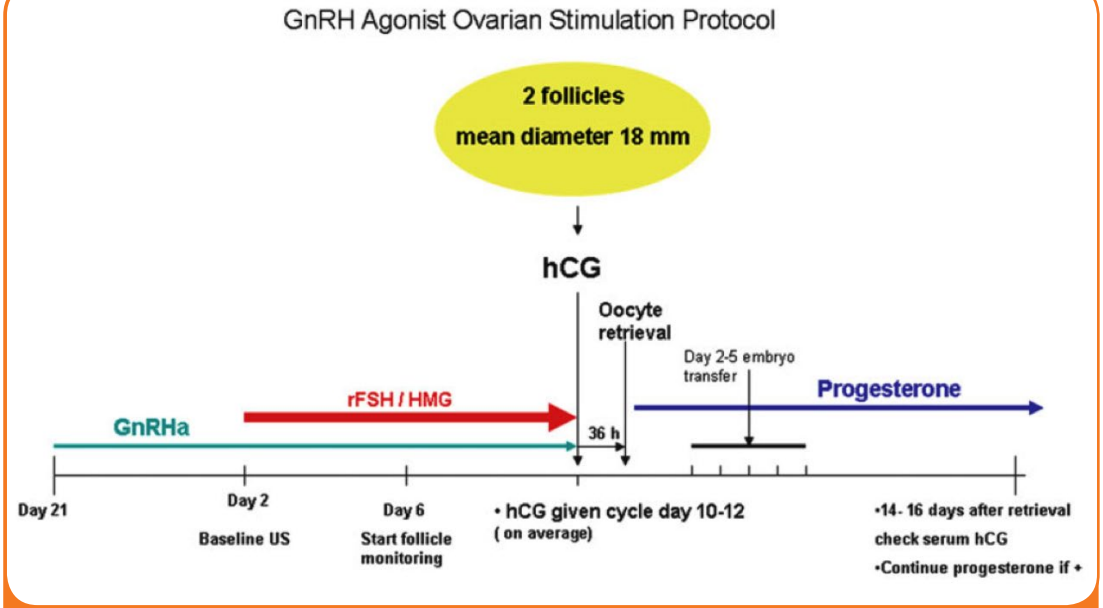
More recently, a pen injector has been developed for use with follitropin alfa FbM. This is a prefilled ready-to-use device and is available in three multidose strengths, equivalent to 300, 450 and 900 IU. The minimum dose increment is 37.5 IU.

(Craenmehr E et al 2001, Platteau P et al 2003)

13. PROTOCOLS FOR ART WITH GONADOTROPINS

Gonadotropins (FSH and HMG) are an essential part of Controlled Ovarian Hyperstimulation (COH) for ART regimens. Most IVF protocols involve treatment with a GnRH analog (agonist or antagonist) for prevention of premature LH surge. Several meta-analyses have shown that the use of a **GnRH agonist** increases the number of oocytes retrieved, increases clinical pregnancy rate and decreases cycle cancelation compared with cycles without an agonist. There are different regimens for gonadotropins like **fixed dose regime, step-up protocol, step-down protocol, chronic low-dose step-up regime, and combined therapy with other drugs** like clomiphene citrate and tamoxifen.

COH with GnRH agonist traditionally involves down-regulation using the **long protocol** [***Figure 1***] i.e. GnRH agonist treatment begins during the midluteal phase of the previous cycle (day 21 of a regular 28 day cycle). In women who do not cycle predictably, oral contraceptives (OC) can be used to control the onset of menses, starting GnRH agonist treatment 1 week before their discontinuation. In India, **leuprolide acetate** (s/c injection) is the most commonly used GnRH agonist. In Europe and elsewhere, **buserelin acetate** (s/c injection or intranasal spray) and **triptorelin** (subcutaneous) are more common; all work equally well. For leuprolide, treatment usually begins with 1.0 mg daily until onset of menses, decreasing to 0.5 mg daily thereafter until hCG is administered. A single dose of a longer-acting depot form of GnRH agonist (leuprolide, goserelin) offers greater convenience, but the total dose and duration of gonadotropin stimulation required are increased significantly. Gonadotropin stimulation begins after confirming that effective pituitary down-regulation has been achieved (**serum estradiol level <50 pg/mL, no follicles >10 mm in diameter**). Some women require longer durations of treatment to achieve suppression.



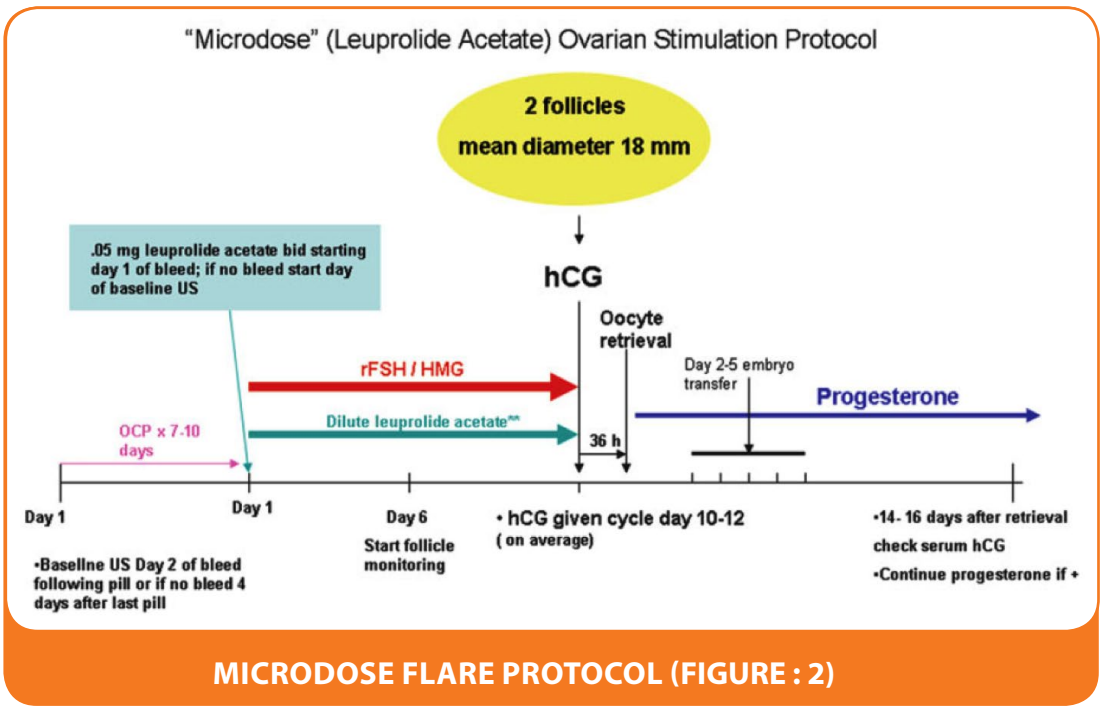
LONG PROTOCOL (FIGURE : 1)

Typical starting doses dose of exogenous gonadotropins range between 150 and 300 IU daily, depending on age, ovarian reserve testing, and the response observed in any previous stimulation cycles. The response to stimulation is monitored with serial measurements of serum estradiol and transvaginal ultrasonography. The first estradiol level usually is obtained after 5 days of stimulation to determine whether the chosen dose of gonadotropins requires adjustment. Thereafter, serum estradiol concentrations and sonography are obtained every 1–3 days, based on the response. In general, stimulation continues until at least two follicles measure 17–18 mm in mean diameter, when others typically measure 14–16 mm. Most women require a total of 7–12 days of stimulation.

The "short" or "flare" protocol is an alternative stimulation protocol, which uses both the brief initial agonistic response to a GnRH agonist (flare) and the suppression that results from longer-term treatment. Here, leuprolide acetate (1.0 mg daily) is administered on cycle days 2–4, continuing thereafter at a reduced dose (0.5 mg daily), and gonadotropin stimulation (225–450 IU daily) begins on cycle day 3. Later adjustments in the dose of gonadotropin stimulation are based on ovarian response. Indications for hCG administration are the same as in the long protocol (as

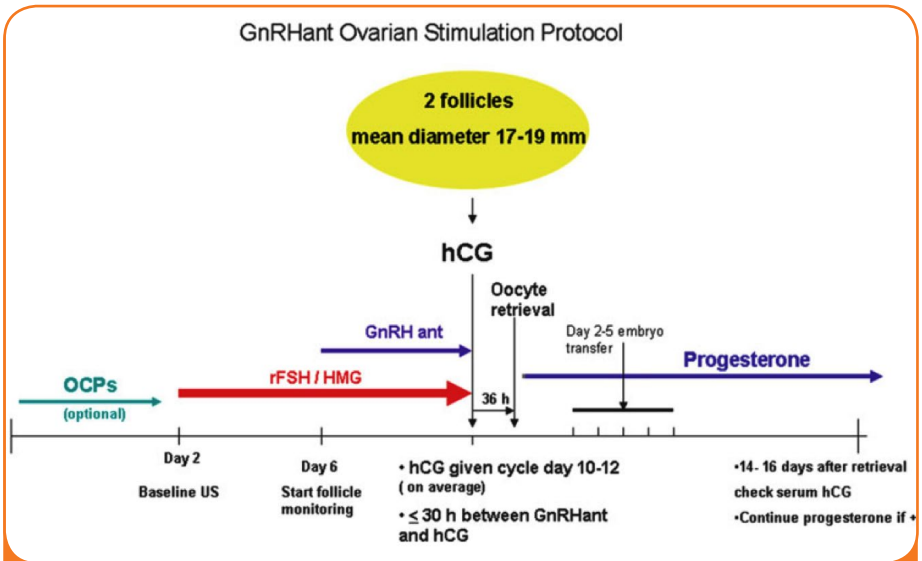
described above). The disadvantage of the flare protocol is decreased scheduling flexibility, unless the onset of menses is controlled by pre-treatment with an OC. The regimen can also result in an increase in serum progesterone and androgen levels, which may adversely affect oocyte quality and fertilization and pregnancy rates.

The "**OC microdose GnRH agonist flare**" stimulation regimen ***[Figure 2]*** is a variation of the standard short protocol involving 14–21 days of preliminary ovarian suppression with a daily OC pill, followed by microdose leuprolide treatment (40 μ g twice daily) beginning 3 days after discontinuation of OC treatment, and high-dose gonadotropin stimulation (300–450 IU daily) starting on day 3 of leuprolide therapy. Its main **advantage over the standard short** protocol is that it does not induce any increases in serum progesterone or androgen concentrations. It may be useful in previous poor responders, in whom it can stimulate increased endogenous FSH release and may yield lower cancellation rates and higher peak serum estradiol levels, transfer rates, and pregnancy rates.



MICRODOSE FLARE PROTOCOL (FIGURE : 2)

In the **GnRH-antagonist protocol** [***Figure 3***], the gonadotropins are started on day 2 of the cycle, and GnRH antagonist is added to prevent the premature LH surge after about 5-6 days, when the leading follicle reaches a diameter of 14mm and/or serum E2 is > 400pg/ml. Though long protocol was considered the 'gold standard' in IVF cycles, the use of antagonist for pituitary suppression and agonist for ovulation trigger eliminates OHSS making ART protocols simpler and patient friendly. **GnRH antagonists** were shown to have several potential advantages over agonists, including a rapid onset of action, lack of hormone withdrawal symptoms, lower dose requirement of gonadotropins, shorter duration of treatment cycle and significantly lower risk of ovarian hyperstimulation syndrome (OHSS).



GNRH ANTAGONIST PROTOCOL (FIGURE : 3)

Individualization of ovarian stimulation protocols is essential for optimizing cycle outcomes as each woman's ovarian response

to stimulation is highly variable. Efforts have been made to identify markers that accurately predict response to the OI regimen to improve the safety, and efficiency of treatment. The selection of an appropriate starting dose of gonadotropins allows physicians to individualize established treatment protocols. This could potentially shorten the time taken to reach the ovulation-triggering threshold and reduce the risk of cycle cancellation because of extreme responses to gonadotropins.

Commonly used **biomarkers predictive of ovarian reserve** and response to treatment include age, BMI, basal FSH, antral follicle count (AFC) and anti-Müllerian hormone (AMH). Other factors studied as potential predictors for ovarian response include inhibin-B, estradiol, ovarian volume and vascular flow. Various algorithms (such as the **CONSORT** treatment algorithm) have been developed to calculate the optimum FSH starting dose. Accurate prediction of ovarian response prior to COS would allow tailoring of treatment in the first treatment cycle. For patients who have had previous treatment, previous response to stimulation can guide the gonadotropin dosage in subsequent cycles. These days, though the most common starting dose for COS is 150–225 IU/day, higher starting doses are used in older patients. **Commonly used starting doses of gonadotropins in first IVF cycles are:**

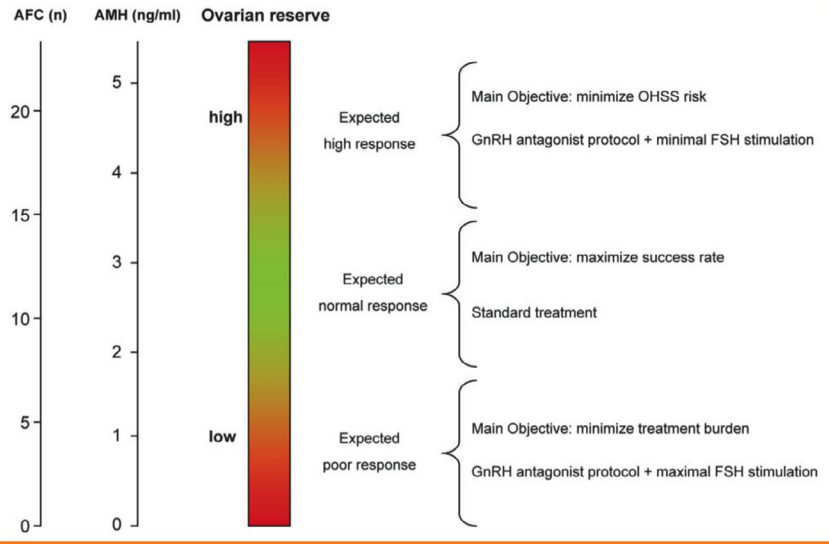
Age < 35 : start 150 IU daily;
Age 35–39 : start 225 IU daily;
Age 40+ : start 300 IU daily.

If a woman has had poor or exaggerated response to treatment using this protocol in previous cycles, the starting dosage should be increased or decreased accordingly. After 5–7 days of stimulation, the dosages may be adjusted upwards or downwards depending on the follicular response (assessed by ultrasound and measurement of serum estradiol).

La Marca suggested that anti-Müllerian hormone (AMH) is a better marker in predicting ovarian response to controlled ovarian stimulation than age of the patient, FSH, estradiol and inhibin B [**Figure 4,5**]. In clinical practice, AMH measurement may be useful in the prediction of poor response and cycle cancellation and also of hyper-response and ovarian hyperstimulation syndrome. As AMH may permit the identification of both the extremes of ovarian stimulation, it plays a significant role in the individualization of treatment strategies in order to reduce the clinical risk of ART along with optimized treatment burden.

Optimal Fertility	Satisfactory Fertility	Low Fertility	Very Low/ Undetectable	High Level
28.6 – 48.5 pmol/L	15.7 – 28.6 pmol/L	2.2 – 15.7 pmol/L	0.0 – 2.2 pmol/L	> 48.5 pmol/L Suspicion of PCOS or Tumour

CORRELATION OF AMH WITH FERTILITY POTENTIAL (FIGURE : 4)



CORRELATION OF AMH WITH FERTILITY AND SUGGESTED TREATMENT PROTOCOLS (FIGURE : 5)

(Hughes EG et al 1992, European and Middle East Orgalutran Study Group 2001, Fluker M et al 2001, Nardo LG et al 2011, Howles CM et al 2010, Olivennes F et al 2009, Popovic-Todorovic B et al 2003)

Luteal Phase Support

Co-treatment with GnRH analogs effectively suppresses endogenous LH secretion. Unfortunately, even though agonist and antagonist treatment ends on the day of hCG administration, residual suppression of endogenous LH does not. Abnormally low levels of LH during the luteal phase may be insufficient to stimulate and maintain the level of luteal function required to promote timely endometrial maturation for implantation or to support an early pregnancy once established. Endogenous LH secretion can remain suppressed for as long as 10 days after treatment with a GnRH agonist ends. As a result, luteal function is inadequate.

Therefore, some form of luteal phase support must be provided for all. Progesterone supplementation is generally started on the day of oocyte retrieval. **It can be given in the form of:**

- Oral micronized progesterone (200–800 mg daily)
- Oral dydrogesterone (20-30mg daily)
- Vaginal 8% gel (90 mg daily)
- Vaginal micronized tablets (200–800 mg daily), and
- Intramuscular injection (25–50 mg daily)

Numerous clinical trials have compared clinical, ongoing, or delivered pregnancy rates or spontaneous abortion rates between groups receiving treatment with different luteal phase support regimens, with varying results. There is no evidence that any treatment regimen is superior, although results achieved with oral micronized progesterone have been inconsistent.

The optimal duration of supplementation also has not been established. Treatment regimens vary widely, from discontinuation of supplementation at the time of the pregnancy test, to continuation throughout the first trimester. Although estradiol supplementation also is commonly administered, there is no evidence that it improves outcomes, compared to those achieved with progesterone supplementation alone.

14. NEW DEVELOPMENTS

Corifollitropin Alfa

In order to increase the duration of action of r-hFSH, reduce the number of injections required and simplify ART regimens, an FSH molecule with an extended duration of therapeutic action has been developed. This long-acting protein, termed as **FSH C- terminal peptide** (FSH-CTP, corifollitropin alfa) was first described by **Bouloux** in 2001. FSH-CTP consists of the alfa subunit of r-hFSH with a hybrid beta subunit (made of the beta subunit of hFSH and the C-terminal part of the beta subunit of hCG which confers an increased half-life on the molecule). FSH-CTP initiates and sustains follicular growth for one week so one dose can replace the first seven daily injections of gonadotropin in COS.

The first live birth resulting from a FSH-CTP stimulation cycle was reported in 2003. In Europe, FSH-CTP is now approved for use in ART cycles along with a GnRH antagonist. Two large multicenter, randomized, double blind studies were conducted to demonstrate the non-inferiority of FSH-CTP to r-hFSH (**ENGAGE study** in 1506 patients of 60–90 kg, and **ENSURE study** in 396 patients weighing <60 kg undergoing ART). Ongoing pregnancy rates per cycle initiated were similar for FSH CTP and r-hFSH. **However, FSH-CTP was associated with a higher incidence of OHSS**. The effects of FSH-CTP cannot be adjusted to individual patient requirements, therefore careful assessment of patient suitability is required before treatment is commenced.

Additional future developments may identify orally active molecules of human FSH or LH receptor agonists that might obviate the need to inject gonadotropin.

(Bouloux PM et al 2001, Beckers NG et al 2003, Devroey P et al 2009, Corifollitropin alfa Ensure Study Group 2010)

PART - 2
Frequently Asked Questions

Ques 1: What factors should be considered in deciding the gonadotropin dose for COS?

Ans : Dose of gonadotropin used for COH needs to be individualized for optimizing cycle outcomes as each woman's ovarian response to stimulation is highly variable. Various factors that need to be considered to decide the starting dose of gonadotropins include age, BMI, basal FSH and estradiol, antral follicle count (AFC) and anti-Müllerian hormone (AMH). Other factors studied as potential predictors for ovarian response include inhibin-B, ovarian volume vascular flow and history of smoking. **Various algorithms have been proposed** to calculate the optimum FSH starting dose e.g CONSORT treatment algorithm, **Popovic-Todovoric [Figure 6]**, **Biasoni et al [Figure 7]**. For patients who have had previous treatment, previous response to stimulation can guide the gonadotropin dosage in subsequent cycles.
(Howles CM et al 2010, Olivennes F et al 2009, Popovic-Todorovic B et al 2003, Biasoni V et al 2011)

Total number of follicles 10 mm day 2–5	FSH score IU/day	rFSH starting dose
<15	90	
15–25	60	
>25	50	
Total ovarian volume day 2–5		Score
<9 ml	90	
9–13 ml	60	
>13 ml	50	
Total Doppler score day 2–5		Score
2–3	30	
4	20	
5	10	
6	0	
Age (years)		Score
>35	20	
>30–≤35	10	
≤30	0	
Smoking habits; cigarettes/day		Score
>10	20	
≤10	10	
Non-smoker	0	
Total FSH score (sum of scores) same as dose IU/day		

POPOVIC-TODOVORIC RFSH DOSAGE NORMOGRAM (FIGURE : 6)

Criteria to establish the starting daily dose of rFSH according to age, body mass index (BMI), basal FSH, and AFC

Clinical characteristics	rFSH starting dose (IU)
Age < 35 + normal BMI + basal FSH < 8 IU/L + AFC > 14	100 - 150
Age < 35 + BMI 25-30 + basal FSH < 8 IU/L + AFC > 14	200
Age 35-40 and/or basal FSH 8-10 IU/L and/or AFC 8-13	150 - 250
Age 35-40 and/or basal FSH 8-10 IU/L and/or AFC 8-13, BMI > 25	300

Patients above 40 years, with BMI > 30 or < 19, basal FSH levels > 10 IU/L and/or AFC < 8 were a priori excluded from the study.

BIASONI CRITERIA FOR STARTING DAILY DOSE OF RFSH (FIGURE : 7)

Ques 2: Which is the preferred gonadotropin in ART cycles?

Ans : The gonadotropins preparations used for COS in ART cycles are r-hFSH, uFSH-HP and hMG. Numerous metaanalyses and RCTs have shown that all commercially available gonadotropins have similar efficacy and safety profiles. There is little difference between r-hFSH and hMG in outcomes, in terms of dose requirement, days of stimulation, number of oocytes retrieved, estradiol and progesterone levels and clinical pregnancy and live birth rate.

(van Wely M et al 2011, Al-Inany H et al 2005)

Ques 3: Does rFSH improve embryo quality or clinical pregnancy rates?

Ans : Few studies have shown that rFSH is more efficient than FSH-HP or HMG because the total gonadotrophin dose required per treatment cycle was lower (a mean of about 400 IU less was necessary with the use of r-hFSH). However, no significant difference was found between the r-hFSH and u-FSH groups in other secondary outcome parameters, such as spontaneous abortion rate, multiple pregnancy rate, OHSS rate, estradiol levels on the day of hCG, the number of follicles, number of retrieved oocytes and embryo quality. While few studies do show higher clinical pregnancy rates with rFSH, others have shown similar outcomes with rFSH and HMG.

(Daya S 2002, Al-Inany H et al 2005)

Ques 4: Is LH supplementation recommended in ovarian stimulation protocols?

Ans : Though LH plays an important role in folliculogenesis, data from studies that employed rLH to supplement FSH stimulation are controversial. A meta-analysis by Daya et al suggested that the level of endogenous LH is sufficient in most cases, and addition of LH might reduce the pregnancy rate. Thus, **LH supplementation has no benefit** in normal responders undergoing COS. Several meta-analyses of studies comparing outcomes in women receiving supplementary r-hLH with those receiving r-hFSH alone showed no differences in outcomes between treatment groups.

However, evidence does suggest that **LH has benefits** in women aged above 35 years, and in poor responders in terms of significant improvement in fertilization and clinical pregnancy rates. LH supplementation is also needed along with FSH for healthy follicular development and oocyte maturation in patients with hypogonadotrophic hypogonadism. However, exposure of the developing follicle to excessive LH results in follicular atresia **(LH-ceiling effect)**.

(Daya S et al 1995, Kolibianakis EM et al 2007, Mochtar MH et al 2007, European Recombinant Human LH Study Group1998)

Ques 5: What strategies can be used to improve COH outcomes in poor responders?

Ans : Various strategies attempted to improve the outcome of poor responders in IVF include:

1. Increasing the starting dose of gonadotropins;
2. Starting stimulation in the late luteal phase;
3. Using adjuvant growth hormone (GH) or GH-releasing factor;
4. Manipulating the use of GnRH agonist (e.g. reducing the dose, stop-protocol, micro-dose flare protocols);
5. Use of GnRH antagonist protocols;
6. Minimal stimulation protocols;
7. Use of the natural cycle.

Ques 6: What strategies can be used to optimize COH in Hyper responders?

Ans : The following strategies can be used for stimulation of high responder patients:

1. Use low doses of gonadotropins (100–150 IU/day) or minimal stimulation protocols
2. Monitor patients at regular, frequent intervals.
3. Resist the tendency to increase the dose, unless there is a total lack of response.
4. Coasting (with-hold gonadotropins for 1-3 days once leading follicles have reached 15-18mm, before hCG trigger)
5. Avoid GnRH agonist flare protocols.
6. Use GnRH antagonist protocol
7. Reducing hCG dose

8. GnRH agonist trigger
9. Cryopreservation of all embryos (cancel fresh ET)

Ques 7: Which is the optimal OI protocol for women with hypogonadotropic hypogonadism (HH)?

Ans : In women with HH, optimal clinical results are achieved by administration of a combination of FSH and LH (either as hMG or a combination of FSH and rLH or low-dose hCG). To avoid multiple follicular development, the lowest effective dose of gonadotropins should be used. Treatment should be monitored by serum estradiol (E2) measurements and ultrasound scans of the ovaries. A common protocol is to administer hMG at a starting dose of 150 IU/day for 5 days and, unless a substantial increase in E2 level occurs, the dose is increased by 33% every 5 days. If recombinant gonadotropin preparations are used, a starting dose of 150 IU rFSH combined with 75IU rLH is usually given. Significantly larger amounts of gonadotropins and a longer stimulation period have been reported for ovulation induction in HH patients. **The response to gonadotropin therapy is considered optimal if three criteria** are met, i.e. at least one follicle reaches a mean diameter of > 17 mm, preovulatory serum E2 level of > 400 pmol/L is obtained, and a midluteal progesterone level of > 25 nmol/L is seen. When follicular response is adequate, ovulation is triggered by a single intramuscular injection of 10000 IU of hCG.

Luteal support (in the form of supplemental exogenous progesterone or 1500–2500 IU of hCG every 3–4 days) is essential in women with HH as endogenous gonadotropin secretion is inadequate to support normal luteal function.

(Messinis IE 2005, Kumbak B et al 2006)

Ques 8: What are the complications associated with the use of gonadotropins?

Ans : **Multifetal gestation** is the most frequent complication of COH. To minimize the risk of multiple pregnancy in an IUI cycle, cycle cancellation should be considered when three or more mature follicles (>16–17 mm) or a large number of intermediate-sized follicles (10–15 mm) are observed or when the serum E2 concentration exceeds 1000 pg/mL. In an IVF cycle, restricting the number of embryos transferred to one or two can minimize the risk of multifetal gestation.

Ovarian hyperstimulation syndrome (OHSS) is the most serious iatrogenic complication associated with ovarian stimulation. OHSS is classified as mild, moderate, severe and critical. Mild manifestations of OHSS (lower abdominal discomfort, mild nausea, vomiting and abdominal distention) are seen in up to one third of COH cycles. Progression of illness is recognized when symptoms persist, worsen, or include ascites demonstrated by increasing abdominal girth or ultrasound. Serious illness exists when pain is accompanied by: 1) rapid weight gain, 2) tense ascites, 3) hemodynamic instability (orthostatic hypotension, tachycardia), 4) respiratory difficulty (tachypnea), 5) progressive oliguria, or 6) laboratory abnormalities. The **pathophysiology of OHSS** is characterized by increased capillary permeability, leading to leakage of fluid from the vasculature, third-space fluid sequestration, and intravascular dehydration. In critical cases, it can lead to multisystem dysfunction, thrombosis, renal and hepatic dysfunction, and pulmonary edema. Vascular endothelial growth factor (VEGF) is one of the factors involved in the pathophysiology of OHSS. In women undergoing ovarian stimulation with gonadotropins, hCG is the usual trigger for OHSS.

The key to **prevention of OHSS** is recognition of risk factors for OHSS (young age, low body weight, polycystic ovary syndrome, high doses of exogenous gonadotropins, high absolute or rapidly rising serum E2 levels, and previous episodes of OHSS). Ovulation induction regimens should be individualized, carefully monitored, and use the minimum dose and duration of gonadotropin therapy necessary. Caution is indicated when any of the following indicators are present: rapidly rising serum E2 levels, E2 concentration > 2500 pg/mL, or a large number of intermediate-sized follicles (10– 14 mm). A lower dose of hCG (5000 IU instead of the standard 10000 IU) or using an agonist trigger (in an antagonist cycle) may be beneficial for patients at high risk for OHSS.

(The Practice Committee of the American Society for Reproductive Medicine 2008, Aboulghar M 2009)

PART - 3

MARKET PREPARATIONS OF GONADOTROPINS AVAILABLE IN INDIA

The various available market preparations of gonadotropins are listed in Table 1.

Table 1: Market preparations of Gonadotropins available in India

Manufacturer	Trade name	Generic Product	Formulations available	Doses available	Price (MRP)	Route of administration
Merck Serono	**Gonal F** (Figure 8)	rFSH (Follitropin alfa)	Vial	75 IU	Rs 1727	s/c
			Vial	1050 IU	Rs 27038	s/c
			Pen	300 IU	Rs 8020	s/c
				450 IU	Rs 11957	s/c
				900 IU	Rs 23768	s/c
	Luveris (Figure 9)	rLH	Vial	75 IU	Rs 2137	s/c
Ferring	**Menopur** (Figure 10)	75unit contains: 75 IU HP-FSH +9.9IU hCG+ 0.04IU LH	Vial	75 IU	Rs 1470	s/c or IM
			Vial	600 IU	Rs 16222	s/c
			Vial	1200 IU	Rs 32444	s/c
	Menogon (Figure 11)	75 IU uFSH + 75 IU uLH	Ampoule	75 IU	Rs 937	IM
MSD	**Recagon** (Figure 12)	rFSH (Follitropin beta)	Vial	50 IU	Rs 1605	s/c
				100 IU	Rs 3208	s/c
			Pen	300 IU	Rs 9626	s/c
				600 IU	Rs 19253	s/c
Intas	**Follisurge** (Figure 13)	rFSH (Follitropin alfa)	PFS	75 IU	Rs 1550	s/c
				150 IU	Rs 3000	s/c
				225 IU	Rs 5600	s/c
				300 IU	Rs 7000	s/c
			Pre-filled pen	450 IU	Rs 11000	s/c
				900 IU	Rs 23000	s/c
			Multidose vial	1200 IU	Rs 24000	s/c
	Menotas HP	HP-FSH + LH (1:1)	Vial	75 IU	Rs 870	s/c or IM
				150 IU	Rs 1745	s/c or IM
	Menotas (Figure14)	uFSH + LH (1:1)	Vial	75 IU	Rs 770	IM
				150 IU	Rs 1000	IM

Bharat Serum	**Folligraf** (Figure 15)	rFSH (Follitropin alfa)	Vial	75 IU	Rs 1600	s/c
			Vial	150 IU	Rs 3200	s/c
			PFS	75 IU	Rs 1700	s/c
				150 IU	Rs 3400	s/c
				225 IU	Rs 5100	s/c
				300 IU	Rs 6600	s/c
			Multidose vial	1200 IU	Rs 24200	s/c
	Humog HP	HP-FSH + LH (1:1)	Vial	75 IU	Rs 980	s/c or IM
			Vial	150 IU	Rs 1600	s/c or IM
	Humog (Figure 16)	uFSH + LH (1:1)	Vial	75 IU	Rs 713	IM
			Vial	150 IU	Rs 1154	IM
			Vial	225 IU	Rs 1678	IM
Bharat Serm - Axis Division	**Diva HMG**	uFSH + LH (1:1)	Vial	75 IU	Rs 713	IM
			Vial	150 IU	Rs 1157	IM
	Diva HMG-HP	HP-FSH + LH (1:1)	Vial	75 IU	Rs 980	s/c or IM
			Vial	150 IU	Rs 1600	s/c or IM
	Diva FSH	uFSH	Vial	75 IU	Rs 700	IM
			Vial	150 IU	Rs 1350	IM
	Gonarec	rFSH (follitropin alfa)	Vial	75 IU	Rs 1890	s/c
Sun Pharma	**GMH**	HP-FSH + LH (1:1)	Vial	75 IU	Rs 985	s/c or IM
			Vial	150 IU	Rs 1485	s/c or IM
	Ovitrop HP	HP-FSH	Vial	75 IU	Rs 1100	s/c or IM
			Vial	150 IU	Rs 1850	s/c or IM
	Ovitrop R	rFSH	Multidose vial	300 IU	Rs 7000	s/c
Emcure	**Materna rFSH**	rFSH (Follitropin alfa)	Vial	75 IU	Rs 2076	s/c
			Vial	150 IU	Rs 4038	s/c
	Materna HMG	HP-FSH + LH (1:1)	Vial	75 IU	Rs 1014	s/c or IM
			Vial	150 IU	Rs 1188	s/c or IM

LG	**Newmon R**	rFSH (follitropin alfa)	PFS	75 IU	Rs 1940	s/c
				150 IU	Rs 3880	s/c
				225 IU	Rs 5820	s/c
				300 IU	Rs 8020	s/c
			Vial	75 IU	Rs 1705	s/c
			Vial	150 IU	Rs 3190	s/c
	IVF-M	uFSH + LH (1:1)	Vial	75 IU	Rs 890	IM
			Vial	150 IU	Rs 1220	IM
Mylan	**My FSH**	HP-FSH	Vial	75 IU	Rs 1300	s/c or IM
		HP-FSH	Vial	150 IU	Rs 1900	s/c or IM
	My HMG	HP-FSH + LH (1:1)	Vial	75 IU	Rs 1200	s/c or IM
			Vial	150 IU	Rs 1600	s/c or IM
Corona	**Eema FSH**	HP-FSH	Vial	75 IU	Rs 1100	s/c or IM
			Vial	150 IU	Rs 2035	s/c or IM
			PFS	150 IU	Rs 2690	s/c or IM
	Eema HMG	HP-FSH + LH (1:1)	Vial	75 IU	Rs 935	s/c or IM
			Vial	150 IU	Rs 1760	s/c or IM
			PFS	150 IU	Rs 1900	s/c or IM
Zydus Healthcare Ltd	**ZyFSH-R**	rFSH (follitropin alfa)	Vial	75 IU	Rs 1978	s/c
			Vial	150 IU	Rs 3846	s/c
	ZyFSH-HP	HP-FSH	Vial	75 IU	Rs 1318	s/c or IM
			Vial	150 IU	Rs 1923	s/c or IM
	ZyHMG-HP	HP-FSH + LH (1:1)	Vial	75 IU	Rs 1088	s/c or IM
			Vial	150 IU	Rs 1747	s/c or IM
	ZyHMG	uFSH + LH (1:1)	Vial	75 IU	Rs 763	IM
			Vial	150 IU	Rs 1083	IM
Bayer	**Menodac**	uFSH + LH (1:1)	Vial	75 IU	Rs 761	IM
			Vial	150 IU	Rs 1080	IM
	Fostine HP	HP-FSH	Vial	75 IU	Rs 1095	s/c or IM
			Vial	150 IU	Rs 1420	s/c or IM

Samarth	**Eugon HP**	HP-FSH + LH (1:1)	Vial	75 IU	Rs 996	s/c or IM
			Vial	150 IU	Rs 1690	s/c or IM
	Euvifol HP	HP-FSH	Vial	75 IU	Rs 1087	s/c or IM
			Vial	150 IU	Rs 1932	s/c or IM
Gufic	**Puregraf HP**	HP-HMG (FSH + LH 1:1)	Vial	75 IU	Rs 825	s/c or IM
			Vial	150 IU	Rs 1530	s/c or IM
	Follicare HP	HP-FSH	Vial	75 IU	Rs 1045	s/c or IM
			Vial	150 IU	Rs 1845	s/c or IM
Sanzyme	**Gynogen HP**	HP-HMG (FSH +LH 1:1)	Vial	75 IU	Rs 1124	s/c or IM
			Vial	150 IU	Rs 1540	s/c or IM
			PFS	150 IU	Rs 1990	s/c or IM
			Multidose vial	600 IU	Rs 5500	s/c or IM
	Endogen	HP HP-FSH	Vial	75 IU	Rs 1397	s/c or IM
			Vial	150 IU	Rs 2090	s/c or IM
Gland Pharma	**Folliglan F**	HP-FSH	Vial	75 IU	Rs 1533	s/c or IM
			Vial	150 IU	Rs 2133	s/c or IM
			PFS	150 IU	Rs 2633	s/c or IM
	Folligan MG	HP-HMG (FSH +LH 1:1)	Vial	75 IU	Rs 1133	s/c or IM
			Vial	150 IU	Rs 1533	s/c or IM
			PFS	150 IU	Rs 1633	s/c or IM
			Multidose vial	600 IU	Rs 5533	s/c or IM
Gynova **a division of Zydus Healthcare Ltd**	**ZyFSH-R**	rFSH (follitropin alfa)	Vial	75 IU	Rs 1978	s/c
			Vial	150 IU	Rs 3846	s/c
	ZyFSH-HP	HP-FSH	Vial	75 IU	Rs 1318	s/c or IM
			Vial	150 IU	Rs 1923	s/c or IM
	ZyHMG-HP	HP-FSH + LH (1:1)	Vial	75 IU	Rs 1088	s/c or IM
			Vial	150 IU	Rs 1747	s/c or IM
	ZyHMG	uFSH + LH (1:1)	Vial	75 IU	Rs 763	s/c or IM
			Vial	150 IU	Rs 1083	s/c or IM

GONAL F (FIGURE : 8)

LUVERIS (FIGURE : 9)

MENOPUR (FIGURE : 10)

MENOGON (FIGURE : 11)

RECAGON (FIGURE : 12)

FOLLISURGE (FIGURE : 13)

MENOTAS (FIGURE : 14)

HUMOG (FIGURE : 16)

FOLLIGRAF (FIGURE : 15)

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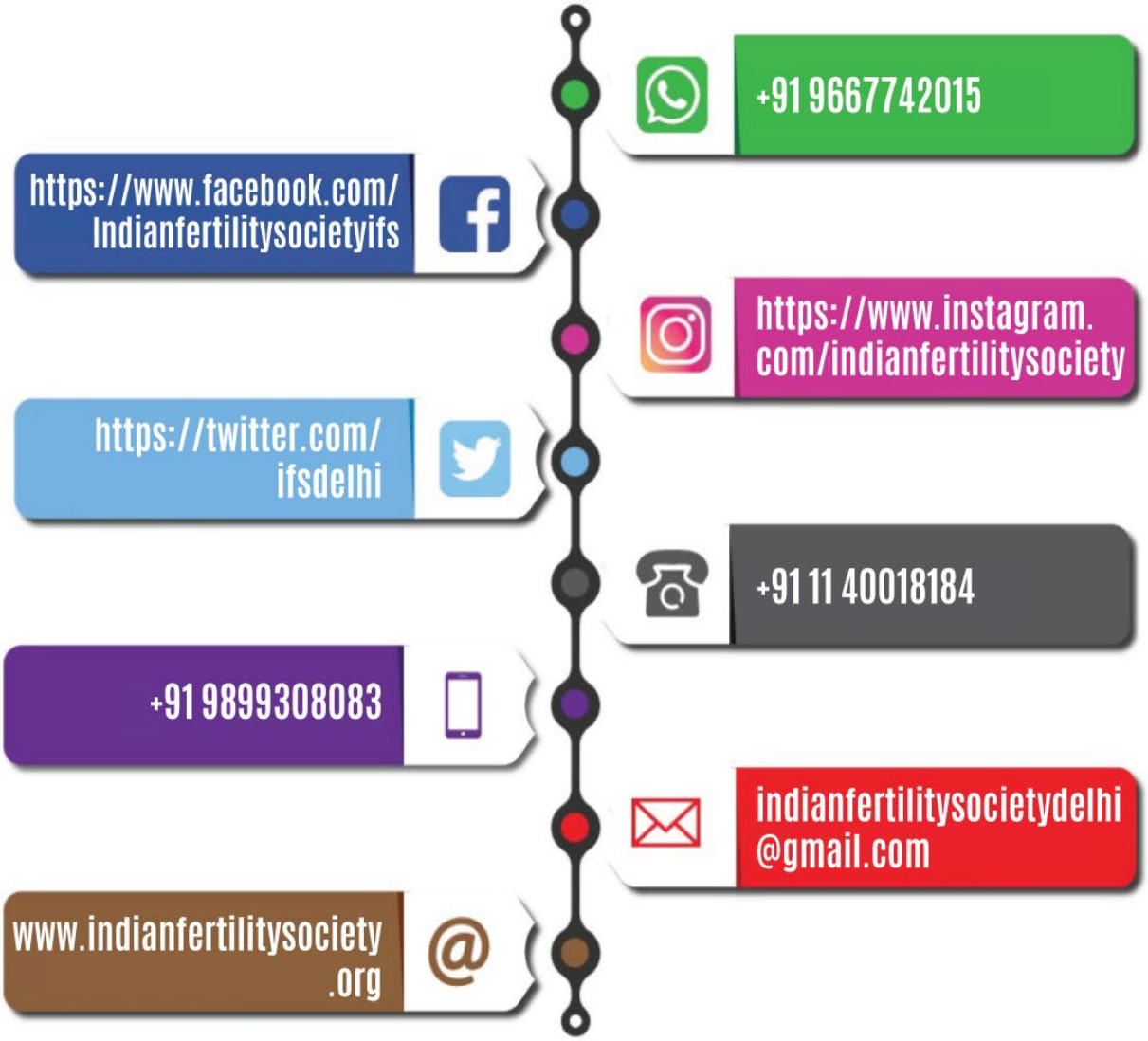

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