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Ovulation Induction Simplified

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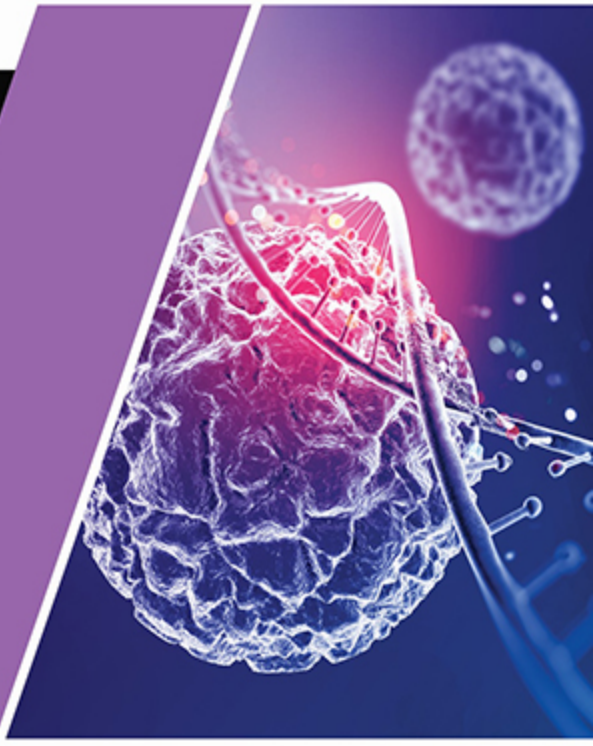

Forewords
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JAYPEE

Contents

SECTION 1: Endocrinology of Nonstimulated and Stimulated Cycles

1. **Endocrinology of Stimulated and Nonstimulated Cycle: Follicular Phase 3**
   Jaideep Malhotra, Kalyani Shrimali, Neharika Malhotra
2. **Luteal Phase Mystery of Nonstimulated and Stimulated Cycles 13**
   Sonal Karia

SECTION 2: Ovarian Reserve Markers

3. **Biomarkers of Ovarian Reserve: Appraisal of Prediction and Results 25**
   Seema Pandey
4. **Markers of Ovarian Reserve 38**
   Elpiniki Chronopoulou, Anil Gudi

SECTION 3: Flow Matters

5. **Color Mapping of Follicle in Controlled Ovarian Hyperstimulation 49**
   Sonal Panchal, Chaitanya Nagori
6. **Evaluation and Monitoring of Endometrium in Controlled Ovarian Hyperstimulation 67**
   Sonal Panchal, M Lipika

SECTION 4: Ovulation Induction/Ovarian Stimulation—Armamentarium of Ovulogens

7. **Selective Estrogen Receptor Modulators: Clomiphene Citrate and Tamoxifen 87**
   Sujata Kar, Megha Gupta
8. **Aromatase Inhibitors 100**
   Rekha Pillai, Hazel Mehlawat, Meenakshi Choudhary
9. **Gonadotropins: Follicle-stimulating Hormone, Luteinizing Hormone, and Human Menopausal Gonadotropin 113**
   Rishma Dhillon Pai, Unnati Mamtora, Arnav Hrishikesh Pai

SECTION 5: Trigger it Right

10. **Human Chorionic Gonadotropin: Not a Panacea Anymore 127**
    Anupama Ravi Futela, Ashadeep Chandrareddy

11. Analog Trigger: Are We Missing the Target? 147
Yuval Atzmon, Einat Shalom-Paz

12. Dual Trigger: It Works! 159
Rachana Sameer Deshpande, Padma Rekha Jirge

SECTION 6: Downregulate it Right

13. Gonadotropin-releasing Hormone Analogs: Agonist and Antagonist 173
Madhuri Patil

14. Pretreatment in In Vitro Fertilization Cycles: Does it Work? 194
Aleyamma TK, Treasa Joseph, Mohan Shashikant Kamath

SECTION 7: Determinants of an Optimal Protocol

15. Determinants of an Optimal Protocol 211
Seema Pandey, Shreya Gowni, Vidhu Modgil

SECTION 8: Ovarian Stimulation Protocols for IUI Cycle

16. Ovarian Stimulation Protocols in Intrauterine Insemination 231
Sunita Tandulwadkar, Bushra Khan, Rashmika Gandhi

17. Ovarian Stimulation Protocols for Normoresponders 245
Laurel Stadtmauer, Xuaochong Liu, Jayapriya Jayakumaran

18. Ovarian Stimulation Protocols for Hyper-responders 257
Seema Pandey, Sini Venugopal

19. Ovarian Stimulation Protocols for Poor Responders 275
Gautam Khastgir, Utpala Sen

20. Stimulation Protocols for Fertility Preservation 288
Kamal Ojha, Biswanath Ghosh Dastidar

SECTION 9: Adjuvants: Do they Work?

21. Adjuvants in Assisted Reproductive Technology 301
Nandita Palshetkar, Rohan Palshetkar

22. Insulin Sensitizers: Metformin and Inositols 310
N Sanjeeva Reddy, Radha Vembu

SECTION 10: Luteal Phase Support

23. Luteal Phase Support in Intrauterine Insemination Cycles 329
Bhavana Mittal, Chandana Bhat

24. Luteal Phase Support in Assisted Reproductive Technology Cycles: Fresh and Frozen Embryo Transfer 339
Anu Chawla, Manisha Nandi

SECTION 11: Complications of Ovarian Stimulation

25. Complications Encountered during Oocyte Retrieval 345
Ameet S Patki, Khyati R Pandya

26. Ovarian Hyperstimulation Syndrome: Prevention and Cure 352
Kedar Ganla, Rana Choudhary, Priyanka Harshavardhan Vora

SECTION 12: Mixed Bag

27. Mild and Minimal Stimulation 369
Bushra Khan, Sunita Tandulwadkar

28. Dual Stimulation 379
Hrishikesh D Pai, Sheetal Sawankar

29. Low-cost In Vitro Fertilization 390
Priya Bhave, Ashita Punjabi Hakhoo

30. Immunotherapy in Assisted Reproduction Treatment 398
Sapna Ahuja

31. Fertility Toolbox 415
Mrinmayi Dharmadhikari, Ameet S Patki

Index 435

Chapter 16

Ovarian Stimulation Protocols in Intrauterine Insemination

Sunita Tandulwadkar, Bushra Khan, Rashmika Gandhi

INTRODUCTION

Infertility has impacted millions worldwide, National Health Service (NHS) UK in 2021 estimated that one in every couple is suffering from inability or difficulty in conceiving. Infertility is commonly defined as the inability of a couple to conceive after 12 months of regular, unprotected intercourse in women <35 years of age, and after 6 months in women 35 years and older.[1]

OVARIAN STIMULATION AND INTRAUTERINE INSEMINATION

Intrauterine insemination (IUI) stands as one of the most performed procedures in assisted reproductive technology for treating infertility. Controlled ovarian hyperstimulation (COH) serves as a crucial initial step in the process of IUI.

Intrauterine insemination can be conducted in either the natural cycle or in conjunction with COH. The objective of IUI is to enhance pregnancy rates by increasing the number of dominant follicles per cycle, achieved through elevating serum follicle-stimulating hormone (FSH) levels, and increasing the number of sperms reaching the fallopian tubes and successfully resulting in higher fertilization. Agents that boost FSH serum levels to stimulate ovary encompass oral ovulogens such as clomiphene citrate (CC), letrozole, and exogenous gonadotropins. Historically, these above-mentioned drugs were developed and utilized to induce follicular growth and ovulation in anovulatory women or in patients with irregular cycles. However, more recently like from the mid-90s evidence developed that ovulation induction is recommended in ovulatory patients as well, especially in unexplained infertility. Cochrane library in 2021 republished their review on drugs used for ovulation induction in IUI since there was no clear consensus from innumerable research conducted on the above topic.[2] The review considered various combinations with clomiphene, letrozole, and gonadotropins alone and in combination, they also considered multifollicular growth versus monofollicular growth in IUI cycles, a fair consideration was emphasized in

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chances of multiple gestation when different protocols were used and main focus was laid on the fact that cycles were cancelled when more than three follicles developed. Although in vitro fertilization (IVF) per-cycle pregnancy rate is higher than in IUI, however, it is also the most expensive and invasive treatment.[3] A randomized controlled trial (RCT) conducted by Bensdorp and colleagues showed that live birth rates (LBRs) between three cycles of IVF with single embryo transfer and six cycles of IUI with ovarian stimulation were similar, and, therefore, IUI-OS should be advised as the treatment of first choice before IVF.[4]

DEVELOPMENT OF OVARIAN STIMULATING AGENTS

In early 20th century, scientists noticed that patients with pituitary lesions had atrophy of gonads, which resulted in discovery of pituitary gonadotropins, previously known as Prolan A and Prolan B by Fevold et al. in 1931.[5] Thereafter, FSH and luteinizing hormone (LH) were both isolated and purified initially from animal serum and later from urine of postmenopausal women which led to the discovery of human menopausal gonadotropin (hMG). Second important discovery was when the first estrogen antagonist tested in cancer patients also induced ovulation.

Different types of ovulation inducing drugs:

- *Oral:*
  - Clomiphene citrate
  - Letrozole
  - Anastrozole
  - Tamoxifen
- *Injectable:*
  - HP-hMG (highly purified human menopausal gonadotropin)
  - RecFSH (recombinant FSH)

CLOMIPHENE CITRATE

Clomiphene citrate belongs to selective estrogen receptor modulators (SERMs) group. They interact with estrogen receptors (ERs) within a target organ. However, CC structurally is a nonsteroidal derivative of triphenylchloroethylene. CC is very similar to estrogen hence it attaches to the ERs easily. Commercially, CC is available as a racemic mixture comprising two isomers: 38% zuclomiphene and 62% enclomiphene.[6]

Mechanism of Action

Clomiphene citrate binds to ERs in the hypothalamus, blocking the estrogen feedback loop and leading to increased levels of GnRH (gonadotropin-releasing hormone), which in turn stimulates pituitary gonadotropin

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secretion and promotes follicular development in the ovaries. CC also exerts direct effects on both the pituitary gland and the ovaries. However, its antiestrogenic effects at the level of the endometrium or cervix can occasionally have adverse effects on fertility in a minority of individuals.[7]

Indications for using CC in IUI patients:

- Anovulatory polycystic ovary syndrome (PCOS)
- Unexplained infertility
- Mild male factor for superovulation

Treatment Protocols

Standard Protocol

A baseline transvaginal ultrasound (TVS) should be performed between day 1 and 3 of the menstrual cycle to confirm the absence of any large follicles or cysts from the previous cycle before initiating treatment. CC therapy is typically initiated between day 2 and 5 of the cycle, starting on the day of spontaneous or induced bleeding, and administered for a total of 5 days. Initiating clomiphene earlier may stimulate the maturation of multiple follicles. The initial dose is usually 50 mg daily for 5 days. Studies have shown that the pregnancy rate remains consistent whether starting at 50 mg or 100 mg per day.[8] Side effects begin at the 50 mg dose, with potentially more serious reactions at 100 mg. Approximately, 50% of patients conceive with the 50 mg dose, and an additional 20% conceive with 100 mg.[9]

Ultrasound monitoring begins from day 9 of the menstrual cycle to track follicular growth and endometrial thickness. This monitoring serves to assess treatment progress and can help differentiate between CC failure (failure to conceive despite successful ovulation) and clomiphene resistance (failure to induce ovulation). If ovulation is not achieved, the dosage is increased incrementally by 50 mg up to a maximum of 150 mg daily for 5 days, although the FDA recommends a maximum daily dose of 100 mg. The highest dosage is typically maintained for 3–4 months before considering the patient unresponsive to CC. Most experts advise against exceeding 150 mg per day due to concerns about efficacy and safety.[7]

Mature follicle is expected to occur 5–10 days after the last day of therapy. When dominant follicle develops, hCG 5,000–10,000 IUI or recombinant hCG 250 μg is given to induce final follicular maturation and to ensure that ovulation is timed optimally with respect to follicular growth and IUI.

Stair-step Protocol

Traditionally stair-step protocol is used in patients where only 5 days of CC has not worked and instead of cancelling the cycle, one can step up the CC dose and monitor after another 5 days. Studies revealed similar LBR as

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standard CC protocol. Stair-step protocol may be available as an alternative for PCOS patients.

Side Effects of Clomiphene Citrate

- Antiestrogenic effects on cervical mucus and endometrial lining can affect the quality of cervical mucus, making it less favorable for sperm transport, reducing its implantation potential.
- Other causes of infertility also associated with ovulatory dysfunction such as tubal factors, severe endometriosis, and male factor infertility.
- *Lack of persistence:* Successful conception with CC often requires consistent timing of intercourse or IUI around ovulation. Lack of persistence in timing attempts to conceive during the fertile window can contribute to lower pregnancy rates despite ovulation induction.[10]

These factors highlight the complexity of achieving pregnancy with CC and underscore the importance of comprehensive evaluation and management tailored to individual patient needs in infertility treatment.

Side effects:

- Vasomotor flushes—10%
- Abdominal distention, bloating, soreness, pain—5.5%
- Breast discomfort—2%
- Nausea, vomiting—2.2%
- Headache—1.3%
- Visual symptoms 1.5%—CC should be promptly discontinued
- Dryness or loss of hair—0.3%
- Ovarian enlargement—5%; delay in next cycle treatment
- Increased risk of ectopic pregnancy
- Multiple pregnancy 5–8%
- Ovarian hyperstimulation syndrome (OHSS)

TAMOXIFEN

Tamoxifen is another SERM and has similar actions like CC without its side effects on cervical mucus and endometrium. It is administered at a dosage of 40 mg daily for 5 days starting between day 2 and 5.

LETROZOLE

Letrozole, as an aromatase inhibitor, functions similarly to CC in initiating gonadotropin release but through a different mechanism. Unlike CC, which blocks ERs to create an apparent estrogen-deficient state in the pituitary, letrozole works by reducing blood estrogen levels through inhibition of aromatase, the enzyme responsible for converting androgens to estrogens. This reduction in estrogen levels leads to a more pronounced initial release of FSH compared to CC.[11]

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Moreover, letrozole offers additional benefits. Despite inducing an estrogen-deficient environment, it does not adversely affect the endometrium or cervical mucus due to its short half-life (approximately 45 hours). In contrast, CC's ER-blocking action persists for about 2 weeks, resulting in an estrogen-deficient state despite adequate estrogen levels in the bloodstream. This difference can impact endometrial receptivity and cervical mucus quality, potentially affecting embryo implantation.

Furthermore, letrozole may enhance follicular sensitivity to FSH by increasing the expression of FSH receptor genes peripherally. This mechanism contributes to improved follicular growth and development, which are crucial for successful ovulation and subsequent embryo implantation.

Overall, compared to CC, letrozole offers superior outcomes in terms of follicular growth, endometrial development, and potentially higher pregnancy rates. These advantages make letrozole a preferred choice for ovulation induction in certain patient populations, particularly those where optimizing endometrial conditions is critical for achieving pregnancy.[11]

Advantages

- *Monofollicular ovulation:* Aromatase inhibitors promote the development of a single dominant follicle, reducing the likelihood of multiple pregnancies compared to agents like gonadotropins. This also lowers the risk of severe OHSS.
- *No antiestrogenic effects on endometrium or cervix:* Unlike CC, aromatase inhibitors do not exert antiestrogenic effects on the endometrium or cervical mucus, potentially improving endometrial receptivity for implantation.
- *High safety profile:* Aromatase inhibitors have a short half-life and are associated with fewer adverse effects compared to other ovulation induction agents. This makes them generally well-tolerated by patients.
- *Higher pregnancy rates:* Studies have shown that aromatase inhibitors may offer higher pregnancy rates compared to CC, particularly in certain patient populations such as those with PCOS.

Treatment Protocol

Standard Protocol

The commonly practiced protocol for letrozole involves a daily dosage of 5 mg taken once daily for 5 consecutive days, typically administered from day 3 to 7 of the menstrual cycle. This regimen was initially adapted from a similar approach used with CC. Cochrane 2022[10] analysis showed that letrozole appears to improve LBRs in infertile women when used in comparison with CC. There is no difference in miscarriage rates and multiple pregnancy rates. Many studies have stated that letrozole and CC have similar

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pregnancy rates whereas there have been few which say that letrozole has better pregnancy rates.[11,12]

Extended Protocol

A longer administration protocol, where letrozole is taken from day 1 to 10 of the cycle at a lower dose of 2.5 mg daily, has been proposed. Comparative studies have shown that this extended 10-day regimen leads to significantly greater numbers of mature follicles and higher pregnancy rates compared to the standard 5-day protocol. Specifically, research indicates an average of 6.7 follicles with the 10-day regimen versus 3.9 follicles with the 5-day regimen. Pregnancy rates also show improvement, with 17.4% achieved with the 10-day protocol compared to 12.4% with the 5-day regimen.[13]

The potential mechanism behind these findings suggests that the longer duration of letrozole treatment allows for more follicular growth and maturation, thereby enhancing the chances of successful ovulation and subsequent pregnancy. This extended protocol may be particularly beneficial for patients who have not responded optimally to the standard 5-day regimen or who require a more robust follicular response.[14]

In clinical practice, the choice between the 5-day and 10-day letrozole protocols should consider individual patient factors, treatment goals, and the need for balancing efficacy with safety.

Aromatase Inhibitors Combined with Gonadotropins in Ovarian Stimulation for IUI

In a sequential regime, letrozole 2.5 mg was given from cycle days 3 to 7 and FSH was added on cycle day 6 and day 8 and ovulation triggered with hCG. The FSH dose required was 50% lower than with standard regimens. In addition, the pregnancy rate with a combination of aromatase inhibitor and FSH was equivalent to FSH alone, and almost twice the level seen with CC and FSH treatment.[15]

Another study[16] compared two groups, a combination of letrozole and FSH or FSH only. The number of growing follicles, the E2 level, and the endometrial thickness were lower in the letrozole group. The pregnancy rates were similar between the two groups, but the multiple pregnancy rate was lower in the combination group ($p < 0.05$).

Gómez et al.[17] randomized patients to undergo treatment with CC/FSH or letrozole/rFSH. Although there was a significantly lower peak serum E level in letrozole/rFSH compared with CC/rFSH (914 ± 187 vs. 1,207 ± 309 pg/mL, respectively; $p < 0.007$), there were no differences in the number of mature (>16 mm) preovulatory follicles. A significantly higher endometrial thickness was observed in the letrozole/FSH group (9.5 ± 1.5 mm vs. 7.3 ± 1.1 mm; $p = 0001$). The clinical pregnancy rates were similar between two groups (23.8% vs. 20%, respectively).

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The risk for multiple pregnancy is about 3–7% overall, and there is no robust evidence proving any teratogenic effects of letrozole as compared with CC.

ANASTROZOLE

Many studies have suggested similar mechanism of action and clinical pregnancy rates as letrozole.[18]

GONADOTROPINS

Gonadotropins were introduced a century ago, a lot of advancement and discovery has been made in last 25 years. Currently, we have the highly purified and rFSH and hMG. Three major gonadotropins are similar in structure as in they are all glycoprotein with similar alpha chain and variable beta chains. Various milestones are described in the **Figure 1**.

Types of Gonadotropins (Table 1)

- *Urinary-derived gonadotropins (uFSH):* These include hMGs, which contain both FSH and LH, and purified FSH (uFSH), extracted from the urine of postmenopausal women.
- *Highly purified human menopausal gonadotropins (HP-hMG):* These are highly purified forms of hMG, with a higher FSH to LH ratio compared to traditional hMG.
- *Highly purified FSH*
- *Recombinant gonadotropins (rFSH):* Produced through recombinant DNA technology, these include recombinant FSH (rFSH) and recombinant LH (rLH).

In Cochrane Database Systematic Review,[19] in which 43 trials involving 3,957 women were included, author concluded that gonadotropins might be more effective in follicular growth during ovarian stimulation in IUI cycles. This review also stated that low dose of gonadotropins was safer especially in PCOS patients, whereas pregnancy rates were not different in low-dose or high-dose gonadotropin cycles.

Comparative Effectiveness of Gonadotropins

Recent studies have provided insights into the comparative effectiveness of various combinations.[2]

- *Gonadotropins versus antiestrogens (13 studies):* For live birth, the results of five studies were pooled and showed improvement in the cumulative LBR for gonadotropins compared to antiestrogens [odds ratio (OR) 1.37, 95% confidence interval (CI) 1.05–1.79; $I^2 = 30\%$]. Although gonadotropins lead to a higher multiple pregnancy rate compared with antiestrogens (OR 1.58, 95% CI 0.60–4.17; $I^2 = 58\%$; 7 studies, 2,139 participants).

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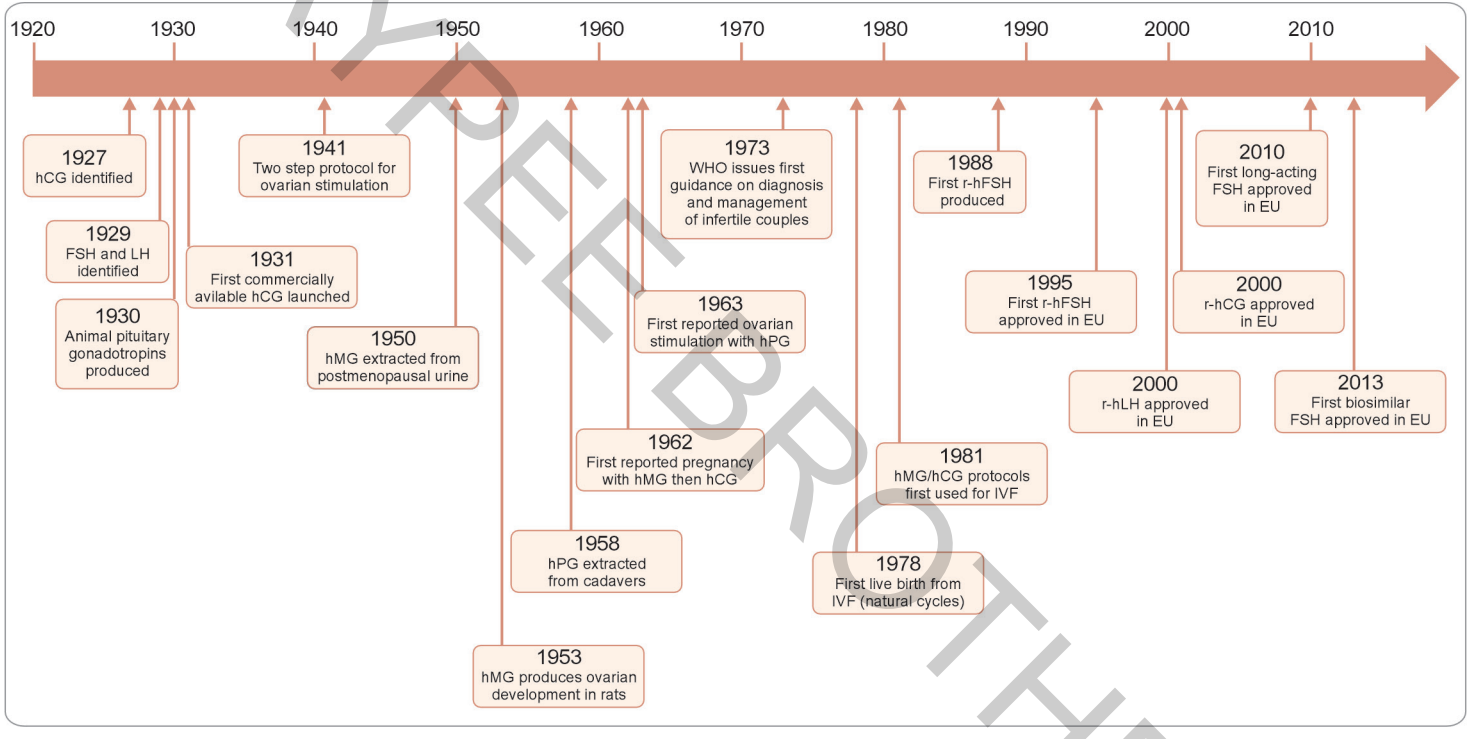

Fig. 1: Milestones in the development of gonadotropin preparations. (FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; hMG: human menopausal gonadotropin; IVF: in vitro fertilization; LH: luteinizing hormone)
Source: Leão Rde B, Esteves SC. Gonadotropin therapy in assisted reproduction: an evolutionary perspective from biologics to biotech. Clinics (Sao Paulo). 2014;69(4):279-93.

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TABLE 1: Differences between gonadotropin formulations.

	Purity (gonadotropin content)	*Mean specific activity (IU/mg protein)*	*LH activity (IU/vial)*	*Injected protein per 75 IU (µg)*
hMG	<5%	~100	75	~750
HP-hMG	<70%	2,000–2,500	75	~33
Rec-hFSH				
Follitropin beta	>99%	7,000–10,000	0	8.1
Follitropin alpha	>99%	13,645	0	6.1
Lutropin alpha (rec-hLH)	>99%	22,000	75	3.7

(FSH: follicle-stimulating hormone; hMG: human menopausal gonadotropin; LH: luteinizing hormone)
Source: Leão Rde B, Esteves SC. Gonadotropin therapy in assisted reproduction: An evolutionary perspective from biologics to biotech. Clinics (Sao Paulo). 2014;69(4):279-93.

- *Aromatase inhibitors versus antiestrogens (8 studies):* Both the drugs have shown similar pregnancy rates.
- *Gonadotropins with GnRH (gonadotropin-releasing hormone) agonist versus gonadotropins alone (4 studies):* Two studies revealed that we are uncertain whether gonadotropins with GnRH agonist lead to a higher multiple pregnancy rate compared to gonadotropins alone (OR 2.53, 95% CI 0.82–7.86; $I^2 = 0$; 2 studies, 264 participants).
- *Gonadotropins with GnRH antagonist versus gonadotropins alone (14 studies):* Three studies reported LBR per couple, but it is uncertain whether gonadotropins with GnRH antagonist improve LBR compared to gonadotropins (OR 1.5, 95% CI 0.52–4.39; $I^2 = 81\%$; 3 studies, 419 participants).
- *Gonadotropins with antiestrogens versus gonadotropins alone (2 studies):* Neither of the studies reported data for LBR. It is uncertain whether gonadotropins combined with antiestrogens lead to a higher multiple pregnancy rate compared with gonadotropins alone, based on one study (OR 3.03, 95% CI 0.12–75.1; 1 study, 230 participants; low-certainty evidence).
- *Aromatase inhibitors versus gonadotropins (6 studies):* Two studies revealed that aromatase inhibitors may decrease LBR compared with gonadotropins (OR 0.49, 95% CI 0.34–0.71; $I^2 = 0\%$; 2 studies, 651 participants; low-certainty evidence).

Rationale for Gonadotropin Use

Gonadotropins are used to directly stimulate the ovaries, promoting the development of multiple follicles. This increases the chances of achieving

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a successful pregnancy in IUI cycles. The goal is to produce one or two dominant follicles while minimizing the risk of multiple pregnancies and OHSS.

There are two primary protocols for ovulation induction: the step-up and step-down protocols. Treatment begins shortly after spontaneous or progesterone-induced bleeding. A baseline vaginal ultrasound scan should be performed to check for ovarian cysts and measure endometrial thickness.

- *Step-up protocol:* After the baseline transvaginal sonography on day 2 of menstrual cycle, gonadotropin at a dose of 37.5–75 U is started depending upon the patients weight for 5 days and it is then stepped up by another 37.5 U. Every 5 days dose can be increased till the time sufficient response is achieved. The gonadotropin dose should not increase above 225 IU/day. A dominant follicle greater than 10 mm is considered an adequate response, and the treatment is continued at the same dose until the day of hCG injection to trigger ovulation.
- *Step-down protocol:* The step-down protocol simulates a natural menstrual cycle. The goal is to quickly achieve an FSH threshold to stimulate a dominant follicle. It begins with 150 IU/day from day 2 of menses until a dominant follicle is observed (>10 mm). The gonadotropin dose is then reduced to 112.5 IU/day, and after 3 days, it is further reduced to 75 IU/day, continuing until the follicle reaches a mature size. If a dominant follicle is not seen after 3–5 days of treatment, the dose is increased by 37.5 IU/day. This protocol typically requires a shorter treatment period but demands strict monitoring.
- *Combination protocols:* Gonadotropins can be used in combination with other agents such as clomiphene or letrozole to enhance follicular development while potentially reducing the amount of gonadotropin required. In such protocols, clomiphene or letrozole is typically administered from cycle days 3–7, followed by gonadotropin injections starting on day 7–9 until the desired follicular response is achieved.[20]

Individualization of Protocol

Foremost point is that indication of ovulation induction should be kept in mind along with duration of infertility, age of female partner, BMI, and serum anti-Mullerian hormone (AMH) levels.

Monitoring

The standard method of monitoring is through vaginal ultrasound scanning (TVS), which is safe, accurate, and effective for evaluating follicular development to be done on day 2 followed by day 7–8 further till the time of trigger by alternate days.

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Timing of Intrauterine Insemination

Ovulation is triggered when at least one follicle or more, measuring ≥18–20 mm, is seen on a transvaginal scan, using either 250 µg of r-hCG or 10,000 IU of urinary hCG. IUI is performed 36–40 hours later and this is done while keeping in mind that the oocyte remains fertilizable for a brief period of time (12–16) hours after ovulation.[21]

Luteal Phase Support

A meta-analysis stated that progesterone luteal phase support improved the chance of a clinical pregnancy after a single OS-IUI cycle in the gonadotropins subgroup [RR 1.56, 95% CI (1.06, 2.31); I^2 = 0%; 6 RCTs, 965 participants; moderate-quality evidence], but not in the gonadotropins + CC [RR 1.39, 95% CI (0.12, 16.33); I^2 = 0%; 2 RCTs, 319 participants].[22]

When to Cancel the Cycle?

A cycle is typically cancelled if more than three follicles have reached a mature size (>16 mm) or if more than four follicles are greater than 12 mm. In such cases, the couple is advised to avoid sexual intercourse. Alternatively, excess follicles can be aspirated, or the cycle can be converted to in vitro fertilization (IVF).

Complications and Side Effects

- Multiple pregnancies
- *Ovarian hyperstimulation syndrome (OHSS):* Usually mild to moderate in IUI cycles

Pregnancy Rates

Pregnancy rates depend on various factors. With gonadotropin stimulation, the pregnancy rate per cycle ranges from 4 to 40%, with a cumulative pregnancy rate of 30–60% in patients under 40 years old after approximately three cycles of IUI. In women under 40, superovulation with gonadotropin and IUI results in a pregnancy rate per cycle of 12.6%, with 11% twin pregnancies and 1.1% triplet pregnancies. For women over 40, the pregnancy rate per cycle is 7.4%, with 4.9% twin pregnancies and 0.7% triplet pregnancies. The number of motile sperm for insemination is also crucial, with the generally accepted cutoff being 1 million motile sperm in the insemination sample.[23]

How Many Cycles Should be done?

In the context of assisted reproductive technologies, we recommend only three cycles of superovulation and IUI. Considerations include cost-effectiveness and the psychological burden of repeated failures to achieve pregnancy.

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Predictive Factors for Successful IUI

- Evidence suggests prewash semen sample of about >5 million and postwash at least 1 million.
- Advanced maternal and paternal age have negative impact on IUI results.[24]
- High DNA fragmentation is not always the cause of fail IUI.
- High BMI can also result in failed cycles.

CONCLUSION

Ovulation induction is a cornerstone of fertility treatment, offering various protocols and medications to optimize outcomes for patients undergoing IUI. Overall, the choice of ovulation induction agent and protocol should be individualized based on the patient's specific clinical scenario, underlying conditions, and response to previous treatments. Advancements in understanding the pharmacodynamics and optimizing the use of these agents continue to improve outcomes, offering hope to many couples struggling with infertility.

KEY POINTS

- Clomiphene citrate has been a long-standing first-line treatment due to its ease of use and favorable cost profile. However, its potential antiestrogenic effects on the endometrium and cervical mucus can sometimes limit its efficacy.
- Letrozole, an aromatase inhibitor, has emerged as an effective alternative, particularly for patients with PCOS. It offers a favorable side effect profile and higher LBRs compared to clomiphene, making it a valuable tool in the fertility specialist's arsenal.
- Gonadotropins provide a more direct stimulation of the ovaries, resulting in higher pregnancy rates, albeit with an increased risk of multiple pregnancies OHSS. Careful monitoring and individualized dosing protocols, such as the step-up and step-down approaches, are essential to mitigate these risks.
- The introduction of GnRH antagonists has further refined ovulation induction protocols. Their use can enhance the number of mature follicles and improve pregnancy rates, as evidenced by recent studies. However, the associated risk of multiple gestations necessitates careful consideration and patient counseling.

REFERENCES

1. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: A committee opinion. Fertil Steril 2020;113(3):533-5.

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2. Cantineau AEP, Rutten AGH, Cohlen BJ. Agents for ovarian stimulation for intrauterine insemination (IUI) in ovulatory women with infertility. Cochrane Database Syst Rev. 2021;(11):CD005356.
3. Tjon-Kon-Fat RI, Bensdorp AJ, Bossuyt PM, Koks C, Oosterhuis GJ, Hoek A, et al. Is IVF - served two different ways - more cost-effective than IUI with controlled ovarian hyperstimulation? Hum Reprod. 2015;30(10):2331-9.
4. Bensdorp AJ, Tjon-Kon-Fat RI, Bossuyt PM, Koks CA, Oosterhuis GJ, Hoek A, et al. Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. BMJ. 2015;9(350):g7771.
5. Fevold SL, Hisaw FL, Leonard SL. The gonad-stimulating and the luteinizing hormones of the anterior lobe of the hypophysis. Am J Physiol. 1931;97:291-301.
6. Mbi Feh MK, Patel P, Wadhwa R. (2024). Clomiphene. [online] Available from https://www.ncbi.nlm.nih.gov/books/NBK559292/. [Last accessed August, 2024]
7. Brown J, Farquhar C. Clomiphene and other antioestrogens for ovulation induction in polycystic ovarian syndrome. Cochrane Database Syst Rev. 2016;(12):CD002249.
8. Speroff L, Fritz MA. Clinical Gynecologic Endocrinology and Infertility, 7th edition. Philadelphia: Lippincot Williams Wilkins; 2005.
9. Osmanlıoğlu Ş, Şükür YE, Tokgöz VY, Özmen B, Sönmezer M, Berker B, et al. Intrauterine insemination with ovarian stimulation is a successful step prior to assisted reproductive technology for couples with unexplained infertility. J Obstet Gynaecol. 2022;42(3):472-7.
10. Teede HJ, Tay CT, Laven JJE, Dokras A, Moran LJ, Piltonen TT, et al.; International PCOS Network. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Eur J Endocrinol. 2023;189(2):G43-G64.
11. Franik S, Le Q-K, Kremer JAM, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for ovulation induction in infertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2022;(9):CD010287.
12. Peng G, Yan Z, Liu Y, Li J, Ma J, Tong N, et al. The effects of first-line pharmacological treatments for reproductive outcomes in infertile women with PCOS: A systematic review and network meta-analysis. Reprod Biol Endocrinol. 2023;21(1):24.
13. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, et al.; NICHD Reproductive Medicine Network. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med. 2014;371(2):119-29.
14. Badawy A, Mosbah A, Tharwat A, Eid M. Extended letrozole therapy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a novel protocol. Fertil Steril. 2009;92:236-9.
15. Pavone ME, Bulun SE. Clinical review: The use of aromatase inhibitors for ovulation induction and superovulation. J Clin Endocrinol Metab. 2013;98(5):1838-44.
16. Nuojua-Huttunen S, Tomas C, Bloigu R, Tuomivaara L, Martikainen H. Intrauterine insemination treatment in subfertility: An analysis of factors affecting outcome. Hum Reprod. 1999;14(3):698-703.

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17. Gómez-Palomares JL, Juliá B, Acevedo-Martín B, Martínez-Burgos M, Hernández ER, Ricciarelli E. Timing ovulation for intrauterine insemination with a GnRH antagonist. Hum Reprod. 2005;20(2):368-72.
18. van Wely M, Kwan I, Burt AL, Thomas J, Vail A, Van der Veen F, et al. Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles. Cochrane Database Syst Rev. 2011;(2):CD005354.
19. Weiss NS, Kostova E, Nahuis M, Mol BJ, van der Veen F, van Wely M. Gonadotrophins for ovulation induction in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2019;(1):CD010290.
20. Cabry-Goubet R, Scheffler F, Belhadri-Mansouri N, Belloc S, Lourdel E, Devaux A, et al. Effect of Gonadotropin Types and Indications on Homologous Intrauterine Insemination Success: A Study from 1251 Cycles and a Review of the Literature. Biomed Res Int. 2017;2017:3512784.
21. Firouz M, Noori N, Ghasemi M, Dashipour A, Keikha N. Comparing the Effectiveness of Doing Intra-uterine Insemination 36 and 42 Hours After Human Chorionic Gonadotropin (HCG) Injection on Pregnancy Rate: A Randomized Clinical Trial. J Family Reprod Health. 2020;14(3):173-9.
22. Casarramona G, Lalmahomed T, Lemmen CHC, Eijkemans MJC, Broekmans FJM, Cantineau AEP, et al. The efficacy and safety of luteal phase support with progesterone following ovarian stimulation and intrauterine insemination: A systematic review and meta-analysis. Front Endocrinol. 2022;13:960393.
23. Cicek OS, Demir M. The impact of gonadotropin type on controlled ovarian stimulation and intrauterine insemination cycle outcomes. J Hum Reprod Sci. 2022;15:51-7.
24. Starosta A, Gordon CE, Hornstein MD. Predictive factors for intrauterine insemination outcomes: A review. Fertil Res Pract. 2020;6(1):23.

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"A book is a garden, an orchard, a storehouse, a party, a company by the way, a counselor, a multitude of counselors."
—*Charles Baudelaire*

Ovulation Induction Simplified is the dream child of MSAR President Dr Sunita Tandulwadkar. This is a book about the intricacies of assisted reproductive technology (ART) in our day-to-day practice. With the help of her coeditors, she has tried to make it practical, to the point, and evidence based. Strong and solid foundation is the way to building the block of success and realizing that the book begins with the basic endocrinology and physiology of an ovarian cycle, stimulated and nonstimulated one. The book has been divided into different sections like armamentarium of drugs which deals with drugs available for ovarian controlled hyperstimulation, downregulation of the cycles, how to trigger, and available protocols followed by luteal phase support. The unique part of the book is that it does not leave the readers on guiding protocols but also talks about the complications of oocyte pick-up (OPU) and discusses the determinants of a successful cycle too. The best part of the book is that each and every topic has been curated by people who are the best in their field. To conclude, *Ovulation Induction Simplified* is a delight to read.



Sunita Tandulwadkar MD (Obs & Gyne) FICS (Gyne-Endoscopy) FICOG is a distinguished figure in the realm of obstetrics and gynecology, in vitro fertilization (IVF), and endoscopy. She is renowned for her exceptional contributions and numerous awards. Hailing from India, her journey began with a strong passion for women's health and reproductive medicine, thus shaping her illustrious career. She currently holds the esteemed position of Head, Department of Obstetrics and Gynecology, Ruby Hall Clinic, Pune, Maharashtra, India, and is also the Chief of Ruby Hall IVF and Endoscopy Centre and the Director of DY Patil IVF and Endoscocpy Centre, Pune, where she leads groundbreaking advancements. Currently, she is the President Elect FOGSI (2025–2026) and President Elect ISAR (2026–2027).

She is a pioneer in endoscopy in India, advocating minimally invasive surgical techniques and conducting innovative research, positively impacting patients. She founded Solo Stem Cells, a stem cells research and application center, pioneering stem cell treatments, including India's first stem cell baby at the age of 45 years. Her accolades include leadership roles in medical organizations, prestigious awards, and serving as a sought-after speaker and keynote address giver. Her philanthropic efforts include co-founding the Solo Research Foundation, dedicated to improving healthcare accessibility. Her legacy embodies unwavering commitment, innovation, and compassion in healthcare, shaping obstetrics and gynecology, IVF, and endoscopy fields, and inspiring countless individuals.



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He has been Chairperson, Perinatology Committee of FOGSI, and on the Governing Council of ICOG for over 12 years. He is the Past President of Mumbai OBGYN Society, Chairperson, West Zone, India RCOG and Country Representative at ASPIRE. He has been a TEDx speaker since 2017, the first gynecologist and infertility specialist doctor from Mumbai. He has been a recipient of FOGSI Corion Award 2003 for best research in India, MOGS Young Scientist Award 2005, and MOGS Dr Ganatra Charitable Medical Centre Award. He has been a recipient of the Dina Patel Gold Medal for standing first in the Fellow of College of Physicians and Surgeons (FCPS) exams. He has won the Indumati Jhaveri prize in the junior category, AICOG, in 1990 and the C S Dawn Award, AICOG, in Chennai in 2015. He has been awarded the prestigious AOFOG—Young Gynecologist Award at Seoul, Korea, in 2005. He has been conferred as a Fellow of the Royal College, London, in September 2008. He is the President of ISAR (Indian Society for Assisted Reproduction), which has more than 6,000 members, for 2 years (2024–2026).



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