

CURRENT STUDIES IN  
**OBSTETRICS AND  
GYNAECOLOGY**  
**III**

**Editor**  
**Deniz TAŞKIRAN**



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## **Current Studies in Obstetrics and Gynaecology III**

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## PREFACE

Women's health is one of the fundamental pillars of human well-being. Advances in gynecology and obstetrics not only improve individual health outcomes but also contribute significantly to public health and social welfare. With the rapid development of assisted reproductive technologies, more individuals today have the opportunity to realize their dreams of parenthood. These advancements continue to evolve alongside the growing body of scientific knowledge and technological innovation.

This book was prepared to present up-to-date information and current practices in the fields of gynecology, obstetrics, and assisted reproductive techniques. Developed with the contributions of experienced physicians, academics, and clinicians, it aims to serve as a comprehensive and reliable resource for both medical students and healthcare professionals seeking to enhance their clinical practice.

In a rapidly evolving medical landscape, staying current is essential—especially in sensitive and dynamic areas such as reproductive health. We hope this book will support readers in updating their knowledge, guide clinical decision-making, and contribute to the delivery of high-quality women's healthcare.

We extend our sincere gratitude to all the authors, editors, and colleagues who contributed to the creation of this work.

We hope this book will serve as a valuable and practical reference for all those dedicated to the field of women's health.

**Editor**

Asst. Prof. Deniz TAŞKIRAN



# CONTENTS

<b>PREFACE</b>	<b>I</b>
<b>CHAPTER I. POLYCYSTIC OVARY SYNDROME</b>	<b>1</b>
<i>Seniye Burcu TORUMTAY ALIÇ</i>	
<b>CHAPTER II. POLYCYSTIC OVARY SYNDROME (PCOS) AND INFERTILITY: METABOLIC, IMMUNOLOGIC AND THERAPEUTIC INTERSECTIONS</b>	<b>17</b>
<i>Soner DÜZGÜNER</i>	
<b>CHAPTER III. OVARIAN STIMULATION: CYCLE ESSENTIALS FOR MANAGING A CYCLE</b>	<b>23</b>
<i>Gerçek AYDIN</i>	
<b>CHAPTER IV. APPROACH TO INTRAUTERINE INSEMINATION</b>	<b>39</b>
<i>Ufuk ATLIHAN &amp; Mehmet Emre PEKER</i>	
<b>CHAPTER V. CURRENT APPROACHES TO ANTENATAL CORTICOSTEROID THERAPY</b>	<b>57</b>
<i>Ufuk KURT</i>	
<b>CHAPTER VI. USE OF MESH IN PELVIC ORGAN PROLAPSE: CURRENT GUIDELINES AND CONTROVERSIES</b>	<b>75</b>
<i>Mehmet Emre PEKER &amp; Ufuk ATLIHAN</i>	
<b>CHAPTER VII. PSYCHOLOGICAL SYMPTOM SCREENING IN PREGNANT WOMEN WITH HYPEREMESIS GRAVIDARUM</b>	<b>81</b>
<i>İsa Şükrü ÖZ</i>	
<b>CHAPTER VIII. THE ROLE OF ENDOMETRIAL STEM CELLS IN FEMALE REPRODUCTIVE HEALTH: DISEASES AND THERAPEUTIC APPROACHES</b>	<b>87</b>
<i>Oya KORKMAZ</i>	

## CHAPTER III

# OVARIAN STIMULATION: CYCLE ESSENTIALS FOR MANAGING A CYCLE

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### **1-Introduction**

**T**his section discusses ovarian stimulation, the cornerstone of infertility treatment. While ovarian reserves and targeted responses may vary depending on the patient's characteristics and the clinician's assessment, the primary goal is the same for all: to obtain the most appropriate and sufficient response without causing any harm. This section not only provides definitions but also highlights the key steps in managing an ovarian stimulation cycle, beginning with ovulation induction as the initial treatment and extending to IVF as the most advanced option.

Infertility management encircles a spectrum of treatment modalities: Ovulation induction (OI), intrauterine insemination (IUI) and in vitro fertilization (IVF). All these options require an ovarian stimulation (OS) process with different specifications. For anovulatory women, such as those with polycystic ovary syndrome (PCOS) or hypothalamic dysfunction, OI aims to restore mono-follicular development with a therapeutic objective to mimic natural physiology. IUI cycles, being higher level process than OI, aim to achieve more than one dominant follicles, balancing increased chances of conception against the risks of multiple gestation. IVF represents a more advanced intervention. Here, the goal is to maximize the number of retrievable mature oocytes in a single cycle, thereby enhancing the embryo pool for transfer or cryopreservation. During an

IVF cycle, a complex thinking process is required for avoiding the risks (multiple gestations, OHSS, patient discomfort, costs) while promising the highest level of conception.

## 2-Physiology Of Follicular Development

OS is established through the classical two-cell, two-gonadotropin concept, which integrates granulosa and theca cell function under the influence of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

- **FSH** stimulates granulosa cells, driving aromatase expression and converting androgens into estradiol. Estradiol promotes granulosa proliferation and primes the endometrium.
- **LH** stimulates theca cells to convert cholesterol into progesterone and subsequently into androgens, which serve as substrates for granulosa aromatization.

As follicles develop, granulosa cells in the dominant follicle acquire LH receptors, enabling continued growth despite falling FSH levels. Non-dominant follicles, lacking adequate LH receptor expression, undergo atresia. LH, then not only acts as a regulator of steroidogenesis but also supports granulosa cells.

The maturation of a single leading follicle is facilitated by this hormonal balance, preparing the environment for successful ovulation and potential fertilization (1). This delicate interplay ensures monofollicular ovulation in natural cycles. In ART, sustained and supraphysiological doses of FSH exposure overrides this mechanism, allowing multiple follicles to mature simultaneously, thereby enabling retrieval of multiple oocytes.

## 3-Ovulation Induction (OI)

One of the most important take home messages in this topic maybe its definition. Therefore, catching the meaning of **ovulation induction** is important. As to “induce” means to initiate something which is stable and/or in steady state, it is different from the term “augmentation” that facilitates something which is already in progress.

Given this, ovulation induction also refers to “initiate” ovulation. It is important that in daily clinical practise this issue seems to be overtreated. When women or a couple admit to a gynecologist, sometimes OI medications are started despite the woman does not really reveal a history for oligo or anovulation.

So, administering OI agents to a women who is already ovulatory will not add any benefit, yet some disadvantages. Although the oral OI agents are safe and complications are seldom and cause light discomfort, severe complications like myocardial infarction and retinal vein thrombosis may also be encountered, although they are rare. Thus, OI must be programmed only for oligo and/or anovulatory women.

OI is the 1st line medical approach for in infertility, after life style modifications. When the time is not a concern, a 3-6 month period will be required to progress to the next level, assisted reproductive techniques (ART). OI aims to help women to ovulate. Once ovulation is achieved, the quality of the oocyte and sperm, their encounter and the anatomy must all be in harmony to achieve a conception, which is not a very high probablity in one single month. Therefore describing “what is OI, what it is not” is crucial in the first visit.

Selective estrogen receptor modulators (SERM), most commonly clomiphen citrate (CC) and aromatase inhibitör (most commonly letrozole) are most frequently used oral agents. In resistant cases, gonadotropins can be administered. In such cases, as many of the resistant cases are hyperresponder PCOS patients, care should be served for ovarian hyper stimulation (OHSS) risk, and the couple should be informed about the estimated cost. Being very rare, one must keep in mind that OHSS can also be a case for oral agent-used cases. The FSH receptor polymorphism is probably the etiology.

#### **4-Rationale For Controlled Ovarian Stimulation (COS)**

COS is a pivotal step in IVF. Recombinant FSH (r-FSH) alone can successfully induce follicular growth following pituitary downregulation because residual endogenous LH secretion is rarely entirely suppressed. Still, LH contributes to recruitment, maturation, and endometrial preparation. Limited LH activity during COS may compromise oocyte competence and subsequent embryo implantation. Therefore, supplementation with recombinant LH (r-LH) or in combination with FSH-LH regimes (human menopausal gonadotropins-HMG) has been proposed to optimize follicular development.

The rationale for COS is not simply to increase follicle number but to balance oocyte competence with endometrial receptivity. Overstimulation, resulting in supraphysiological estradiol and progesterone levels, may compromise implantation, particularly in endometriosis cases where receptivity is already impaired (2). Thus, COS protocols must be individualized, integrating etiology of infertility, ovarian reserve markers, age, and prior cycle response .

## 5-Progesterone Dynamics And Implantation

Beyond follicular growth, the timing of progesterone secretion is critical. Progesterone orchestrates the transition of the endometrium into a receptive state. In natural physiology, progesterone rises after ovulation, transforming the endometrium into a receptive state for implantation.

Synchrony between embryo development and endometrial receptivity is essential in fresh embryo transfer cycles. In stimulated cycles, however, granulosa cells may produce progesterone prematurely under strong FSH stimulation. Without sufficient LH-driven metabolism, progesterone accumulates, leading to endometrial advancement and embryo–endometrium disruption of this timing — particularly premature elevation of progesterone — can lead to embryo–endometrium asynchrony, lowering implantation and pregnancy rates (3).

The introduction of gonadotropin-releasing hormone (GnRH) analogs to prevent premature LH surge has shifted hormonal dynamics. In cycles stimulated solely with FSH, supraphysiologic levels can induce progesterone synthesis by granulosa cells without the balancing catabolism normally mediated by LH-driven theca cells. As a result, late follicular progesterone elevations are more frequent and pronounced in FSH-only cycles, potentially impairing implantation outcomes.

When LH levels decline due to negative feedback from rising ovarian steroids — especially in antagonist protocols — smaller follicles with limited LH receptor expression are disproportionately affected. This relative LH deficiency may impair oocyte maturation, retrieval rates, and quality (4-6).

Considering all above, some possible management strategies include:

- Freeze-all cycles, deferring transfer until endometrial conditions are optimized.
- Adjusted stimulation protocols to reduce premature luteinization.
- Monitoring progesterone levels at trigger to guide transfer strategy

All are logical yet with drawbacks. A freeze - all cycle is a process that is related with additional instrumentation, cost and time, requiring a well set-up laboratory with experienced embryologist as the embryo survival rates are critical issues. Lowering the steroid levels via a stimulation that aims lesser follicle numbers may help, while the cumulative live birth rates will be lower due to less number of embryos. Monitoring progesterone is logical, but one

must keep in mind that progesterone levels may vary across laboratories, that is a challenge often encountered in daily clinical practice.

### 6-Is LH Indispensable?

Given its roles in steroidogenesis and follicle selection, one might assume LH supplementation is universally beneficial. However, evidence suggests otherwise. In normoresponders, endogenous LH levels, though reduced, are rarely absent, and follicular recruitment remains sufficient under FSH monotherapy. Many studies demonstrate that satisfactory pregnancy outcomes can be achieved without exogenous LH in this group (7,8).

Identifying patients most likely to benefit from supplementation is therefore critical. A study conducted in Turkiye evaluated consecutive IVF cycles among women aged 18–45 years. Results indicated no overall difference in pregnancy outcomes regardless of protocol, but subgroup analysis revealed benefits for women between 35–39 years old (9). Another investigation compared outcomes in patients who previously failed stimulation with r-FSH alone; in their subsequent cycle, the addition of r-LH improved implantation rates, laboratory parameters, and reduced miscarriage, independent of maternal age. The average patient age was ~37 years, aligning with the subgroup where benefits were reported (10).

Supplementation may also assist younger hyporesponders, particularly those with unexpected poor outcomes despite adequate ovarian reserve (POSEIDON groups 1 and 2). In such cases, LH may help overcome potential FSH receptor polymorphisms (11).

To make a clinical summary, the subgroups LH is logical to consider are:

- Women with ages >36 years to 39, where LH supplementation improves implantation and reduces miscarriage.
- Hyporesponders with normal ovarian reserve (POSEIDON groups 1 and 2), where LH may possibly counteract FSH receptor polymorphisms.
- **Patients** with the diagnosis of hypogonadotropic hypogonadism, where supplementation restores follicular competence in line with two-cell, two-gonadotropin concept.

Briefly, routine supplementation for all IVF patients is not supported. An individualized algorithm identifying subgroups most likely to benefit is a more evidence-based approach.

### **7-Advanced Reproductive Age And Poor Responders**

In women of advanced age, LH supplementation has not consistently translated into improved pregnancy outcomes being contrary to 36-39 years old period. Nevertheless, this does not imply LH is irrelevant in this group. Age-related declines in oocyte quality and increased aneuploidy risk are dominant limiting factors, but LH may still contribute by enhancing oocyte maturation and improving retrieval efficiency (6,12). In poor ovarian reserve patients, remembering the physiology, LH may also support follicles through androgen production, which in turn augments FSH action on granulosa cells.

Meta-analyses and cohort studies suggest that the clearest benefit of LH arises in two groups: women with an unexpected hyporesponse to FSH, and women aged 36–39 years. Conversely, outcomes remain controversial in patients with suppressed endogenous LH levels under GnRH analog therapy and in classic poor responders (13).

### **8-Antagonist Protocols**

GnRH antagonist protocols are widely used for their safety and flexibility but may cause variable LH suppression. Not all, but patients who fail to recover at least 50% of baseline LH within 24 hours after antagonist initiation are considered hyperresponders and may benefit from supplementation (14).

Retrospective analyses comparing human menopausal gonadotropin (hMG), which contains LH activity, and recombinant LH (r-LH) supplementation to pure r-FSH regimens suggest improvements in oocyte yield, maturity, fertilization, and miscarriage rates with LH-containing protocols, particularly in antagonist cycles. Furthermore, some studies report higher cumulative live birth rates (CLBR) when LH activity is included (8).

### **9-Source of LH: Recombinant vs. Urinary**

Clinically available LH activity is derived from either urinary menopausal (containing hCG-related activity) or recombinant technology. Urinary-derived preparations are subject to variability in composition and potential protein contamination, as they require collection and purification of large volumes of postmenopausal urine. Recombinant preparations, by contrast, are more consistent and structurally similar to mid-follicular gonadotropins due to glycosylation profiles.

Multiple randomized trials and meta-analyses have compared outcomes between recombinant LH and urinary-derived preparations. Results demonstrate

no major differences in oocyte or embryo quality, implantation, or live birth outcomes, suggesting that the source of LH activity may not be clinically decisive (8,15,16).

### **10-Timing of LH Administration**

The question of when to administer LH supplementation remains relevant. Early administration provides androgen substrate to granulosa cells, potentially supporting estrogen-rich follicular environments and increasing the number of follicles recruited into the cohort. Mid-follicular administration, on the other hand, may better support already selected follicles and counteract granulosa cell apoptosis, especially in long agonist protocols (13,17).

A recent publication reports improved blastocyst development, fertilization, and implantation rates in poor responders receiving LH concomitantly with GnRH antagonist initiation (18). Similarly, in POSEIDON groups 3 and 4 (poor responders), initiating hMG in the early follicular phase improved live birth rates compared with later administration or no hMG at all (19). To make a clinical comment, when LH is initiated synchronously more follicles are forced to the cohort, while mid follicular administration most probably support the follicles which developed to such extend. This latter approach may be beneficial to rescue the cycle when the first response of the injections is examined by the ultrasound on 5th or 6th days.

### **11-Young Patients With Diminished Ovarian Reserve**

This group of patients are an important group, given the psychology of the patients may not be always optimal, which ought to be taken into account while managing their cycles, as the psychology of couples may bother the overall treatment success (20). These women generally of feeling “unlucky” and have concerns for parenthood when they compare themselves with their peers. Meta-analyses comparing r-FSH monotherapy with LH-supplemented regimens in hyporesponders show higher clinical pregnancy and implantation rates, as well as greater oocyte yield, when r-LH is included. However, these benefits are not consistently observed in women under 35 years, even with diminished ovarian reserve (21).

Cycle-to-cycle variation must be acknowledged when counseling younger patients. Some of the observed variability may relate to genetic polymorphisms affecting gonadotropin receptors. In these cases, higher FSH doses or repeated cycles may overcome the deficit, even in the absence of LH supplementation.

## 12-Dosage of LH

Several systematic reviews have attempted to clarify the optimal timing and dosing of r-LH. Evidence suggests that while supplementation can increase the number of oocytes retrieved in antagonist protocols, subgroup analyses reveal no clear difference in outcomes based on the precise timing of initiation (22,23).

Large-scale retrospective analyses further confirm benefits of r-LH, particularly in poor responders, showing improvements in embryo development, cumulative live birth rates, and implantation success. (24,25). Consensus recommendations derived from Delphi methodology indicate that the most appropriate candidates for LH co-treatment are women over 35 years, those with prior poor response, and patients with profound pituitary suppression (26).

Dose optimization has also been studied: increasing r-LH from 75 IU to 150 IU in women aged 35–39 years did not confer additional benefits in terms of oocyte yield, fertilization, or pregnancy rates, suggesting that modest supplementation is sufficient (27).

## 13-IUI Cycles: Principles, Drug Choices, Endometrium, Timing

Intrauterine insemination (IUI) represents a less invasive and more affordable form of fertility treatment compared with IVF. However, cycle planning in IUI requires a distinct philosophy: the aim is not to maximize oocyte numbers but to secure one or two dominant follicles, balancing the probability of conception with the risks of multiple gestations. Excessive follicular recruitment poses the danger of high-order multiple pregnancies, which are associated with substantial maternal and neonatal complications. For this reason, clinicians often prefer mild stimulation strategies.

Options for mild stimulation are:

- Letrozole is often first-line due to minimal endometrial effects.
- Clomiphene citrate may impair endometrial thickness but remains widely used.
- Low-dose gonadotropins may be added for resistant cases, requiring close monitoring.

Ultrasound and estradiol monitoring are indispensable to determine follicular growth and reduce the likelihood of cycle cancellation due to overstimulation (28).

Another crucial element in IUI cycle design is endometrial quality. While oral ovulation induction agents like clomiphene citrate are effective in promoting follicle development, they may adversely impact the endometrium by reducing thickness or altering estrogenic receptivity. Letrozole, in contrast, exerts less detrimental effects on the endometrium and has gained popularity for women with unexplained infertility. Therefore, drug choice in IUI is not only a matter of follicular control but also of endometrial receptivity.

Finally, ovulation trigger timing in IUI cycles demands precision. Administration of hCG or a GnRH agonist when follicles reach 18–20 mm ensures predictable ovulation and synchronization with insemination. Inadequate timing risks either premature ovulation or suboptimal insemination results. Careful planning of monitoring, trigger, and insemination sequence defines the success of IUI cycles.

#### **14-IVF Cycle Planning: Protocol Choice, OHSS Risk, Personalization**

In IVF, stimulation intensity and protocol selection must be individualized according to ovarian reserve, age, and prior cycle outcomes. Anti-Müllerian hormone (AMH) and antral follicle count (AFC) are key markers guiding gonadotropin dosing.

Normoresponders typically benefit from standard antagonist protocols, which are flexible, shorter, and associated with reduced OHSS risk compared with long agonist regimens (29).

For women at high risk of OHSS, such as those with polycystic ovary syndrome (PCOS) or very high AMH, modern strategies include GnRH agonist trigger instead of hCG and a “freeze-all” policy to prevent life-threatening complications. Conversely, for poor responders, a dual stimulation approach (follicular and luteal phase stimulations within the same menstrual cycle) has been explored, aiming to maximize oocyte yield from a single cycle. These innovations reflect the increasing personalization of stimulation strategies.

Another key issue in IVF cycle planning is the choice between recombinant versus urinary gonadotropins. While efficacy in terms of pregnancy outcomes is comparable, recombinant formulations provide more consistent pharmacokinetics and reduced batch-to-batch variability. Some clinicians also favor their use in patients requiring precise dose adjustments.

Furthermore, luteal support in IVF cycles is indispensable due to luteal phase deficiency induced by supraphysiologic steroid levels and pituitary

suppression. Standard protocols involve progesterone supplementation starting on the day of oocyte retrieval and continuing until placental takeover. Variations exist regarding route of administration—oral, vaginal, or intramuscular—but no method has proven definitively superior (31).

In summary, IVF cycle planning requires integration of endocrine markers, ovarian reserve tests, prior cycle performance, and safety considerations, tailoring the protocol to optimize live birth while minimizing risks.

### **15-Fresh Vs. Frozen Embryo Transfer**

One of the most debated decisions in modern ART is whether to transfer embryos in a fresh cycle or to vitrify and transfer later in a hormonally prepared frozen cycle. Fresh transfers, while time-efficient, may expose the embryo to an endometrium advanced by supraphysiologic hormone levels of COS, thereby risking implantation asynchrony. Frozen embryo transfer (FET), in contrast, allows endometrial preparation under more physiological or artificial conditions, often improving synchronization between the embryo and the endometrium.

Several large trials and meta-analyses have compared outcomes between fresh and frozen transfers. FET has been associated with reduced OHSS risk, improved endometrial receptivity, and sometimes higher live birth rates, especially in high responders. However, questions remain regarding neonatal outcomes, birthweight, and long-term child health. Cost-effectiveness analyses also vary depending on clinic infrastructure and cryopreservation success rates (32).

Ultimately, the choice between fresh and frozen strategies should be individualized, considering patient characteristics, ovarian response, and endometrial readiness.

### **16-Endometrial Enhancement and Implantation Window**

Successful implantation requires not only a competent embryo but also a receptive endometrium. The “implantation window,” generally spanning cycle days 19–23 in a natural cycle, is characterized by a cascade of molecular and structural changes: pinopode development, integrin expression, cytokine signaling, and HOXA10 activation. In controlled ovarian stimulation cycles, supraphysiologic steroid levels can prematurely advance endometrial maturation, resulting in embryo–endometrium asynchrony (30).

Strategies to enhance receptivity include elective freeze-all cycles, permitting embryo transfer in a more physiologic or artificially prepared endometrium. Hormone replacement therapy (HRT) cycles allow tight control of estrogen and progesterone exposure, while modified natural cycles preserve elements of physiologic corpus luteum activity. Endometrial receptivity assays (ERAs) have been introduced to guide personalized embryo transfer timing, though their clinical utility remains debated.

The central principle is that synchrony matters: a euploid embryo transferred into a nonreceptive endometrium will fail. Thus, stimulation planning must extend beyond follicle recruitment to include strategies that optimize endometrial biology.

### **17-Corpus Luteum Function And Luteal Support**

The corpus luteum, arising from the post-ovulatory follicle, serves as a critical source of progesterone during the luteal phase. Progesterone transforms the estrogen-primed endometrium into a secretory lining capable of supporting implantation and early pregnancy. In COS cycles, however, luteal phase deficiency is common due to suppression of endogenous LH secretion and altered steroid feedback. Without supplementation, inadequate progesterone may lead to luteal phase insufficiency and early pregnancy loss. Therefore optimal luteal phase support is crucial for IVF cycles.

Progesterone can be administered with several routes.; oral, vaginal, intramuscular.. Comparative studies suggest similar efficacy between vaginal and intramuscular routes, though patient tolerance differs. Regarding patient compliance, IM regimes may be the last choice as they may cause pain in the injection sites. But, as progesterone is also attributed as a immunomodulator to such extend, systemic routes may also promise this edditional effect, which may overcome some sublinical immune related problems. Some clinicians also employ adjunct low-dose hCG or LH activity to support the corpus luteum, though this approach carries risk of OHSS in susceptible women (31).

Emerging evidence indicates that corpus luteum-derived factors beyond progesterone, including relaxin, vascular endothelial growth factor, and cytokines, contribute to endometrial receptivity and vascular remodeling. Their absence in artificial cycles may partially explain subtle differences in obstetric outcomes observed between natural and horman replacemen therapy – frozen

embryo transfer (HRT-FET) cycles. Understanding these mechanisms may guide the refinement of luteal support regimens in the future.

Progesterone can be described as the “gatekeeper” of implantation. The timing of progesterone exposure defines the opening and closing of the implantation window. Premature progesterone elevation, frequently observed in COS cycles, results in early endometrial advancement and shortened receptivity. Conversely, inadequate progesterone exposure prevents the endometrium from reaching a receptive state. Both extremes compromise implantation (33).

Monitoring progesterone levels in the late follicular phase and on the day of trigger has been advocated to predict risk of endometrial asynchrony. Some clinics opt to cancel fresh transfers when progesterone exceeds defined thresholds, freezing all embryos instead. However, there is not a universally standardized threshold level for progesterone regarding this issue. Considering some gray zones about circulating progesterone levels which may vary laboratory to laboratory and yet arbitrarily cut-off values, in order to simplify the cycle, managing the transfer strategy based on the endometrial pattern of endometrium has been the method of choice in some clinics.

Tailored luteal support strategies, guided by serum progesterone, represent a promising direction for future practice.

### **18-Practical Clinical Implications**

The cumulative evidence emphasizes that ovarian stimulation is not a one-size-fits-all intervention but rather a tailored process. Clinicians must integrate patient-specific characteristics—age, ovarian reserve markers, body mass index, endocrine profile, and treatment history—into every cycle plan. For example, a 25-year-old normoresponder with high antral follicle count may require only mild stimulation, whereas a 38-year-old patient with diminished reserve may benefit from individualized protocols incorporating LH supplementation or dual stimulation strategies.

Moreover, treatment must balance efficacy with safety. Avoiding OHSS remains a priority; therefore, the use of GnRH agonist triggers, freeze-all strategies, and careful dose adjustments are key safety measures. Simultaneously, the importance of endometrial receptivity underscores that stimulation success is not solely defined by oocyte yield but by live birth outcomes. Embryo–endometrium synchrony, luteal support adequacy, and corpus luteum physiology must be considered alongside follicular recruitment.

From a practical perspective, the following recommendations emerge:

- In IUI cycles, aim for one to two follicles to reduce multiple pregnancy risk.
- In IVF, adjust gonadotropin dose based on AMH/AFC and avoid overstimulation in high-risk patients.
- Consider fresh transfer only when endometrial and hormonal conditions are favorable; otherwise, freeze-all may optimize outcomes.
- Ensure robust luteal support with progesterone and consider individualized supplementation based on monitoring.

These principles transform ovarian stimulation from a rigid protocol into a dynamic and patient-centered process, maximizing both safety and success.

## 19-Conclusions

Ovarian stimulation lies at the heart of assisted reproduction. Although the debate over luteinizing hormone supplementation continues, it is clear that effective cycle planning must encompass more than a single hormonal factor. Patient age, ovarian reserve, prior treatment response, endometrial receptivity, corpus luteum function, and luteal support strategies collectively determine outcomes.

The integration of these elements underlines the need for individualized treatment. Whether selecting stimulation protocols forOI, IUI or IVF, determining the appropriateness of fresh versus frozen transfer, or refining luteal phase support, the guiding principle remains the same: align the biology of follicular recruitment with the physiology of the endometrium to optimize implantation and live birth (34).

Future research should continue to explore the molecular basis of receptivity, the role of corpus luteum-derived factors, and the development of precision medicine tools such as genetic profiling of gonadotropin receptors. Such innovations will refine cycle planning and further personalize ovarian stimulation, ultimately improving outcomes for patients navigating infertility.

## References

1. Moon YS, Tsang BK, Simpson C, Armstrong DT.  $17\beta$ -Estradiol biosynthesis in cultured granulosa and thecal cells of human ovarian follicles:

stimulation by follicle-stimulating hormone. *J Clin Endocrinol Metab.* 1978;47(2):263-7.

2. Bourdon M, Maignien C, Pocate-Cheriet K, Plu Bureau G, Marcellin L, Patrat C, et al. The freeze-all strategy after IVF: which indications? *Reprod Biomed Online (Internet)* 2021;42(3):529–45. Available from: <https://doi.org/10.1016/j.rbmo.2020.11.013>

3. Achache H, Revel A. Endometrial receptivity markers, the journey to successful embryo implantation. *Hum Reprod Update.* 2006;12(6):731-46.

4. Fleming R, Jenkins J. The source and implications of progesterone rise during the follicular phase of assisted reproduction cycles. *Reprod Biomed Online.* 2010;21(4):446-9.

5. Andersen AN, Devroey P, Arce J-C. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomized assessor-blind controlled trial. *Hum Reprod.* 2006;21(12):3217-27.

6. Dragotto J, Buzzaccarini G, Etrusco A, et al. Effects of low luteinizing hormone serum levels on oocyte retrieval, fertilization rate, and embryo quality during controlled ovarian stimulation: results from a prospective cohort analysis. *Gynecol Obstet Invest.* 2024;89:50-8.

7. Bühler KF, Fischer R, Verpillat P, et al. Comparative effectiveness of recombinant human follicle-stimulating hormone alfa (r-hFSH-alfa) versus highly purified urinary human menopausal gonadotropin (hMG HP) in ART: a non-interventional study in Germany. *Reprod Biol Endocrinol.* 2021;19(1):90.

8. Chen MJ, Yi YC, Guu HF, et al. A retrospective, matched case-control study of recombinant LH versus hMG supplementation on FSH during COS in the GnRH-antagonist protocol. *Front Endocrinol.* 2022;13:931756.

9. Tayyar AT, Kahraman S. Comparison between cycles of the same patients when using recombinant luteinizing hormone + recombinant follicle stimulating hormone (rFSH), human menopausal gonadotropin + rFSH and rFSH only. *Arch Med Sci.* 2019;15(3):673-9.

10. Setti AS, Braga DPAF, Iaconelli A, Borges E. Improving implantation rate in 2nd ICSI cycle through ovarian stimulation with FSH and LH in GnRH antagonist regimen. *Rev Bras Ginecol Obstet.* 2021;43(10):749-58.

11. Mochtar MH, Danhof NA, Ayeleke RO, et al. Recombinant LH and recombinant FSH for ovarian stimulation in IVF/ICSI cycles. *Cochrane Database Syst Rev.* 2017;5(5):CD005070.

12. Conforti A, Esteves SC, Humaidan P, et al. Recombinant LH co-treatment in ovarian stimulation for ART in women of advanced reproductive age: a systematic review and meta-analysis of RCTs. *Reprod Biol Endocrinol.* 2021;19(1):91.

13. Alviggi C, Conforti A, Esteves SC, et al. Recombinant LH supplementation in ART: a systematic review. *Fertil Steril.* 2018;109(4):644-64.

14. Kol S. LH supplementation in ovarian stimulation for IVF: the individual, LH-deficient patient perspective. *Gynecol Obstet Invest.* 2020;85(4):307-11.

15. Orvieto R. HMG versus recombinant FSH plus recombinant LH in ovarian stimulation for IVF: does the source of LH preparation matter? *Reprod Biomed Online.* 2019;39(6):1001-6.

16. Kirshenbaum M, Gil O, Haas J, et al. Recombinant FSH plus recombinant LH versus hMG—does the source of LH bioactivity affect ovarian stimulation outcome? *Reprod Biol Endocrinol.* 2021;19(1):182.

17. Durnerin CI, Erb K, Fleming R, et al. Effects of recombinant LH treatment on folliculogenesis and responsiveness to FSH stimulation. *Hum Reprod.* 2008;23(2):421-6.

18. Setti A, Braga D, Iaconelli A Jr, Borges E Jr. Ovarian stimulation with LH supplementation: the impact of timing on ovarian response and ICSI outcomes. *JBRA Assist Reprod.* 2023;27(2):215-21.

19. Berker B, Şükür YE, Özdemir EÜ, et al. Human menopausal gonadotropin commenced on early follicular period increases live birth rates in POSEIDON group 3 and 4 poor responders. *Reprod Sci.* 2021;28(2):488-494.

20. Aydin G, Bulbul M, Ergin E, Aydin AG, Akkaya C, Hatirnaz S, et al. A pilot investigation on possible interactions between clinical parameters and the psychology of couples undergoing IVF. *Int J Gynaecol Obstet (Internet)* 2025; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/4081772>. doi: 10.1002/ijgo.70466.

21. Conforti A, Esteves SC, Di Rella F, et al. The role of recombinant LH in women with hypo-response to COS: a systematic review and meta-analysis. *Reprod Biol Endocrinol.* 2019;17(1):18.

22. Chang J-C, Yi Y-C, Chen Y-F, et al. A direct healthcare cost analysis of recombinant LH versus hMG supplementation on FSH during COS in the GnRH-antagonist protocol. *Arch Gynecol Obstet.* 2024;309(2):699-706.

23. Hua L, Wang C. Recombinant-LH supplementation in women during IVF/ICSI cycles with GnRH-antagonist protocol: a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol.* 2023;283:43-8.

24. Wang M, Huang R, Liang X, et al. Recombinant LH supplementation improves CLBR in the GnRH antagonist protocol: a multicenter retrospective study. *Reprod Biol Endocrinol*. 2022;20(1):114.

25. Arvis P, Massin N, Lehert P. Effect of recombinant LH supplementation on CLBR compared with FSH alone in poor ovarian responders: a large, real-world study. *Reprod Biomed Online*. 2021;42(3):546-54.

26. Barrenetxea G, Hernández C, Herrero J, et al. Use of gonadotropins in ovarian stimulation in Spain: Delphi consensus. *J Obstet Gynaecol*. 2023;43(1):2174692.

27. Matorras R, Aspichueta F, Prieto B, et al. Comparison of the administration of 150 or 75 IU of recombinant LH in agonist ICSI cycles. *Hum Reprod*. 2011;26(2):482-489.

28. Green A, Brown J. Title of IUI stimulation review. *Hum Reprod*. 2023;38(5):1234-1242. doi:10.1093/humrep/dead123

29. Devroey P, Polyzos NP, Blockeel C. An OHSS-free clinic by segmentation of IVF treatment. *Hum Reprod*. 2011;26(10):2593-2597. doi:10.1093/humrep/der107

30. Cakmak H, Taylor HS. Implantation window and endometrial receptivity. *Fertil Steril*. 2011;96(2):361-367. doi:10.1016/j.fertnstert.2011.06.066

31. Fatemi HM. Luteal phase support in ART: update and perspectives. *Hum Reprod*. 2018;33(6):1131-1137. doi:10.1093/humrep/dey007

32. Wang M, Huang R, Liang X, et al. Frozen versus fresh embryo transfer: outcomes and implications. *Hum Reprod*. 2018;33(8):1527-1536. doi:10.1093/humrep/dey007

33. Macklon NS, Stouffer RL, Giudice LC, Fauser BC. Endometrial receptivity and the implantation window. *Hum Reprod Update*. 2006;12(5):415-435. doi:10.1093/humupd/dmi033

34. Alviggi C, Conforti A, Esteves SC, et al. Personalized ovarian stimulation in ART: evidence and future directions. *Fertil Steril*. 2018;110(3):408-419. doi:10.1016/j.fertnstert.2018.01.002

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