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Review Article

Pharmacologic Strategies, Clinical Outcomes, and Safety Considerations in Intrauterine Insemination: A Focused Narrative Review

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Abstract

Background: Intrauterine insemination (IUI) is a widely used first-line assisted reproductive technology (ART) in which pharmacologic interventions largely determine efficacy and safety. Therefore, this study aimed to synthesize and critically evaluate evidence on pharmacologic strategies utilized in IUI, focusing on clinical outcomes, safety profiles, and unresolved clinical controversies.

Methods: A narrative review was conducted using PubMed, Scopus, and Web of Science to identify English-language studies (2000–2025) addressing the pharmacologic management of IUI cycles. Randomized controlled trials, systematic reviews, meta-analyses, and major clinical guidelines were prioritized in this review.

Results: Based on the findings, ovarian stimulation agents, such as clomiphene citrate, aromatase inhibitors, and gonadotropins, demonstrated differing efficacy–risk profiles. Notably, it was revealed that mild stimulation protocols provide the most favorable balance between pregnancy rates and complications. Nonetheless, evidence supporting emerging technologies (e.g., artificial intelligence-guided protocols and biomarker-driven dosing) remains preliminary.

Conclusion: Overall, pharmacologic management is central to IUI success. Individualized, evidence-based stimulation strategies emphasizing safety over maximal follicular recruitment should guide clinical practice.

Keywords: Intrauterine insemination, Pharmacologic strategies, Ovarian stimulation, Fertility, ART, Safety

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Introduction

Intrauterine insemination (IUI) is a well-established assisted reproductive technology that offers a less invasive but more affordable treatment option for selected infertility indications.[1,2] While the technical aspects of sperm preparation and uterine insemination are standardized, pharmacologic management is the primary determinant of IUI success and safety. In addition, controlled ovarian stimulation, ovulation triggering, and luteal phase support are essential components that directly influence follicular development, endometrial receptivity, and pregnancy outcomes.[1,3]

Previous reviews have comprehensively addressed the indications, effectiveness, and procedural aspects of IUI.[1,3,4] However, rapid evolution in reproductive pharmacology has introduced new challenges related to drug selection, dosing, risk mitigation, and personalization of therapy.[5,6] Moreover, the same pharmacologic strategies that enhance pregnancy rates increase the risks of multiple gestations and ovarian hyperstimulation syndrome (OHSS), indicating the need for evidence-based balance rather than maximal stimulation.[7-9]

Accordingly, this review specifically focuses on pharmacologic strategies in IUI, synthesizing current evidence on commonly utilized agents, their clinical outcomes, and associated complications. In addition, it highlights unresolved clinical questions, limitations of emerging technologies, and ethical considerations relevant to drug-based IUI management. This targeted approach aims to support informed clinical decision-making and patient-centered counseling.

Pharmacologic Agents Used in Intrauterine Insemination

Ovarian Stimulation Agents

Controlled ovarian stimulation is employed to overcome ovulatory dysfunction or modestly increase the number

of available oocytes per cycle.[10,11] Clomiphene citrate, aromatase inhibitors (primarily letrozole), and exogenous gonadotropins are some of the commonly used agents. Each class substantially differs in mechanism of action, endometrial effects, and risk profile.[12,13]

Although clomiphene citrate is widely employed due to its low cost and oral administration, its anti-estrogenic effects on the endometrium and cervical mucus may adversely affect implantation.[14-16] Accordingly, aromatase inhibitors have emerged as preferred first-line agents in certain populations, particularly women with polycystic ovary syndrome, due to more favorable endometrial effects and lower multiple pregnancy rates.[17,18] Moreover, gonadotropins are associated with higher pregnancy rates but confer a significantly increased risk of OHSS and multifetal gestation, necessitating intensive monitoring.[7,10,12,17]

Ovulation Triggering

Ovulation is typically triggered using human chorionic gonadotropin (hCG) once adequate follicular development is achieved. Gonadotropin-releasing hormone agonist triggers may be considered in selected high-risk patients in order to reduce OHSS risk, although their routine use in IUI remains limited.[19,20]

Luteal Phase Support

Progesterone supplementation is typically administered following ovulation induction, particularly in cycles using gonadotropins or clomiphene citrate.[21,22] While luteal support is extensively practiced, evidence regarding optimal formulation, dose, and necessity in all IUI cycles remains heterogeneous, representing an ongoing area of clinical debate.[23,24]

Clinical Outcomes of Pharmacologically Managed Intrauterine Insemination

Pregnancy outcomes following IUI are modest and highly dependent on patient selection and pharmacologic strategy.[1,25] Female age, ovarian reserve, and stimulation response are the strongest predictors of success in this regard. Mild stimulation protocols aiming for one to two mature follicles provide the most desirable balance between pregnancy rates and safety, whereas aggressive stimulation confers limited benefits with disproportionate risk.[26-28]

The success of pharmacologically managed IUI is determined by the interaction between patient-specific characteristics and drug-related factors. Generally, female age, ovarian reserve, stimulation protocol, follicular response, sperm quality, and endometrial receptivity influence pregnancy outcomes.[29,30] The central roles of pharmacologic decision-making in modulating these variables and balancing efficacy with safety are summarized in Figure 1.

Table 1 summarizes essential patient-related and pharmacologic factors affecting the success of IUI and their clinical implications.

Drug-Related Risks and Complications

Multiple Gestations

Multiple pregnancy remains the most critical complication of medicated IUI.[31] The risk increases with the number of developing follicles and is the highest in gonadotropin-stimulated cycles.[32] Evidence supports the use of mild stimulation protocols targeting one to two mature follicles to reduce this risk.[33]

Ovarian Hyperstimulation Syndrome

OHSS is an iatrogenic complication that is primarily associated with gonadotropin use. Although OHSS is less frequent in IUI than in in vitro fertilization, severe cases can occur. Individualized dosing, close ultrasound monitoring, and strict cancellation policies are essential preventive measures for this type of syndrome.[7, 10, 12]

Ectopic Pregnancy

Stimulated cycles may slightly increase the risk of ectopic pregnancy, particularly in women with underlying tubal pathology. Accordingly, it is recommended that effective methods, such as early monitoring, serial β-hCG measurements, and transvaginal ultrasonography, be considered for these women.[34,35]

Drug-Specific Adverse Effects

Clomiphene citrate may cause vasomotor symptoms and anti-estrogenic endometrial effects, while letrozole is generally well tolerated but may be associated with fatigue or dizziness. Moreover, gonadotropins can cause injection-site reactions and ovarian discomfort.[36]

Likewise, pharmacologic stimulation in IUI is associated with well-recognized risks, including multiple

Table 1. A Summary of the Key Pharmacologic and Patient-Related Factors Influencing IUI Success and Their Clinical Implications

Factor	Clinical Impact	Pharmacologic Implications
Female age	Declining pregnancy rates with increasing age	It may warrant limited IUI attempts and early escalation to IVF.
Ovarian reserve (AMH/AFC)	Predicting response to stimulation	It guides drug selection and starting dose.
Stimulation protocol	Determining follicular yield and risk	Mild stimulation is preferred to reduce the number of multiples.
Number of mature follicles	Increasing pregnancy and multiple risks	It targets 1–2 follicles and is cancelled if excessive.
Endometrial receptivity	Being essential for implantation	It avoids anti-estrogenic effects and considers progesterone.
Sperm quality	Limiting fertilization potential	It determines the suitability of IUI vs. IVF/ICSI.

Note. IUI: Intrauterine insemination; AMH: Anti-mullerian hormone; AFC: Antral follicle count; IVF: In vitro fertilization; ICSI: Intracytoplasmic sperm injection.

gestations, OHSS, ectopic pregnancy, and medication-specific adverse effects.[37,38] These complications are largely preventable through individualized dosing, mild stimulation protocols, close monitoring, and strict cycle cancellation criteria. Figure 2 illustrates an overview of the major pharmacologic risks of IUI, including multiple gestations, ovarian hyperstimulation syndrome, ectopic pregnancy, and medication-specific adverse effects, and corresponding preventive strategies.

Challenges and Limitations in Intrauterine Insemination Pharmacotherapy

Despite widespread use, IUI pharmacotherapy faces inherent limitations. Inter-individual variability in ovarian

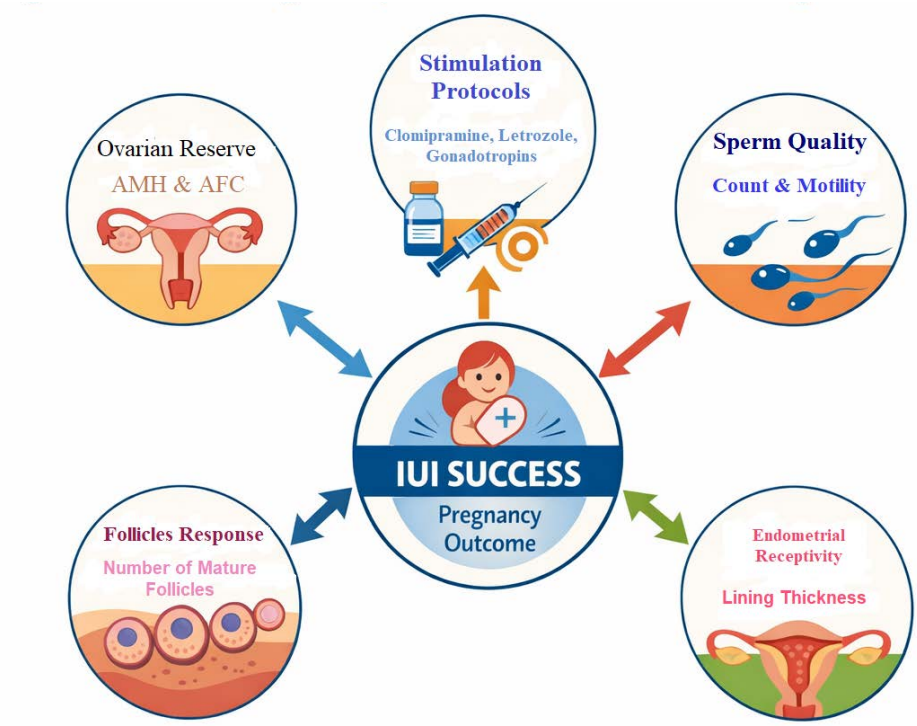

Figure 1. Pharmacologic and Patient-Related Factors Influencing IUI Success: A Schematic Representation of How Ovarian Reserve, Stimulation Protocol, Follicular Response, Sperm Quality, and Endometrial Receptivity Interact to Determine Pregnancy Outcomes in Medicated IUI Cycles
Note. IUI: Intrauterine insemination; AMH: Anti-mullerian hormone; AFC: Antral follicle count

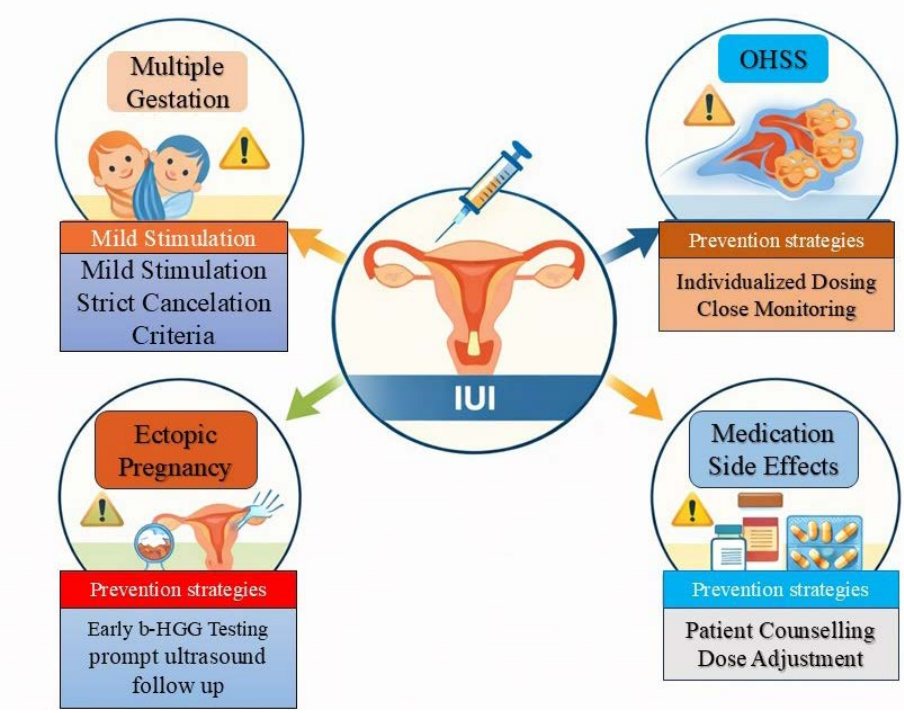

Figure 2. Drug-Related Risks and Complications Associated With IUI
Note. IUI: Intrauterine insemination; hCG: Human chorionic gonadotropin; OHSS: Ovarian hyperstimulation syndrome

Table 2. Drug-Related Risks and Complications in Medicated IUI

Complication	Clinical Significance	Prevention/Management
Multiple gestation	Increased maternal and neonatal morbidity	Mild stimulation and strict cancellation criteria
OHSS	Potentially severe iatrogenic complication	Individualized dosing and close monitoring
Ectopic pregnancy	Increased risk in stimulated cycles	Early β-hCG and ultrasound follow-up
Drug side effects	Effects on adherence and quality of life	Patient counseling and dose adjustment
Psychological burden	Stress and emotional fatigue	Counseling and realistic expectation setting

Note. OHSS: Ovarian hyperstimulation syndrome; IUI: Intrauterine insemination; hCG: Human chorionic gonadotropin.

response complicates protocol selection, and success rates decline sharply with advancing maternal age.[39,40] Likewise, IUI is ineffective in cases of severe male factor infertility, where in vitro fertilization or intracytoplasmic sperm injection is necessary.[41] Additionally, the cumulative cost of repeated medicated cycles raises concerns regarding cost-effectiveness and timely escalation of care.[42] Table 2 outlines common drug-related complications in IUI and recommended preventive strategies.

Innovations and Future Directions

Biomarker-Guided Stimulation

Markers such as anti-Müllerian hormone and antral follicle count are increasingly used to guide starting doses of stimulation drugs.[43] Although these biomarkers improve the prediction of ovarian response, their ability to independently improve live birth rates remains unproven.[44,45]

Artificial Intelligence and Predictive Modeling

AI-based models have been proposed to optimize drug selection and dosing. However, most existing studies are retrospective, and external validation is limited. Currently, these tools should be considered investigational rather than standard of care.[46]

Other Emerging Technologies

Approaches such as microfluidic sperm selection and molecular endometrial receptivity testing demonstrate theoretical promise but lack sufficient prospective evidence to support routine use in IUI cycles.[47]

Ethical Considerations and Patient Counseling

Ethical practice in pharmacologic IUI requires transparent communication regarding expected success rates, drug-related risks, and alternatives.[48,49] Further, counseling should explicitly address the risk of multiple gestations, the potential need for cycle cancellation, and financial considerations. Moreover, shared decision-making is essential to align treatment intensity with patient values and risk tolerance.[49,50]

Conclusion

Pharmacologic management is the cornerstone of modern intrauterine insemination, exerting a decisive influence on both efficacy and safety. Existing evidence supports the use of mild, individualized stimulation protocols that prioritize risk reduction over maximal follicular recruitment. While emerging technologies may enhance future personalization, their current role remains investigational.

Key Clinical Takeaways

Drug selection and dosing should be individualized based on ovarian reserve and risk profile.

In addition, mild stimulation offers the best balance between pregnancy rates and safety.

Multiple gestation and OHSS remain the principal preventable complications.

Clear patient counseling and ethical risk management are integral to high-quality IUI care.

Continued emphasis on evidence-based pharmacologic strategies and patient-centered decision-making will ensure that IUI remains a relevant and responsible first-line fertility treatment.

Ethics statement

Not applicable.

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None.

Conflict of interests declaration

There is no conflict of interest.

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Data availability statement

Not applicable.

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