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ADVANCES IN PHARMACOLOGY OF ASSISTED REPRODUCTIVE TECHNOLOGY: IMPROVING OOCYTE YIELD AND ENDOMETRIAL RECEPTIVITY

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ABSTRACT

Background: Infertility affects 10–15% of couples worldwide, and Assisted Reproductive Technology (ART) has transformed its management. Despite advances, live birth rates remain modest at 30–40% per cycle. Optimizing ovarian stimulation and endometrial receptivity is critical for improving outcomes, with pharmacology playing a central role. **Objective:** To provide a comprehensive overview of pharmacological agents and protocols in ART, emphasizing mechanisms of action, clinical applications, safety, and emerging individualized strategies. **Methods:** Narrative review of recent clinical trials, meta-analyses, and guidelines. Agents discussed include selective estrogen receptor modulators, aromatase inhibitors, gonadotropins, GnRH analogs, hCG, progesterone, and adjunctive therapies such as metformin, cabergoline, glucocorticoids, and anticoagulants. **Results:** Pharmacological strategies maximize oocyte yield, prevent premature LH surges, and enhance implantation. Clomiphene citrate and letrozole remain first-line oral agents; recombinant gonadotropins and hMG support controlled ovarian hyperstimulation. GnRH antagonists reduce OHSS risk, while luteal support with progesterone is essential. Adjuncts such as cabergoline and CoQ10 improve safety and outcomes in high-risk groups. Emerging approaches, including long-acting gonadotropins and guided dosing, support personalized therapy. **Conclusion:** Pharmacology underpins ART success by balancing efficacy and safety. Advances in gonadotropin formulations, GnRH analogs, and adjunctive agents have improved outcomes, yet challenges like OHSS and implantation variability persist. Precision medicine approaches incorporating pharmacogenomics and tailored stimulation represent the next frontier in ART.

KEYWORDS: Assisted reproductive technology, ovarian stimulation, implantation, pharmacology, luteal support.

1. INTRODUCTION

Infertility, defined as the inability to conceive after 12 months of unprotected intercourse affects an estimated 10–15% of couples of reproductive ages worldwide and represents a major public health challenge.[1] Beyond its clinical implications, infertility carries significant psychological, social, and economic burdens, particularly in regions where childbearing is central to cultural identity and marital stability.

Since the birth of the first test-tube baby in 1978, Assisted Reproductive Technology (ART) has transformed infertility management, offering options such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) to millions of couples.[2] ART has progressed remarkably, yet live birth rates remain limited, averaging only 30–40% per treatment cycle globally.[3] Improving these outcomes requires addressing two pivotal determinants of success: adequate ovarian stimulation to yield multiple high-quality oocytes and sufficient endometrial receptivity to support implantation.[4]

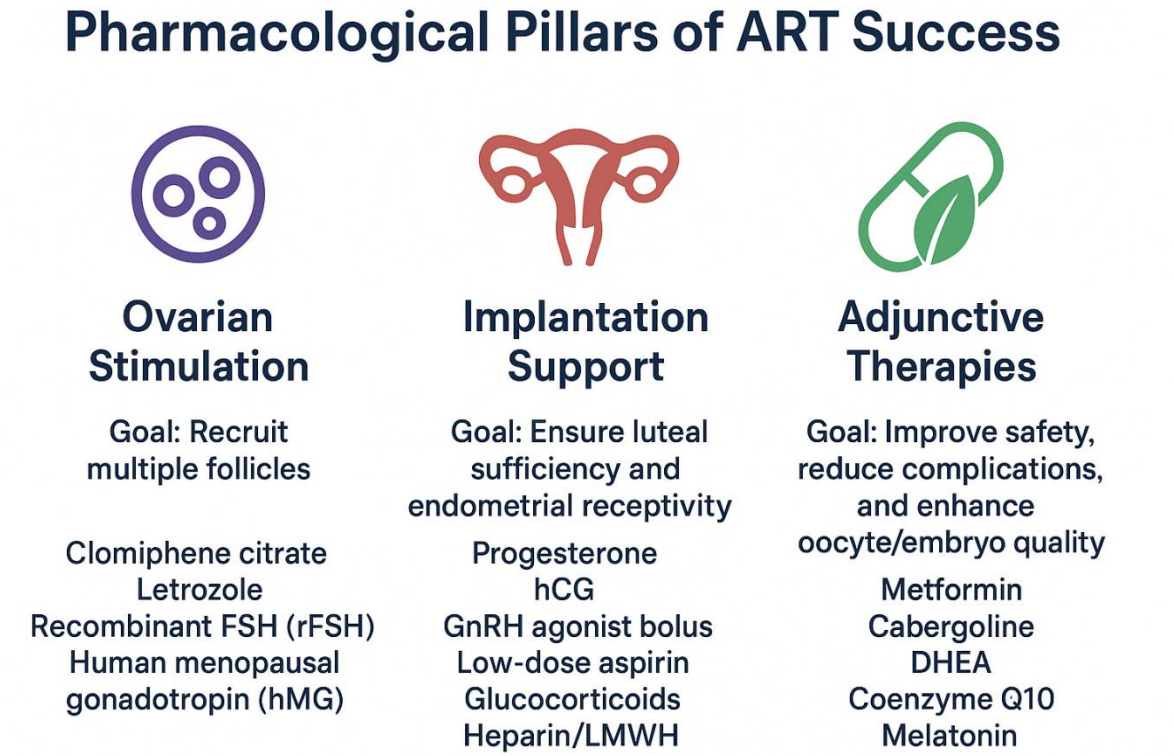
Pharmacology lies at the heart of both processes. Controlled ovarian hyperstimulation relies on exogenous gonadotropins and adjunctive agents to stimulate

follicular development while preventing premature luteinizing hormone surges. Similarly, implantation often requires pharmacological support of the luteal phase and, in some cases, immunomodulation or vascular modulation to optimize endometrial receptivity. However, despite advances in drug formulations and stimulation protocols, significant challenges persist, including ovarian hyperstimulation syndrome (OHSS), interindividual variability in drug response, and suboptimal implantation rates. These gaps highlight the need for a more precise understanding of pharmacological mechanisms, individualized stimulation protocols, and integration of pharmacogenomic insights into ART practice.

This review aims to provide a comprehensive examination of the pharmacological strategies underpinning ART, focusing on ovarian stimulation, luteal phase and implantation support, adjunctive therapies, and emerging innovations. Emphasis is placed on mechanisms of action, pharmacokinetics, clinical applications, safety considerations, and the future role of personalized, pharmacogenomic driven ART.

Table 1: Pharmacological Pillars of ART Success.

Pillar	Goal	Key Pharmacological Agents
Ovarian Stimulation	Recruit multiple follicles and optimize oocyte yield	Clomiphene citrate, Letrozole, Recombinant FSH (rFSH), Human menopausal gonadotropin (hMG), GnRH agonists/antagonists, Hcg
Implantation Support	Ensure luteal sufficiency and endometrial receptivity	Progesterone, hCG, GnRH agonist bolus, Low-dose aspirin, Glucocorticoids, Heparin/LMWH, Growth factors (e.g., G-CSF)
Adjunctive Therapies	Improve safety, reduce complications, and enhance oocyte/embryo quality	Metformin, Cabergoline, DHEA, Coenzyme Q10, Melatonin, Antioxidants, Immunomodulators (IVIG, intralipids)



2. Ovarian Stimulation in ART

2.1 Rationale

The natural menstrual cycle usually produces only one dominant follicle, limiting the number of oocytes available for fertilization. Controlled ovarian hyperstimulation (COH) in Assisted Reproductive Technology (ART) aims to recruit multiple follicles, thereby increasing the number of retrievable oocytes and enhancing the probability of fertilization, embryo selection, cryopreservation, and ultimately live birth.[5] The concept of cumulative live birth rate (CLBR) across fresh and frozen transfers has increasingly replaced per-cycle pregnancy rate as the most meaningful outcome.[6]

Overstimulation carries the risk of ovarian hyperstimulation syndrome (OHSS), impaired oocyte/embryo competence, and reduced endometrial receptivity.[7,8] Therefore, modern ART emphasizes

individualized protocols based on ovarian reserve markers (AMH, AFC), age, prior response, and genetic or metabolic background.[9,10]

Recent insights have reshaped stimulation strategies, with the follicular wave theory supporting DuoStim/Shanghai protocols that allow double stimulation in the same cycle particularly for poor responders and fertility preservation, while artificial intelligence and predictive modelling are being explored for dosing and trigger timing to enhance personalization, and the POSEIDON criteria (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) have redefined poor responders into distinct low prognosis subgroups, improving both counselling and patient stratification.[11–13]

2.2 Core Pharmacological Agents

2.2.1 Clomiphene Citrate (CC)

- Mechanism: A selective estrogen receptor modulator (SERM) that blocks hypothalamic estrogen receptors, reducing negative feedback and increasing GnRH, FSH, and LH.[14]
- Clinical Role: Commonly used in mild stimulation or cost-saving protocols, sometimes combined with gonadotropins.[15]
- Limitations: Long half-life and anti-estrogenic effects on the endometrium may compromise implantation.[16]

2.2.2 Letrozole

- Mechanism: Third-generation aromatase inhibitor that suppresses estrogen synthesis, thereby increasing endogenous FSH release.[17]
- Clinical Role: First-line therapy in women with PCOS; associated with higher live birth rates compared to clomiphene citrate.[18]
- Advantages: Minimal anti-endometrial effects, shorter half-life, and lower risk of multiple pregnancies.[18]

2.2.3 Gonadotropins

- Recombinant FSH (rFSH): High-purity formulation with predictable pharmacokinetics; forms the standard backbone of controlled ovarian hyperstimulation (COH).[19].
- Human Menopausal Gonadotropin (hMG): Contains both FSH and LH activity; useful in women with LH deficiency or poor responders.[20]
- Individualization: Dosing guided by AMH, AFC, and patient profile; excessive FSH may impair oocyte quality.[21]
- LH Supplementation: rLH or hMG may improve outcomes in select POSEIDON groups.[13,22]

2.2.4 GnRH Agonists and Antagonists

- Agonists: Initially cause a gonadotropin "flare" followed by pituitary desensitization; used in long and flare protocols.[23]
- Antagonists: Provide immediate suppression, shorter duration, and lower risk of OHSS.[24]
- Recent Evidence: Fixed antagonist timing improves live birth rates in unexpected poor responders (POSEIDON 1) compared to flexible initiation.[25]

2.2.5 Human Chorionic Gonadotropin (hCG) and Alternatives

- Role: Mimics the LH surge to induce final oocyte maturation.[26]
- Risks: Increases the risk of OHSS, especially in high responders.[27]
- Alternatives:
  - Recombinant hCG (rhCG) for consistent pharmacokinetics.
  - GnRH agonist trigger in antagonist cycles to lower OHSS, with modified luteal support.[28]
  - Dual trigger (GnRH agonist + low-dose hCG) enhances mature oocyte yield and embryo competence.[29]

2.3 Ovarian Stimulation Protocols

2.3.1 Long GnRH Agonist Protocol

- Initiation: Luteal phase of the preceding cycle.
- Advantages: Strong suppression and follicular synchrony.[23]
- Limitations: Long duration and higher OHSS risk.[24]
- Recent Data: Early follicular long-acting agonist protocols outperformed mid-luteal and antagonist protocols in POSEIDON 1 & 3 patients.[30]

2.3.2 GnRH Antagonist Protocol

- Initiation: Mid-follicular phase (fixed or flexible).
- Advantages: Shorter duration, safer (lower OHSS risk), allows use of agonist trigger.[24]
- Limitations: Slightly less follicular synchrony than agonist protocols.
- Recent Insights: In young patients with high ovarian reserve, antagonist protocols yield higher cumulative live birth rates with lower OHSS.[6]

2.3.3 Short / Microdose Flare Protocol

- Mechanism: Early follicular GnRH agonist "flare."
- Clinical Role: Poor responders or women with diminished ovarian reserve.
- Update: Short agonist stops (SAS) protocols increase oocyte yield in POSEIDON-defined poor responders.[31]

2.3.4 Mild / Minimal Stimulation Protocols

- Strategy: Low-dose gonadotropins ± CC or letrozole.
- Advantages: Lower cost and reduced OHSS risk.
- Limitations: Lower oocyte yield; suitable only for selected patients.[32]

2.3.5 Individualized / POSEIDON-Based Protocols

- Approach: Stratify patients by ovarian reserve and age.[23]

- Strategies: rLH supplementation, oocyte/embryo accumulation, and tailored dose escalation.
- Evidence: POSEIDON stratification better predicts euploid embryo yield than Bologna criteria.[33]

2.3.6 Novel / Hybrid Strategies

- Double Stimulation (DuoStim / Shanghai Protocol): Two retrievals per cycle, particularly useful for poor prognosis patients.[11]
- Progestin-Primed Ovarian Stimulation (PPOS): Prevents premature LH surge; suited for freeze-all cycles, though live birth rates may be slightly lower than antagonist protocols.[34]
- Dual Trigger and AI-Driven Timing: Emerging strategies to optimize oocyte maturation and retrieval outcomes.[12,29]

3. Luteal Phase Support in ART

3.1 Rationale

Controlled ovarian hyperstimulation disrupts the natural luteal phase by suppressing LH secretion, leading to inadequate progesterone support for endometrial receptivity.[35] Supplementation is therefore essential to maintain implantation potential and early pregnancy until placental takeover at 8–10 weeks.[36]

3.2 Pharmacological Agents

Progesterone

- Routes: Vaginal (gel, capsules), intramuscular, or oral formulations.[37]
- Efficacy: Vaginal progesterone is widely used due to local endometrial delivery with fewer systemic side effects.[38]
- Limitations: Oral micronized progesterone has variable bioavailability.[39] Recent studies suggest dydrogesterone as a promising oral option with comparable efficacy to vaginal preparations.[40]

Human Chorionic Gonadotropin (hCG)

- Mechanism: Stimulates corpus luteum progesterone production.[41]
- Limitations: Increases OHSS risk, limiting its use in high responders.[42] Current practice recommends restricted use to low-risk patients.[43]

GnRH Agonists

- Mechanism: Pulsatile LH release from pituitary to support luteal function.[44]
- Clinical Role: Sometimes used as adjuncts to progesterone in antagonist cycles, with evidence of improved implantation and live birth outcomes.[45,46]

3.3 Protocol Considerations

- Duration: Support is typically continued until at least a positive pregnancy test, often extended to 8–10 weeks gestation.[36,47]
- Comparative Efficacy: Progesterone remains the gold standard, while hCG use is now restricted.[43]
- Innovations: Combination approaches (progesterone + low-dose GnRH agonist) may optimize implantation while minimizing OHSS.[45,48]

4. Implantation Enhancers and Endometrial Modulators

4.1 Rationale

Even with optimal ovarian stimulation and embryo quality, implantation failure remains a major limiting factor in ART. Strategies to improve endometrial receptivity and uterine perfusion have been investigated to address recurrent implantation failure (RIF).[49]

4.2 Pharmacological and Adjuvant Approaches

Low-Dose Aspirin (LDA)

- Mechanism: Improves uterine blood flow via platelet inhibition and enhanced prostacyclin activity.[50]
- Evidence: Mixed; some recent meta-analyses show no consistent benefit in unselected IVF populations.[51]

Glucocorticoids

- Mechanism: Immunomodulatory, reducing endometrial NK cell activity.[52]
- Clinical Role: Investigated in women with suspected immune-mediated implantation failure.[53]
- Controversy: Evidence remains weak, and risks of systemic side effects limit routine use.[54]

Anticoagulants (Heparin, LMWH)

- Mechanism: Improve uterine microcirculation and counteract prothrombotic states.[55]
- Evidence: Demonstrated benefit in antiphospholipid antibody-positive women, but little role in unselected IVF patients.[56]

Antioxidants and Adjuvant Supplements

- Agents: Coenzyme Q10, melatonin, vitamins C/E reduce oxidative stress, potentially enhancing oocyte and endometrial quality.[57]
- Evidence: Small-scale RCTs show encouraging results, but insufficient evidence for routine clinical use.[58]

Growth Factors and Intrauterine Infusions (e.g., G-CSF, PRP)

- Mechanism: Enhance endometrial proliferation and receptivity.[59]
- Evidence: Early trials suggest improved outcomes in thin endometrium or RIF, but results remain inconsistent and larger trials are needed.[60,61]

5. Adjunctive Pharmacological Strategies

Dopamine agonists (cabergoline)

Multiple randomized controlled trials (RCTs) and meta-analyses have shown that cabergoline reduces the risk of moderate-to-severe ovarian hyperstimulation syndrome (OHSS) when used prophylactically in

high-risk women undergoing controlled ovarian stimulation. It does so without a significant negative impact on clinical pregnancy rates or the number of oocytes retrieved in most studies. For example, a meta-analysis of RCTs found that cabergoline reduced the risk of moderate-severe OHSS (RR ~0.38, 95 % CI 0.29-0.51) while having no clinically relevant effect on clinical pregnancy or oocyte yield.[62,63]

A more recent meta-analysis comparing calcium infusion to cabergoline found no significant difference in overall OHSS rates between the two but suggested calcium may reduce the rate of severe OHSS more than cabergoline in some analyses. Pregnancy outcomes were similar.[64]

Coenzyme Q10 (CoQ10)

In women with diminished ovarian reserve (DOR), pretreatment with CoQ10 has been shown in RCTs to improve several IVF/ICSI outcomes: increased number of retrieved oocytes, higher clinical pregnancy rates, more optimal embryos, lower cycle cancellation rates, and lower miscarriage rates compared to controls.[65]

In addition, CoQ10 supplementation during in vitro maturation (IVM) of human oocytes enhances oocyte maturation rates and reduces post-meiotic aneuploidy rates in older women (38 - 46 years) when compared to no supplementation; effects are less evident in younger women.[66]

Machine learning / AI for dose selection

Recent observational studies show that using machine learning (ML) models to help select the starting dose of FSH in ovarian stimulation can improve planning. For example, one large analysis (n =2,713 development, 774 validation) demonstrated that an ML model including age, AMH, AFC, BMI, and prior live births achieved a higher performance in dose recommendation (measured by a performance score relating to metaphase II oocytes and dose) compared to clinicians' prescriptions.[67]

Another study compared AI-assisted FSH dosing in real-world usage: using AI to help select starting and total FSH doses led to significantly lower FSH doses without reducing the number of metaphase II oocytes retrieved.[68]

6. Pharmacokinetics, Pharmacodynamics, and Safety

Interindividual variability and dosing

Evidence supports that patient factors such as age, AMH, AFC, BMI influence ovarian response and require individualized dosing. The ML models above incorporate such biomarkers in dose prediction showing tangible gains.[67,68]

OHSS risk and prevention

Cabergoline remains one of the safer adjuncts in women at high risk of OHSS, as noted. Calcium infusion may be an alternative in certain high-risk settings for severe OHSS prevention, but more high-quality RCTs are required.[64]

Safety data from the ML/AI studies to date do not show increased adverse events when lower FSH dosing is used or when the starting dose is guided by ML rather than standard clinician choice.[67,68]

7. Future Directions (based on current published evidence)

Because we are restricting to solid published evidence, future directions are necessarily modest and should focus on what has been demonstrated and what still requires confirmation. These include conducting larger RCTs to define the comparative effectiveness of calcium versus cabergoline for severe OHSS prevention across different patient subgroups (e.g., PCOS, high ovarian reserve), performing additional trials of CoQ10 in varying age groups and ovarian reserve statuses to determine optimal dosing, timing, and safety, initiating prospective multi-center studies to evaluate ML/AI-based decision support for FSH dosing in terms of live birth outcomes, OHSS incidence, cost, and patient satisfaction, and exploring how biomarkers and patient genetic or physiologic variability can be integrated into PK/PD models and AI tools for enhanced precision.

8. CONCLUSION

Pharmacology is at the heart of ART success, governing both ovarian stimulation and implantation outcomes. Advances in gonadotropin formulations, GnRH analogs, and adjunctive agents have greatly improved safety and efficacy, yet challenges such as OHSS and variable implantation rates persist. The future lies in personalized, pharmacogenomic-driven protocols to optimize both efficacy and safety, moving ART closer to precision medicine.

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The authors declare no conflict of interests.

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