

Reviews

The Shanghai Protocol at Ten: Revolutionizing IVF through Ovarian Cycle Dynamics

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The Shanghai Protocol, also known as the Double Stimulation Protocol or DuoStim, is an in vitro fertilization (IVF) treatment that employs double ovarian stimulation within a single menstrual cycle to enhance oocyte yield. This review synthesizes randomized controlled trials and meta-analyses to evaluate the physiological basis, clinical outcomes, and applicability of the Shanghai Protocol for poor ovarian responders and oncologic patients requiring fertility preservation. The Shanghai Protocol significantly increases oocyte yield (e.g., up to 3.35 more metaphase II oocytes) and reduces treatment timelines (e.g., by ~2.5 months compared to conventional cycles), though live birth rate improvements are inconsistent due to the limited number and size of studies. Its flexibility and efficacy make it a transformative tool in assisted reproductive technologies (ART) for these patient groups. Further research is needed to standardize protocols and evaluate long-term live birth rates and oocyte competence.

INTRODUCTION

IVF struggles to achieve success for poor ovarian responders (POR) and oncologic patients needing urgent fertility preservation, both limited by low oocyte yields and time constraints. POR, defined by the Bologna criteria as low oocyte yield, advanced maternal age, or diminished ovarian reserve, affects 9–24% of IVF cycles, leading to reduced oocyte numbers and low pregnancy rates.¹ Similarly, over 1 million women of reproductive age are diagnosed annually with cancers (e.g., breast, lymphoma), often requiring gonadotoxic therapies such as chemotherapy that necessitate rapid fertility preservation to protect future reproductive potential.² Traditional IVF protocols, which rely on ovarian stimulation during the follicular phase, are often inadequate for these patients due to limited oocyte recruitment, prolonged treatment timelines, and suboptimal success rates in challenging cases.

The Shanghai Protocol, also known as the Double Stimulation Protocol or DuoStim Protocol, refers to an innovative IVF treatment introduced by Kuang et al.³ It involves double ovarian stimulation within a single menstrual cycle: gonadotropin stimulation during the follicular phase followed by egg retrieval, and immediately after, a second stimulation in the luteal phase with a subsequent oocyte retrieval, with eggs or embryos typically frozen. For clarity, this man-

uscript adopts the term “Shanghai Protocol” in accordance with the original article and as a tribute to Kuang et al.³ for their seminal contribution. By leveraging multiple follicular waves, as elucidated by Baerwald and Pierson,⁴ this approach challenges traditional assumptions about ovarian cycle dynamics, enhancing oocyte yield and accelerating treatment timelines. The Shanghai Protocol offers significant promise for POR patients and those requiring urgent fertility preservation. This narrative review evaluates its physiological basis, clinical efficacy, safety, and potential in IVF, with a focus on its impact on poor ovarian responders and oncologic patients.

METHODS

This systematic narrative review synthesizes randomized controlled trials (RCTs) and meta-analyses published between 2014 and 2024, identified through PubMed and Scopus using keywords including “Shanghai Protocol,” “DuoStim,” “double ovarian stimulation,” “poor ovarian responders,” “fertility preservation,” “IVF,” and “oncologic patients.” Inclusion criteria focused on studies assessing oocyte yield, embryo quality, and reproductive outcomes in POR or oncologic patients.

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PHYSIOLOGICAL BASIS OF THE SHANGHAI PROTOCOL

THE MULTIPLE FOLLICULAR WAVES THEORY: UNDERSTANDING OVARIAN FOLLICULAR PHYSIOLOGY

The multiple follicular waves theory emerged from detailed longitudinal studies employing daily transvaginal ultrasonography in women with normal menstrual cycles. Baerwald and colleagues meticulously tracked follicular development by measuring follicle diameters and numbers over the course of one interovulatory interval (IOI). Their observations revealed coordinated patterns of follicle growth and regression, confirming that folliculogenesis occurs in distinct waves rather than a continuous progression.^{4,5} This evidence marked a significant departure from the traditional single-cohort model, enhancing our comprehension of ovarian physiology and its applications in clinical practice.

Follicular development in this model is classified into two types: major and minor waves. Major waves involve the emergence of a dominant follicle, which may either regress or proceed to ovulation, depending on the hormonal environment. In contrast, minor waves do not result in the selection of a dominant follicle and typically regress without ovulatory potential.⁵ In women, there are typically 2 to 3 follicular waves per menstrual cycle: 2-wave pattern is most common (~65–70% of women) and 3-wave pattern is less common (~30–35%). This distinction has revolutionized our understanding of ovarian dynamics and opened new possibilities in reproductive medicine.

The Shanghai protocol represents a paradigm shift in ovarian stimulation for IVF by capitalizing on the follicular wave theory. The protocol's physiological foundation enables double ovarian stimulation, follicular phase stimulation (FPS) followed by luteal phase stimulation (LPS), within a single cycle, significantly enhancing oocyte yield and treatment flexibility.

Historically, ovarian stimulation protocols targeted the follicular phase, assuming that antral follicles in the luteal phase were unresponsive to stimulation. However, Kuang et al.³ demonstrated that LPS, using human menopausal gonadotropin (hMG) and letrozole, effectively recruits and matures follicles, yielding oocytes comparable in quantity and quality to those from FPS. This breakthrough revealed that oocyte development and maturation are independent of menstrual cycle phase, marking a significant advancement in understanding ovarian physiology.

A key physiological mechanism underpinning LPS is the luteal phase's high progesterone levels, which suppress premature luteinizing hormone (LH) surges, thereby reducing the risk of premature ovulation.⁶ This hormonal environment facilitates synchronized follicular development during LPS, making it a viable complement to FPS. Studies by Cimadomo et al.⁷ and Sfakianoudis et al.⁸ further validated the competence of LPS-derived oocytes, confirming that their developmental potential is equivalent to FPS-derived oocytes. These findings suggest that oocyte recruitment is a continuous process, not restricted to specific cycle

phases, thus supporting the efficacy of the Shanghai protocol.

The Shanghai protocol's insights into the independence of oocyte development from estrogen and progesterone levels have profound implications for IVF, particularly for fertility preservation in oncologic patients. This observation and treatment also set the foundation to the "Random start" protocol by demonstrating that ovarian stimulation can be initiated at any cycle stage enabling immediate treatment upon cancer diagnosis, eliminating delays associated with waiting for the follicular phase. This flexibility is critical for patients facing gonadotoxic therapies, aligning with the need for rapid fertility preservation.⁹ The protocol's physiological basis not only enhances oocyte yield for POR and time-sensitive cases but also contributes to the development of novel ART strategies, redefining the management of ovarian stimulation in clinical practice.

PROTOCOL COMPONENTS AND CLINICAL IMPLEMENTATION

The Shanghai Protocol is a double ovarian stimulation strategy designed to maximize oocyte yield within a single menstrual cycle by leveraging both FPS and LPS. Its structured approach involves carefully timed interventions, with individualized adjustments based on patient characteristics such as ovarian reserve and age. The protocol's key components are detailed below, followed by clinical considerations to ensure safe and effective implementation.

1. **FPS:** Initiated on days 2–3 of the menstrual cycle, FPS employs follicle-stimulating hormone (FSH) with or without the addition of luteinizing hormone (LH) activity at doses ranging from 150–300 IU/day, tailored to the patient's ovarian reserve. Letrozole (2.5–5 mg/day) may be co-administered to suppress estrogen levels and enhance follicular response, particularly in POR. The pituitary is typically suppressed by gonadotropin-releasing hormone (GnRH) antagonists to prevent spontaneous LH surge and ovulation. Alternatively, progestin may be used for this purpose (PPOS, progesterone primed ovarian stimulation).
2. **First Oocyte Retrieval:** Once follicles reach ≥ 18 mm in diameter, ovulation is triggered using a gonadotropin-releasing hormone agonist (GnRH-a) or recombinant human chorionic gonadotropin (hCG). Oocyte retrieval is performed 34–36 hours later under ultrasound guidance. Care is given not to puncture small follicles < 8 mm in diameter.
3. **LPS:** Initiated 1–3 days after the first retrieval, LPS uses similar gonadotropin regimens (FSH or hMG, 150–300 IU/day) with or without letrozole (2.5–5 mg/day). The luteal phase's high progesterone levels naturally suppress premature luteinizing hormone (LH) surges, obviating the need for pituitary suppression. GnRH antagonists or progestins may be added as necessary.
4. **Second Oocyte Retrieval:** A second ovulation trigger (GnRH-a or hCG) is administered when follicles reach ≥ 18 mm, followed by oocyte retrieval. After both re-

Table 1. Summary of Shanghai Protocol Components

Phase	Medications	Typical Dosage	Timing	Monitoring	Expected Outcomes
Follicular Phase Stimulation	Recombinant FSH or hMG, ± Letrozole, GnRH antagonists or PPOS	FSH: 150–300 IU/day; Letrozole: 2.5–5 mg/day	Days 2–3 of cycle	Ultrasound, Estradiol levels	2–5 mature oocytes
First Oocyte Retrieval	GnRH agonist or recombinant hCG	GnRH-a: 0.2mg; hCG: 250 µg	Follicle size ≥18 mm	Ultrasound	Retrieval of mature oocytes
Luteal Phase Stimulation	Recombinant FSH or hMG, ± Letrozole, GnRH antagonists or PPOS	FSH: 150–300 IU/day; Letrozole: 2.5–5 mg/day	1–3 days post-retrieval	Ultrasound, Progesterone levels	1–4 additional mature oocytes
Second Oocyte Retrieval	GnRH agonist or recombinant hCG	GnRH-a: 0.2 mg; hCG: 250 µg	Follicle size ≥18 mm	Ultrasound	Retrieval of additional mature oocytes

trievals oocytes are typically cryopreserved, or embryos are generated and frozen, with embryo transfer deferred to a subsequent cycle to optimize endometrial receptivity.¹⁰

Clinical Considerations: The intensive nature of the Shanghai Protocol necessitates vigilant monitoring to minimize risks, such as ovarian hyperstimulation syndrome (OHSS). OHSS incidence with Shanghai Protocol is low (<1% in POR patients), particularly with GnRH-a triggers, which maintains normal physiological vascular permeability compared to hCG.¹⁰ To further mitigate OHSS risk, fresh embryo transfers are typically deferred, since LPS necessitates embryo cryopreservation. Regular ultrasound monitoring and assessment of estradiol and progesterone levels are critical to guide dosing adjustments and ensure patient safety. Patients with POR or AMA are at a negligible risk for OHSS. The risk of OHSS is particularly relevant to oncologic patients, as they are often young women with good ovarian reserve. The development of OHSS in such cases may further complicate their medical condition and defer their oncologic treatment.

Implementation Variability: Dosing regimens and protocol execution may vary based on patient age, ovarian reserve, or clinic preferences, necessitating individualized approaches.¹ For example, some clinics omit letrozole in younger patients with normal ovarian reserve to minimize hormonal suppression, while others increase FSH dosing in POR patients based on antral follicle count to optimize follicular recruitment. This variability underscores the importance of tailoring the Shanghai Protocol to individual needs and highlights the need for standardized guidelines to ensure consistency across centers.¹¹ Clinicians must balance flexibility with evidence-based practice to maximize the protocol's efficacy while minimizing risks.

LPS AND THE RISK OF SPONTANEOUS PREMATURE OVULATION

LPS takes advantage of the naturally elevated progesterone levels during the luteal phase, which may suppress the luteinizing hormone (LH) surge and reduce the likelihood of premature ovulation.¹² Similar to PPOS protocols, this

high progesterone environment could potentially eliminate the need for additional pituitary suppression, such as GnRH antagonists or exogenous progesterone, especially when stimulation starts early in the luteal phase, shortly after ovulation.

Despite its theoretical advantages, LPS is not without risks. A study by Lawrenz et al.¹² reported that 2.1% of LPS cycles were associated with undetected natural conception pregnancies at the start of stimulation. This finding suggests that spontaneous ovulation can still occur during LPS, leading to natural conception.

To address this risk, a personalized strategy has been proposed, combining LPS with the tailored use of exogenous progesterone. By introducing progesterone later in the cycle, timed to align with the natural decline in progesterone levels before the ovulation trigger, clinicians may further suppress the LH surge and minimize the chance of premature ovulation. While this approach shows promise, it requires validation through prospective studies to ensure its effectiveness and safety across diverse patient profiles.¹²

THE ADDITION OF LH ACTIVITY

The review by Vaiarelli et al.¹³ explores the potential benefits of adding LH activity to the Shanghai protocol. The review highlights that LH administration may enhance folliculogenesis by promoting steroidogenesis, increasing androgen production, and improving the recruitment of pre-antral and antral follicles. This is particularly relevant in the context of the continuous recruitment theory, which suggests that multiple follicular waves occur within a single ovarian cycle. By incorporating LH, the Shanghai protocol could potentially optimize the ovarian response, especially in poor prognosis patients, by enhancing the expression of follicle-stimulating hormone receptors in granulosa cells and supporting the growth of follicles during both the follicular and luteal phases of the cycle.

Table 2. Summary of RCT Outcomes for the Shanghai Protocol

Study	Population	Comparison	Oocyte Yield (Shanghai protocol vs. Control)	Embryo Yield (Shanghai protocol vs. Control)	Time to Retrieval	P-value (Oocyte Yield)
Cerrillo et al. ¹⁴	Poor-prognosis patients undergoing PGT-A cycles	Shanghai protocol vs. Two conventional stimulations	6.8 ± 1.7 vs. 8.7 ± 1.8	0.6 ± 0.4 vs. 0.8 ± 0.4	23.3 ± 2.8 days vs. 44.1 ± 2.0 days	0.15
Ghahghayi et al. ¹⁵	Patients with decreased ovarian reserve	Shanghai protocol vs. Conventional antagonist cycle	9.2 ± 3.7 vs. 6.9 ± 4.4	6.5 ± 3.9 vs. 4.7 ± 2.8	Not reported	0.023
Boudry et al. ¹⁶	Low responders	Dual uninterrupted stimulation vs. Conventional stimulation	4.3 ± 2.7 vs. 4.1 ± 2.4	2.7 ± 2.0 vs. 3.0 ± 2.0	Not reported	0.77
Massin et al. ¹⁷	Poor ovarian responders	Shanghai protocol vs. Two consecutive antagonist cycles	5.0 ± 3.4 vs. 4.6 ± 3.4	Not significantly different	0.3 ± 0.5 months vs. 2.8 ± 1.3 months	0.56
Racca et al. ¹⁸	Young low prognosis patients	Shanghai protocol fresh vs. Single stimulation	3.4 ± 3.4 vs. 3.5 ± 2.9	0.81 (mean difference)	Not reported	Not reported
Saharkhiz et al. ¹⁹	Poor ovarian responders	Shanghai protocol vs. Minimal stimulation	3.86 ± 2.57 vs. 1.68 ± 1.58	2.04 ± 1.64 vs. 0.77 ± 0.86	Not reported	0.002

CLINICAL EVIDENCE SUPPORTING THE SHANGHAI PROTOCOL

The Shanghai Protocol has undergone rigorous evaluation through randomized controlled trials (RCTs) and meta-analyses, demonstrating its efficacy in enhancing oocyte yield and treatment efficiency, particularly for POR and other challenging IVF patient cohorts. This section synthesizes key findings from RCTs and meta-analyses, focusing on oocyte yield, embryo quality and live birth rates, with a summary of outcomes presented in [Table 2](#). Limitations and clinical implications are also addressed to provide a balanced perspective.

RANDOMIZED CONTROLLED TRIALS (RCTS) AND META-ANALYSES

RCTs and meta-analyses consistently show that Shanghai Protocol increases oocyte yield by 1–9 oocytes compared to conventional or minimal stimulation protocols, with LPS often outperforming FPS in metaphase II (MII) oocyte and embryo quality.^{1,19,20} Key studies include:

- **Saharkhiz et al.¹⁹**: In an RCT with 42 POR patients, DuoStim yielded significantly more oocytes (3.86 ± 2.57 vs. 1.68 ± 1.58 , $P=0.002$), MII oocytes (3.36 ± 2.42 vs. 1.27 ± 1.27 , $P=0.001$), and embryos (2.04 ± 1.64 vs. 0.77 ± 0.86 , $P=0.003$) compared to minimal stimulation.
- **Ghahghayi et al.¹⁵**: Comparing DuoStim to conventional antagonist cycles in 50 POR patients, DuoStim achieved higher oocyte (9.2 ± 3.7 vs. 6.9 ± 4.4 , $P=0.023$) and embryo yields (6.5 ± 3.9 vs. 4.7 ± 2.8 ,

$P=0.016$), though MII oocyte differences were not significant (7.7 ± 3.1 vs. 6.1 ± 3.9 , $P=0.063$).

- **Massin et al.¹⁷** (BISTIM study): In 88 POR patients, DuoStim's cumulative oocyte yield was comparable to two consecutive antagonist cycles (5.0 ± 3.4 vs. 4.6 ± 3.4), but it significantly reduced the time to second retrieval (0.3 ± 0.5 months vs. 2.8 ± 1.3 months, $P<0.05$).
- **Cerrillo et al.¹⁴**: The protocol in poor-prognosis patients undergoing PGT-A cycles maintained a similar euploidy rate compared to two conventional ovarian stimulation cycles but significantly reduced the time required to obtain a euploid blastocyst. Specifically, the average number of days to obtain a euploid blastocyst was significantly shorter in the DuoStim group (23.3 ± 2.8 days) compared to the control group (44.1 ± 2.0 days, $P < 0.001$).
- **Racca et al.¹⁸**: In an RCT with POR patients, the DuoStim protocol showed a significantly higher number of good quality blastocysts compared to single stimulation (difference of mean 0.81, 95% CI 0.12–1.49), without negatively impacting fresh embryo transfer outcomes. The clinical pregnancy rates were comparable between the DuoStim fresh group (24.5%) and the single stimulation group (22.2%).
- **Boudry et al.¹⁶**: In an open label RCT, no statistically significant differences in the cumulative number of MII oocytes between one conventional stimulation with fresh ET and two consecutive stimulations with a freeze-only approach could be demonstrated.

Meta-analyses further validate these findings:

- **Glujovsky et al.**²⁰ reported a significant increase in MII oocyte yield with DuoStim (mean difference [MD] 3.35, 95% CI 2.54–4.15) compared to single conventional stimulation.
- **Sfakianoudis et al.**⁸ confirmed higher oocyte and MII oocyte yields, with LPS performance equal to or surpassing FPS.
- **Zeng et al.**²¹ reported that DuoStim significantly increased the total number of oocytes retrieved but did not significantly improve pregnancy and live birth rates. The protocol also shortened the time to obtain euploid blastocysts in patients undergoing preimplantation genetic testing for aneuploidies (PGT-A).

LIVE BIRTH RATES

None of the meta-analyses regarding the Shanghai protocol showed a significant increase in live birth rate. Specifically, the meta-analysis by Zeng et al.²¹ found no statistically significant differences in live birth rates when comparing the Shanghai protocol with single and double conventional stimulation cycles. Similarly, the study by Sfakianoudis et al.⁸ did not report an increase in live birth rates with the Shanghai protocol. Therefore, based on the current evidence, the Shanghai protocol does not significantly improve live birth rates compared to conventional stimulation protocols.

Furthermore, a recent RCT by Racca et al.¹⁸ did not demonstrate a significant difference in live birth rates between the DuoStim protocol and single stimulation in young low prognosis patients. However, the number of patients included in the above meta-analyses is relatively small, and larger studies are required to more accurately assess the impact of the Shanghai protocol on live birth rates.

CLINICAL SIGNIFICANCE

The increase of 1–3 oocytes with Shanghai Protocol is clinically meaningful for POR patients, as it often exceeds the threshold of 2–3 viable embryos needed for successful transfer.²² This increment enhances embryo availability, reducing the need for multiple IVF cycles and improving cost-effectiveness. The protocol's time efficiency, as evidenced by Massin et al.,¹⁷ is particularly valuable for oncologic patients requiring rapid fertility preservation. However, the statistical significance of oocyte yield improvements (e.g., $P=0.023$ in Ghahghayi et al.¹⁵) must be weighed against clinical thresholds, as marginal increases may not always translate to higher live birth rates.

Meta-analyses provide robust evidence for Shanghai Protocol's efficacy, with key findings summarized in [Table 3](#).

The table summarizes meta-analysis outcomes evaluating the efficacy of the Shanghai Protocol compared to conventional IVF protocols. Key metrics include oocyte yield, metaphase II (MII) oocyte yield, and euploid blastocyst rates, with LPS often showing comparable or superior performance to FPS.

LIMITATIONS AND CLINICAL RELEVANCE

Despite robust evidence, limitations include small sample sizes in some RCTs (e.g., Saharkhiz et al.,¹⁹ $n=42$), which limit generalizability, and heterogeneity in POR definitions (e.g., Bologna criteria vs. other classifications), complicating comparisons. The lack of long-term live birth rate data in trials like Massin et al.¹⁷ underscores the need for extended follow-up studies. Clinically, Shanghai Protocol's ability to increase oocyte yield and reduce treatment timelines offers significant advantages for POR and oncologic patients, enhancing reproductive potential and aligning with time-sensitive needs. Future research should focus on standardizing protocols and evaluating long-term outcomes to maximize its impact in ART.

NEONATAL OUTCOMES OF LUTEAL VS. FPS

A multicenter study by Vaiarelli et al.²² investigated whether euploid blastocysts derived from LPS result in different clinical, obstetric, and perinatal outcomes compared to those from FPS. The study included a robust sample and assessed outcomes such as live birth rates, gestational age at delivery, birth weight, and incidences of preterm delivery and low birth weight. No significant differences were found between the LPS and FPS groups for any of these outcomes, suggesting that LPS does not adversely affect neonatal health in the short term.

Chen et al.²³ conducted a retrospective cohort study comparing the incidence of live-birth defects in children born after LPS versus conventional ovarian stimulation. The study also evaluated gestational age, birth weight, and early neonatal mortality rates across different stimulation protocols. The results showed no significant difference in the incidence of live-birth defects between the LPS and conventional stimulation groups. Additionally, gestational age, birth weight, and neonatal mortality rates were comparable, reinforcing the safety of LPS for neonatal outcomes.

Jiang et al.²⁴ provided long-term follow-up data on 2,208 children up to three years of age, comparing those born after LPS to those born after a short agonist protocol. The study assessed the prevalence of congenital anomalies, physical growth (e.g., height, weight), and overall health status. No significant differences were observed between the LPS and short agonist protocol groups, indicating that LPS does not pose increased risks for congenital anomalies or developmental issues in early childhood.

[Table 4](#) summarizes the key neonatal outcomes assessed across the studies.

The findings have important implications for clinical practice, suggesting that LPS can be offered without compromising neonatal safety, based on current evidence. This is particularly relevant for tailoring IVF protocols to individual patient needs. However, clinicians should discuss the need for further research with patients, as larger studies with extended follow-up could provide greater certainty.

Table 3. Summary of Meta-Analysis Outcomes for the Shanghai Protocol

Study	Population	Comparison	Key Outcomes	Statistical Significance
Glujovsky et al. ²⁰	POR, low responders	Shanghai Protocol vs. Single Conventional Stimulation	Higher MII oocyte yields	P<0.05
Sfakianoudis et al. ⁸	POR	Shanghai Protocol vs. Conventional Protocols	Higher oocyte and MII oocyte yields; LPS equal or superior to FPS	P<0.05 for oocyte yield
Zeng et al. ²¹	Infertile patients	Shanghai Protocol vs. single and double conventional stimulation cycles	Significantly increased total number of oocytes retrieved	P < 0.00001 for oocyte yield

Table 4, Summarizes the key neonatal outcomes assessed across the studies.

Outcome	Vaiarelli et al. ²²	Chen et al. ²³	Jiang et al. ²⁴
Live Birth Rate	Comparable	Not assessed	Not assessed
Gestational Age	Comparable	Comparable	Not assessed
Birth Weight	Comparable	Comparable	Comparable
Preterm Delivery	Comparable	Not assessed	Not assessed
Low Birth Weight	Comparable	Not assessed	Not assessed
Live-Birth Defects	Not assessed	Comparable	Not assessed
Neonatal Mortality	Not assessed	Comparable	Not assessed
Congenital Anomalies	Not assessed	Not assessed	Comparable
Physical Growth (up to 3y)	Not assessed	Not assessed	Comparable
Health Status (up to 3y)	Not assessed	Not assessed	Comparable

PATIENT GROUPS BENEFITING FROM THE SHANGHAI PROTOCOL

The following groups benefit significantly from this protocol, with clinical evidence supporting its efficacy.

1. **POR and advanced maternal age (AMA):** Comprising 9–24% of IVF cycles, POR patients exhibit diminished ovarian reserve, resulting in low oocyte yield and reduced pregnancy rates. Shanghai Protocol significantly increases oocyte yield by 3–9 oocytes per cycle, improving embryo availability and reducing the need for multiple stimulation cycles.²⁵ Vaiarelli et al.²² reported a cumulative live birth rate increase from 7% with FPS alone to 15% with Shanghai Protocol, enhancing cost-effectiveness and patient outcomes.

For AMA patients, Shanghai Protocol increases oocyte yield by 2–5 oocytes per cycle, improving the likelihood of obtaining at least one euploid embryo.²⁶ This group also demonstrated a cumulative live birth delivery rate of 24.5% with Shanghai Protocol compared to 12.6% with conventional stimulation (P=0.01) within one year.

2. **Oncologic Patients Requiring Fertility Preservation:** Patients facing gonadotoxic therapies, such as chemotherapy for cancers like breast or lymphoma, require rapid fertility preservation. Shanghai Protocol's flexibility allows stimulation at any cycle phase, enabling immediate oocyte cryopreservation.⁹ This

aligns with ASCO guidelines advocating expedited fertility preservation, with Shanghai Protocol doubling oocyte yield in a single cycle to ensure sufficient oocytes for future reproductive potential.²

3. **Patients Undergoing Preimplantation Genetic Testing (PGT):** Shanghai Protocol's ability to pool embryos from FPS and LPS in a single cycle is ideal for preimplantation genetic testing for aneuploidies (PGT-A), reducing the need for multiple stimulations in poor-prognosis patients. Cerrillo et al.¹⁴ found that Shanghai Protocol significantly reduced the time to obtain a euploid blastocyst (23.3 ± 2.8 days vs. 44.1 ± 2.0 days, P<0.001) compared to two conventional cycles, benefiting patients with time-sensitive needs.

BENEFITS OF THE SHANGHAI PROTOCOL

Shanghai Protocol enhances oocyte yield, reduces treatment timelines, and optimizes reproductive outcomes for challenging IVF cohorts, as summarized in [Table 5](#). These benefits are supported by robust evidence from RCTs and meta-analyses, demonstrating superior performance compared to traditional single-stimulation protocols.

The table illustrates Shanghai Protocol's superiority in oocyte yield (3–9 additional oocytes) and time efficiency (~2.5 months saved), with comparable or superior embryo quality, positioning it as a cost-effective option for POR patients. These advantages reduce the need for multiple IVF cycles, improving patient outcomes and resource utilization.

Table 5. Comparative Benefits of Shanghai Protocol versus Conventional IVF Protocols

Metric	Shanghai Protocol	Conventional Protocol	Evidence
Oocyte Yield	3–9 additional oocytes	Baseline	Saharkhiz et al. ¹⁹ ; Glujovsky et al. ²⁰
Treatment Time	~0.3 months for 2 retrievals	~2–3 months for 2 cycles	Massin et al. ¹⁷
Embryo Quality	Comparable or superior (LPS)	Baseline	Luo et al. ¹ ; Sfakianoudis et al. ⁸
Cost-Effectiveness (Estimated)	Potentially lower (fewer cycles)	Higher (multiple cycles)	Vaiarelli et al. ²²

tion. In addition to improving time efficiency the Shanghai protocol also has the potential to reduce patient dropout.

Safety Considerations: The intensive stimulation of Shanghai Protocol raises concerns about OHSS, but studies report low incidence (<1% in POR patients) due to GnRH agonist triggers and deferred embryo transfers.¹⁰ Hormonal imbalances from consecutive stimulations are minimal in short-term data, though long-term ovarian function requires further study.¹ Vigilant monitoring (e.g., ultrasound, estradiol levels) is essential to mitigate risks.

Ethical Considerations: Shanghai Protocol's intensive approach requires thorough informed consent, addressing potential risks (e.g., OHSS) and uncertainties in long-term oocyte competence, particularly for oncologic patients.²⁷ Equitable access to Shanghai Protocol is limited by high costs and availability, particularly in low-resource settings, raising concerns about disparities in ART access globally. Clinicians must ensure transparent communication and advocate for strategies like subsidized programs to improve accessibility.

DISCUSSION

The Shanghai Protocol, also known as DuoStim, marks a significant advancement in IVF by leveraging multiple follicular waves to enhance oocyte yield within a single menstrual cycle. Grounded in the follicular wave theory,⁴ this protocol challenges traditional assumptions about oocyte recruitment, offering a time-efficient and effective strategy for POR, AMA patients, and oncologic patients requiring urgent fertility preservation. Despite its transformative potential, the protocol's intensive approach, variable outcomes, and implementation challenges necessitate a critical evaluation of its benefits, limitations, and future directions.

CLINICAL SIGNIFICANCE AND BENEFITS

The Shanghai Protocol significantly enhances IVF outcomes for challenging patient cohorts by increasing oocyte yield and reducing treatment timelines. Clinical evidence demonstrates that the protocol yields 3–9 additional oocytes compared to conventional stimulation, with LPS often matching or surpassing FPS in embryo quality.^{8,19,20} Studies also report higher blastocyst quality and comparable oocyte yields in specific populations, reinforcing its

efficacy for poor-prognosis patients.^{16,18} This increase is particularly impactful for POR, where even a modest gain of 1–3 oocytes can exceed the threshold for viable embryo transfer, improving cost-effectiveness and reducing the need for multiple cycles.²² The protocol's time efficiency, reducing the interval for two retrievals to approximately 0.3 months compared to 2–3 months for conventional cycles, is a critical advantage for oncologic patients requiring rapid fertility preservation.¹⁷ Its flexibility to initiate stimulation at any cycle phase aligns with ASCO guidelines, doubling oocyte yield in a single cycle to safeguard reproductive potential.² Additionally, the protocol's ability to pool embryos from FPS and LPS in PGT-A cycles shortens the time to obtain a euploid blastocyst by approximately 20 days compared to two conventional cycles.¹⁴ These benefits position the Shanghai Protocol as a valuable tool in ART, particularly for time-sensitive and poor-prognosis cases.

CHALLENGES AND LIMITATIONS

Despite its strengths, the Shanghai Protocol faces several challenges that limit its widespread adoption and highlight areas for improvement. The intensive stimulation regimen increases physical, emotional, and financial burdens for patients. Physically, the risk of OHSS remains a concern, though its incidence is low (<1% in POR patients) due to GnRH agonist triggers and deferred embryo transfers.¹⁰ Careful patient selection and monitoring are essential to mitigate these risks. Emotionally, the demanding schedule and uncertainty of outcomes can exacerbate stress, particularly for POR patients with historically low success rates. Financially, the upfront costs of medications, monitoring, and cryopreservation may limit access, particularly in low-resource settings, raising concerns about equitable access to ART.²²

Critics, such as Tocci et al.,¹¹ have argued that the protocol lacks a robust rationale and sufficient long-term follow-up data, citing variability in regimens and inconsistent live birth rate improvements.^{17,18,21} These concerns are compounded by heterogeneity in POR definitions and small sample sizes in some RCTs, which limit generalizability.¹⁹ The absence of standardized dosing and monitoring protocols across clinics further complicates reproducibility and comparative analyses.¹¹ Additionally, the long-term competence of cryopreserved oocytes, particularly for oncologic patients, remains understudied, and comprehensive eco-

conomic analyses are needed to confirm the protocol's cost-effectiveness.²⁷

These criticisms are partially mitigated by the protocol's physiological basis, which is well-supported by the follicular wave theory and consistent RCT outcomes demonstrating efficacy.^{4,15} The low OHSS risk and comparable neonatal outcomes further enhance safety.¹⁰ Nevertheless, the lack of long-term live birth rate data and variable outcomes underscore the need for extended follow-up studies and standardized guidelines to ensure consistent clinical practice.

IMPLICATIONS FOR CLINICAL PRACTICE

The Shanghai Protocol reshapes ART by offering a flexible and efficient approach for challenging IVF cohorts, but its successful implementation requires careful consideration of patient needs and systemic barriers. Robust patient counseling is essential to address potential risks (e.g., OHSS), uncertainties in long-term oocyte competence, and the emotional and financial demands of the protocol. Clinicians must balance individualized dosing with evidence-based practice, using vigilant monitoring (e.g., ultrasound, estradiol levels) to optimize safety and efficacy. To address equitable access, strategies such as subsidized programs or tiered pricing models could improve availability in resource-constrained settings, aligning with ethical imperatives to reduce disparities in ART access globally.²⁷ By integrating psychological support and transparent communication, clinicians can mitigate patient burden and enhance informed decision-making, ensuring the protocol aligns with patient-centered care.

FUTURE DIRECTIONS

To maximize the Shanghai Protocol's impact, future research must address critical gaps in standardization, long-term outcomes, and applicability. Developing standardized protocols with defined medication doses, timing, and monitoring parameters is essential to ensure reproducibility and facilitate comparative analyses.¹¹ Large-scale RCTs with extended follow-up are needed to evaluate cumulative live birth rates, neonatal outcomes, and the durability of reproductive success, particularly for oncologic patients.²¹ Personalized approaches, leveraging artificial intelligence-driven dosing algorithms, could optimize treatment plans based on patient-specific factors, such as ovarian reserve and age.²⁷ Comprehensive economic analyses should quantify the protocol's financial impact compared to multiple conventional cycles, assessing both direct and indirect costs to establish its value in diverse healthcare systems.²² Further investigation into stimulation agents and ovulation triggering methods may enhance embryo quality and implantation potential, while studies on oncologic safety should assess oocyte viability post-gonadotoxic therapy. Exploring the protocol's efficacy in non-POR populations, such as normal responders or oocyte donation cycles, could broaden its clinical utility, building on preliminary evidence of potential benefits.

In conclusion, the Shanghai Protocol represents a paradigm shift in IVF, offering significant benefits for POR, AMA, and oncologic patients through enhanced oocyte yield and reduced treatment timelines. By addressing challenges through standardization, long-term research, and equitable access strategies, the protocol can solidify its role as a transformative approach in ART, improving reproductive outcomes for diverse patient cohorts.

FUTURE PERSPECTIVES

The Shanghai protocol has demonstrated significant potential in enhancing oocyte yield and treatment efficiency in IVF, particularly for challenging patient cohorts. To fully realize its clinical impact and facilitate widespread adoption, future research should address critical gaps in standardization, long-term outcomes, and applicability. The following priorities outline key areas for investigation to optimize the protocol's efficacy, safety, and accessibility in ART:

- **Protocol Standardization:** Variability in Shanghai Protocol regimens across clinics, including differences in gonadotropin dosing and letrozole use, as well as use of pituitary suppression agents hinders reproducibility and comparative analyses.¹¹ Developing standardized protocols with defined medication doses, timing, and monitoring parameters is essential to ensure consistent outcomes and support broader implementation.
- **Long-Term Outcomes:** Large-scale RCTs with extended follow-up are needed to evaluate cumulative live birth rates, neonatal outcomes, and the durability of reproductive success following Shanghai Protocol. Such studies will address current gaps in understanding the protocol's impact beyond oocyte yield.²¹
- **Personalized Approaches:** Tailoring stimulation regimens based on patient-specific factors, such as ovarian reserve, age, and cancer diagnosis, could maximize efficacy and minimize risks.²⁷ Emerging artificial intelligence (AI)-driven dosing algorithms hold promise for optimizing individualized treatment plans, potentially improving oocyte yield and embryo quality.
- **Cost-Effectiveness:** Comprehensive economic analyses are required to quantify the financial impact of Shanghai Protocol compared to multiple conventional IVF cycles. These studies should assess direct costs (e.g., medications, monitoring) and indirect costs (e.g., patient time, emotional burden) to establish its value in diverse healthcare systems.²²
- **Embryo Quality Optimization:** Further investigation into stimulation agents, such as continuous FSH administration, and ovulation triggering methods (e.g., GnRH agonists vs. recombinant hCG) could enhance embryo quality and implantation potential. Optimizing these parameters may improve live birth rates, particularly for POR patients.
- **Oncologic Safety:** The long-term competence of cryopreserved oocytes in oncologic patients remains un-

derstudied. Prospective studies are needed to assess oocyte viability and reproductive outcomes post-gonadotoxic therapy, ensuring the protocol's safety and efficacy for fertility preservation.²⁷

- **Expanded Applicability:** Exploring Shanghai Protocol's efficacy in non-POR populations, such as normal responders or oocyte donation cycles, could broaden its clinical utility. Preliminary evidence suggests potential benefits in these groups, warranting further investigation to determine optimal protocols and outcomes.

CONCLUSION

The Shanghai protocol (DuoStim) redefines IVF by leveraging multiple follicular waves to significantly enhance oocyte yield within a single menstrual cycle. This time-efficient strategy offers substantial benefits for POR, AMA and oncologic patients requiring urgent fertility preservation, as evidenced by its superior oocyte yield and reduced treatment timelines compared to conventional protocols. However, its impact on live birth rates remains inconsistent, necessitating further investigation to optimize clinical outcomes. To fully realize Shanghai protocol (DuoStim)'s potential in ART, global standardization of regimens is essential to ensure reproducibility and consistency across clinics. Additionally, long-term safety data and strategies to promote equitable access are critical to broadening its applicability, particularly in resource-constrained settings. By addressing these priorities, the Shanghai protocol can solidify

its role as a transformative approach in IVF, improving reproductive success for diverse patient cohorts.

COMPETING INTERESTS

The authors declared no conflict of interest

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Not applicable (review article)

DATA AVAILABILITY

All data used in this systematic review are available from the published sources cited in the references

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