ALIVE

ART LEARNING INITIATIVES FOR EXPERTS

Issue 12

PCOS and Infertility: Managing Current Challenges Part 3

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CONTENTS

Foreword

Triggering for oocyte maturation, luteal phase support and subsequent fresh or frozen embryo transfer are important steps in IVF program to achieve optimal reproductive outcomes in women with or without PCOS. Of late, the concept of "patient-friendly" IVF is a repeated theme in the field of ART. Individualization of triggers for ovulation induction, LPS are much debated topics in the field of ART today. Continuous research is underway for these stages of ART to maximize efficacy and safety, minimize the treatment burden and adverse effects for the patients undergoing IVF and deliver successful outcomes.

This issue explores different aspects of ovulation triggering, luteal phase support, choosing fresh or frozen embryo transfer and the role of personalizing these stages to make IVF a safer alternative for infertile couples to enjoy the bliss of parenthood.

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Introduction

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2. *Sawankar SG, Malhotra J, Bora NM, et al. Pharmacological Options to Trigger Final Oocyte Maturation in In Vitro Fertilization. J South Asian Feder Obst Gynae 2020;12(1):38-44.*
3. *Shahar Kol, Ofer Fainaru. Chapter 23 - The Role of GnRH Agonist Triggering in GnRH Antagonist-Based Ovarian Stimulation Protocols, Editor(s): Peter C.K. Leung, Eli Y. Adashi, The Ovary (Third Edition), Academic Press, 2019, Pages 363-377.*
4. *Deepika K, Baiju P, Gautham P et al. Repeat Dose of Gonadotropin-releasing Hormone Agonist Trigger in Polycystic Ovarian Syndrome Undergoing In Vitro Fertilization Cycles Provides a Better Cycle Outcome - A proof-of-concept Study. J Hum Reprod Sci. 2017;10(4):271-280.*
5. *Engmann L, Benadiva C, Humaidan P. GnRH agonist trigger for the induction of oocyte maturation in GnRH antagonist IVF cycles: a SWOT analysis. Reprod Biomed Online. 2016;32(3):274-85.*

Triggering final oocyte maturation is a pivotal step in modern patient-tailored IVF/ICSI treatment for securing the optimal number of mature oocytes without compromising fertilization, embryo development and live birth.

It is well known that hCG and GnRH agonists (GnRHa) are the most commonly used triggers. While hCG was the first triggering agent clinically available, the GnRH agonists, of late, have dominated the IVF arena, given their capacity to induce pituitary downregulation and to minimize the risk of premature luteinization during ovarian stimulation.

GnRHa trigger has been a boon in polycystic ovarian syndrome (PCOS) patients undergoing in IVF cycles, as it significantly reduces or nearly eliminates the risk of OHSS.

Despite several advantages of GnRHa triggering, some studies have reported poor reproductive outcomes and a worldwide survey has shown that GnRHa trigger is used only in 5.2% to 36.1% of cases.

However, a plethora of old as well as recent clinical evidences show that GnRH agonist trigger has better advantages over hCG trigger in delivering better reproductive outcomes.

A prospective, randomized, double-blind, proof-of-concept study by Deepika et al., showed that a repeat dose of GnRHa trigger 12 h following the first dose yielded a better maturity of oocytes, higher number of blastocysts, and a trend towards higher clinical pregnancy than a single dose in PCOS patients (n=125; Group A: single dose of GnRHa 0.2 mg, 35 h prior to oocyte retrieval, and Group B: 0.2 mg GnRHa 35 h prior to oocyte retrieval + repeat dose of 0.1 mg 12 h following the 1st dose) undergoing IVF in antagonist cycles.

Comparison of triggers in PCOS women-GnRHa vs hCG trigger: *Clinical evidences*

1. *Youssef MA, Van der Veen F, Al-Inany HG et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. Cochrane Database Syst Rev. 2014;2014(10):CD008046.*
2. *Bourdon M, Peigne M, Solignac C et al. Gonadotropin-releasing hormone agonist (alone or combined with human chorionic gonadotropin) vs. human chorionic gonadotropin alone for ovulation triggering during controlled ovarian stimulation for in vitro fertilization/intracytoplasmic sperm injection: a systematic review and meta-analysis. Fertil Steril Rev 2021;2:353-370.*
3. *Deepika K, Suvarna R, Sumi M et al. HCG trigger versus GnRH agonist trigger in PCOS patients undergoing IVF cycles: frozen embryo transfer outcomes. JBRA Assist Reprod. 2021;25(1):48-58.*
4. *Farag AH, NasrEl-deen MH and Hassan RM. Triggering ovulation with gonadotropin-releasing hormone agonist versus human chorionic gonadotropin in polycystic ovarian syndrome. A randomized trial. Middle East Fertility Society Journal. 2015;20:217-223.*
5. *Le MT, Nguyen DN, Zolton J et al. GnRH Agonist versus hCG Trigger in Ovulation Induction with Intrauterine Insemination: A Randomized Controlled Trial. Int J Endocrinol. 2019 Mar 13; 2019:2487067.*
6. *Humaidan P, Kol S, Papanikolaou EG; Copenhagen GnRH Agonist Triggering Workshop Group. GnRH agonist for triggering of final oocyte maturation: time for a change of practice? Hum Reprod Update. 2011;17(4):510-524.*

Some studies have evaluated the results comparing the GnRHa and hCG trigger in women with PCOS.

A Cochrane review study evaluated the effectiveness and safety of GnRH agonists vs. hCG for triggering final oocyte maturation in IVF and ICSI for women undergoing COH in a GnRH antagonist protocol. However, out of the 17 RCTs (n = 1847) included in the review, only two studies had PCOS patients.

Review results showed that final oocyte maturation triggering with GnRH agonist instead of hCG in fresh autologous GnRH antagonist IVF/ICSI treatment cycles prevented OHSS [(mild, moderate or severe; OR 0.15; eight RCTs, 989 women, moderate-quality evidence (Figure 1)]. This showed that with the use of a GnRH agonist, for a woman with a 5% risk of OHSS using hCG, the rate would be between nil and 2%.

In donor-recipient cycles, use of GnRH agonists instead of hCG resulted in a lower incidence of OHSS (OR 0.05; three RCTs, 374 women), with no evidence of a difference in live birth rate.

However, GnRH agonist trigger in fresh autologous cycles was associated with a lower live birth rate, a lower ongoing pregnancy rate (pregnancy >12 weeks) and a higher rate of early miscarriage (< 12 weeks) suggesting probable benefits with freeze-all policy.

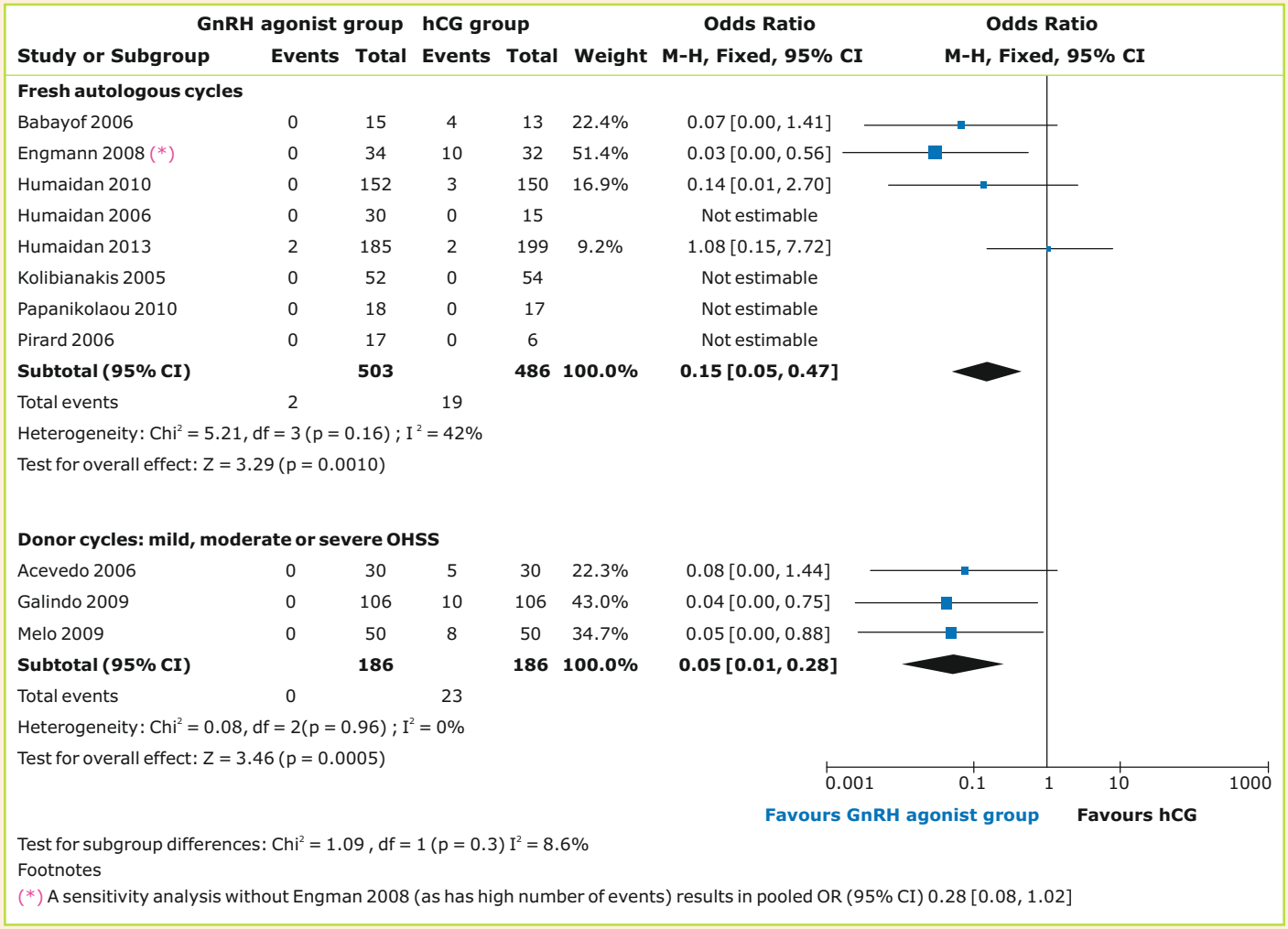

Figure adapted from Youssef MA et al. Cochrane Database Syst Rev. 2014;2014(10):CD008046.

Figure 1. GnRH agonist versus hCG for oocyte maturation triggering showing OHSS incidence per women randomly assigned

Another systematic review and meta-analysis of 29 studies (few studies including PCOS women and total n=26 studies including 2,755 women; 1,419 had GnRHa triggering and 1,336 had hCG alone for triggering) evaluated GnRHa triggering improved oocyte maturation, pregnancy outcomes, and safety compared with hCG triggering during controlled ovarian stimulation.
The results were as follows:

- GnRHa trigger compared with hCG alone resulted in significantly higher number of retrieved and mature oocytes (p=0.01 and p=0.04 respectively)
- GnRHa alone for triggering was beneficial in preventing OHSS, especially for "high" responders, compared with hCG alone (OR=0.01)
- After **dual triggering (GnRHa+hCG)**, there was a statistically significantly higher number of retrieved and mature oocytes and clinical pregnancy rate compared with hCG alone but no reduction in the OHSS risk.

Deepika et al., in a prospective, observational cohort study evaluated the outcomes following the transfer of embryos in frozen embryo transfer (FET) cycles obtained from GnRHa trigger and hCG trigger in PCOS patients of Asian origin undergoing an antagonist protocol [Group A: GnRHa trigger (n=92) and Group B: hCG trigger (n=101)].
The study results showed that cumulative live birth rate per stimulation cycle favoured GnRHa trigger against the hCG trigger [55.4% vs. 36.6%; p=0.009 respectively; OR=2.15; p=0.008].
A significantly higher number of mature oocytes (19.1±11.7 versus 14.1±4.3; p<0.001) and blastocysts (4.2±1.63 versus 3.26±1.22; p<0.001; Table 1) were available in the GnRHa group compared to the hCG group.
The incidence of moderate to severe OHSS in the hCG group was very high compared to 0% in GnRHa group (p<0.001).
In PCOS patients undergoing IVF, hCG trigger should be replaced by a GnRHa trigger with vitrification of all embryos followed by FET.

Table 1. Embryological and cycle outcomes

Variables	Group A (GnRHa) (n=92)	Group B (hCG) (n=101)	p value
Number of oocytes	23.5±7.8	20.8±5.4	0.006
Mature oocytes (MII)	19.1±11.7	14.1±4.3	<0.001
Fertilized oocytes (2PN)	15.6±5.6	11.7±3.6	<0.001
Top quality cleavage embryos	12.9±3.32	9.09±2.99	<0.001
Blastocysts	4.2±1.63	3.26±1.22	<0.001
Blastocyst conversion	59.9%	58.2%	0.689
OHSS n (%)	1 (0.52%)	91 (47.4%)	<0.001

Values are expressed as mean± SD. p<0.05= statistically significant.

Table adapted from Deepika K et al. JBRA Assist Reprod. 2021;25(1):48-58.

Farag et al., in a prospective study compared GnRH agonist and hCG for triggering ovulation in 85 infertile PCOS women who had ovulation induction with clomiphene citrate. GnRH agonist 0.2 mg (group 1) or hCG 10,000 IU (group 2) was given to trigger ovulation.
The results showed similar cumulative pregnancy rates (17.14% versus 20% respectively;

p = 0.332; Table 2). The ovulation rates were 80% versus 68.6% (p = 0.413); 94.3% versus 90.9% (p =0.669); 97.1% versus 93.7% (p = 0.603) in the two groups respectively for 3 cycles of induction. A total of seven patients developed mild OHSS while no patients had moderate/severe OHSS.
Triggering with GnRHa in PCOS may be an effective alternative to hCG without compromising luteal function and pregnancy rates after repeated cycles of treatment.

Table 2. Comparison between groups in the study

Studied parameters	Studied groups		p value
	Group 1 (GnRHa) (n =35)	Group 2 (hCG) (n=35)	
Clinical pregnancy n(%)			
After 1st cycle	0(0%)	2(5.7%)	0.493
After 2nd cycle	0(0%)	1(3%)	0.485
After 3rd cycle	6(17.1%)	4(12.5%)	0.736

Table adapted from Farag AH et al. Middle East Fertility Society Journal. 2015;20:217-223.

Le et al., in a prospective, randomized, comparative study assessed the clinical pregnancy rates (CPRs) in 197 infertile patients who were administered either GnRHa or hCG for ovulation trigger (n=98 cycles vs. n=99 cycles respectively) in intrauterine insemination (IUI) cycles. PCOS was the cause for infertility in average 34% cases (GnRHa triggered cycles 34.7% and 33.3% for hCG triggered cycles).
After adjusting for body mass index (BMI) and infertility duration, there was no difference in CPR between the two groups (OR 0.58, 95% CI 0.27-1.25, p=0163; Table 3).

Table 3. Intervention outcomes after BMI and infertility adjustment in GnRHa and hCG triggered cycles

Outcomes	GnRHa-triggered cycles (n = 98)	hCG-triggered cycles (n = 99)	p value
Ovulation rate	OR 0.56 CI: 95% (0.23–1.38)		0.207
Biochemical pregnancy rate	OR 0.47 CI: 95% (0.23–0.98)		0.044
Clinical pregnancy rate	OR 0.58 CI: 95% (0.27–1.25)		0.163

Table adapted from Le MT et al. Int J Endocrinol. 2019; 2019:2487067.

This study showed that GnRHa can be used to trigger ovulation in stimulated and natural cycles with IUI.

A review of nine trials by Humaidan et al., showed no OHSS after GnRHa triggering [0% incidence in the GnRHa group: risk difference 5%] in fresh IVF cycles with ET. In oocyte donation cycles (4 trials) the OHSS incidence was 0%. The delivery rate improved significantly after modified luteal support [6% risk difference in favor of the hCG group when compared with initial studies with conventional luteal support [18% risk difference].
The results showed that GnRHa triggering is a valid alternative to hCG triggering, resulting in elimination of OHSS.

Individualization of trigger in PCOS

1. *Maghraby H, Saleh H, Fourtia IL et al. The dilemma of the trigger timing in IVF: a review. Middle East Fertility Society Journal. 2024, 29:8.*
2. *Kol S, Homburg R, Alsbjerg B, Humaidan P. The gonadotropin-releasing hormone antagonist protocol--the protocol of choice for the polycystic ovary syndrome patient undergoing controlled ovarian stimulation. Acta Obstet Gynecol Scand. 2012;91(6):643-647.*

Several factors need to be considered when deciding the time of the trigger: the size of the leading follicles, distribution of the follicular cohort, the duration of stimulation, the protocol used for stimulation, and ovarian response status.
Of late, individualization/personalization of therapy is gaining importance in all fields of medicine. "Patient-friendly" IVF is a repeated theme in the field of ART.

In recent times, there is a question whether there is a need to individualize the timing of trigger according to the predicted pattern of ovarian response or in other words, whether the predicted response to ovarian stimulation affect the trigger timing.
Individualized criteria for timing of ovulation trigger in poor responders are not yet established. There is also no absolute consensus on the best time for triggering ovulation in women with PCOS.

According to published data, there are no interventional studies investigating specific criteria for the timing of final oocyte maturation for PCOS women. There are only a few studies investigating the effect of the duration of ovarian stimulation in PCOS women separately.
Some authors have hypothesised that it might be preferable to administer the trigger earlier in high responders than in normal and poor responders to avoid premature progesterone rise and consequently poor outcomes.

Maghraby et al., in their paper suggest the following aspects for individualization of trigger:

1. The timing of triggering of final oocyte maturation in ICSI cycles (stimulation phase length) should be individualized on a case-by-case basis.
2. The decision of administration of the trigger in ICSI cycles is multifactorial and many factors should be considered while making such decision as:
   i. Leading follicles size (16-22 mm) is associated with the optimum oocyte maturation ratio.
   ii. Size of the remaining cohort of follicles should be proportionally large follicles (≥ 14 mm).
   iii. The protocol used for ovarian stimulation:
      - For GnRH agonist protocol: prolongation of stimulation 24-48 h in agonist cycles would result in higher oocyte yield and more mature oocyte and in turn better outcomes.
      - For GnRH antagonist protocol: prolongation of stimulation beyond the precise timing (criteria) of trigger seems to have no added benefits in case of poor and high responders.

Luteal phase support for PCOS

1. *Kicińska AM, Stachowska A, Kajdy A et al. Successful Implementation of Menstrual Cycle Biomarkers in the Treatment of Infertility in Polycystic Ovary Syndrome-Case Report. Healthcare (Basel). 2023;11(4):616.*
2. *Harzif AK, Pratamasari SMR, Rumapea CTP et al. The efficacy of luteal phase support in women with polycystic ovary syndrome following assisted reproductive technology: a systematic review. Middle East Fertil Soc J. 2024;29:40.*
3. *Zhao J, Hao J, Li Y. Individualized luteal phase support after fresh embryo transfer: unanswered questions, a review. Reprod Health. 2022;19(1):19.*
4. *Humaidan P, Papanikolaou EG, Kyrou D et al. The luteal phase after GnRH-agonist triggering of ovulation: present and future perspectives. Reprod Biomed Online. 2012;24(2):134-141.*
5. *Haahr T, Roque M, Esteves SC and Humaidan P (2017) GnRH Agonist Trigger and LH Activity Luteal Phase Support versus hCG Trigger and Conventional Luteal Phase Support in Fresh Embryo Transfer IVF/ICSI Cycles-A Systematic PRISMA Review and*

Meta-analysis. Front. Endocrinol. 8:116.
6. *Alyasin A, Mehdinejadiani S, Ghasemi M. GnRH agonist trigger versus hCG trigger in GnRH antagonist in IVF/ICSI cycles: A review article. Int J Reprod Biomed. 2016;14(9):557-566.*
7. *Humaidan P, Engmann L, Benadiva C. Luteal phase supplementation after gonadotropin-releasing hormone agonist trigger in fresh embryo transfer: the American versus European approaches. Fertil Steril. 2015;103(4):879-885.*

Polycystic ovary syndrome is the most common cause of anovulatory infertility. Absent, impaired, or rare ovulation induces progesterone deficiency in the luteal phase, which is a critical problem in PCOS. A luteal phase insufficiency/defect with all of its clinical consequences is routinely observed among women with PCOS.

Luteal phase support is a crucial aspect of ART entailing administration of medications like progesterone, progestins, hCG, or GnRH agonists to bolster implantation success and early embryonic growth, enhancing the corpus luteum's function.
It should also be noted that LPS does not have so many choices as the individualized COS protocols and endometrium preparation protocols.
The efficacy of LPS in women with PCOS undergoing ART is an important concern in reproductive medicine. The most plausible reason for the luteal-phase defect seen in stimulated GnRH antagonist cycles triggered with a GnRHa seems to be a lack of endogenous LH activity during the early to mid-luteal phase, which necessitates a modification of the standard luteal-phase supplementation currently used after hCG triggering to secure the reproductive outcome.

Consequently, in the modified LPS, one bolus of hCG administered either at the time of triggering (dual trigger) or after oocyte retrieval rescues the luteal phase after GnRHa triggering, resulting in a reproductive outcome comparable with that of hCG triggering. At the same time, the risk of OHSS seems to be decreased, even in the OHSS high-risk patient.

Two different modified LPS strategies have been proposed to overcome the luteal phase deficiency in the last decade.
In the "European approach" the endogenous steroid (progesterone and estradiol) production by the corpora lutea is boosted by exogenous LH activity, i.e., LH or hCG after GnRHa trigger.
The other approach is called the "American approach" or the intensive LPS in which luteal progesterone and estradiol are administered exogenously and doses adjusted according to serum steroid levels, thus, disregarding the function of the corpora lutea.
Luteal phase supplementation is yet to be well studied in women with PCOS undergoing ART.

A systematic review of 5 studies comprising a total of 818 patients evaluated the effectiveness of LPS in women with PCOS undergoing ART, with a focus on pregnancy rates as the primary endpoint. Letrozole, clomiphene citrate, and human menopausal gonadotropin as ovulation induction agents and different forms of progesterone for LPS (oral, intramuscular, and intravaginal) were used in the studies.
Results demonstrated inconsistent efficacy of LPS, with some studies showing significant improvements in pregnancy rates with LPS, while others showed no statistically significant difference. The review results suggested that LPS may improve pregnancy rates in women with PCOS undergoing ART but is influenced by the choice of ovulation induction agent and the route of progesterone administration.
Researchers opined that **personalized treatment** approaches considering patient response and emerging evidence are essential.

Why individualization in LPS is important? – Clinical evidences

1. Boynukalin FK, Tohma YA, Yarkıner Z et al. (2024) Individualized luteal phase support in frozen-thawed embryo transfer after intramuscular progesterone administration might rectify live birth rate. Front. Endocrinol. 15:1412185.
2. Benadiva C, Engmann L. Luteal phase support after gonadotropin-releasing hormone agonist triggering: does it still matter? Fertil Steril. 2018;109(5):763-767.
3. Lawrenz B, Coughlan C, Fatemi HM. Individualized luteal phase support. Curr Opin Obstet Gynecol. 2019;31(3):177-182.
4. Zhao J, Hao J, Li Y. Individualized luteal phase support after fresh embryo transfer: unanswered questions, a review. Reprod Health. 2022;19(1):19.
5. Álvarez M, Gaggiotti-Marre S, Martínez F et al. Individualised luteal phase support in artificially prepared frozen embryo transfer cycles based on serum progesterone levels: a prospective cohort study. Hum Reprod. 2021;36(6):1552-1560.
6. Durdag GD, Bektas G, Turkyilmaz E et al. Effect of Individualized Progesterone Supplementation for Luteal Support in Frozen-Thawed Cycles on Pregnancy Outcome. Gynecol Obstet Reprod Med 2022;28(1):50-55.

In recent years, increasing attention has been paid to the individualization of ovarian stimulation (OS) and LPS in ART. Individualization is crucial to maximize efficacy and safety and to minimize the treatment burden, side effects, and cost. At the same time, a paradigm shift has occurred from fresh embryo transfers (ETs) to frozen embryo transfers (FETs) in IVF treatments, and the individualization of LPS in FET cycles has become the centre of attention.

Developing an individualized approach to managing the luteal phase and optimizing conception rates without increasing the risk of OHSS is essential for the clinician. Several factors may be predictive of clinical outcomes and OHSS development, and formulation of management guidelines can be tailored to a patient's response. It should be noted that current developments in ART are characterized by a trend toward embryo vitrification and subsequent FET.

However, a 'freeze-all-strategy' may not apply to all patients and management of an adequate LPS is crucial in order to achieve a pregnancy after FET. The most common approach for LPS is the administration progesterone (oral, intramuscular, and intravaginal). The uniformity of LPS is not in keeping with the diversity and developments of individualized ovarian stimulation treatment. Thus, there is a need for individualization of the LPS and to achieve this, reproductive medicine specialists need to be aware of the impact of ovarian stimulation on the luteal phase and the available approaches for LPS.

However, individualization of LPS has not been yet well implemented to date.

It is the task of the reproductive medicine specialist to individualize LPS according to the patient's specific characteristics, needs and desires and the type of treatment performed.

Individualization of LPS after GnRH agonist trigger can be performed with the use of low hCG dosages or even without any additional hCG, according to the progesterone levels in the early and mid-luteal phase.

The greatest indication for individualization of the luteal phase is following GnRH agonist trigger in high responder patients in order to tailor LPS to the patient-specific pattern of luteolysis and minimize the risk of causing OHSS with unnecessary high hCG dosages. Future studies should develop an algorithm, which provides the minimal-required hCG dosage, depending on the systemic progesterone levels.

Recent studies have shown that many modified LPS programs are used in ART cycle. In hCG cycles used for final oocyte maturation, the progesterone with or without low dose of hCG may be adequate to maintain pregnancy. However, in the GnRHa for trigger cycles, individualized low dose of hCG administration with or without progesterone is suggested.

Zhao et al., in their paper opined that infertile women should be provided individualized based on their specific characteristics, desires and the treatment protocol. They recommended to initiate the LPS between 24 and 72 h after oocyte retrieval and continue at least until the hCG test is positive (Figure 2). The addition of estradiol and the route of progesterone administration appear to be independent of the improvement in outcomes.

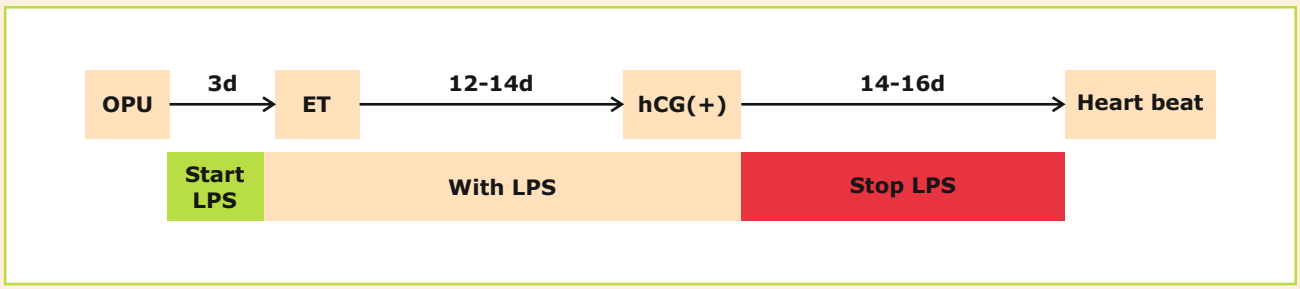

Figure adapted from Zhao J et al. Reprod Health. 2022;19(1):19.

Figure 2. Optimal initiation and duration of LPS
OPU oocyte pick-up, ET embryo transfer, LPS luteal phase support

Alvarez et al., in a prospective, observational cohort study showed that individualized LPS with subcutaneous progesterone coadministered with vaginal progesterone before FET under hormone replacement treatment therapy resulted in excellent ongoing pregnancy rates and live birth rates. A total of 574 cycles (453 patients) were analysed: 348 cycles (leading to 342 euploid FET) with adequate P4 on the day previous to FET, and 226 cycles (leading to 220 euploid FET) under iLPS after low P4 on the previous day to FET, but restored P4 levels on the transfer day. Overall, the study included 574 HRT FET cycles (453 patients). However, this study did not include women with PCOS.

Boynukalin et al., in a retrospective, cohort study evaluated whether individualized LPS improved pregnancy outcomes in cases with a low serum P concentration and the effectiveness of rescue protocol using IM progesterone (IM-P) in FET. This study included 637 single or double blastocyst FETs receiving 100 mg IM-P after incremental estrogen treatment. Patients with serum P concentrations <20.6 ng/ml on the ET day were administrated 400 mg vaginal progesterone for rescue and the results were compared in patients who did not need rescue vaginal P (ET-day P concentration ≥ 20.6 ng/ml). **PCOS was the cause of infertility in 18.8% and 16.1% patients described above respectively along with other causes** (Table 4).

Table 4. Comparison of outcomes in the study

	ET-day P concentration < 20.6 ng/ml	ET-day P concentration ≥ 20.6 ng/ml	p value
Clinical pregnancy rate	45/85 (52.9%)	326/552 (59.6%)	0.287
Live birth rate	40/85 (47.1%)	280/552 (50.7%)	0.526
Miscarriage rate	5/45 (11.1%)	46/326 (14.1%)	0.583

Table adapted from Boynukalin FK et al. Front. Endocrinol. 2024;15:1412185.

Rescue vaginal P administration for low ET day serum P concentrations following IM-P resulted in comparable live birth rates.

Durdag et al., in a prospective cohort study (n=30) evaluated mid-luteal serum progesterone levels and pregnancy outcomes after providing individualized LPS in hormonally replaced FET cycles. Vaginal progesterone treatment was supported by 100 mg IM-P according to serum P levels as individualized LPS. PCOS was one of the causes of infertility in 3 patients in this study.
The results showed no significant difference between mid-luteal progesterone levels of the

patients whose transfer day progesterone was above and below 10 ng/mL (p=0.481). No significant difference was found in pregnancy outcomes in the study with individualized progesterone application (Table 5).

Table 5. Pregnancy rates due to progesterone values at transfer day and 8th day

	Pregnancy (–) (n=14)	Pregnancy (+) (n=16)	p value
PG <10 ng/mL at transfer day	50.0%	50.0%	0.765
PG ≥10 ng/mL at transfer day	44.4 %	55.6%	
PG <10 ng/mL at 8th day	71.4%	**28.6%**	***0.204***
PG ≥10 ng/mL at 8th day	39.1%	**60.9%**	

PG: Progesterone

Table adapted from Durdag GD et al. Gynecol Obstet Reprod Med 2022;28(1):50-55.

Studies on individualization of LPS in PCOS patients are less and further studies are necessary to determine the optimal LPS for each individual patient.

Freeze all policy

1. *Celada P, Bosch E. Freeze-all, for whom, when, and how. Ups J Med Sci. 2020;125(2):104-111.*
2. *Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. Fertil Steril. 2016;106(7):1634-1647.*
3. *Leathersich S, Roche C and Hart R. Minimising OHSS in women with PCOS. 2025; Front. Endocrinol. 16:1507857.*
4. *Borges E Jr, Braga DP, Setti AS, Vingris LS, Figueira RC, Iaconelli A Jr. Strategies for the management of OHSS: Results from freezing-all cycles. JBRA Assist Reprod. 2016;20(1):8-12.*

The 'freeze-all' practice refers to the cryopreservation of all mature oocytes or viable embryos after ovarian stimulation OS. The development of the vitrification technique has been crucial to make this approach a reality, since it increases the post-thaw survival rates and permits comparable implantation rates with fresh embryos.
The application of 'freeze-all' approach was primarily illustrated in protocols to avoid OHSS by delaying implantation. The freeze-only strategy of IVF provides a number of opportunities to optimize the overall outcome in several every-day situations in daily practice (Figure 3).

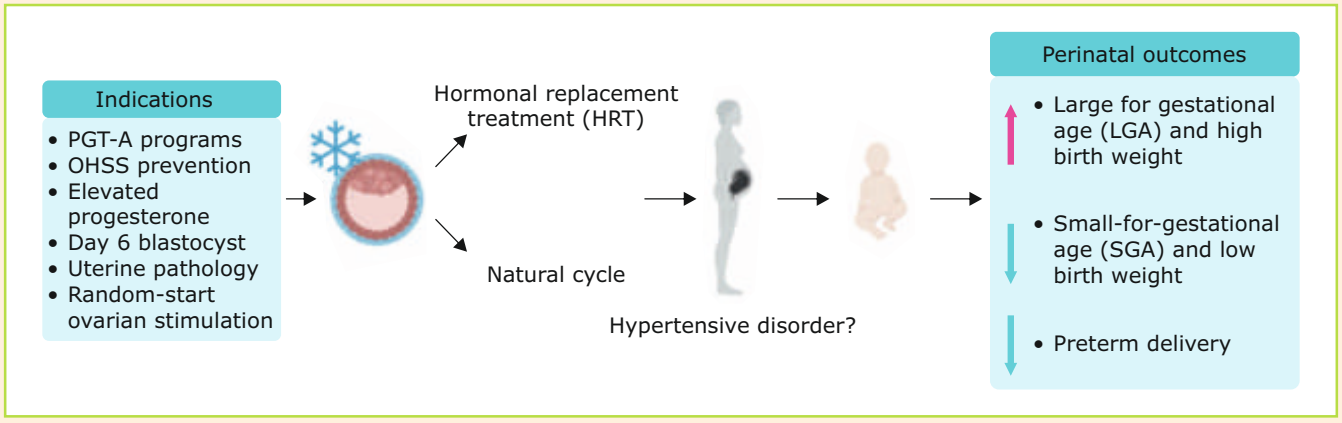

Figure adapted from Celada P et al. Ups J Med Sci. 2020;125(2):104-111.

Figure 3. Overview of Embryo cryopreservation

ASRM guidelines 2016 recommends that there is fair evidence that cryopreservation prevents OHSS. (Grade B).

Avoiding a fresh embryo transfer through cryopreservation of all embryos ("freeze-all" strategy) reduces the incidence of OHSS in cycles at high risk, including for women with PCOS. It avoids the risk of late OHSS that comes with increasing levels of endogenous hCG and allows the use of a GnRH agonist trigger without additional LPS.

Furthermore, a planned FET, rather than fresh embryo transfer may also be associated with increased live birth rates and improved obstetric and neonatal outcomes in hyperstimulated cycles, further improving the safety and long-term outcomes of IVF.

The cryopreservation of all embryos can prevent pregnancy-induced late OHSS. However, it cannot prevent early OHSS if hCG is used to trigger oocyte maturation. The use of GnRHa as a trigger for final oocyte maturation in antagonist IVF cycles has been proposed as a method for preventing ovarian OHSS. From a clinical point of view, the most significant benefit of GnRHa trigger is its ability to induce a quick and reversible luteolysis and thus reduce the risk of OHSS development.

GnRH agonist trigger with or without freeze-all strategy – Clinical evidences

1. *Kol S, Humaidan P. GnRH agonist triggering: recent developments. Reprod Biomed Online. 2013;26(3):226-230.*
2. *Borges E Jr, Braga DP, Setti AS et al. Strategies for the management of OHSS: Results from freezing-all cycles. JBRA Assist Reprod. 2016;20(1):8-12.*
3. *Wang Q, Wan Q, Li T et al. Effect of GnRH agonist trigger with or without low-dose hCG on reproductive outcomes for PCOS women with freeze-all strategy: a propensity score matching study. Arch Gynecol Obstet. 2024;309(2):679-688.*
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6. *Atkinson P, Koch J, Ledger WL. GnRH agonist trigger and a freeze-all strategy to prevent ovarian hyperstimulation syndrome: a retrospective study of OHSS risk and pregnancy rates. Aust N Z J Obstet Gynaecol. 2014;54(6):581-585.*

The use of GnRHa trigger will prevent OHSS even in extreme cases if a freeze-all policy is adopted. With the current improvement in cryo-technology, an excellent OHSS risk-free cumulative pregnancy rate has previously been reported.

Moreover, in earlier studies, not much was known about clinical outcomes when GnRH agonist or hCG were used to trigger ovulation in freeze-all IVF cycles.

However, of late, several studies using GnRH agonist trigger with or without freeze-all strategy are reported in literature.

Results of some studies with and without PCOS women are discussed here.

A retrospective cohort study compared the effect of GnRHa trigger (0.2 mg) alone versus dual trigger (0.2 mg GnRHa + 1000/2000 IU hCG) on reproductive outcomes in patients with PCOS who received the freeze-all strategy in 615 cycles.

After propensity score matching (PSM), patients with dual trigger (n = 176) had more oocytes retrieved, mature oocytes, and 2PN embryos compared to that with GnRHa trigger alone. However, there was no significant difference in the oocytes maturation rate, normal fertilization rate, and frozen embryos between the two groups. The OHSS (14.8% vs. 2.8%, $p<0.001$) and moderate/severe OHSS (11.4% vs. 1.7%, $p<0.001$) were significantly higher in dual-trigger group than in GnRHa-alone group. The pregnancy and single neonatal outcomes were comparable between the two groups ($p>0.05$).

For PCOS women with freeze-all strategy, GnRHa trigger alone decreased the risk of OHSS

without damaging oocyte maturation and achieved satisfactory pregnancy outcomes.

Bosdou et al., in their systematic review and meta-analysis (total 8 trials; high responders (n=4); normal responders (n = 4); total 5265 patients); explored whether the outcomes of comparison of live birth rates between the first frozen embryo transfer (ET) and a fresh embryo transfer (fresh ET group) differed based on the type of ovarian response. This study included women with PCOS. In high responders, a significantly higher probability of live birth was observed in the frozen ET group compared with the fresh ET group (RR: 1.18, three studies=3398 patients; Figure 4).

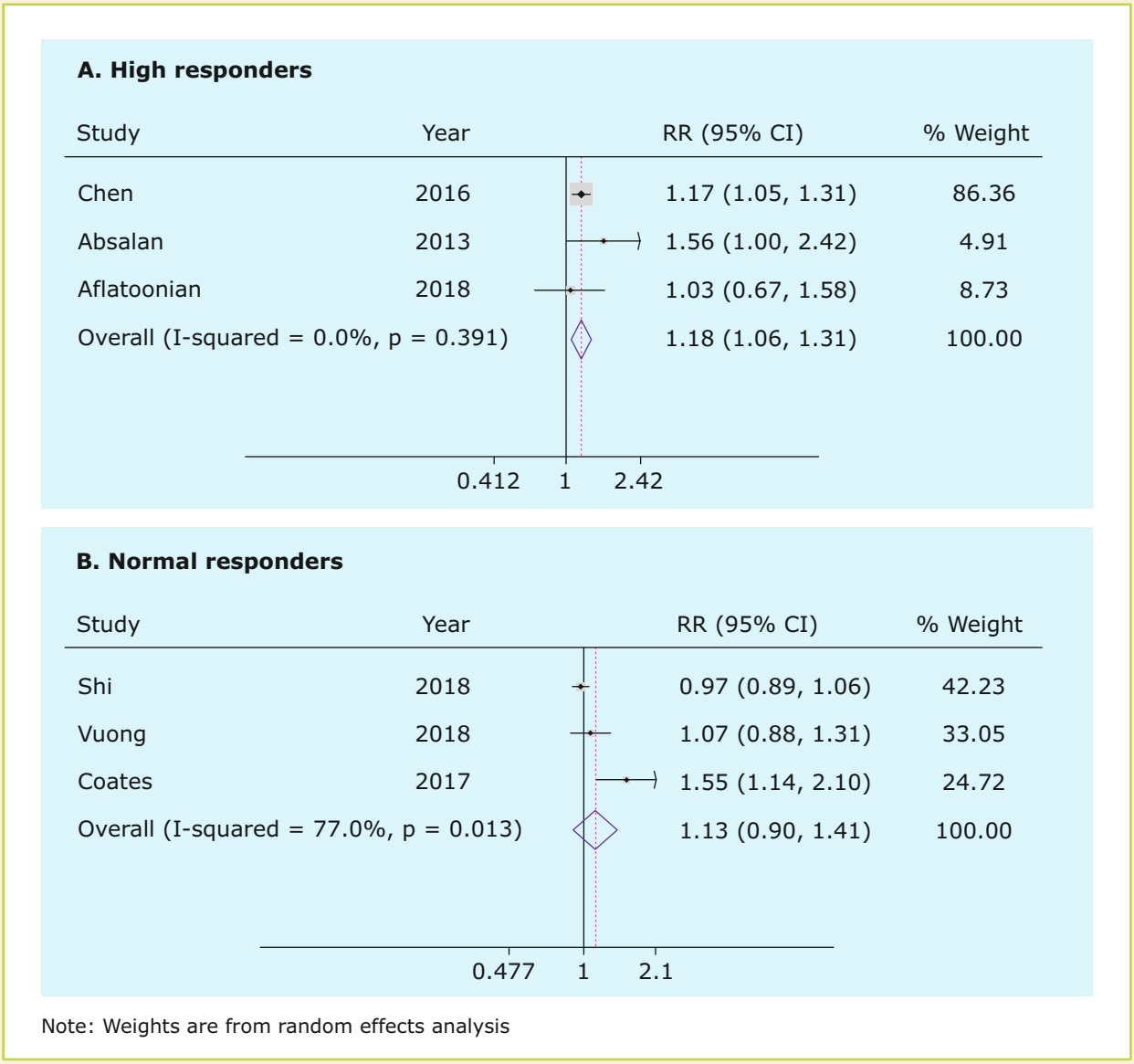

Figure adapted from Bosdou JK et al. Hum Reprod. 2019;34(3):491-505.

Figure 4. Live birth in (A) high responders (fixed effects model) and (B) normal responders (random effects model).

The risk of moderate/severe OHSS was significantly lower in the frozen ET group when compared with the fresh ET group both in high (RR: 0.19, single study; n=1508 patients) and normal responders (RR: 0.39, two studies; n = 2939 patients).
There is a higher probability of live birth after the first frozen ET, in a freeze-only cycle strategy, compared with the first fresh ET in high responders but not in normal responders.

Riberio et al., investigated whether freeze-all strategy in high-responders increase pregnancy rates and improve safety outcomes compared with GnRH agonist triggering followed by low-dose hCG intensified LPS with a fresh embryo transfer. PCOS was one of the cause of infertility in this study **(24.8% in fresh transfer and 26% in freeze-all group)** along with other causes.
A total of 209 women with an excessive response to ovarian stimulation undergoing IVF/ICSI in a GnRH antagonist cycle were included.
Women were randomized either to cryopreserve all good-quality embryos followed by a FET in a subsequent artificial cycle or to perform a fresh ET with intensified LPS following GnRH agonist trigger.
The findings showed that intention-to-treat clinical pregnancy and live birth rates after the first embryo transfer did not vary significantly among the fresh embryo transfer and freeze-all study arms 51/105 (48.6%) versus 57/104 (54.8%) and 41/104 (39.4%) versus 42/101 (41.6%), respectively (Figure 5).
However, moderate-to-severe OHSS occurred solely in the group that received low-dose hCG (9/105, 8.6% vs. 0/104; p<0.01) and who attempted a fresh embryo transfer.

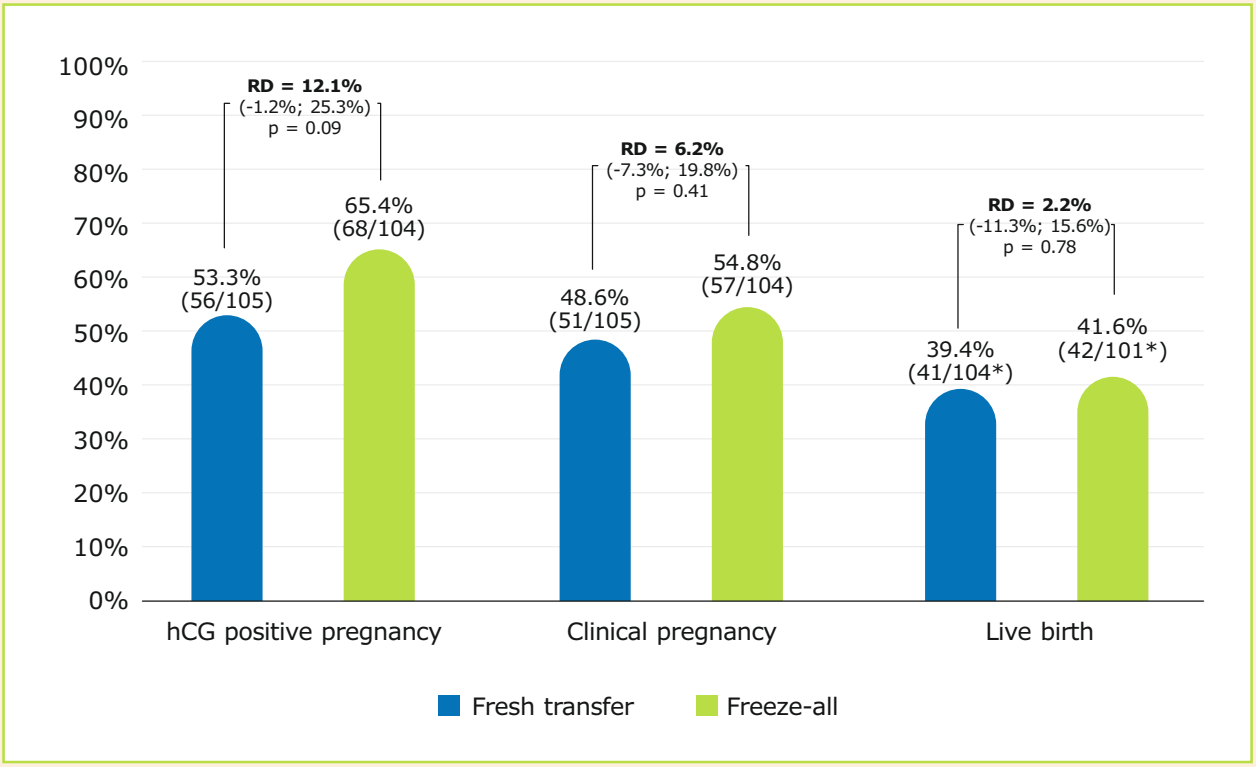

Figure adapted from Santos-Ribeiro S et al. Hum Reprod. 2020;35(12):2808-2818.

Figure 5. Pregnancy (intention to treat) outcomes following the first embryo transfer
*Excluding four patients lost to follow-up (one in the fresh transfer and four in the freeze-all arms, respectively). RD, risk difference

This study showed that pregnancy rates after agonist triggering followed by either fresh embryo transfer with intensified LPS using low-dose hCG or the freeze-all strategy did not vary significantly. However, moderate-to-severe OHSS occurred more frequently in women who attempted a fresh embryo transfer.

Borges et al., compared GnRHa (n=74) or hCG trigger (n=49) in OHSS patients for clinical outcomes when fresh versus freeze-thawed embryo transfers were performed in cycles with a high number of retrieved oocytes. PCOS women were not included in this study.
There was decreased serum estradiol level, a decreased number of retrieved oocytes, an increased MII retrieved rate, and decreased fertilization rate in the hCG compared with the GnRHa trigger. No significant differences were noted concerning clinical outcomes.
The clinical pregnancy rate was higher among freeze-all cycles, as well as the implantation and cumulative pregnancy rates, when compared with fresh embryo transfer cycles.
GnRHa triggering may be a good alternative to prevent the OHSS in patients presenting an extreme ovarian response to COS, leading to similar clinical outcomes, when compared to hCG trigger. The strategy of freezing-all embryos not only decreased the risk of OHSS but also lead to a better pregnancy rate (Table 6).

Table 6. Clinical outcomes from freeze-all cycles using hCG or GnRH agonist trigger

Cycle outcomes	hCG	GnRH agonist	p value
Number of cycles	49	74	
Clinical pregnancy rate	44.8%	50.0%	0.483
Single pregnancy rate	72.7%	75.6%	0.856
Twin pregnancy rate	22.7%	24.3%	0.585
Triplet pregnancy rate	4.5%	0	0.935
Miscarriage rate	29.7%	14.6%	0.164
Implantation rate	39.0%	37.1%	0.885
Cumulative pregnancy rate	53.0%	59.5%	0.483

Table adapted from Borges E Jr et al. JBRA Assist Reprod. 2016;20(1):8-12.

Atkinson et al., in their retrospective study evaluated OHSS and pregnancy rates in 123 women undergoing COH using an antagonist protocol, GnRH agonist trigger and freezing of all oocytes or embryos. Out of 123 women, 25.2% were undergoing oocyte freezing and 74.8% underwent embryo freezing. PCOS women were included in this study.
Results showed no cases of OHSS, either early or late onset. The pregnancy rate was 31.7% after the first frozen cycle transfer with a cumulative pregnancy rate of 50% after two frozen embryo transfers.
Researchers concluded that a GnRH agonist trigger and a freeze-all approach prevents OHSS with a good pregnancy rate.

OHSS Free clinic by segmentation

1. *Roque M. Freeze-all policy: is it time for that? J Assist Reprod Genet. 2015;32(2):171-176.*
2. *Devroey P, Polyzos NP, Blockeel C. An OHSS-Free Clinic by segmentation of IVF treatment. Hum Reprod. 2011;26(10):2593-2597.*
3. *Castillo JC, Haahr T, Martínez-Moya M et al. Gonadotropin-releasing hormone agonist for ovulation trigger - OHSS prevention and use of modified luteal phase support for fresh embryo transfer. Ups J Med Sci. 2020;125(2):131-137.*
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5. *Thakre N, Homburg R. A review of IVF in PCOS patients at risk of ovarian hyperstimulation syndrome. Expert Rev Endocrinol Metab. 2019;14(5):315-319.*
6. *Blockeel C, Drakopoulos P, Santos-Ribeiro S et al. A fresh look at the freeze-all protocol: a SWOT analysis. Hum Reprod. 2016;31(3):491-497.*

OHSS is an iatrogenic, potentially lethal, and still one of the major complications encountered during COS in approximately 1-14% of ART cycles. The prevention of OHSS is the most important aspect of its management. The balance between the desire for pregnancy and the patients' safety is a top priority. The concept of an OHSS-free clinic has become a reality.

This approach should include pituitary down-regulation using a GnRH antagonist, ovulation triggering with a GnRH agonist and vitrification of oocytes or embryos. Devroey and colleagues introduced the concept of an OHSS-free clinic which virtually eliminates the onset of early and late OHSS. The strategy to obtain an OHSS-free clinic is closely related to the segmentation concept.

It consists of the following segments:

1. Segment A involves optimization of the ovarian stimulation, including GnRH agonist triggering in a GnRH antagonist cycle
2. Segment B then consists of optimum cryopreservation methods for oocyte or embryo vitrification.
3. Segment C includes embryo replacement in a receptive, non-stimulated endometrium in a natural cycle or with artificial endometrial preparation.

By segmenting the treatment into these steps, the concern about specific and adequate LPS after GnRHa triggering disappears.

An additional benefit of postponing embryo transfer is avoiding embryo exposure to non-physiologic, elevated circulating steroid levels observed in fresh transfer IVF cycles. In recent years, the pregnancy and live birth rates after the FETs have improved, most certainly as a result of the use of vitrification for embryo cryopreservation. It is necessary to note that segmentation cycle requires very precise planning in the process of frozen-thawed embryos which is not available in all IVF centers.

There is adequate new data to suggest that women who are at a high risk of OHSS due to PCOS should be given an agonist trigger and the embryos frozen. The freeze all strategy in PCOS patients at risk of OHSS has improved pregnancy rates with a negligible risk of OHSS. This makes it a safe option which must surely be universally adopted.

- Segmentation of the protocol for PCOS women undergoing IVF makes an OHSS-free clinic a plausible proposition
- Segmentation of an IVF cycle in PCOS woman makes it safer and has better outcomes.

Thakre et al., in their paper opined that women with PCOS who thought undergoing IVF was a bane, can now be successfully and safely treated due to recent advances in IVF. The principal steps needed to achieve this are as follows:

- GnRH antagonist protocol in all cases which is no longer disputed
- More intense monitoring than the average IVF patient
- GnRH agonist trigger is a welcome innovation and step forward; doses probably still need some fine tuning which may be individually applied

- Freezing all the embryos at blastocyst stage and FET. Vitrification of embryos and improvements of blastocyst culture now make this a very viable option. The best protocol for frozen/thawed embryo replacement is yet to be decided.

The concept of OHSS free clinic by segmentation is outlined in the figure 6.

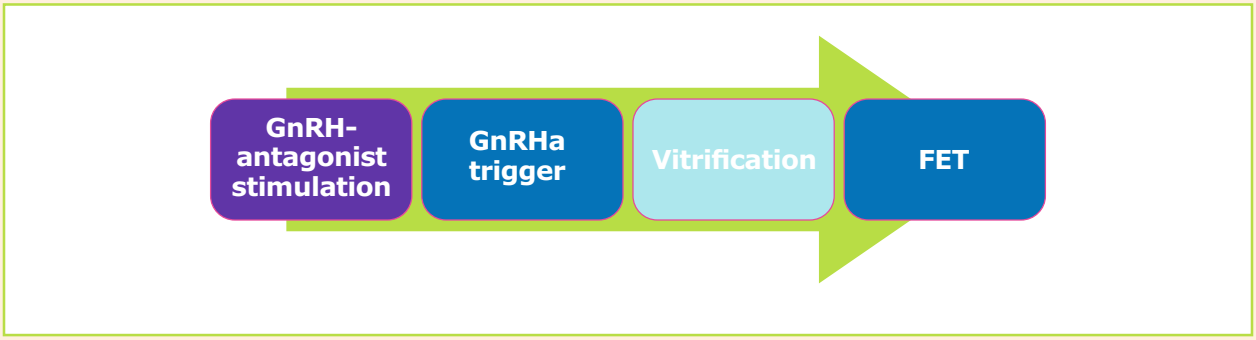

Figure adapted from Blockeel C et al. Hum Reprod. 2016;31(3):491-497.

Figure 6. The OHSS free-clinic segmentation protocol
GnRHa, GnRH agonist; FET, frozen embryo transfer

OHSS free clinic by Freeze all + GnRH Antagonist use + GnRH Agonist triggering: Clinical evidences

1. *Teede HJ, Tay CT, Laven JJE et al. International PCOS Network. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Eur J Endocrinol. 2023 Aug 2;189(2):G43-G64.*
2. *Griesinger G, Schultz L, Bauer T et al. Ovarian hyperstimulation syndrome prevention by gonadotropin-releasing hormone agonist triggering of final oocyte maturation in a gonadotropin-releasing hormone antagonist protocol in combination with a "freeze-all" strategy: a prospective multicentric study. Fertil Steril. 2011;95(6):2029-33, 2033.e1.*
3. *Krishna D, Dhoble S, Praneesh G et al. Gonadotropin-releasing hormone agonist trigger is a better alternative than human chorionic gonadotropin in PCOS undergoing IVF cycles for an OHSS Free Clinic: A Randomized control trial. J Hum Reprod Sci 2016;9:164-172.*
4. *Beydilli Nacak G. Tozkir E. Ozkaya E et al. Comparison of hCG Versus Gonadotropin-Releasing Hormone Agonist to Induce Oocyte Maturation in Assisted Reproductive Technology Cycles: A Retrospective Cohort Study. Gynecol Obstet Reprod Med. 2021;27(2):143-149.*
5. *ELhelw EM, El Serour AGEA, Rady MS et al. Freeze-all policy versus luteal phase support with low dose of human chorionic gonadotrophin for high-responder patients undergoing intracytoplasmic sperm injection on pregnancy outcomes: a retrospective cohort observational study. Middle East Fertility Society Journal. 2022;27:20.*
6. *Fernández-Sánchez M, Fatemi H, García-Velasco JA et al. Incidence and severity of ovarian hyperstimulation syndrome (OHSS) in high responders after gonadotropin-releasing hormone (GnRH) agonist trigger in "freeze-all" approach. Gynecol Endocrinol. 2023;39(1):2205952.*

According to the 2023 guideline for the assessment and management of PCOS, triggering final oocyte maturation with a GnRH agonist and freezing all suitable embryos is recommended, in an IVF/ICSI cycle with a GnRH antagonist protocol, where a fresh embryo transfer is not intended or where there is an increased risk of OHSS.

A prospective, clinical cohort study assessed the OHSS incidence and cumulative live birth rate in 51 patients undergoing ovarian stimulation in a GnRH antagonist protocol and receiving a GnRH agonist triggering followed by cryopreservation of all two pronuclei (2PN)-stage zygotes by two methods, vitrification or slow-cooling, for later ET. About 18/51 patients were classified by the investigators as having PCOS. Out of 51 patients, 48 patients underwent at least one frozen-thawed ET. The cumulative live birth rate was 37.3%. The live birth rate per first frozen-thawed ET was 5.9% and 19.4% in the slow-cooling and vitrification group, respectively (difference: 13.5%). Three cases of OHSS II and one early-onset case of OHSS III occurred. Researchers

suggested that elective cryopreservation of zygotes or embryos after agonist triggering as first choice for OHSS prevention in high-risk patients on a GnRH antagonist protocol.

Deepika et al., in a prospective, randomized control trial evaluated whether GnRHa trigger is a better alternative to hCG in Indian PCOS women undergoing IVF cycles with GnRH antagonist for the prevention of OHSS. A total of 227 patients were divided into Group A (study group): GnRHa trigger 0.2 mg (n = 92) and Group B (control group): 250 µg of recombinant hCG as trigger (n = 101) 35 h before oocyte retrieval. OHSS incidence was the primary outcome. The results showed that the incidence of moderate to severe OHSS in the hCG group was 37.6% and 0% in the GnRHa group ($p < 0.001$; Table 7).

Table 7. Primary outcomes in the study

OHSS magnitude	Trigger group, n (%)		p value
	Group A (GnRHa), n=92	Group B (hCG), n=101	
None	91 (90.1)	10 (9.9)	<0.001
Mild	1 (1.9)	53 (98.1)	<0.001
Moderate	0	35 (100)	<0.001
Severe	0	3 (100)	<0.001

Table adapted from Krishna D et al. J Hum Reprod Sci 2016;9:164-72.

The GnRHa group had significantly more mature oocytes retrieved, more fertilized oocytes, and a higher number of top-quality cleavage embryos on day 3 than the hCG group. The most effective strategy which virtually eliminates the occurrence of OHSS in PCOS women in antagonist IVF cycles is the use of GnRHa trigger in combination with cryopreservation leading to an **"OHSS free clinic,"** which can soon be a reality.

Nacak et al., compared cycle characteristics and outcomes using a protocol consisting of a GnRH agonist trigger or hCG trigger after cotreatment with GnRH antagonist. In this retrospective study, 33 patients with PCOS, polycystic ovarian morphology, or previous high response underwent ovulation trigger by GnRH agonst trigger (study group) and 132 patients underwent ovulation trigger by hCG (control group). The rates of patients with PCOS were similar between the two groups (50.8% vs. 51.5%, $p>0.05$). Among 33 women who underwent agonist trigger, freeze all strategy was indicated for 21 cases, whereas among 132 women in the control group freeze all strategy was preferred in 10 cases ($p<0.001$). There was a positive pregnancy test obtained in 70 women in the control group and 13 cases in the study group ($p=0.161$). There was a single case with mild OHSS in the study group whereas, in the control group, 19 OHSS cases were observed ($p=0.07$). GnRH agonist trigger after GnRH antagonist cotreatment and freeze-all strategy reduces the risk of OHSS in high-risk patients undergoing IVF without affecting pregnancy rates.

ELhelw et al., in a retrospective, cohort, observational study evaluated the benefits of freeze-all policy vs. LPS with hCG on the incidence of pregnancy outcomes in high responder patients undergoing ICSI. The study participants underwent GnRH antagonist protocol cycle and were divided into two groups i.e. Group A (n=78): Fresh embryo transfer (ET) and Group B (n=65): **cycle segmentation (freeze-all group)**. PCOS was one of the cause of infertility in this study

(23.07% in Group A and 21.53% patients in Group B) along with other causes. Both groups underwent final oocyte maturation by GnRH-agonist triggering followed by LPS with hCG (Group A), while in (Group B; no LPS), all the embryos were cryopreserved to be transferred in a subsequent artificial prepared cycle. The primary outcome measure was the clinical pregnancy rate at 7 weeks of gestational age. The study results showed that the incidence of clinical pregnancy rate, implantation rate and live birth rates were significantly lower in Group A than compared to group B (Table 8).

Table 8. ICSI Outcomes in the study groups

ICSI cycle outcomes	Group A (n = 78)	Group B (n = 65)	p value
Daily exogenous gonadotrophine dose (UI)	168.3 ± 38.7	165.7 ± 39.9	0.804
Retrieved oocytes (n)	12.7 ± 3.2	14.1 ± 3.5	0.158
Mature oocytes (n)	10.2 ± 3.2	11.1 ± 3.7	0.711
Fertilization rate (%)	73.8	76.9	0.456
Embryo transfer (n)	1.2 ± 0.4	1.3 ± 0.4	0.684
Implantation rate (%)	22/78 (28.20%)	28/65 (43.07%)	< 0.001*
Clinical pregnancy rate/first ET%	19/78 (24.35%)	26/65 (40%)	< 0.001*
Live birth rate/first ET%	14/78 (17.94%)	21/65 (32.30%)	< 0.001*
Clinical miscarriage	5/19 (26.05%)	5/26 (19.2%)	< 0.001*
Ectopic pregnancy	0	0	
Mild OHSS	5/78 (6.41%)	5/65 (7.69%)	0.623
Moderate to severe OHSS	5/78 (6.41%)	0	0.023*

Data are presented as mean (SD), number, and proportion (%). E2, estradiol; ET, embryo transfer; OHSS, ovarian hyperstimulation syndrome.
*p < 0.05 is statistically significant

Table adapted from ELhelw EM et al. Middle East Fertility Society Journal. 2022;27:20.

The cycle segmentation strategy resulted in better pregnancy rates with less incidence of moderate to severe OHSS compared with original fresh ET in high-responder women performing ICSI.

Although the combination of GnRH antagonist protocol with GnRHa triggering, followed by freezing all embryos is thought to completely avoid OHSS, a recent study by Sanchez et al., showed that high responders (n=77) receiving GnRH agonist triggering followed by freeze all approach may experience signs and symptoms of mild OHSS.
Overall, only 17/77 high responders (22%) developed signs and symptoms of mild OHSS which lasted 6-21 days. Researchers opined that patients should still be informed about these adverse events when receiving GnRH-a triggering.

What Guidelines say?

1. *Ovarian stimulation for IVF/ICSI UPDATE 2025. Accessed from website https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Guidelines-in-development/Update_OS as on 04.09.2025.*
2. *Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. Fertil Steril. 2024;121(2):230-245.*
3. *Teede HJ, Tay CT, Laven JJE et al. International PCOS Network. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Eur J Endocrinol. 2023 Aug 2;189(2):G43-G64.*

ESHRE 2025 recommendations: Ovulation triggering, LPS, Freeze-all strategy

- For final oocyte maturation, hCG is preferred, unless the patient is at risk of early OHSS, in which case GnRH agonist triggering is advised. **[2025] GPP**
- The use of GnRH agonist for final oocyte maturation is not recommended in the general IVF/ICSI population with fresh transfer, regardless of luteal phase support (with or without LH-activity). **[updated] Strong** ⊕⊕□□
- In patients at risk of OHSS, the use of a GnRH agonist for final oocyte maturation is probably recommended over hCG in cases where no fresh transfer is performed. **[2019] Conditional** ⊕□□□
- The addition of hCG to GnRH agonist as a dual trigger for final oocyte maturation is probably not recommended for high responders. **[2025] Conditional** ⊕□□□
- In hCG triggered ovarian stimulation cycles, hCG as luteal phase support in standard dosages of 1500 IU is not recommended. **[updated] Strong** ⊕⊕□□
- A freeze-all strategy is recommended to minimise the risk of late-onset OHSS. **[updated] Strong** ⊕⊕□□
- A GnRH agonist trigger is recommended for final oocyte maturation in women at risk of OHSS combined with a freeze-all strategy to minimise the risk of severe OHSS. **[updated] Strong** ⊕□□□
- If a GnRH agonist protocol with hCG trigger is used in high responders, a freeze-all strategy is recommended to decrease the risk of late-onset OHSS. **[updated] GPP**
- A GnRH agonist bolus, in addition to progesterone for luteal phase support in hCG triggered cycles is probably not recommended. **Conditional** ⊕⊕□□
- Repeated GnRH agonist injections, alone or in addition to progesterone for luteal phase support in hCG triggered cycles is probably not recommended. **[reworded] Conditional** ⊕□□□
- A reduced gonadotropin dose is probably recommended to decrease the risk of OHSS in predicted high responders. **[2025] Conditional** ⊕□□□
- The GnRH antagonist protocol is recommended for predicted high responders. However, if GnRH agonist protocols are used, a reduced gonadotropin dose is recommended to decrease the risk of OHSS. **[updated] Strong** ⊕□□□

ASRM 2024 guideline recommendations for prevention of moderate and severe ovarian hyperstimulation syndrome

- It is recommended to employ ovarian stimulation protocols using gonadotropin-releasing hormone (GnRH) antagonists over protocols using GnRH agonists when there is concern for OHSS. **(Strength of evidence: A; strength of recommendation: strong)**
- It is recommended to dose gonadotropins based on individualized ovarian reserve testing to decrease the risk of OHSS. **(Strength of evidence: B; strength of recommendation: moderate)**
- It is recommended to use a GnRH agonist to trigger oocyte maturation as a first-line strategy to reduce the risk of moderate-to-severe OHSS. **(Strength of evidence: A; strength of recommendation: strong)**
- It is recommended to add adequate luteal support when using a GnRH agonist as a trigger and planning a fresh embryo transfer. **(Strength of evidence: A; strength of recommendation: strong)**

- It is not recommended to use a lower dose for the human chorionic gonadotropin (hCG)-only trigger as a strategy to reduce the risk of moderate-to-severe OHSS. **(Strength of evidence: C; strength of recommendation: weak)**
- It is recommended to consider a freeze-only cycle and subsequent frozen embryo transfer in patients at risk for OHSS on the basis of a high ovarian response or elevated serum estradiol levels. Multiple high-quality studies have reported a significant reduction in rates of moderate or severe OHSS when this strategy is employed. **(Strength of evidence: A; strength of recommendation: strong)**
- It is not recommended to administer a luteal GnRH antagonist alone to reduce rates of moderate-to-severe OHSS. Most studies report no reduction in rates of moderate-to severe OHSS or in signs or symptoms associated with OHSS. Some low-quality evidence suggests modest symptomatic improvement in women with OHSS who received a GnRH antagonist after the hCG trigger. **(Strength of evidence: C; strength of recommendation: weak)**

PCOS 2023 guideline recommendations

- The use of a GnRH antagonist protocol for women with PCOS undergoing IVF/ICSI is recommended as it enables the use of an agonist trigger, with the freezing of all embryos generated if required, without compromising the cumulative live birth rate, to reduce the risk of significant ovarian hyperstimulation syndrome.

Summary

Triggering for oocyte maturation is an important step in IVF cycles. Although hCG is the most commonly used trigger, of late, GnRH agonist triggering is gaining importance, especially in PCOS patients as it significantly reduces the risk of OHSS. Now, clinical evidences have shown that triggering with GnRHa in PCOS women may be an effective alternative to hCG without compromising luteal function and pregnancy rates.

Of late, individualization/personalization of therapy is gaining importance in all fields of medicine.

Although there is no absolute consensus on the best time for triggering ovulation in women with PCOS, published data states that timing of triggering of final oocyte maturation in ICSI cycles should be individualized on a case-by-case basis for optimal results.

Luteal phase support is a crucial aspect of ART and does not have so many choices as the individualized COS protocols and endometrium preparation protocols. Increasing attention is being paid to individualization of LPS also in ART to maximize efficacy and safety and to minimize the treatment burden, side effects and cost. However, clinical studies on LPS individualization are warranted.

The balance between the desire for pregnancy and the patients' safety is a top priority in ART and this has shown that the concept of an OHSS-free clinic has become a reality. OHSS-free clinic by segmentation of IVF treatment has reduced/minimized the concern about specific and adequate LPS after GnRHa triggering and also nearly eliminated the risk of OHSS. Clinical evidences demonstrate that cycle segmentation strategy results in better pregnancy rates with less incidence of moderate to severe OHSS.

Segmentation of IVF protocol even for PCOS women undergoing IVF makes an OHSS-free clinic now a plausible proposition. Segmentation of IVF cycle in PCOS women makes it safer and has better outcomes. However, segmentation cycle requires very precise planning in the process of frozen-thawed embryos which is not available in all IVF centres.

Feedback form

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Issue 12 | October 2025

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Scientific content	1	2	3	4	5	6	7	8	9	10
Relevance of the topic	1	2	3	4	5	6	7	8	9	10
Impact on my daily practice	1	2	3	4	5	6	7	8	9	10
Innovation	1	2	3	4	5	6	7	8	9	10
Overall level of satisfaction	1	2	3	4	5	6	7	8	9	10

What aspects of the Newsletter issue 12 did you find particularly interesting and/or informative?

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Please suggest topics/areas that you would like to be covered in future issues of the Alive Newsletter?

_____

How can the subsequent Newsletter issues be improved?

_____

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