ALIVE

ART LEARNING INITIATIVES FOR EXPERTS

Issue 11

PCOS and infertility: Managing current challenges part 2

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Foreword

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Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder that affects fertility in reproductive-aged women and has a profound impact on their emotional health as well.

Due to chronic anovulation, women with PCOS undergo ovulation induction as the first step in their infertility management. Ovarian stimulation is a challenge to the clinicians in women with PCOS due to diversity of the disease. This necessitates thorough evaluation of the patient as there are several stimulation protocols available which have their own advantages and disadvantages.

This issue highlights about different ovarian stimulation protocols available for women with PCOS undergoing IVF, their uses and which would be the best protocol amongst the available ones.

The issue also highlights about different triggers available that enable to obtain higher percentage of mature oocytes and number of top-quality embryos thus enabling better IVF outcomes in women with PCOS.

I am excited to share that I was appointed an **Emeritus Professor of Human Genetics** at Andhra University in June 2024. The **Academy of Clinical Embryologists awarded me the Lifetime Achievement Award** by ACE in 2024 at the annual meet in Pune.

Choosing an ovarian stimulation protocol in PCOS Women: *What are the different OS protocols available?*

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10. *Kol S, Homburg R, Alsbjerg B et al. 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.*
11. *Guan S, Feng Y, Huang Y, Huang J. Progestin-Primed Ovarian Stimulation Protocol for Patients in Assisted Reproductive Technology: A Meta-Analysis of Randomized Controlled Trials. Front Endocrinol (Lausanne). 2021 Aug 31;12:702558.*
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Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder, typically characterized by anovulation, infertility, obesity, insulin resistance and polycystic ovaries. According to 28 June 2023 WHO statistics, PCOS affects an estimated 8-13% of reproductive-aged women. PCOS accounts for ≥80% of women with anovulatory infertility.

As chronic anovulation is the main problem in PCOS patients, ovulation induction (OI) is considered as one of first options infertility management in women with PCOS history. Although optimal infertility treatment for PCOS patients is still a matter of debate, *in vitro* fertilization (IVF) remains a reasonable option in PCOS women who are refractory to conventional infertility treatment modalities or who have coexisting infertility factors.

Patients with PCOS face several challenges in IVF due to diversity of ovarian stimulation (OS) protocols, risk of ovarian hyper stimulation syndrome (OHSS), higher serum estradiol level, faster endometrial maturation, approaches like freeze all embryos policies. Adoption of an optimal OS protocol in these patients to overcome these challenges is highly important.

Today, many controlled OS strategies have been offered for the treatment of patients with PCOS undergoing IVF.

Short-acting GnRH agonist long protocol, also known as "long protocol" which starts from mid-luteal phase, has been the gold standard for pituitary downregulation method in COS worldwide nowadays, especially in young normo-gonadotropic women. The long protocol has plenty of advantages, such as maintaining stable and low LH and progesterone levels throughout the stimulation phase, synchronized follicular development, good number of retrieved oocytes and short learning curve.

Published data is available regarding early-follicular long-acting GnRH agonist long protocol and midluteal short-acting GnRH agonist long protocol.

GnRH agonist use in PCOS patients has been associated to prevent premature luteinizing hormone (LH) surge while the follicles are still immature resulting in a higher clinical pregnancy rate (CPR) and lower cycle cancellation rate (CCR). GnRH agonist administration causes gonadotropin suppression via pituitary desensitization after transient period of gonadotropin hypersecretion (flare up).

Due to the flare-up phase, GnRH agonist protocols are associated with some disadvantages like prolonged protocol duration, higher risk of formation ovarian cysts and development of hypo-estrogenic side effects. In addition, their use is associated with an increased risk of developing OHSS.

To overcome these issues, **GnRH antagonists** have been introduced to routine practice as alternatives to GnRH agonists. Unlike the indirect pituitary suppression induced by GnRH agonists, GnRH antagonists immediately and competitively occupy the GnRH receptors, which helps to overcome the unfavourable effects of GnRH agonist protocols. GnRH antagonists are usually scheduled during COS based on the progression of follicles development; detecting a leading follicle ≥ 12-14 mm diameter (Flexible protocol), or they are used from Day 5/ Day 6 of stimulation onward (Fixed protocol).

The GnRH antagonist protocol is associated with a significant reduction in the occurrence of OHSS.

Despite the overall effectiveness of GnRH analogs, the LH surge still occurs in 3-10% of all IVF cycles.

The predictive factors of ovarian sensitivity of PCOS patients to gonadotropins include fasting blood insulin, anti-Mullerian hormone (AMH), baseline follicular stimulating hormone (FSH), age and body mass index (BMI).

Consequently, other alternative OS protocols have also been proposed by various researchers.

Progestin-primed ovarian stimulation (PPOS) protocol is a new ovarian stimulation regimen based on a freeze-all strategy that uses progestin as an alternative to a GnRH analog for suppressing a premature LH surge during the follicular phase. This new OS regimen has been proved to effectively prevent a premature LH surge and does not compromise oocyte competence in cycles followed by embryo cryopreservation. It has been widely used in patients undergoing IVF since 2016 and has showed good IVF outcomes.

Researchers have tried PPOS protocols using oral medroxyprogesterone acetate and Corifollitropin alfa. However, a recently published systematic review and meta-analysis by Yang et al., (2023) states that there is currently no evidence to support that PPOS could reduce the risk of OHSS, increase oocyte maturation, or improve pregnancy outcomes in women with PCOS undergoing IVF/ICSI when compared to GnRH analogue protocols. They also opined that this protocol could be patient-friendly and a viable alternative for PCOS patients, especially when frozen-thawed embryo transfer is planned.

A schematic representation of OS with GnRH analogues and progestins is shown in Figure 1.

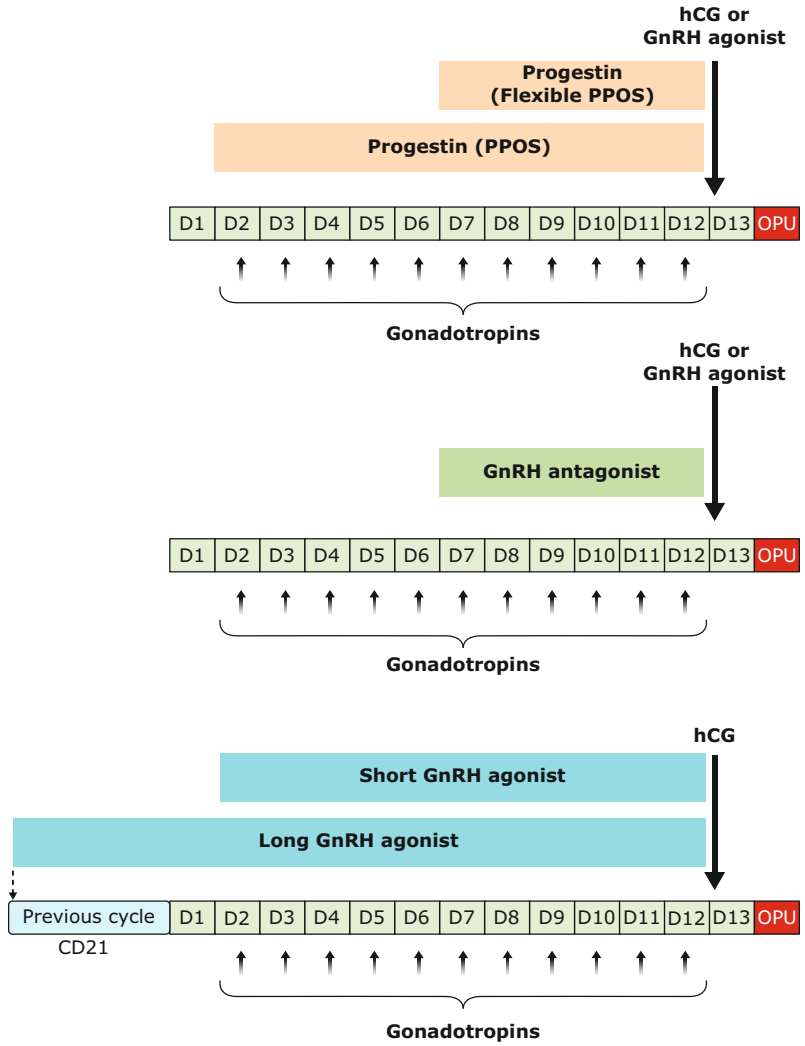

Figure adapted from Ata B et al. Hum Reprod Update. 2021;27(1):48-66.

Figure 1. Schematic representation of ovarian stimulation protocols for ART.
CD, cycle day; OPU, oocyte pick-up; PPOS, progestin-primed ovarian stimulation.

Choosing proper medications can be an important tool to achieve a desired OS outcome and reduce associated complications, such as OHSS. In this regard, the mild ovarian stimulation (mild-OS) and minimal ovarian stimulation (minimal-OS) protocols are cost effective alternatives.

Mild-OS refers to a protocol, which decreases the dose or duration of gonadotropin administration in comparison with common protocols in the single OS cycle with GnRH-antagonists. In this definition, mild-OS targets to obtain a maximum of 10 oocytes/time. In the mild OS protocol, 100–150 IU of gonadotropin is administered at the beginning of the follicular phase.

To prevent luteinizing hormone (LH) peak, the GnRH-antagonist is administered in a daily dose after 5–7 days.

Minimal-OS refers to a protocol, which aims to achieve a maximum of five oocytes. According to the International Society for Mild Approaches in Assisted Reproduction (ISMAAR), minimal-OS aims to obtain 2–7 oocyte. Minimal-OS is performed by administrating antiestrogenic factors (such as clomiphene citrate (CC)) or aromatase inhibitors (such as letrozole) alone or in combination with a small dose of gonadotropin. Figure 2 outlines different stimulation protocols.

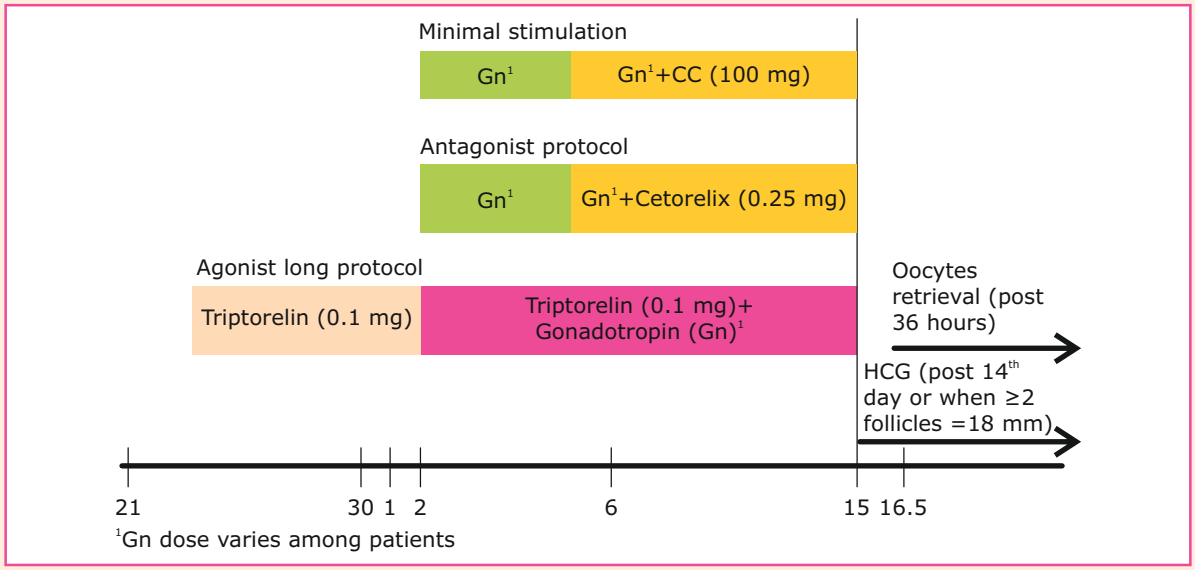

Figure adapted from Shrestha D et al. Ann Transl Med. 2015;3(10):137.

Figure 2. Stimulation procedures for agonist long, antagonist and minimal stimulation protocols for IVF. Gn, gonadotropin mixtures; CC, clomiphene citrate.

Elasy et al., proposed a new soft protocol in PCOS ovrian stimulation without prior pituitary desensitization followed by fresh embryo transfer. A simple OS protocol used small doses of gonadotropins in the predicted high responders and avoided pituitary downregulation by using an agonist or antagonist. Alternatively, non-steroidal anti-inflammatory (NSAID) was used to prevent premature LH surge.

The study showed 56.2% biochemical pregnancies, 50.2% implantation rate, 49.9% clinical pregnancy rate and 8.5% miscarriage rate.

Despite availability of different types of OS protocols, according to evidence, there is an agreement only in using GnRH-antagonists to OS in patients with PCOS; whereas, there is no agreement on the optimal medication and gonadotropin administration for OS to achieve the best fertility outcome in these patients. Randomized control trials (RCTs) on mild/minimal OS protocols in women with PCOS history are scant.

GnRH Agonist *vs*. Antagonist Protocols – *Moving towards antagonist...*

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5. *Kadoura S, Alhalabi M, Nattouf AH. Conventional GnRH antagonist protocols versus long GnRH agonist protocol in IVF/ICSI cycles of polycystic ovary syndrome women: a systematic review and meta-analysis. Sci Rep. 2022;12(1):4456.*
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7. *Balen AH, Morley LC, Misso M et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. Hum Reprod Update. 2016;22(6):687-708.*
8. *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;189(2):G43-G64.*
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The use of GnRH antagonist protocol has several advantages against the agonist protocol.
GnRH antagonists competitively inhibit endogenous GnRH, suppress the pituitary gonadotropin output and produce an immediate and rapid decrease in FSH and LH levels without a flare effect. Administration of GnRH antagonists in the late follicular phase prevents premature LH surge and premature luteinization.
The short acting nature of GnRH antagonists allows them to be administered only when there is a risk for an LH surge. This is in contrast to GnRH agonists where pituitary downregulation occurs only after 7-10 days. Both agonists and antagonists can suppress elevated circulating LH concentrations, but the smaller follicular cohorts observed in antagonist cycles may help to reduce the risk of OHSS in women with PCOS who tend to be high responders.
Furthermore, GnRH antagonist cotreatment allows final oocyte maturation to be triggered with a bolus of GnRH agonist instead of human chorionic gonadotropin (hCG), which is known to either totally eliminate or significantly reduce the risk of OHSS in the high-risk patient.
Thus, for the oocyte donor it is now generally recommended that OS should be performed with GnRH antagonist cotreatment, because this protocol eliminates OHSS and gives less discomfort for the donor in the "luteal phase", i.e. the days following oocyte aspiration, as well as an excellent reproductive outcome in the recipient.
All these ensure a short and simple IVF cycle and better patient compliance.

In a nutshell, GnRH antagonists have the following advantages:

- **Short duration of treatment**
- **Shorter stimulation of FSH / Lower requirement of gonadotropins**
- **Adaptability of Flexible or Fixed protocol**
- **No flare effect unlike agonists**
- **Can be administered when there is a risk for an LH surge**
- **Allows trigger with GnRH agonist instead of hCG for final oocyte maturation**
- **Lower risk of developing OHSS**
- **Less discomfort for the donor in the "Luteal phase"**
- **Less expensive**
- **Better patient compliance**

Published data is also available for GnRH antagonist protocols introduced to suppress gonadotropin levels, not only during the mid-follicular phase but also during the early follicular phase either as an early-late flexible protocol or an early fixed protocol.
According to the 2016 World Health Organization (WHO) guidelines, IVF with the GnRH

antagonist protocol is the treatment of choice for patients with PCOS. Figure 3 outlines the consensus algorithm for OI in PCOS.

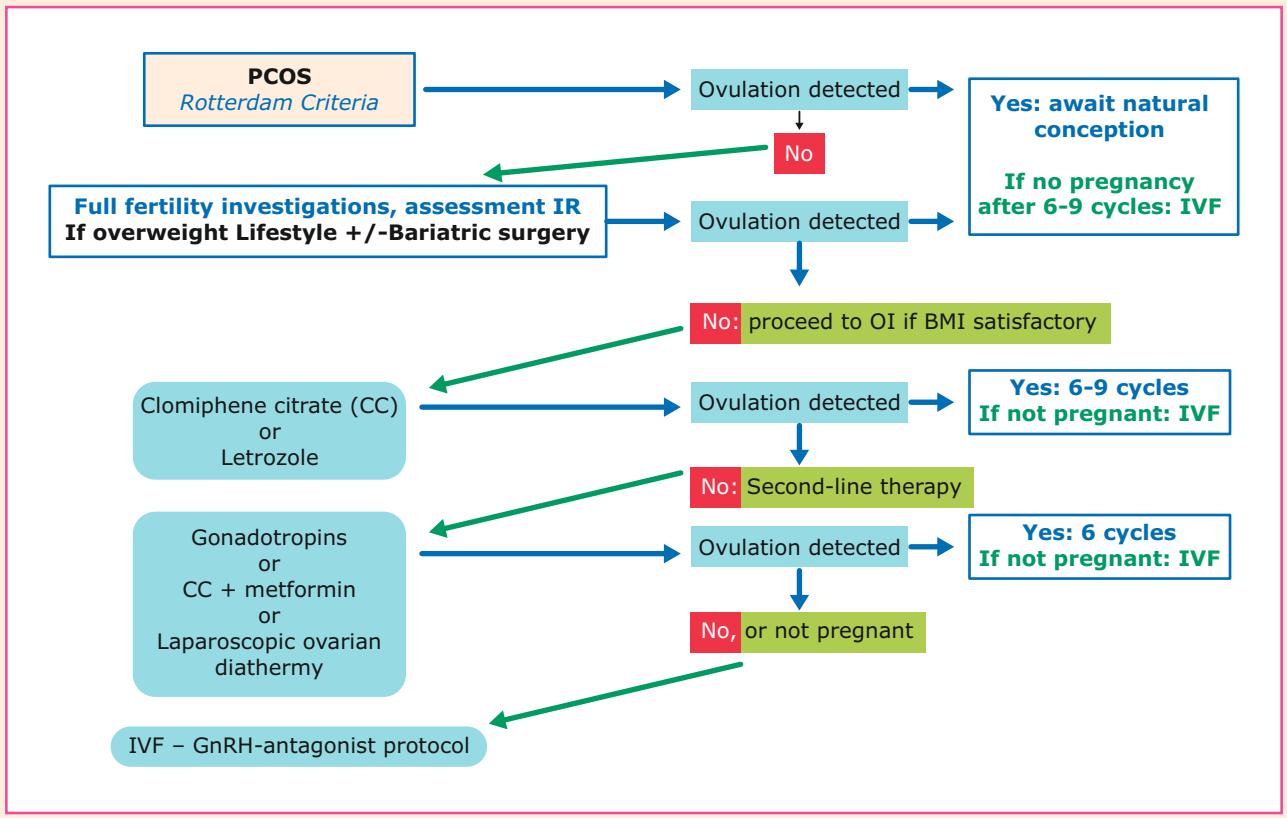

Figure adapted from Balen AH al. Hum Reprod Update. 2016;22(6):687-708.

Figure 3. Consensus Algorithm for ovulation induction in PCOS.

According to the Recommendations from the 2023 international evidence-based guideline for the assessment and management of PCOS, GnRH antagonist protocol cannot be recommended over GnRH agonist long protocol for women with PCOS undergoing IVF/ICSI to improve clinical pregnancy or live birth rate.

However, 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 OHSS.

The 2020 ESHRE guidelines for ovarian stimulation in IVF/ICISI strongly recommend that the GnRH antagonist protocol for women with PCOS with regards to improved safety and equal efficacy (Box).

High responder

The GnRH antagonist protocol is recommended for women with polycystic ovary syndrome (PCOS), with regards to improved safety and equal efficacy. (Lambalk et al., 2017)

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The following section explores clinical evidence supporting the GnRH antagonist protocol, which is becoming increasingly preferred in clinical practice, especially for women with PCOS

Clinical Evidences - GnRH Agonist *vs*. Antagonist Protocols in women with PCOS

1. *Wang D, Chu T, Yu T et al. Is early-follicular long-acting GnRH agonist protocol an alternative for patients with polycystic ovary syndrome undergoing in vitro fertilization? Reprod Biol Endocrinol. 2022;20(1):137.*
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12. *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.*

GnRH Agonist Protocol only

An early-follicular long-acting GnRH-agonist long protocol can be used as an ideal ART pregnancy assistance program for PCOS women

Wang et al., in a retrospective study compared the clinical and perinatal outcomes of PCOS women undergoing IVF/ICSI treatment with either an early-follicular long-acting GnRH-agonist (GnRH-a) long protocol (EFLL) or a midluteal short-acting GnRH-a long protocol (MLSL).

Patients underwent either MLSL (1179 cycles) or EFLL (2390 cycles). Pregnancy outcomes, perinatal and maternal complications were the primary outcome measures.

Results portrayed that fresh embryo transfer (59.12% *vs*. 55.47%, p=0.038), clinical pregnancy (75.23% *vs*. 53.82%, p=0.001), and live birth rates (63.27% *vs*. 42.05%, p=0.010) were higher in the EFLL group. However, the proportion of patients "freezing all" for high risk of OHSS (24.27% *vs*. 32.06%, p=0.001) and ectopic pregnancy (1.51% *vs*. 5.97%, p=0.002) were lower in the EFLL group than in the MLSL group (Table 1).

Based on these results it could be inferred that EFLL can be used as an ideal ART pregnancy assistance program for PCOS women.

Table 1. Comparison of laboratory parameters and clinical outcomes

	MLSL	EFLL	p value
Length of stimulation (d)	11.894 ± 2.139	14.725 ± 2.660	< 0.001
Total dosage of Gn (IU)	1666.979 ± 706.009	2263.929 ± 909.607	< 0.001
E2 on trigger day (pg/ml)	6360.655 ± 3283.401	3992.922 ± 2227.219	< 0.001
LH on trigger day (mIU/ml)	1.446 ± 0.693	0.738 ± 0.957	< 0.001
Endometrial thickness on trigger day (mm)	11.240 ± 2.554	12.134 ± 2.360	< 0.001
No. of oocytes retrieved (n)	16.906 ± 7.813	18.078 ± 7.978	< 0.001
No. of 2PN (n)	10.905 ± 5.987	10.852 ± 5.963	0.804
No. of transferable embryos	6.559 ± 4.004	5.832 ± 3.415	< 0.001
High-quality embryos rate (%)	59.37 (7531/12684)	54.23 (13892/25619)	< 0.001
Moderate to severe OHSS rate (%)	2.46 (29/1179)	3.22 (77/2390)	0.207
"Freezing all" for high risk of OHSS (%)	32.06 (378/1179)	24.27 (580/2390)	< 0.001
Implantation rate (%)	37.85 (436/1152)	56.76 (1368/2410)	< 0.001
Biochemical pregnancy rate (%)	58.87 (385/654)	79.23 (1120/1413)	< 0.001
Clinical pregnancy rate (%)	53.82 (352/654)	75.23 (1063/1413)	< 0.001
Live birth rate (%)	42.05 (275/654)	63.27 (894/1413)	0.010
Full-term birth rate (%)	32.87 (215/654)	50.88 (719/1413)	< 0.001
Spontaneous abortion rate (%)	8.26 (54/654)	10.83 (153/1413)	0.070
PTB rate (%)	8.10 (53/654)	11.11 (157/1413)	0.518

Note: Categorical data: % (n/N)
Gn gonadotropin, LH luteinizing hormone, OHSS ovarian hyperstimulation syndrome, PTB preterm birth

Table adapted from Wang D et al. Reprod Biol Endocrinol. 2022;20(1):137.

GnRH Antagonist Protocol only

Modified COS can significantly improve clinical outcomes and eliminate OHSS

A retrospective cohort study by Yanagihara et al., analyzed therapeutic efficacy of a modified COS protocol for PCOS that does not cause OHSS while maintaining oocyte quality.

ART clinical outcomes, embryonic development, and hormone levels were analyzed in 175 PCOS patients treated with four COS (GnRH agonist based long protocol, Group A; GnRH antagonist protocol with HCG trigger, Group B; GnRH antagonist protocol with GnRH agonist trigger, Group C, and the modified COS group).

Of 175 patients with PCOS, 45 and 130 patients underwent 47 and 136 oocyte retrieval cycles, 75 and 250 embryo transfer cycles with the modified COS, and with conventional methods, respectively.

Results showed that cumulative pregnancy rate at one trial was a significantly higher result than in Group A and higher than in Groups B and C (cumulative pregnancy rate at one trial of Group A, B, C, and modified COS: 40.0%, 54.5%, 56.3%, and 72.3%, respectively).

With this method, not clinically problematic OHSS and higher clinical outcomes than in conventional methods were observed (Table 2). Therefore, modified COS can significantly improve clinical outcomes and eliminate OHSS.

Table 2. Comparison of clinical outcome between modified COS and conventional treatments

	Group A[a] 60 women (60 cycles)	Group B[a] 38 women (44 cycles)	Group C[a] 32 women (32 cycles)	Modified COS 45 women (47 cycles)	p-value (Group A *vs.* Modified COS)	p-value (Group B *vs.* Modified COS)	p-value (Group C *vs.* Modified COS)
Clinical pregnancy rate	28.7% (33/115)	42.0% (34/81)	42.6% (23/54)	48.0% (36/75)	0.0068	0.4497	0.5431
Clinical pregnancy (n)[b]	24	23	18	34	NA	NA	NA
Cumulative pregnancy rate	40.0% (24/60)	54.5% (24/44)	56.3% (18/32)	72.3% (34/47)	0.0009	0.0776	0.1388
Miscarriage rate	24.2% (8/33)	29.4% (10/34)	30.4% (7/23)	19.4% (7/36)	0.6293	0.3311	0.3331
Live birth rate	18.3% (21/115)	27.2% (22/81)	25.9% (14/54)	36.0% (27/75)	0.0059	0.2347	0.2254
Cumulative live birth rate	30.0% (18/60)	38.6% (17/44)	37.5% (12/32)	57.4% (27/47)	0.0043	0.0727	0.0817
Gestational duration (wks)[c]	39.33 ± 1.25	39.62 ± 0.93	38.90 ± 2.18	39.67 ± 1.48	0.748	0.892	0.590
Birth weight (g)[c]	2949.05 ± 333.21	3007.71 ± 511.38	2982.78 ± 556.73	3014.13 ± 490.39	0.803	0.951	0.863

[a]A: GnRH agonist-based long protocol, B: GnRH antagonist-based protocol with HCG trigger protocol, C: GnRH antagonist protocol with GnRH agonist trigger.
[b]Patients number.
[c]Mean ± standard deviation.

Table adapted from Yanagihara Y et al. Reprod Med Biol. 2021;21(1):e12429.

Comparison of GnRH Antagonist *vs.* Agonist Protocols

Conventional GnRH antagonist protocols represent a safer and more cost-effective choice for PCOS women undergoing IVF/ICSI cycles than the standard long GnRH agonist protocol

A systematic review and meta-analysis of 10 studies by Kadoura et al., compared the effects of GnRH antagonist and GnRH agonist protocols on IVF/ICSI outcomes in women with PCOS (n=1214).
Live birth rate, ongoing pregnancy rate, and OHSS rate were the primary outcomes.
Results demonstrated GnRH antagonist protocols resulted in a significantly lower OHSS rate (risk ratio (RR)= 0.58; p=0.0002, Figure 4), shorter stimulation duration (weighted mean difference (WMD)=−0.91 day; p=0.0009), lower gonadotropin consumption (WMD=−221.36 IU; p<0.0001), lower E2 levels on hCG day (WMD=−259.21 pg/ml; p=0.02), thinner endometrial thickness on hCG day (WMD=−0.73 mm; p=0.001), and lower number of retrieved oocytes (WMD=−1.82 oocytes; p=0.03).
The researchers concluded that conventional GnRH antagonist protocols represent a safer and more cost-effective choice for PCOS women undergoing IVF/ICSI cycles than the standard long GnRH agonist protocol without compromising the IVF/ICSI clinical outcomes.

Study or Subgroup	GnRH Antagonist Events	Total	GnRH agonist Events	Total	Weight	Risk ratio M-H Random, 95% CI
Bahceci et al., 2005	3	73	5	75	4.1%	0.62 [0.15, 2.49]
Choi et al., 2005	1	22	2	21	1.5%	0.48 [0.05, 4.88]
Ghaebi et al., 2018	8	50	26	50	16.8%	0.31 [0.15, 0.61]
Haydardedeoglu et al., 2012	5	150	6	150	5.9%	0.83 [0.26, 2.67]
Hosseini et al., 2010	25	57	35	55	63.1%	0.69 [0.48, 0.98]
Kurzawa et al., 2008	0	37	2	37	0.9%	0.20 [0.01, 4.03]
Mokhtar et al., 2015	0	50	0	50		Not estimable
Shin et al., 2018	2	14	3	13	3.0%	0.62 [0.12, 3.13]
Trenkic et al., 2016	3	45	7	45	4.8%	0.43 [0.12, 1.55]
Total (95% CI)		**498**		**496**	**100.0%**	**0.58 [0.44, 0.77]**
Total events:	47		86			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.54$, df = 7 (p = 0.59); $I^2 = 0\%$

Test for overall effect: Z = 3.77 (p = 0.0002)

Test for subgroup differences: Not applicable

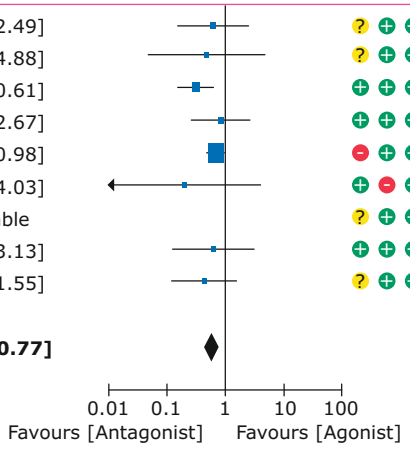

Figure adapted from Kadoura S et al. Sci Rep. 2022;12(1):4456.

Figure 4. Forest plot: OHSS rate per PCOS randomization women. (A) Bias arising from the randomization process; (B) Bias due to deviations from intended interventions; (C) Bias due to missing outcome data;(D) Bias in measurement of the outcome; (E) Bias in selection of the reported result and (F) overall bias.

GnRH antagonist protocol is significantly better than GnRH agonist protocol for reduction of OHSS rate in women with PCOS

Lin et al., conducted a meta-analysis 9 RCTs to compare IVF outcomes for GnRH agonist long and GnRH antagonist protocols in women with PCOS.

The main outcomes measured in this study included clinical pregnancy rate (CPR), ongoing pregnancy rate (OPR) and OHSS rate.

Results showed that the CPR-per-embryo transferred was similar in the two groups (relative risk (RR): 0.97).

After meta-analysis of 4 of the RCTs, it was determined that a GnRH antagonist protocol was better than an agonist long protocol to reduce the rate of severe OHSS (odds ratio (OR): 1.56, Figure 5).

GnRH antagonist protocol was significantly better than GnRH agonist protocol for reduction of OHSS rate. Whereas, with regards to CPR both the protocols were similar in PCOS women.

Study or Subgroup	GnRHa long protocol Events	Total	GnRH antagonist protocol Events	Total	Weight	Odds Ratio M-H Random, 95% CI Year
Rafal Kurzawa, 2008	2	37	0	33	18.1%	4.72 [0.22, 101.93] 2008
Ensieh, 2010	0	45	5	45	19.2%	0.08 [0.00, 1.51] 2010
Trifon G, 2010	6	110	5	110	36.2%	1.21 [0.36, 4.09] 2010
Chung-Hoon Kim, 2012	8	103	1	105	26.5%	8.76 [1.08, 71.33] 2012
Total (95% CI)		**295**		**293**	**100.0%**	**1.56 [0.29, 8.51]**
Total events	16		11			

Heterogeneity: $Tau^2 = 1.69$; $Chi^2 = 7.22$, df = 3 (p = 0.07); $I^2 = 58\%$

Test for overall effect: Z = 0.51 (p = 0.61)

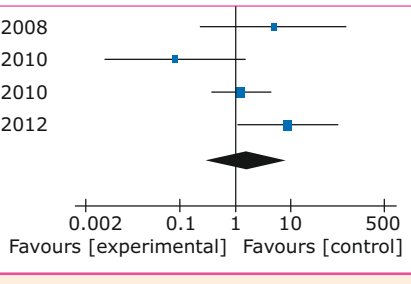

Figure adapted from Lin H et al. PLoS One. 2014;9(3):e91796.

Figure 5. Severe OHSS rate of GnRH long agonist protocol versus GnRH antagonist protocol per woman.

The incidence of OHSS rate was significantly lower in women undergoing the GnRH antagonist protocol

A Systematic review and Meta-analysis of 11 studies was conducted by Yang et al., to evaluate the effectiveness and safety of long-acting GnRH agonist follicular (n=1994) and antagonist protocols (n=1678) among women undergoing IVF. Results revealed that OHSS rate (relative risk (RR): 1.63; p=0.0058, Figure 6) was lower in the GnRH antagonist protocol compared to the long-acting GnRH agonist protocol group. Live birth rate (RR: 1.61; p<0.001), clinical pregnancy rate (RR: 1.44; p<0.001), and implantation rate (RR: 1.58; p=0.001) were higher in the long-acting GnRH agonist follicular protocol compared with the antagonist protocol group. No difference was observed in miscarriage rate (RR: 0.98; p=0.98) between the groups.
The incidence of OHSS rate was significantly lower in women undergoing the GnRH antagonist protocol. However, the long-acting GnRH agonist follicular protocol was beneficial in improving live birth rate, clinical pregnancy rate, and implantation rate.

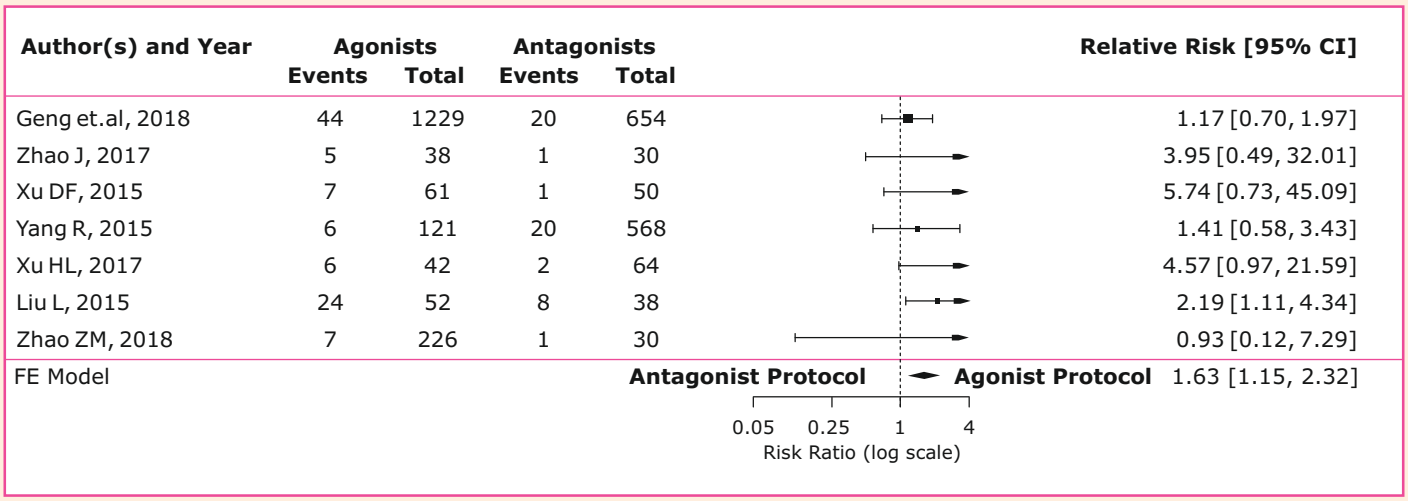

Figure adapted from Yang R et al. Adv Ther. 2021;38(5):2027-2037.

Figure 6. Forest plot comparing the OHSS rate of patients between the long-acting GnRH agonist follicular group and the GnRH antagonist protocol groups.
CI, Confidence interval; FE, Fixed effect; GnRH, Gonadotropin-releasing hormone; OHSS, Ovarian hyperstimulation syndrome.

Early administration of a GnRH antagonist led to reduced incidence of moderate-to-severe OHSS in high-risk subjects with a better clinical pregnancy rate per embryo transfer

Shin et al., in a multi-center randomized parallel-group trial evaluated the efficacy and safety of a fixed early GnRH antagonist protocol (n=14) against conventional midfollicular GnRH antagonist protocol (n=11) and a long GnRH agonist protocol (n=11) for IVF in patients with PCOS (Figure 7). The primary endpoint of this study was the number of oocytes retrieved, and the secondary endpoints included the rate of moderate-to-severe OHSS and the clinical pregnancy rate.
Results demonstrated that the median total number of oocytes was similar among three groups (early, 16; conventional, 12; agonist, 19; p=0.111). The early GnRH antagonist protocol showed statistically non-significant associations with a higher clinical pregnancy rate (early, 50.0%; conventional, 11.1%; agonist, 22.2%; p=0.180) and lower incidence of moderate-to-severe OHSS (early, 7.7%; conventional, 18.2%; agonist, 27.3%; p=0.463), especially among subjects

at high risk for OHSS (early, 12.5%; conventional, 40.0%; agonist, 50.0%; p=0.324) (Table 3). Early administration of a GnRH antagonist led to reduced incidence of moderate-to-severe OHSS in high-risk subjects with a better clinical pregnancy rate per embryo transfer.

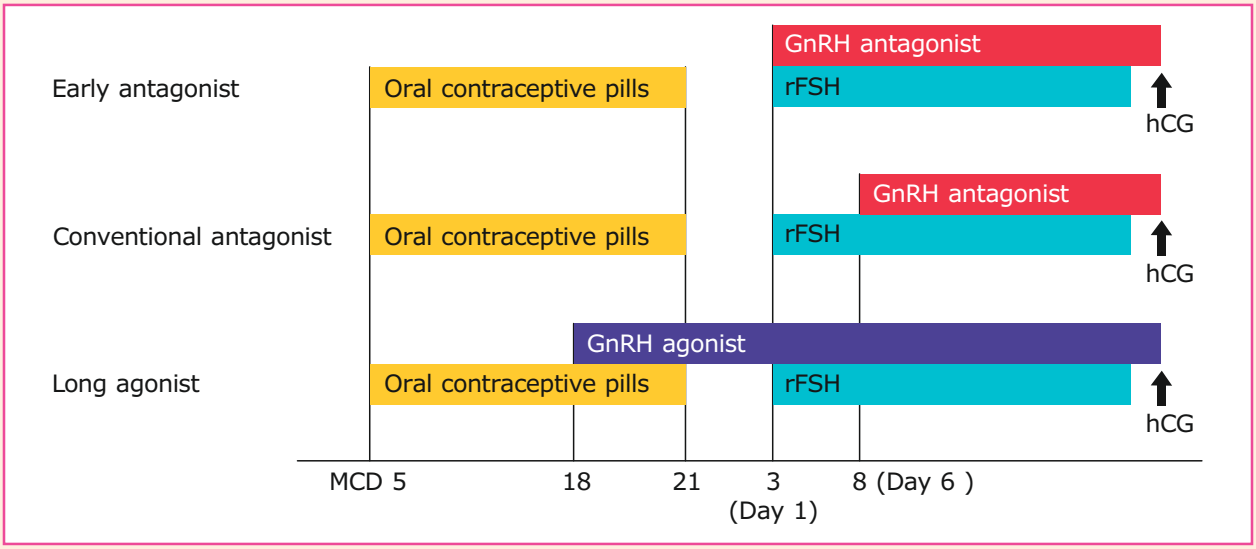

Figure adapted from Shin JJ et al. Clin Exp Reprod Med. 2018;45(3):135-142.

Figure 7. Schematic representation of each *in vitro* fertilization protocol.
GnRH, Gonadotropin-releasing hormone; rFSH, Recombinant follicle-stimulating hormone; hCG, Human chorionic gonadotropin; MCD, Menstrual cycle day.

Table 3. IVF outcomes of study groups

Variable	Early antagonist (n=14)	Conventional antagonist (n=11)	Long agonist (n=11)	p-value
Clinical pregnancy per embryo transfer (%)	4/8 (50.0)	1/9 (11.1)	2/9 (22.2)	0.180
Moderate-to-severe OHSS	1/13 (7.7)	2/11 (18.2)	3/11 (27.3)	0.463
Moderate-to-severe OHSS among cycles with hCG day E_2>2,000 pg/mL	1/8 (12.5)	2/5 (40.0)	3/6 (50.0)	0.324

Values are presented as number (%) or median (range).
ICSI, intracytoplasmic sperm injection; NA, not applicable; OHSS, ovarian hyperstimulation syndrome; E_2, estradiol; hCG, human chorionic gonadotropin.

Table adapted from Shin JJ et al. Clin Exp Reprod Med. 2018;45(3):135-142.

GnRH antagonist protocol may be preferred to reduce OHSS incidence rates without compromising the pregnancy outcome for PCOS patients treated by ICSI

A cross-sectional study conducted by Behery et al., compared the efficacy of GnRH agonist long mid-luteal protocol (Group 1; n=200) against fixed (day 7) GnRH antagonist protocol (Group 2; n=200) in patients with PCOS treated by ICSI. Incidence rate of OHSS was the primary outcome measured in this study. Results demonstrated that rates of OHSS significantly differed between the groups where the rates were 15%, 6%, and 1.5% *vs*. 4.5%, 2.5%, and 0.05% with p=0.04 for mild, moderate, and severe form of OHSS respectively in group 1 and group 2 (Figure 8). Hence, antagonist protocol may be preferred with regards to reduction of OHSS incidence rates without compromising the pregnancy outcome for PCOS patients treated by ICSI.

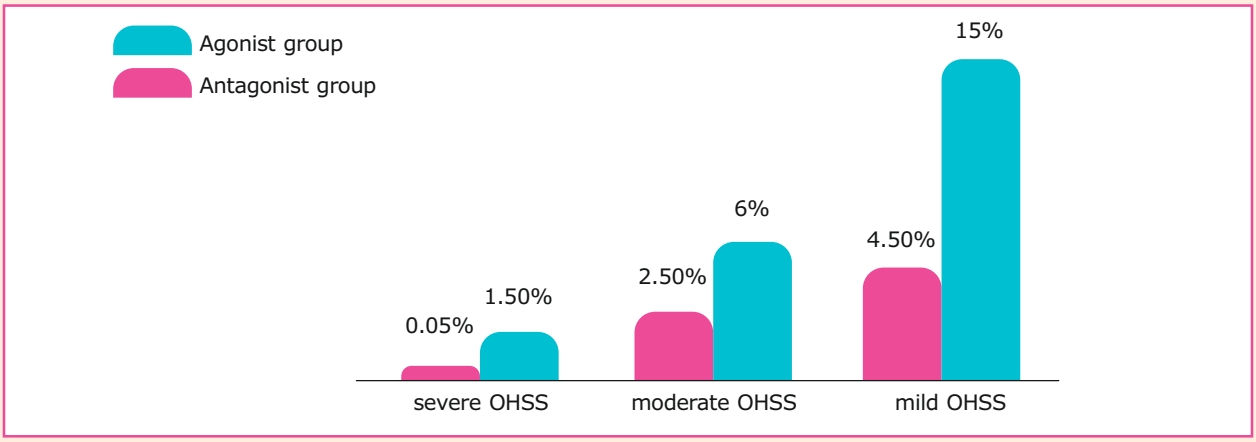

Figure adapted from Behery MA et al. Middle East Fertility Society Journal. 2020 Jan;24:1-7.

Figure 8. Bar chart representing the percentages of different forms of OHSS in both groups.

GnRH antagonist protocol is an equally effective but safer protocol in PCOS patients compared with the long agonist protocol

A single-center prospective controlled study carried out by Kaur et al., compared long agonist (n=60) and antagonist (n=40) protocol in PCOS women. Live birth rate and clinical pregnancy rate were the primary outcomes measured in this study, and rate of OHSS was considered as one of the secondary outcomes. Results demonstrated that there were no significant differences observed between the groups in live birth rate and clinical pregnancy rate.

Furthermore, rate of OHSS was significantly higher in the agonist group. Number of oocytes retrieved, number of follicles and peak estradiol levels were significantly more in the agonist group (Table 4). These findings implied that GnRH antagonist protocol is an equally effective but safer protocol in PCOS patients compared with the long agonist protocol.

Table 4. Pregnancy outcome and OHSS rate in the agonist and antagonist groups

	Long agonist (n = 60)	Antagonist (n = 40)	p value
Implantation rate	19.5%	18.87%	1.000
Clinical pregnancy rate	23 (38.3%)	15 (37.5%)	0.933
Multiple pregnancy rate	6 (10.0%)	3 (7.5%)	0.446
Miscarriage rate	2 (3.3%)	2 (5.0%)	1.000
Ectopic pregnancy rate	2 (3.3%)	1 (2.5%)	1.000
Live birth rate	19 (31.7%)	12 (30%)	0.860
OHSS rate	16 (26.7%)	2 (5.0%)	**0.007** Highly significant**

Embryo transfer was cancelled and all embryos cryopreserved in two cases of early onset OHSS detected within 3 days post oocyte retrieval; **indicates p value is significant

Table adapted from Kaur H et al. J Hum Reprod Sci. 2012;5(2):181-186.

Flexible GnRH antagonist protocol is strongly recommended for patients under 30 years old and with high ovarian reserve (AFC>24)

Zhang et al., conducted a retrospective cohort study to compare the cumulative live birth rates (cLBRs) after the first ART cycle using flexible GnRH-antagonist protocol (n=1640) *vs*. standard long GnRH agonist protocol (n=2762) for COS in infertile women with different ages and ovarian

reserve. Results depicted that the cLBRs of women in the antagonist and long agonist protocols group were 45.3 and 50.0% respectively. Subgroup multivariable regression analysis showed that in patients with low ovarian reserve (AFC≤7), the cLBR was significantly lower in the antagonist group than in the long agonist protocol group (OR: 0.62), which effect was more robust in younger patients (<30 y) (OR: 0.29). The analysis also revealed remarkably lower cLBR in patients above 40 years regardless of their AFC, although the difference was not statistically significant. The cLBR was higher in cycles with antagonist protocol than with the long agonist protocol (OR:1.43) in patients with high ovarian reserve (AFC>24), and the effect was of statistical significance in younger patients (<30y) (OR: 1.78) (Table 5).

This study strongly recommended flexible GnRH antagonist protocol for patients under 30 years old and with high ovarian reserve (AFC>24). For the other groups of patients in the present cohort, antagonist protocol was slightly favored because it had lower OHSS in general and in patients with PCOS according to previous publications.

Table 5. Comparison of cLBRs of flexible GnRH antagonist protocol *vs*. GnRH agonist long protocol using multivariable regression analysis in subgroup patients with different AFCs and of different ages

	Non-adjusted	p	Adjusted	p	p for interaction
Basal AFC ≤7	0.50 (0.35, 0.73)	0.0003	0.62 (0.41, 0.94)	0.026	***0.013***
Basal AFC >7, ≤24	0.99 (0.86, 1.15)	0.902	1.02 (0.88, 1.19)	0.805	
Basal AFC >24	1.35 (0.94, 1.96)	0.109	1.43 (0.96, 2.12)	0.079	
Female age <30 y	0.98 (0.81, 1.19)	0.828	1.01 (0.82, 1.23)	0.952	***0.526***
Female age ≥30 y, <40 y	0.89 (0.75, 1.06)	0.191	0.92 (0.77, 1.10)	0.347	
Female age ≥40 y	0.67 (0.26, 1.73)	0.412	0.58 (0.21, 1.58)	0.288	
Total	0.95 (0.84, 1.08)	0.424	1.00 (0.87, 1.14)	0.985	

The cLBR was not significantly different between the two groups after adjusting for confounders of female age, female BMI, infertility duration, infertility diagnosis, infertility factors and method of fertilization in general population [adjusted OR 1.00 95%CI (0.87, 1.14)]. However, whether adjusting for confounders or not, a significant decrease of cLBR was seen in GnRH antagonist group for patients with basal AFC<7 [non-adjusted OR 0.50 95%CI (0.35, 0.73), adjusted OR 0.62 95%CI (0.41, 0.94)]. p for interaction test between GnRH analogs and AFCs was statistical significant, indicating that patients with basal AFC < 7 might be really a special population that should not be treated with GnRH antagonist. Significant changes of cLBR in other subgroup patients were not seen. The italic values represent that the differences are statistically significant.

Table adapted from Zhang W et al. Front Endocrinol (Lausanne). 2020 May 8;11:287.

GnRH agonist protocol may result with higher LBR than antagonist protocol with satisfied lower OHSS rates for PCOS women in fresh embryo transfer cycles

Zhai et al., evaluated depot GnRH agonist protocol versus GnRH antagonist protocol in IVF outcomes for PCOS patients in a retrospective study of Chinese cohort. The cohort consisted of 533 patients with 470 in the depot GnRH agonist group and 63 in the GnRH antagonist group. Fresh live birth rate (LBR) was the primary outcome measure and severe OHSS is one of the outcome measures of this study.

Results implied that LBR was higher in depot GnRH agonist group compared with GnRH antagonist group (49.79% *vs*. 34.92%; p=0.027). LBR was higher in depot GnRH agonist group compared with GnRH antagonist group based on multivariable logistic regression (odds ratio (OR)=1.83, p=0.032) and after propensity score matching (50.32% *vs*. 35.48%; p=0.033). The OHSS rates were similar between the two groups (p=0.561) (Table 6). Depot GnRH agonist protocol may result with higher LBR than antagonist protocol with satisfied lower OHSS rates for PCOS women in fresh embryo transfer cycles.

Table 6. ART outcomes

		Depot GnRH Agonist Group (n=470)	GnRH Antagonist Group (n=63)	p value
Gn total dose	Mean(SD)	2717.10(1198.34)	2300.71(1372.14)	0.011
	Median (IQR)	2475(1806.25-3300)	1800(1575-2700)	<0.001
Number of oocytes retrieved	Mean(SD)	12.15(5.13)	12.13(5.25)	0.970
	Median (IQR)	12(8-16)	11(8-16)	0.849
Clinical pregnancy rate	Yes	277 (58.94%)	37 (58.73%)	0.975
	No	193 (41.06%)	26 (41.27%)	
LBR	Yes	234 (49.79%)	22 (34.92%)	0.027
	No	236 (50.21%)	41 (65.08%)	
OHSS	Yes	35 (7.4%)	6 (8.5%)	0.561
	No	435 (92.6%)	57 (90.5%)	

Abbreviations: ART, assisted reproductive technology; SD, standard deviation; IQR, the interval of quartile range (Q1-Q3); LBR, live birth rate; OHSS, ovarian hyperstimulation syndrome.

Table adapted from Zhai J et al. J Multidiscip Healthc. 2023;16:2781-2792.

A very recent publication revealed that shorter ovarian stimulation is detrimental to fresh embryo transfer outcomes in PCOS women undergoing GnRH antagonist protocol.
In the study that included patients depending on their Gn duration, ≤8 days (n=501) and >8 days (n=1326), the clinical pregnancy rate, ongoing pregnancy and live birth rate were significantly decreased in the ≤8 days group in fresh embryo transfer (50% *vs*. 66.20%, 45.56% *vs*. 59.08%, 40% *vs*. 56.49%). PCOS women with Gn duration ≤8 days were associated with poor clinical pregnancy,ongoing pregnancy and live birth rate. Although shorter Gn duration (≤8 days) was not associated with impaired embryo outcomes in GnRH antagonist protocol, it was detrimental to clinical pregnancy outcomes in fresh embryo transfer cycle. Over and above all these evidences, in the era of "personalized treatment", clinicians are obliged to consider each individual patient prior to stimulation to determine the most appropriate protocol, combining the lowest treatment burden and risk with the highest chance of conception.

Triggering in PCOS patients

1. *Bourdon M, Peigné M, Solignac C et al. GnRHa (alone or combined with hCG) versus hCG alone for ovulation triggering during controlled ovarian stimulation for IVF/ICSI: a systematic review and meta-analysis. Fertil Steril Rev 2021;2:353-370.*
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. *Atkinson P, Koch J, Susic D, Ledger WL. GnRH agonist triggers and their use in assisted reproductive technology: the past, the present and the future. Womens Health (Lond). 2014;10(3):267-276.*
4. *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.*
5. *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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9. *Orvieto R. Triggering final follicular maturation--hCG, GnRH-agonist or both, when and to whom? J Ovarian Res. 2015 Aug 21;8:60.*
10. *Rahav Koren R, Miller N, Moran R et al. GnRH agonist-triggering ovulation in women with advanced age. Sci Rep. 2022;12(1):16401.*
11. *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.*
12. *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;10:271-80.*

In ART, COS protocols help to obtain mature oocytes that can then be fertilized by IVF/ICSI. The final oocyte maturation step is an essential component of IVF protocols. In natural menstrual cycles, the increasing estradiol level from the dominant follicle in association with a small increase in the progesterone level leads to enhanced LH and FSH release that results in final oocyte maturation and triggering of ovulation. The same condition of triggering is generated after COS in ART. Several options are available in ART to trigger oocyte maturation. Figures 9 and 10 outline different trigger approaches available.

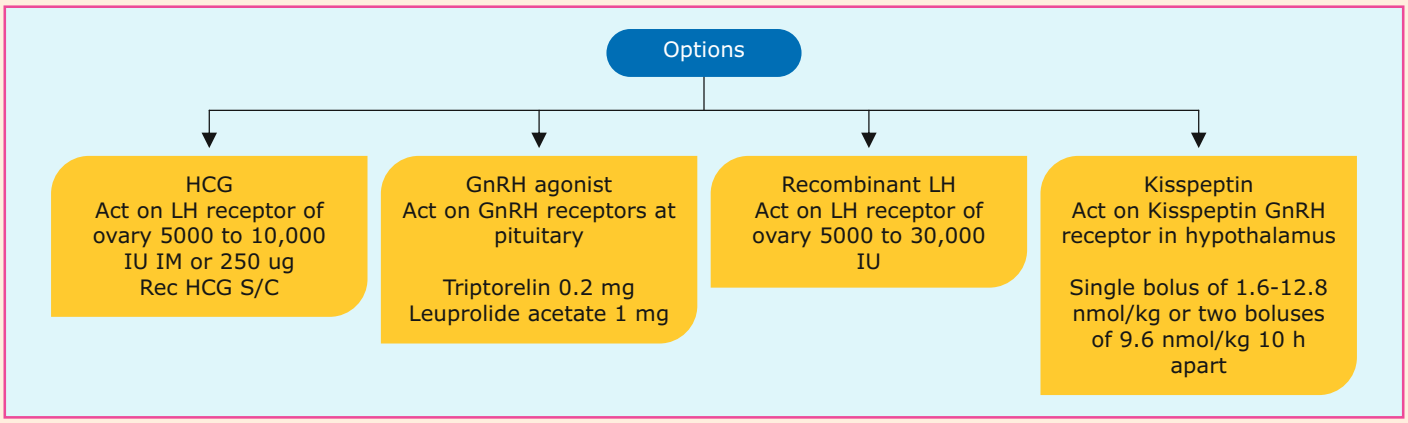

Figure adapted from Sawankar SG et al. J South Asian Feder Obst Gynae. 2020;12(1):38-44.

Figure 9. Various options to trigger oocyte maturation.

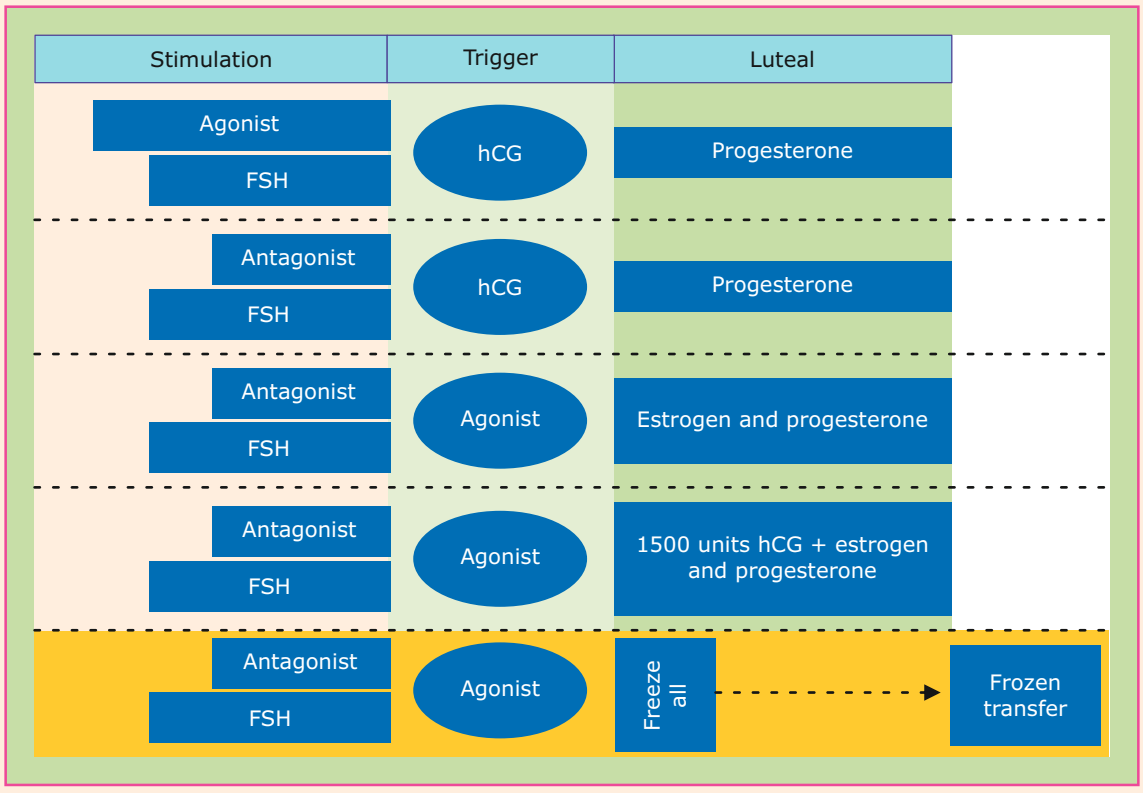

Figure adapted from Atkinson P et al. Womens Health (Lond). 2014;10(3):267-276.

Figure 10. Summary of approaches with human chorionic gonadotropin and agonist triggers.
FSH: Follicle stimulating hormone; hCG: Human chorionic gonadotropin.

Risk comparing GnRH Agonist trigger *vs*. hCG trigger

The exogenous human chorionic gonadotropin (hCG) has a high degree of homology (both structural and biological similarities) with LH, binds to the same receptor (LHCGR), and therefore has been used for several years to trigger ovulation in ART.
Traditionally a bolus of hCG has been the gold standard for ovulation induction and final oocyte maturation in ART cycles as a surrogate for the natural mid-cycle LH surge for several decades.
However, a longer half-life of hCG compared with that of LH, produce a prolonged luteotropic effect which leads to OHSS, a serious iatrogenic complication of ART.
The long half-life and sustainable luteotropic activity of hCG raise significantly vascular permeability stimulated by vascular endothelial growth factor (VEGF) as the major vascular mediator of OHSS. Some studies have also suggested a negative impact of hCG on endometrial receptivity and oocyte quality.
PCOS patients undergoing IVF have a high risk of developing OHSS triggered by exogenous and/or endogenous hCG.
On the contrary, induction of final oocyte maturation with a bolus of GnRH agonists (GnRHa) in patients undergoing ovarian stimulation for IVF could be considered to be more physiologic because the elicited surge mimics the natural cycle surge of gonadotropins (Figure 11).

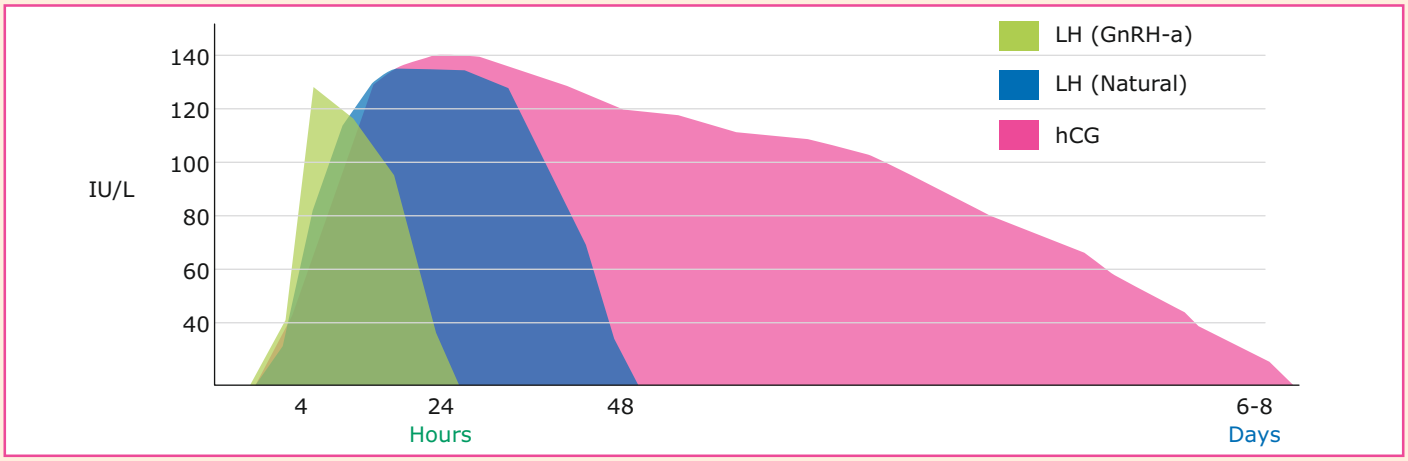

Figure adapted from Castillo JC et al. Ups J Med Sci. 2020;125(2):131-137.

Figure 11. Comparison of ovulation triggers. Schematic graphic showing LH activity of different types of trigger agents when compared with natural mid-cycle surge.
GnRHa: gonadotrophin-releasing hormone agonist; hCG: human chorionic gonadotropin.

Advantages of using GnRHa in the final oocyte maturation

Some studies have demonstrated that the use of GnRHa in the final oocyte maturation has similar or better results compared to hCG trigger. Unlike hCG trigger, GnRH-a trigger stimulates FSH surge in addition to LH surge. FSH surge, in the mid-cycle, has a specific effect on oocyte maturation and leads to a further expansion of cumulus cells surrounding the oocyte and release of proteolytic enzymes involved in the process of ovulation. GnRH-a trigger with effects of FSH along with the LH in the final follicular maturation, may result a more physiological maturity.
GnRHa also significantly decreases the risk of OHSS and when used instead of hCG trigger provides an opportunity to continue the cycle and fresh embryo transfer. Recent modifications of luteal phase after GnRH-a trigger make it possible to transfer embryo in the same cycle for many women at the risk of OHSS and provide a good outcome. In addition, reduction of immature

oocyte syndrome is as a result of GnRH-a trigger.

The advantages of GnRHa trigger use over hCG are as follows:

1. GnRH agonist has shorter half-life (60 min) than hCG (> 24 hours).
2. GnRH agonist induces more physiologic surge of ovulatory LH and FSH *vs*. hCG
3. Number of oocytes retrieved, percentage of mature oocytes and number of top-quality embryos are either comparable or in favor of the GnRHa trigger
4. While both LH and hCG act on the same LH receptor, accumulating evidence suggests that LH has a greater impact on AKT and extracellular signal regulated protein kinase (ERK1/2) phosphorylation, responsible for granulosa cells proliferation, differentiation and survival, while hCG generates higher intracellular cAMP accumulation, which stimulates steroidogenesis (progesterone production).

Orvieto et al., in their paper discuss about the use of GnRHa and hCG in final follicle maturation in patients at risk to develop severe OHSS.

- One bolus of 1500 IU hCG 35 h after the triggering bolus of GnRHa, i.e. one hour after oocyte retrieval, was demonstrated to rescue the luteal phase, resulting in a reproductive outcome comparable with that of hCG triggering, and with no increased risk of OHSS.
- One bolus of 1500 IU hCG concomitant with GnRHa (dual trigger), 34-36 h before oocyte retrieval was suggested as a method which improves oocyte maturation, while providing more sustained support for the corpus luteum than can be realized by the GnRHa-induced LH surge alone. Although acceptable rates of fertilization, implantation, clinical pregnancy, ongoing pregnancy rates, and early pregnancy loss were achieved in high responders after dual trigger, the incidence of clinically significant OHSS was not eliminated, but rather reduced to 0.5%.

Figure 12 outlines the GnRHa and hCG trigger in patients at risk to develop severe OHSS.

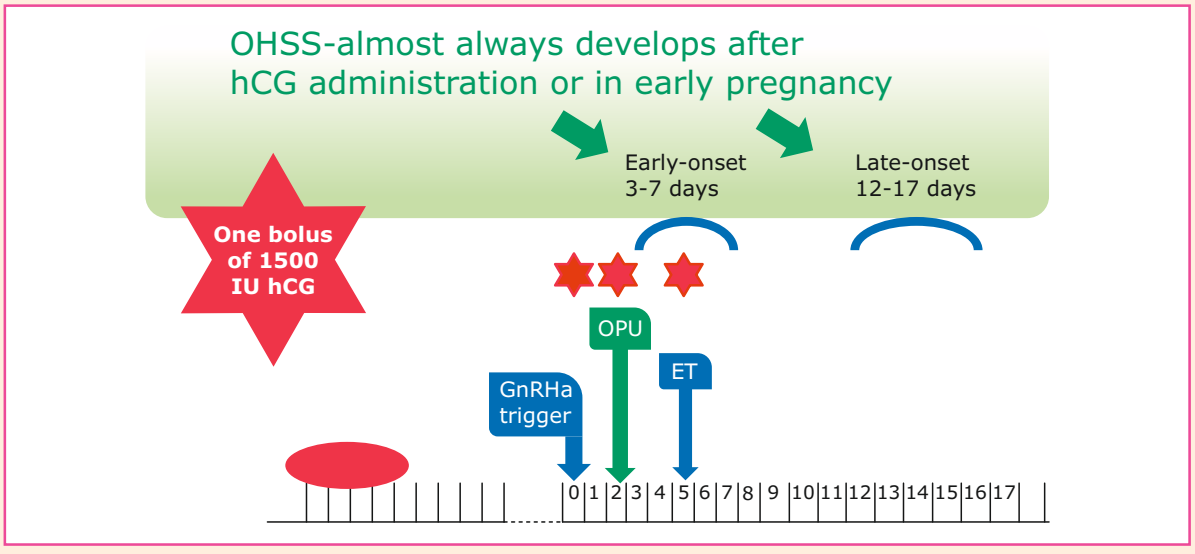

Figure adapted from Orvieto R. J Ovarian Res. 2015 Aug 21;8:60.

Figure 12. GnRHa and hCG trigger in patients at risk to develop severe OHSS.

Table 7 outlines the effect of GnRHa versus hCG trigger on the different follicular maturation variables following an IVF treatment cycle.

Table 7. The effect of GnRHa versus hCG trigger on the different follicular maturation variables following an IVF treatment cycle

Authors	#oocytes	#MII oocytes	#MII to #oocytes	#top quality embryos
Fauser et al.	=		=	=
Kolibianakis et al.	=	=	=	
Humaidan et al.	=		>	
Acevedo et al.	=	=	=	=
Erb et al.	>	>		>

>In favor of GnRHa

Table adapted from Orvieto R. J Ovarian Res. 2015 Aug 21;8:60.

However, despite all these advantages of GnRHa trigger, poor reproductive outcomes have been associated with the GnRHa trigger, including lower ongoing pregnancy rate, lower live birth rate and a higher rate of miscarriage compared to hCG trigger.
This poor outcome is attributed to luteal phase defect and premature luteolysis because of a shorter LH surge associated with the GnRHa trigger compared to the LH surge associated with a natural cycle.
The causes of lower pregnancy rates, could probably, be due to sub-optimal yields of mature oocytes, possible adverse effects on oocyte, embryo, endometrium and luteal phase.
In addition, there are concerns regarding the effectiveness of GnRHa to yield optimal mature oocytes, with a few cases of empty follicle syndrome (EFS) and immature oocyte syndrome being reported. This has led to the clinicians been skeptical of using GnRHa as the trigger of choice even in indicated cases such as **PCOS and hyper-responders**.
A worldwide survey has shown that GnRHa trigger is used only in 5.2% to 36.1% of cases.

Summary

Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder, typically characterized by anovulation, infertility, obesity, insulin resistance and polycystic ovaries. Ovulation induction is considered one of first options infertility management in women with PCOS history. Today, many controlled OS strategies have been offered for the treatment of patients with PCOS undergoing IVF. A plethora of clinical evidence demonstrate that the use of GnRH antagonist protocol has several advantages against the GnRH agonist protocol. Major guidelines strongly recommend GnRH antagonist protocol for women with PCOS with regards to improved safety and significant reduction of OHSS in women with PCOS. Several options are available in ART to trigger oocyte maturation. Studies have demonstrated that the use of GnRHa in the final oocyte maturation has similar or better results compared to hCG trigger which has been the gold standard for ovulation induction and final oocyte maturation in ART cycles.

Feedback form

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Thank you for going through the contents of **ALIVE Newsletter Issue 11.** To ensure that future issues will be of interest to you, we would greatly appreciate your feedback on the format and content of this issue.

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Satisfaction Score for ALIVE Newsletter Issue 11 - PCOS and Infertility: Managing current challenges : part 2 ; January 2025

Rating Scale	Poor ----------Excellent (Please circle the appropriate rating)									
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 11 did you find particularly interesting and/or informative?

_____

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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