ALIVE

ART LEARNING INITIATIVES FOR EXPERTS

Issue 10

PCOS and Infertility : Managing current challenges part 1

January 2024

MERCK

CONTENTS

expert insights

Dr. G. A. Rama Raju

Director,
Krishna IVF Clinic,
Visakhapatnam, India.

Polycystic ovary syndrome (PCOS) is a complex heterogeneous multisystem disorder with a high global prevalence. Infertility is a prevalent presenting feature of PCOS. The complex etiology of PCOS poses as a challenge even today for clinicians to manage the syndrome effectively as different neuroendocrine mechanisms appear to be involved in mediating the development of PCOS.

In patients with PCOS, polyfollicular development during controlled ovarian hyperstimulation (COH) in IVF/ICSI occurs easily and this is a difficult problem to manage. The risk of OHSS is high in PCOS women compared to non-PCOS women. Early detection and prevention in advance of OHSS in PCOS patients is extremely important to the safety of COH treatment.

In this issue an effort is made to discuss the importance of early detection of OHSS, its primary and secondary prevention, various factors increasing the risk of OHSS in PCOS, relation between different biomarkers, and OHSS and prediction models for OHSS in PCOS.

In addition, the role of Metformin in IVF and its efficacy on biomarkers like AMH and AFC in PCOS patients is also outlined.

An effort is also made to develop a complete checklist that can be a guidance to clinicians on OHSS prevention in Fertility treatment.

PCOS and Infertility: Managing Current Challenges

Is PCOS Really an Enigma? Introduction and Challenges

1. *Joham AE, Piltonen T, Lujan ME et al. Challenges in diagnosis and understanding of natural history of polycystic ovary syndrome. Clin Endocrinol (Oxf). 2022;97(2):165-173.*
2. *Li M, Ruana X and Mueck AO. Management strategy of infertility in polycystic ovary syndrome. Global Health Journal.2022;6(2):70-74.*
3. *Che Y, Yu J, Li YS et al. Polycystic Ovary Syndrome: Challenges and Possible Solutions. J Clin Med. 2023;12(4):1500.*
4. *Copp T, Muscat DM, Hersch J et al. The challenges with managing polycystic ovary syndrome: A qualitative study of women's and clinicians' experiences. Patient Educ Couns. 2022;105(3):719-725.*
5. *Costello MF, Misso ML, Balen A et al for International PCOS Network. Evidence summaries and recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome: assessment and treatment of infertility. Hum Reprod Open. 2019;2019(1):hoy021.*
6. *Hoeger KM, Dokras A and Piltonen T. Update on PCOS: Consequences, Challenges, and Guiding Treatment. The Journal of Clinical Endocrinology & Metabolism. 2021;106(3): e1071–e1083.*
7. *Dumesic DA, Abbott DH, Sanchita S et al. Endocrine-Metabolic Dysfunction in Polycystic Ovary Syndrome: an Evolutionary Perspective. Curr Opin Endocr Metab Res. 2020;12:41-48.*
8. *Stener-Victorin E, Padmanabhan V, Walters KA et al. Animal Models to Understand the Etiology and Pathophysiology of Polycystic Ovary Syndrome. Endocr Rev. 2020;41(4):bnaa010.*
9. *Liao B, Qiao J and Pang Y (2021) Central Regulation of PCOS: Abnormal Neuronal-Reproductive-Metabolic Circuits in PCOS Pathophysiology. Front. Endocrinol. 12:667422.*
10. *Hiam D, Moreno-Asso A, Teede HJ et al. The Genetics of Polycystic Ovary Syndrome: An Overview of Candidate Gene Systematic Reviews and Genome-Wide Association Studies. J Clin Med. 2019;8(10):1606.*
11. *Palomba S, Santagni S, Falbo A, La Sala GB. Complications and challenges associated with polycystic ovary syndrome: current perspectives. Int J Womens Health. 2015;7:745-763.*
12. *https://aura.abdn.ac.uk/bitstream/handle/2164/18654/Copp_etal_The_challenges_with_AAM.pdf?sequence=1*
13. *Li F, Chen Y, Niu A (2021) Nomogram Model to Predict the Probability of Ovarian Hyperstimulation Syndrome in the Treatment of Patients With Polycystic Ovary Syndrome. Front. Endocrinol. 12:619059.*

Polycystic ovary syndrome (PCOS) is a complex heterogeneous multisystem disorder affecting 8%-13% of reproductive-aged women and 3%-11% of adolescent girls depending on the diagnostic criteria used and the population studied. Some publications also state that the global prevalence of PCOS ranges from 6% to 21%.

PCOS includes a wide range of heterogeneous symptoms on a spectrum of severity and is associated with adverse reproductive, metabolic and psychological outcomes. The etiology of PCOS is still unclear and is likely to be a mix of environmental factors, genetic causes and *in utero* exposure. In women of reproductive age, PCOS leads to oligo or anovulation, hyperandrogenism, and polycystic ovarian changes.

Infertility is a prevalent presenting feature of PCOS with ~75% of these women suffering infertility due to anovulation, making PCOS by far the most common cause of anovulatory infertility.

PCOS is also burdened with insulin resistance that is worsened by hyperandrogenism-related adipose tissue accumulation and dysfunction with lipotoxicity and oxidative stress.

Different animal models have successfully outlined the neuroendocrine mechanisms potentially involved in mediating the development of PCOS (Figure 1). Animal models have identified that alterations in GABA, KNDy, and AMH brain-specific signaling are likely involved in GnRH neuron hyperactivity in PCOS.

A brief explanation of roles of GABA, KNDy, AMH and GnRH in the complex mechanism of PCOS is outlined below.

1. GnRH Neuron Hyperactivity in PCOS: Gonadotropin-releasing hormone (GnRH) neurons play a critical role in the regulation of the reproductive system. In PCOS, these neurons can become hyperactive, leading to an imbalance in the reproductive hormones.

2. GABA (Gamma-Aminobutyric Acid): GABA is a major inhibitory neurotransmitter in the brain. Alterations in GABA signaling could disrupt the normal inhibitory control over GnRH neurons, potentially contributing to their hyperactivity in PCOS.
3. KNDy Neurons: KNDy neurons, which express Kisspeptin, Neurokinin B and Dynorphin, are crucial in regulating GnRH secretion. Changes in the activity of these neurons can significantly impact GnRH neuron activity. In PCOS, altered KNDy neuron signaling might contribute to the dysregulation of GnRH secretion.
4. AMH (Anti-Müllerian Hormone): AMH is produced by ovarian granulosa cells and is often elevated in women with PCOS. AMH can influence GnRH neuron activity, and its elevated levels in PCOS might contribute to the hyperactivity of these neurons.

The interplay between these factors in PCOS is complex and involves feedback mechanisms between the brain and the ovaries. Understanding these interactions is crucial for developing targeted treatments for PCOS, particularly those that address the neuroendocrine components of the disorder.

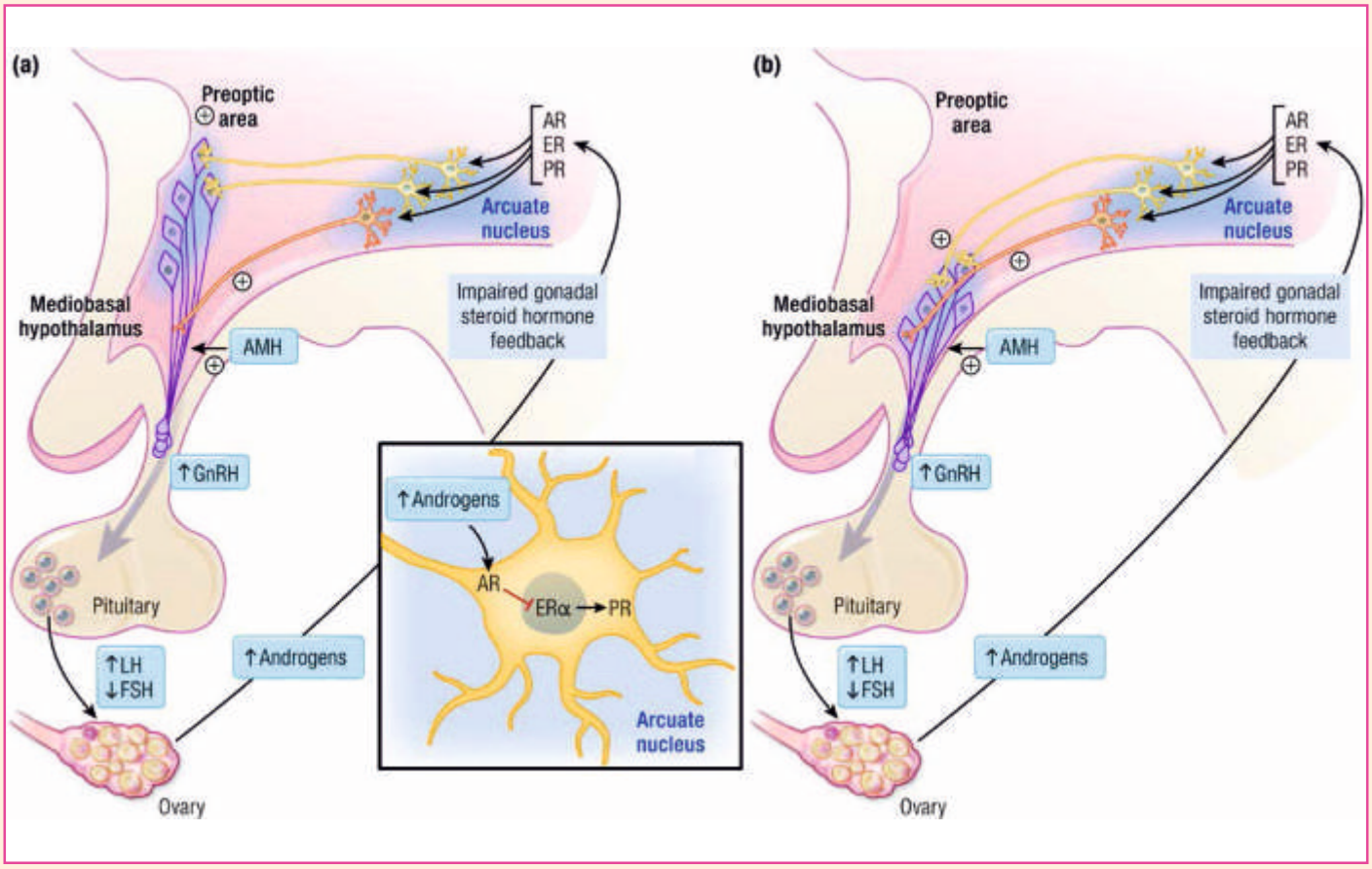

Figure adapted from Stener-Victorin E et al. Endocr Rev. 2020;41(4):bnaa010.

Figure 1. Neuroendocrine mechanisms potentially involved in mediating the development of PCOS. Panel (a) illustrate rodent and panel (b) primate hypothalamus-pituitary-gonadal feed-back loops.

The genome-wide association studies have identified a total of 19 risk gene loci for PCOS located in the neuroendocrine, metabolic, and reproductive pathways (Table 1).

Table 1. SNPs identified by Genome-Wide Association Studies (GWAS) in Polycystic Ovary Syndrome (PCOS). NIH, National Institute of Health.

Study	Diagnostic Criteria	Gene Locus	SNPs	Nearest Gene
Chen et al., 2011	Rotterdam	2p16.3	rs13405728	*LHCGR, STON1-GTF2A1L*
		2p21	rs12468394 rs13429458 rs12478601	*THADA*
		9q33.3	rs10818854 rs2479106 rs10986105	*DENND1A*
Shi et al., 2012	Rotterdam	2p16.3	rs13405728	*LHCGR, STON1-GTF2A1L*
		2p16.3	rs2268361 rs2349415	*FSHR*
		2p21	rs12468394 rs13429458 rs12478601	*THADA*
		9q33.3	rs10818854 rs2479106 rs10986105	*DENND1A*
		9q22.32	rs4385527 rs3802457	C9orf3
		11q22.1	rs18974116	*YAP1*
		12q13.2	rs705702	*RAB5B, SUOX*
		12q14.3	rs2272046	*HMGA2*
		16q12.1	rs4784165	*TOX3*
		19p13.3	rs2059807	*INSR*
		20q13.2	rs6022786	*SUMO1P1*
Lee et al., 2015	Rotterdam	8q24.2	rs10505648	*KHDRBS3, LINC02055*
Hwang et al., 2012	Rotterdam	12p12.2	rs10841843 rs6487237 rs7485509	*GYS2*
Hayes et al., 2015	NIH	8p32.1	rs804279	*GATA4, NEIL2*
		9q22.32	rs10993397	*C9orf3*
		11p14.1	rs11031006	*ARL14EP, FSHB*
Day et al., 2015	NIH	2q.34	rs1351592	*ERBB4*
		11q22.1	rs11225154	*YAP1*
		2q21	rs7563201	*THADA*
		11p14.1	rs11031006	*FSHB*
		5q31.1	rs13164856	*RAD50*
		12q21.2	rs1275468	*KRR1*

SNPs = single nucleotide polymorphisms

Table adapted from Hiam D et al. J Clin Med. 2019;8(10):1606.

Moreover, animal studies and human data show the syndrome having transgenerational origins, with a 5-fold higher risk for daughters born to mothers with PCOS for inheriting the syndrome. Thus, the pathogenesis of PCOS is complex and multifactorial, including genetic, environmental, and transgenerational components (Figure 2).

However, new insights into the pathophysiology of PCOS suggest that there may be antenatal drivers for development of PCOS, specifically, evidence of hyperandrogenism in mothers appears to influence development of PCOS features in offspring. The role for abnormal AMH in the pathophysiology is also emerging, but AMH is not yet a diagnostic tool for PCOS.

Studies have shown that PCOS is a really challenging and heterogenous condition for both

clinicians as well as the patients.
Women with PCOS present an adverse reproductive profile, including a high risk of pregnancy-induced hypertension, preeclampsia, and gestational diabetes mellitus. Patients with PCOS present not only a higher prevalence of classic cardiovascular risk factors, such as hypertension, dyslipidemia and Type 2 Diabetes Mellitus, but also of non-classic cardiovascular risk factors, including mood disorders, such as depression and anxiety.
In one of the very first studies published by Copp et al., exploring the views of both clinicians' and women's experiences with managing PCOS, several challenges ushered in.
Clinicians raised a number of challenges regarding PCOS diagnosis. These included the lack of standardisation regarding diagnostic cut-offs, the potential for misdiagnosis due to overlap with other conditions, limitations in evidence regarding long-term implications (including by PCOS phenotype) and the risk of under- and overdiagnosis.
On the contrary, women with PCOS reported significant dissatisfaction with the diagnostic process, inadequate information and treatment prescribed (about oral contraceptives or fertility drugs), difficulties in weight management, trying complementary and alternative management, increased psychological distress etc.

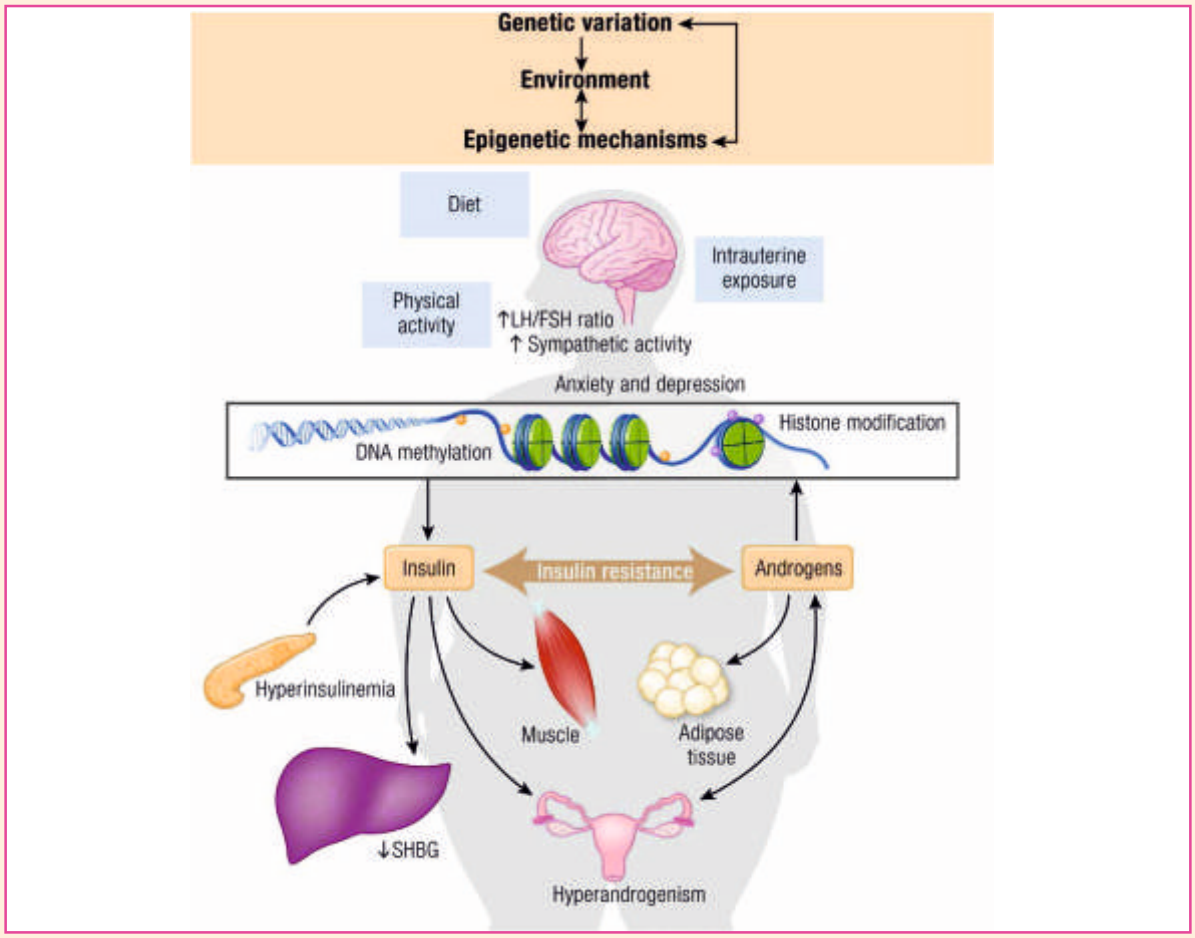

Figure adapted from Stener-Victorin E et al. Endocr Rev. 2020;41(4):bnaa010.

Figure 2. Hypothetical contribution of environmental, epigenetic and genetic factors in the pathophysiology of PCOS.

In patients with PCOS, polyfollicular development during controlled ovarian hyperstimulation (COH) in IVF/ICSI occurs easily and this is a difficult problem. Ovarian hyperstimulation syndrome (OHSS) is a common iatrogenic complication occurring after ovulation hyperstimulation and increases the complications in the perinatal period of pregnant women.
Owing to the threshold window of follicle stimulating hormone (FSH), which is difficult to control, the risk of OHSS is greatly increased in patients with PCOS infertility receiving COH in IVF/ICSI.
Therefore, early detection and prevention in advance of OHSS in PCOS patients are extremely important to the safety of COH treatment.

Importance of early detection and preventing OHSS

1. *Fiedler K, Ezcurra D. Predicting and preventing ovarian hyperstimulation syndrome (OHSS): the need for individualized not standardized treatment. Reprod Biol Endocrinol. 2012;10:32.*
2. *Smith V, Osianlis T, Vollenhoven B. Prevention of Ovarian Hyperstimulation Syndrome: A Review. Obstet Gynecol Int. 2015;2015:514159.*
3. *Agarwal S, Krishna D, Rao KA. Prevention and Management of Ovarian Hyperstimulation Syndrome. Int J Infertil Fetal Med. 2019;10(3):46–51.*

OHSS is a rare, iatrogenic complication of controlled ovarian stimulation (COS).
The incidence of moderate to severe OHSS is between 3.1 and 8% of IVF cycles but can be as high as 20% in high-risk women. The exact cause of OHSS is still unknown. Human Chorionic Gonadotrophin (hCG) exposure, however, is thought to be a critical mediator of the syndrome. The role of hCG can be further elucidated via the two distinct clinical presentations observed in OHSS: the "early" and "late" forms. "Early" OHSS occurs within 9 days of hCG being administered as an ovulatory trigger and reflects the effect of exogenous hCG on ovaries that have already been hyperstimulated by gonadotrophins. "Late" OHSS, on the other hand, occurs more than 10 days after the use of hCG as an ovulatory trigger.

Prevention of OHSS

As on date, there is no perfect strategy which completely eliminates OHSS. However, there are factors which we can take into consideration to reduce its incidence.

Identifying "at-risk" women: Awareness of risk factors is important for clinicians to predict and preempt occurrence of OHSS to reduce its incidence as a complication of COS.

Primary risk factors: Young age, low BMI, PCOS, high AMH, and previous history of OHSS.

Secondary Risk Factors: Rapidly rising E_2 level (E_2 5,000 ng/L and/or ≥18 follicles), >14 follicles with a diameter of 11 mm on trigger day.

Prevention strategies for OHSS can be studied as primary and secondary. Primary prevention is based on assessment of a patient's profile and identifying risk factors and working on them. Secondary prevention helps in early diagnosis and intervention. Deterrence and early detection of OHSS are the most important strategies for the patient's safety.

primary prevention

1. *Jahromi NB, Parsanezhad ME, Shomali Z et al. Ovarian Hyperstimulation Syndrome: A Narrative Review of Its Pathophysiology, Risk Factors, Prevention, Classification, and Management. Iran J Med Sci. 2018;43(3):248-260.*
2. *Velthuis E, Hubbard J, Longobardi S et al. The Frequency of Ovarian Hyperstimulation Syndrome and Thromboembolism with Originator Recombinant Human Follitropin Alfa (GONAL-f) for Medically Assisted Reproduction: A Systematic Review. Adv Ther. 2020;37(12):4831-4847.*
3. *Humaidan P, Polyzos NP, Alsbjerg B et al. GnRHa trigger and individualized luteal phase hCG support according to ovarian response to stimulation: two prospective randomized controlled multi-centre studies in IVF patients. Hum Reprod. 2013;28(9):2511-2521.*

1. **Ovulation induction regimens:** The risk of OHSS should be assessed individually based on the history, physical examination, ultrasound results, and the Antral Follicle Count (AFC). Patients with PCOS are at a higher risk for OHSS. The minimum gonadotropin dose should be used for ovulation induction in patients with PCOS, and step-up regimens are considered superior to step-down regimens.
   In a systematic review and meta-analysis of 45 studies involving 5186 patients exposed to GONAL-f (5240 treatment cycles), the authors recommend a starting dose of less than 150 IU of r-hFSH to mitigate the risk of OHSS and maximize the probability of a safe, fresh embryo transfer after ovarian stimulation for ART treatment in patients with potential/expected ovarian hyper response based on patient characteristics and also biomarkers like AMH and AFC.
   In expected high responders younger than 35 years old presenting with an AMH of 7.7 ng/mL, to avoid cycle cancellation or freeze-all cycles due to excessive ovarian response and related OHSS risk, the r-hFSH starting dose calculated using the existing nomograms would be either 100-112.5 IU, 75-100 IU or 100-125 IU, all of which are lower, as recommended before, than a standard dose of 150 IU.
2. **Metformin:** A recent Cochrane Review, which was based on 8 randomized controlled trials with 798 cases, concluded that Metformin significantly reduced the risk of OHSS by 63%.
3. **Individualizing the treatment regimens of IVF:** COS should be individualized, and gonadotropin administration should be tailored to every single woman separately to prevent OHSS.
4. **Laparoscopic ovarian drilling (LOD) in patients with PCOS:** The main advantage of LOD is decreasing the dose and duration of gonadotropins required for ovulation induction.
5. **Human chorionic gonadotropin alternatives for ovulation triggering:** The drug of choice to trigger the final maturation of follicles should be selected based on the predicted risk of OHSS development.
   A study by Humaidan et al., evaluated whether a GnRH agonist (GnRHa) trigger followed by a bolus of 1,500 IU hCG in a group of patients at risk of OHSS would reduce the OHSS incidence compared with hCG trigger. The study was based on the results of 390 IVF patients from two large prospective, randomized, controlled, multi-centre studies.
   According to the study results, one bolus of 1,500 IU hCG after GnRHa trigger reduced the OHSS rate in patients with 15-25 follicles ≥11 mm and secured the ongoing pregnancy rate. On the contrary, in patients at low risk of OHSS, the administration of two boluses of 1,500 IU hCG after GnRHa trigger led to induction of OHSS.
6. **GnRH antagonist as an alternative to the long agonist IVF protocol:** It has been proven that patients who are at a high risk for developing OHSS would have a minimal risk after undergoing GnRH antagonist protocols.

secondary prevention

1. *Fiedler K, Ezcurra D. Predicting and preventing ovarian hyperstimulation syndrome (OHSS): the need for individualized not standardized treatment. Reprod Biol Endocrinol. 2012 Apr 24;10:32.*
2. *Jahromi NB, Parsanezhad ME, Shomali Z et al. Ovarian Hyperstimulation Syndrome: A Narrative Review of Its Pathophysiology, Risk Factors, Prevention, Classification, and Management. Iran J Med Sci. 2018;43(3):248-260.*

Different ways of Secondary prevention of OHSS can be done by implementing these techniques:

1. **Cancelling ovulation induction:** As OHSS is associated with hCG, terminating the ovulation cycle by cancelling the hCG trigger in the presence of several risk factors for OHSS

is the most effective technique to prevent OHSS.

2. **Coasting - withholding exogenous gonadotropins:** Coasting has been shown to reduce the incidence of OHSS in high-risk patients without affecting cycle outcome.
3. **Individualizing the hCG trigger dose:** Theoretically, decreasing the standard dose of hCG administered to trigger oocyte maturation (10000 IU) might prevent OHSS.
4. **Employing a dopamine agonist:** Administration of a dopamine agonist, such as cabergoline or guinagolide, from the day of hCG trigger can reduce the incidence of OHSS by inhibiting the phosphorylation of VEGFR-2 in response to hCG.
5. **Employing a GnRH agonist trigger:** The risk of OHSS can be reduced by using a GnRHa trigger, instead of an hCG trigger, in patients undergoing COS with a GnRH-antagonist protocol.
6. **Intravenous fluids at time of oocyte retrieval:** Albumin has both osmotic and transport functions, properties that underscore its potential for the prevention of OHSS.
7. **Cryopreservation of oocytes and embryos:** Cryopreservation is considered a traditional approach for the prevention of OHSS in COS.
8. ***In vitro* maturation (IVM) of immature oocytes:** IVM can be considered as another alternative method for fertility treatment in over-responding patients who are at high risk for OHSS.
9. **Vasopressin-induced vascular endothelial growth factor (VEGF) secretion blockade:** VEGF plays a critical role in the pathogenesis of OHSS by increasing vascular permeability. Relcovaptan is a non-peptide vasopressin receptor antagonist that has the ability to inhibit the VEGF by adjusting vascular smooth muscle proliferation and vasoconstriction.

VEGF – A role in the occurrence of OHSS

1. *Fang L, Li Y, Wang S et al. TGF-β1 induces VEGF expression in human granulosa-lutein cells: a potential mechanism for the pathogenesis of ovarian hyperstimulation syndrome. Experimental & Molecular Medicine (2020) 52:450-460.*
2. *Naredi N, Talwar P, Sandeep K. VEGF antagonist for the prevention of ovarian hyperstimulation syndrome: Current status. Med J Armed Forces India. 2014;70(1):58-63.*
3. *McElhinney B, Ardill J, Caldwell C et al. Variations in serum vascular endothelial growth factor binding profiles and the development of ovarian hyperstimulation syndrome. Fertil Steril. 2002;78(2):286-290.*
4. *Pietrowski D, Szabo L, Sator M et al. Ovarian hyperstimulation syndrome is correlated with a reduction of soluble VEGF receptor protein level and a higher amount of VEGF-A. Hum Reprod. 2012 Jan;27(1):196-199.*

Vascular endothelial growth factor (VEGF) was originally described as an endothelial cell-specific mitogen. VEGF can increase vascular permeability and stimulate angiogenesis.

OHSS is related to increased capillary permeability and fluid retention brought about by many biochemical mediators, the most important being vascular endothelium growth factor.

A relation between hCG, VEGF and OHSS has been clearly explained.

The exogenous administration of hCG is the most important prerequisite for the development of OHSS after COH because the syndrome does not develop if hCG is withheld. hCG *per se*, has no vasoactive property and the angiogenic molecule, VEGF has been implicated as the most important mediator of hCG-dependent ovarian angiogenesis. VEGF mRNA levels increases after hCG administration in granulosa cells and VEGF stimulates angiogenesis and vascular hyperpermeability by interacting with its VEGF receptor 2 (VEGFR-2), thus contributing to occurrence of OHSS.

Other pathogenetic forerunners postulated for OHSS are: the immune system and the rennin angiotensin system (RAS). Ovarian RAS, very similar to the action of VEGF, brings about new vessel formation and increased capillary permeability leading to ovarian enlargement and

extracellular fluid sequestration, a characteristic feature of OHSS.
The entire interplay of several mediators involved in the process is outlined in Figure 1.

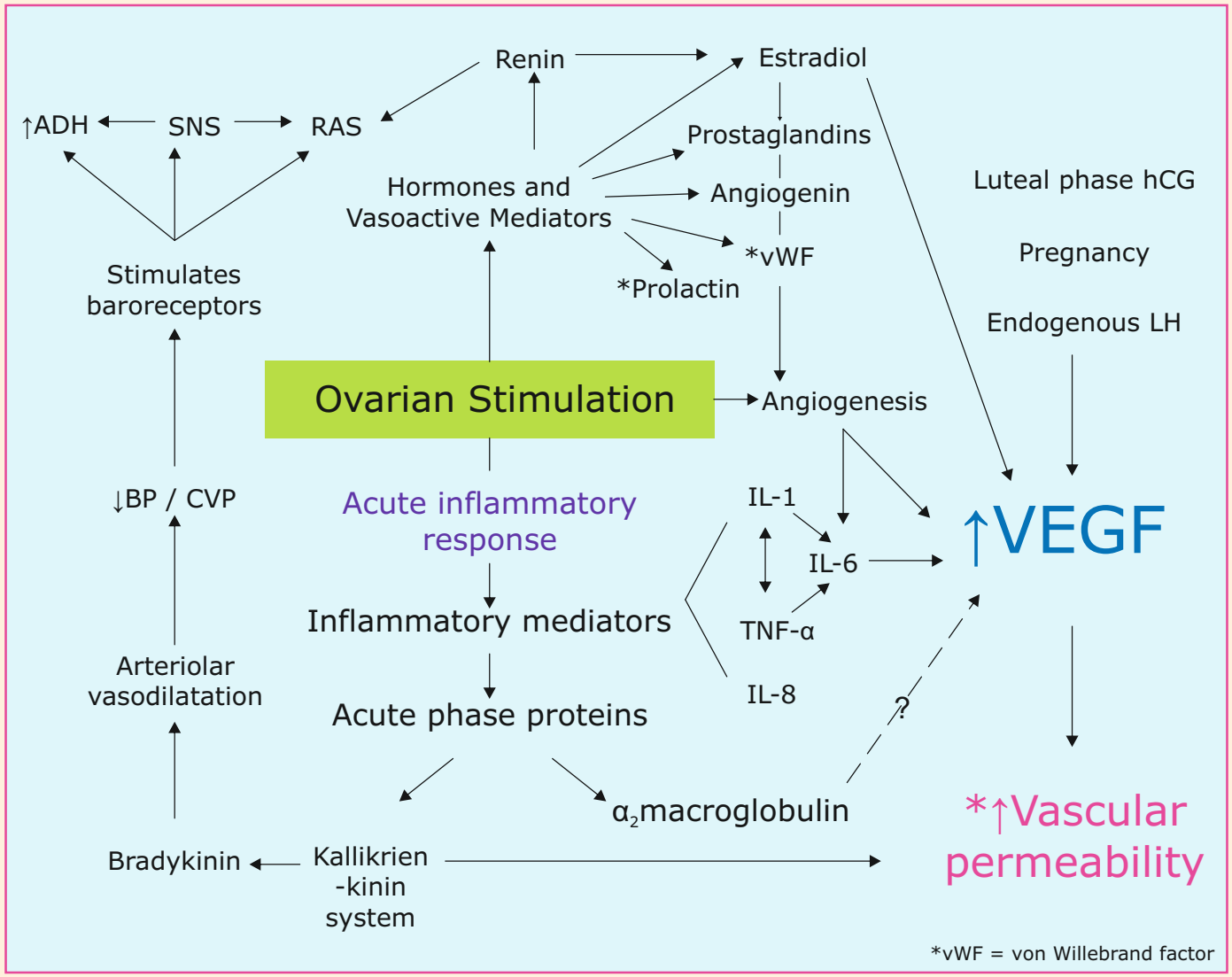

Figure adapted from McElhinney B et al, Fertil Steril. 2002;78(2):286-290.

Figure 1. Cascade of events leading to the development of OHSS.

In a nutshell, the potential role of the VEGF/VEGF-receptor (VEGF-R) system in the occurrence of OHSS is based on three lines of evidence.

1. First, VEGF increases the vascular permeability of endothelial cells which could lead to a shift in fluids from the inner space of the endothelial vasculature to the third space.
2. Second, the occurrence of OHSS is strongly correlated with the application of hCG during IVF therapy, leading to a strong increase in VEGF expression by granulosa cells of the corpus luteum.
3. Third, in OHSS patients the amount of VEGF in the follicular fluid is frequently higher than in persons not affected by this complication.

Hyper-responders vs. PCOS

1. *Vembu R, Reddy NS. Serum AMH Level to Predict the Hyper Response in Women with PCOS and Non-PCOS Undergoing Controlled Ovarian Stimulation in ART. J Hum Reprod Sci. 2017;10(2):91-94.*
2. *Gat I, Shlush E, Quach K, Librach CL. The continuum of high ovarian response: a rational approach to the management of high responder patient subgroups. Syst Biol Reprod Med. 2015;61(6):336-44.*
3. *Elasy AN, Abedlghany AM. Soft ovarian stimulation protocol in polycystic ovary syndromes women inspired by gonadotropin stimulated intrauterine insemination cycles converted to rescue IVF: time to shift the focus "retrospective study". Middle East Fertil Soc J. 2023.28:3.*
4. *Sun B, Ma Y, Li L et al. (2021) Factors Associated with Ovarian Hyperstimulation Syndrome (OHSS) Severity in Women With Polycystic Ovary Syndrome Undergoing IVF/ICSI. Front. Endocrinol. 11:615957.*
5. *Tummon I, Gavrilova-Jordan L, Allemand MC, Session D. Polycystic ovaries and ovarian hyperstimulation syndrome: a systematic review. Acta Obstet Gynecol Scand. 2005;84(7):611-616.*

By definition, the hyper response includes a number of oocytes retrieved above a certain threshold, the development of ovarian hyper stimulation syndrome (OHSS) or cycle cancellation due to the hyper response or a combination of these three entities.
High responders are characterized by an exaggerated response accompanied with a higher risk for OHSS. The importance of chronology in the assessment of high responders is summarized in Figure 1.

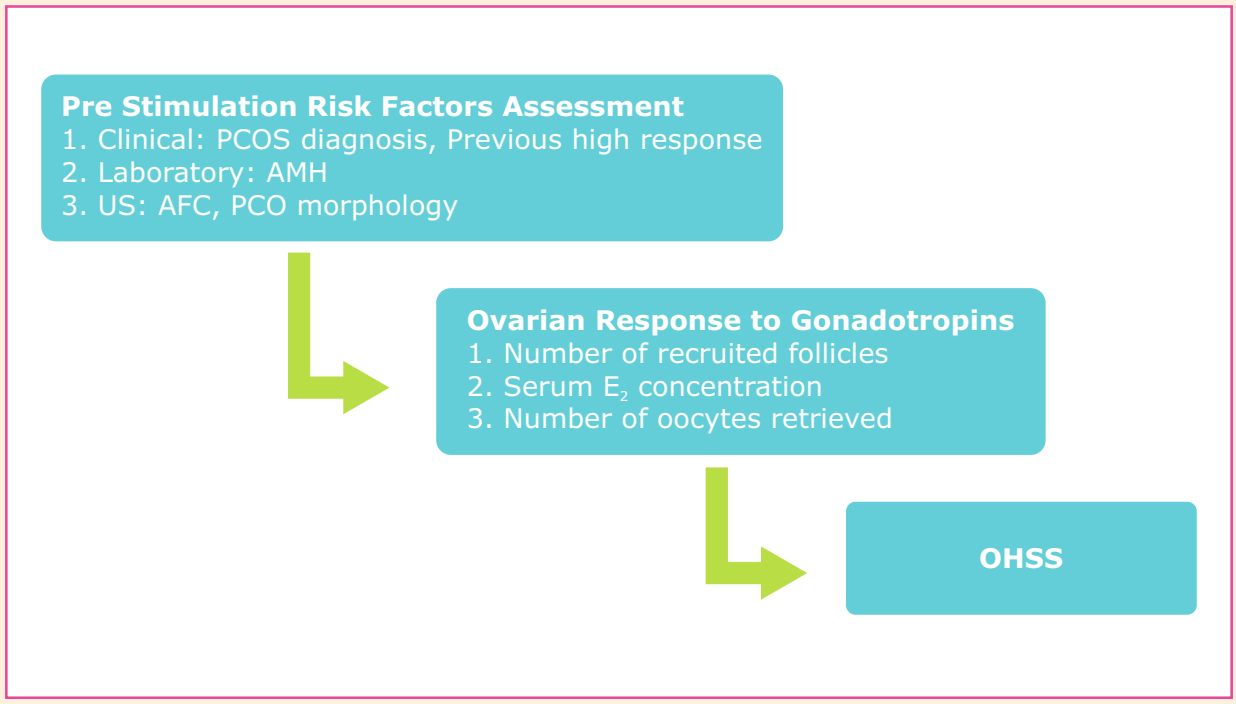

Figure adapted from Gat I et al. Syst Biol Reprod Med. 2015;61(6):336-44.

Figure 1. Chronological evaluation of high ovarian response and OHSS development.
PCOS = polycystic ovary syndrome; AMH = anti-mu¨llerian hormone; AFC = antral follicle count; PCO = polycistic ovary; US = ultrasound; OHSS = ovarian hyperstimulation syndrome; E2 = estradiol.

Ovarian response to gonadotropin stimulation is a wide continuum and often unpredictable. This heterogeneity requires careful stepwise assessment and evaluation. A clear separation should be drawn between risk factors for a high ovarian response and the actual response exhibited by a patient to stimulation. Similarly, it is important to distinguish between high ovarian response and development of clinically significant OHSS.

Among hyper-responders, where follicular recruitment is excessive, a decision should be made to either cancel the cycle or allow a rescue IVF.
On the contrary, PCOS is a critical risk factor for OHSS. Women with PCOS usually have higher AFCs and AMH and serum E_2 levels. Due to the high sensitivity of polycystic ovaries to COH, controlling COH in patients with PCOS is difficult, and thus, COH may result in OHSS.
Tummon et al., in a systematic review assessed and quantified the relationship between polycystic ovaries (PCOs) and OHSS. Ten studies, meeting inclusion and exclusion criteria, were analyzed. When PCO were present, the combined odds ratio for OHSS was 6.8 (95% CI 4.9-9.6) suggesting a significant and consistent relationship between PCO and OHSS.
Considering the eight cohort studies alone, the relative risk for OHSS was 5.7 (95% CI 4.0–8.9), as shown in Figure 2.

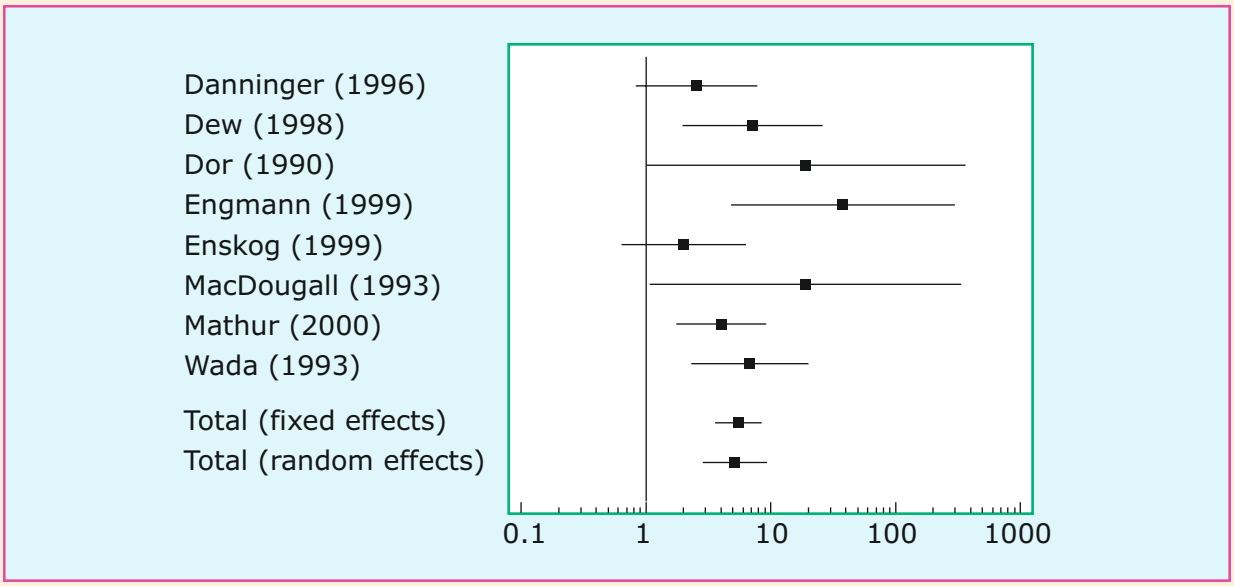

Figure adapted from Tummon I et al. Acta Obstet Gynecol Scand. 2005;84(7):611-616.

Figure 2. Forest plot of cohort studies showing odds ratios with 95% confidence interval.

The figure explains that the risk of OHSS increases as the numerical value of odds ratio increases. As the square boxes in the forest plot graph move away from numerical value 1, the risk for OHSS increases.

phenotypes of pcos

1. *Lizneva D, Suturina L, Walker W et al. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril. 2016 Jul;106(1):6-15.*
2. *Elsayed AM, Al-Kaabi LS, Al-Abdulla NM et al. Clinical Phenotypes of PCOS: a Cross-Sectional Study. Reprod Sci. 2023 May 22.*
3. *Sachdeva G, Gainder S, Suri V et al. Comparison of the different PCOS phenotypes based on clinical metabolic, and hormonal profile, and their response to clomiphene. Indian J Endocr Metab 2019;23:326-331.*

Over the last several decades, although significant efforts have been made to classify PCOS, the global consensus regarding a PCOS criterion remains controversial.
Some progress has been achieved more recently with the introduction of a novel phenotypic approach to the diagnosis. Three sets of diagnostic criteria have been proposed over the past three decades (Table 1).

Table 1. Evolution of the diagnostic criteria for polycystic ovarian syndrome.				
Parameter	NIH 1990	ESHRE/ASRM 2003	AE-PCOS 2006	NIH 2012 extension of ESHRE/ASRM 2003
Criteria	HA OA	HA OD PCOM	1. HA 2. Ovarian dysfunction (OD and/or PCOM)	1. HA 2. OD 3. PCOM
Limitations	1.Two of two criteria required Exclusion of related or mimicking etiologies	1. Two of three criteria required	1. Two of two criteria required	1. Two of three criteria required; and 2. Identification of specific phenotypes included: A: HA + OD + PCOM B: HA + OD C: HA + PCOM D: OD + PCOM

Note: AE-PCOS = Androgen Excess & PCOS Society; ASRM = American Society for Reproductive Medicine; ESHRE = European Society for Human Reproduction and Embryology; HA = hyperandrogenism; NIH = National Institutes of Health; OA = oligo-anovulation; OD = ovulatory dysfunction; PCOM = polycystic ovarian morphology.

Table adapted from Lizneva D et al. Fertil Steril. 2016 Jul;106(1):6-15.

In 2012, the NIH came up with four PCOS phenotypes that are based on either two or all three of the Rotterdam criteria being present.
The NIH consensus panel proposed the phenotypic approach to classify PCOS (Table 2).
Phenotype A (full-blown syndrome PCOS: HA+OD+PCO) includes hyperandrogenism (HA) (clinical or biochemical), ovulatory dysfunction (OD), and polycystic ovaries (PCO) (HA+OD+PCO).
Phenotype B (non-PCO PCOS: HA+OD) includes hyperandrogenism (HA) and ovulatory dysfunction (OD).
Phenotype C (ovulatory PCOS: HA+PCO) includes hyperandrogenism (HA) and polycystic ovaries (PCO).
Phenotype D (non-hyperandrogenic PCOS: OD+PCO) includes ovulatory dysfunction (OD) and polycystic ovaries (PCO).
Table 2. summarizes these four PCOS phenotypes.

Table 2. Classification of polycystic ovarian syndrome phenotypes.				
Parameter	Phenotype A	Phenotype B	Phenotype C	Phenotype D
PCOS features	HA/OD/PCOM	HA/OD	HA/PCOM	OD/PCOM
HA	+	+	+	-
OD	+	+	-	+
PCOM	+	-	+	+
NIH 1990 criteria	x	x		
Rotterdam 2003 criteria	x	x	x	x
AE-PCOS 2006 criteria	x	x	x	

Note: AE-PCOS = Androgen Excess & PCOS Society; HA = hyperandrogenism; NIH = National Institutes of Health; OD = ovulatory dysfunction; PCOM = polycystic ovarian morphology.

Table adapted from Lizneva D et al. Fertil Steril. 2016 Jul;106(1):6-15.

causes of primary and secondary pcos

1. *Khadilkar SS. Can Polycystic Ovarian Syndrome be cured? Unfolding the Concept of Secondary Polycystic Ovarian Syndrome! J Obstet Gynaecol India. 2019;69(4):297-302.*
2. *Gambineri A, Cecchetti C, Altieri P et al., PCOS. Chapter 2 - Secondary PCOS: Well-defined causes, leading to the PCOS phenotype. 15-22. https://doi.org/10.1016/B978-0-12-823045-9.00008-0.*

Etiologically, PCOS is classified as Primary and Secondary PCOS.
A concept of secondary PCOS is being described recently. This condition, even though rare, is completely curable, as majority of these factors are treatable.
Primary PCOS: Primary PCOS is the most common variety of PCOS without any known cause. Proposed theory suggests that there is functional ovarian hyperandrogenism (FOH) along with disturbance of hypothalamo-pituitary–ovarian (HPO) axis function.
Secondary PCOS: The PCOS arising due to well-defined causes other than HPO axis dysfunction is labelled as secondary PCOS. The causes of secondary PCOS are listed in Table 1.

Table 1. Secondary causes mimicking PCOS.

Adipose tissue and Skin	Thyroid	Pituitary	Adrenal	
Obesity	Hypothyroidism	Prolactinoma	Glucocorticoid-suppressible FAH	Glucocorticoid-non-suppressible FAH
Lipodystrophy syndromes	Autoimmune thyroiditis	Hyperprolactinaemia	CAH: classic and non-classic 21-hydroxylase deficiency	Cushing's syndrome
SSIR		ACTH secreting tumour, Cushing's disease	Other less common enzymes deficiency[a]	Androgen-secreting tumours
Idiopathic Hirsuitism		Acromegaly		Glucocorticoid resistance

Ovaries	Neuroendocrine	Drug induced
DSD	Epilepsy	Androgenic drugs
Androgen-secreting tumours {sertoli leydig cell tumour}		Valproic acid

FAH = functional adrenal hyperandrogenism, DSD = disorders of sex development, SSIR = syndrome of severe insulin resistance, CAH = congenital adrenal hyperplasia
[a]11Beta-hydroxylase, cortisone reductase deficiency, DHEA sulphotransferase deficiency

Table adapted from Khadilkar SS. J Obstet Gynaecol India. 2019;69(4):297-302.

clinical categories as per core features and comorbidities

Khadilkar in her paper has described a new nomenclature, "HA-PODS" -- **"hyperandrogenic persistent ovulatory dysfunction syndrome"**. With unfolding the concept, the secondary PCOS, the nomenclature has added secondary PCOS categories (Table 2).
The author opines that in her clinical practice, this nomenclature has been extremely useful to prevent diagnostic pitfalls and to plan the management of PCOS. **The author also opines that secondary causes of PCOS, even though rare, are completely curable.**
She also opines that clinical categorization by HA-PODS nomenclature of both primary and secondary PCOS can minimize diagnostic and therapeutic pitfalls and will serve as a checklist to ensure that appropriate investigation is ordered and specific treatment is initiated as per diagnostic code. This can go a long way in establishing uniformity in diagnosis, treatment and research, which is the need of the hour.

Table 2. Clinical and etiological categories of PCOS.			
HA-PODS-primary		HA-PODS-secondary	
IR	Insulin resistance	PRL	Hyperprolactinaemia
O	Obesity	THY	Thyroid disorders
DM	Diabetes mellitus	CAH	Congenital adrenal hyperplasia
D	Dyslipidaemia	SSIR	Syndrome of severe insulin resistance
C-EH	Cancer/endometrial hyperplasia	LD	Lipodystrophy
HT	Hypertension	AST	Androgen-secreting tumour
SA	Sleep apnoea	Cush	Cushing's syndrome
CV	Cardiovascular disease	DI	Drug (Valproic acid) Induced
FL	Fatty liver		
MS	Metabolic syndrome		

Table adapted from Khadilkar SS. J Obstet Gynaecol India. 2019;69(4):297-302.

Gambineri et al., describe the well-defined endocrinopathies that lead to secondary forms of PCOS, in particular, hyperprolactinemia, thyroid disorders, non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21-NCAH), Cushing's syndrome, acromegaly and severe insulin resistance states.

Different secondary forms of PCOS are as follows:

1. **PCOS - Secondary to hyperprolactinemia:** The literature available describes a high prevalence (50%-67%) of hyperprolactinemia in women with clinical, hormonal, or ultrasound features of PCOS. Prolactin, therefore, needs to be measured in the diagnostic approach to PCOS.
2. **PCOS - Secondary to thyroid disorders:** Thyroid hormones participate in the regulation of follicular development and modulate the production of ovarian steroids. Hypothyroidism decreases sex hormone binding globulin (SHBG) synthesis and secretion by the liver, with a consequent increased peripheral bioavailability of estrogens and, particularly, androgens, thus producing a condition of "functional" hyperandrogenism. On the other hand, hyperthyroidism causes hyperandrogenism through an increased ovarian production rate of testosterone and androstenedione by a direct stimulatory effect. All these alterations contribute to producing a form of PCOS secondary to thyroid disorders.
   Primary hypothyroidism may also cause PCOS through an increase in prolactin which is due to pituitary stimulation by TRH (thyrotropin-releasing hormone) and to peripheral insulin resistance and the subsequent hyperinsulinemia which frequently follows hypothyroidism.
   Interestingly, PCOS is also frequently associated with increased TSH levels without primary hypothyroidism.
   Therefore, TSH and thyroid hormones in the circulation should be measured in the diagnostic approach to PCOS.
3. **PCOS - Secondary to non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency:** The known prevalence of this disease among the PCOS population is between 1% and 3%, but increases to 33% in PCOS women with basal 17-OH progesterone (17-OHP) in the follicular phase of the menstrual cycle of ≥2.00 ng/mL measured by routine immunoassay. Therefore, 21-NCAH should always be considered in the diagnosis of PCOS.

4. **PCOS - Secondary to Cushing syndrome:** Cushing's syndrome (CS) is a rare disorder, with an annual incidence of 2–3 cases/million inhabitants and, in females, it is frequently characterized by hirsutism, acne, menstrual irregularity, infertility, hyperandrogenemia, and, therefore, with a PCOS-like phenotype.
   Hypercortisolism inhibits GnRH pulsatility and decreases gonadotropin responsiveness to GnRH, thus reducing LH and FSH secretion from the pituitary. In addition, it decreases the ovarian LH-receptor level thereby impairing LH action at the ovary, and directly inhibits ovarian estradiol and progesterone production. Cushing's syndrome also causes functional hyperandrogenism by reducing the hepatic synthesis of SHBG.
   When hypercortisolism is severe, hypogonadotropic hypogonadism develops. In such cases, hyperinsulinemia as a consequence of peripheral insulin resistance may act as a co-gonadotropin stimulator of the ovaries, thus maintaining ovarian steroid output and contributing to the development of PCOS.
5. **PCOS - Secondary to acromegaly:** Acromegaly can also be frequently accompanied by a PCOS-like phenotype which is derived from the direct effect of excessive GH/ IGF-1 (insulin-like growth factor 1) secretion on the ovaries and/or from insulin resistance secondary to GH excess. Blood measurement of IGF-1, therefore, needs to be performed in the diagnostic approach to PCOS to exclude acromegaly.
6. **PCOS - Secondary to severe insulin resistance states:** Clinicians who deal with PCOS should always consider the existence of a form of PCOS secondary to a severe state of insulin resistance (SSIR), whose prevalence was recently described to be 1.6%. The reported causes of SSIR are primary defects in insulin signal transduction or adipose tissue dysfunctions due to lipodystrophy or, more frequently, severe obesity.
   Almost all women with SSIR develop a secondary form of PCOS and present acanthosis nigricans, which are considered the clinical marker of severe IR (insulin resistance), due to a condition of "partial IR".

Factors increasing risk of OHSS in PCOS

1. *Sun B, Ma Y, Li L et al. (2021) Factors Associated with Ovarian Hyperstimulation Syndrome (OHSS) Severity in Women With Polycystic Ovary Syndrome Undergoing IVF/ICSI. Front. Endocrinol. 11:615957.*

Age, PCOS, low BMI, high antral follicle count (AFC), increased anti-Muller hormone (AMH) levels, and elevated serum E_2 concentrations are risk factors for OHSS. Published data exploring the factors increasing the risk of OHSS in PCOS is sparse.

A retrospective study by Sun et al., examined the risk factors for OHSS and their effect on OHSS severity in patients with PCOS undergoing IVF/ ICSI. The study reviewed the records of 2,699 women included in this study.

The association between each of the interrogated risk factors (including female age, BMI, AFC, basal serum E_2, and the number of oocytes retrieved) and OHSS were analyzed. The effects of each risk factor on OHSS severity were further explored.

According to the results, 75.2% had a normal response to COH and 24.8% developed OHSS. Patients with OHSS were younger and had lower BMIs and basal serum follicle-stimulating hormone (FSH) and E_2 levels but higher AFCs than those in the normal group.

AFC demonstrated a strong correlation with OHSS, with a cutoff value of 24 in patients with PCOS. A total of 19.5% of the patients had mild OHSS, while 80.5% had moderate OHSS. Basal serum E_2 showed a strong correlation with OHSS severity, with a cutoff value of 37.94 pg/ml.

Table 1 shows a logistic regression analysis for OHSS severity. The basal serum FSH, E_2, and

Testosterone levels and AFC were significant predictors.
The study demonstrated that AFC was a strong marker of OHSS, and basal serum E_2 is the best predictor of OHSS severity in women with PCOS undergoing IVF treatment.

Table 1. Logistic regression analysis for ovarian hyperstimulation syndrome (OHSS) severity.

	Beta	Standard Error	Wald Chi-Square Value	p value	OR (95% CI)
Age					
≤25 y					1.00 (Reference)
25-30 y	0.1989	0.1738	1.3102	0.2524	0.79(0.39–1.60)
30-35 y	0.056	0.1995	0.0788	0.7789	0.69(0.33–1.46)
>35 y	-0.6846	0.3089	4.9123	0.0267	0.33(0.12–0.89)
Antral follicular count*	0.2607	0.2465	1.1179	0.2904	1.30(0.80–2.10)
Baseline hormone levels					
FSH (mIU/ml)*	-0.3403	0.2129	2.5557	0.1099	0.71(0.47–1.08)
E_2 (pg/ml)*	0.4736	0.2206	4.6098	0.0318	1.61(1.04–2.47)
T*	0.1378	0.2264	0.3707	0.5426	1.15(0.74–1.79)
Long-acting protocol	-1.047	0.2122	24.3475	<0.0001	0.35(0.23–0.53)

*Select patients with less than the median values served as the reference groups. The median value for the antral follicular count and FSH, E_2 and T levels was 24, 5.49, 37.94, and 0.37, respectively.
FSH = follicle-stimulating hormone; E_2 = estradiol; T = testosterone.

Table adapted from Sun B et al. Front. Endocrinol. 2021;11:615957.

According to the table, AFC was the best predictor of OHSS among all the variables analyzed and the results suggest that AFC is also the most important risk factor for OHSS in women with PCOS.
Upon exploring the effects of each risk factor on OHSS severity in PCOS women, the following observations were made:

1. **Female Age and OHSS:** This study showed that age may also be used to assess the risk of OHSS and OHSS severity. Young women with high AFCs, high serum E_2 levels and a high number of retrieved oocytes are more susceptible to OHSS. The younger the patients are, the greater the possibility of developing severe OHSS.
2. **BMI and OHSS:** BMI is another patient characteristic that needs to be considered when assessing the risk of developing OHSS and OHSS severity.
3. **AFC and OHSS:** Markers for ovarian reserve, especially serum AMH and AFC, may also be used to assess the risk of OHSS. Based on the data in this study, AFC levels predicted OHSS.
4. **Basal serum E_2, the number of oocytes retrieved and OHSS:** The development of OHSS is almost always accompanied by elevated E_2 levels, and estrogen has been implicated as a potential etiologic factor. Basal serum E_2 showed a stronger correlation with OHSS severity in this study.
   In this study, the number of retrieved oocytes in the OHSS group was higher than that in the normal group (22.96 ± 7.93 vs. 15.31 ± 6.84), but the rate of good-quality embryos was lower (49.06 ± 22.13 vs. 58.54 ± 27.86). Compared with the mild OHSS group, the moderate OHSS group generally had more oocytes retrieved.
   These results may help clinicians pay more attention to the basal serum E_2 and the number of retrieved oocytes of patients with PCOS, which may prevent the occurrence of OHSS in PCOS women.

Risk of OHSS in PCOS and non-PCOS women

1. *Vembu R, Reddy NS. Serum AMH Level to Predict the Hyper Response in Women with PCOS and Non-PCOS Undergoing Controlled Ovarian Stimulation in ART. J Hum Reprod Sci 2017;10:91-94.*
2. *Alhilali MJ, Parham A, Attaranzadeh A et al. Polycystic Ovary Syndrome Develops the Complications of Assisted Reproductive Technologies. Arch Razi Inst. 2022;77(4):1459-1464.*
3. *Ashrafi M, Bahmanabadi A, Akhond MR et al. Predictive factors of early moderate/severe ovarian hyperstimulation syndrome in non-polycystic ovarian syndrome patients: a statistical model. Arch Gynecol Obstet. 2015;292(5):1145-1152.*
4. *Izhar R, Husain S, Tahir MA et al. Antral follicle count and anti-Müllerian hormone level as predictors of ovarian hyperstimulation syndrome in women with polycystic ovarian syndrome undergoing controlled ovarian stimulation. J Ultrason 2021; 21: e200-e205.*

Clinical studies have shown that risk of OHSS is high in PCOS women compared to non-PCOS women.

Vembu et al., conducted a prospective cohort study to compare the outcome of stimulation in PCOS and non-PCOS groups. The study included 246 women undergoing ICSI among which 31.3% were in PCOS group, and 68.7% were in non-PCOS group. According to the results, in the PCOS group, 22.1% had OHSS and only 4.7% had OHSS in non-PCOS group (p=0.0005; Figure 1).

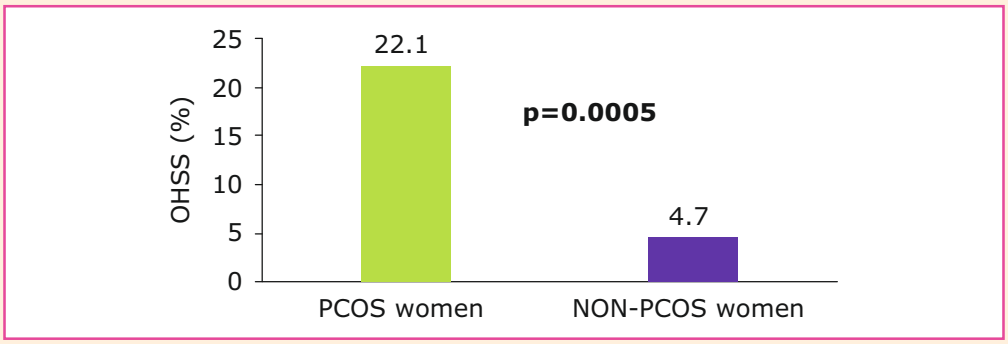

Figure 1. High incidence of OHSS in PCOS women compared to Non-PCOS women.

Another study by Alhilali et al., investigated the relationship between PCOS and non-PCOS patients with the risk of moderate-to-severe OHSS in ICSI treatment patients. The study included 60 patients in the reproductive ages (20-38), including OHSS patients and age-matched normoresponders.

The incidence of OHSS in PCOS patients increased significantly up to 13.9 times higher than in patients without PCOS (OR=13.900; p=0.007; Table 1).

Table 1. Patients and ICSI cycles characteristics of the three groups of the study.

	Normoresponders	Low-risk OHSS	High-risk OHSS	p value
Number of patients	19	13	28	-
Female age (year)	32.11 (20-38)	29.0 (23-35)	29.46 (23-38)	NS
PCOS				
Yes n (%)	0 (0)	3 (5)	7 (11.6)	0.007
No n (%)	19 (31.7)	10 (16.7)	21(35)	

Table adapted from Alhilali MJ et al. Arch Razi Inst. 2022;77(4):1459-1464.

Moreover, moderate-to-severe OHSS increased significantly (OR=3.860; p=0.043) in patients with primary infertility than those with secondary infertility.
The present study revealed that the severity of OHSS increased in PCOS patients especially when they had primary infertility.

Ashrafi et al., in a retrospective study evaluated the predictive factors of early moderate/severe OHSS in non-PCOS patients. In this study, 86 non-PCOS patients who developed moderate-to-severe OHSS out of 7073 patients treated with IVF/ICSI cycles were analyzed with 172 non-PCOS patients without developing OHSS as control group.
The regression analysis revealed that the variables, including age [odds ratio (OR) 0.9, antral follicles count (OR 4.3), infertility cause (tubal factor, OR 11.5), hypothyroidism (OR 3.8) and positive history of ovarian surgery (OR 0.2) were the most important predictors of OHSS.
According to the results, the predictive regression model based on primary characteristics of non-PCOS patients had equal specificity in comparison with two mentioned strong predictive variables namely **number of follicles and serum estradiol level on hCG day.**

Izhar et al., in a prospective cohort study compared the rate of OHSS in women with and without PCOS. Among 689 women included in the study, 276 (40.1%) had PCOS, and 476 (59.9%) were used as the controls. OHSS occurred in 19.6% of the cases, and in 7.7% of the controls (p <0.001) demonstrating that OHSS was common in cases than controls.

Relation between AMH, AFC and OHSS

1. *Smith V, Osianlis T, Vollenhoven B. Prevention of Ovarian Hyperstimulation Syndrome: A Review. Obstet Gynecol Int. 2015;2015:514159.*
2. *Sun B, Ma Y, Li L et al. (2021) Factors Associated with Ovarian Hyperstimulation Syndrome (OHSS) Severity in Women With Polycystic Ovary Syndrome Undergoing IVF/ICSI. Front. Endocrinol. 11:615957.*
3. *Lee TH, Liu CH, Huang CC et al. Serum anti-Müllerian hormone and estradiol levels as predictors of ovarian hyperstimulation syndrome in assisted reproduction technology cycles. Hum Reprod. 2008;23(1):160-167.*
4. *Jayaprakasan K, Chan Y, Islam R et al. Prediction of in vitro fertilization outcome at different antral follicle count thresholds in a prospective cohort of 1,012 women. Fertil Steril. 2012;98(3):657-663.*
5. *Ocal P, Sahmay S, Cetin M et al. Serum anti-Müllerian hormone and antral follicle count as predictive markers of OHSS in ART cycles. J Assist Reprod Genet. 2011;28(12):1197-203.*
6. *Izhar R, Husain S, Tahir MA et al. Antral follicle count and anti-Müllerian hormone level as predictors of ovarian hyperstimulation syndrome in women with polycystic ovarian syndrome undergoing controlled ovarian stimulation. J Ultrason 2021; 21: e200–e205.*
7. *Broer SL, Dólleman M, Opmeer BC et al. AMH and AFC as predictors of excessive response in controlled ovarian hyperstimulation: a meta-analysis. Hum Reprod Update. 2011;17(1):46-54.*

Hormonal markers like Anti-Mullerian Hormone (AMH) are increasingly being utilized in predicting ovarian response to stimulation. Ultrasonographic markers, such as the antral follicle count (AFC), are also another facet worthy of mention in the prediction of OHSS.
The current literature indicates that AMH values >3.4 ng/ml and AFC >24 are particularly associated with an increased risk of OHSS in patients undergoing fertility treatment.
Lee et al., in a study to determine whether the serum AMH levels can predict OHSS prior to selection of COS protocols (262 IVF cycles) showed that the basal serum AMH level predicted OHSS better than age and BMI with a sensitivity of 90.5% and specificity of 81.3%. The basal serum AMH level could be utilized effectively to predict OHSS and thus to direct the selection of mild COS protocols.
Figure 1 shows the ROC curve for the three predicting factors for OHSS which can be determined prior to ovarian stimulation: patient age, BMI and basal serum AMH level.

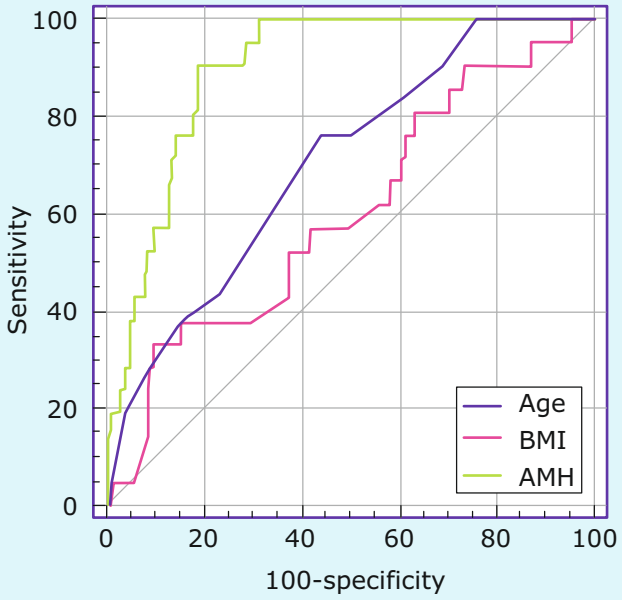

Figure adapted from Lee TH et al. Hum Reprod. 2008;23(1):160-167.

Figure 1. Comparison of predictive values for OHSS using the ROC_{AUC}
The ROC_{AUC} of the basal serum AMH level was larger than that of age (p= 0.002) and BMI (p< 0.001).

Jayaprakasan et al., in their prospective study of 1012 subjects, noted an AFC ≥ 24 to be correlated with an increased risk of moderate to severe OHSS in comparison to an AFC < 24 (8.6% versus 2.2%).
Ocal et al., conducted a study to evaluate predictive role of day-3 serum AMH levels and AFC in OHSS in patients undergoing IVF/ICSI cycles. The study included 41 women with moderate/severe OHSS and 41 age matched women without OHSS.
The study results showed that mean AFC and AMH were significantly higher in women with OHSS compared to women without OHSS (p = 0.049, p < 0.0001 and p < 0.0001, respectively; Table 1). The cut-off value for AMH 3.3 ng/mL provided the highest sensitivity (90%) and specificity (71%) for predicting risk of OHSS. The cut-off value for AFC was 8 with 78% sensitivity and 65% specificity.
The researchers concluded that measurement of basal serum AMH and AFC can be used to determine the women with high risk for OHSS.

Table 1. Mean AMH and AFC levels in the study.

	OHSS present (n=41)	OHSS absent (n=41)	p value
AMH (ng/mL) mean±SD	6.9±3.9	2.9±2.0	<0.0001[a]
AFC mean±SD	12.9±6.8	8.2±6.0	<0.0001[a]

[a]Mann Whitney U test

Table adapted from Ocal P et al. J Assist Reprod Genet. 2011 Dec;28(12):1197-203.

Izhar et al., conducted a prospective cohort study to determine the cut-off for the AFC and the AMH level predictive of OHSS in both PCOS and non-PCOS women.
Among 689 women included in the study, the cut-off value for AFC and AMH in women with PCOS

were 18 and 6.425 ng/ml, respectively, but the values for non-PCOS women were lower, 10 and 3.95 ng/ml, respectively (Table 2). The findings showed that group-specific values should be used to identify and counsel women undergoing COS.

Table 2. AUC for AFC and AMH to predict hyper-response.

AFC	CUT-OFF	AUC	95% (CI)	Sensitivity	Specificity
PCO	18	0.969	(0.939–0.992)	94.4%	97.3%
Control	10	0.972	(0.975–0.997)	93.8%	97.1%
AMH					
PCO	6.425 ng/ml	0.972	(0.946–0.990)	92.6%	93.7%
Control	3.95 ng/ml	0.974	(0.956–0.993)	93.6%	94.5%

Table adapted from Izhar R et al. J Ultrason 2021; 21: e200–e205.

A Meta-analysis of 9 studies reporting on AMH and five reporting on AFC by Broer et al., showed that summary estimates of sensitivity and specificity for AMH were 82 and 76%, respectively, and 82 and 80%, respectively, for AFC. Both AMH and AFC are accurate predictors of excessive response to ovarian hyperstimulation.

Prediction Models for OHSS in PCOS

1. *Cao M, Liu Z, Lin Y et al. (2022) A Personalized Management Approach of OHSS: Development of a Multiphase Prediction Model and Smartphone-Based App. Front. Endocrinol. 13:911225*
2. *Griesinger G, Verweij PJ, Gates D et al. Prediction of Ovarian Hyperstimulation Syndrome in Patients Treated with Corifollitropin alfa or rFSH in a GnRH Antagonist Protocol. PLoS One. 2016;11(3):e0149615.*
3. *Madrazo I, Vélez MF, Hidalgo JJ et al. Prediction of severe ovarian hyperstimulation syndrome in women undergoing in vitro fertilization using estradiol levels, collected ova, and number of follicles. J Int Med Res. 2020 Aug;48(8):300060520945551.*
4. *Li F, Chen Y, Niu A et al. Nomogram Model to Predict the Probability of Ovarian Hyperstimulation Syndrome in the Treatment of Patients With Polycystic Ovary Syndrome. Front Endocrinol (Lausanne). 2021;12:619059.*

A variety of measures have been proposed to be useful in the prevention of OHSS, including decreased gonadotropin consumption, modification/customization of different protocols and cryopreservation of all embryos. Despite the increasing methods of preventing OHSS, moderate/severe OHSS still occurred on a worldwide scale. Complete prevention of OHSS seems to be impossible. Therefore, an early prediction and prevention of OHSS is critical to reduce the morbidity of OHSS.

Several predictive models for OHSS have been proposed although not in PCOS patients.

Griesinger et al., proposed a prediction of OHSS in patients treated with Corifollitropin alfa or rFSH in a GnRH antagonist protocol. The optimal threshold of follicles ≥11 mm on the day of hCG to identify those at risk was 19 follicles for both moderate to severe OHSS and for severe OHSS.

Cao et al., built multiphase prediction models based on big data and constructed a user-friendly smartphone-based app for the personalized management of women at risk of moderate/severe OHSS.

Madrazo et al., proposed prediction of severe OHSS in women undergoing IVF using estradiol levels, collected ova, and number of follicles. The number of ova collected and the fold increase in serum E_2 from Day 3 to Day 10 could predict development of OHSS.

However, Li et al., proposed a Nomogram model to predict the probability of OHSS in the treatment of patients with PCOS.

Nomogram to predict the probability of OHSS in PCOS

1. *Li F, Chen Y, Niu A et al. Nomogram Model to Predict the Probability of Ovarian Hyperstimulation Syndrome in the Treatment of Patients With Polycystic Ovary Syndrome. Front Endocrinol (Lausanne). 2021;12:619059.*

A retrospective study by Li et al., explored the risk factors of OHSS in patients with PCOS undergoing IVF/ICSI and to establish a nomogram model evaluate the probability of OHSS in PCOS patients. The researchers retrospectively analyzed clinical data from 4,351 patients with PCOS receiving IVF/ICSI and divided the clinical cases into a modeling group (3,231 cases) and a verification group (1,120 cases) according to a ratio of about 3:1.

Univariate and multivariate logistic regression analyses showed that **FSH** (OR, 0.901; p<0.001), **AMH** (OR, 1.259; p<0.001), **E_2** value on the day of hCG injection (OR, 1.122; p<0.001), **total dosage of Gn used** (OR, 1.010; p=0.041), and **follicle number on the day of hCG injection** (OR, 0.134; p=0.020; Figure 1) were the independent risk factors for OHSS in PCOS patients.

The AUC of the modeling group was 0.827 (95% CI, 0.795–0.859), and the AUC of the verification group was 0.757 (95% CI, 0.733–0.782).

According to the researchers, the newly established nomogram model has proven to be a novel tool that can effectively, easily and intuitively predict the probability of OHSS in the patients with PCOS, by which the clinician can set up a better clinical management strategy for conducting a precise personal therapy.

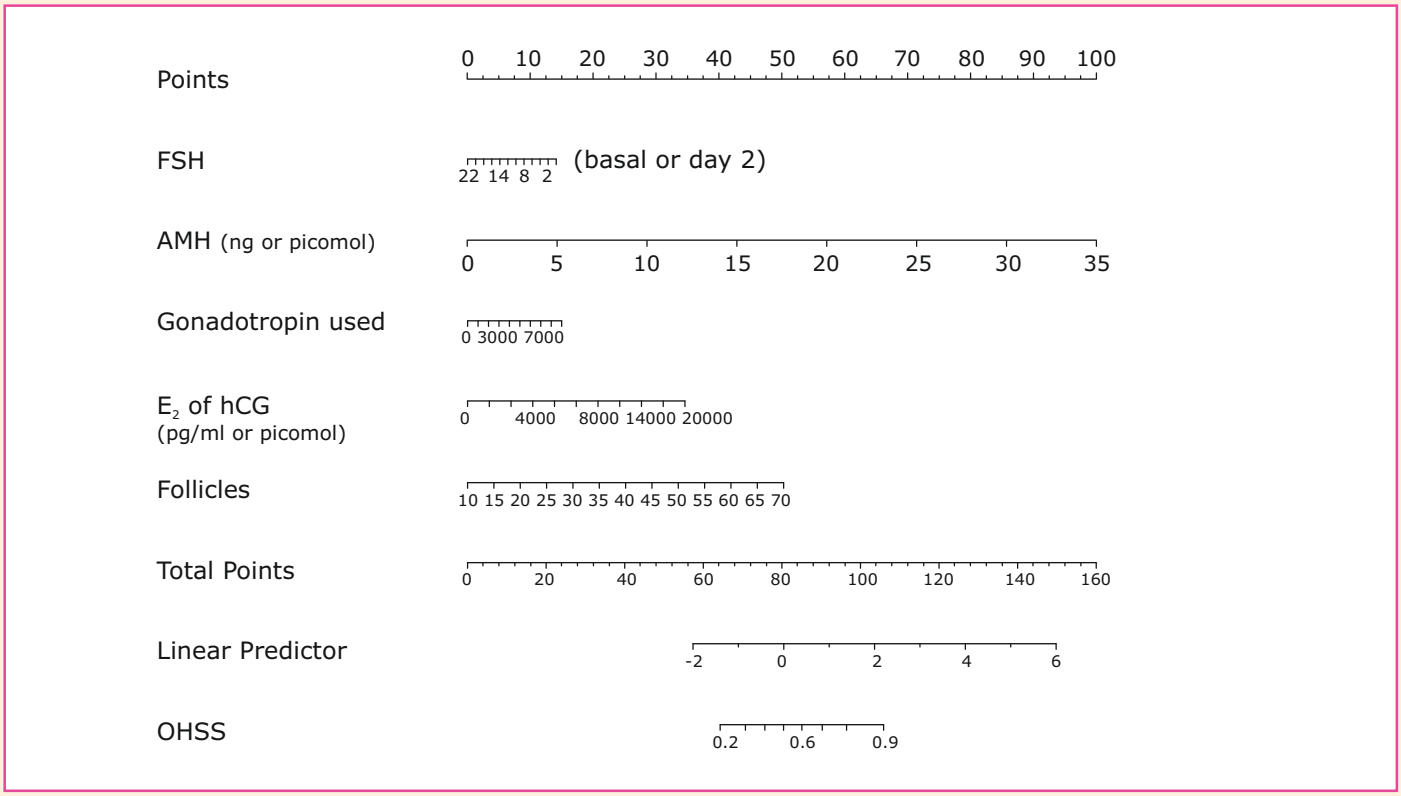

Figure adapted from Li F et al. Front Endocrinol (Lausanne). 2021;12:619059.

Figure 1. **Nomogram to predict the probability of OHSS in PCOS related infertility patients.** The probability of OHSS is calculated by drawing a line to the point on the axis for each of the following variables: FSH, AMH, E_2 value on the day of hCG injection, total dosage of Gn used and follicle number on the day of hCG injection. The points for each variable are summed and located on the total points line. Next, a vertical line is projected from the total points line to the predicted probability bottom scale to obtain the individual probability of OHSS.

Management

1. *Wu Y, Tu M, Huang Y et al. Association of Metformin With Pregnancy Outcomes in Women With Polycystic Ovarian Syndrome Undergoing In Vitro Fertilization: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3(8):e2011995.*
2. *Zhou Z, Chen H, Chu L et al. The effects of metformin on anti-Müllerian hormone levels in patients with polycystic ovary syndrome: a systematic review and meta-analysis. J Ovarian Res. 2023;16(1):123.*
3. *Foroozanfard F, Samimi M, Almadani KH et al. Effect of metformin on the anti-Müllerian hormone level in infertile women with polycystic ovarian syndrome. Electron Physician. 2017 Dec 25;9(12):5969-5973.*
4. *Saleh BO, Ibraheem WF, Ameen NS. The role of anti-Mullerian hormone and inhibin B in the assessment of metformin therapy in women with polycystic ovarian syndrome. Saudi Med J. 2015 May;36(5):562-567.*
5. *Chhabra N, Malik S. Effect of insulin sensitizers on raised serum anti-mullerian hormone levels in infertile women with polycystic ovarian syndrome. J Hum Reprod Sci. 2018; 11:348-352.*

Metformin in IVF and its effect on AMH and AFC

Targeting insulin resistance has improved ovulation and fertility in women with PCOS. During the last decades, this recognition led to many studies regarding the possible role of insulin-sensitizing agents, particularly metformin, in the treatment of PCOS.
Metformin, a biguanide, is widely used among women with PCOS undergoing IVF/ICSI.

Results of a Systematic review and meta-analysis of 12 RCTs, which collectively included 1,123 women with PCOS undergoing infertility treatment with IVF/ICSI-ET demonstrated that Metformin treatment was associated with a decreased risk of OHSS but had no association with the overall clinical pregnancy rate or live birth rate among women with PCOS undergoing IVF/ICSI-ET.

Effect on AMH and AFC : clinical evidences

In a recently published (June 2023) Systematic review and Meta-analysis by Zhou et al., 14 studies involving 257 women with PCOS were included to analyze whether Metformin treatment in patients with PCOS results in a decrease of AMH levels.
The results showed that there was a significant decrease in AMH levels after Metformin treatment [SMD (95% CI) of -0.70 (-1.13 to -0.28); p=0.001; Figure 1].
Metformin exhibited a strong inhibitory effect on AMH levels for PCOS patients with age less than 28 [SMD-1.24, p=0.008].
Additionally, AMH levels significantly slid down in PCOS patients with no more than 6 months Metformin treatment [SMD-1.38, p=0.0007], or with no more than a dose of 2000 mg/day [SMD -0.70, p=0.001].
This meta-analysis provided quantitative evidence demonstrating that metformin significantly decreased AMH levels, especially for young patients and those with AMH levels at baseline higher than 4.7 ng/ml.

A pre and post clinical trial by Foroozanfard et al., assessed the effect of Metformin on AMH level in PCOS patients suffering from infertility. Thirty infertile patients with PCOS were enrolled according to the Rotterdam criteria. The serum AMH level was recorded before and after 8 weeks of treatment with Metformin (1500 mg daily).
Serum AMH level was significantly decreased after 8 weeks of treatment with Metformin [10±3.75 (ng/ml) *versus* 7.8±3.7 (ng/ml)] (p=0.008). Also, AMH level change was directly associated to BMI in PCOS patients. Eight weeks' treatment with Metformin significantly decreased AMH levels in this study.

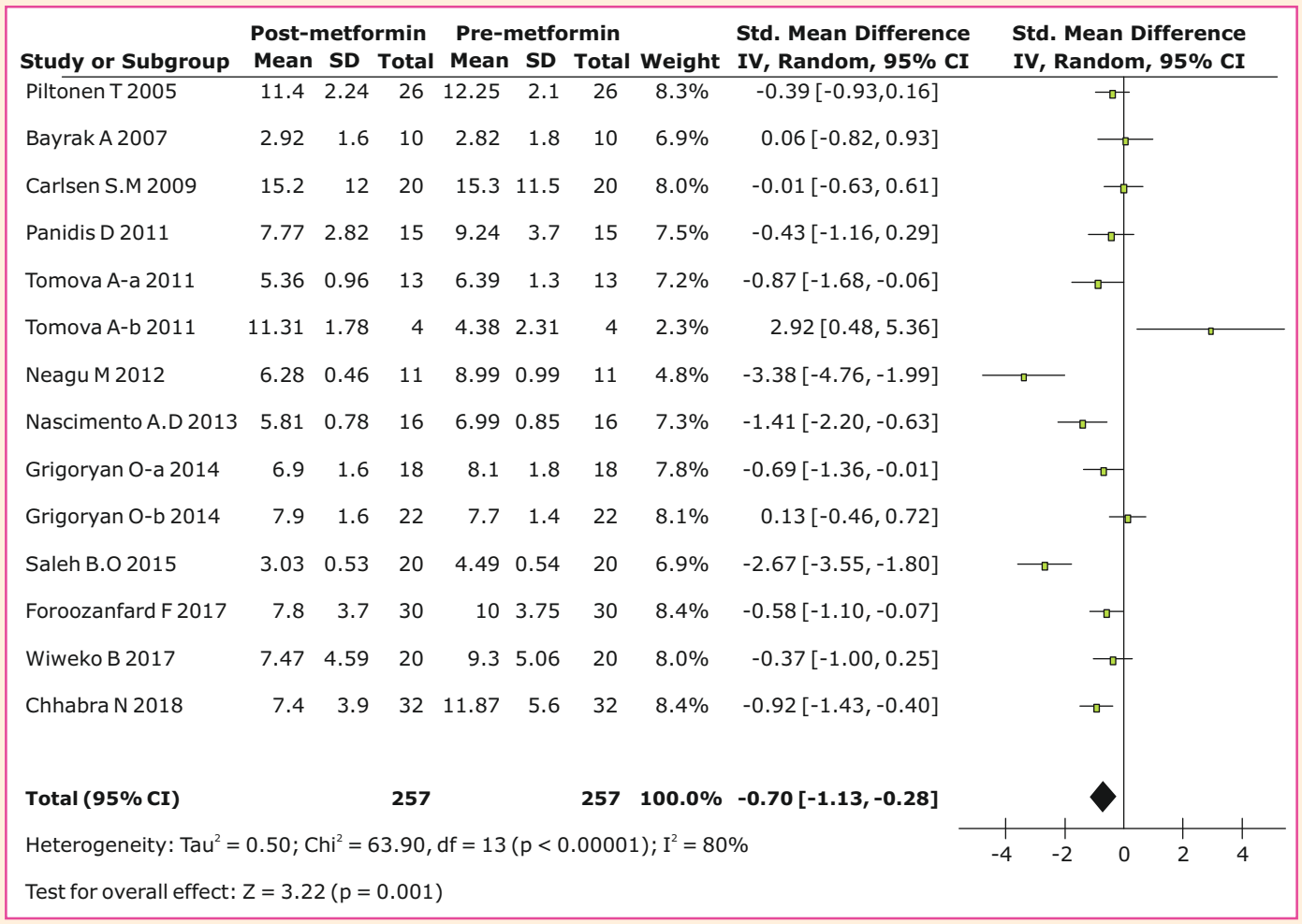

Figure adapted from Zhou Z et al. J Ovarian Res. 2023;16(1):123.

Figure 1. Meta-analysis of serum AMH levels in women with PCOS before and after metformin administration from 14 studies using a random-effect model.

Saleh et al., in a cross-sectional study evaluated the role of Metformin therapy on AMH levels in PCOS women.

About 38 women with PCOS, aged 18-38 years, were classified into:

- Group I (GI, n=20)
- Group II included women in GI that were followed up after they were treated with Metformin hydrochloride 500 mg 3 times daily for 3 months and
- Group III (GIII) included 18 women that were already on metformin hydrochloride treatment 500 mg 3 times daily for 6 months to 3 years.

The mean serum AMH levels was significantly decreased in post Metformin treatment women (3 months; GII; Table 1) compared with those before treatment (GI), and those women on prolonged treatment (GIII) ($p<0.01$ for both).

However, there was no significant difference in serum AMH between GI and GIII.

Table 1. Mean ± standard error of mean values of AMH in different groups of women with PCOS.			
Parameter	Group I, n=20	Group II, n=20	Group III, n=18
AMH (ng/ml)	4.49 ± 0.54	3.03 ± 0.53*	4.88 ± 0.91
*significant difference between Group II and each of Group I and Group III (p=0.001)			

Figure adapted from Saleh BO et al. Saudi Med J. 2015;36(5):562-567.

In conclusion, serum AMH was a useful prognostic biochemical marker for Metformin treatment in PCOS women.

Chabra et al., in a prospective interventional randomized single-center study, studied the effect of insulin sensitizers (Metformin, Myoinositol and their combination) on raised serum AMH levels in 105 infertile women with PCOS. Patients were randomized into three equal groups of 35 each. Group A received Metformin alone, Group B Metformin plus myoinositol, and Group C only Myoinositol.
The results showed a reduction in AMH in all groups of insulin sensitizers with significant fall in the Metformin only group (Table 2).

Table 2. Comparison of anti-Mullerian hormone levels and antral follicle count before and after treatment with insulin sensitizers.							
	Metformin (*n*=32)		Metformin + myoinositol (*n*=32)		Myoinositol (*n*=31)		*p**
	Before	After	Before	After	Before	After	
AMH	11.87±5.6	7.4±3.9	10.78±4.2	10.5±4.1	10.7±3.5	9.3±4.2	0.012
AFC	13.06±1.8	9.8±1.7	12.28±1.5	9.69±2.6	14.26±2	12.48±1.9	0.000
*Univariate analysis. AMH=Anti-Mullerian hormone, AFC=Antral follicle count							

Figure adapted from Chhabra N et al. J Hum Reprod Sci. 2018; 11:348-352.

There was also a fall in the AFC but it was not statistically significant.
The researchers concluded that therapy with insulin sensitizers in PCOS women reduces the AMH levels, converts irregular menstrual cycles to regular and reduces clinical hyperandrogenism.

summary

Polycystic ovary syndrome (PCOS) is a complex heterogeneous multisystem disorder with a global prevalence ranging from 6% to 21%. The etiology of PCOS is still unclear and is likely to be a mix of environmental factors, genetic causes and *in utero* exposure. Infertility is a prevalent presenting feature of PCOS with ~75% of these women suffering infertility due to anovulation. In patients with PCOS, polyfollicular development during controlled ovarian hyperstimulation (COH) in IVF/ICSI occurs easily and this is a difficult problem. OHSS is a common iatrogenic complication and incidence of moderate to severe OHSS is between 3.1 and 8% of IVF cycles but can be as high as 20% in high-risk women. As on date, there is no perfect strategy which completely eliminates OHSS. However, several techniques/strategies can be implemented for primary and secondary prevention of OHSS.

Hormonal markers like Anti-Mullerian Hormone (AMH) are increasingly being utilized in predicting ovarian response to stimulation. Antral follicle count (AFC) is also another facet worthy of mention in the prediction of OHSS. A newly established nomogram model has proven to be a novel tool that can effectively, easily and intuitively predict the probability of OHSS in the patients with PCOS. Metformin, a biguanide, is widely used among women with PCOS undergoing IVF/ICSI. Results of meta-analysis provide quantitative evidence demonstrating that Metformin significantly decreased the risk of OHSS among women with PCOS undergoing IVF/ICSI-ET and also significantly decreased AMH levels, especially in young patients and those with AMH levels at baseline higher than 4.7 ng/ml.

Fertility Treatment and OHSS Prevention Master Form

Date:_____

Patient Name:_____

Personal Information:

- Age:_____
- BMI:_____

General Health Assessment:

- Current Medications:_____
- Known Allergies:_____

PCOS and OHSS Risk Assessment:

- Diagnosis of PCOS: Yes / No
- Symptoms of PCOS (e.g., irregular periods, hirsutism):_____
- Previous OHSS: Yes / No
- Severity of Previous OHSS (if applicable):_____

Baseline Hormonal and Ovarian Reserve Evaluation:

- FSH:_____IU/L
- LH:_____IU/L
- Estradiol (E_2):_____pg/mL
- AMH:_____ng/mL
- Antral Follicle Count:_____
- Ovarian Volume:_____
- FSHR Genotype Known: Yes / No (If yes, details:_____)

Treatment Plan:

- Proposed Stimulation Protocol (Type/Dose):_____
- Planned Medications (including Metformin, Dopamine Agonist):_____
- Individualized Considerations (ICOS):_____

Ovulation Trigger Plan:

- Chosen Trigger (e.g., hCG, GnRH agonist):_____
- Dose:_____
- Recent Estradiol Level before Trigger:_____pg/mL

Primary Prevention Strategies:

- Use of Metformin: Yes / No
- Use of GnRH Antagonist: Yes / No
- Additional Medications:_____

Secondary Prevention Strategies:

- Plan for Coasting (if applicable):_____
- HCG Trigger Dose Individualization:_____
- Plan for Cryopreservation of Oocytes and Embryos:_____
- Intravenous Fluids at Time of Oocyte Retrieval:_____

Early Detection of OHSS Checklist:

- Rapid weight gain (>2.2 pounds/1 kg in 24 hours)
- Severe abdominal pain
- Severe, persistent nausea and vomiting
- Blood clots
- Decreased urination
- Shortness of breath
- Tight or enlarged abdomen

Late-Onset OHSS Checklist (Post-Pregnancy Confirmation):

- Persistent or worsening of early OHSS symptoms post pregnancy confirmation
- Rapid weight gain (more than 2.2 pounds/1 kg in 24 hours)
- Ascites or fluid accumulation in the abdomen
- Difficulty breathing or shortness of breath
- Decreased urinary output
- Blood clots
- Severe abdominal pain and bloating

Contact Healthcare Provider if:

- Experiencing symptoms of OHSS
- Breathing problems or leg pain during treatment

feedback form

ALIVE
ART LEARNING INITIATIVES FOR EXPERTS

Issue 10 | January 2024

Thank you for going through the contents of **ALIVE Newsletter Issue 10.** 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.

Name:_____

Email ID:_____

Contact No:_____

Satisfaction Score for ALIVE Newsletter - PCOS and Infertility : Managing Current challenges Part 1 : Issue 10; January 2024

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 10 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?

_____

Steps to scan QR code

1) Open the Camera application either from the lock screen or tapping on the icon from your home screen.
2) Hold your device steady for 2-3 seconds towards the QR Code.
3) Click on the notification to open the content of the QR Code.

Disclaimer: *This information is being collected for informational purpose only which will help us in evaluating the quality and content of the Newsletter and making improvements in future.*

MERCK

For the use of a Registered Medical Practitioner or Hospital or Laboratory only.

XXXXXXXXXXXXXXXX

Merck Specialities Pvt. Ltd.
Godrej One, 8th Floor, Pirojshanagar Nagar, Eastern Express Highway,
Vikroli East, Mumbai, Maharashtra 400079, India.