Optimising Ovarian Stimulation:
Improving Outcomes Across the Patient Spectrum

Learning Objectives

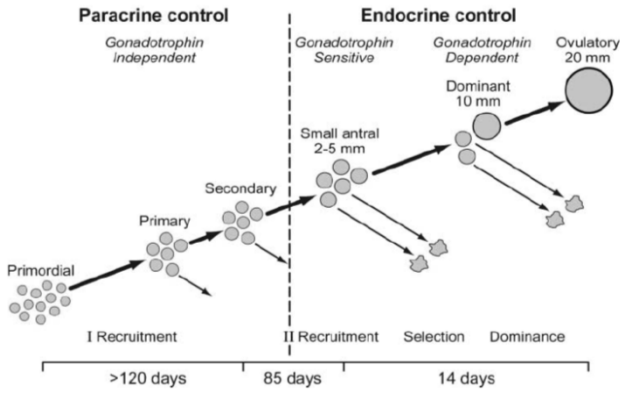
After this section, participants should better understand:

- The process of folliculogenesis
- How to optimise ovarian stimulation across various etiologies of infertility

Oocyte Pool: *Current Dogma*

- Women are born with a complement of oocytes for life
- Composed of primordial follicles
  - Contain oocytes arrested in meiotic prophase I
- Remain quiescent until recruited into maturation
- Enter maturation through complex signals
  - Bidirectional signals between oocyte and surrounding somatic granulosa cells

Folliculogenesis

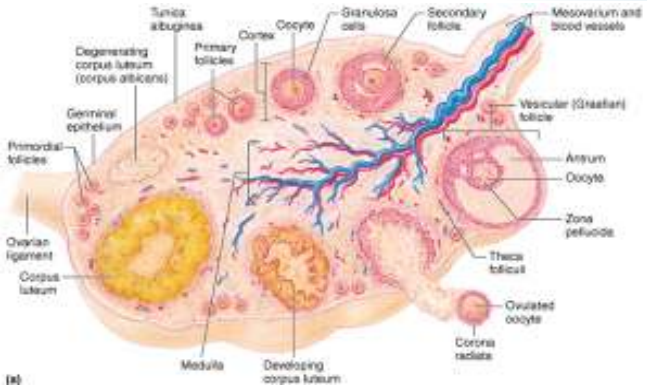


Folliculogenesis

Adapted from Baird DT, Mitchell A. Hormonal control of folliculogenesis: the key to successful reproduction. *Ernst Schering Res Found Workshop*. 2002;(41):1-9.; McGee EA, Hsueh AJ. Initial and cyclic recruitment of ovarian follicles. *Endocr Rev*. 2000;21:200-214.

Follicular Development in the Ovary

Follicular development in the ovary



From Knight PG, Glister C. Local roles of TGF-beta superfamily members in the control of ovarian follicle development. *Anim Reprod Sci.* 2003;78:165-183. Reproduced with permission.

Optimising Ovarian Stimulation:
Improving Outcomes Across the Patient Spectrum

Characteristics of Ovarian Pool and Ageing

Varying oocyte number at birth between individuals
Varying pace of follicular recruitment between individuals
Decreasing pace of follicular recruitment between individuals and over time
Fewer primordial follicles available for folliculogenesis
Increasingly poor quality of eggs over time
Decreasing embryo quality over time
Decreasing spontaneous fecundity with age
Decreasing oocyte and embryo numbers in *in vitro* fertilisation (IVF)
Decreasing pregnancy rates in IVF and other infertility treatments
Increasing aneuploidy with advancing age

Gleicher N, Weghofer A, Barad DH. Defining ovarian reserve to better understand ovarian aging. *Reprod Biol Endocrinol*. 2011;9:23.

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Ovarian Stimulation Protocols

- Ovarian stimulation (OS) protocols are utilised to induce multiple follicle development, as part of IVF or other infertility treatments
- There are many OS protocols, *and…*
- There are many drugs and drug combinations for use in these OS protocols
- Standardised OS protocols are not suitable for all patient demographics, *as…*
- There is great heterogeneity in the populations undergoing OS, especially for IVF
- Individualised ovarian stimulation (iOS) protocols are the future

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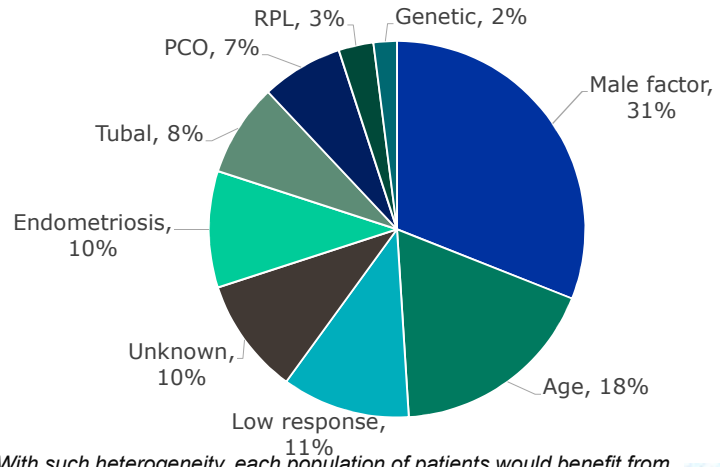
Optimising Ovarian Stimulation: Improving Outcomes Across the Patient Spectrum

Heterogeneity of Populations Undergoing OS for IVF



With such heterogeneity, each population of patients would benefit from individual assessment and personalised ovarian stimulation protocol.

PCO: polycystic ovary; RPL: recurrent pregnancy loss

Bosch E, Ezcurra D. Individualised controlled ovarian stimulation (iCOS): maximising success rates for assisted reproductive technology patients. *Reprod Biol Endocrinol.* 2011;9:82.

Assessing Ovarian Function

- Potential predictors of ovarian function
  - **Biochemical**
    - Follicle-stimulating hormone (FSH)
    - Estradiol (E2)
    - Inhibin A/B
    - Anti-Müllerian hormone (AMH)
  - **Imaging**
    - Antral follicle count (AFC)
    - Ovarian volume
  - **Dynamic tests**
    - Clomiphene citrate challenge test (CCCT)
    - Inhibin and E2 response to FSH (EFORT)

Conclusions

- Assessing ovarian function is essential to determine an appropriate ovarian stimulation protocol
- Individualised ovarian stimulation (iOS) protocols are essential for the best chance of successful outcome and to minimise the risk of ovarian hyperstimulation

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Learning Objectives

After this section, participants should better understand:

- Definitions of controlled ovarian stimulation (COS) and controlled ovarian hyperstimulation (COH)
- Medications used for COS and COH
- Factors to be considered in choosing COS/COH protocols
- Why it is necessary to individualise protocols

Ovarian Stimulation: Definitions

- **COS** is intended for non-assisted reproductive technology (ART) cycles (such as intrauterine insemination, timed intercourse) in which the ovaries are stimulated to ovulate 1 or 2 oocytes with mild pharmacological treatment
- **COH** is intended for ART cycles (such as IVF) in which the ovaries are stimulated to grow 10-12 mature oocytes for IVF with the administration of injectable medications
- The injectable medications used to achieve COH are called gonadotropins

Medications used for COS/COH

- Clomiphene citrate (CC)
- Metformin
- Aromatase inhibitors (letrozole)
- Dopamine agonists
- FSH
- Luteinising hormone (LH)
- Human chorionic gonadotropin (hCG)
- Human menopausal gonadotropin (hMG)
- Gonadotropin-releasing hormone (GnRH) agonist or antagonist

Clomiphene Citrate (CC)

- Most commonly used agent for infrequent/absent ovulation; often combined with intrauterine insemination (IUI)
- Causes pituitary FSH secretion
  - FSH stimulates development of ovarian follicles
- Induces ovulation in approximately 80% of properly selected women
- Mostly mild side effects, including hot flashes
- Ovarian hyperstimulation possible but infrequent
- When combined with IUI, dosage is usually 50 or 100 mg per day given from days 2-6 *or* 3-7 *or* 5-9 of menstrual cycle

Insulin Sensitising Drugs - Metformin

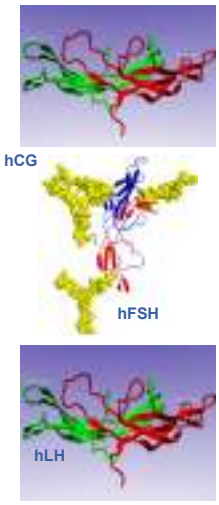
- Insulin resistance and hyperinsulinemia common in polycystic ovary syndrome (PCOS)
- In some women with PCOS, CC alone may fail to induce ovulation; thus, it is combined with metformin
- Metformin alone can restart cyclic ovulation and menses; however, its use is off-label
- Gastrointestinal side effects are common with metformin
  - Liver and kidney function tests should be performed
- Other diabetes drugs (rosiglitazone and pioglitazone) have been used for this purpose but are more hepatotoxic

Aromatase Inhibitors - Letrozole

- Aromatase inhibitors reduce estrogen levels
- Use is off-label
- Pregnancy rates are comparable to CC
- Initial reports claiming possible risk for congenital abnormalities have not been substantiated

The Gonadotropins

- **hCG:** extracted from the urine of pregnant women or produced by recombinant technology
- **hMG:** composed of FSH and LH extracted from the urine of post-menopausal women
- **FSH:** extracted from the urine of post-menopausal women or produced by recombinant technology
- **LH:** produced by recombinant technology
- **GnRH:** either agonist or antagonist



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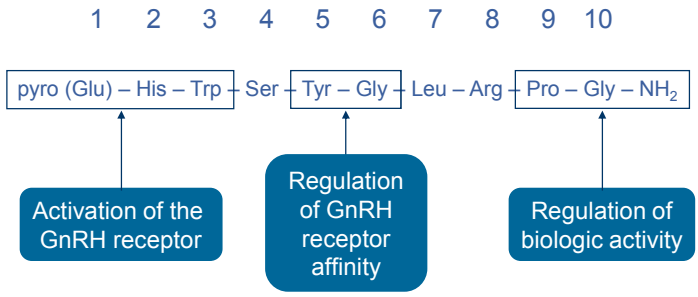
Structure of GnRH



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GnRH Analogs (Agonists/Antagonists)

- GnRH agonists
  - Leuprolide acetate
  - Buserelin acetate
  - Triptorelin acetate
  - Nafarelin acetate
- GnRH antagonists
  - Cetrorelix acetate
  - Ganirelix acetate

Factors Affecting Choice of Protocol for COH

- Patients
  - Age (baseline FSH, E_2)
  - Antral follicle count (5-6 per ovary)
  - AMH
  - Etiology of infertility
  - History of prior stimulation
  - Body weight (expressed as body mass index [BMI])
- ART Centers
  - Flexibility
  - Experience
  - Cryopreservation

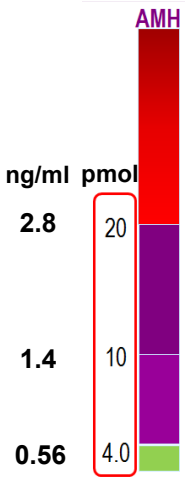
An Ideal Test for Ovarian Reserve

- Qualitative assessment of the fulfillment of criteria investigated for each ovarian reserve test

	AMH	AFC	FSH	Inhibin B	E2
Biologically plausible	+++	++/+++	++	++/+++	+
Cross-sectional relation with age	++/+++	+++	++	+	–
Mean longitudinal decline	+++	+	+/++	+/++	–
Consistency of individual change	+++	++/+++	+	+	–

Adapted from van Rooij IA, Broekmans FJ, Scheffer GJ, et al. Serum antimullerian hormone levels best reflect the reproductive decline with age in normal women with proven fertility: a longitudinal study. *Fertil Steril.* 2005;83:979-987.

AMH-based Strategy for Individualising the ART Protocol (AMH Gen II Assay)



	REGIMEN	FSH Dose
		nWT/obese
High Responders (150IU daily)	Antagonist: r-hFSH +(r-hLH) hMG	150/225
Normal Responders	Agonist: r-hFSH or hMG	225/300
Reduced Responders Negligible response	Agonist + FSH, e.g. CC; flare up	225/300

Nelson SM, La Marca A. The journey from the old to the new AMH assay: how to avoid getting lost in the values. *Reprod Biomed Online.* 2011;23:411-420.

Rationale for iOS

- A substantial number of patients show low or no response to standard OS protocols
- iOS protocols:
  - Improve overall outcome
  - Decrease number of cancelled cycles
  - Decrease patient costs
  - Increase number of healthy live births

How many Eggs for a Successful Outcome?

- Better success with 10-15 eggs

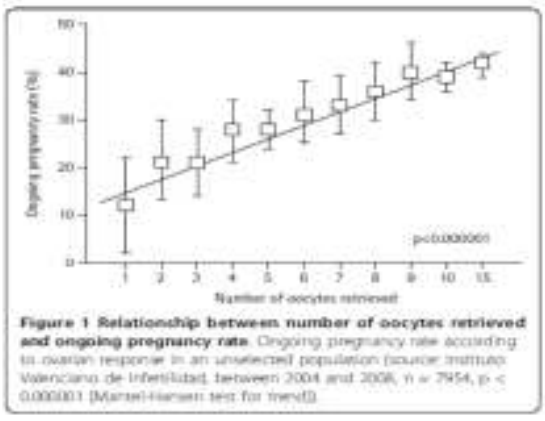


Figure 1 Relationship between number of oocytes retrieved and ongoing pregnancy rate. Ongoing pregnancy rate according to ovarian response in an unselected population (source: Instituto Valenciano de Infertilidad, between 2004 and 2008, n = 7954, p < 0.000001 [Mantel-Haenszel test for trend]).

Patrizio P, Sakkas D. From oocyte to baby: a clinical evaluation of the biological efficiency of in vitro fertilization. *Fertil Steril*. 2009;91:1061-1066.

Conclusions

- iOS protocols have potential to improve pregnancy rates
- Multiple medications are commonly used for COS and COH
- CC is most common for infrequent or absent ovulation
- Metformin + CC is commonly used in PCOS
- Multiple factors affect protocol choice for COH

Learning Objectives

After this section, participants should better understand:

- The description of the most common COH protocols for IVF
- The use of a long-luteal phase GnRH agonist
- The role of a GnRH antagonist
- The role of a microdose GnRH agonist
- How to individualise OS
- The approach to poor responders

The Main COH Protocols

- GnRH antagonist
- Short (flare up) GnRH agonist
- Long (luteal phase) GnRH agonist
- Minidose GnRH agonist

GnRH Agonists

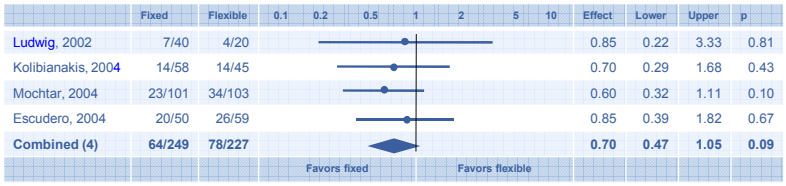
- Used to prevent premature LH surge
- Started on cycle day 21 of the preceding luteal phase
- Dosing options
  - 0.50 mg (10 units) daily until the day hCG is administered
  - 0.50 mg (10 units) daily, reduced to 0.25 mg (5 units) at the start of gonadotropins

GnRH Antagonists

- Used to prevent premature LH surge
- Started on day 5 or 6 of COH or when follicle is about 13 mm and E2 concentrations are 200-400 pg/mL
- 2 dosing options:
  - 0.25 mg once daily until the day hCG is administered
  - Single 3-mg dose, equivalent to 4 days of LH suppression

Antagonist Protocols

- Fixed versus flexible
  - Fewer gonadotropins in flexible protocols
  - Fewer ampoules of GnRH-antagonist on flexible protocols
  - No significant difference in pregnancy rate



- Single versus multiple dose
  - 73% in the single-dose group received 1 injection
  - No significant difference in the pregnancy rate

Table adapted from Al-Inany H, et al. *Reprod Biomed Online*. 2005;10:567-570.; Mochtar MH, et al. *Hum Reprod*. 2004;19:1713-1718.; Ludwig M, et al. *Hum Reprod*. 2002;17:2842-2845.; Kolibianakis E, et al. *Acta Obstet Gynecol Scand*. 2004;83:1216-1217.; Escudero E, et al. *Fertil Steril*. 2004;81:562-566.

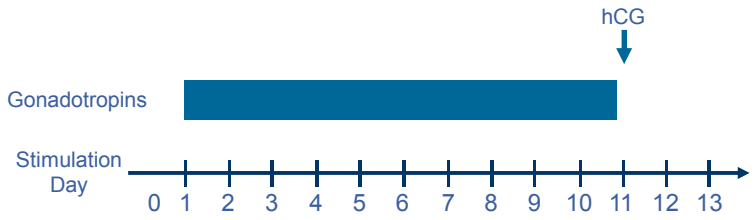
GnRH Antagonist vs. Agonists

- Equally effective at preventing spontaneous LH surge
- GnRH antagonists
  - Associated with lower risk of ovarian hyperstimulation syndrome (OHSS)
  - Lower amounts of gonadotropins needed for stimulation
  - Debate about slightly lower pregnancy and implantation rates versus GnRH agonists

Orvieto R, Patrizio P. GnRH agonist versus GnRH antagonist in ovarian stimulation: an ongoing debate. *Reprod Biomed Online*. 2013;26:4-8.

COH Protocol General Rule

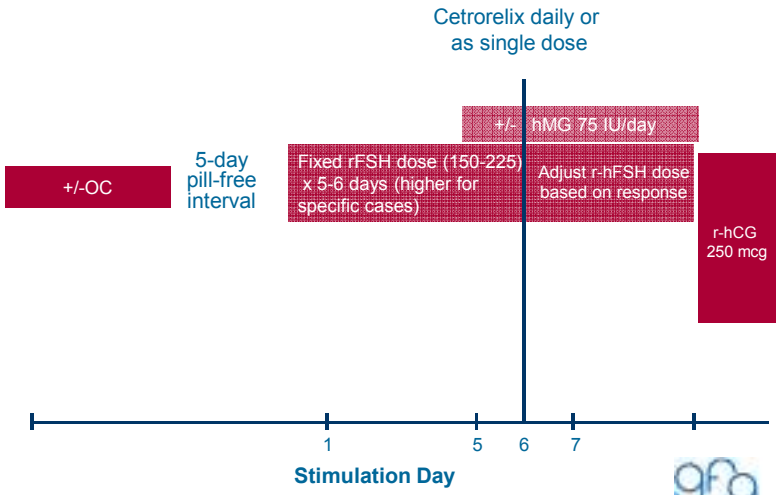
- Gonadotropin dose usually unchanged for the first 4 or 5 days of stimulation
- Dose adjusted according to ovarian response and E2 level until criteria for hCG administration have been met



COH: Long or Luteal Phase GnRH Agonist

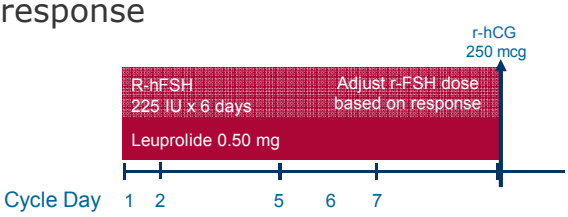
- Use GnRH agonist beginning on day 21 of previous menstrual cycle (luteal phase)
  - Goal: hormonal suppression (downregulation) by the time of menses
- After confirming hormonal suppression on day 2 or 3 of menses, gonadotropin treatment is started
- GnRHa is continued until day of hCG administration to prevent the endogenous LH surge, which can cause premature ovulation

COH: GnRH Antagonist Protocol



COH: Short or Flare GnRH Agonist

- Medications (GnRH agonists and gonadotropins) started at menses onset
  - Induces "flare-up" of FSH followed by downregulation
  - Prevents premature LH surge
- Gonadotropins added from cycle day 2
- Used in patients known or expected to have a poor response



Optimising Ovarian Stimulation:
Improving Outcomes Across the Patient Spectrum

COH: Mini-dose GnRH Agonist

- Short GnRH agonist protocol used in poor responders
  - Increases stimulatory response and prevents LH surge
  - Decreases cycle cancellations
- GnRH agonist started on cycle day 2 together with gonadotropins if endogenous FSH <15 IU/L
- 10% of the normal dose of GnRH agonist (50 µg leuprolide acetate twice a day)

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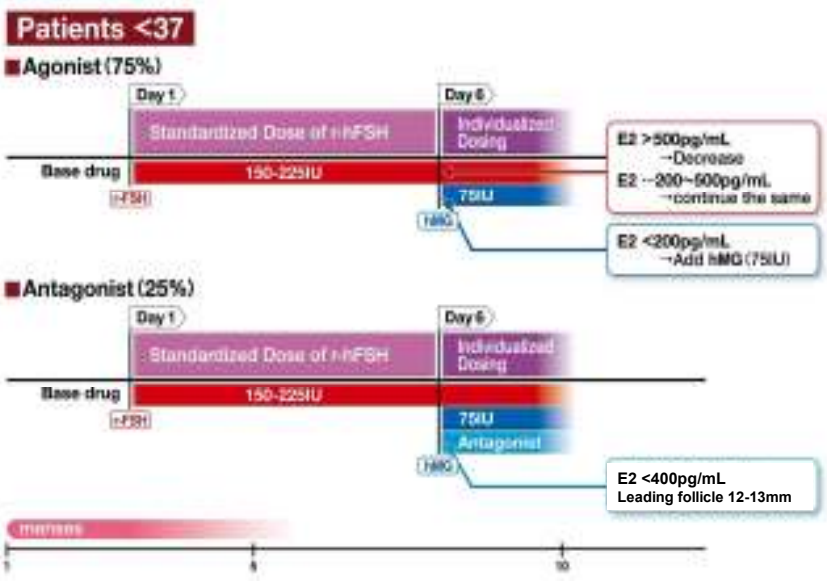
Agonist and Antagonist Regimens for IVF



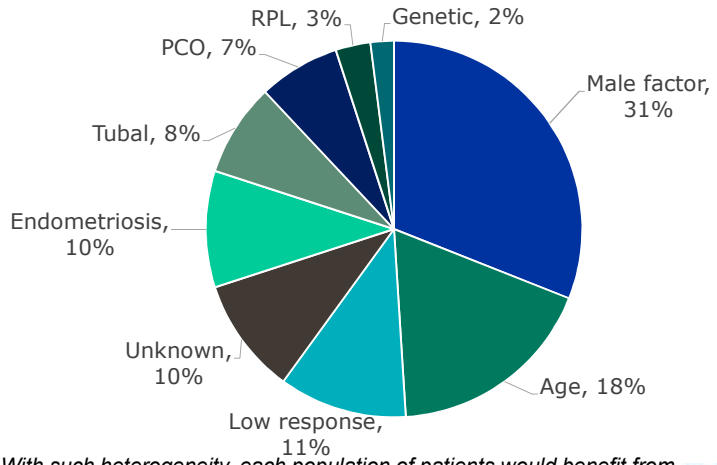
Optimising Ovarian Stimulation:
Improving Outcomes Across the Patient Spectrum

Personalising the Protocols

- "Standard patient" is one in whom a normal response to COH is expected
- Definition:
  - Age <40 years
  - Regular menstrual cycle (21-35 days)
  - Basal FSH <10 IU/L and E2 <50 pg/mL
  - Normal AMH and BMI

Shanbhag S, Aucott L, Bhattacharya S, Hamilton MA, McTavish AR. Interventions for 'poor responders' to controlled ovarian hyperstimulation (COH) in in-vitro fertilisation (IVF). *Cochrane Database Syst Rev*. 2007;(1):CD004379.; Griesinger G, Diedrich K, Tarlatzis BC, Kolibianakis EM. GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis. *Reprod Biomed Online*. 2006;13:628-638.

Heterogeneity of Populations Undergoing OS for IVF



With such heterogeneity, each population of patients would benefit from individual assessment and personalized ovarian stimulation protocol.

PCO: polycystic ovary; RPL: recurrent pregnancy loss

Bosch E, Ezcurra D. Individualised controlled ovarian stimulation (iCOS): maximising success rates for assisted reproductive technology patients. *Reprod Biol Endocrinol*. 2011;9:82.

Heterogeneity of Populations Undergoing OS for IVF (con't.)

	≤35		36-40		>40	
BMI	<25	≥25	<25	≥25	<25	≥25
Normo-ovulatory	31.9%	5.6%	19.3%	4.1%	7.0%	1.8%
Anovulation/PCO	4.5%	2.5%	1.4%	0.9%	0.06%	0.04%
Low responders	4.4%	0.7%	3.6%	0.6%	0.34%	0.06%
Endometriosis	5.7%	0.4%	2.7%	0.2%	0.18%	0.02%

Bosch E, Ezcurra D. Individualised controlled ovarian stimulation (iCOS): maximising success rates for assisted reproductive technology patients. *Reprod Biol Endocrinol*. 2011;9:82.

Poor Responders

- Most challenging patients
- Despite multiple treatment cycles with various protocols, outcome is suboptimal
- No commonly accepted definition
- Criteria may include one or more of the following:
  - Poor ovarian reserve markers
  - Low number of antral follicles
  - Low peak estradiol level
  - High gonadotropin dosage
  - Prolonged days of stimulation
  - Prior cancelled cycles due to poor response

Tests Predictive of Decreased Ovarian Reserve and High Probability of Poor Response

- Abnormalities of the 3 following hormonal levels measured together on cycle day 3:
  1. High FSH (>9 mIU/mL)
  2. High FSH/LH ratio (>2)
  3. High E2 (>50 pg/mL)
- Low basal AFC and reduced ovarian volume
- Low AMH

Muasher SJ, Oehninger S, Simonetti S, et al. The value of basal and/or stimulated serum gonadotropin levels in prediction of stimulation response and in vitro fertilization outcome. *Fertil Steril*. 1988;50:298-307.; Luk J, Patrizio P. Superovulation protocols. In: Coward K, Wells D, eds. *Textbook of Clinical Embryology*. Cambridge University Press: London, United Kingdom; 2013.

Strategies to Treat Poor Responders

- High dose of gonadotropins
- GnRH agonist
  - Reducing the dose
  - Stop-protocol
  - Mini-dose flare protocols
- GnRH antagonist protocols
- Minimal stimulation (CC/gonadotropins/GnRH antagonist)
- Starting antagonist in late luteal phase
- Natural cycle or IVM

Leong M, Patrizio P. Poor responders: how to define, diagnose and treat? IVF Worldwide website. http://www.ivf-worldwide.com/survey/poor-responders/results-poor-responders.html. Updated 2012. Accessed June 8, 2013.

Poor Responders

- There is no best protocol for poor responders
- All protocols have advantages and disadvantages
- The real issue is the limited number of follicles available for recruitment
- No protocol can convert a poor responder to a good responder

Conclusions

- GnRH antagonist and agonist protocols are common for COS
- The protocols are equally effective but GnRH antagonists are associated with a lower risk of OHSS
- Multiple variations in protocols exist to allow for individualisation
- The heterogeneity of populations undergoing OS for IVF demand this protocol individualisation
- There is no best protocol for poor responders

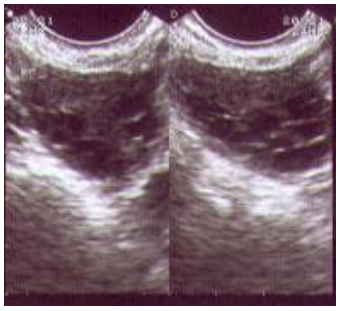
Learning Objectives

After this section, participants should better understand:

- OS protocols in PCOS, including
  - Low-dose step-up
  - Step-down
  - Metformin
  - Antagonist protocol/GnRH agonist trigger
- Natural cycle IVF and *in vitro* maturation (IVM)

PCOS and IVF

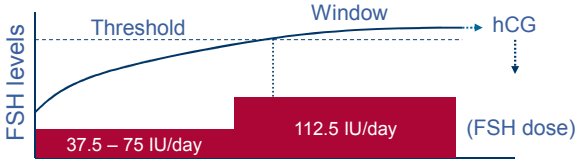
- OS = difficult and potentially risky
  - Exaggerated "explosive" response
  - OHSS
  - Multiple pregnancies
  - No response
- Goal: Maximise pregnancy rate but minimise OHSS and multiple pregnancies



Ultrasound view of polycystic ovaries

PCOS: Gonadotropin Protocols

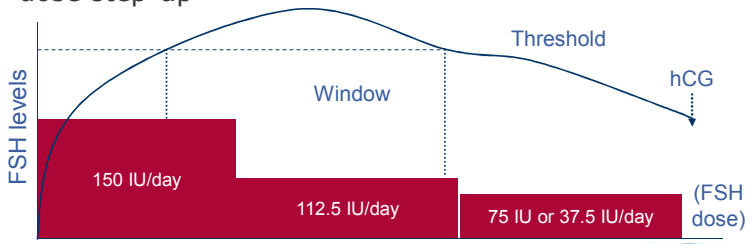
- Low-dose step-up protocol
  - Initiate treatment with FSH 37.5-75 IU/day x 14 days
  - If no response, ↑ FSH by 37.5 IU x 7 days up to maximum of 225 IU/day
  - 72% ovulation rate, 45% pregnancy rate
    - Multiple pregnancy 6-18%, OHSS 1%
  - No response: patients who are obese and patients with high basal LH



Adapted from Rinaudo PF, Patrizio P. Gonadotropin treatment of PCOS: is there a preferred protocol of treatment? In: Bed-Rafael Z, Lobo R, Shoham Z, eds. *The Third World Congress on Controversies in Obstetrics, Gynecology & Infertility.* Pianoro, Italy: Monduzzi Editore; 2002:197-209.

PCOS: Gonadotropin Protocols

- Step-down protocol
  - FSH 150 IU/day until 12-13 mm follicle
  - FSH 112.5 IU/day for 2-3 days
  - FSH 75 IU/day or 37.5 IU/day until hCG
  - Fewer days of stimulation and is as effective as low-dose step-up



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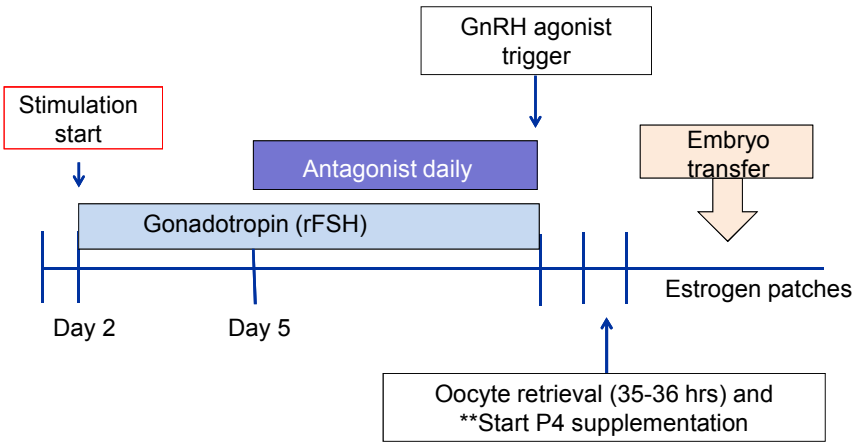
PCOS: Metformin Protocol

- Pre-treatment or co-treatment with metformin in IVF
  - Does not improve response to stimulation
  - May improve pregnancy rates
  - Reduces the risk of OHSS

Tang T, Glanville J, Orsi N, Barth JH, Balen AH. The use of metformin for women with PCOS undergoing IVF treatment. *Hum Reprod*. 2006;21:1416-1425.; Kjøtrød SB, von Düring V, Carlsen SM. Metformin treatment before IVF/ICSI in women with polycystic ovary syndrome; a prospective, randomized, double blind study. *Hum Reprod*. 2004;19:1315-1322.

Antagonist Protocol and GnRH Agonist Trigger (PCOS Patients)



Natural Cycle IVF and IVM*

- PCOS patients are extremely sensitive to stimulation with gonadotropins
- Patients at risk of developing OHSS
- Patients with poor ovarian response

Disadvantages of Natural Cycle IVF Alone

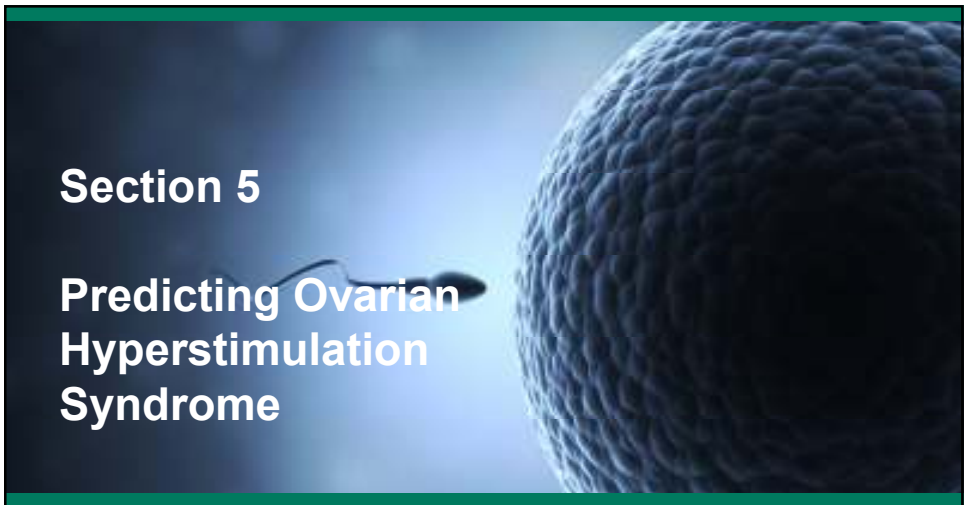
- If no egg is retrieved, then the cycle is lost
- If no fertilisation occurs, then no embryo is available for transfer
- Low efficiency resulting in a lower pregnancy rate and a high miscarriage rate

*IVM = in vitro maturaton

Chian RC, Buckett WM, Abdul Jalil AK, et al. Natural-cycle in vitro fertilization combined with in vitro maturation of immature oocytes is a potential approach in infertility treatment. *Fertil Steril*. 2004;82: 1675-1678.

Conclusions

- OS in patients with PCOS carries risk of OHSS
- Various protocols have been developed to best match a particular patient with the optimal protocol
- Safer stimulation through personalisation leads to better outcome



Learning Objectives

After this section, participants should better understand:

- OHSS
- Use of the CONSORT criteria and iOS as primary prevention criteria
- Secondary prevention for OHSS
- Management strategies when prevention fails

Ovarian Hyperstimulation Syndrome

- Substantial evidence that ART is safe and effective
- Serious complication is OHSS
  - Rare iatrogenic complication of OS
- Occurs is approximately 1.4% of all cycles
- *Primary prevention* of OHSS is key
  - Assess individual risk; use appropriate OS protocol
- *Secondary prevention: be prepared*
  - Cycle cancellation
  - Coasting
  - Reduce hCG trigger dose or, if possible, GnRH trigger
  - Others

OHSS Pathophysiology

- Fluid shift due to increased vascular permeability
- hCG implicated as major cause
- Also implicated:
  - Prostaglandins (PGs)
  - Inhibin
  - Renin-angiotensin aldosterone system (RAAS)
  - Inflammatory mediators
  - Vascular endothelial growth factor (VEGF)
- VEGF is a major mediator
  - VEGF receptor 2 is unregulated in response to hCG
  - Peak levels coincide with maximal vascular permeability

OHSS Symptoms

OHSS Stage	Clinical Features	Laboratory Features
Mild	• Abdominal distension/ discomfort • Mild nausea/vomiting • Enlarged ovaries	• No important alterations
Moderate	• Mild features • Ultrasonographic evidence of ascites • Diarrhoea	• Elevated hematocrit (>41%) • Elevated WBC (>15,000) • Hypoproteinemia

OHSS Symptoms (con't.)

OHSS Stage	Clinical Features	Laboratory Features
Severe	• Mild and moderate features • Hydrothorax • Severe dyspnea • Oliguria/anuria • Intractable nausea/vomiting • Tense ascites • Low blood/central venous pressure • Rapid weight gain (>1 kg in 24 hr) • Syncope • Severe abdominal pain • Venous thrombosis	• Hemoconcentration (Hct >55%) • WBC >25,000 • CrCl <50 mL/min • Cr >1.6 • Na^+ <135 mEq/L • K^+ >5 mEq/L • Elevated liver enzymes

Cr: creatinine; CrCl: creatinine clearance; Hct: hematocrit; K^+: potassium; Na^+: sodium; WBC: white blood cell

OHSS Risk Factors

Risk Factor	Threshold of Risk
Primary risk factors (patient-related)	
• High basal AMH	• >3.36 ng/mL
• Young age	• <33 years
• Previous OHSS	• Moderate and severe cases, particularly those with hospitalisation
• PCO-like ovaries	• >24 antral follicles in both ovaries combined

OHSS Risk Factors (con't.)

Risk Factor	Threshold of Risk
Secondary risk factors (ovarian response-related)	
On day of hCG trigger	
• High number of medium/ large follicles	• ≥13 follicles ≥11 mm in diameter or >11 follicles ≥10 mm in diameter
• High or rapidly rising E2 levels and high number of follicles	• E2 5,000 ng/L and/or ≥18 follicles
• Number of oocytes retrieved	• >11

Preventing OHSS: *Primary Prevention*

- Prevention is a multistage process
- Primary prevention: recognize risk factors
- Use of iOS allows appropriate drug and dose selection as opposed to a standardised protocol
- Based on a study of 1,378 patients, best predictors include:
  - Basal FSH, BMI, age, number of follicles <11 mm at screening
  - ***CONSORT* algorithm*** includes these biomarkers and has been suggested as a means to select the starting gonadotropin dose

*CONsistency in recombinant FSH Starting dOses for individualised tReatmenT

Acceptability of the CONSORT Calculator

- Physicians were asked to rate the calculator on user-friendliness and ease of use (using semantic scales)
- Acceptability was defined as the proportion of physicians for whom the CONSORT calculator was acceptable (moderately friendly/very friendly and easy/very easy to use) for 75% of their patients
- Rate was expressed as a percentage

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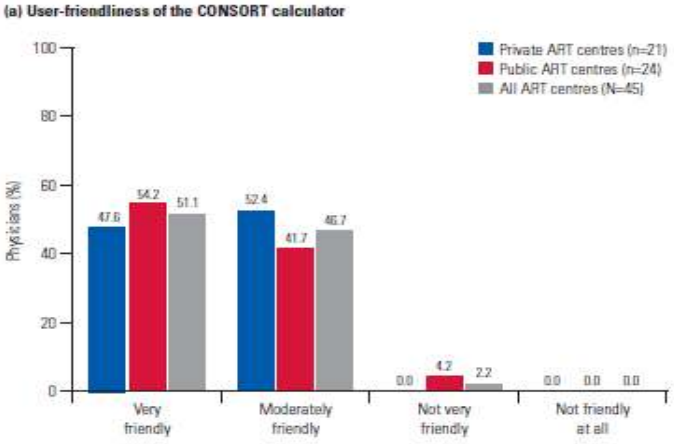
Acceptability of CONSORT



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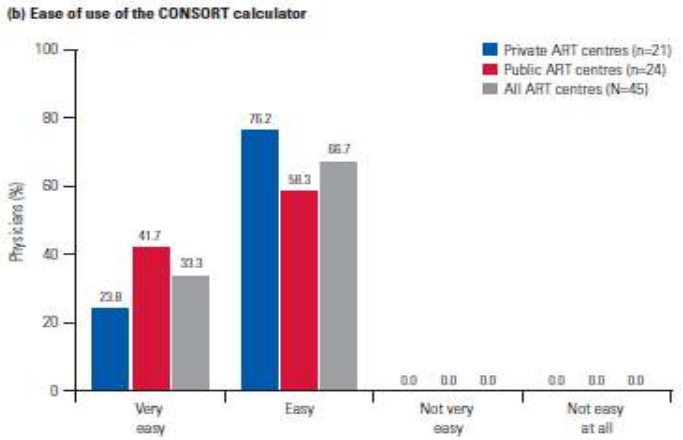
Acceptability of CONSORT (con't.)



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Assessed Patient Population

Baseline patient characteristics (N=193)		
	Mean±SD[a]	Range
Age, years[b]	30.2±2.74	22-35
BMI, kg/m^2	22.4±3.10	17.4-30.9[c]
Baseline FSH level, IU/L	6.4±1.66	2.0-11.3
AFC	16.2±7.23	6-48
Indication for ART[d] n(%)		
Male infertility	138 (71.5%)	
Tubal pathology	34 (17.6%)	
Idiopathic infertility	22 (11.4%)	
Ovulatory disorder	21 (10.9%)	
Other	8 (4.1%)	

AFC, antral follicle count; ART, assisted reproductive technologies; BMI, body mass index; FSH, follicle stimulation hormone; IU, international unit; SD, standard deviation
[a]Unless stated otherwise
[b]n=192 (data missing for one patient); one patient was aged 35.09 years, despite this minor protocol deviation, this patient was included in the analysis.
[c]Three patients had a BMI ≥30 kg/m^2 (30.5, 30.9 and 30.1 kg/m^2), despite this minor protocol deviation, they were included in the analysis.
[d]Patients could have more than one indication for ART, percentages are calculated for all patients in the secondary analysis population (N=193).

Comparative Analyses

COS characteristics in the three CONSORT groups (for patients who had a COS cycle started; complementary analysis population, N=181)

Characteristic[a]	CONSORT-supported (n=40)	CONSORT-influenced (n=51)	CONSORT-rejected (n=90)	All patients (N=181)
r-hFSH starting dose, IU[b]	121.9±22.1	133.8±45.2	175.8±53.2	152.1±51.5
Total r-hFSH dose, IU[b]	1416.6±518	1580.1±659	1932.1±743	1719.0±707
Duration of COS, days	11.1±2.10	11.2±2.20	10.5±1.84	10.9±2.02

COS, controlled ovarian stimulation; IU, international units; r-hFSH, recombinant human follicle-stimulation hormone
[a]Data are mean±standard deviation
[b]Supported versus rejected, p<0.0001 (Wilcoxon test)

Treatment Outcomes

Treatment outcomes for patients who had a COS cycle started (complementary analysis population, N=181)

	CONSORT-supported (n=40)	CONSORT-influenced (n=51)	CONSORT-rejected (n=90)	All patients (N=181)
Cancelled COS cycles, n (%) Inadequate response Other	4 (10.0%) 2 (5.0%) 2 (5.0%)	8 (15.7%) 5 (9.8%) 3 (5.9%)	10 (11.1%) 3 (3.3%) 7 (7.8%)	22 (12.2%) 10 (5.5%) 12 (6.6%)
Number of oocytes retrieved per patient, mean±SD[a]	9.92±4.24	9.77±5.54	11.64±6.81	10.74±6.01
Cancelled embryo or blastocyst transfers, n (%)	1 (2.5%)	2 (3.9%)	3 (3.3%)	6 (3.3%)
Number of embryos/blastocysts transferred per patient, mean±SD	1.53±0.56	1.54±0.60	1.41±0.59	1.47±0.59

COS, controlled ovarian stimulation; SD, standard deviation
[a]Per patient with oocyte retrieval attempted, CONSORT-approved versus CONSORT-rejected, P=0.37 (Wilcoxon test); CONSORT-influenced + CONSORT-supported versus CONSORT-rejected, p=0.15 (Wilcoxon test)
[b]n=149

Optimising Ovarian Stimulation:
Improving Outcomes Across the Patient Spectrum

Pregnancy Outcomes (CONSORT Calculator)

Pregnancy outcomes for patients who had a COS cycle started (complementary analysis population, N=181)

Outcome, n (%)	CONSORT-supported (n=40)	CONSORT-influenced (n=51)	CONSORT-rejected (n=90)	All patients (N=181)
Clinical pregnancy[a]				
Per started COS cycle[b]	18 (45%)	18 (35.3%)	22 (24.4%)	58 (32.0%)
Per transfer[c]	18 (51.4%)	18 (48.6%)	22 (31.0%)	58 (40.6%)
Implantation Biochemical pregnancy only or spontaneous miscarriage	3 (7.5%)	2 (3.9%)	14 (5.6%)	20 (11.5%)

COS, controlled ovarian stimulation
[a]6 weeks of amenorrhoea
[b]Supported versus rejected, p=0.02; supported + influenced versus rejected, p=0.03
[c]Calculated as a proportion of the total number of patients undergoing embryo or blastocyst transfer (CONSORT-supported, n=35; CONSORT-influenced, n=37; CONSORT-rejected, n=71; all patients, N=143)
[d]6 weeks of amenorrhoea; percentages calculated per standard COS cycle for each group

Preventing OHSS: *Secondary Prevention*

- Secondary prevention of OHSS includes:
  - *In vitro* oocyte maturation
  - Coasting (conflicting data)
  - Decreasing hCG trigger dose
  - Using a GnRH agonist trigger
  - Oocyte retrieval with cryopreservation; transfer in unstimulated cycle
  - Cabergolin (dopamine agonist)

OHSS: *If Prevention Fails*

- Mild OHSS (which occurs in most stimulated patients) usually requires no intervention
- Moderate OHSS not associated with ascites or enlarged ovaries usually requires no intervention
- Treat both symptomatically
- Severe OHSS must be treated and may be life-threatening
  - Maintain circulatory volume
  - Restore electrolyte balance
  - Employ paracentesis as necessary

Conclusions

- OHSS can be a serious complication of OS
- The clinical symptoms and severity help to determine appropriate interventions, as do patient risk factors
- Primary prevention is the key to avoid OHSS
- The CONSORT calculator or other algorithms may help in this effort

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