Optimising Ovarian Stimulation: Improving Outcomes Across the Patient Spectrum

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Section 1
Follicular Development and Impact of Ovarian Ageing
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
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Folliculogenesis


Follicular Development in the Ovary

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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

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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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.

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

Section 2

Introduction to Ovarian Stimulation Protocols
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
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**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

Structure of GnRH

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>pyro (Glu) – His – Trp – Ser + Tyr – Gly + Leu – Arg + Pro – Gly – NH₂</td>
<td></td>
<td></td>
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</tbody>
</table>

- Activation of the GnRH receptor
- Regulation of GnRH receptor affinity
- Regulation of biologic activity
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

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An Ideal Test for Ovarian Reserve

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

<table>
<thead>
<tr>
<th>Test Characteristics</th>
<th>AMH</th>
<th>AFC</th>
<th>FSH</th>
<th>Inhibin B</th>
<th>E2</th>
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<tbody>
<tr>
<td>Biologically plausible</td>
<td>+++</td>
<td>++/+++</td>
<td>++</td>
<td>++/+++</td>
<td>+</td>
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<tr>
<td>Cross-sectional relation with age</td>
<td>++/+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Mean longitudinal decline</td>
<td>+++</td>
<td>+</td>
<td>+/+</td>
<td>+/+</td>
<td>–</td>
</tr>
<tr>
<td>Consistency of individual change</td>
<td>+++</td>
<td>++/+++</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>AMH</th>
<th>REGIMEN</th>
<th>FSH Dose</th>
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<tbody>
<tr>
<td>ng/ml</td>
<td>pmoL</td>
<td>nWT/obese</td>
</tr>
<tr>
<td>2.8</td>
<td>20</td>
<td>150/225</td>
</tr>
<tr>
<td>1.4</td>
<td>10</td>
<td>225/300</td>
</tr>
<tr>
<td>0.56</td>
<td>4.0</td>
<td>225/300</td>
</tr>
</tbody>
</table>

Agonist: r-hFSH or hMG

Agonist + FSH, e.g. CC; flare up

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

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

<table>
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<tr>
<th></th>
<th>Fixed</th>
<th>Flexible</th>
<th>4.5</th>
<th>8.2</th>
<th>12</th>
<th>22</th>
<th>38</th>
<th>54</th>
<th>75</th>
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<tbody>
<tr>
<td>Ludwig, 2002</td>
<td>7/40</td>
<td>4/20</td>
<td>0.85</td>
<td>0.22</td>
<td>3.33</td>
<td>0.81</td>
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<tr>
<td>Kolibianakis, 2004</td>
<td>14/58</td>
<td>14/45</td>
<td>0.70</td>
<td>0.29</td>
<td>1.68</td>
<td>0.43</td>
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<tr>
<td>Mochtar, 2004</td>
<td>23/101</td>
<td>34/103</td>
<td>0.60</td>
<td>0.32</td>
<td>1.11</td>
<td>0.10</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Escudero, 2004</td>
<td>20/50</td>
<td>26/59</td>
<td>0.85</td>
<td>0.39</td>
<td>1.82</td>
<td>0.67</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Combined (4)</td>
<td>64/249</td>
<td>78/227</td>
<td>0.70</td>
<td>0.47</td>
<td>1.05</td>
<td>0.09</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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


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

**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
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)

Agonist and Antagonist Regimens for IVF

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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


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

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

<table>
<thead>
<tr>
<th></th>
<th>≤35</th>
<th>36-40</th>
<th>&gt;40</th>
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<tbody>
<tr>
<td>BMI</td>
<td>&lt;25</td>
<td>≥25</td>
<td>&lt;25</td>
</tr>
<tr>
<td>Normo-ovulatory</td>
<td>31.9%</td>
<td>5.6%</td>
<td>19.3%</td>
</tr>
<tr>
<td>Anovulation/PCO</td>
<td>4.5%</td>
<td>2.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Low responders</td>
<td>4.4%</td>
<td>0.7%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>5.7%</td>
<td>0.4%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>


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

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

Optimising Ovarian Stimulation: Improving Outcomes Across the Patient Spectrum
**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
Section 4

Adjusting Ovarian Stimulation in Polycystic Ovary Syndrome

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)

Optimising Ovarian Stimulation:
Improving Outcomes Across the Patient Spectrum
Optimising Ovarian Stimulation: Improving Outcomes Across the Patient Spectrum

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

**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


**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


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**Optimising Ovarian Stimulation: Improving Outcomes Across the Patient Spectrum**
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Antagonist Protocol and GnRH Agonist Trigger (PCOS Patients)

Gonadotropin (rFSH) Antagonist daily

Day 2

Stimulation start

Antagonist daily

GnRH agonist trigger

Day 5

GnRH agonist trigger

Embryo transfer

Estrogen patches

Oocyte retrieval (35-36 hrs) and **Start P4 supplementation

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

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**

<table>
<thead>
<tr>
<th>OHSS Stage</th>
<th>Clinical Features</th>
<th>Laboratory Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Abdominal distension/diastasis</td>
<td>No important alterations</td>
</tr>
<tr>
<td></td>
<td>Mild nausea/vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enlarged ovaries</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Mild features</td>
<td>Elevated hematocrit (&gt;41%)</td>
</tr>
<tr>
<td></td>
<td>Ultrasonographic evidence of ascites</td>
<td>Elevated WBC (&gt;15,000)</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>Hypoproteinemia</td>
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</tbody>
</table>
OHSS Symptoms (con’t.)

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

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

OHSS Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Threshold of Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary risk factors (patient-related)</td>
<td></td>
</tr>
<tr>
<td>• High basal AMH</td>
<td>&gt;3.36 ng/mL</td>
</tr>
<tr>
<td>• Young age</td>
<td>&lt;33 years</td>
</tr>
<tr>
<td>• Previous OHSS</td>
<td>Moderate and severe cases, particularly those with hospitalisation</td>
</tr>
<tr>
<td>• PCO-like ovaries</td>
<td>&gt;24 antral follicles in both ovaries combined</td>
</tr>
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OHSS Risk Factors (con’t.)

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

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

Acceptability of CONSORT (con’t.)


Assessed Patient Population

<table>
<thead>
<tr>
<th>Baseline patient characteristics (N=193)</th>
<th>Mean ± SD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30.2 ± 2.74</td>
<td>22-35</td>
</tr>
<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>22.4 ± 3.10</td>
<td>17.4-30.9&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Baseline FSH level, IU/L</td>
<td>6.4 ± 1.66</td>
<td>2.0-11.3</td>
</tr>
<tr>
<td>AFC</td>
<td>16.2 ± 7.23</td>
<td>6-48</td>
</tr>
</tbody>
</table>

Indication for ART<sup>d</sup> 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-stimulating hormone; IU, international unit; SD, standard deviation  
<sup>a</sup>Unless stated otherwise  
<sup>b</sup>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.  
<sup>c</sup>Three patients had a BMI $\geq 30$ kg/m<sup>2</sup> (30.5, 30.9 and 30.1 kg/m<sup>2</sup>), despite this minor protocol deviation, they were included in the analysis.  
<sup>d</sup>Patients could have more than one indication for ART, percentages are calculated for all patients in the secondary analysis population (N=193).  

Optimising Ovarian Stimulation: Improving Outcomes Across the Patient Spectrum
### Comparative Analyses

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

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

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)**

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

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)

<table>
<thead>
<tr>
<th>Outcome, n (%)</th>
<th>CONSORT-supported (n=40)</th>
<th>CONSORT-influenced (n=51)</th>
<th>CONSORT-rejected (n=90)</th>
<th>All patients (N=181)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancy&lt;sup&gt;a&lt;/sup&gt; Per started COS cycle&lt;sup&gt;b&lt;/sup&gt; Per transfer&lt;sup&gt;c&lt;/sup&gt;</td>
<td>18 (45%) 18 (51.4%)</td>
<td>18 (35.3%) 18 (48.6%)</td>
<td>22 (24.4%) 22 (31.0%)</td>
<td>58 (32.0%) 58 (40.6%)</td>
</tr>
<tr>
<td>Implantation Biochemical pregnancy only or spontaneous miscarriage</td>
<td>3 (7.5%) 2 (3.9%)</td>
<td>14 (5.6%)</td>
<td>20 (11.5%)</td>
<td></td>
</tr>
</tbody>
</table>

CONSORT, controlled ovarian stimulation
<sup>a</sup>6 weeks of amenorrhoea
<sup>b</sup>Supported versus rejected, p=0.02; supported + influenced versus rejected, p=0.03
<sup>c</sup>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)
<sup>d</sup>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
Optimising Ovarian Stimulation:
Improving Outcomes Across the Patient Spectrum

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Optimising Ovarian Stimulation: Improving Outcomes Across the Patient Spectrum
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