International Federation of Gynecology and Obstetrics

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REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

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OHSS PREVENTION

Learning objectives

- Identify patients at high risk of OHSS
- Establish a set of tools that reduce risk

False reassurance! Saving Mothers

- *“Gratifyingly, no maternal deaths appeared to have occurred as a direct result of pregnant women dying of ovarian hyperstimulation syndrome following assisted fertility therapy…,*

- *but one or two cases did occur in non-pregnant women, which are not currently classified as maternal deaths”.*

Iatrogenic

Estimated mortality:

1: 450,000- 500,000

Brinsden PR, et al., Br J Obstet Gynaecol, 1995, 102:767–772.

1-3: 100,000

Confidential Inquiry into Maternal and Child Health, 2007

Pathophysiology

Increased vascular permeability:

- fluid shift from the vascular system into third space i.e. peritoneal space, lungs etc.
- fall in intravascular volume,
- haemoconcentration,
- thromboembolic events
- renal failure, ARDS and death

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OHSS is a potentially life threatening complication of ART and other infertility treatments.

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"OHSS – a disease of the past"

Fertil Steril. 2004 Jan;81(1):1-5.

Luteolysis induced by a gonadotropin-releasing hormone agonist is the key to prevention of ovarian hyperstimulation syndrome.

Kol S.

Department of Obstetrics and Gynecology, Rambam Medical Center, Haifa, Israel. s_kol@rambam.health.gov.il

2004

Abstract

OBJECTIVE: To review the available knowledge on the use of GnRH agonist for ovulation triggering as a means to prevent ovarian hyperstimulation syndrome (OHSS).

DESIGN(S): Review of pertinent English language studies published over the past 15 years.

RESULT(S): The available literature suggests that while GnRH agonist effectively induces final oocyte maturation and ovulation, it also completely and reliably prevents clinically significant OHSS. The mechanism of action in the context of OHSS prevention involves complete, quick, and irreversible luteolysis

CONCLUSION(S): Controlled ovarian stimulation protocols based on GnRH antagonist to prevent premature LH rise and GnRH agonist for ovulation triggering provide a safe and OHSS-free clinical environment. Adequate luteal support compensates for luteolysis and assures good clinical outcome. The fertility community is urged to adopt these protocols. This will make OHSS a disease of the past.

PMID: 14711532 [PubMed - indexed for MEDLINE]

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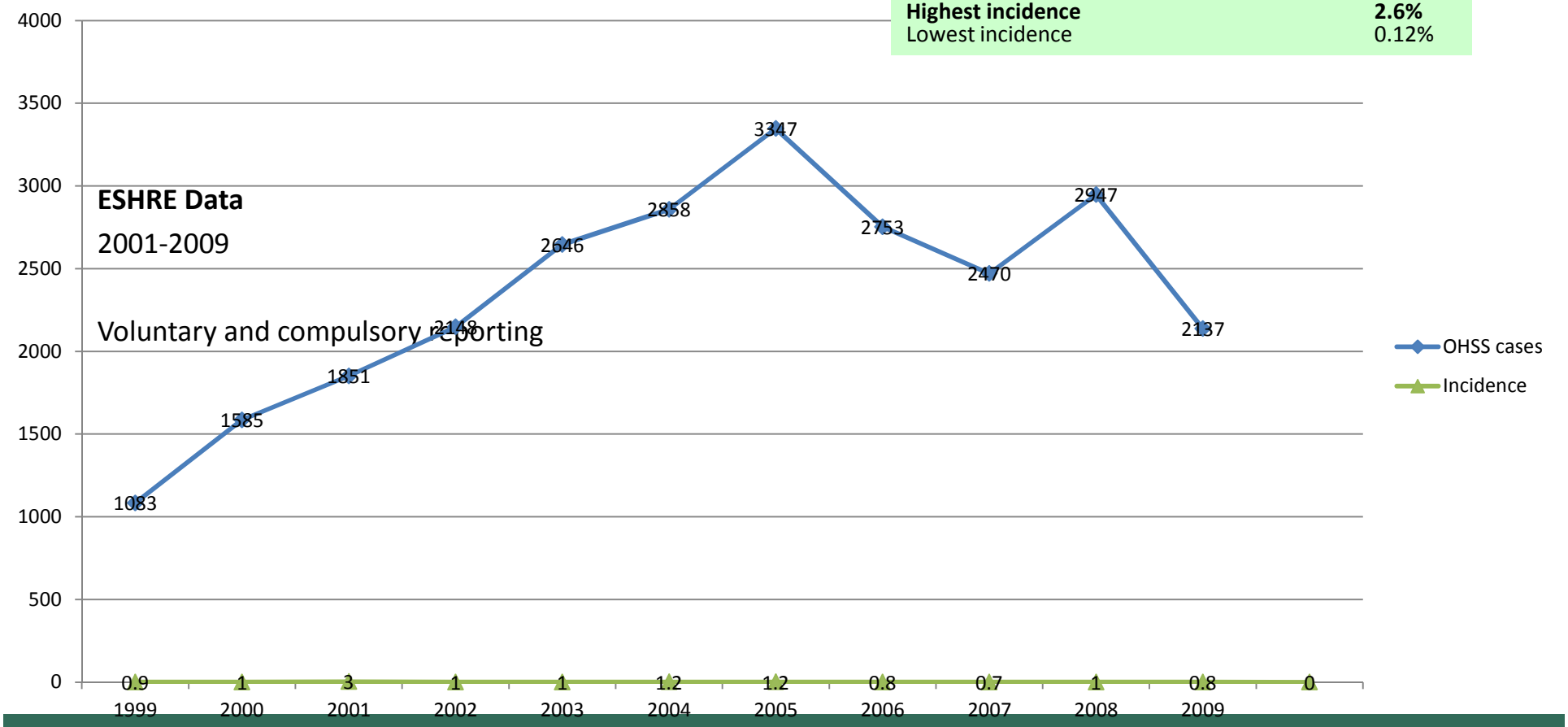
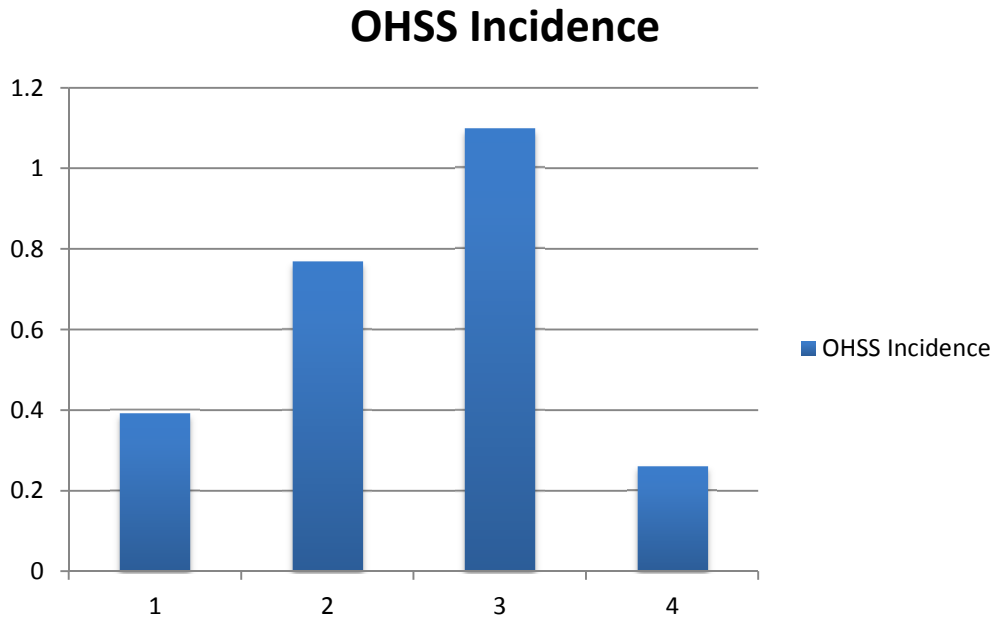
OHSS Incidence in Europe

Countries	34
Reporting OHSS cases	27
No OHSS	1
Highest incidence	**2.6%**
Lowest incidence	0.12%



OHSS Incidence by country 2009 (1death)

	Cycles	OHSS	Incidence
Group 1 (1/5)	2044	8	0.39%
Group 2 (2/17)	73440	564	0.76%
Group 3 (3/7)	101283	1112	1.09%
Group 4 (2/5)	173647	453	0.26%



1= <1000 cycles/year
2= 1000-9999 cycles/year
3= 10,000-49,999 cycles/year
4= Over 50,000 cycles/ year

Significant underreporting
Different practices in different countries

Awareness

What does the literature say?

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OHSS, death (n=15)

Acta Obstet Gynecol Scand
Minerva Ginecol
Int J Legal Med
Med Hypotheses
Anesth Analg
Human Reprod
Int J Cardiol
Aust NZJ Obstet Gynaecol
Pathology
Acta Genet Med Gemellol
J Am Coll Surg

Before 2000	**7**
2000-2009	**7**
After 2009	**1**

4

Deaths

2006	**ARDS**	**Italy**
1995	**Cerebral infarction**	**NZ**

OHSS, lethal (n=8)

Radiographics
Ann NY Acad Sci (anaesthesia)
Gynecol Endocrinol
Cochrane Database
Eur J Ophtalmol
J Clin Endocrinol Metab
Acta Obstet Gynecol Scand

Before 2000	**2**
2000-2009	**4**
After 2009	**2**

2

Deaths 0

OHSS, fatal (n=25)

Radiographics
Gynecol Endocrinol
Cochrane Database
Acta Obstet Gynecol Scand
Acta Med Port
Int J Legal Med
Reprod Biol Endocrinol
Ann Fr Anest Reanim
Sem Reprod Med
Rozhl Chir
RBM on line
J Emerg Med
Med Hypotheses
Crit Care Med
Mol Endocrinol
Best Pract Res Clin Obstet Gyanecol
Hum Reprod Update
Eur J Gastroenterol Hepatol
Pathol International
EJOGR
Pathology
Hum Reprod

7

Before 2000	**4**
2000-2009	**14**
After 2009	**7**

Deaths	**2006**	**ARDS**	**Italy**
			2000
	ARDS	**Japan**	
	1995	**Cerebral infarction**	**NZ**

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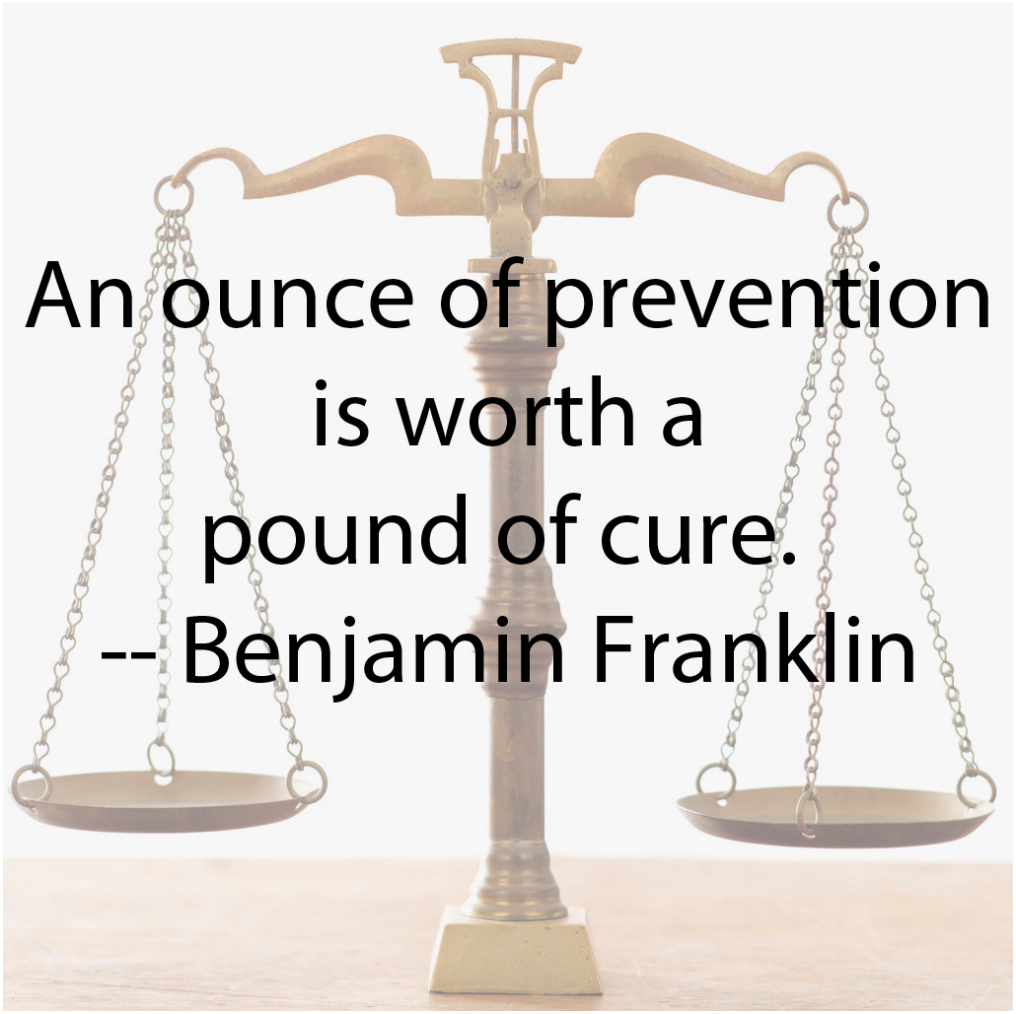
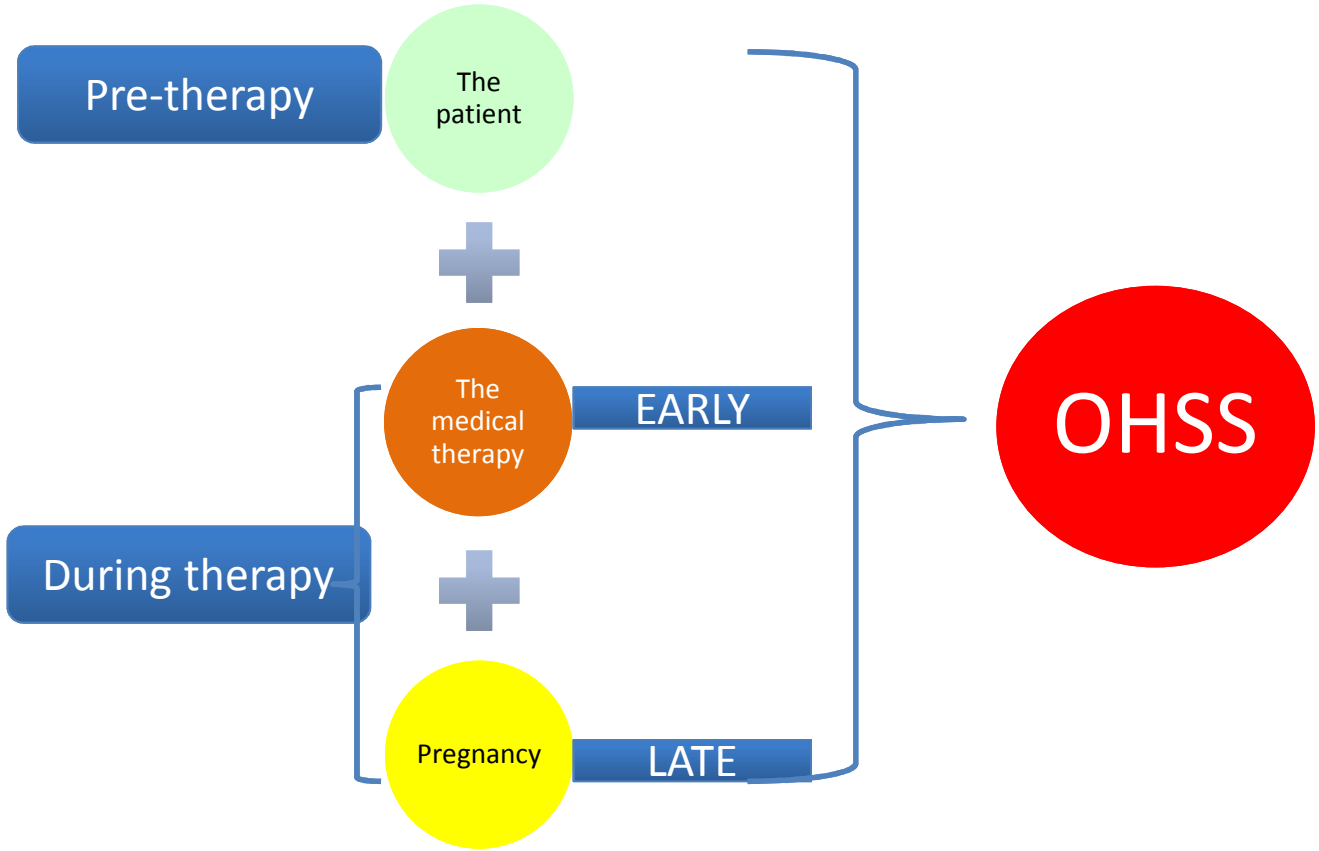


Strategy - prevention



Think *EARLY and LATE*

EARLY OHSS

- presents within 9 days after OR
- reflects excessive ovarian response / over-stimulation.

LATE OHSS (pregnancy related)

- presents after this period usually triggered by hCG from an early pregnancy
- more likely to be severe and to last longer than early OHSS.

Mathur et al., 2000, Fertil Steril 73, 901-12

Total prevention

- OHSS does not develop if:
  - hCG is not administered
  - downregulation is continued

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Risk reduction

- **Identify** (Recognise patients at risk)
- **Act** (*Early OHSS*: Change plans during stimulation)
- **Prevent** (*Early OHSS*: Cancel or trigger with spray)
- **Safe** (*Late OHSS*: Freeze all)

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EARLY OHSS risk reduction

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Identify

Step I **Identify**

Identify

- Previous OHSS
- Young age (less than 30 years old)
- PCOS
- High antral follicle count (ovarian volume)
- High AMH
- Thin habitus
- OTHERS (Egg donors, oncology females)

Intervention

- Low starting FSH dose

  Marci R et al., Fertil Steril, 2001

- **PCOS**
  - Use Metformin if tolerated (OR 0.27, 95% CI 0.16 to 0.47)

    Tso et al., 2009, Cochrane Database Syst Rev 2: CD006105.
  - Antagonist always
    - Lower peak E2 levels
    - Lower number of oocytes
    - Lower OHSS

      Ragni G, 2005, *Hum Reprod,* 20 (9): 2421-5
    - Risk reduction (45*, 7511*)

      There was a statistically significant lower incidence of OHSS in the GnRH antagonist group (29 RCTs; OR 0.43, 95% CI 0.33 to 0.57).

      Al-Inany HG , *Cochrane Database of Systematic Reviews*, 2011, Issue 5. Art. No.: CD001750.

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Step I **Identify**

Identify

- Young age (less than 30 years old)
- Thin habitus
- PCOS
- High AMH
- High antral follicle count (ovarian volume)
- Previous OHSS
- OTHERS (Egg donors, oncology females)

Intervention

- Use ANTAGONIST protocol
- Use low FSH starting dose (125 or 150IU)

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Antagonist protocol?

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Step II **ACT**

Step II Act

- *Cycle cancellation (GnRH agonist cycles)*
- FSH dose reduction
- Trigger
- Dopamine agonists

Step II **Cancel cycle**

- Reduce FSH dose
- Cycle cancellation (agonist protocols)

  – If high E_2 levels on first day of scan
    - Define level (over 7,000pmol/L)

  – High E2, rapid E2 increase
  – Very large number of small follicles

Step II **Assess risk**

E_2 level	Numbers	Admitted	Mild	Moderate	Severe
Less 15,000 pmol/L	1243	0	0	0	0
15-19,999 pmol/L	106	14 (13.2%)	5 (4.7%)	7 (6.6%)	2 (1.9%)
20-24,999 pmol/L	34	8 (23.5%)	1 (2.9%)	1 (2.9%)	6 (17.6%)
>25,000 pmol/L	11	3(27.3%)	0	1(9.1%)	2(18.2%)
All >15,000 pmol/L	**151**	**25 (16.6%)**	**6 (3.9%)**	**9 (5.9%)**	**10 (6.6%)**

Long GnRH agonist protocol

Mocanu et al., Hum Fertil, 2005

Step II **Trigger control**

- **Trigger**
  - Agonist treatments
    - Lower hCG dose (5000IU)?

      The incidence of OHSS was not reduced in the high-risk population even with lower dose of u-HCG. ….the dose of u-HCG for final oocyte maturation for women referred for IVF needs to be individualized.

      Tsoumpou I, et al., Reprod Biomed Online, 2009
  - Antagonist treatment
    - GnRHa (OR 0.10, 95% CI 0.01 to 0.82; 5 RCTs)

      Youssef MA et al., Cochrane Database Syst Rev. 2011 Jan 19;(1):CD008046

Step II **Dopamine agonists**

- Reduces OHSS (OR=0.4)

Tang et al., Cochrane Database Syst Rev. 2012 Feb 15;2CD008605

Cabergoline appears to reduce the risk of OHSS in high-risk women, especially for moderate OHSS

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Step II Act

Stimulation control	• Reduce FSH dose (high E2 and large number of follicles) • Cancel treatment (high E2 and fast increase, LP treatments)
Trigger control	• **Do not administer trigger** • If antagonist therapy use agonist for trigger • If agonist therapy use 5000IU hCG if safe • **Establish a threshold for E2 level at trigger**
VEGF pathway control	• Use dopamine agonists (cabergoline)
Endogenous LH release prevention	• Continue the agonist or antagonist until bleed if cycle cancelled

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LATE OHSS prevention

Step III **PREVENT late OHSS**

Identify

- High number of follicles aspirated
- Large number of oocytes (>20)
- Above ceiling oestradiol levels
- Ascites
- Abdominal discomfort

Odds of admission with OHSS

E_2 level	Admitted (%)	OR
15,0000- 19,999 pmol/L	13.2%	1
20,000 [illegible]	[illegible]	2.02
Over 2[illegible]	[illegible]	2.46
All E_2 over 15,000 pmol/L		
Less 20 oocytes	8.5%	1
20-24 oocytes	13.3%	1.65
25-29 oocytes	15.6%	1.99
Over 30 oocytes	38.5%	6.7

2.13

Long GnRH agonist protocol

Mocanu et al., Hum Fertil, 2005

Progesterone and only progesterone

- There was a significantly higher risk of ovarian hyperstimulation syndrome (OHSS) when hCG was used (**OR 3.62**, 95% CI 1.85 to 7.06).

van der Linden*, et al., Cochrane Database of Systematic Reviews 2011*, Issue 10. Art. No.: CD009154.

Step III **Dopamine agonists**

- A statistically significant reduction in OHSS was observed in the cabergoline treated group (OR **0.40**, 95% CI 0.20 to 0.77; 2 RCTs, 230 women) with a number needed to treat (NTT) of 7.

Tang H., *et al.,* Cochrane Database Syst Rev. 2012 Feb 15;2:CD008605.

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Step III **Dopamine agonists**

- Significantly reduces risk of early OHSS.
- Does not eliminate risk of late OHSS.

Carizza et al., Reprod Biomed Online, 2008

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To transfer or not to transfer?

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Why transfer if patient is categorised as high OHSS risk?

Word of warning

Hum Reprod. 2013 Sep;28(9):2522-8.
Severe early ovarian hyperstimulation syndrome following GnRH agonist trigger with the addition of 1500 IU hCG. *Seyhan A et al., Canada*

It would be prudent to avoid hCG luteal rescue and freeze all embryos for future transfer in such women particularly when there are ≥18 follicles with 10-14 mm diameters even with few larger follicles.

Assisted conception

- A woman known to be at risk of ovarian hyperstimulation syndrome (OHSS) underwent superovulation and had a large number of oocytes collected and embryo transfer performed.
- She subsequently developed abdominal pain, collapsed within two weeks of the procedure and died a few days later.

- She had been counselled about the risks of superovulation but embryo transfer should not be performed when there is a high risk of OHSS.

“FREEZE ALL”

Good practice:

- ≥ 20 oocytes are collected
- E2 above 15,000 pmol/L
- Patient unwell
- Ascites

Step III Late OHSS prevention

Identify

- High number of follicles aspirated
- Large number of oocytes (>20)
- Above ceiling oestradiol levels
- Ascites
- Abdominal discomfort

Stay safe

- Dopamine agonists (Cabergoline 0.5mg daily)
- **Progesterone only for luteal support in all cycles**
- Freeze all

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Special considerations

ONCOFERTILITY and OOCYTE DONORS

- Risk of OHSS.
- The patient
  - does not need eggs/ embryos (OD)
  - is about to embark on life-saving therapy (OF)

NO

- **Acceptable to have OHSS?**

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ONCOPATIENTS and DONOR OOCYTES

ALWAYS

- Use antagonist protocol.
- Trigger final maturation with GnRH analogues.

- Use dopamine agonists?

Discussed

- **I**dentify
  - Recognise the high risk patients before they start therapy.
  - Educate patients and staff.
- **A**ct
  - Use antagonist always
  - Monitor closely, reduce gonadotrophins if high E2 levels and high number of follicles evident.
- **P**revent
  - Cancel treatment.
  - hCG 5000 IU or Gn-RHa trigger.
  - Dopamine agonists.
- **S**afe
  - Progesterone only.
  - Freeze all embryos.
  - Dopamine agonists.

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Thank you