ORDINE
MEDICI CHIRURGHI
E ODONTOIATRI
DELLA PROVINCIA
DI BRESCIA
COMMISSIONE CULTURA
Coordinatore: Dott. Germano Bettoncelli

Convegno

L'INFERTILITÀ DI COPPIA:
DALLA MEDICINA GENERALE AL CENTRO DI
PROCREAZIONE MEDICALMENTE ASSISTITA (PMA)

7 ottobre 2017 - ore 8.00

PMA:
Complicanze e rischi

Dr.ssa Chiara Fratus - Dir. Medico UO
Ginecologia e Ostetricia Manerbio
ASST Garda

Dr.ssa Silvia Bonetti -Dir. Medico UO
Ginecologia e Ostetricia Istituto
Clinico Città di Brescia

COMPLICANZE E RISCHI

COMPLICANZE E RISCHI

complicanze minori

piccole ecchimosi ed indolenzimento nella sede di iniezione
molto comuni

cefalea, cambiamenti d'umore
comuni

reazioni allergiche (ECCIPIENTI: lattosio)
rare

Complicanze chirurgiche

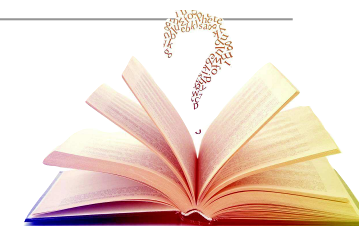
CORRESPONDENCE

Clinical complications after transvaginal oocyte retrieval in 7,098 IVF cycles

We report the complications observed after transvaginal oocyte retrieval guided by ultrasound in 7,098 IVF cycles. The frequency of severe complications in our patients was 0.08%, of which four cases were intraperitoneal bleeding (0.06%) and two were cases of ovarian abscess (0.003%). (Fertil Steril® 2011;95:293–4. ©2011 by American Society for Reproductive Medicine.)

Key Words: Transvaginal oocyte retrieval, peritoneal bleeding, pelvic abscess, IVF cycle

emoperiotoneo severo 0.06%
ascesso pelvico 0.03%



emoperitoneo 0.34%

Bodri D, Guillen JJ, Polo A, Trullenque M, Esteve C, Coll O. Complications related to ovarian stimulation and oocyte retrieval in 4052 oocyte donor cycles. Reprod Biomed Online 2008;17:237–43

ascesso pelvico 0.24%

Roest J, Mous HV, Zeilmaker GH, Verhoeff A. The incidence of major clinical complications in a Dutch transport IVF programme. Hum Reprod Update 1996;2:345–53

Distribuzione delle complicanze verificatesi nell'applicazione delle tecniche a fresco secondo la tipologia della complicanza, nell'anno 2015.

Tipo di complicanza	N	%
OHSS (% sui cicli iniziati)	181	0,33
Sanguinamento (% sui prelievi)	71	0,14
Infezione (% sui prelievi)	5	0,01
Complicanze (% su cicli iniziati)	**257**	**0,46**

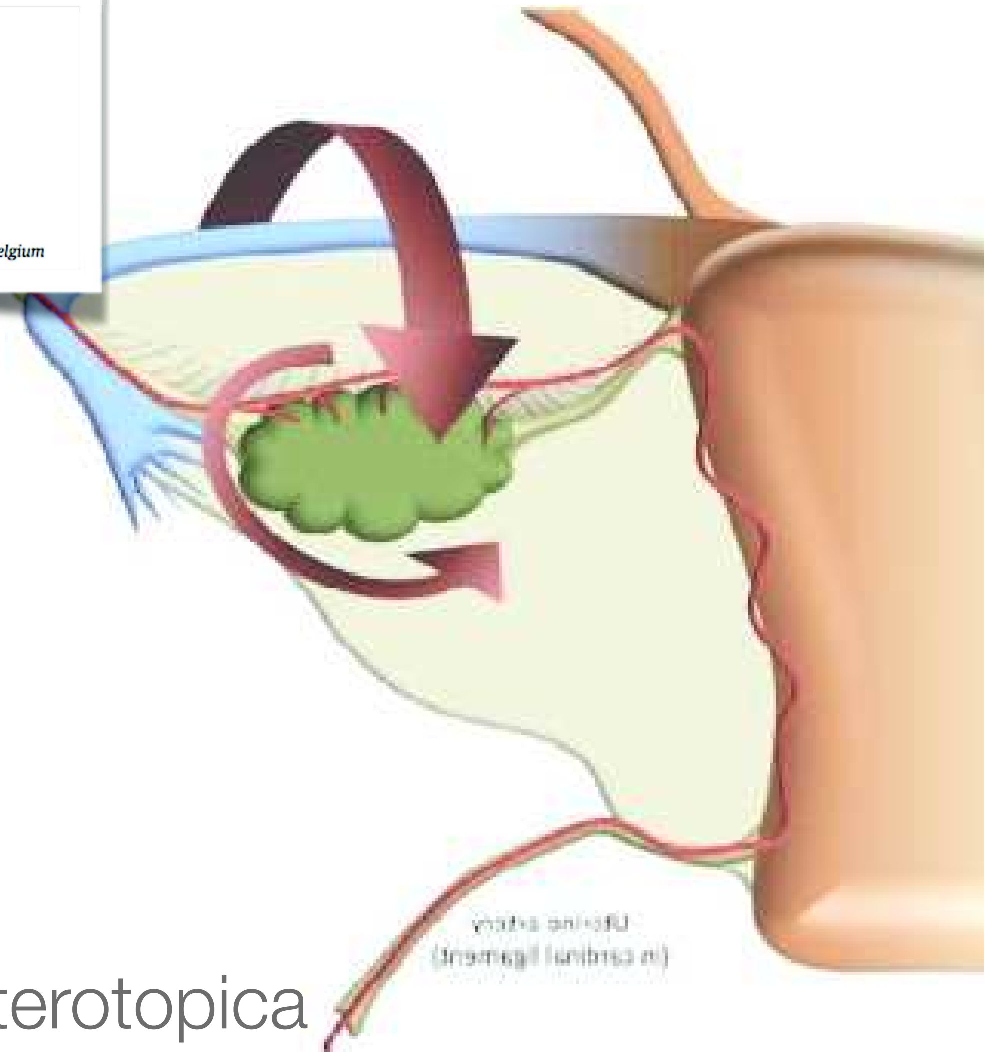
Torsione ovarica

10

Ovarian hyperstimulation syndrome and complications of ART

Veerle Vloeberghs, MD [1], Karen Peeraer, MD [1], Anne Pexsters, MD [2],
Thomas D'Hooghe, MD, PhD [*]

Leuven University Fertility Center, Department Obstetrics and Gynecology, UZ Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium



0.08-0.2%

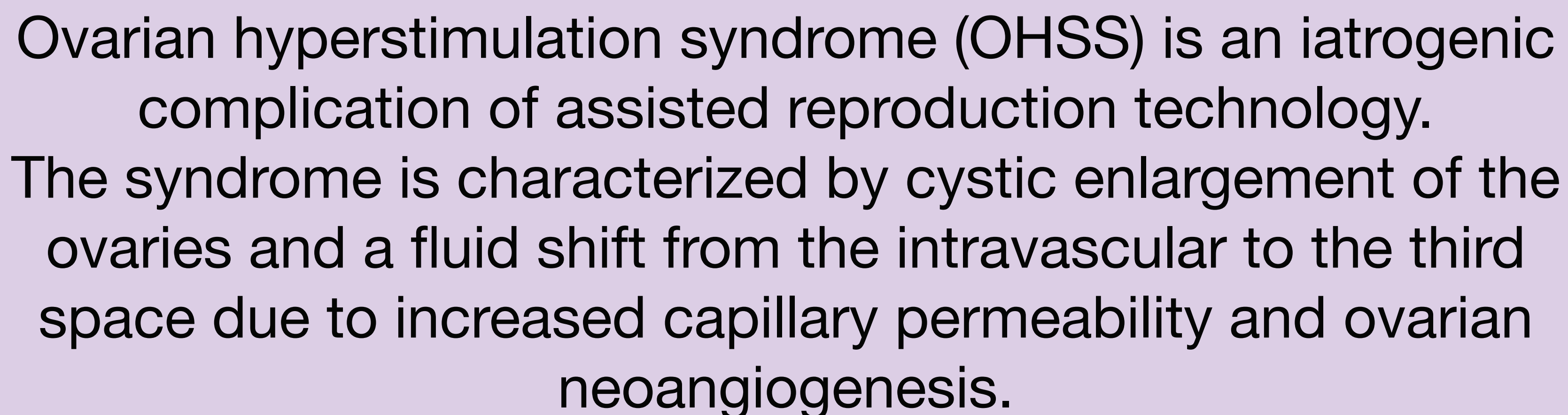
Fattori predisponenti:

-ovaie iperstimolate

- gravidanza

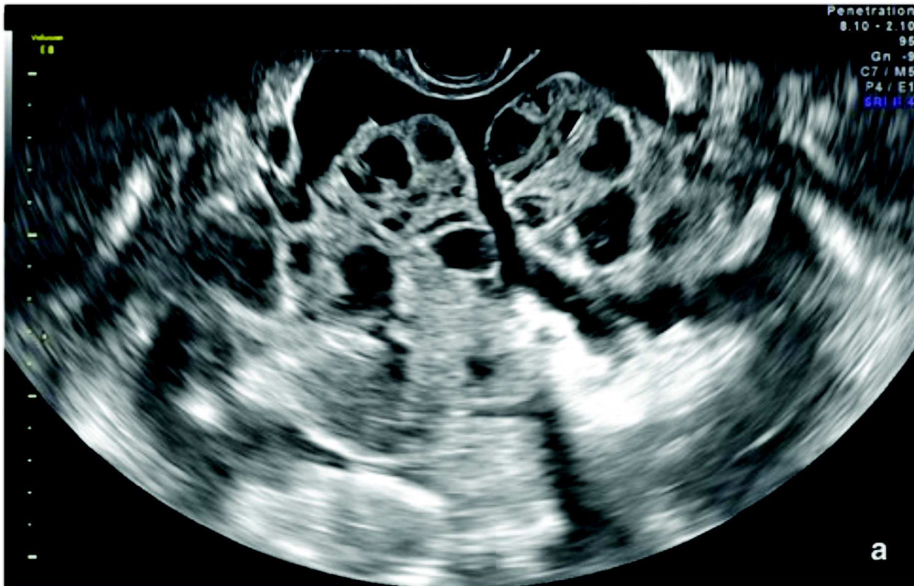
DD: gravidanza ectopica/eterotopica

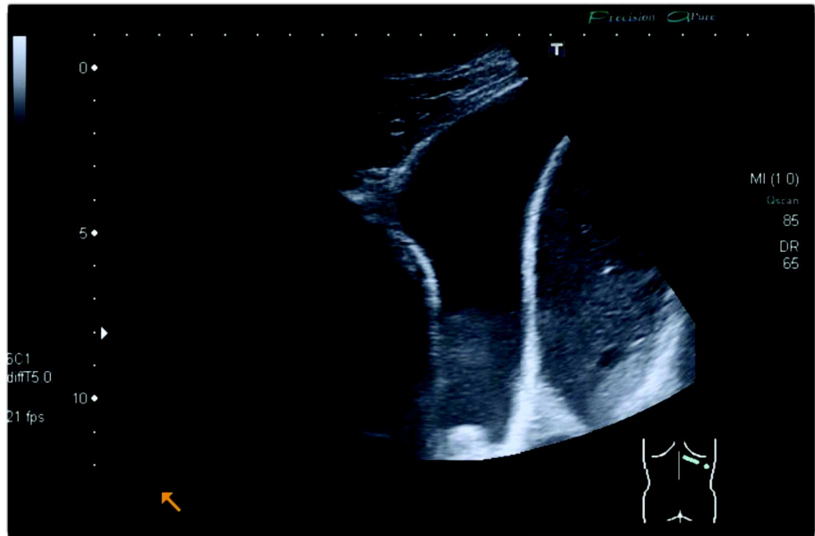
OHSS - definizione

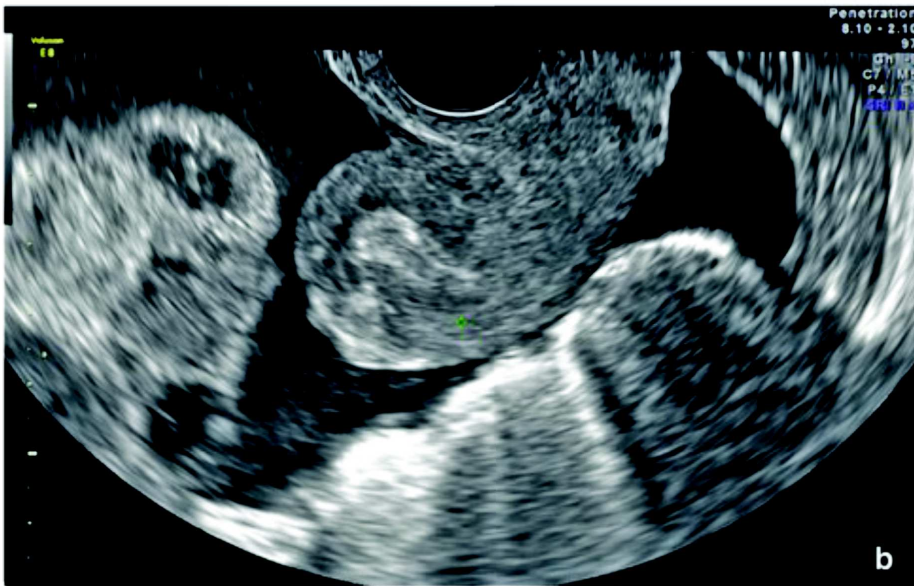


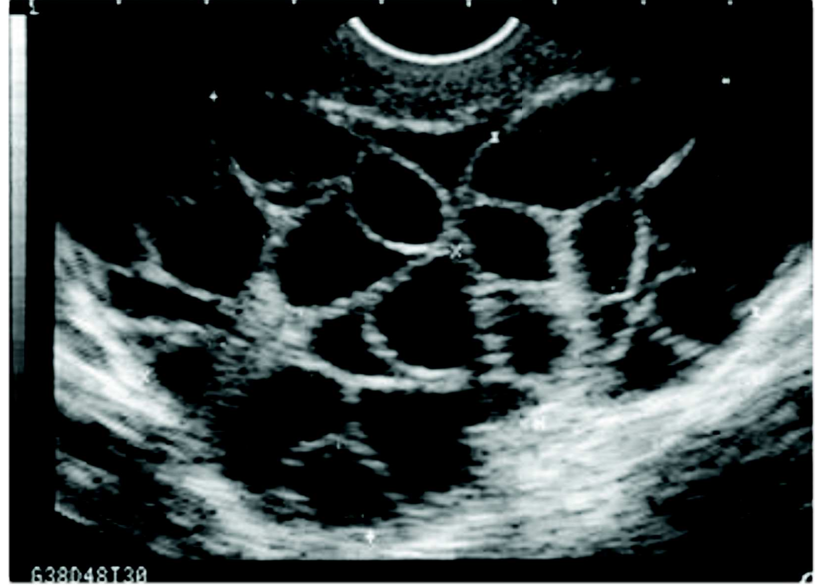
casi aneddotici di OHSS su gravidanza spontanea

OHSS







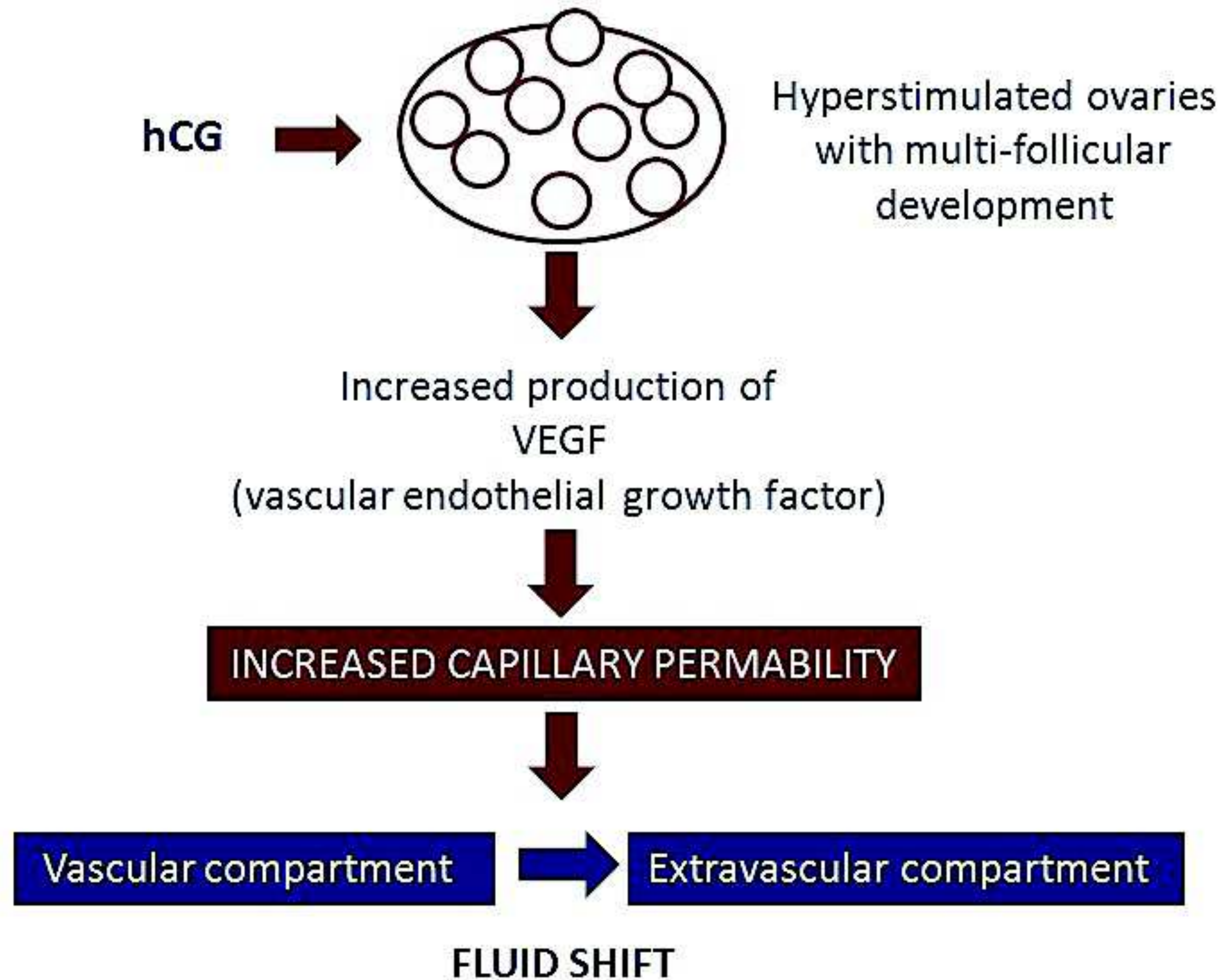


OHSS - fisiopatologia

J Assist Reprod Genet (2010) 27:121–128
DOI 10.1007/s10815-010-9387-6
GONAD PHYSIOLOGY AND DISEASE

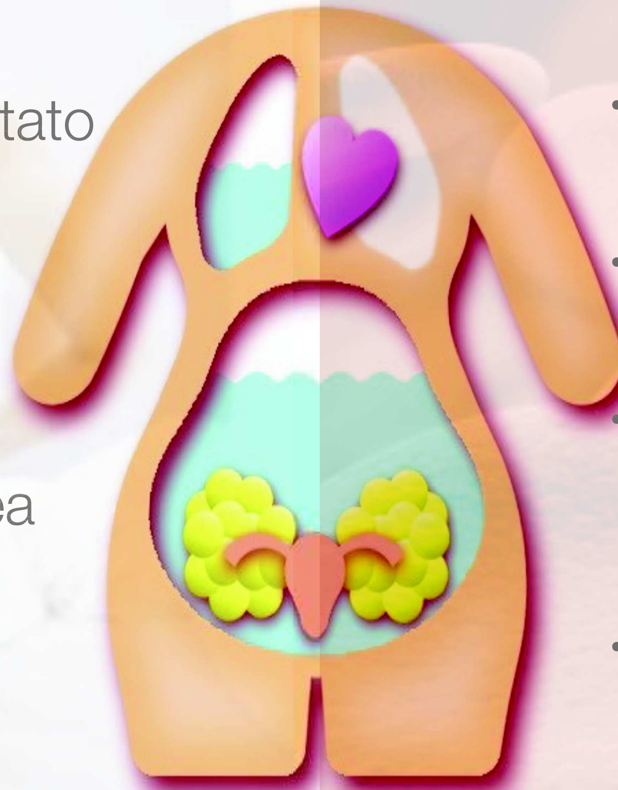
Ovarian hyperstimulation syndrome: pathophysiology and prevention

Carolina O. Nastri · Rui A. Ferriani · Isa A. Rocha · Wellington P. Martins



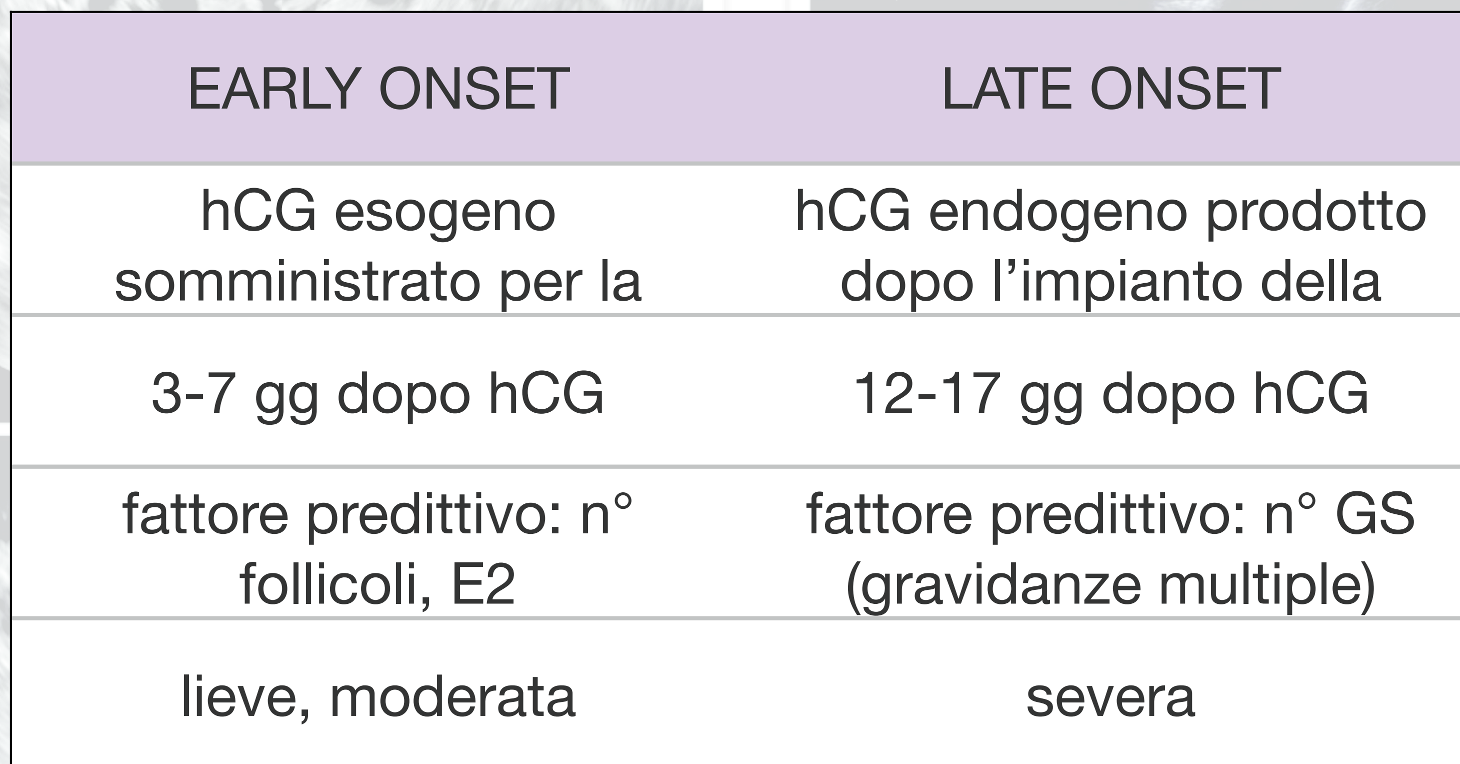
OHSS- quadro clinico

- ovaie di volume aumentato
- dolore/ tensione addominale
- nausea, vomito, dispnea
- ascite, versamento pleurico/pericardico



- ipovolemia
- oliguria/anuria
- emoconcentrazione
- iponatremia, iperpotassiemia
- ipoalbuminemia
- trombosi
- ARDS

OHSS - classificazione



EARLY ONSET	LATE ONSET
hCG esogeno somministrato per la	hCG endogeno prodotto dopo l’impianto della
3-7 gg dopo hCG	12-17 gg dopo hCG
fattore predittivo: n° follicoli, E2	fattore predittivo: n° GS (gravidanze multiple)
lieve, moderata	severa

OHSS - classificazione

Royal College of Obstetricians & Gynaecologists

The Management of Ovarian Hyperstimulation Syndrome

Green-top Guideline No. 5

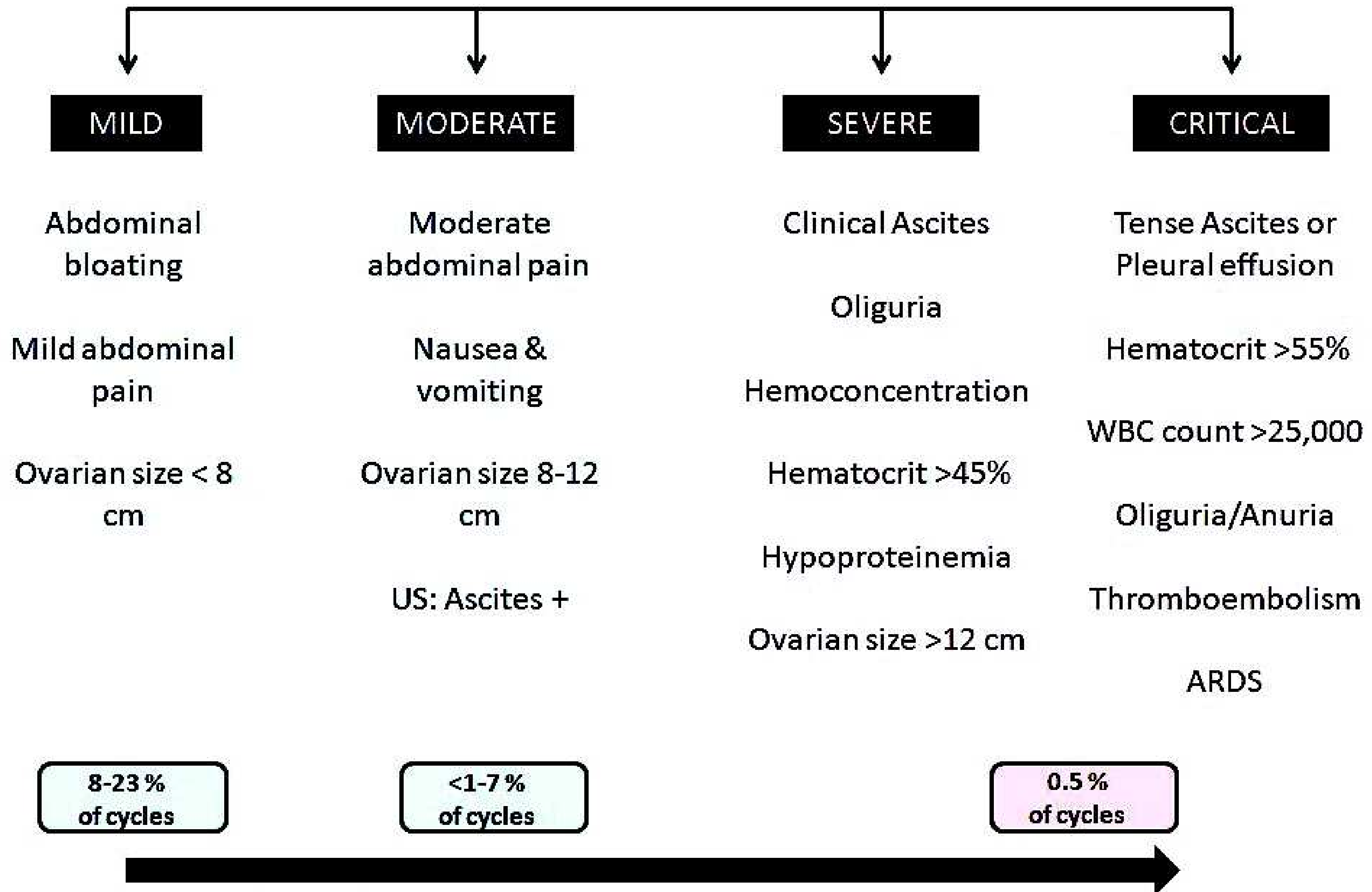
February 2016

Category	Features
Mild OHSS	Abdominal bloating Mild abdominal pain Ovarian size usually < 8 cm[a]
Moderate OHSS	Moderate abdominal pain Nausea ± vomiting Ultrasound evidence of ascites Ovarian size usually 8–12 cm[a]
Severe OHSS	Clinical ascites (± hydrothorax) Oliguria (< 300 ml/day or < 30 ml/hour) Haematocrit > 0.45 Hyponatraemia (sodium < 135 mmol/l) Hypo-osmolality (osmolality < 282 mOsm/kg) Hyperkalaemia (potassium > 5 mmol/l) Hypoproteinaemia (serum albumin < 35 g/l) Ovarian size usually > 12 cm[a]
Critical OHSS	Tense ascites/large hydrothorax Haematocrit > 0.55 White cell count > 25 000/ml Oliguria/anuria Thromboembolism Acute respiratory distress syndrome

[a] Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction because of the effect of follicular aspiration. Women demonstrating any feature of severe or critical OHSS should be classified in that category.

OHSS - classificazione

Royal College of Obstetricians & Gynaecologists



OHSS - epidemiologia

3 - 6% OHSS moderata

0,1 - 3% OHSS severa

Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. Hum Reprod Update 2002;8:559–77.

Vlahos NF, Gregoriou O. Prevention and management of ovarian hyperstimulation syndrome. Ann N Y Acad Sci. 2006;1092:247–64. doi: 10.1196/annals.1365.021

0,3% ospedalizzazione

Kupka MS, Ferraretti AP, de Mouzon J, Erb K, D'Hooghe T, Castilla JA, et al.; European IVF-Monitoring Consortium, for the European Society of Human Reproduction and Embryology (ESHRE).Assisted reproductive technology in Europe, 2010: results generated from European registers by ESHRE. Hum Reprod 2014;29:2099–113.

Some degree of ovarian hyperstimulation occurs in all women who respond to ovulation induction, but this should be distinguished from OHSS

OHSS - gestione clinica

In most cases OHSS is **self-limiting** and requires **supportive** management and monitoring while awaiting resolution.

VALUTAZIONE AMBULATORIALE

- Bilancio entrate-uscite (se postivo > 1000 ml/24h: valutazione urgente)
- paracetamolo/oppioidi (no FANS)
- profilassi antitromboembolica

OSPEDALIZZAZIONE

- scarso controllo del dolore
- inadeguata idratazione
- OHSS severa/critica

OHSS - prevenzione

Prevention of OHSS

Before

- Identification of risk factors to individualize COS
- Correct adaptation of stimulation protocols
- Monitoring COS using USG and E2 assays constitutes the `gold standard'
- Use of Gn Rh antagonist
- Cycle cancellation or Coasting

During

- Limit the dose or concentration of hCG
- Use Rec LH/ GnRH agonist to trigger ovulation
- IVM
- Prophylactic Albumin/ starch in high risk
- Transfer of single embryo ↓ MP Rate thus OHSS

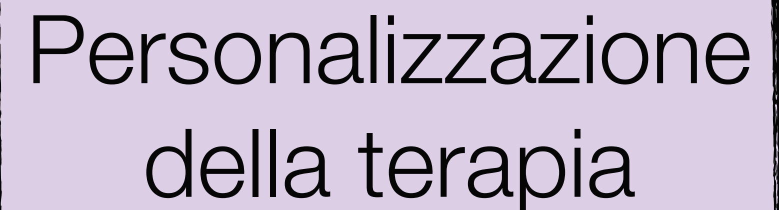
After

- Cryopreservation of all Embryos for transfer in subsequent cycle
- Using progesterone instead of hCG for luteal Phase support
- Dopamine agonist
- Use of Antagonist post cryofreezing all embryos or with Fresh ET?

OHSS - prevenzione primaria

Fattori di rischio

- giovane età
- pregressa OHSS
- AFC elevata
  (n° dei follicoli 2-10 mm in fase follicolare precoce)
- AMH elevato
- basso BMI
- PCO / PCOS



OHSS - prevenzione secondaria

crioconservazione degli embrioni/ovociti ed embriotransfer nei cicli successivi

OHSS - prospettive

l'incidenza dell'OHSS è in netta riduzione

COMPLICANZE DELLA GRAVIDANZA

GRAVIDANZA ECTOPICA

Refaat et al. Reproductive Biology and Endocrinology (2015) 13:30
DOI 10.1186/s12958-015-0025-0

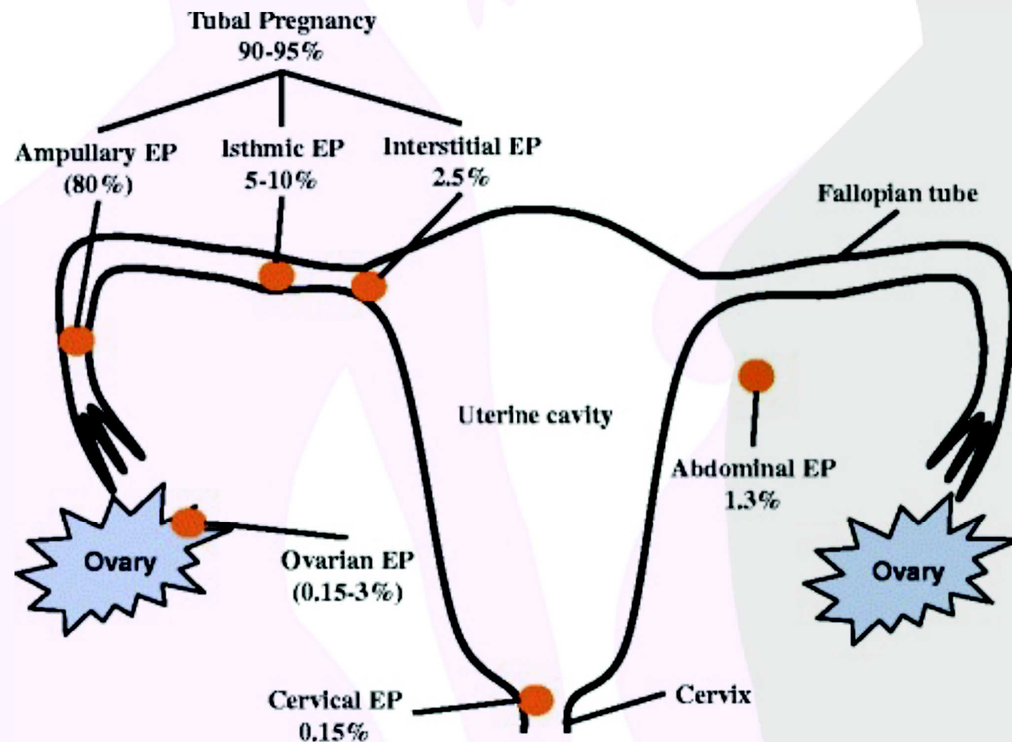
RB&E REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY

REVIEW — Open Access

Ectopic pregnancy secondary to in vitro fertilisation-embryo transfer: pathogenic mechanisms and management strategies

Bassem Refaat[1*], Elizabeth Dalton[2] and William L Ledger[2]

Ectopic pregnancy (EP) is a form of abnormal pregnancy in which the fertilised ovum implants outside the intrauterine cavity, with the ampullary region of the Fallopian tube being the most common site of implantation



Fattori di rischio:

fattore tubarico
endometriosi
pregressa PID
pregressa gravidanza ecopica
pregressa chirurgia tubarica

GRAVIDANZA ECTOPICA - ETEROTOPICA

gravidanza spontanea

EP: 1-2%

HP: 1/30.000

ART

EP: 2,1-8,6 % (fino a 11% in pazienti con fattori di rischio)

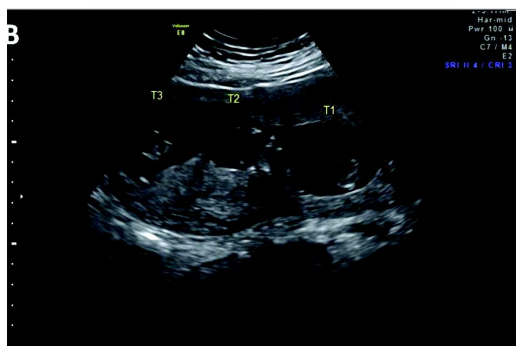
HP: 0.8%

Infertility is a problem affecting 8-12% of couples worldwide. The associations between infertility and EP are complex, as one of them could be simultaneously a cause and the other a consequence. There is an increased risk of developing EP following fertility treatment, which could be due to the effects of the treatment or the pre-existing disorder.

GRAVIDANZE MULTIPLE

Tab. 4.33: Distribuzione percentuale del genere delle gravidanze (singole, gemellari, trigemine o quadruple) secondo le classi di età delle pazienti ottenute da tecniche applicate nell'anno 2015.

Classi di età delle pazienti	Gravidanze totali da tecniche di II e III livello	Gravidanze singole %	Gravidanze gemellari %	Gravidanze trigemine %	Gravidanze quadruple %
≤ 34 anni	5.503	81,7	17,4	0,8	0,05
35-39 anni	5.773	84,3	14,9	0,8	-
40-42 anni	2.028	87,8	11,5	0,6	0,05
≥ 43 anni	410	95,1	4,6	0,2	-
Totale	**13.714**	**84,1**	**15,1**	**0,8**	**0,03**



GRAVIDANZE MULTIPLE

Tab. 4.31: Distribuzione percentuale secondo la tecnica utilizzata del genere delle gravidanze (singole, gemellari, trigemine o quadruple) ottenute da tecniche applicate nell'anno 2015.

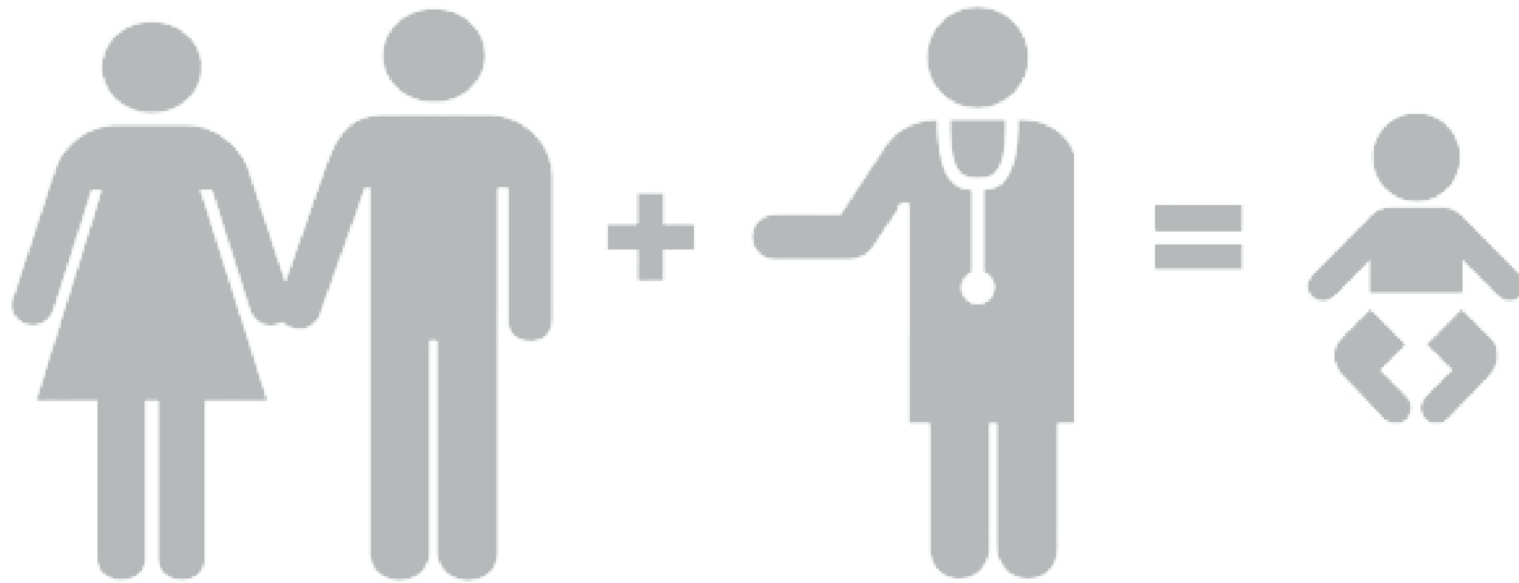
Tipo di Gravidanze	FIVET %	ICSI %	FER %	FO %	II e III livello totale %
Gravidanze singole	82,2	82,0	89,8	89,0	84,1
Gravidanze gemellari	17,0	17,0	9,8	10,6	15,1
Gravidanze trigemine	0,7	1,0	0,4	0,4	0,8
Gravidanze quadruple	0,06	0,04	-	-	0,03
Totale	**100**	**100**	**100**	**100**	**100**

FER (Frozen Embryo Replacement)
FO (Frozen Oocyte)

CONCLUSIONI

bassa percentuale di complicanze

si può affermare che la PMA si basa su tecniche che si possono definire sicure



I HAVE A DREAM…

Grazie per l'attenzione

OHSS - classificazione

Table I. Classification of ovarian hyperstimulation syndrome (OHSS)

Study	Mild	Moderate	Severe		
Rabau *et al.* (1967)	Grade 1: estrogen >150 µg and pregnanediol >10 mg 24 h Grade 2: + enlarged ovaries and possibly palpable cysts Grade 1 and 2 were not included under the title of mild OHSS	Grade 3: grade 2 + confirmed palpable cysts and distended abdomen Grade 4: grade 3 + vomiting and possibly diarrhoea	Grade 5: grade 4 + ascites and possibly hydrothorax	Grade 6: grade 5 + changes in blood volume, viscosity and coagulation, time	
Schenker and Weinstein (1978)	Grade 1: estrogen >150 µg/24 h and pregnanediol >10 mg 24 h Grade 2: grade 1+ enlarged ovaries, sometimes small cysts	Grade 3: grade 2 + abdominal distension Grade 4: grade 3 + nausea, vomiting and/or diarrhoea	Grade 5: grade 4 + large ovarian cysts, ascites and/or hydrothorax	Grade 6: marked haemoconcentration + increased blood viscosity and possibly coagulation abnormalities	
Golan *et al.* (1989)	Grade 1: abdominal distension and discomfort Grade 2: grade 1 + nausea, vomiting and/or diarrhoea, enlarged ovaries 5–12 cm	Grade 3: grade 2 + ultrasound evidence of ascites	Grade 4: grade 3 + clinical evidence of ascites and/or hydrothorax and breathing difficulties	Grade 5: grade 4 + haemoconcentration, increase blood viscosity, coagulation abnormality and diminished renal perfusion	
Navot *et al.* (1992)			Severe OHSS: variable enlarged ovary; massive ascites ± hydrothorax; Hct >45%; WBC >15 000; oliguria; creatinine 1.0–1.5; creatinine clearance ≥50 ml/min; liver dysfunction; anasarca	Critical OHSS: variable enlarged ovary; tense ascites ± hydrothorax; Hct >55%; WBC ≥25 000; oliguria; creatinine ≥1.6; creatinine clearance <50 ml/min; renal failure; thromboembolic phenomena; ARDS	
Rizk and Aboulghar (1999)		Discomfort, pain, nausea, distension, ultrasonic evidence of ascites and enlarged ovaries, normal haematological and biological profiles	Grade A: Dyspnoea, oliguria, nausea, vomiting, diarrhoea, abdominal pain, clinical evidence of ascites, marked distension of abdomen or hydrothorax, US showing large ovaries and marked ascites, normal biochemical profile	Grade B: Grade A plus massive tension ascites, markedly enlarged ovaries, severe dyspnoea and marked oliguria, increased haematocrit, elevated serum creatinine and liver dysfunction	Grade C: Complications as respiratory distress syndrome, renal shut-down or venous thrombosis

OHSS - fisiopatologia

Estradiol	Estradiol level is a reliable predictor of OHSS during ART
	OHSS can occur despite low estradiol levels
	High estradiol concentrations are not sufficient to induce OHSS
	Currently considered a mere marker of granulose activity
hCG	Fundamental for triggering OHSS
	hCG alone is not sufficient to induce OHSS
Interleukins	Some interleukins are associated with OHSS, and elevated concentrations are associated with increased vascular permeability, hemoconcentration, elevated plasma estradiol concentration, and inhibition of hepatic albumin production
Renin-angiotensin system	There is a direct correlation between plasma renin activity and the severity of OHSS
	All hypovolemic conditions are associated with a secondary reactive hyperaldosteronism via renin-angiotensin cascade activation
	Renin-angiotensin system activation is probably the effect and not the cause of OHSS
VEGF	VEGF expression is associated with OHSS increased vascular permeability
	VEGF levels are elevated during ovarian stimulation with exogenous FSH, which is enhanced after hCG administration

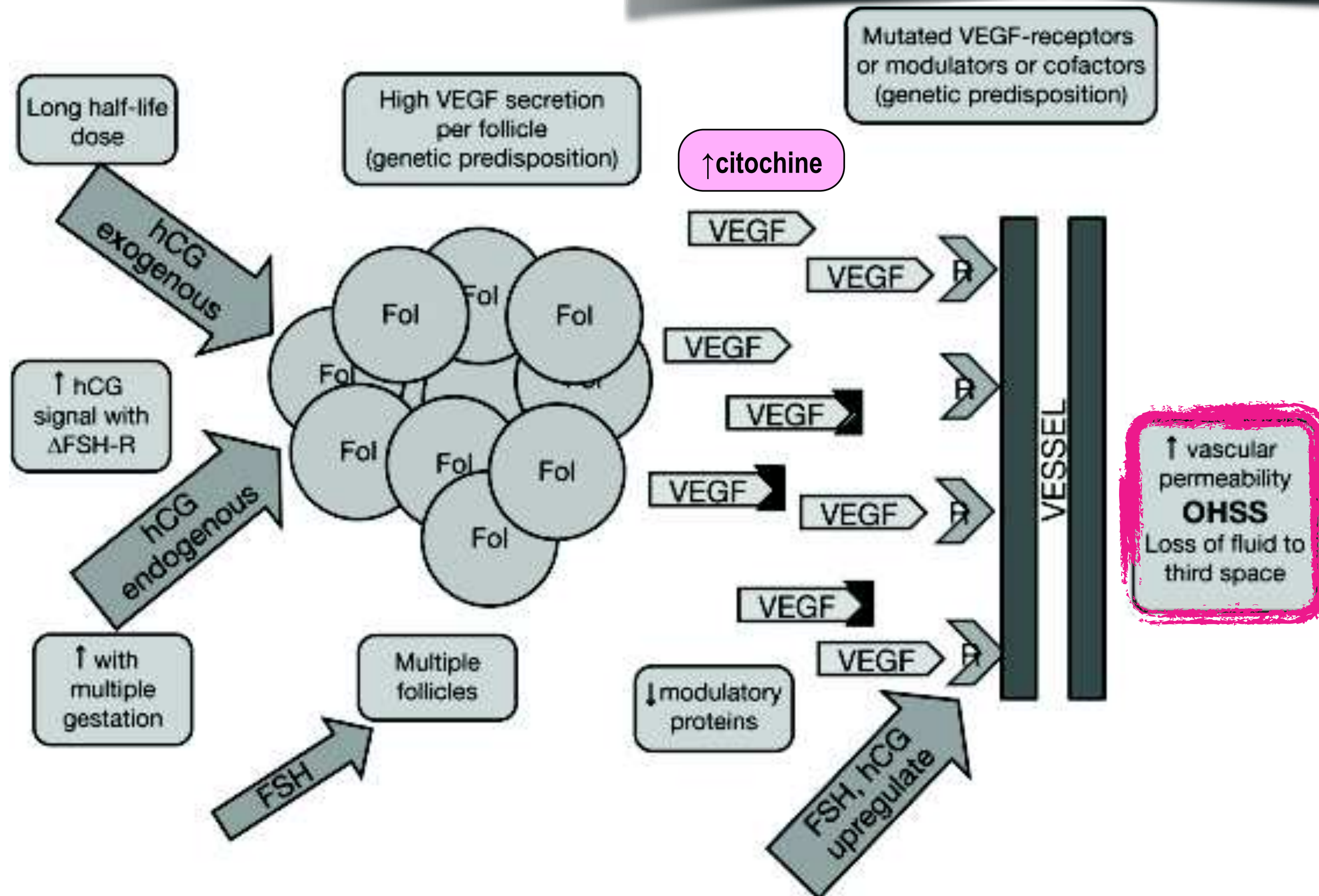
OHSS - fisiopatologia

J Assist Reprod Genet (2010) 27:121–128
DOI 10.1007/s10815-010-9387-6

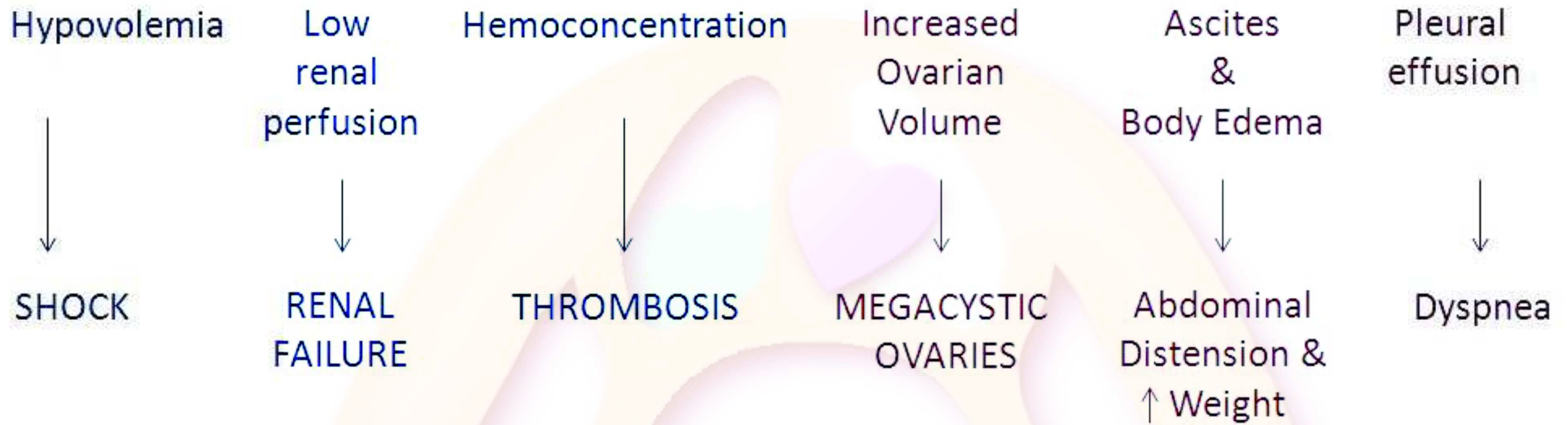
GONAD PHYSIOLOGY AND DISEASE

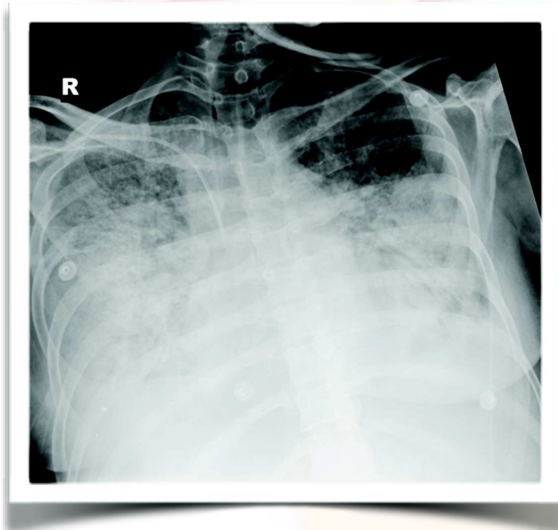
Ovarian hyperstimulation syndrome: pathophysiology and prevention

Carolina O. Nastri · Rui A. Ferriani · Isa A. Rocha · Wellington P. Martins

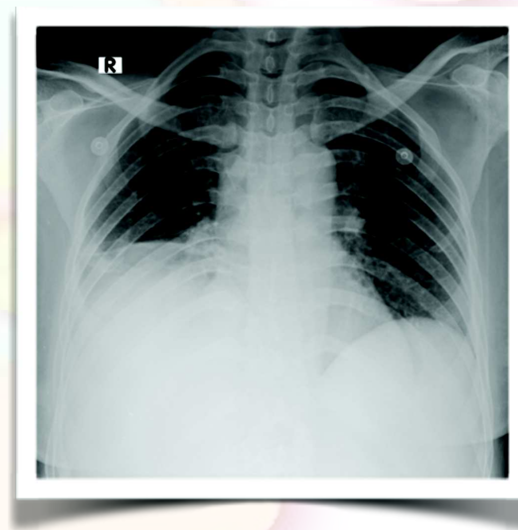


OHSS- quadro clinico





ARDS



IDROTORACE

OHSS- quadro clinico

- Clinical manifestations reflect the extent of fluid shift into the third space

- Clinical spectrum ranges from:

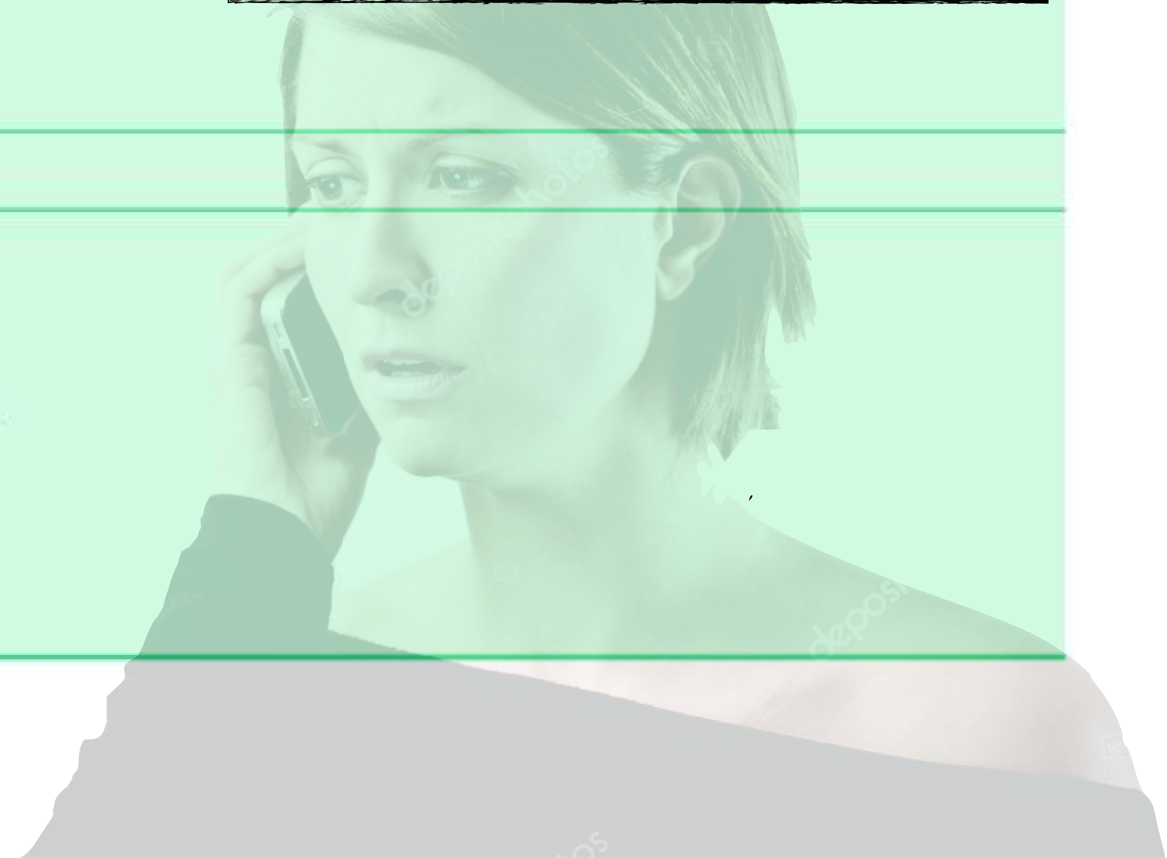
  - ✓ Abdominal bloating (commonest)
  - ✓ Nausea & vomiting
  - ✓ Weight gain
  - ✓ Dyspnea
  - ✓ Oliguria & Anuria
  - ✓ Venous thrombosis
  - ✓ Thrombo-embolism & Arrythmias
  - ✓ ARDS (adult respiratory distress syndrome)
  - ✓ Sepsis
  - ✓ Death

Increasing severity

OHSS - gestione clinica

porre la diagnosi
stabilire la severità

necessaria visita specialistica



History
Time of onset of symptoms relative to trigger
Medication used for trigger (hCG or GnRH agonist)
Number of follicles on final monitoring scan
Number of eggs collected
Were embryos replaced and how many?
Polycystic ovary syndrome diagnosis?
Symptoms
Abdominal bloating
Abdominal discomfort/pain, need for analgesia
Nausea and vomiting
Breathlessness, inability to lie flat or talk in full sentences
Reduced urine output
Leg swelling
Vulval swelling
Associated comorbidities such as thrombosis