REPRODUCTIVE MEDICINE & ASSISTED
RM&ART
REPRODUCTIVE TECHNIQUES SERIES

Ovarian Hyperstimulation Syndrome

edited by
Jan Gerris
Annick Delvigne
François Olivennes

CRC Press
Taylor & Francis Group

OVARIAN HYPERSTIMULATION SYNDROME

Edited by

Jan Gerris MD PhD

*Division of Gynecology
University Hospital Ghent
Ghent, Belgium*

Annick Delvigne MD PhD

*Center for Reproductive Medicine
St Pierre Hospital
Brussels, Belgium*

François Olivennes MD PhD

*Unit of Reproductive Medicine
Obstetrics and Gynecology Service II, Cochin Hospital
Paris, France*

CRC Press

Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

First published 2006 by Informa Healthcare

Published 2018 by CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

© 2006 by Taylor & Francis Group, LLC
CRC Press is an imprint of Taylor & Francis Group, an Informa business

No claim to original U.S. Government works

ISBN 13: 978-1-84214-328-5 (hbk)

This book contains information obtained from authentic and highly regarded sources. While all reasonable efforts have been made to publish reliable data and information, neither the author[s] nor the publisher can accept any legal responsibility or liability for any errors or omissions that may be made. The publishers wish to make clear that any views or opinions expressed in this book by individual editors, authors or contributors are personal to them and do not necessarily reflect the views/opinions of the publishers. The information or guidance contained in this book is intended for use by medical, scientific or health-care professionals and is provided strictly as a supplement to the medical or other professional's own judgement, their knowledge of the patient's medical history, relevant manufacturer's instructions and the appropriate best practice guidelines. Because of the rapid advances in medical science, any information or advice on dosages, procedures or diagnoses should be independently verified. The reader is strongly urged to consult the relevant national drug formulary and the drug companies' and device or material manufacturers' printed instructions, and their websites, before administering or utilizing any of the drugs, devices or materials mentioned in this book. This book does not indicate whether a particular treatment is appropriate or suitable for a particular individual. Ultimately it is the sole responsibility of the medical professional to make his or her own professional judgements, so as to advise and treat patients appropriately. The authors and publishers have also attempted to trace the copyright holders of all material reproduced in this publication and apologize to copyright holders if permission to publish in this form has not been obtained. If any copyright material has not been acknowledged please write and let us know so we may rectify in any future reprint.

Except as permitted under U.S. Copyright Law, no part of this book may be reprinted, reproduced, transmitted, or utilized in any form by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying, microfilming, and recording, or in any information storage or retrieval system, without written permission from the publishers.

For permission to photocopy or use material electronically from this work, please access www.copyright.com (<http://www.copyright.com/>) or contact the Copyright Clearance Center, Inc. (CCC), 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400. CCC is a not-for-profit organization that provides licenses and registration for a variety of users. For organizations that have been granted a photocopy license by the CCC, a separate system of payment has been arranged.

Trademark Notice: Product or corporate names may be trademarks or registered trademarks, and are used only for identification and explanation without intent to infringe.

Visit the Taylor & Francis Web site at
<http://www.taylorandfrancis.com>

and the CRC Press Web site at
<http://www.crcpress.com>

Although every effort has been made to ensure that all owners of copyright material have been acknowledged in this publication, we would be glad to acknowledge in subsequent reprints or editions any omissions brought to our attention.

A CIP record for this book is available from the British Library.

Library of Congress Cataloging-in-Publication Data

Data available on application

Composition by Parthenon Publishing

Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Ascites fluid is characterized by a high concentration in proteins (4.8 g/100 ml), a low leukocyte count and the presence of relatively high numbers of red blood cells.

The extravascular protein-rich exudate accumulated in the peritoneum, in the pleura (hydrothorax) (Figure 3) and even in the pericardiac space is associated with intravascular volume depletion and hemoconcentration, activation of vasoconstrictor and antinatriuretic factors, severe hypoalbuminemia and sometimes

vulvar or generalized edema (anasarca). The cardiovascular effects include arterial hypotension, reduced fluid volume, low central venous pressure, tachycardia, increased cardiac output, low peripheral resistance, increased vascular stasis, hemoconcentration and hypercoagulation.

The associated hypovolemia can induce oliguria and electrolyte imbalance. Oliguria exists in about 30% of cases, and renal failure secondary to hypoperfusion or to compressive obstruction occurs in about 1.4% of the severe forms of OHSS^{21,25}. Decreased renal perfusion induces stimulation of renal tubules and resorption of sodium and water, resulting in clinical manifestations of oliguria and sodium retention. Electrolyte imbalance is then observed, typically hyponatremia and hyperkalemia.

Figure 1 Thin line of ascites hardly discernible from usual discrete intra-abdominal bleeding as the result of ovarian puncture

Figure 2 Uterus floating in echographically obvious large quantity of ascites

Figure 3 Hydrothorax (usually right-sided)

Figure 4 Two severely enlarged ovaries in OHSS patient undergoing laparotomy. Courtesy Dr G I Serour, Egypt

Together with ascites, the associated paralytic ileus can impair diaphragmatic movement to such an extent that respiratory problems ensue. If pleural effusion also develops, lung function may be seriously affected, leading to adult respiratory distress syndrome (ARDS).

Pleural effusion can complicate massive ascites or exist as an isolated manifestation of OHSS without peritoneal fluid accumulation. Liver dysfunction can also occur. Thromboembolic phenomena constitute the ultimate complication of OHSS and are capable, despite appropriate treatment, of killing the patient²⁶.

Such an array of potential severity of side-effects is rarely encountered, especially for a treatment applied for non-lethal pathology. The challenge for assisted reproductive technologies in the future is certainly an improvement of the baby take-home rate without impairment of women's health and their long- or short-term quality of life.

REFERENCES

1. Rydberg E, Pedersen-Bjergaard K. Effect of serum gonadotrophin and chorionic gonado-

trophin on the human ovary. *JAMA* 1943; 121: 1117-22.

2. Davis E, Hellebaum AA. Observations on the experimental use of gonadotropic extracts in the human female. *J Clin Endocrinol* 1944; 4: 400-9.
3. Esteban-Altirriba J. Le syndrome d'hyperstimulation massive des ovaires. *Rev Franç Gynécol Obstet* 1961; 56: 555-64.
4. Rotmensch S, Scommegna A. Spontaneous ovarian hyperstimulation syndrome associated with hypothyroidism. *Am J Obstet Gynecol* 1989; 160: 1220-2.
5. Le Dall R. Le syndrome d'hyperlutéinisation massive des deux ovaires par injection intermestive d'hormones gonadotropes. Thesis (no. 915), Paris, 1957.
6. Zalel Y, Katz Z, Caspi B, et al. Spontaneous ovarian hyperstimulation syndrome concomitant with spontaneous pregnancy in a woman with polycystic ovary disease. *Am J Obstet Gynecol* 1992; 167: 122-4.
7. Ayhan A, Tuncer ZS, Aksu AT. Ovarian hyperstimulation syndrome associated with spontaneous pregnancy. *Hum Reprod* 1996; 11: 1600-1.
8. Lipitz S, Grisaru D, Achiron R, et al. Spontaneous ovarian hyperstimulation mimicking an ovarian tumour. *Hum Reprod* 1996; 11: 720-1.
9. Olatunbosun OA, Gilliland B, Brydon LA, et al. Spontaneous ovarian hyperstimulation syndrome in four consecutive pregnancies. *Clin Exp Obstet Gynecol* 1996; 23: 127-32.
10. Abu-Louz SK, Ahmed AA, Swan RW. Spontaneous ovarian hyperstimulation syndrome with pregnancy. *Am J Obstet Gynecol* 1997; 177: 476-7.
11. Di Carlo C, Bruno P, Cirillo D, et al. Increased concentrations of renin, aldosterone and Ca125 in a case of spontaneous, recurrent, familial, severe ovarian hyperstimulation syndrome. *Hum Reprod* 1997; 12: 2115-17.
12. Nappi RG, Di Naro E, D'Aries AP. Natural pregnancy in hypothyroid woman complicated by spontaneous ovarian hyperstimulation syndrome. *Am J Obstet Gynecol* 1998; 178: 610-11.

Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

IVF cycles with embryo transfer was considered, the incidence was 17% ($n = 18$). An additional group, using a cohort of 78 early- and late-OHSS patients, determined the oocyte number and peak E_2 level that best discriminated cycles with and without OHSS⁸. These authors calculated the sensitivity and specificity for different cut-off limits: only a moderately significant positive likelihood ratio (LR; 6.37) was obtained for an E_2 level > 2642 pg/ml, while a moderately significant negative LR (0.13) was obtained for an E_2 level < 1847 pg/ml.

Although mean serum E_2 levels are significantly higher in patients who develop OHSS compared with controls, serum E_2 alone is not a sufficiently predictive factor. Indeed, an extensive overlap of serum E_2 values was found between controls and OHSS patients in two series of 54 OHSS patients² and 128 patients⁹ (Figure 1).

Some authors studied the predictive value of measuring the *early cycle serum E_2 level* to estimate cycle outcome in IVF. E_2 was measured in

the mid-follicular phase (day 9) during COH (long gonadotropin-releasing hormone (GnRH) agonist and human menopausal gonadotropin (hMG) started on day 3), and excessive ovarian responsiveness was defined by $E_2 > 4000$ pg/ml on the day of hCG administration or the necessity for coasting based on $E_2 > 3000$ pg/ml before the day of hCG injection. With a serum E_2 level > 800 pg/ml on cycle day 9, 55.8% of patients fulfilled the criteria for excessive ovarian responsiveness, but none of the patients with a serum E_2 level < 300 pg/ml met the criteria. According to these previous data, the authors recommended decreasing the hMG dose on day 9 in order to tailor the ovarian response¹⁰.

D'Angelo *et al.* studied the predictive value of different serum E_2 cut-off levels on days 11 and 8 of COH in a retrospective case-control study of 80 patients¹¹. A serum E_2 of 3354 pg/ml on day 11 of COH gave a sensitivity and specificity of 85% for the detection of women at risk for OHSS (only mild and moderate OHSS were recorded in the studied patients). Moreover,

Figure 1 Overlap of estradiol values between OHSS and control patients⁹

Figure 2 Frequency histogram of estradiol (E_2) value (pg/ml) which was chosen by physicians ($n = 141$) as value for administration of human chorionic gonadotropin (hCG) when applying coasting as preventive measure

constitute a risk factor for OHSS. Moreover, according to different authors, the size of follicles which should be considered a threshold value for risk is variable. Blankstein *et al.*²⁵ in 1987 evaluated a cohort of 65 patients treated with COH and found that patients with OHSS had significantly more follicles at the time of hCG than did patients without OHSS. In moderate to severe OHSS, 95% of the preovulatory follicles were < 16 mm and 55% < 9 mm; in contrast, in mild OHSS, 69% were follicles of intermediate size (9–15 mm). Although this study is often cited as a reference, its results should be distinguished from those of other reports, because the stimulation conditions were quite different. For example, hCG was administered to all patients when their 24-h urinary excretion of E_2 was between 80 and 180 μ g, independent of any maturation criteria assessed by ultrasound.

A significant correlation was found between the presence of multiple (> 4.2) secondary follicles of size 14–16 mm and severe OHSS²⁶, while others^{2,27} found that during ovarian induction and IVF cycles, respectively, follicles of 12–14 mm or < 18 mm were associated with an increased risk of OHSS.

Finally, it was observed that, during IVF, OHSS patients had more follicles > 15 mm in size¹⁵.

The discussion regarding follicular size may be obsolete, because stimulation criteria are totally different according to whether ovarian induction or IVF is applied. Furthermore, the error in follicle measurement and counting is related to their number⁶. Hence, the risk of OHSS is often related to the total number of developing follicles and to the number of collected oocytes (90% of follicles seen)⁶. In the latter study, no patient developed severe OHSS

Figure 3 Overlap of number of oocytes retrieved between OHSS and control patients²⁰

patients who underwent IVF³¹. In addition, a significant correlation was found between the baseline number of follicles, the number of oocytes retrieved and OHSS.

Some investigators furthermore evaluated the intraovarian blood flow, and identified a close correlation between OHSS severity and lowered resistance to blood flow in the stimulated ovaries³². However, the predictive value of these data should be validated in larger series. Agrawal *et al.* suggested that within ovarian and uterine blood vessels, blood flow velocities were higher in the early follicular phase and on the day of hCG administration in women with polycystic ovaries/polycystic ovarian syndrome (PCO/PCOS)³³. A positive correlation was observed between serum vascular endothelial growth factor (VEGF) and E₂ concentrations on the days of hCG administration and oocyte retrieval, and between serum VEGF concentration and Doppler blood flow velocities through-

out the IVF cycle³³. Quantification of the Doppler signal in PCOS using three-dimensional power Doppler ultrasonography was recently published by Pan *et al.*³⁴. These authors found that mean ovarian volume was significantly higher ($p < 0.05$) in women with PCOS compared with women with normal ovaries. The vascularization flow index (VFI), flow index (FI) and vascularization index (VI) were significantly higher ($p < 0.05$) in women with PCOS compared with women with normal ovaries. The authors concluded that this observation may help to explain the excessive response often seen during gonadotropin administration in women with PCOS³⁴. However, other investigators have concluded that polycystic ovaries are not associated with an inherent disturbance in blood flow dynamics of the uterine and ovarian arteries, as measured by color Doppler, and that an increased sensitivity of polycystic ovaries to

Figure 4 (a) Thickened endometrium during ovarian stimulation. (b, c) Multifollicular ovarian development in left and right ovaries accompanied by small quantities of free abdominal fluid. Courtesy Dr D Navot and Dr Z Levine, USA

Table 3 Secondary risk factors predicting OHSS

Serum estradiol > 3000 pg/ml at hCG injection

Serum estradiol > 800 pg/ml at day 9

Serum estradiol > 3354 pg/ml at day 11

> 20 follicles at the end of the follicular phase of COH with GnRH agonist

> 13 follicles at the end of the follicular phase of COH with GnRH antagonist

> 15 oocytes retrieved

hCG, human chorionic gonadotropin; COH, controlled ovarian hyperstimulation; GnRH, gonadotropin-releasing hormone

REFERENCES

1. Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. *Hum Reprod* 2002; 6: 559–77.
2. Navot D, Relou A, Birkenfeld A, et al. Risk factors and prognostic variables in the ovarian hyperstimulation syndrome. *Am J Obstet Gynecol* 1988; 159: 210–15.
3. Haning RV Jr, Austin CW, Carlson LH, et al. Plasma estradiol is superior to ultrasound and urinary estriol glucuronide as a predictor of ovarian hyperstimulation during induction of ovulation with menotropins. *Fertil Steril* 1983; 40: 31–6.
4. Crooke AC. Induction of ovulation with gonadotrophins. *Br Med Bull* 1970; 26: 17–21.
5. Diamond MP, Wentz AC. Ovulation induction with human menopausal gonadotropins. *Obstet Gynecol Surv* 1986; 41: 480–90.
6. Asch RH, Li HP, Balmaceda JP, et al. Severe ovarian hyperstimulation syndrome in assisted reproductive technology: definition of high risk groups. *Hum Reprod* 1991; 6: 1395–9.
7. Morris RS, Wong IL, Kirkman E, et al. Inhibition of ovarian-derived prorenin to angiotensin cascade in the treatment of ovarian hyperstimulation syndrome. *Hum Reprod* 1995; 10: 1355–8.
8. Mathur RS, Akande AV, Keay SD, et al. Distinction between early and late ovarian hyperstimulation syndrome. *Fertil Steril* 2000; 73: 901–7.
9. Delvigne A, Demoulin A, Smits J, et al. The ovarian hyperstimulation syndrome in in-vitro fertilization: a Belgian multicentric study. I. Clinical and biological features. *Hum Reprod* 1993; 8: 1353–60.
10. Ho H-Y, Lee RK, Lin MH, Hwu YM. Estradiol level on day 9 as a predictor of risk for ovarian hyperresponse during controlled ovarian hyper-

Table 4 Diagnostic criteria of complications of iatrogenic CHSSE

Complications	Diagnostic criteria
Torsion	Reactive or strenuous activity followed by extreme abdominal pain and nausea
Ovarian haemorrhage	Abdominal trauma or strenuous activity followed by severe abdominal pain, distension, hypotension, severe pallor, low Hb level and ultrasound scan
Thromboembolism which may be arterial or venous in various sites including upper and lower limbs, neck and intracerebral vessels	A possible positive family history of thrombosis and/or thrombophilias, signs depend upon sites of thromboembolism Usually presents between 7 and 10 weeks' gestation. Positive specific tests for blood hypercoagulability: MBS and MBSA
Hepatocellular and cholestatic disorders	Usually in third trimester Mild to moderate increase in AST and ALT May persist for > 2 months
Impaired renal function and azotemia	Oliguria or anuria Serum creatinine > 1.5 mg/dl Creatinine clearance < 150 ml/min Sodium < 135 mEq/l Potassium > 5.0 mEq/l Hyperkalemic acidosis
Temporary failure of transplanted kidney	Azotemia
Bilateral or unilateral hydropneumothorax	Chest tightness, dry cough and dyspnea Chest ultrasonography or chest X-ray
ARDS	Rapid respiratory insufficiency Chest X-ray or ultrasonography Blood gases assessment Lung function tests MBS and MBSA
Pulmonary embolism	Fever, dyspnea, wheeze and haemoptysis Chest X-ray, MBS and MBSA
Pericardial effusion	Supraventricular arrhythmias Echocardiography

ARDS, adult respiratory distress syndrome; Hb, haemoglobin; MBS, magnetic resonance imaging; MBSA, magnetic resonance angiography; AST, aspartate aminotransferase; ALT, alanine aminotransferase

artery presents with a picture of cerebral infarct. Deep vein thrombosis presents with pain and swelling of the leg.

Duplex Doppler ultrasonographic examination and magnetic resonance angiography of suspected occluded vessels based on the clinical manifestations will help in the diagnosis and initiation of treatment before the onset of serious complications.

Liver dysfunction

Liver dysfunction is a rare complication of severe OHSS. More recently it has been reported even in moderate OHSS^{39,65}. Both hepatocellular and cholestatic disorders were reported. Abnormal hepatic function has been increasingly recognized as a complication of severe OHSS that may persist for more than 2 months. Liver biopsy shows significant morphological abnormalities only at the ultrastructural level.

Midgley *et al.*⁶⁶ describe a case of recurrent cholestasis following OHSS during a twin pregnancy. On the first occasion cholestasis developed unusually in the first trimester, and on the second occasion it developed in the third trimester as usual. In a large prospective longitudinal study of 50 consecutive patients with ascites due to severe OHSS, Fabregues *et al.*⁶⁷ showed that 15 patients (30%) had abnormal liver tests characterized by a mild to moderate increase in aspartate aminotransferase (AST) (mean 103 ± 17.1 IU/l and alanine aminotransferase (ALT) (76 ± 8.3 IU/l), which was associated in some cases with an increase in γ -glutamyl transpeptidase or alkaline phosphatase. All abnormalities reverted to normal after resolution of the syndrome. The death of a patient, with an unrevealed history of hepatitis C, from hepatorenal failure following moderate OHSS has been reported by Serour *et al.*³⁹. Davis *et al.*⁶⁸ describe a case of severe OHSS with

Figure 1 Severe abdominal distension in a patient with severe OHSS. Picture taken on day 16 after embryo transfer. The patient was pregnant with twins. Courtesy Dr J Gerris, Belgium

Figure 2 Vulvar edema in a patient with OHSS. Courtesy Dr J J Amy, Belgium

Figure 3 Three subsequent images of thorax X-ray in the same patient, showing severe resolving and resolved hydrothorax. Courtesy Dr J Gerris, Belgium

15. Yordan Y, Cammash CD, Homborg S, et al. Spontaneous ovarian hyperstimulation syndrome and deep vein thromboses in pregnancy: case report. *Hum Reprod* 1999; 14: 2245–48.
16. He (Qing) C, Elm-Jori P, Sung-Hoon K, et al. Ovarian hyperstimulation syndrome complicating a spontaneous singleton pregnancy: case report. *J Assist Reprod Genet* 2000; 19: 190–3.
17. Zanel F, Fioristi R, Ben-Shefiel Z, et al. Recurrent spontaneous ovarian hyperstimulation syndrome associated with polycystic ovary syndrome. *Gynaecol Endocrinol* 1996; 9: 113–16.
18. Oltmannsmeier CH, Gölzhauf H, Hopewell JS, et al. Spontaneous ovarian hyperstimulation syndrome in three consecutive pregnancies. *Clin Exp Obstet Gynaecol* 1996; 23: 124–32.
19. Di Carlo C, Rocco PA, Cicillo G, et al. Increased concentration of oestrin, androstenedione and Ca^{25} in a case of spontaneous recurrent foetal loss: severe ovarian hyperstimulation syndrome. *Hum Reprod* 1992; 13: 2105–17.
20. Edi-Olegbe KDO, Hopkins MC. Recurrent idiopathic ovarian hyperstimulation syndrome in pregnancy. *Br J Obstet Gynaecol* 1982; 100: 959–61.
21. Dellacasa A, Simini G, Oltmannsmeier H, et al. New insights into the pathophysiology of ovarian hyperstimulation syndrome. What makes the difference between spontaneous and iatrogenic syndrome? *Hum Reprod* 2004; 19: 486–91.
22. Smith GL, Oltmannsmeier H, Dellacasa A, et al. Ovarian hyperstimulation syndrome due to a mutation in the follicle-stimulating hormone receptor. *N Engl J Med* 2003; 34: 2760–61.
23. Nazzari C, Montan P, Hsiao T, et al. A chimeric gonadotropin-sensitive mutation in the follicle-stimulating hormone receptor as a cause of familial gestational spontaneous ovarian hyperstimulation syndrome. *N Engl J Med* 2002; 34: 2752–61.
24. The Practice Committee of the American Society for Reproductive Medicine. Ovarian hyperstimulation syndrome. *Fertil Steril* 2000; 54: 1209–14.
25. Righesi PC. Severe OHSS: how many cases are preventable? *Hum Reprod* 2000; 15: 8–10.
26. Mitchell ST, Elchesser HA, Williams K. Ovarian hyperstimulation syndrome associated with clomiphene citrate. *West Indian Med J* 2000; 49: 327–9.
27. Sills JS, Najjar RA, Mowery M. Ovarian hyperstimulation and nephrotoxicity following accidental daily clomiphene citrate use over three consecutive months. *Bleed Thromb* 2000; 8: 540–3.
28. ESHRE Special interest group (SIG) guidelines on ovarian hyperstimulation syndrome (OHSS) 2005. <http://www.eshre.com/home>
29. Navot N, Reich RA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. *Fertil Steril* 1992; 58: 249–61.
30. Seaman GJ, Rhodes VC, Saitan M, et al. Complications of assisted reproductive techniques: a review. *Assist Reprod* 1990; 4: 214–22.
31. Mihalas JG III, Althos GF. The ovarian hyperstimulation syndrome. *Fertil Steril* 2000; 73: 483–96.
32. Persadli AP. The ovarian hyperstimulation syndrome (OHSS): definitions, clinical symptoms, classification and incidence. In: Cammash AP, Gnanapavan L, Tarleton BC, eds. *Ovarian Hyperstimulation Syndrome*. Series: Fertil Steril Series. Boston: Christchurch Press, 1992; 1: 1–101.
33. Ludwig M, Feldmann SB, Denney R, et al. Significant reduction of the incidence of ovarian hyperstimulation syndrome (OHSS) by using LH/LH antagonist octreotide (Octanide) in controlled ovarian stimulation for assisted reproduction. *Andr Gynaecol Obstet* 2000; 86: 29–31.
34. Aboulghar M, Mansour R, Seaman GJ, et al. Ovarian hyperstimulation syndrome: modern concepts in pathophysiology and management. *Andro Res Fertil Soc J* 1996; 1: 3–16.
35. Schacter JC. Prevention and treatment of ovarian hyperstimulation syndrome. *Hum Reprod* 1990; 16: 653–6.
36. Al-Khawaf T, Gudzinski J. Prevention and treatment of ovarian hyperstimulation syndrome. *Best Pract Res Clin Obstet Gynaecol* 2000; 14: 249–61.

to be 1/500 000. In reality, the true incidence could be significantly higher.

The only way to obtain a better idea of the true incidence is to strive towards prospective registration of all fertility treatments (ovulation induction, IUI, IVF/ICSI), as well as of their most important complications. This chapter aspires no more than to create the awareness that, in the long term, such registries are unavoidable. It is unacceptable that young women should die while being treated for a problem that, in one case out of two, is not theirs.

For the issue of multiple pregnancy, centers worldwide have come a long way in registering the incidence of this most frequent complication. Expressing the efficacy of a center by an indicator called CUSIDERA (cumulative singleton delivery rate) and its safety by another indicator called CUTWIDERA (cumulative twin delivery rate) could be one way of reporting multiples, as suggested by Germond *et al.*¹⁵.

In contrast, few countries ask their centers to report the incidence of OHSS, and if they do, lethal cases are not reported. Such reports could help in understanding the direct mechanisms of death as well as help in suggesting measures to prevent the death of these patients.

Moreover, before such a register of complications could have any usefulness (apart from creating unwanted reactions from an incompletely informed public), there must be unity of definition of OHSS, when it is mild, moderate and serious, and a guarantee of anonymity to avoid under-reporting. National and supranational registries, such as the American Society for Reproductive Medicine (ASRM), the European IVF Monitoring (EIM) program and the World Registry on assisted reproductive technologies (ART) should ask their accredited members to report all cases of severe OHSS and all cases of maternal mortality, whatever the cause of death.

Figure 1 Thrombi (arrowheads) in right arteria basilaris of patient who died of thromboembolic complications of OHSS. Courtesy of Dr R Bernardus, The Netherlands

ACKNOWLEDGMENTS

The authors thank Dr A Th Alberda, Sint Franciscus Gasthuis, Rotterdam; Dr D A Gietelink, Amphia Ziekenhuis, Breda, The Netherlands; and Dr M Camus, Center for Reproductive Medicine of the VUB, Brussels, for their contribution to the manuscript.

REFERENCES

1. Delvigne A. Request for information on unreported cases of severe ovarian hyperstimulation syndrome (OHSS) [Letter]. *Hum Reprod* 2005; 20: 2033.
2. Esteban-Altirriba J. Le syndrome d'hyperstimulation massive des ovaires. *Rev Fr Gynecol Obstet* 1961; 56: 555.
3. Figueroa-Casas P. Reaccion ovarica monstruosa a las gonadotrofinas a proposito de un caso fatal. *Ann Cirug* 1958; 23: 116.

- Low body weight*;
- Allergies*.

*Scientific evidence to confirm these factors is weak.

Criteria for defining a patient as being at risk of OHSS during stimulation for IVF

- Serum estradiol value > 3000/4000 pg/ml:
No clear cut-off value;
Poor predictive value (8–23%);
Not a mediator as OHSS possible with low estradiol;
The slope of the estradiol rise is the main risk factor and of more importance than the maximum estradiol value;
- Follicle numbers > 30–35 in both ovaries:
No clear cut-off value (10–35);
Variation due to operator and technique;
- Other predictors not used as routine:
Vascular endothelial growth factor (VEGF) > 200 pg/ml.

Clinical diagnosis and staging

Most common symptoms and signs.

Clinical symptoms

- Lower abdominal discomfort;
- Progressive increase in umbilical circumference;
- Nausea, vomiting;
- Dyspnea;
- Diarrhea;
- Respiratory distress;
- Rapid weight gain;
- Oliguria, anuria.

Paraclinical signs

- Enlarged ovaries;
- Ascites;
- Pleural effusion (right > left);
- Thromboembolism (especially from upper-body veins);
- Pericardiac effusion.

Hypercoagulability or thrombotic history;

Unconnected haemocoagulation after 48 h of the usual intravenous treatment.

Low-dose aspirin

For prevention of thrombotic complications;

Patient's value are immobilised because of obesity (not recommended if active bleeding).

Aspirin: contraindications

Abdominally or regionally;

Proposed: if patient discomfort is important, or systematically, or when biological anomalies are not corrected by the usual intravenous treatment (persistent haemocoagulation and/or renal failure).

Cardinal measure: 41 within 12 h;

Unconnected guidance recommended.

better and disseminate uniform guidelines for prevention and treatment. Most of these classification systems are based on the severity of the disease, which is in turn based on a combination of the severity of the patient's symptoms as well as severity of the physical, laboratory and radiological signs of the disease (Table 1). Five major schemes have been suggested to classify OHSS.

Robson (1967)

Although pregnant mare serum gonadotropin was used clinically as early as the 1930s to induce ovulation, the results of these early trials were disappointing. Gonadotropin treatments began to enter the clinical armamentarium in

1958, when a combination of follicle stimulating hormone derived from cadaveric human pituitary glands and human chorionic gonadotropin (hCG) successfully induced ovulation and pregnancy². With the use of these agents, and with the later introduction of clomiphene citrate³ and human menopausal gonadotropins⁴, experience with the spectrum of ovarian hyperstimulation syndrome unfortunately grew.

The original classification, suggested by Robson et al. in 1967¹⁰, categorises the syndrome into six grades by levels of increasing severity. Grade 1 disease is defined by the presence of supraphysiological levels of estradiol and progesterone, as measured by 24-hourly excretion greater than 150 µg and 10 µg, respectively.

Table 1. Classification of OHSS

Mild	Moderate	Severe	Critical ^a
Bloating	Perilting	Massive ascites	Tense ascites
Nausea	Abdominal pain	Hypotension	Hypovolaemia
Abdominal distension	US evidence of ascites	Hct > 45%	Pericardial effusion
Ovaries ≤ 5 cm	Hct > 40%	WBC > 15 000/mm ³	Hct > 55%
	WBC > 10 000/mm ³	Oliguria	WBC > 25 000/mm ³
	Ovaries > 5 cm	Oestrogens 1–1.5 mg/dl	Oliguria or anuria
		Oestrogens clearance ≥ 50 ml/min	Oestrogens > 1.5 mg/dl
		Hepatic dysfunction	Oestrogens clearance < 50 ml/min
		Azosaemia	Renal failure
		Ovaries variably enlarged	Thromboembolic phenomena
			ARDS
			Ovaries variably enlarged

US, ultrasound; Hct, haematocrit; WBC, white blood cell count; ARDS, adult respiratory distress syndrome

Grade 2 adds to these laboratory measurements the presence of enlarged ovaries and, questionably, palpable cysts. Interestingly, Kaban did not define grades 1 and 2 as OHSS at all, and felt that these grades were expected by-products of ovarian stimulation and required no attention or treatment.

In the Kaban classification system, grade 3 disease adds the presence of abdominal distension and definitively palpable ovarian cysts, and grade 4 includes vomiting and possibly diarrhea. ¹⁰ Kaban, patients with grades 3 and 4 OHSS are at possible risk for future worsening and complications, and require observation but no intervention. Grades 5 and 6, in this system, require hospitalization with aggressive observation and intervention. Grade 5 is defined by fluid shifts and fluid spacing leading to ascites and hyothorax, and grade 6 is defined by hematological changes in blood volume, blood viscosity and coagulation time.

Schenker (1978)

Schenker and Weinstein¹¹ modified the Kaban classification system to group the grades into a less cumbersome mild/moderate/severe terminology, but maintained the grading system as well. In the Schenker scheme, grades 1 and 2 are termed mild OHSS, and include the same definitions: urinary excretion of estradiol and progesterone for grade 1, and enlarged ovaries with small cysts for grade 2. Grades 3 and 4 are termed moderate OHSS, and include abdominal distension for grade 3, and nausea, vomiting and/or diarrhea for grade 4. Grades 5 and 6 are defined as severe disease, including large ovarian cysts and ascites and/or hyothorax for grade 5, and haemoconcentration, increased blood viscosity and coagulation changes for grade 6.

Golan (1988)

While the Kaban and Schenker classification systems seemed at the time to be comprehensive,

they suffer from several drawbacks. First, they focus more on ovarian response, particularly in the lower grades of the disease, than on the clinical syndrome. Second, they are difficult to incorporate into the clinical setting, as 24-h urinary hormones are not routinely measured. Third, they incorporate unnecessarily cumbersome subdivisions; simple classification as mild, moderate and severe OHSS would be adequately descriptive and more clinically useful. Finally, these schemes were developed through observation of women undergoing ovulation induction. More recently, with the evolution of assisted reproductive technologies (ART) and routine use of controlled ovarian hyperstimulation (COH) in ART patients, the laboratory and clinical findings in the lower grades of the Kaban and Schenker classifications are routinely observed and may reflect not a syndrome but an acknowledgment that COH has indeed been achieved. Therefore, there was a need for a simpler, more clinically useful and more relevant system.

Golan et al. in 1989¹² attempted such a revision of these older systems by classifying OHSS into mild, moderate and severe, eliminating hormone measurements from the system, and including in the mild category clinical symptoms previously classified as moderate disease prior to the days of routine COH for ART. Golan institutes a grading scheme, defining grades 1 and 2 as mild OHSS, grade 3 as moderate OHSS and grades 4 and 5 as severe OHSS. In the mild category, grade 1 includes abdominal discomfort and distension, and grade 2 adds enlarged ovaries to 5–10 cm and nausea, vomiting and/or diarrhea. For moderate OHSS, Golan introduces the use of ultrasound, defining ultrasound evidence of ascites as grade 3, even if the degree of ascites is not detectable clinically. Severe OHSS features respiratory symptoms such as dyspnea and tachypnea and clinical evidence of ascites and/or hyothorax as grade 4, and haemoconcentration, oliguria, increased blood viscosity, coagulation abnormalities, hypotension, and

serum oestradial levels dropped to $<3000\text{ ng/ml}$ and follicles with a diameter $\geq 18\text{ mm}$ were present.²⁰

We used the criteria of Golan et al. to classify OHSS.²¹ According to these criteria, patients with moderate to severe OHSS requiring bedrest or admission to hospital were marked in our database.

Student's *t* test was used to evaluate statistical differences between continuous variables. *P* values < 0.05 were considered significant. Confidence interval analysis was performed to compare the incidence of OHSS in singleton versus twin conception cycles.

Evaluation of pregnancy rate, multiple pregnancy rate and incidence of OHSS

Over this 7-year period, 44 cases of OHSS occurred in 5833 cycles (1.52%). The incidence of ovarian hyperstimulation syndrome was

fairly stable over this period, varying between 0.5 and 2.4% with an average of 1.52% per cycle. The effect of the evolution of implementation of SET on the ongoing pregnancy rate, the multiple pregnancy rate and the incidence of OHSS is shown in Figure 1. Of the 44 cases of OHSS, eight cases occurred in a non-conception cycle during the first week after oocyte retrieval. Thirty-six cases of OHSS occurred in 3065 non-conception cycles (4.0%). There were 50 cases in 757 singleton conception cycles (6.1%) and six cases in 157 twin pregnancy cycles (3.8%) (odds ratio 1.06, 95% confidence interval 0.44–2.64).

Analysis of cycle-related variables

We analyzed cycle-related variables in non-conception cycles (early OHSS) and conception cycles (late OHSS). In the latter group a comparison was made between singleton and twin pregnancies. A total of 48 cases were analyzed (four cases from 2005 were also included).

Figure 1 Evolution of pregnancy rate, multiple pregnancy rate and incidence of OHSS

CHAPTER 9

Pathophysiology of the ovarian hyperstimulation syndrome

Annick Delwigne

INTRODUCTION

The ovarian hyperstimulation syndrome (OHSS) is characterized by an increase in size of the ovaries, with the appearance of multiple cysts, and by an increase in the vascular permeability of ovarian vessels causing ascites, pleural effusion, and sometimes pericardiac effusion. The severe form is also accompanied by electrolyte disturbances, as well as by cardiopulmonary, hepatic, renal and hemodynamic disturbances, leading to an increased thromboembolic risk. The dominant finding is bilateral multicystic enlargement of the ovaries. Ultrapathological examination of these ovaries reveals multiple corpora lutea, follicle cysts and massive edema of the ovarian stroma. It has been suggested that formation of the cysts is a direct reaction to stimulation with gonadotropins, since similar ovarian observations exist in other conditions associated with high levels of endogenous gonadotropins such as hydatidiform mole, choriocarcinoma and multiple pregnancy.

Animal experiments have shown that the main pathological feature of OHSS is an increase in capillary permeability, as demonstrated in a rabbit experimental model using intravenous dyes¹. Furthermore, angiogenesis is

also enhanced in OHSS. It has been demonstrated in animals that the amount of fluid shifting from the intravascular space into the abdominal cavity depends on the presence of the ovaries. The latter, however, do not have to be in the peritoneal cavity². Neither estrogen nor a progestin in excessive amounts caused ascites in female rabbits³. Moreover, OHSS cannot be induced in male animals or in mice treated with large doses of gonadotropins.

Consequently, the following principles can be considered as established: first, the presence of an ovary is a prerequisite condition for OHSS; second, a vasoactive mediator secreted by the ovaries plays a major role in the development of OHSS, after ovarian stimulation. This factor is probably secreted into the peritoneal cavity and liberated in the systemic circulation where it can exert its action.

Some investigators have hypothesized that ascites in women with OHSS contains this chemical ovarian product responsible for OHSS. This hypothesis has been confirmed by *in vitro* permeability experiments, using follicular fluid and ascites of patients suffering from OHSS⁴.

Subsequently, much research has been directed toward identifying this mediator either in the blood or in the ascites of patients with

production enhances vWF concentrations. The increased vWF on the day of embryo transfer has been shown to be related to the severity of OHSS, and an elevation of vWF precedes the clinical manifestations in severe OHSS². This increase has not been observed in follicular fluid, suggesting that vWF is not produced by the ovary. vWF may be of endothelial origin and influenced by vasoactive ovarian factors. Higher plasma levels of vWF in OHSS patients compared with high responders on the day preceding oocyte retrieval lasted until after embryo transfer and were maintained well into the late luteal phase². In high responders without OHSS, the levels of vWF also increased during the pre-ovulatory phase, but decreased from the day of oocyte retrieval onward. Subsiding levels of vWF in patients with severe OHSS indicate improvement of the disease. This test might become clinically useful as an additional "discriminating parameter" or "prognostic marker". It is likely that vWF plays a role in the cascade that leads to OHSS, but suffers as a consequence of the activation of endothelial cells by a factor of ovarian origin, thus as its causal factor.

Endothelin-1, another vasoconstrictor that increases capillary permeability, was found to be 100–200-fold higher in follicular fluid than in plasma. In OHSS patients, serum endothelin-1 level is elevated but in parallel with other neuroendocrine vasoactive factors, and without correlation with the OHSS grading, suggesting a homeostatic response rather than an initiating role in OHSS⁴.

Contribution of neuroendocrine and hemodynamic changes to arteriolar vasodilatation

Palacki et al. evaluated systemic, endogenous vasoactive neuroendocrine factors in severe OHSS during the appearance of the syndrome for a period of 4–5 weeks⁹. The authors recorded increased hematocrit, decreased mean arterial pressure, increased cardiac output and reduced

peripheral vascular resistance. This was accompanied by marked increases in plasma renin, norepinephrine, antidiuretic hormone (ADH) and atrial natriuretic peptide levels. The authors compared previous results in women with and without hyperconcentration: similar values were observed except for renin, norepinephrine and ADH, which were found to be higher in OHSS patients. These observations suggest that OHSS is associated with arteriolar vasodilatation. Indeed, if circulatory dysfunction were to be due solely to an extravascular shift, contraction of the circulating blood volume should induce a reduction in cardiac output, an increase in peripheral vascular resistance and a decrease in atrial natriuretic peptide. In contrast, cardiac output and atrial natriuretic peptide are increased and peripheral vascular resistance is markedly reduced, indicating a marked peripheral arteriolar vasodilatation. The simultaneous occurrence of these disorders leads to hyperdynamic circulatory dysfunction, with marked stimulation of the sympathetic nervous system, renin-angiotensin system and ADH.

Exorcisman et al. observed an alteration of osmoregulation during OHSS, with an excretory threshold for arginine vasopressin secretion that is reset to lower plasma osmolality during superovulation¹⁰. This means, however, body tonicity is maintained in OHSS patients until at least 10 days after the administration of hCG. These authors suggest that a decrease in plasma osmolality and plasma sodium levels is due to altered osmoregulation rather than to electrolyte losses.

CONCLUSION (Figure 1)

The main hypothesis concerning the development of OHSS is that regulation of the inflammation-like evolution process is disturbed. This leads to overproduction of local proinflammatory factors in the ovary. In turn, this results in secondarily increased capillary leakage and transmission of inflammatory mediators to other

Figure 1 Pathophysiology of OHSS. TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VEGFR-1, VEGF receptor-1; RAS, prorenin–renin–angiotensin system; vWF, von Willebrand factor

Figure 2 (a) Images of cut surface of ovary of OHSS patient and (b) edema of the alveoli of the lungs of same patient. Reproduced from reference 11, with permission

compartments. In the most severe form of OHSS, this process also leads to systemic manifestations.

In addition to the shift of fluid to extravascular spaces, OHSS is consistently associated with marked arteriolar vasodilatation.

Figure 1 Schematic representation of the follicle stimulating hormone (FSH) receptor with locations of the D567N/G and T449I/A mutations (gray circles) identified in patients presenting spontaneous OHSS. The locations of polymorphisms T307A and N680S of the FSH receptor are represented by black triangles

Figure 2 Functional characteristics of the four follicle stimulating hormone (FSH) mutant receptors identified in patients presenting spontaneous OHSS. Levels of cyclic adenosine monophosphate (cAMP) observed using COS-7 cells transfected with wild-type human FSH receptor (wt hFSHr), D567N, D567G mutants (a) and T449I, T449A mutants (b) after stimulation with recombinant human (rh) FSH (10 IU/ml) and increasing concentrations of recombinant human chorionic gonadotropin (rhCG) (100–300 IU/ml). Each graph represents the mean $\pm$ SEM of at least two separate experiments

Future work should aim to identify susceptibility genes in the development of iatrogenic OHSS. The individual response to controlled ovarian hyperstimulation is most likely a polygenic trait, as recently suggested by de Castro et al., who provided evidence of genetic interactions between the PSEI receptor and estrogen receptors α and β genes in relation to controlled ovarian hyperstimulation outcome²⁹. The genetic background of the patient probably also plays a role in susceptibility to the increase of vascular permeability. Two clinical entities have been described in iatrogenic OHSS: early forms occurring 3–7 days after triggering of ovulation by hCG, and late forms developing 12–17 days after ovulation in close association with an initiated pregnancy^{30,31}. The early pattern is related to an excessive response to gonadotropin stimulation, while the late pattern is more likely to be severe and is induced by endogenous hCG in conception cycles. Although the clinical sequences of the syndrome are very similar in both forms, it is possible that susceptibility to one or the other form differs between both patterns: in the early form, the genetic background of the patient could influence the ovarian hyper-response to exogenous PSEI, while in the late form, it would be more implicated in stimulation of the corpus lutea by hCG. OHSS can indeed be viewed as a tremendous exaggeration of the local inflammatory-like reactions which accompany angiogenesis during corpus luteum formation in a normal menstrual cycle, with a massive release of vasoactive molecules such as vascular endothelial growth factor^{32,33}, angiotensin II^{34,35} and various interleukins²⁸. As the release of these molecules reaches a threshold, physiological control mechanisms can be overstretched, leading to development of the symptoms of the syndrome. The respective genes of these vasoactive molecules could also constitute candidate susceptibility genes in the development of iatrogenic OHSS. These association studies will require large series of patients, which will most probably only be obtained

through multicentric studies. The identification of patients susceptible to elicit a hyperresponse to standard stimulation treatments would allow adaptation of their treatment and avoidance, if not completely at least to a large extent, of OHSS, which remains a frequent and potentially life-threatening complication of IVF.

ACKNOWLEDGMENTS

We thank members of the Laboratory of Research in Human Reproduction and of the Institut de Recherches Interdisciplinaires en Biologie Humaine et Moléculaire (IRBHM) for helpful support and discussion.

REFERENCES

1. Zaki N, Chvicko E, Ben-Rafael Z, et al. Recurrent spontaneous ovarian hyperstimulation syndrome associated with polycystic ovary syndrome. *Gynecol Endocrinol* 1995; 9: 310–15.
2. Okturkbasan OA, Gilliland E, Eryilmaz LH, et al. Spontaneous ovarian hyperstimulation syndrome in four consecutive pregnancies. *Clin Exp Obstet Gynecol* 1996; 23: 123–24.
3. Ekl-Kragle M, Hopkins BE. Recurrent idiopathic ovarian hyperstimulation syndrome in pregnancy. *Br J Obstet Gynaecol* 1987; 104: 382–4.
4. De Carlo C, Erone P, Ciniello D, et al. Increased concentrations of neurotrophins and Ca²⁺ in a case of spontaneous, recurrent, familial, severe ovarian hyperstimulation syndrome. *Hum Reprod* 1997; 12: 3115–17.
5. Ludwig M, Gembrecht C, Buser O, et al. Ovarian hyperstimulation syndrome (OHSS) in a spontaneous pregnancy with fetal and placental triploidy: information about the general pathophysiology of OHSS. *Hum Reprod* 1995; 10: 3082–87.
6. Nagai EC, Di Mario R, Davies AP, et al. Natural pregnancy in hypothyroid women complicated

Figure 1 Vascular permeability in three groups of animals injected with saline during 5 consecutive days (control group), 10 IU pregnant mare's serum gonadotropin (PMSG group) or PMSG and 10 IU human chorionic gonadotropin (hCG) (OHSS group). EB, Evans blue

results of these experiments showed that in narrow correlation to vascular permeability (Figure 1), ovarian mRNA VEGF expression increased during the time course, reaching peak values after 48 h, whereas no significant change in expression was observed in the mesentery (Figure 2). To demonstrate further the ovarian origin of VEGF, we showed that vascular permeability was not altered when ovariectomized rats were treated with PMSG + hCG⁴¹.

In addition, we also analyzed which of the VEGF isoforms were expressed by the ovaries of hyperstimulated animals with specific primers for conventional RT-PCR. The ovary expressed VEGF₁₂₀ and VEGF₁₆₄ isoforms. We showed that there was also an increase of VEGFR-2 expression in the ovaries, coincidental in time with

maximal vascular permeability⁴², demonstrating the involvement of the VEGF/VEGFR-2 system in OHSS. Immunohistochemistry showed VEGF in granulosa and in the zona pellucida of preovulatory and atretic follicles, and in granulosa-lutein and endothelial cells of whole corpus luteum^{41,42}.

In summary, these experiments showed that the VEGF system (ligand and receptor 2) is up-regulated in the ovaries of hyperstimulated animals, coincidental in time with maximal vascular permeability, clearly suggesting a crucial role for locally (ovary)-produced VEGF in OHSS. Although VEGF measurements in the serum/plasma of these animals would have provided us with more evidence to confirm the role of VEGF in OHSS, unfortunately VEGF

Figure 2 Vascular endothelial growth factor (VEGF) mRNA expression in ovary and mesentery of OHSS animals. Adapted from reference 41. hCG, human chorionic gonadotropin

measurements in the serum of these animals were (are) in all cases below the limit of detection of the most sensitive enzyme-linked immunosorbent assay (ELISA) kits used.

Prevention of development of OHSS by interference with VEGF pathway

After the role of VEGF in establishing vascular permeability was demonstrated, a series of blocking experiments was designed through the administration of SU5416, a VEGFR-2 inhibitor, as a new strategy to prevent and treat OHSS by inhibiting an increase of vascular permeability. Since this was a totally new concept, primarily designed to be employed as an antiangiogenic approach in cancer patients, we attempted several protocols of SU5416 administration in order

to block iVP in our OHSS animal models. We found that SU5416 should be administered after hCG, with a single injection of hCG being as effective as multiple injections⁴¹ (Figure 3). The reasons for this behavior can be found in the observation that the syndrome develops only during corpus luteum formation after the ovulation process.

In any case, the ability to reverse hCG action on vascular permeability by targeting the VEGFR-2 employing SU5416 not only confirmed the key role of VEGF in OHSS, but also provided new insights into the development of strategies to prevent and treat the syndrome based on its pathophysiological mechanism, rather than using empirical approaches as we do today. In fact, tumor growth, neoangiogenesis

Figure 3 Reversal of increased vascular permeability employing SU5416 (48 h after human chorionic gonadotropin (hCG) administration). Adapted from reference 41. EB, Evans blue; q24, injection of SU5416 every 24 h; q48, injection of SU5416 every 48 h; hCG, injection of SU5416 just after hCG administration

and ascites formation have been prevented in animals with different ovarian neoplasms by targeting the VEGF system^{43,44}, and specifically the Flk-1 receptor with SU5416⁴⁵. Herein, we present evidence that the same approach can be used in the OHSS model.

Gene expression in hyperstimulated ovaries

In the previous experiments, we showed that inhibition of VEGF action was accompanied by reduced vascular permeability. However, the use of such strategies employing antiangiogenic drugs (in cancer patients) has been abandoned in women due to side-effects of these compounds^{46–48}. Aiming to find a specific non-toxic treatment for OHSS, we reverted to our hypothesis utilizing microarray technology in order to investigate all the genes potentially involved in

the development of OHSS. We looked at the expression of gene products regulated under OHSS conditions. This approach resulted in the development of new approaches to block the onset of the syndrome by employing dopamine agonists.

Microarray technology has become one of the most powerful techniques to check, in a single experiment, all the possible genes which are up- or down-regulated under the effects of administration of one or several compounds. We compared ovarian gene expression in animals subjected to different regimens of gonadotropins, including control animals and stimulated rats developing OHSS⁴⁹. Forty-eight hours after hCG, vascular permeability was measured, and mRNA from ovaries extracted to perform gene expression profiles in microarray filters containing 14 000 genes. In the microarray

Figure 4 Reversal of increased vascular permeability with bromocriptine (Br2) in rat OHSS model. EB, Evans blue

chemical nature of these drugs and not to the molecular mechanism. Levels of VEGFR-2 phosphorylation in the ovaries of OHSS animals before and after the administration of dopamine agonists are currently being studied. If dopamine agonists are really able to block VEGFR-2 phosphorylation, the next question would be: what is their molecular mechanism of action? We do not know whether dopamine agonists block iVP by competing with VEGF for VEGFR-2 binding, if they directly affect VEGFR-2 conformation or whether these effects are mediated through binding to their own dopamine receptors. As this is a new area of research, more studies are needed in order to elucidate this question.

THE ROLE OF VEGF IN OTHER STRATEGIES USED TO REDUCE OHSS INCIDENCE

Although based on an empirical approach, some clinical strategies developed to reduce the inci-

dence of OHSS, e.g. using different hormones to trigger ovulation, or coasting, have been successful in achieving this purpose. Here, we focus on recent data providing evidence that the effectiveness of both of these approaches is at least partially related to targeting the VEGF system. The rationale for using LH as a trigger for ovulation by reducing VEGF levels and, hence, OHSS is provided by studies performed on OHSS in animal models. Findings regarding the role of VEGF in coasting were made in OHSS patients.

Using hormones other than hCG to trigger ovulation: studies in an animal model

In many mammalian species, including humans, the mid-cycle surge of luteinizing hormone (LH) initiates a series of events included under the term ovulation, comprising oocyte maturation, follicular rupture and luteinization of granulosa and theca cells. The LH surge is accompanied by a follicle stimulating hormone

Figure 5 Number of oocytes recovered, vascular permeability and VEGF expression after using different hormones to trigger ovulation. EB, Evans blue; hCG, human chorionic gonadotropin; PMSG, pregnant mare's serum gonadotropin; FSH, follicle stimulating hormone; LH-10, 10 IU luteinizing hormone; LH-60, 60 IU LH

OHSS in women undergoing controlled ovarian stimulation (COS);

- (2) To investigate the mechanism by which coasting may act, hypothesizing the possibility that coasting acts through VEGF regulation;
- (3) To determine which follicle population is more likely to be affected by coasting.

A total of 160 women (patients and oocyte donors) undergoing coasting and 116 controls were included in the study. Serum, follicular fluid and granulosa cells were collected on the day of oocyte retrieval. VEGF concentrations were determined using ELISA. Real-time PCR was performed to evaluate VEGF gene expression in granulosa cells. Cell death was studied by flow cytometry⁶⁶.

Follicular cells aspirated from coated patients showed a ratio in favor of apoptosis, especially in smaller follicles (48 vs. 26%, $p < 0.05$). Follicular fluid determinations

confirmed that coating reduces VEGF protein secretion (1413 vs. 3538 pg/ml, $p < 0.001$) and gene expression (two-fold decrease) in granulosa cells (Figure 6). Follicular fluid VEGF

Figure 6 The vascular endothelial growth factor/glyceraldehyde-3-phosphate dehydrogenase (VEGF/GAPDH) ratio was used to compare VEGF expression between coated and non-coated patients. (a) Typical logarithmic curve observed during PCR amplification. At the beginning of the reaction increases in cDNA expression are linear (log-linear phase), so quantification is performed during this phase. When the reaction becomes saturated, quantification cannot be performed accurately (non-log-linear phase) as products are overexpressed. (b) Temperature of melting (TM) for the GAPDH and VEGF cDNA PCR products in the fusion curve. As the temperature increases, double DNA strings separate and the dye intercalated between them can be measured. The maximum dye expression coincides with TM which is characteristic for each PCR product. As observed a single peak means that only the one expected product was amplified. (c) VEGF levels are expressed as the VEGF/GAPDH ratio, where GAPDH expression is used to normalize results, so VEGF expression could be compared at the same level. * $p < 0.05$

Figure 7 Measurements of free vascular endothelial growth factor (VEGF) and ratios of free VEGF/ α_2 -macroglobulin (A2M) and free VEGF/total VEGF in non-risk, risk without and risk with OHSS during the time course, 0, 3, 6, 10 and 14 (pregnancy test) days after oocyte retrieval. * $p < 0.05$

REFERENCES

1. Pellicer A, Albert C, Mercader A, et al. The pathogenesis of ovarian hyperstimulation syndrome: in vivo studies investigating the role of interleukin-1, interleukin-6, and vascular endothelial growth factor. *Fertil Steril* 1999; 71: 482-9.
2. Schenker JG, Weinstein D. Ovarian hyperstimulation syndrome: a current survey. *Fertil Steril* 1978; 30: 255-68.
3. Knox GE. Antihistamine blockade of the ovarian hyperstimulation syndrome. *Am J Obstet Gynecol* 1974; 118: 992-4.
4. Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive

Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Figure 2 The management and clinical course of a polycystic ovarian disease (PCOD) patient post-ovulation induction, presenting with late onset of severe OHSS. y, years; hMG, human menopausal gonadotropin; hCG, human chorionic gonadotropin; d, days; Hb, hemoglobin; HT, hematocrit; w, weeks

Figure 3 The management and clinical course of a patient who underwent *in vitro* fertilization–intracytoplasmic sperm injection (IVF–ICSI) treatment and was admitted with early onset of OHSS. She conceived; however, the pregnancy terminated with a missed abortion. See Figure 2 for definitions

reported in 1995 in a small group of in vitro fertilisation patients. In that report, no cycles were cancelled, none of the patients developed severe OHSS and pregnancy rates were reported as high²⁴. Other centers had similar experiences and did not find an adverse effect on in vitro fertilisation cycle parameters²⁵.

Lee et al., however, in a much larger study, did not find equivalent results²⁶. Four out of 20 women treated by coasting still developed OHSS. Multiple regression analysis determined that other factors were more likely to be responsible for the better outcomes in those patients who did not develop OHSS.

One problem with these studies is the lack of uniformity in how coasting was performed. The time point in the cycle at which coasting was to be started and the duration of coasting varied significantly. A Cochrane review concluded that insufficient evidence existed to permit the recommendation of coasting as a valid means to reduce the risk of OHSS²⁷. The most recent data also suggest that coasting is associated with a significant incidence of premature luteinisation and, if needed for more than 4 days, that the implantation rate is reduced²⁸.

TREATMENT BY OVER-HYDRATION AND ASPIRATION

A number of authors have advocated the use of extensive fluid hydration combined with paracentesis for the treatment of OHSS and ascites. There are two underlying theories for the use of over-hydration. The first recognises the fact that thromboembolic phenomena have been responsible for the majority of fatal complications of OHSS, and can be responsible for significant morbidity such as stroke or pulmonary embolus²⁹. By hydrating the patient, it is hoped that this will maintain intravascular volume, reduce haemoconcentration and therefore lessen the chance for thrombosis. In addition, maine-

tenance of intravascular volume may improve renal perfusion and assist with natural diuresis.

However, due to the increased vascular permeability, a significant amount of the fluid given for hydration will leave the intravascular space and increase the ascites, thus necessitating paracentesis. Aspiration of the ascitic fluid by paracentesis provides some immediate relief to the patient. It is also hoped that decreasing the intra-abdominal pressure will increase venous return to the heart and improve renal perfusion and ultimately speed the resolution process.

Edaru et al. were the first to propose abdominal paracentesis for the treatment of OHSS³⁰. Later, transvaginal ultrasound guided paracentesis was found to be an acceptable alternative³¹.

Protocol for management of OHSS with over-hydration and paracentesis³²

- [1] Patients are advised to maintain a fluid intake of 1000–1500 ml daily;
- [2] Patients are instructed to contact the nursing staff if they experience an increase in abdominal girth of more than 1–2 cm, weight gain of > 1 kg in 24 h, shortness of breath, nausea, vomiting, diarrhea, or a subjective decrease in urine output;
- [3] Patients reporting these signs or symptoms undergo blood evaluations and are instructed to increase fluid by 500 ml/day if haemoconcentration is observed;
- [4] The patients then undergo transvaginal ultrasound-guided paracentesis with drainage of ascites fluid.

A typical hydration/aspiration protocol of the type used by many American infertility programs is given above. Many authors have published case series with various modifications of this protocol. In addition to vigorous oral hydration, Alkoulthas et al. advocated intensive intravenous hydration to reduce

- (5) Anti-emetics for nausea (Zofran ODT[®] 8mg every 8h as needed);
- (6) If hemoglobin is $>15\text{ g/dL}$, start Dosemod[®] 40mg every day;
- (7) Patient to measure input and output every day and phone the results to the office;
- (8) Patient also to call the office if she has any of the following:
 - (a) Sudden weight gain;
 - (b) Shortness of breath;
 - (c) Brain resistant to medication;
 - (d) Nausea resistant to medication or emesis.

Am-patient management

- (1) Dextrose 5% in half normal saline (D50/4.5NS) + 10mEq/L KCl to match urine output;
- (2) 250ml of salt-poor (25% albumin) intravenously over 2h;
- (3) Upon completion of albumin drip, administer furosemide 20mg intravenous push;
- (4) If patient has persistent oliguria, start renal-dose dopamine (2-3mg/kg/min);
- (5) Paracentesis reserved for refractory tense ascites or severe dyspnea.

Hydroxyethyl starch

Hydroxyethyl starch is a highly branched anglican that resembles glycogen. Its molecular weight ranges from 200 to 1000kDa. At that size, it is potentially large enough to avoid leaking out of the vasculature. Abramson et al. compared the use of 6% hydroxyethyl starch solution with use of albumin in 16 patients with severe CHSS²². Eighty percent of patients in the albumin group required paracentesis compared with only 32% in the starch group. Hospital stay

averaged 3 days less in the starch group. Levin et al. used a 10% solution and also showed efficacy²³. Dextran 40 has also been used as a plasma expander in the treatment of CHSS. Compared with 25% albumin, dextran 40-treated patients had less time to resolution of hemocoagulation without affecting the pregnancy or miscarriage rate²⁴. The potential advantages of synthetic colloid expanders in the treatment of CHSS include lower cost and lower risk for infection compared with the blood-derived albumin. In theory they may be more effective, since their size would limit their leakage out of the vasculature.

Dopamine

Dopamine is also an effective treatment for CHSS by virtue of its ability, at low doses, to effect dilatation of the renal vasculature, improve renal blood flow and thereby promote diuresis. Ferranti et al. were the first to report the use of intravenous dopamine for the treatment of CHSS²⁵. We also reported a series of patients successfully treated in this way²⁶.

One problem with dopamine is that it must be given intravenously. Although low-dose dopamine has a vasodilatory effect in selected tissues, high concentrations achieved locally as a result of intravenous (IV) site extravasation can still cause severe vasoconstriction and ischemic tissue injury. Because of this risk, most hospitals restrict by protocol the use of IV dopamine to an intensive-care setting with a higher nurse/patient ratio, so that the IV sites can be monitored more closely. This, of course, dramatically increases the cost of treatment. Treatment consists of the administration of subcutaneous phentolamine into the area of ischemia. Typically, dramatic resolution of ischemic changes rapidly follows phentolamine injection with no untoward effects.

Turnock et al. reported the use of a novel dopamine derivative for the treatment of CHSS²⁷. Decarpanine is a synthetic, orally

Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Table 4 Characteristics of repeated out-patient paracentesis in 53 women with late-onset ovarian hyperstimulation syndrome (OHSS) (July 1987–July 2004)

	Number	Elapsed days	Volume drained ^a (ml)	Colloid ^a administration ^a
First paracentesis	53	17.6 ± 3.9 days post-hCG	1941 ± 706	3853 (73%)
Second paracentesis	23	3.1 ± 1.7 days later	3245 ± 930	3033 (93%)
Third paracentesis	11	4.2 ± 2.3 days later	2458 ± 1279	511 (45%)
Fourth or more	6	5.3 ± 2.9 days later	2110 ± 745	293 (33%)

^a250ml of 25% albumin or 500ml of 10% hydroxyethyl starch

colloid products⁵. Preliminary evidence suggests that colloid alternatives such as hydroxyethyl starch may be equally effective^{20–22}. Since late 2001, it has been our practice to administer 500ml of 10% hydroxyethyl starch to most patients undergoing their first paracentesis, and as needed for subsequent procedures if urine output has been marginal despite appropriate fluid intake (Table 4). The administration of more than 1500ml hydroxyethyl starch in a 24-h period has been associated with bleeding complications²³.

Anticoagulation

Correction of hemoconcentration is probably the single most important step in reducing the risk of thromboembolism²⁴. Gentle mobilization, leg exercises and CUP (anticoagulant) stockings are also helpful, and are easy to incorporate in an out-patient management routine. The thromboembolic risks that accompany immobility are intuitively much higher in hospitalized patients confined to bed with an intravenous line and an indwelling urinary catheter than they are in women following a regimen of rest and limited activities at home.

The role of subcutaneous heparin remains controversial; some authors use it routinely in hospitalized patients, while others reserve it for those with abnormal coagulation parameters, or

a suspicious personal or family history²⁵. It has not been our practice to anticoagulate patients unless they have a positive history for thromboembolism. The sole thrombotic episode in the series described in Table 5 involved an axillary vein thrombosis more than 3 weeks after clinical resolution of the OHSS. The woman was subsequently found to have a thrombophilic disorder.

RESULTS OF OUT-PATIENT MANAGEMENT OF OHSS

During a 17-year period (July 1987–July 2004) we performed more than 4300 IVF cycles and identified 58 patients (0.4%) who developed moderate to severe OHSS and required drainage of ascitic fluid. Two of these 58 women were managed outside our standard protocol; one woman required a sole thoracentesis in a local hospital out-patient clinic, and one woman was hospitalized at a distant center for albumin and paracentesis because it was not feasible for her to travel to us for management. Both were pregnant and delivered healthy singleton and triplet pregnancies, respectively.

The remaining 56 women underwent at least one out-patient paracentesis in our free-standing clinic and are summarized in Table 5. Of these, two women were hospitalized briefly to

Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

165. Thirumaru K, Searle T, Quinn A, et al. The value of routine estradiol monitoring in assisted conception cycles. *Acta Obstet Gynecol (Scand)* 2002; 81: 521-4.
166. Aloubayse WL. Prediction of ovarian hyperstimulation syndrome (OHSS). Estradiol level has an important role in the prediction of OHSS. *Hum Reprod* 2002; 17: 1140-1.
167. The ESHERE Group Workshop. Infertility revisited: the state of the art today and tomorrow. *Hum Reprod* 1996; 11: 1793-807.
168. Ufanga A, Davies B, Salek E, et al. Value of the serum estradiol level for predicting ovarian hyperstimulation syndrome: a retrospective case-control study. *Fertil Steril* 2004; 81: 222-6.

Only one prospective randomized study, involving 50 patients, affected by PCOS has been carried out²⁶. PCOS patients who failed to become pregnant during a previous trial, or whose cycle had been cancelled for high OHSS risk, were randomized between classical IVF treatment versus electrocautery of one ovary, 11 week before ovarian stimulation. The pregnancy and miscarriage rates were identical, but the rate of cancelling for risk of OHSS was significantly lower in the randomized group. There was no advantage in terms of miscarriage rate, which remained high in both groups.

Finally, a retrospective comparison was made of 15 women with clomiphene-resistant PCOS, treated by laparoscopic ovarian diathermy before IVF, and 16 PCOS patients who did not receive surgical pretreatment²⁸. In this study there was only a trend toward a lower risk of miscarriage (38.9% vs. 66.7%) and OHSS (0% vs. 4.3%), and higher chances of pregnancy (38.9% vs. 10.5%) in the group which had been surgically pretreated, but these differences were not statistically significant.

Minimal ovarian destruction is necessary to sensitize PCOS to exogenous gonadotropins. However, in order to avoid OHSS, a considerable amount of healthy ovarian destruction is required, with the drawback that, under these conditions, the ovarian reserve may be hampered.

Summary

Since only preliminary data are available and in view of the possible side-effects (adhesions and loss of ovarian tissue) and its invasive character, this approach should be restricted to rebel cases of OHSS in patients suffering from PCOS, and applied only as a last resort.

REDUCTION OF THE NUMBER OF TRANSFERRED EMBRYOS

Late-onset OHSS may be induced or aggravated by the rising hCG produced by early pregnancy

As hCG secretion is higher in multiple pregnancies, it can be postulated that by reducing the number of conceptuses the incidence or severity of OHSS will decrease. In these conditions, a reduction of the number of transferred embryos could be an efficient preventive method for high-risk patients.

Scobie *et al.*²⁹ observed, in a retrospective study, a higher number of days of hospital stay in relation to the number of conceptuses.

De Guberung *et al.*³⁰ evaluated the incidence of single-embryo transfer (SET) and its subsequent decline in twin pregnancies. The authors evaluated the possible consequences of decreasing multiple pregnancy on OHSS incidence. Over a 5-year period, SET increased from 13 to 45%, which was associated with a decrease in multiple pregnancies from 33.6 to 11.7%. During this period, the incidence of OHSS did not decrease (20.5–3.4%). Moreover, the proportions of OHSS among singleton (3.33%) and twin (3.73%) conception cycles were similar. It seems clear from this study that the late form of OHSS is related more to the presence of hCG than to its level.

In a recent Belgian study³¹, multiple pregnancies were equally high among early- and late-OHSS cases (40.0% and 45.5%, respectively), but only in the group of late-OHSS cases was significant compared with the non-OHSS population reached (45.2% vs. 35.1%). This late form, closely associated with multiple pregnancies, is more likely to be severe.

According to these three preliminary studies, it is more the severity than the incidence of OHSS that is dependent on the level of hCG, resulting from multiple pregnancy.

CONCLUSIONS

In the prevention of any disease, it should be emphasized that the possibility of primary prevention depends on two main requirements. First, the etiology of the disease must be known,

188. Bodiker TC, Shrivakunt H, Auckhil S, et al. Severity of ovarian hyperstimulation syndrome: its relation to number of oocytes. *Int J Fertil Women* 2004; 49: 36–42.
189. De Meschong JC, Wanggelschoes DC, Nam Nguyen P, et al. Singleton pregnancies are less affected by ovarian hyperstimulation syndrome as twin pregnancies. *Fertil Steril* 2004; 82: 1690–3.
190. Mapanislaom BL, Tournaye H, Verpoest W, et al. Early and late ovarian hyperstimulation syndrome: early pregnancy outcomes and profile. *Hum Reprod* 2005; 20: 526–31.
191. Leif JOC, Vindén SC. Combined approach as an effective method in the prevention of severe ovarian hyperstimulation syndrome. *Int J Obstet Gynecol Reprod Biol* 2001; 97: 200–12.

Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Figure 1 Frequency distribution of number of oocytes in patients hospitalized with OHSS

Exactly half of the patients hospitalized were pregnant and the other half were not. Neither the multivariate analysis nor a direct comparison of the groups of pregnant versus non-pregnant women hospitalized because of severe OHSS showed any difference in cost between groups ($\text{€}1299 \pm (\text{SD}) 941$ versus $\text{€}1445 \pm (\text{SD}) 989$ for non-pregnant versus pregnant patients, respectively).

Discussion

In Belgium, the total cost of one IVF/ICSI cycle, including gonadotropins, averages about $\text{€}4000$. When considering only treatments conducted in both centers as contributing to this analysis,

this means that for a total expense of 6238 (total number of cycles) $\times \text{€}4000 = \text{€}24\,952\,000$ needed for primary treatment over the period of time considered, an additional total expense of 77 (hospitalized OHSS cases) $\times \text{€}1539 = \text{€}118\,503$ is incurred for direct costs due to OHSS hospitalization. This does not include indirect costs due to working incapacity, and additional direct and indirect costs for OHSS patients who manage to escape hospitalization but nevertheless need extra consultation, sonography, blood tests and mostly analgesic drugs. These costs were not analyzed in this study, but may be estimated to be at least the same amount as the direct costs. This means that the total costs for OHSS

Figure 2 Frequency distribution of costs for hospitalized patients with OHSS

(about €237 000 with 1.23% severe cases) constitute approximately 1% of the primary treatment costs (€237 000 from €24 952 000).

More than half of these patients obtained an ongoing pregnancy, and it is therefore not possible to say that all these cases could have been prevented by not administering human chorionic gonadotropin (hCG) as an ovulation trigger. However, about two-thirds of patients clearly had the early form of the syndrome with a short hospitalization period, whereas one-third had a pregnancy enhanced form. Therefore, it makes sense to consider what the effect would have been if another ovulation trigger, e.g. recombinant luteinizing hormone (LH), had been used. It may be assumed that two-thirds of all OHSS

cases could have been prevented in doing so, resulting in a saving of at least two-thirds of €237 000, i.e. approximately €158 000.

In terms of prevention, the administration of recombinant (rec)LH could theoretically reduce the incidence of OHSS if compared with the use of hCG to induce ovulation. We tried to calculate what the savings would be if recLH were to be used in all patients treated with IVF, or in a risk group. In Belgium, 1 ampoule of 5000 IU of hCG (required to induce ovulation in a patient at risk of OHSS) costs €4.65. If we hypothesize that (at least) two-thirds of all cases of OHSS could be prevented by administering recLH instead of hCG, the dose required might cost €158 000/6238 = approx. €25 as an equivalent.

Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Index

- activated protein C (APC) resistance 45
- adult respiratory distress syndrome (ARDS)
- 31, 36
 - management 174
 - with over-hydration therapy 162
- alfentanil administration 151, 163, 173–4, 184, 262–3
- adverse effects 235–7
- propylactic uses 180, 233–7, 276–8, 285
- allergy 114
- anaphylaxis hypersensitivity
- angiotensin 85
- angiotensin II 89–91, 100–2
- see also renin-angiotensin system (RAS)
- angiotensin II receptor blocker (ARB) 162
- angiotensin-converting enzyme (ACE) 88, 100
- ACE inhibitors (ACEis) 100, 103–3, 152, 171
- anatomical model 131
- anticoagulant treatment 152–3, 151–2, 174, 182, 268
- risks 49
- antigen-presenting cells (APCs) 109
- antiphospholipid syndrome 50
- antipruritic/antidominant administration 152
- aspirin 2–4, 31, 35, 100, 132–3, 159
- biochemical mediators of CHSS 83–4
 - management 152–3, 150–1, 174, 175, 183–4, 238
 - over-hydration therapy 161–3
 - see also peracetamol
- renin-angiotensin system and 100
- WBC concentration 90
- see also vascular permeability changes
- Belgium, lethal cases 81, 84
- blood flow
- hemodynamic changes 19–30, 86, 100–2
 - intensive care 19
- body mass index (BMI) 19, 192
- as risk factor 19
- brimonidine (Bri) 127
- C-reactive protein (CRP) 21
- cardiac complications 35
- classification of CHSS 71–5, 264
- by disease onset 75
 - by disease severity 71–4
 - Golan (1989) 73–4, 264
 - Karot (1983) 74
 - Salen (1997) 72–3
 - Stok (1989) 74
 - Schmidt (1998) 75
 - used for 71
- clonidine citrate 39, 195
- coasting 129–30, 161, 216–20, 236–44, 247–63, 285–6
- advantages of 247
 - criteria for 240, 236–6
 - duration 242, 264–1, 236
 - efficacy 242–3, 260
 - Cochrane review 260
- CaMKII agonist/TF cycles 254–6
- CaMKII antagonist/TF cycles 255
- mechanism of action 223–60, 247–53
- oxo-TF cycles 254
- physician attitudes towards 253
- pregnancy rate and 261–2
- timing of 242, 254–60

- granulosa cells 301, 349
- health-economic aspects 353–71
- hemocoelocentesis 21, 31, 46, 132, 382
management 382
- hemodynamic changes 19–20, 46, 100–2
- hemorrhage, ovarian 31, 382
- hepatitis 152–3, 150, 179, 195
propylactic use 50
risks of 49
- hepatic dysfunction 34–5
- histamine 49
- human chorionic gonadotropin (hCG) 77, 81,
200, 281
avoidance of 160, 207–10
delay of see coasting
FSH receptor activation 123–5
ovulation induction 196, 204–5, 251
timing of administration 260
- human leukocyte antigen (HLA) 108
- human menopausal gonadotropin (hMG) 195
- hydrothorax 2, 56
- hydroxyethyl starch (HES) 151, 169, 185
propylactic use 227, 239–20, 205
- hypercoagulability 30, 45–9
in pregnancy 42–4
see also anticoagulant treatment
- hyperostotic tubinosis of the first trimester 27
- hypersensitivity 106–10
inflammation in 114
- hypohyponatremia 27
- hypovolemia 2, 30
- immunological dysregulation 100–2, 114–15
see also inflammation
- in vitro fertilisation (IVF) 27–8, 192
coasting
GnRH agonist cycles 254–9
GnRH antagonist cycles 258
complications 271
costs of 267
FSH receptor mutation and 125–7
natural IVF 194
OHSS prevention 102–4
in-patient management 164, 287
- incidence 8, 281–2
in ovulation induction 39
- indomethacin 171
- inflammation 44, 100, 108–10
hypersensitivity 109–10
in folliculogenesis 112–13
in hypersexuality 114
in ovulation induction 105–19
in polycystic ovarian syndrome (PCOS) 112
non-specific inflammatory response 106
possible pathological mechanisms in OHSS
110–12
glucocorticoids 111–12
IL-10 116–11
regulatory T cells and IL-2 111
specific inflammatory response 109
- inhibins 20
- interleukins 94
hypersensitivity and 109
IL-1 113–14
IL-2 111, 114
IL-8 113
IL-10 109, 109–12, 114, 115
inflammatory responses 108
- intravenous fluid administration 150, 287
- kidney dysfunction see renal complications
- kinin–kallikrein system 45
- laser vaporisation, ovarian 329–32
- late OHSS 75, 280
- lethal cases 152–65
Belgium 60, 64
case reports from the literature 62–3
importance of registries 64–5, 271–2
lessons from 62–4
Netherlands 59–61, 63–6
- likelihood ratio (LR) 8
- liver dysfunction 34–5
- luteal phase
GnRH agonist-induced 207
monitoring 179–80
- lutinisation 114
- lutinizing hormones (LH)
LH surge 209–9

- GnRH agonist-induced 207
 - hyperstimulation 190
 - ovulation induction 135-9, 205-6, 222
- management of OHSS 149-52, 171-2, 287-8
 - ACE inhibitors 199
 - albumin administration 151, 163, 173-4, 184, 287-8
 - anticoagulation 151-2, 155, 288
 - antiprostaglandin administration 152
 - conservative management protocol 162-4
 - diagnosis 164-5
 - dual renin-angiotensin blockade therapy 152
 - fluid restriction 162
 - guidelines 166-70
 - hospitalisation 149-50, 287
 - hydration 151, 163, 287
 - medical approach 171-8
 - over-hydration therapy 161-3
 - paracentesis 152-3, 161-2, 174-5, 162-4
 - plasma expanders 151, 164, 287
 - surgery 175
 - see also out-patient management
- miscarriages 153-5
- multiple pregnancies 77
 - OHSS relationships 77-81, 153
 - single embryo transfer studies 78-81, 222
- mutations, FSH receptor gene 121-3, 127-8
 - idiopathic OHSS and 125-7
 - spontaneous OHSS and 123-5
- ovaries 30, 35
- Stewart classification scheme 74
- Netherlands, lethal cases 58-61, 63-4
- obstetrical outcome 152-6
- oliguria 3, 30-1, 174
- oocyte quality, crossing impact 260-2
- out-patient management 162-4, 170-2, 230
 - anticoagulation 155
 - clinical assessment 163
 - colloid replacement 164-2
 - guidelines 160
 - initial phase monitoring 173-80
 - outcome 165-7
 - paracentesis 162-4
 - progressive symptoms 160
 - rehydration 163
- ovarian cyst rupture 175
- ovarian enlargement 8
 - see also ovarian volume
- ovarian haemorrhage 32, 262
- ovarian hyperstimulation syndrome (OHSS) 391
 - biochemical mediators of 63-8
 - classification 71-5, 264
 - by disease onset 75
 - by disease severity 71-4
 - need for 70
 - clinical manifestations 2-4, 19-21, 262
 - mild OHSS 29
 - severe OHSS 29-31, 166-71
 - complications 31-7
 - critical see critical OHSS
 - definition 2, 391
 - difficulties 7
 - fetal ovarian hyperstimulation 25
 - genetic aspects 131-8
 - gene expression 135-7
 - gonadotroph adenomas and 26-7
 - health-economic aspects 267-71
 - historical perspective 1-3
 - in IVF fertilisation programs 27-8
 - in ovulation induction 26-31
 - patients at risk 28-9
 - in spontaneous pregnancy 27
 - incidence 4, 281-2
 - laboratory findings 31
 - lethal cases 59-65
 - Belgium 61, 64
 - case reports from the literature 62-3
 - importance of oggistics 64-5, 271-2
 - lessons from 63-4
 - Netherlands 59-61, 63-4
 - multiple pregnancy relationships 77-81
 - single embryo transfer studies 78-81, 222
 - obstetrical outcome 152-6
 - post-term infants 25-6
 - symptoms 392