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Attualità cliniche e di laboratorio.
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EVENTO SENZA FINI DI LUCRO

PROCEDURE DI PROCREAZIONE MEDICALMENTE ASSISTITA E RISCHIO TROMBOEMBOLICO

ELVIRA GRANDONE
UNITA' DI RICERCA IN ATEROSCLEROSI E TROMBOSI
I.R.C.C.S. «CASA SOLLIEVO DELLA SOFFERENZA»
S. GIOVANNI ROTONDO

Quesiti

- Quando una profilassi con Eparina a Basso Peso Molecolare?
- Quale eparina e quali dosaggi? Quanto tempo proseguire con eventuale profilassi?
- Come comportarsi relativamente al trasferimento di embrioni in caso di S. da Iperstimolazione?

Delivery rate according to maternal age

For women ≥ 40 years undergoing IVF treatment,
the delivery rates vary from 1.4% in Czech Republic to 22.2% in Serbia.
For ICSI the DRs vary from 3.0% in Iceland to 22.2% in Albania.

Human Reproduction, Vol.32, No.10 pp. 1957-1973, 2017
Advanced Access publication on August 28, 2017 doi:10.1093/humrep/deu264

human
reproduction

ESHRE PAGES

Assisted reproductive technology in Europe, 2013: results generated from European registers by ESHRE[†]

The European IVF-monitoring Consortium (EIM)[‡] for the European
Society of Human Reproduction and Embryology (ESHRE)

C. Calhaz-Jorge^{1,2}, C. De Geyter^{2,3}, M.S. Kupka^{2,4}, J. de Mouzon^{2,5},
K. Erb^{1,6}, E. Mocanu^{2,7}, T. Motrenko^{2,8}, G. Scaravelli^{1,9}, C. Wyns^{2,10},
and V. Goossens²

¹Faculdade de Medicina da Universidade de Lisboa, Portugal; ²ESHRE Central Office, Meentzstraat 40, Grimbergen B-1852, Belgium; ³University
Women's Hospital of Basel, Switzerland; ⁴Erkrankungs- und Reproduktionsmedizin, Seestrasse 10, Kiel, Schleswig-Holstein; ⁵Abt. Gynäkologie
Srasse im Gynäkologikum Hamburg, Germany; ⁶INSERM, France; ⁷Odense University Hospital, Fertility Clinic, Denmark; ⁸HAIR Unit,
Rovarda Hospital, Ireland; ⁹Thomas Reproduction Centre Borko, Montenegro; ¹⁰National Health Institute, Women, Child and Adolescent
Health Unit, Italy; ¹¹UCLouvain, Belgium

[†]Correspondence address: Reproductive Medicine Unit, Faculdade de Medicina da Universidade de Lisboa, Av. Egas Moniz 1649-015 Lisbon,
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Submitted on June 20, 2017; accepted on July 31, 2017

European Society of Human Reproduction and Embryology (ESHRE)

2012 clinical pregnancy rate per embryo transfer

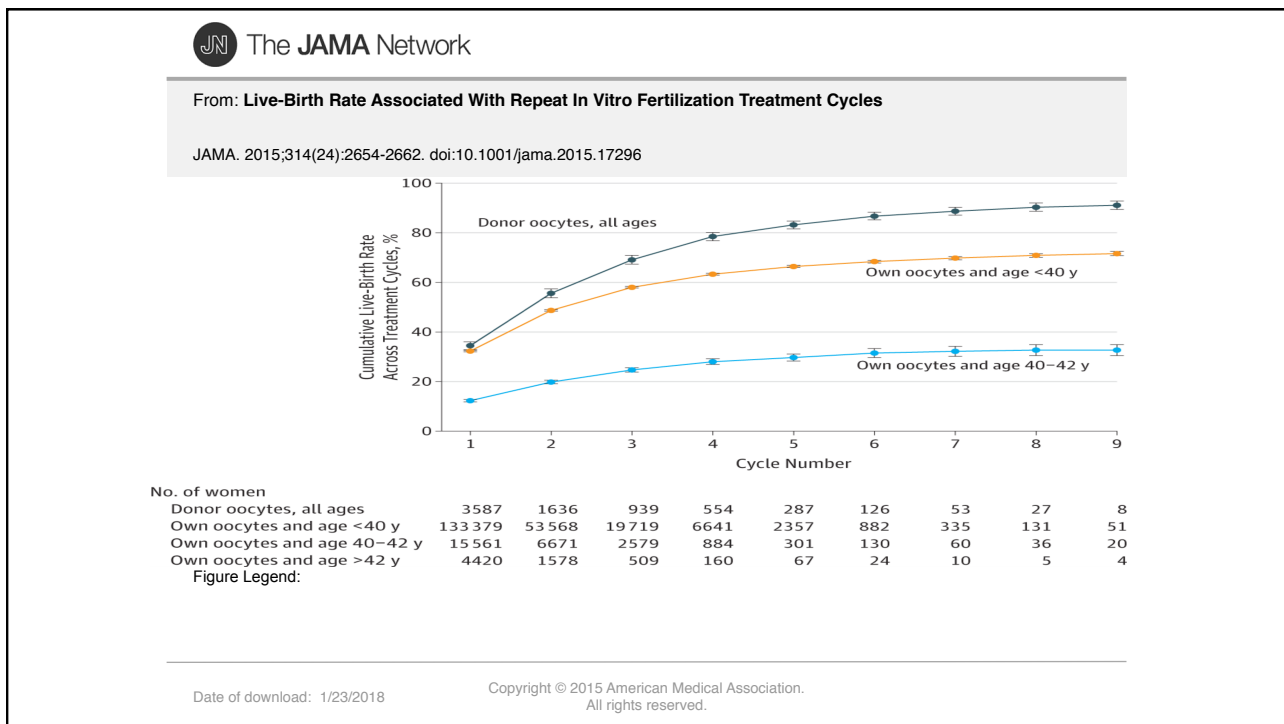
33.8% after IVF,

32.3 % after ICSI,

23.1% after frozen embryo transfer

48.4% after egg donation

ESHRE, Hum Reprod. 2016



OHSS


- OHSS is an exaggerated response to ovulation induction therapy. It is typically associated with exogenous (human menopausal and human chorionic) gonadotrophin stimulation.
- Its severe form occurs in **0.8% to 2.0%** of patients undergoing induction of ovulation
- Hypotension, Pleural effusion (more, and more frequently on the right side); Adult form of respiratory distress syndrome (ARDS); Pericardial effusion; Ascites; Oliguria and anuria; Death (3/100,000 cycles)

Cantwell R, et al. BJOG 2011; Braat DM, et al. Hum Reprod 2010.

OHSS

Moderate OHSS i.e ultrasound evidence of Ascites on day of IUI warns gynecologist to take action

- **Infact , Action should be taken on day of trigger itself**



PCOD

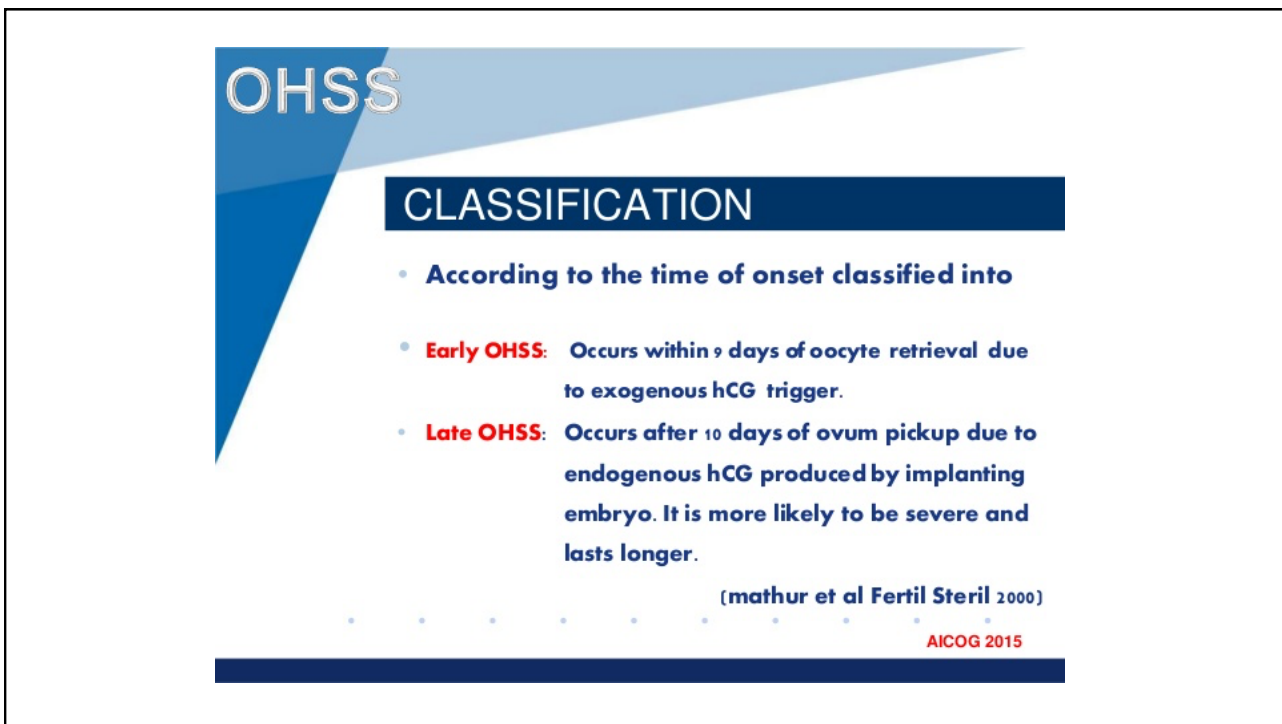
Ascites

OHSS

CLASSIFICATION (Golan et al 1989)

MILD	Grade 1: abdominal distension and discomfort Grade 2: grade 1 + nausea,vomiting and/or Diarrhoea, enlarged ovaries (5-12 cm).
MODERATE	Grade 3: grade 2 + ultrasound evidence of ascites
SEVERE	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

AICOG 2015



The slide features a blue and white geometric design. The text 'OHSS' is in the top left. A dark blue bar contains the word 'CLASSIFICATION'. Below it, a bulleted list describes two types of OHSS. At the bottom right, there is a citation '(mathur et al Fertil Steril 2000)' and the text 'AICOG 2015'.

OHSS

CLASSIFICATION

- According to the time of onset classified into
- **Early OHSS:** Occurs within 9 days of oocyte retrieval due to exogenous hCG trigger.
- **Late OHSS:** Occurs after 10 days of ovum pickup due to endogenous hCG produced by implanting embryo. It is more likely to be severe and lasts longer.

(mathur et al Fertil Steril 2000)

AICOG 2015

LMWH

The proper dosage and the duration of LMWH administration in relation to IVF are **uncertain** as they cannot be determined from the literature. The Royal College of Obstetricians and Gynecologists states that LMWH should be given on an individualized basis in cases of OHSS (**RCOG: Ovarian Hyperstimulation Syndrome. In. https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg_5_ohss.pdf; 2016.**)

Thromboprophylaxis with LMWH during pregnancy is related to a relative risk-reduction of up to 88% at appropriate doses of LMWH (**Greer IA, Blood 2005; Lindqvist PG, AOGS. 2011; Roeters van Lennep JE, J Thromb Haemost. 2011; Lindqvist PG, J Thromb Haemost. 2011.**)

However, LMWH in pregnancy has been reported to be related to a low (2%) but increased risk of bleeding, post-partum hemorrhage and hematomas (**Lindqvist PG, Thromb Haemost. 2000; Sirico A, J Matern Fetal Neonatal Med, 2018.**)

The occurrence of osteoporosis in relation to LMWH thromboprophylaxis seems to be substantially lower than with unfractionated heparin (**Galambosi PJ, Eur J Obstet Gynecol Reprod Biol. 2012.**)

5.0 VTE in Patients Using Assisted Reproductive Technology

5.1.1. For women undergoing assisted reproduction, we recommend against the use of routine thrombosis prophylaxis (Grade 1B).

5.1.2. For women undergoing assisted reproduction who develop severe ovarian hyperstimulation syndrome, we suggest thrombosis prophylaxis (prophylactic LMWH) for 3 months postresolution of clinical ovarian hyperstimulation syndrome rather than no prophylaxis (Grade 2C).

CHEST

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**Introduction to the Ninth Edition :
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Gordon H. Guyatt, Elie A. Akl, Mark Crowther, Holger J. Schünemann,
David D. Gutterman and Sandra Zeilman Lewis

Chest 2012;141:48S-52S
DOI:10.1378/chest.11.2286

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy

Shannon M. Bates,^{1,2} Anita R.
Ian A. Greer,^{1,1} John J. Riva,^{1,2}

Prevention of VTE

^{3,9} Sara R. Vazquez,¹⁰
Rochwerger^{13,17}

Question 11: Should anticoagulant prophylaxis vs no anticoagulant prophylaxis be used for prevention of VTE in women undergoing assisted reproduction?

Recommendation 14

In unselected women undergoing assisted reproductive therapy, the ASH guideline panel *suggests against* prophylactic antithrombotic therapy to prevent VTE (conditional recommendation, low certainty in evidence about effects ⊕⊕○○).

Recommendation 15

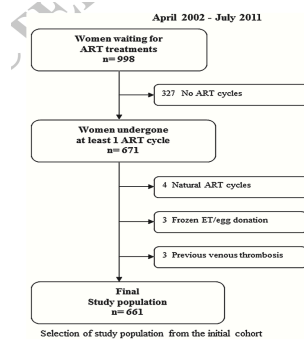
For women undergoing assisted reproductive therapy who develop severe ovarian hyperstimulation syndrome, the ASH guideline panel *suggests* prophylactic antithrombotic therapy to prevent VTE (conditional recommendation, low certainty in evidence about effects ⊕⊕○○).

Journal of Thrombosis and Thrombolysis
https://doi.org/10.1007/s11239-017-1584-z



1 **Venous thromboembolism in assisted reproductive technologies:**
2 **comparison between unsuccessful versus successful cycles in an Italian**
3 **cohort**

4 Michela Villani¹ · Giovanni Favuzzi¹ · Pasquale Totaro² · Elena Chinni¹ · Gennaro Vecchione¹ · Patrizia Vergura¹ ·
5 Lucia Fischetti¹ · Maurizio Margaglione³ · Elvira Grandone¹



Patient	Age	BMI	Varicose veins	Thrombophilia	Family history for VTE	OHSS	Thrombotic event, details	Antithrombotic prophylaxis
1	34	25.7	No	aPL syndrome	n.a.	Yes	Isolated PE	No
2	45	30.8	No	No	No	Yes	Isolated PE	No

n.a. not available, PE pulmonary embolism

Table 4 Logistic regression analysis

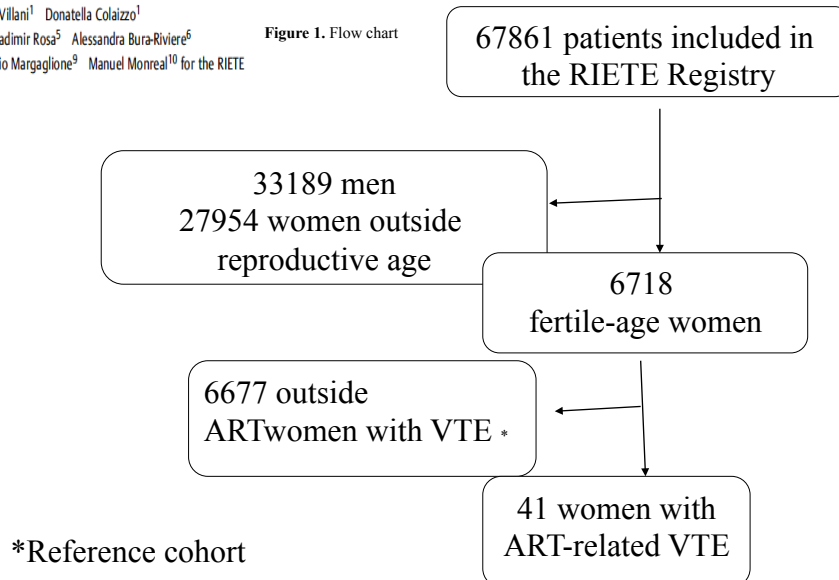
Variables	p	OR	95% CI
Pregnancy	0.02	13.94	1.41–137.45
BMI	0.03	1.23	1.01–1.49

Villani M. et al, JTT, 2017,

Venous Thromboembolism in Women Undergoing Assisted Reproductive Technologies: Data from the RIETE Registry

Elvira Grandone¹ Pier Paolo Di Micco² Michela Villani¹ Donatella Colaizzo¹
Carmen Fernández-Capitán³ Jorge Del Toro⁴ Vladimir Rosa⁵ Alessandra Bura-Riviere⁶
Isabelle Quere⁷ Ángeles Blanco-Molina⁸ Maurizio Margaglione⁹ Manuel Monreal¹⁰ for the RIETE Investigators

Figure 1. Flow chart



Venous Thromboembolism in Women Undergoing Assisted Reproductive Technologies: Data from the RIETE Registry

Elvira Grandone¹ Pier Paolo Di Micco² Michela Villani¹ Donatella Colaizzo¹
Carmen Fernández-Capitán³ Jorge Del Toro⁴ Vladimir Rosa⁵ Alessandra Bura-Riviere⁶
Isabelle Quere⁷ Ángeles Blanco-Molina⁸ Maurizio Margaglione⁹ Manuel Monreal¹⁰ for the RIETE Investigators

- Overall, 41 (0.6%) out of 6718 women of childbearing age with VTE had an ART-related event.
- 23 had isolated DVT (56.1%), 12 isolated PE (29.3%), and 6 both (14.6%).
- VTE occurred in 20 successful and 21 unsuccessful (i.e.: not resulting in a clinical pregnancy) ART cycles.
- Logistic regression showed that **isolated PE** was significantly more frequent than DVT alone or combined with PE in unsuccessful IVF (OR: 4.13, 95%CI: 1.4-12.4), as well as in contraceptive users (OR: 2.96, 95%CI: 1.95- 4.5) and in puerperium (OR: 1.96, 95%CI: 1.16- 3.3).
- After grouping isolated PE and DVT+PE, we found that PE was significantly more frequent in women with unsuccessful IVF and higher BMI (OR: 5.0, 95%CI: 1.2-20.7 and OR: 1.0, 95%CI: 1.0-1.1, respectively).

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OHSS: STRATEGIE DI PREVENZIONE

Human Reproduction Vol.21, No.11 pp: 2836-2837, 2006
Advance Access publication September 11, 2006

doi:10.1093/humrep/del059

Ganirelix acetate causes a rapid reduction in estradiol levels without adversely affecting oocyte maturation in women pretreated with leuprolide acetate who are at risk of ovarian hyperstimulation syndrome*

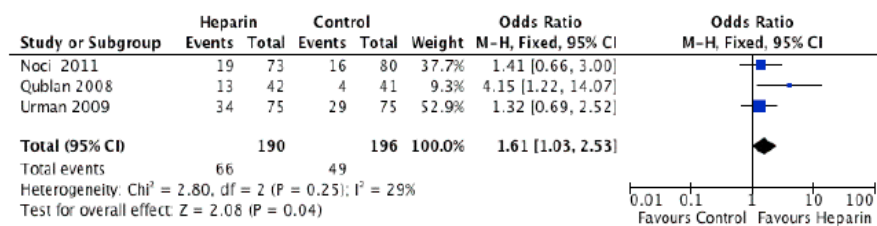
Robert L.Gustofson^{1,2,3}, James H.Segar^{1,2,3} and Frederick W.Larsen^{1,2,4}

- **Riconoscimento delle pz a rischio (habitus, PCO, pregressi OHSS, trombofilie ereditaria o acquisite (???) pregresse TVP)**
- **Personalizzazione del dosaggio FSH**
- **Attento monitoraggio endocrino ed ecografico**
- **Aspirazione di tutti i follicoli durante il pick-up ovocitario**
- **Non procedere alla somministrazione di r-hCG**
- **Ridurre il dosaggio di u-hCG a 7500/5000 U (discusso)**
- **Utilizzo di analogo del GnRH in alternativa ad hCG (non applicabile a cicli in cui si era usato l'analogo per la soppressione ipofisaria)**
- **Congelamento ovocitario/embrionario con differimento del transfer**

Quesiti

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Figure 5. Forest plot of comparison: I Heparin versus control, outcome: I.2 Clinical Pregnancy Rate per woman.



Heparin for assisted reproduction (Review)

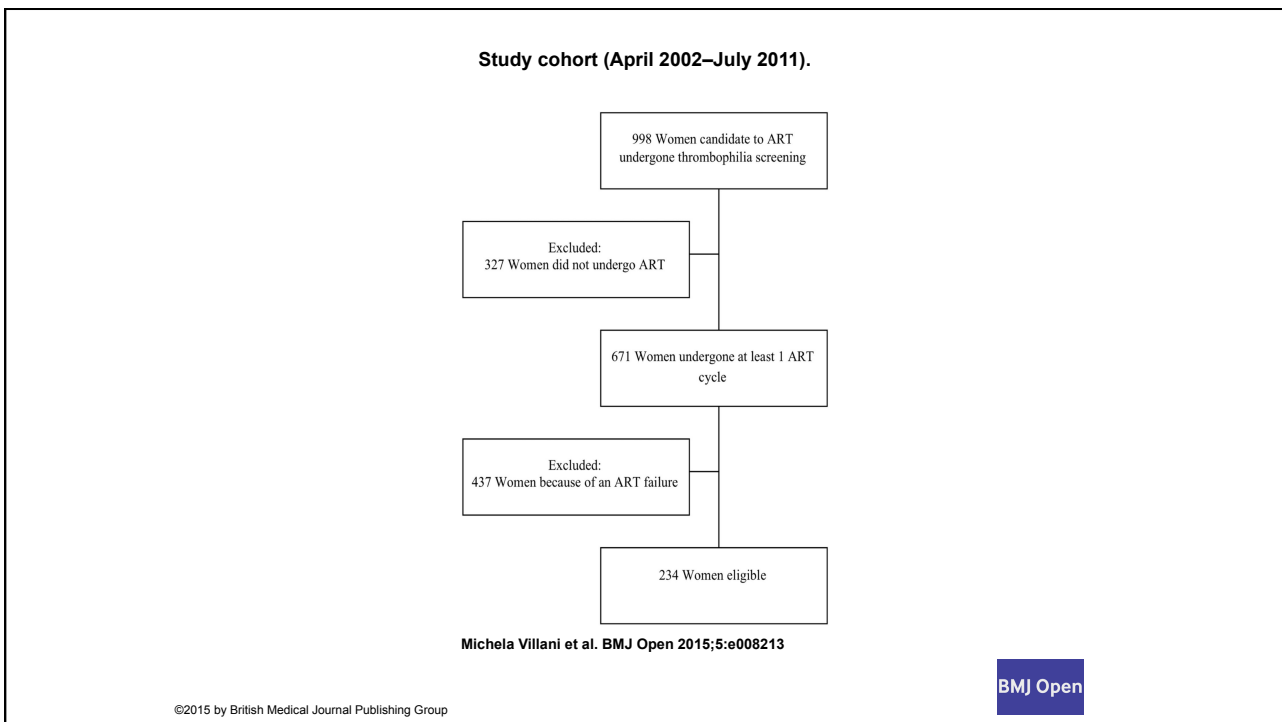
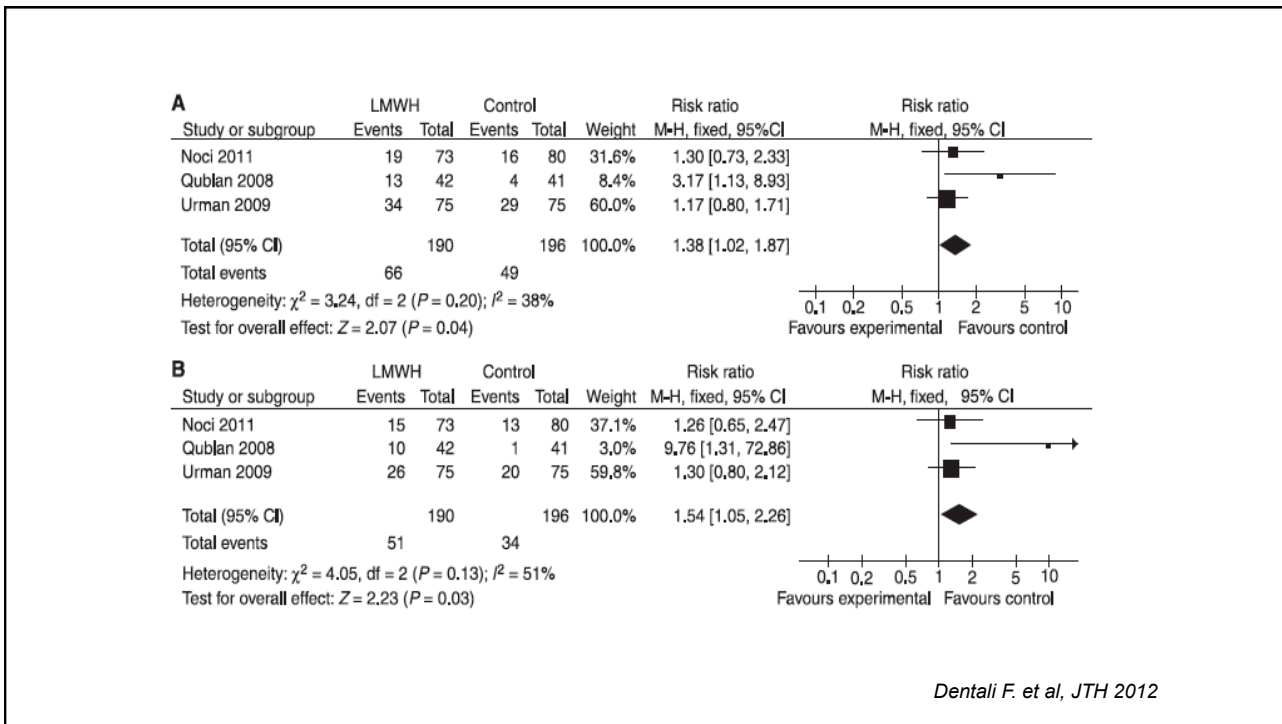
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Heparin for assisted reproduction (Review)



WILEY



VTE in SUCCESSFUL CYCLES

The frequency of TE during pregnancy in patients after IVF, **with or without OHSS** varies between **0.8 and 25/ 1000**, compared with **0.17–2.5/1000** in the background pregnant population

Sennstrom M, et al. AOGS, 2017

AOGS SYSTEMATIC REVIEW

Thromboembolism and in vitro fertilization – a systematic review

MARIA SENNSTROM¹, KARIN ROVA² , MARGARETA HELLGREN³, RAGNHILD HJERTBERG⁴, EVA NORD¹, LARS THURN^{2,5}  & PELLE G. LINDQVIST^{2,6} 

Table 2. Time from embryo transfer (ET) to thromboembolism.

Year (ref)	Author	Study design	Venous thromboembolism (VTE)		Arterial thromboembolism (ATE)			
			n	Days after ET	OHSS n/total n	n	Days after ET	OHSS n/total n
1995 (8)	Kodama H	Case ser	0	na	na	1	11	1/1
1998 (19)	Aboulghar MA	Case ser	0	0	0	2	7 and 9	2/2
2006 (12)	Chan WS	R-case ser	10	Mean 57 (14–105)	0	0	na	na
			24	Mean 24 (3–49) OHSS	24	0	na	na
2007 (20)	Girolami A	R-case ser	0	na	na	10	Mean 9 (3–28)	na
2009 (24)	Salomon O	Case ser	5	49–63	5/5	0	na	na
2009 (17)	Chan WS	R-case ser	61 [†]	Mean 42	47/60	35	Mean 11	27/31
2012 (5)	Rova K	Cohort	32	Mean 60 (OHSS)/mean 68 (no OHSS)	19/32	na	na	na
2012 (23)	Fleming T	Case ser	2	8 and 35	2/2	0	na	na
2015 (11)	Villani M	Case-con	1*	112	0	0	na	na

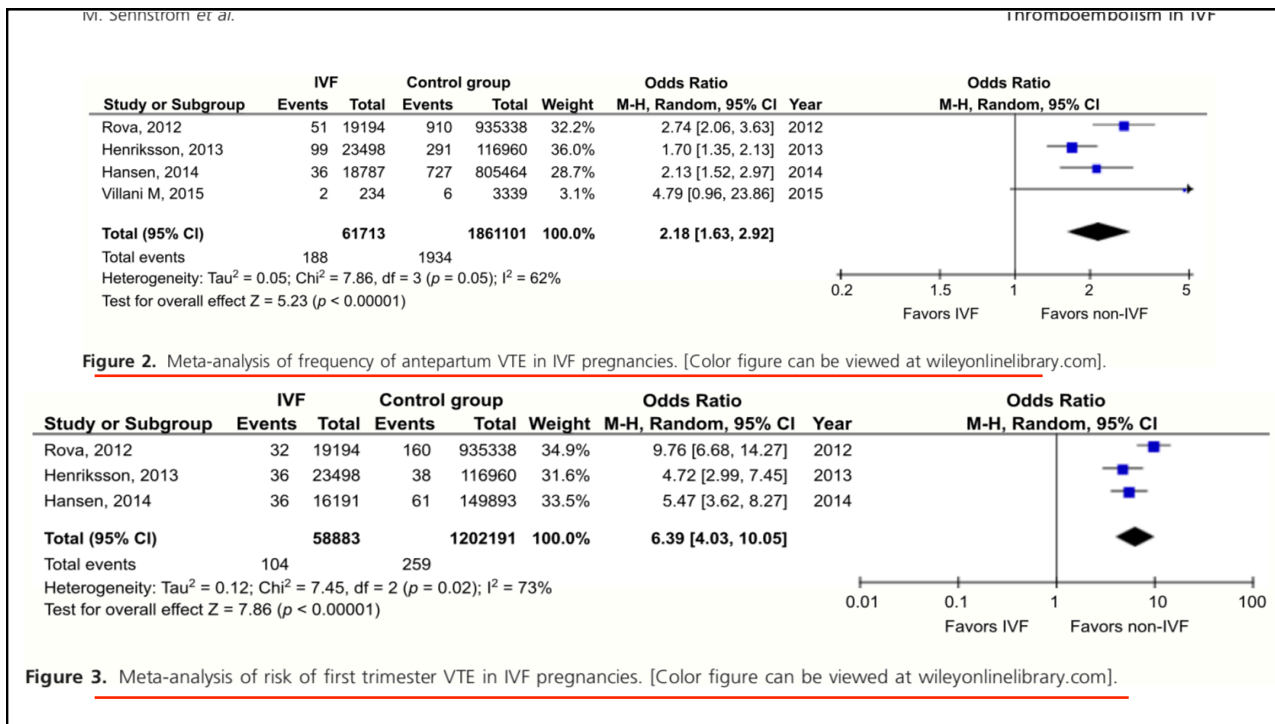
case ser, case series; ET, embryo transfer; na, not applicable; R-case ser, review case series; ref, reference number.

OHSS n/total n = number of OHSS related VTE/IVF as compared with total number VTE/IVF.

*One pulmonary embolism, time of PE not reported.

[†]2 VTE in the same patient.

Sennstrom M, AOGS 2017



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David O. Gutterman and Sandra Zelman Lewis
Chest 2012;141:48S-52S
DOI:10.1378/chest.11-2286

Table 3. Thromboprophylaxis and in vitro fertilization.

Year	Author	Study design	Prophylaxis (n)	VTE (n)	ATE (n)	TE (n)	Type of prophylaxis	Start-duration
2006	Yinon Y	Cohort	24	0	0	0 TE	LMWH* (n = 19) LMWH* + ASA (n = 5)	OI – 6–12 weeks pp
2012	Fleming T	Case ser	2	2	0	2 UBVTE	LMWH	(1) 8 days after ET, (2) Before OI
2015	Villani M	Case-con	23 (3 OHSS)	0	0	0 TE	LMWH or LMWH + ASA [†]	na [‡]

case-con, case-control; case ser, case series; LMWH, low-molecular-weight heparin; na, not applicable; OHSS, ovarian hyperstimulation syndrome; OI, ovarian induction; pp, postpartum; TE, thrombotic event; UBVTE, upper body VTE.

*LMWH 0.6–1 mg/kg.
[†]LMWH + ASA doses not specified.
[‡]Unknown start of thromboprophylaxis.

OPEN REMARKS

- Who is at higher risk? Successful cycles, or...
- LMWH for prophylaxis: duration, doses, brand
- What about fetal/ neonatal outcome?
-

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[Home](#) > [Find Studies](#) > [Study Record Detail](#) Text Size ▾

Recurrent Failures in assisted Reproductive Techniques (The FIRST Registry)

<p>This study is currently recruiting participants. (see Contacts and Locations)</p> <p><i>Verified February 2016</i> by Casa Sollievo della Sofferenza IRCCS</p> <p>Sponsor: Casa Sollievo della Sofferenza IRCCS</p> <p>Information provided by (Responsible Party): Elvira Grandone, MD, Head of Unit, Casa Sollievo della Sofferenza IRCCS</p>	<p>ClinicalTrials.gov Identifier: NCT02685800</p> <p>First received: February 10, 2016 Last updated: February 15, 2016 Last verified: February 2016 History of Changes</p>
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