Caso Clinico su prevenzione del Tromboembolismo Venoso e mancato impianto in corso di induzione ovarica (Procreazione Medicalmente Assistita)

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

CASO CLINICO

- Donna di 40 anni, con ridotta riserva ovarica (orme anti-mulleriano: 0,4 ng/ml; vn: 0,7-1,0 ng/ml).
- BMI 25; Non varici; Non storia personale o familiare di TEV
- 3 pregressi tentativi falliti di procreazione medicalmente assistita (ICSI) per sterilità maschile
- La paziente viene stimolata con follitropina alfa; si ottengono due follicoli "dominanti", si effettua il "pick-up"
- Il giorno successivo manifesta: tensione addominale, improvviso aumento di peso, contestuale contrazione della diuresi, aumento della sensazione di sete. Le indagini strumentali e biochimiche documentano una Sindrome da Iperstimolazione Ovarica (OHSS) severa.

Quesiti

- E' utile istituire una profilassi con Eparina a Basso Peso Molecolare?
- In caso affermativo, quando, quale eparina e quali dosaggi? Quanto tempo proseguire con eventuale profilassi?
- E' prudente trasferire in utero una o due blastocisti? In caso affermativo, è opportuno praticare profilassi con eparina a basso peso molecolare?

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/dex264

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[2,6], E. Mocanu[2,7], T. Motrenko[2,8], G. Scaravelli[2,9], C. Wyns[2,10], and V. Goossens[2]

[1]Faculdade de Medicina de Universidade de Lisboa, Portugal [2]ESHRE Central Office, Meerstraat 60, Grimbergen B-1852, Belgium [3]University Women's Hospital of Basel, Abteilungsleiter gyn. Endokrinologie und Reproduktionsmedizin, Switzerland [4]Kinderwunschzentrum Altonaer Strasse im Gynaekologicum Hamburg, Germany [5]INSERM, France [6]Odense University Hospital, Fertility Clinic, Denmark [7]HARI Unit, Rotunda Hospital, Ireland [8]Human Reproduction Centre Budva, Montenegro [9]National Health Institute, Woman, Child and Adolescent Health Unit, Italy [10]UCLouvain, Belgium

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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

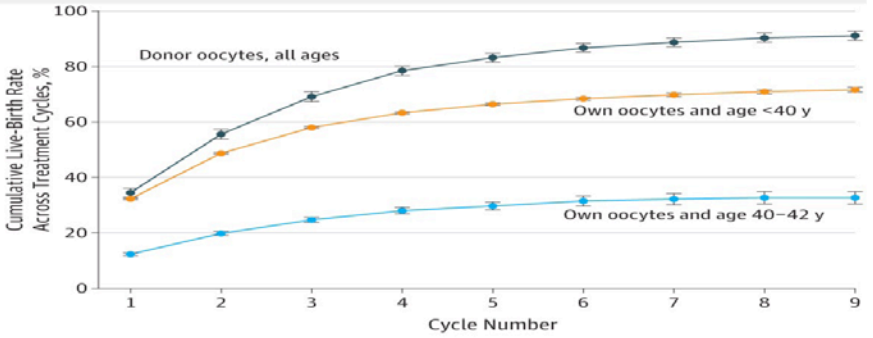
48.4% after egg donation

ESHRE, Hum Reprod. 2016

The JAMA Network

From: **Live-Birth Rate Associated With Repeat In Vitro Fertilization Treatment Cycles**

JAMA. 2015;314(24):2654-2662. doi:10.1001/jama.2015.17296



No. of women									
Donor oocytes, all ages	3587	1636	939	554	287	126	53	27	8
Own oocytes and age <40 y	133 379	53 568	19 719	6641	2357	882	335	131	51
Own oocytes and age 40–42 y	15 561	6671	2579	884	301	130	60	36	20
Own oocytes and age >42 y	4420	1578	509	160	67	24	10	5	4

Figure Legend:

OHSS

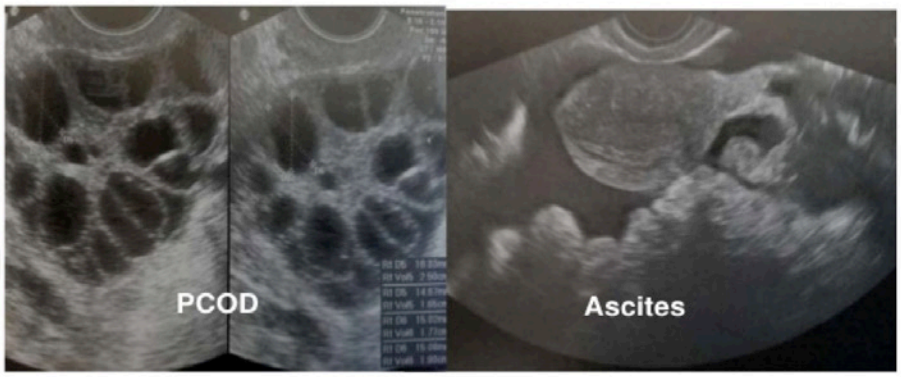
- OHSS is an exaggerated response to ovulation induction therapy. It is tipically associated with exogenous (human menopausal and human chorionic) gonadotrophin stimulation.
- Its severe form occurs in **0.8% to 2.0%** of patients undergoing induction of ovulation
- Hypotension, Pleural effusion (more, 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**



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

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

GRADING OHSS

DEGREE	GRADE	CLINICAL FEATURES
MILD	GRADE 1	Abdominal distention, pain.
	GRADE 2	Vomiting ,diarrhea, ovary enlargement less than 5 cms, weight gain less than 3kg.
MODERATE	GRADE 3	Mild OHSS + Ultrasound evidence of ascites, electrolyte disturbances, ovarian size upto 10cms,weight gain of 10lbs.
SEVERE	GRADE 4	Moderate OHSS + ovary size > 12cm, weight gain > 5kg.
	GRADE 5	Grade 4 + tense ascites, hydrothorax.
	GRADE 6	Grade 5 + haemoconcenteration , coagulation abnormalities, renal dysfunction, respiratory failure

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, LMHW 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
Official publication of the American College of Chest Physicians

CHEST ONLINE

Introduction to the Ninth Edition : Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Gordon H. Guyatt, Elie A. Akl, Mark Crowther, Holger J. Schünemann, David D. Gutterman and Sandra Zelman Lewis

Chest 2012;141;48S-52S
DOI 10.1378/chest.11-2286

Quesiti

- E' utile istituire una profilassi con Eparina a basso peso Molecolare?
- In caso affermativo, quando, quale eparina e quali dosaggi? Quanto tempo proseguire con eventuale profilassi?
- E' prudente trasferire in utero una o due blastocisti? In caso affermativo, è opportuno praticare profilassi con eparina a basso peso molecolare?

OHSS: STRATEGIE DI PREVENZIONE

Human Reproduction Vol.21, No.11 pp. 2830–2837, 2006 doi:10.1093/humrep/del059
Advance Access publication September 11, 2006.

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.Segars[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

- E' utile istituire una profilassi con Eparina a basso peso Molecolare?
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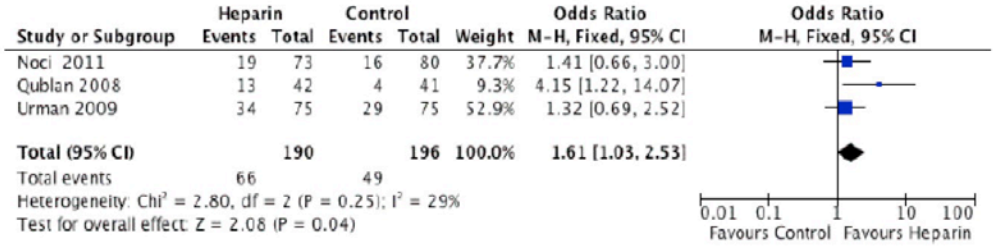
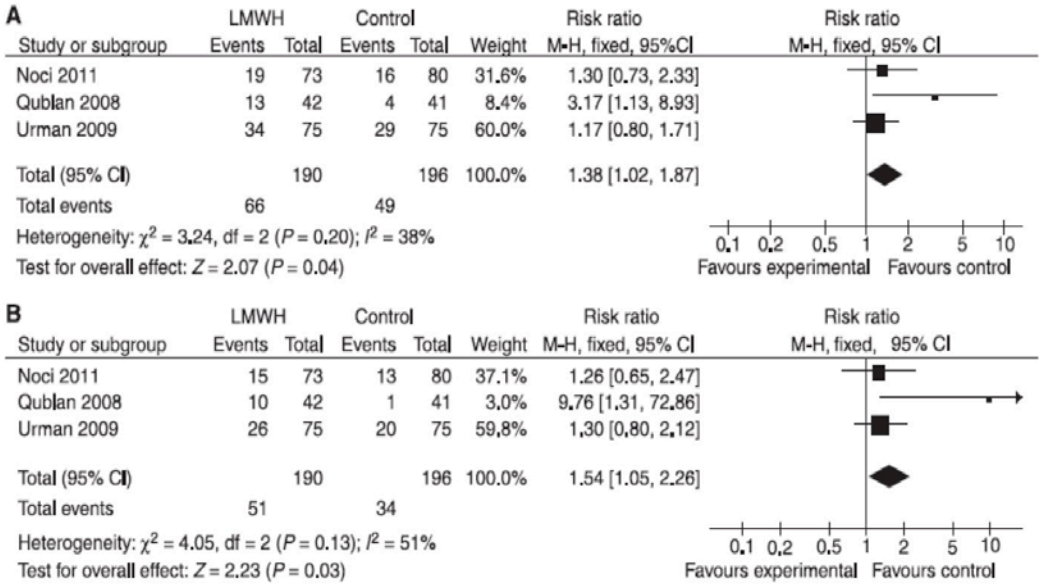
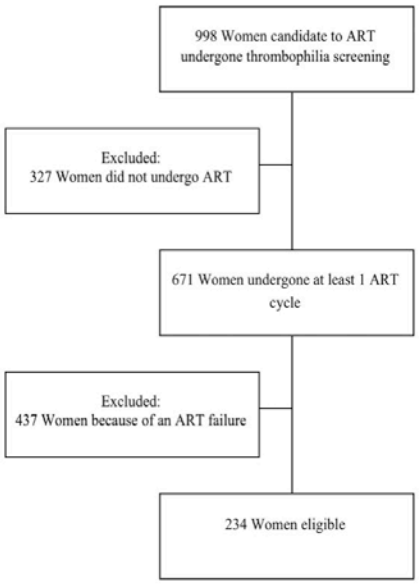
Figure 5. Forest plot of comparison: 1 Heparin versus control, outcome: 1.2 Clinical Pregnancy Rate per woman.





Dentali F. et al, JTH 2012

Study cohort (April 2002–July 2011).



Michela Villani et al. BMJ Open 2015;5:e008213

BMJ Open

Table 3 Age and live births in the reference cohort and general population from the same geographical area

	Maternal age				Live births number
	15 years	20–29 years	30–39 years	40 years	
Reference cohort (n=3339), % 2010–2012	3.7	34.4	55.1	6.8	3451
General population from the same geographical area (n=106 265), % 2008–2010	2.3	32.4	59.5	5.8	107 461

Villani M et al BMJ Open 2015

Table 4 Characteristics of women from the reference cohort experiencing venous thrombosis

Patient	Age at event	BMI	Thrombophilia	Additional risk factors	Type of event	Antithrombotic prophylaxis
1	31	37.1	No	No	Antepartum SVT in the left leg	None
2	33	18.3	No	Previous SVT after Caesarean section	Antepartum DVT in the left leg	None
3	28	17.3	FVL heterozygous	Family history for VTE	Antepartum (37 weeks) DVT in the right leg	LMWH*†
4	33	NA	NA	No	Postpartum SVT in the right leg	None
5	37	NA	NA	No	Postpartum bilateral SVT	None
6	43	NA	NA	No	Antepartum DVT in the left leg	None
7	22	NA	NA	No	Postpartum DVT in the left leg	None
8	35	NA	NA	No	Postpartum bilateral SVT	None
9	36	21.3	FVL heterozygous+ PC deficiency	Previous DVT during oral contraceptive	Antepartum (21 weeks) DVT in the left leg	LMWH*‡
10	33	18.7	FVL heterozygous	No	Antepartum DVT in the left leg	None
11	35	NA	NA	No	Postpartum SVT in the right leg	None

*Started when pregnancy test was positive.
†Treatment withdrawn for physician's choice at 32 weeks.
‡Treatment withdrawn for patient's choice at 20 weeks.
BMI, body mass index; DVT, deep vein thrombosis; FVL, factor V Leiden LMWH, low-molecular-weight heparin; NA, not available; PC, protein C; PE, pulmonary embolism; SVT, superficial vein thrombosis.

Villani M et al BMJ Open 2015

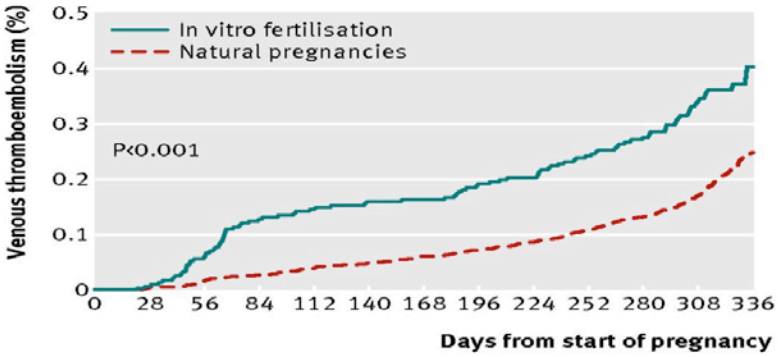
Table 1 Baseline characteristics of the study sample (N=234)

Age years, median (range)	34 (23–46)
BMI, median (range)	22.4 (16.7–35.9)
Smoking habits, n/N (%)	
Unknown	7 (3)
No smokers	186 (79.5)
1–10 cigarettes per day	31 (13.2)
10–20 cigarettes per day	7 (3)
>20 cigarettes per day	1 (0.4)
Not provided	2 (0.9)
Infertility factors, n/N (%)	
Male	92 (39.3)
Female	50 (21.3)
Unexplained	79 (33.8)
Mixed	10 (4.3)
Unknown	3 (1.3)
FVL, n/N (%)	11 (4.7)
PTm, n/N (%)	10 (4.3)
Severe thrombophilias*, n/N (%)	3 (1.3)

*Either homozygosis for FVL or PTm; double mutation, FVL or PTm and/or natural anticoagulants deficiency.
BMI, body mass index; FVL, factor V Leiden; PTm, prothrombin mutation.

Villani M et al BMJ Open 2015

VTE IN PREGNANCIES AFTER ART



Henriksson P et al. BMJ 2013;346:bmj.e8632

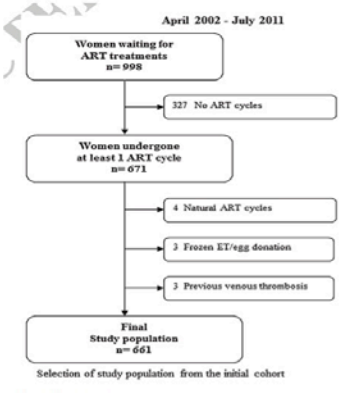
BMJ

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

CrossMark

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

Michela Villani[1] · Giovanni Favuzzi[1] · Pasquale Totaro[2] · Elena Chinni[1] · Gennaro Vecchione[1] · Patrizia Vergura[1] · Lucia Fischetti[1] · Maurizio Margaglione[3] · Elvira Grandone[1]



Selection of study population from the initial cohort

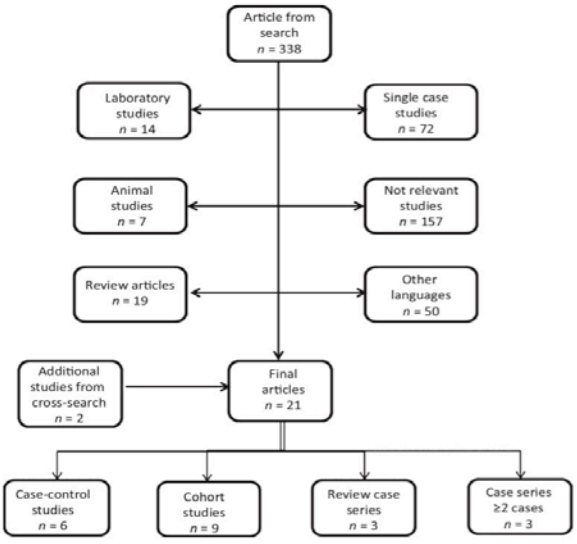
Patient	Age	BMI	Varicose veins	Thrombophilia	Family history for VTE	OHSS	Thrombotic event, details	Antithrombotic prophylaxis
1	34	25.7	No	aPL syndrome	n.a.	Yes	Isolated PE	No
2	45	30.8	No	No	No	Yes	Isolated PE	No

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, *in press*



ure 1. Flow chart of articles identified in searches.

AOGS SYSTEMATIC REVIEW

Thromboembolism and in vitro fertilization – a systematic review

MARIA SENNSTRÖM[1], KARIN ROVA[2], MARGARETA HELLGREN[3], RAGNHILD HJERTBERG[4], EVA NORD[1], LARS THURN[2,5] & PELLE G. LINDQVIST[2,6]

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

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

			Venous thromboembolism (VTE)			Arterial thromboembolism (ATE)		
Year (ref)	Author	Study design	*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

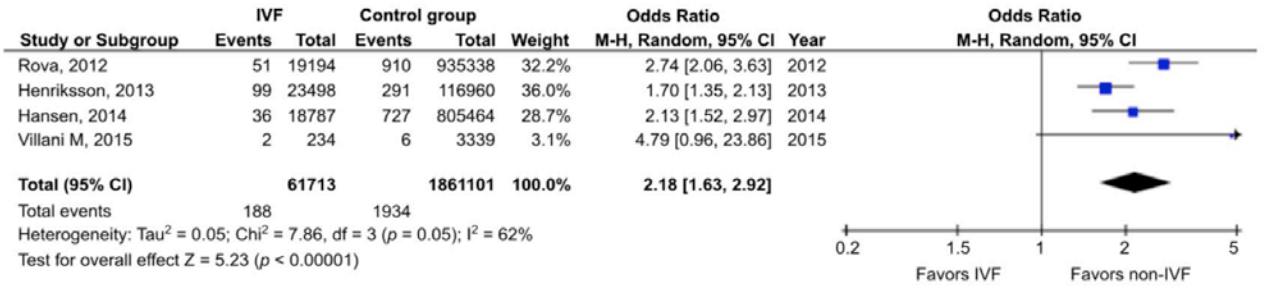

Figure 2. Meta-analysis of frequency of antepartum VTE in IVF pregnancies. [Color figure can be viewed at wileyonlinelibrary.com].

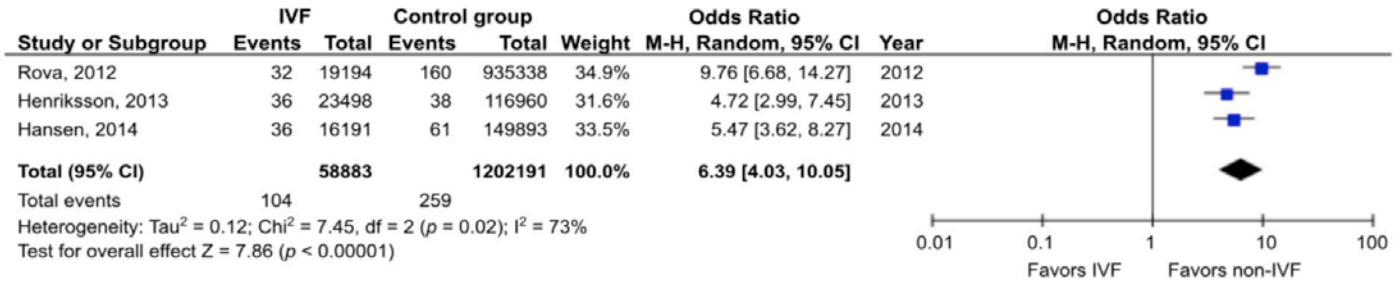

Figure 3. Meta-analysis of risk of first trimester VTE in IVF pregnancies. [Color figure can be viewed at wileyonlinelibrary.com].

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 appliccable; 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.

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†LMWH + ASA doses not specified.
‡Unknown start of thromboprophylaxis.

Thrombosis during ART

VTE: 40–42 days after ET

◆ The incidence of VTE in relation to IVF has been reported at approximately 0.1%-0.5% of treatment cycles (*Mara M, Ceska Gynekol 2004; Grandone E, Hum Reprod 2004; Chan WS, Ginsberg JS. J Thromb Haemost 2006*).

◆ If OHSS: VTE risk lasts from several days to weeks after OHSS is resolved *(Chan and Dixon, 2008)*.

Arterial thrombosis: 10 days after ET *(Chan WS. Curr Opin Obstet Gynecol 2009; Chan WS, Dixon ME Thromb Res 2008)*

The risk of VTE related to OHSS in the first trimester is 1.7%. Therefore, in the absence of additional risk factors for VTE, LMWH is recommended to be administered to OHSS patients dur- ing the whole first trimester, but not thereafter (Rova K, Fertil Steril. 2012;).

CERCABates SM. Anticoagulation and in vitro fertilization and ovarian stimulation. Hematology Am Soc Hematol Educ Program. 2014;2014:379–86.

Prevention and Treatment of VTE in ART

No controlled studies in this area. Clinically, progression of thromboembolism is seen in 10% of cases and along with the presentation in unusual sites suggests that adequate anticoagulation must be implemented promptly.

LMWH is now part of many recommended OHSS treatment protocols **(RCOG) (*Al-Shawaf and Grudzinskas, 2003*).**

However, despite prophylactic (***Hignett et al., 1995; Arya et al., 2001***) and even therapeutic anticoagulation (***McGowan et al., 2003***), thrombosis has been described in association with OHSS.

Factors affecting success/failure

- maternal age,
- reproductive history,
- cause of infertility,
- lifestyle factors,
- quality of the embryos, number of embryos transferred,
- endometrial receptiveness

Qublan HS. Et al. J Obstet Gynaecol. 2005

VTE in Assisted Reproductive Technologies (ART)

Epidemiology

Risk factors

Possible strategies to treat and prevent the events

Has thrombophilia a role?

- The relationship between thrombophilia and ART outcomes is debated (*Penzias AS. Fertil Steril. 2012*)

- Factor V Leiden ? Severe thrombophilias? Association in women with previous implantation failures ? (*Di Nisio M. et al. Blood. 2011*).

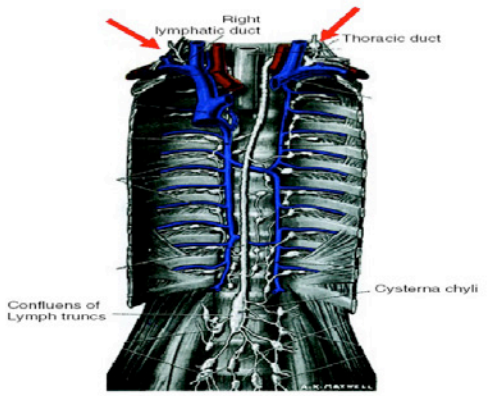

Fig. 1. The largest lymphatic vessel in the body is the thoracic duct. Together with the right lymphatic duct it collects most of the lymph in the body and drains into the systemic blood circulation. The thoracic duct drains into the junction of the left subclavian vein and left jugular vein, the right lymphatic duct into the venous angle on the right side at the jugular vein and the subclavian vein (arrows). Both thoracic and lymphatic duct empty lymph and chyle into the venous system as a return pathway of the systemic loop. In women with ovarian hyperstimulation syndrome, ascites with very high concentrations of estradiol are collected from the peritoneal space into the cisterna chyli, transported via the thoracic and lymphatic duct to the chest, and drained into the junction of the subclavian vein and jugular veins. This phenomenon represents a local trigger for a thrombotic event extending from that anatomical site. Reprinted from *Gray's Anatomy* (1989), p. 841 [4], with permission from Elsevier.

Risk of VTE in pregnancy after ART

- The increased risk is restricted **to the first trimester , (OR) 9.8 95% CI 6.7, 14.3,** with background rates of incidence in the second and third trimesters, the initial post-partum period and in the first three years after an IVF cycle *(Rova K et al, F&S 2012)*.

- Women who experience OHSS show almost a **100-fold increased risk of VTE** during the **first trimester** as compared to **natural pregnancy** (OR 87.3 95% CI 54.1, 140.8) *(Rova K et al, F&S 2012).*

Occurrence of Vein Thromboses in women undergone ART (successful cycles)

Patients	Age at events	BMI	tHcy	Cycle	Type of event	Thrombophilia OHSS	Antithrombotic prophylaxis
1	30	22.3	7.23	1	SVT in the left leg at 12 weeks of pregnancy	no	LMWH*
2	38	20.4	6.0	3	PE during twin pregnancy ended with IUFD (22 weeks)	no	none
3	40	35.9	4.76	3	DVT in the right leg at 18 weeks of pregnancy	PTm heterozygous	none

* Started when pregnancy test was positive

Incidence: 8.5/1000 vs 1.8/1000

After the exclusion of women with previous VTE p: 0.054; OR: 7.2, 95% CI 0.91 to 45.6.

Villani M., et al, BMJ Open, 2015

Quesiti clinici

- E' utile istituire una profilassi con Eparina a basso peso Molecolare?
- In caso affermativo, quando, quale eparina e quali dosaggi? Quanto tempo proseguire con eventuale profilassi?
- E' prudente trasferire in utero una o due blastocisti? In caso affermativo, è opportuno praticare profilassi con eparina a basso peso molecolare?

Table 2 Information on unsuccessful and successful ART cycles

	Unsuccessful cycles (N = 1518)	Successful cycles (N = 318)	p	OR	95% CI
Period of study, n/N of ART cycles (%)					
≤ 2002: 164 ART cycles	139 (84.8)	25 (15.2)	–	–	–
2003–2005: 386 ART cycles	336 (87)	50 (13)	–	–	–
2006–2008: 600 ART cycles	498 (83)	102 (17)	–	–	–
2009–2011: 686 ART cycles	545 (79.4)	141 (20.6)	–	–	–
ART procedure, n/N (%)					
IUI	262 (17.2)	27 (8.5)	< 0.001	2.25	1.46–3.49
IVF	642 (42.3)	153 (48.1)	n.s.	–	–
ICSI	555 (36.6)	133 (41.8)	n.s.	–	–
Controlled ovarian stimulation	17 (1.1)	5 (1.6)	n.s.	–	–
Canceled cycle[a]	42 (2.8)	0 (0)	0.001	n.a.	n.a.
Antithrombotic prophylaxis, n/N (%)					
ASA	341 (22.5)	74 (23.3)	n.s.	–	–
LMWH	52 (3.4)	22 (6.9)	n.s.	–	–
LMWH + ASA	12 (0.8)	13 (4.1)	< 0.001	5.35	2.27–12.64
OHSS, n/N (%)	37 (2.4)	12 (3.8)	n.s	–	–
Venous thrombosis, n/N (%)	0 (0)	2 (0.6)	0.04	n.a.	n.a.
Pulmonary embolism, n/N (%)	2 (0.1)	1 (0.3)			

IUI intrauterine insemination, *IVF* in-vitro fertilization, *ICSI* intracytoplasmatic sperm injection, *ASA* acetylsalicylic acid, *LMWH* low-molecular-weight heparin, *OHSS* ovarian hyperstimulation syndrome

[a]ART cycle in which ovarian stimulation has been carried out with the intention to treat, but which did not proceed to follicular aspiration or, in the case of a thawed embryo, to embryo transfer

Villani M. et al, JTT, 2017, *in press*

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Recurrent Failures in assisted Reproductive Techniques (The FIRST Registry)

This study is currently recruiting participants. (see Contacts and Locations)

Verified February 2016 by Casa Sollievo della Sofferenza IRCCS

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Information provided by (Responsible Party):
Elvira Grandone, MD, Head of Unit, Casa Sollievo della Sofferenza IRCCS

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START-ORTOPEDIA

CHIRURGIA ELETTIVA ED IN EMERGENZA (PROTESI ANCA- GINOCCHIO; FRATTURA FEMORE) IN PAZIENTI ANTICOAGULATI

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