Anticoagulazione nelle Procedure di Fecondazione Assistita

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The FIRST Study

recurrent ***F***ailures in ass***I***sted ***R***eproductive ***T***echniques

A potential benefit of low-molecular-weight heparin (LMWH) in improving ART outcomes, independently of the presence of thrombophilia, has been suggested (Grandone E. et al, PLoS One 2014; Dentali F. al., J Thromb Haemost. 2011; Nelson SM. Hum Reprod Update 2008).

It was hypothesised that heparin can modulate many physiological processes required for blastocyst apposition, adherence and implantation with a potential role in improving pregnancy rates and outcomes.

Several factors could be involved in this process: age, quality of the embryos, number of embryos transferred, success of embryo transfer and endometrial receptiveness.

Thrombophilia?

recurrent ***F***ailures in ass***I***sted ***R***eproductive ***T***echniques

The FIRsT Registry

During this study we will collect and evaluate clinical data regarding the first cycle in women with previous ART failures.

The impact of thrombophilia will be evaluated if available.

OUTLINES

- VTE in ART: risk factors and possible strategies to prevent the events
- Pregnancy Outcomes after ART: possible role for antithrombotic prophylaxis

- VTE in ART: risk factors and possible strategies to prevent events
- Pregnancy Ouctcomes after ART: possible role for antithrombotic prophylaxis

IVF/ICSI

- There has been a huge increase in the worldwide use of IVF since the first successful cycle report by Edwards and Steptoe in 1978.
- In Italy, in 2010 more than 90.000 cycles have been recorded, with more than 12.000 newborns

ART and Thrombosis

- Arterial thrombosis ; VTE
- **O**varian **H**yper **S**timulation **S**yndrome (OHSS): 3-8% successful cycles
- Magnitude of the risk
- VTE in pregnancies after ART (successful cycles)

Thrombosis during ART: features

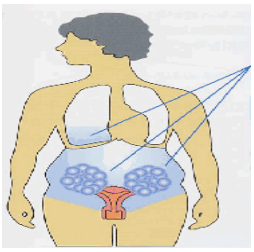
Arterial thrombosis: **10 days after ET** *(Chan WS. Curr Opin Obstet Gynecol 2009; Chan WS, Dixon ME Thromb Res 2008)*

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)*.

OHSS



- Hypotension
- Pleural effusion (more, and more frequently on the right side)
- Adult form of respiratory distress syndrome (ARDS)
- Pericardial effusion
- Ascites
- Oliguria and anuria
- Multiple organ failure
- Death (3/100,000 cycles) **Cantwell R, et al.BJOG 2011; Braat DM, et al. Hum Reprod 2010.**

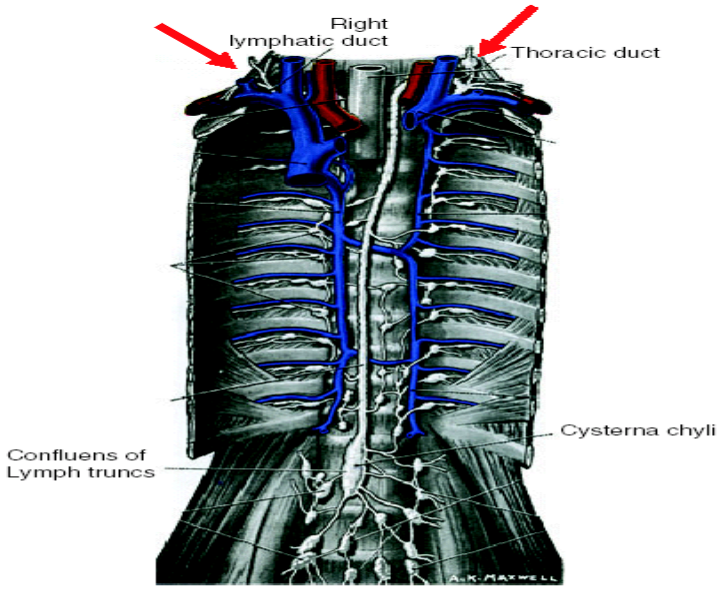


Fig. 1. The largest lymphatic vessel in the body is the thoracic duct. Together with the right lymphatic duct it collects most of the lymph in the body and drains into the systemic blood circulation. The thoracic duct drains into the junction of the left subclavian vein and left jugular vein, the right 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.

OHSS as a “thrombophilia”

- OHSS is an exaggerated response to ovulation induction therapy. It is tipically associated with exogenous (human menopausal and human chorionic) gonadotrophin stimulation
- It is rarely observed with use of other agents, such as clomiphene citrate and gonadotrophin -releasing hormones.
- Its severe form occurs in 0.8% to 2.0% of patients undergoing induction of ovulation.

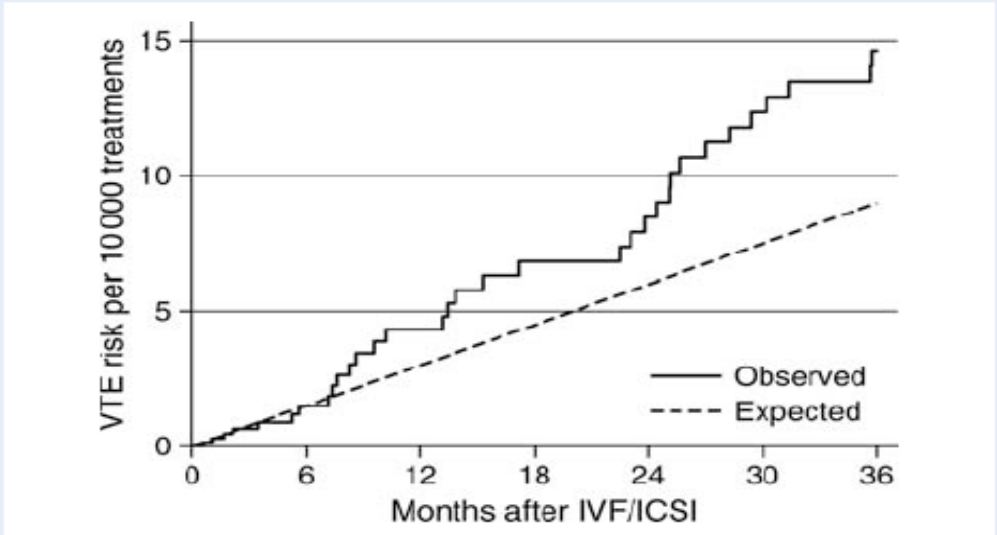


Figure 1 Cumulative incidence of venous thrombosis (VTE) for the first three years after IVF or ISCI, compared to the incidence in the reference population.

30 884 Danish women undergoing 75 141 treatments from 1994 to 2005.

Hansen et al, Hum Reprod 2012

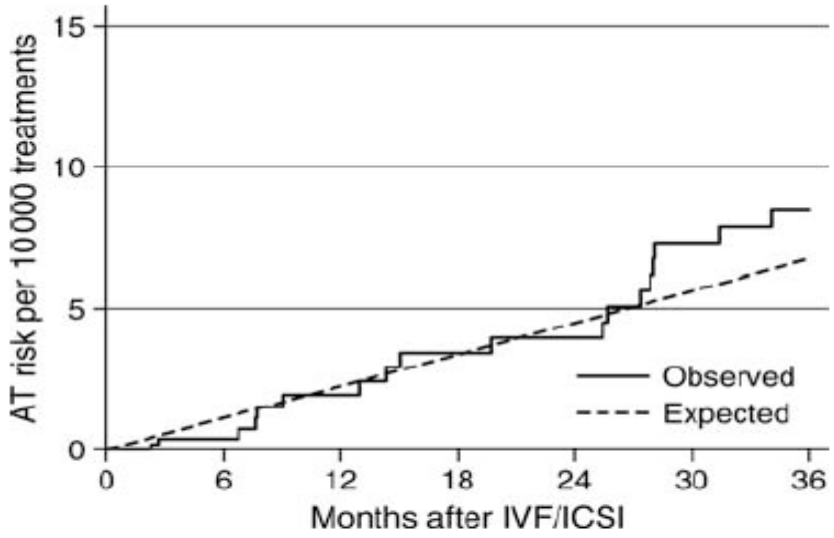


Figure 2 Cumulative incidence of arterial thrombosis (AT) for the first three years after IVF or ISCI, compared to the incidence in the reference population.

Hansen et al, Hum Reprod 2012

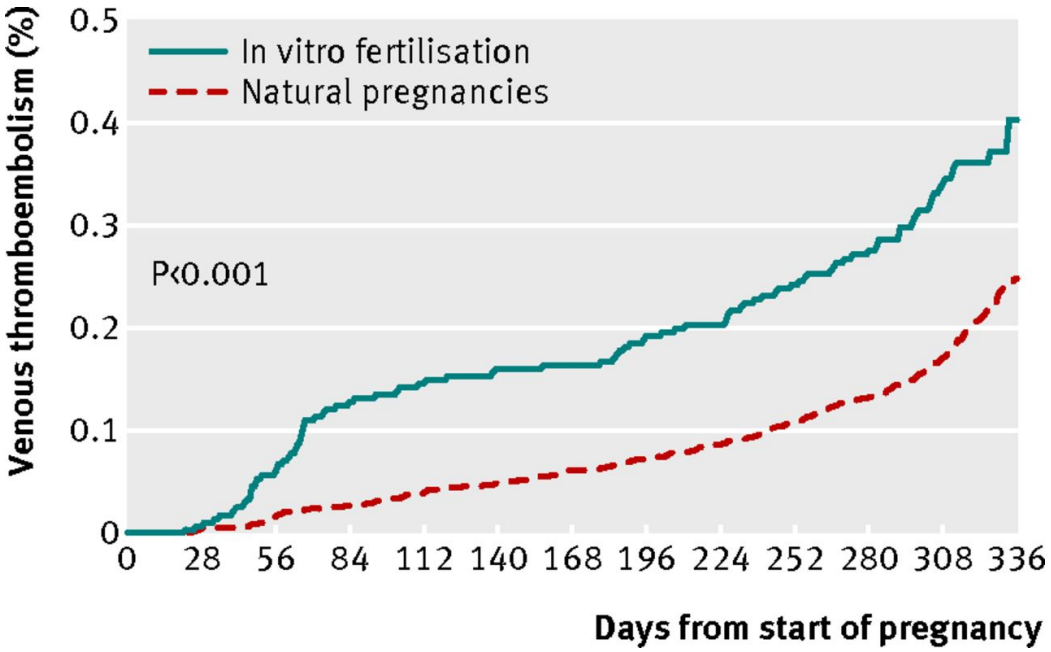
Table II **Incidence rates of venous and arterial thromboses within the first 6 and 12 months after IVF or ISCI.**

	Venous thrombosis	Arterial thrombosis
Reference incidence rate	3.0	2.25
Within 6 months		
Events	7	2
Time at risk (years)	24 686	24 687
Incidence rate (95% CI)	2.8 (1.1–5.8)	0.8 (0.1–2.9)
Incidence rate ratio (95% CI)	0.95 (0.38–1.95)	0.36 (0.04–1.30)
Within 12 months		
Events	14	6
Time at risk (years)	36 856	36 861
Incidence rate (95% CI)	3.8 (2.1–6.4)	1.6 (0.6–3.5)
Incidence rate ratio (95% CI)	1.27 (0.69–2.12)	0.72 (0.27–1.57)

Incidence rate ratios were calculated by comparison to reference populations of young Danish females.
Incidence rates are per 10 000 years at risk.

Hansen et al, Hum Reprod 2012

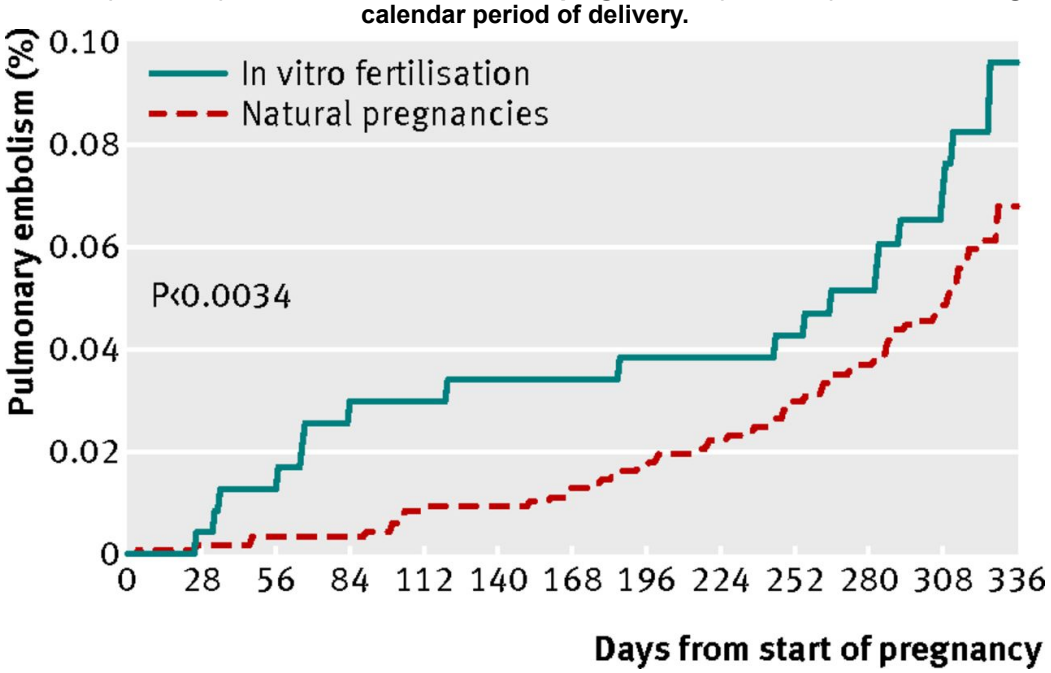
VTE IN PREGNANCIES AFTER ART



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

BMJ

Fig 2 Proportional hazard regression of pulmonary embolism in pregnant women after in vitro fertilisation (n=23 498) and in women with natural pregnancies (n=11 960) matched on age and calendar period of delivery.



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

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Risk of VTE in pregnancy after ART

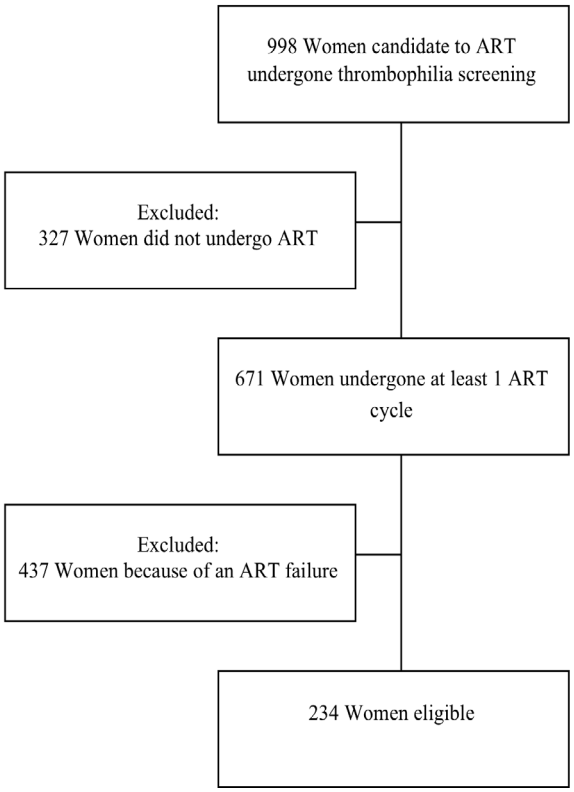
- The increased risk is restricted **to the first trimester , (OR) 9.8 95% CI 6.7, 14.3,** with background rates of incidence in the second and third trimesters, the initial post-partum period and in the first three years after an IVF cycle *(Rova K et al, F&S 2012)***.**

- 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).*

Risk factors identifiable prior to and during ovarian stimulation	
Previous venous or arterial thrombembolism	Age over 35 years
Obesity (body mass index $\geq$30 kg/m^2)	Prolonged travel
Gross varicose veins	Dehydration
Previous intravenous drug abuse	Ovarian hyperstimulation
Prolonged bed rest	Immobility
Medical conditions	Inflammatory conditions, systemic lupus erythematosus, hyperlipidaemia, sickle cell anaemia, ulcerative colitis, diabetes mellitus, Cushing's syndrome, nephrotic syndrome, malignancy, myeloproliferative disorders and liver disease
Inherited thrombophilia[§]	Odds ratio (95% confidence intervals)
Factor V Leiden heterozygous	9.32 (5.44–12.70)
Factor V Leiden homozygous	34.40 (9.86–120.05)
Antithrombin deficiency	4.69* (1.30–16.96)
Protein C deficiency	4.76 (2.15–10.57)
Prothrombin G20210A heterozygous	6.80 (2.46–19.77)
Prothrombin G20210A homozygous	26.36 (1.24–559.29)
Family history of VTE in one or more first degree relatives[γ]	2.7 (95% CI, 1.8–3.8)
Acquired thrombophilia	
Lupus anticoagulant[†]	Five associations with odds ratio of 5.7–9.4 and all significant at 95% CI
Anticardiolipin antibodies[†]	Eight associations with deep vein thrombosis were analysed in four studies: one had a significant 95% CI but only for IgG anticardiolipin antibody titers exceeding the 95th percentile (i.e. 33 GPL units)

[§]Data derived from pregnancy related risk of VTE (Robertson *et al*., 2006).
[γ]Data derived from non-pregnant related risk of VTE (Noboa *et al*., 2008).
[†]Data derived from non-pregnant related risk of VTE (Galli *et al*., 2003b).
*Antithrombin deficiency odds ratio is a serious underestimate of risk for VTE, given 73% of affected individuals have a VTE (see text for full details).

Figure 1. Study cohort (April 2002 – July 2011)



Villani M, et al, BMJ Open 2015

Age years, median (range)	**34 (23 - 46)**
Body Mass Index (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)**

Villani M., et al, BMJ Open 2015

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

Maternal age yrs	15	20-29	30-39	40	Live births number
Reference cohort (n= 3359), % 2010-2012	3.7	34.4	55.1	6.8	3451
General population from the same geographical area (n= 106265) , % 2008-2010	2.3	32.4	59.5	5.8	107 461

Patients	Age at events	BMI	tHcy	Cycle	Type of event	Thrombophilia OHSS	Antithrombotic prophylaxis
1	31	37.1	n.a.	-	SVT in the left leg	no	none
2	33	18.3	n.a.	-	DVT in the left leg	Previous SVT after Caesarean section	none
3	28	17.3	n.a.	-	DVT in one leg at 37 weeks of pregnancy	FVL heterozygous	LMWH*
4	33	n.a.	n.a.	-	SVT in the right leg	n.a.	n.a.
5	37	n.a.	n.a.	-	Bilateral SVT	n.a.	n.a.
6	43	n.a.	n.a.	-	DVT in the left leg	n.a.	none
7	22	n.a.	n.a.	-	DVT in the left leg	n.a.	n.a.
8	35	n.a.	n.a.	-	Bilateral SVT	n.a.	none
9	36	21.3	n.a.	-	DVT in the left leg at 21 weeks of pregnancy	FVL + PC deficiency Previous DVT	LMWH* (the event occurred during a suspension period)
10	33	18.7	n.a.	-	DVT in the left leg at 11 weeks of pregnancy	FVL heterozygous	n.a.
11	35	n.a.	n.a.	-	SVT in the right leg	n.a.	n.a.

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

Two-tailed Fisher exact test
p: 0.06; OR: 3.9, 95%CI: 0.87-15.3.
After the exclusion of women with previous VTE
p: 0.054; OR: 7.2, 95% CI: 0.91 to 45.6.

Patients	Age at events	BMI	Hcy	Cycle	Type of event	Thrombophilia (PTm)	Antithrombotic prophylaxis
1	30	22.3	7.23	1	SVT in the left leg at 12 weeks of pregnancy	no	LMWH*
2	33	20.4	5.0	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

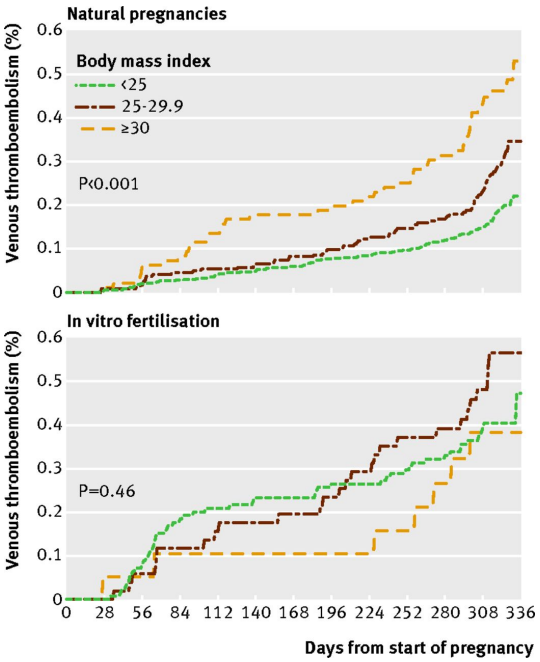
Incidence: 8.5/1000 vs 1.8/1000

Villani M., et al, BMJ Open, 2015

Preventing VTE in ART

- Many additional risk factors for VTE could be present in women approaching ART (eg: age, BMI, prolonged bed rest).
- They are more frequent in clinical practice as compared to OHSS.
- RCOG guidelines suggest to consider LMWH in all these cases .

Fig 4 Proportional hazard regression of venous thromboembolism in three strata for body mass index (<25, 25-29.9, and ≥30) in pregnant women after in vitro fertilisation (n=23 498) and in women with natural pregnancies (n=116 960) matched on age and calendar period of delivery .



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BMJ

LMWH for preventing VTE in ART
VTE following ovulation induction

- 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.

- The future risk of **recurrence** in patients who develop these complications is unknown; however, extrapolation from pregnancy-related studies suggest a **2–8%** risk in the absence of anticoagulation which would be useful in counselling such patients (**Brill-Edwards et al., 2000; Pabinger et al., 2005; De Stefano et al., 2006**).

LMWH for preventing VTE in ART

- Heparin should ameliorate the risk of thrombotic complications associated with OHSS, and thromboprophylaxis using pregnancy related LMWH doses is now part of many recommended 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.

- This resistance to heparin may reflect localized excessive activation of coagulation and elevated concentrations of estradiol impairing the endothelium's antithrombotic properties (***Bauersachs et al., 2007***).

LMWH for preventing VTE in ART

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THROMBOPROPHYLAXIS

•Antithrombotic prophylaxis in 23/234 (9.8 %) women, 8/23 (34.8 %) were thrombophilic (3 FVL heterozygotes, 3 PTm heterozygotes, 1 carried a protein S deficiency combined with FVL and 1 a confirmed presence of antiphospholipid antibodies).

•No treatment in 211: 16 carried thrombophilia (8 were FVL heterozygotes, 7 PTm heterozygotes and 1 protein S deficient).

•When we compared the incidence of thrombotic events in presence or absence of prophylaxis with LMWH, we found no significant difference between the groups (thromboses: 1/23 vs 2/211, p: ns).

Villani M et al, BMJ Open

Prevention and treatment of thrombosis in ART

•No prospective trials to compare the effects of unfractionated or different LMWHs during ART in patients at high risk or suffering from VTE have yet been published.

•The application of heparin is again based on biological plausibility rather than on prospective randomised trials.

•The adequate duration of thromboprophylaxis (or VTE treatment) remains unclear as well.

CHEST 2012

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).

Possible strategies to reduce VTE risk

Clinical Situation	Suggested Management
Risk Factors for VTE present prior to controlled ovarian stimulation but no previous VTE or thrombophilia	Risk Assessment for VTE If multiple risk factors or single major risk factor, consider prophylaxis with LMWHs
OHSS	Prophylactic doses of LMWHs
Thrombophilia without previous VTE	Surveillance or Prophylactic doses of LMWHs (LMWHs if Antithrombin deficiency)

Nelson S.M., 2009, adapted

Venous thrombosis during assisted reproduction: Novel risk reduction strategies

- Complete abolition of OHSS is however now a reality by avoiding exposure to exogenous hCG.
- This can be achieved by segmentation of the IVF cycle using a GnRH agonist for final oocyte maturation and then freezing all oocytes or embryos with subsequent replacement of a single embryo in the context of a frozen embryo transfer.
- This novel approach will ensure a VTE risk equivalent to natural conception and can be combined with conventional thromboprophylaxis strategies.

Nelson S.M., Thromb Res 2013

SCENARI POSSIBILI

Per le Tecniche di II livello:

- Presenza della SOLA trombofilia LIEVE o di n. 1 fattore di rischio aggiuntivo: NO PROFILASSI
- Presenza della SOLA trombofilia SEVERA: PROFILASSI CON EBPM
- Presenza di n. 2 fattori di rischio (compresa trombofilia lieve): VALUTARE PROFILASSI
- Presenza di n. 3 fattori di rischio (compresa trombofilia lieve): SI PROFILASSI
- **OHSS: SEMPRE PROFILASSI con EBPM, da estendere anche in eventuale gravidanza per almeno 3 mesi**

Per le tecniche di I livello

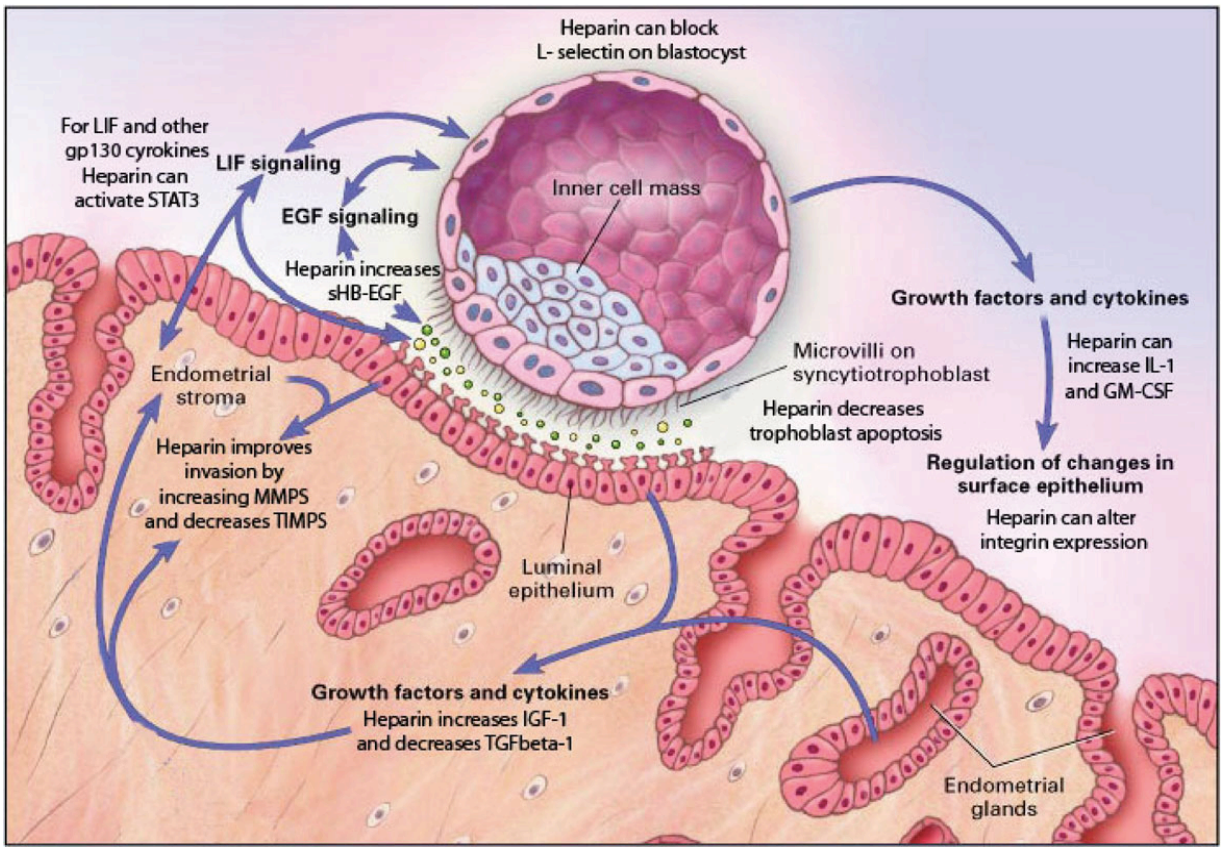
- Se su ciclo spontaneo: NO PROFILASSI
- Se si induce l' ovulazione con farmaci : stesso schema delle tecniche di II livello

Quando iniziare la profilassi nelle donne candidate?: All' inizio del ciclo di induzione della super-ovulazione e fino al test di gravidanza, se positivo rivalutare la donna ed i fattori di rischio.

Quali molecole? Enoxaparina 4000UI/die; Nadroparina 3800UI/die (se peso >70Kg)- 2850UI/die (peso<70Kg); Dalteparina 5000UI/die.

- VTE in ART: Risk factors and possible strategies to prevent events

- Pregnancy Ouctcomes after ART: possible role of antithrombotic prophylaxis



Norwitz ER, NEJM 2001

Table VII. Studies of heparin in assisted conception.

Study	Intervention	Outcome of patients receiving treatment	Outcome of patients in control arm	Conclusion
Kutteh *et al.* (1997)	Two centre comparator study. In centre 2 women with positive APA initiated aspirin 81 mg/day at the time of gonadotrophin start and s.c. heparin 5000 units twice daily beginning on the night of aspiration	10/19 (52.6%) pregnant 8/19 (42.1%) clinical pregnancies	8/17 (42.1%) pregnant 6/17 (35.3%) clinical pregnancies	No significant differences in implantation, pregnancy or clinical pregnancy rates
Qublan, personal communication	Double-blind placebo controlled RCT of 81 women with inherited or acquired thrombophilia and ≥3 failed embryo transfers. Women started s.c. enoxaparin 40 mg once daily on day of embryo transfer.	31% pregnant 23.8% live births	9.6% pregnant 2.8% live births	LMWH improves pregnancy and live birth rate in women with thrombophilia and ≥3 failed embryo transfers ($P < 0.05$)
Schenk *et al.* (1996)	Single centre non-randomised study. APA positive women given heparin and LDA compared with seronegative women	18/35 (51.4%) pregnant	12/40 (30%) seronegative women pregnant	Heparin and aspirin improves implantation rate in APA positive women ($P < 0.05$)
Sher *et al.* (1994)	Single centre non-randomized study. APA positive women initiated aspirin 81 mg/day and s.c. heparin 5000 units twice daily beginning on Day 2 of stimulation	82/169 (49%) pregnant	4/25 (16%) seropositive women pregnant 47/171 (27%) seronegative women pregnant	Heparin and aspirin improves implantation rate in APA positive women ($P < 0.05$) and when compared with seronegative women ($P < 0.001$)
Sher *et al.* (1998)	Multiphase study. APA positive women initiated aspirin 81 mg/day and s.c. heparin 5000 units twice daily beginning on Day 2 of stimulation. Those that declined treatment were control group	417/923 (46%) live births	22/127 (17%) live births	Heparin and aspirin improves live birth rate in APA positive women ($P < 0.001$)
Stern (2003)	Double-blind placebo controlled RCT crossover trial of women either APA or ANA and ≥10 embryos transferred and not achieved pregnancy. Women initiated aspirin 100 mg/day and s.c. heparin 5000 units twice daily beginning on day of embryo transfer	23/158 (15%) pregnant 18/296 (6%) live births per embryo	25/142 (18%) pregnant 17/259 (7%) live births per embryo	Heparin and aspirin from day of embryo transfer does not improve pregnancy or live birth rates in women seropositive for APA or ANA and ≥10 embryos transferred

LDA=low dose aspirin.
APA=antiphospholipid antibody.
ANA=anti nuclear antibody.

Efficacy of low molecular weight heparin in patients undergoing *in vitro* fertilization or intracytoplasmic sperm injection

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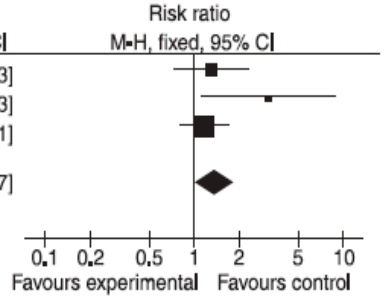
A

Study or subgroup	LMWH Events	LMWH Total	Control Events	Control Total	Weight	Risk ratio M-H, fixed, 95%CI
Noci 2011	19	73	16	80	31.6%	1.30 [0.73, 2.33]
Qublan 2008	13	42	4	41	8.4%	3.17 [1.13, 8.93]
Urman 2009	34	75	29	75	60.0%	1.17 [0.80, 1.71]
Total (95% CI)		190		196	100.0%	1.38 [1.02, 1.87]
Total events	66		49			

Heterogeneity: $\chi^2 = 3.24$, df = 2 ($P = 0.20$); $I^2 = 38\%$

Test for overall effect: $Z = 2.07$ ($P = 0.04$)

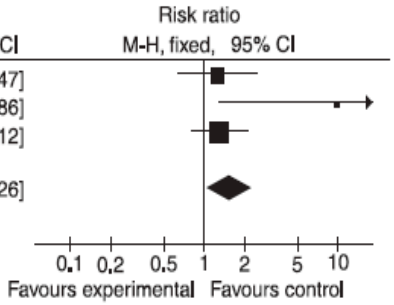


B

Study or subgroup	LMWH Events	LMWH Total	Control Events	Control Total	Weight	Risk ratio M-H, fixed, 95% CI
Noci 2011	15	73	13	80	37.1%	1.26 [0.65, 2.47]
Qublan 2008	10	42	1	41	3.0%	9.76 [1.31, 72.86]
Urman 2009	26	75	20	75	59.8%	1.30 [0.80, 2.12]
Total (95% CI)		190		196	100.0%	1.54 [1.05, 2.26]
Total events	51		34			

Heterogeneity: $\chi^2 = 4.05$, df = 2 ($P = 0.13$); $I^2 = 51\%$

Test for overall effect: $Z = 2.23$ ($P = 0.03$)



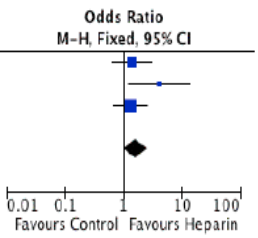
Dentali F. et al, JTH 2012

Figure 5. Forest plot of comparison: 1 Heparin versus control, outcome: 1.2 Clinical Pregnancy Rate per woman.

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Noci 2011	19	73	16	80	37.7%	1.41 [0.66, 3.00]
Qublan 2008	13	42	4	41	9.3%	4.15 [1.22, 14.07]
Urman 2009	34	75	29	75	52.9%	1.32 [0.69, 2.52]
Total (95% CI)		**190**		**196**	**100.0%**	**1.61 [1.03, 2.53]**
Total events	66		49			

Heterogeneity: $Chi^2 = 2.80$, df = 2 (P = 0.25); $I^2 = 29\%$

Test for overall effect: Z = 2.08 (P = 0.04)



Journal of Thrombosis and Haemostasis, **10**: 2075–2085 DOI: 10.1111/j.1538-7836.2012.04886.x

ORIGINAL ARTICLE

Low-dose aspirin for *in vitro* fertilization or intracytoplasmic sperm injection: a systematic review and a meta-analysis of the literature

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Aspirin to prevent Implantation Failure: A meta-analysis

Inclusion Criteria: RCT comparing low-dose aspirin with placebo/no treatment in IVF/ ICSI women were included. Pooled ORs and 95% CIs were calculated.
Results: 17 studies , 6403 patients included. The use of aspirin did not improve live birth/ pregnancy rate compared with placebo or no treatment (1.08; 95% CI, 0.90, 1.29). Pregnancy rates in patients randomized to low dose aspirin : OR, 1.19; 95% CI, 1.01, 1.39, but miscarriage rates were not (OR, 1.18; 95% CI, 0.82, 1.68).

No substantial efficacy of aspirin. Further high-quality studies evaluating the possible efficacy of aspirin in selected groups of patients are warranted.

Figure 1. Flow diagram of enrolled women.

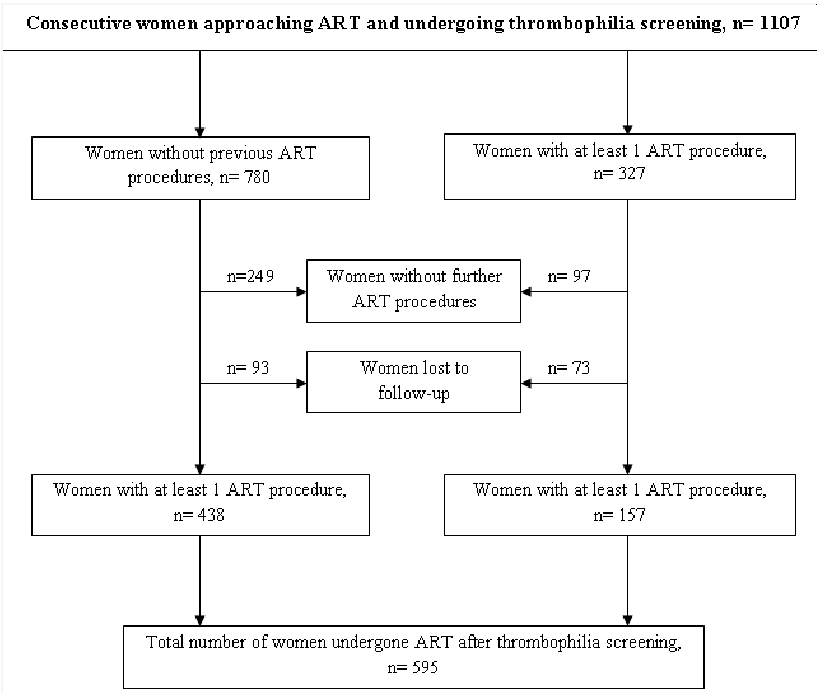

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Table 1. Baseline characteristics and obstetric history of study participants (N=1107)

Age [yrs], median (range)	**35 (18-49)**
Smoking habits, n/N (%)	**233/1107 (21)**
1 - 10 cigarettes per day, n (%)	*154 (66.1)*
10 - 20 cigarettes per day, n (%)	*61 (26.2)*
> 20 cigarettes per day, n (%)	*3 (1.3)*
**Missing, n (%)*	*15 (6.4)*
Infertility factors	
Male factor, n/N (%)	*361/1107 (32.6)*
Pelvic/Tubal factor, n/N (%)	*243/1107 (21.9)*
Unexplained, n/N (%)	*335/1107 (30.3)*
Mixed, n/N (%)	*57/1107 (5.1)*
**Unknown, n/N (%)*	*111/1107 (10.1)*
Women with at least one natural conception, n/N (%)	**173/1107 (15.6)**
Natural conceptions, n	*337*[Δ]
Live births, n (%)	*52 (15)*
Pregnancy losses, n (%)	*208 (62)*
Women with at least 1 ART procedure, n/N (%)	**327/1107 (29.5)**
Type of ART procedure	
IUI, n (%)	*64 (19.6)*
IVF, n (%)	*121 (37)*
ICSI, n (%)	*90 (27.5)*
IUI+IVF+ICSI, n (%)	*49 (15)*
**Missing, n (%)*	*3(0.9)*
Outcome of ART procedure, n	*946*
Clinical pregnancies, n (%)	*131*[□] *(13.8)*
Live births, n (%)	*21 (16)*
Pregnancy losses, n (%)	*103 (78.6)*
FVL, n/N (%)	**45/1107 (4)**
PTm, n/N (%)	**57/1107 (5)**
Severe thrombophilias, n/N (%)	**13/1107 (1)**

*Information not provided by couples
[Δ]32 ectopic pregnancies, 1 ongoing pregnancy, 44 termination
[□]3 ectopic pregnancies, 3 ongoing pregnancy, 1 termination

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Table 3. Clinical pregnancies and live births according to the type of treatment in the prospective cohort. Logistic regression.

	Clinical pregnancies			Live births		
	Ra	OI 95%		Ra	OI 95%	
Ageatscreening	<0.	0.9	0.09	<0.	0.9	0.09
Treatment ASA	0.1	1.4	0.29	0.3	1.2	0.48
Treatment LMW	0.0	2.6	1.53	0.0	2.9	1.55
Combination	0.0	4.9	1.174	0.0	4.0	1.141

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Regular Article

Clinical Pregnancies and Live Births in women approaching ART: A follow-up analysis of 157 women after thrombophilia screening

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Introduction: The role of thrombophilia screening and antithrombotic therapy in unselected women undergone Assisted Reproductive Technologies (ART) is largely unknown. Nonetheless, in many Countries infertile women undergo thrombophilia screening and/or antithrombotic therapy.
Materials and Methods: We carried out a follow-up study. The original sample (n = 1107) consisted of infertile women observed in 13 years. A cohort of 157 women with at least 1 cycle before thrombophilia test and 1 after test was investigated. All underwent thrombophilia screening; an antithrombotic treatment was prescribed in 216 out of 801 cycles. Clinical pregnancy and live birth rates were the main clinical objectives.
Results: Overall, 15 (9.6%) women carried thrombophilia. The Cox regression showed that LMWH alone or combined with ASA was significantly associated with the outcome "live birth" "live births" (p: 0.015, HR: 2.8, 95%CI: 1.2-6.6 for combined therapy), independently of the carriership of thrombophilia. Women with a lower number of attempts had a higher likelihood of delivering a live-born child using the combined therapy (p < 0.001, HR: 0.7, 95%CI: 0.7-0.8), independently of the presence of thrombophilia.
Conclusions: A potential benefit of LMWH in improving number of live births, independently of the presence of thrombophilia, is suggested. Universal thrombophilia screening before ART is not useful to discriminate women with a worse pregnancy prognosis.

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Panel a. Odds Ratio with 95%CI for the outcome "Clinical Pregnancy"

Factors	*P*-value	OR (95 % CI)
Antithrombotic treatment yes/no	0.027	1.59 (1.05 – 2.41)
Type of antithrombotic treatment		
Reference (no treatment)		*1*
• *ASA*	*n.s.*	*1.18 (0.71 – 1.95)*
• *LMWH*	*n.s.*	*2.37 (0.87 – 6.21)*
• *Combined treatment*	*<0.001*	*8.27 (2.72 – 25.49)*
Thrombophilia yes/no	n.s.	1.48 (0.82 – 2.66)

Panel b. Odds Ratio with 95%CI for the outcome "Live Birth"

Factors	*P*-value	OR (95 % CI)
Antithrombotic treatment yes/no	n.s.	1.35 (0.77 – 2.37)
Type of antithrombotic treatment		
Reference (no treatment)		*1*
• *ASA*	*n.s.*	*0.73 (0.32 – 1.59)*
• *LMWH*	*<0.001*	*4.90 (1.75 – 13.29)*
• *Combined treatment*	*0.007*	*4.43 (1.15 – 15.76)*
Thrombophilia yes/no	n.s.	1.20 (0.53 – 2.75)

Conclusions

- VTE risk during and after an ART cycle is slightly increased as compared to that after natural conception
- LMWHs could have a role in lowering the VTE risk in (after) ART, especially in women with OHSS or thrombophilia
- Studies are needed to define when to start and the duration of thromboprophylaxis
- A role of LMWHs in improving live-birth rate is likely, but more evidence is needed

For the full protocols and details about data collection,

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