FERTILITA' E PROBLEMI DELLA GRAVIDANZA

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Outlines

- Drugs: Aspirin, LMWHs, DOACs
- Risk Factors: Thrombophilia
- Research agenda: Biomarkers ?

Aspirin and Pregnancy

- Aspirin acts by neutralizing the activity of cyclooxygenase (COX) enzyme. COX (COX1, COX2) enzymes catalyze the formation of cyclic prostanoids, such as thromboxane A2 (TXA2) and prostacyclin, as well as other prostaglandins .

- Arachidonic acid (AA) is the common precursor of the prostanoid synthesis. Prostanoids have a role in health and diseases, mainly displayed in the inflammation and platelet aggregation .

- Activation of platelets is associated with production of TXA2, which helps to recruit platelets and amplify the process of their activation .

- **Decidualization and invasive throphoblast are key step of normal placental function and, in turn, of a physiological pregnancy.**

- **Invasive throphoblast has the role of promoting a favourable utero-placental circulation, characterised by low resistance, which facilitates the marked increase in blood flow carrying supplies and oxygen to the foetus.**

- It has been documented that aspirin is able to induce the shift in the balance between TXA2 and prostaciclin, leading to vasodilatation and enhanced blood flow.

Table 1. Use of Aspirin to prevent GVCs: evidence from RCTs and prospective studies

Reference	Year	Type	N of women/studies	Enrollment criteria	Outcome	Use of aspirin
Kaandorp SP (65)	2010	RCT	384 women	Pregnancy loss	Live birth	NR
Clark P (66)	2010	RCT	294 women	Pregnancy loss	Live birth	NR
Henderson JT (73)	2014	RCTs, cohort studies	21 RCTs, 2 cohort studies	High risk of pre-eclampsia	Pre-eclampsia, foetal growth restriction, preterm birth	R
Villa PM (74)	2014	RCT	152 women	At risk for pre-eclampsia	Pre-eclampsia, foetal growth restriction, preterm birth	NR
Bujold E (69)	2013	RCTs	34 RCTs	At risk for pre-eclampsia	Severe pre-eclampsia, foetal growth restriction, preterm birth	R
Siristatidis CS (90)	2010	RCTs	2653 women (13 RCTs)	IVF/ICSI	Clinical pregnancy, live birth, pregnancy loss	NR
Dentali F (85)	2012	RCTs	6403 women (17 RCTs)	IVF/ICSI	Clinical pregnancy, live birth	NR
Grandone E (86)	2014	Prospective cohort	1107 women	IVF/ICSI	Clinical pregnancy, live births	NR
Grandone E (87)	2014	Follow-up analysis	157 women	IVF/ICSI	Clinical pregnancy, live birth	NR

NR: Not Recommended
R: Recommended

Grandone E et al, Expert Opinion in Pharmacotherapy, 2015

Aspirin in IVF

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.

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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Main results

The search identified 13 trials as eligible for inclusion in the review, including a total of 2653 participants with a mean age of 35 years. Ten studies used a dose of 100 mg and three used 80 mg of aspirin per day. In most of them, aspirin was commenced immediately at the start of down-regulation, while the duration of treatment varied widely. Eight studies provided a placebo for the control group.

There was no evidence of a difference between the aspirin group and the group receiving no treatment or placebo in rates of live birth (RR 0.91, 95% CI 0.72 to 1.15, 3 RCTs, n = 1053, I^2 = 15%, moderate-quality evidence). In addition, clinical pregnancy rates were also similar for the two groups (RR 1.03, 95% CI 0.91 to 1.17, 10 RCTs, n = 2142, I^2 = 27%, moderate-quality evidence); sensitivity analysis, excluding studies at high risk of bias, did not change the effect estimate. There was no evidence of a difference between groups in terms of multiple pregnancy as confirmed by ultrasound (RR 0.67, 95% CI 0.37 to 1.25, 2 RCTs, n = 656, I^2 = 0%, low-quality evidence), miscarriage (RR 1.10, 95% CI 0.68 to 1.77, 5 RCTs, n = 1497, I^2 = 0%, low-quality evidence), ectopic pregnancy (RR 1.86, 95% CI 0.75 to 4.63, 3 RCTs, n = 1135, I^2 = 0%, very low quality evidence) or vaginal bleeding (RR 1.01, 95% CI 0.14 to 7.13, 1 RCT, n = 487, very low quality evidence). Data were lacking on other adverse effects.

The overall quality of the evidence ranged from very low to moderate; limitations were poor reporting of study methods and suspected publication bias.

Authors' conclusions

Currently there is no evidence in favour of routine use of aspirin in order to improve pregnancy rates for a general IVF population. This is based on available data from randomised controlled trials, where there is currently no evidence of an effect of aspirin on women undergoing ART, as there is no single outcome measure demonstrating a benefit with its use. Furthermore, current evidence does not exclude the possibility of adverse effects.

Cochrane, May 2016

Heparins
Pregnancy

- Both unfractioned- (UFH) and low molecular weight- heparins (LMWHs) exert their role by interacting with Antithrombin (AT).
- Heparin-AT complex is able to accelerate the inhibition of thrombin, and also that of factors (F) Xa, IXa, XIa and XIIa by antithrombin.
- However, thrombin and FXa are more available to the Heparin-AT inhibition in respect to other factors [*Hirsch J, Chest 2001*].
- LMWHs have advantages over UFH in terms of pharmacokinetics and convenience of administration.

Grandone E. et al, Exp Opin Pharmacoth, 2015

F.C.S.A.

Federazione Centri per la diagnosi della trombosi e per la Sorveglianza delle terapie Anti-trombotiche (FCSA)

Segreteria: Via Pace 9, Milano

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Proposta relativa alla prescrivibilità e rimborsabilità delle eparine a basso pm (EBPM)

Luigi Ria

Elvira Grandone

Francesco Marongiu

Table 2. Use of LMWHs to prevent GVCs or VTE: evidence from RCTs and prospective studies

Reference	Year	Type	N of women/studies	Enrollment criteria	Outcome	Use of LMWHs
Kaandorp (65)	2010	RCT	384 women	Pregnancy loss	Live birth	NR
Clark (66)	2010	RCT	294 women	Pregnancy loss	Live birth	NR
Rodger (78)	2014	RCT	292 women	High risk of GVCs or VTE, with thrombophilia	Composite (GVCs/VTE)	NR
Pasquier (67)	2015	RCT	258 women	Pregnancy loss , no thrombophilia	Live birth	NR
Schleussner (68)	2015	RCT	449 women	Pregnancy loss	Live birth	NR
Rodger (80)	2014	Meta-analysis	848 women (6 RCTs)	Previous placenta-mediated GVCs	Pre-eclampsia, Small for Gestational Age newborns, placenta abruptio, IUFD	R
Akthar (83)	2013	Systematic Review	386 women (3RCTs)	IVF/ICSI	Live birth	R *
Dentali (89)	2011	Systematic Review and meta-analysis	405 women (3RCTs)	IVF/ICSI	Live birth	R *
Dodd (15)	2013	Systematic Review	2592 women (16 RCTs)	Pregnant women	Pregnancy-related VTE	NR *

DOI: 10.1111/1471-0528.13706
www.bjog.org

A comparison
pharmacologic
caesarean deli

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Accepted 13 August 2015. Published Onli

ral obstetrics

axis after
lines

A
l Surgeons, 622 West

Table 1. Summary of major society guideline recommendations for obstetric thromboprophylaxis for patients who have undergone caesarean delivery

ACOG
Perioperative mechanical thromboprophylaxis recommended for all patients undergoing caesarean delivery
Pharmacologic prophylaxis (LMWH or UFH) recommended for
- High-risk thrombophilias
- Any prior VTE event
- A family history of VTE and a thrombophilia

Chest
Pharmacologic prophylaxis (LMWH) recommended for one major or two or more minor risk factors
Mechanical prophylaxis recommended for those with contraindications to pharmacologic prophylaxis
Major risk factors (one needed for prophylaxis)
Immobility (strict bed rest ≥1 week in the antepartum period)
Postpartum haemorrhage ≥1000 mL with surgery
Previous VTE
Pre-eclampsia with fetal growth restriction
Thrombophilia
- Antithrombin deficiency
- Factor V Leiden (homozygous or heterozygous)
- Prothrombin G20210A (homozygous or heterozygous)

Medical conditions
- Systemic Lupus erythematosus
- Heart disease
- Sickle cell disease

Blood transfusion
Postpartum infection
Minor risk factors (two needed for prophylaxis)
BMI >30 kg/m²
Multiple pregnancy
Emergency caesarean
Smoking >10 cigarettes/day
Fetal growth restriction
Thrombophilia
- Protein C deficiency
- Protein S deficiency

Pre-eclampsia

RCOG
Risk factors (LMWH recommended for any of the following risk factors)
Previous VTE
Antenatal anticoagulation
Caesarean in labour
Asymptomatic thrombophilia
Prolonged admission
Major medical co-morbidities (e.g. heart or lung disease, systemic Lupus erythematosus, cancer, inflammatory conditions, nephrotic syndrome, sickle cell disease, intravenous drug user
Age >35
BMI >30 kg/m²
Parity ≥3
Smoker
Any surgical procedure
Gross varicose veins

Under RCOG guidelines, 85.0% of patients would receive post-caesarean pharmacologic prophylaxis (95% CI 80.5–88.6%). In comparison, 1.0% of patients would receive pharmacologic prophylaxis under ACOG guidelines (95% CI 0.3–3.0%) and 34.8% of patients would receive prophylaxis under Chest guidelines (95% CI 29.6–40.4%).

Heparin use according to different GL

Risk factors according to different GL

The most common risk factors for prophylaxis using RCOG criteria were caesarean during labour, maternal age ≥35, and obesity. Other risk factors included pre-eclampsia, infection, and high parity. Leading indications for prophylaxis based on Chest guidelines included emergency caesarean, pre-eclampsia, obesity, multiple gestation, and postpartum haemorrhage. Prophylaxis based on ACOG recommendations resulted in three women receiving prophylaxis, all on the basis of having a prior event.

Palmerola KL et al, BJOG 2015

Table 3. Summary of indications to the use of Aspirin or LMWHs in pregnancy to prevent recurrent GVCs or first VTE

Complication	Aspirin	LMWH
Early Pregnancy loss	Not Indicated	Not Indicated°
Early Pregnancy loss in APS	**Indicated**	**Indicated**
Intrauterine Foetal Death*	Not Indicated	***Probably indicated***
Intrauterine Foetal Death in APS	**Indicated**	**Indicated**
Pre-eclampsia	**Indicated**	***Probably indicated***
Small for Gestational Age Newborn	Not Indicated	***Probably indicated***
Pregnancy loss after an ART attempt	Not Indicated	***Probably indicated***
Prevention of first VTE	Not Indicated	**Indicated**

° More research needed for women carrying inherited thrombophilia
* Included that associated with inherited thrombophilia

Grandone E et al, Expert Opinion in Pharmacotherapy, 2015

Anticoagulants in Pregnancy

•Warfarin is generally not used, particularly in the first trimester, because it may be teratogenic.

•Synthetic heparin pentasaccharides (eg, fondaparinux, idraparinux) are avoided because due to a paucity of safety data for these agents.

•Monitoring of anticoagulant activity tends to be more vigilant because less is known about the appropriate dosing of anticoagulants during pregnancy.

DOACs

- Direct Oral Anticoagulants (DOACs) -Dabigatran, rivaroxaban and apixaban - are direct oral anticoagulants, acting on thrombin (dabigatran) and factor Xa (rivaroxaban and apixaban), all approved for the treatment of VTE in the nonpregnant population.
- We do not still have data for the use of DOACs during pregnancy in humans.
- Preclinical animal studies and human placental models demonstrate they cross the placenta.
- Furthermore, they have been shown to cause maternal hemorrhagic complications and a significant increase in foetal toxicity with a reduction of live-born foetuses, and a lower foetal weight [Cutts BA, et al, Am J Obstet Gynaecol. 2013; Turpie AG et al. Thromb Haemost. 2012].
- DOACs were found in breast milk in animals; therefore they are not advised in pregnancy or during breast-feeding [Vanassche T, et al. 2015].

Pregnancy and breastfeeding

Animal studies of dabigatran and rivaroxaban demonstrated pregnancy loss and fetal harm http://www.bayer.ca/files/, http://www.boehringeringelheim.ca/content/dam/internet/opu/ca_EN/documents], and one study demonstrated that dabigatran does cross the human placenta [Obstet Gynecol 2014].

A case report of maternal rivaroxaban use during weeks 1–19 of pregnancy (when pregnancy discovered at week 19, the patient was switched to enoxaparin) resulted in a full-term, low growth percentile, otherwise healthy infant [Thromb Haemost 2014].

Apixaban has no human data in pregnancy, but showed no maternal or fetal harm in animal studies [http://www.pfizer.ca/en/our_products/products/monograph/313.].

Edoxaban animal studies demonstrated no fetal harm. The edoxaban VTE treatment trial reported 10 pregnancies, with edoxaban exposure during the first 6 weeks of gestation (4 full-term births, 2 pre-term births, 1 first-trimester spontaneous abortion, and 3 elective pregnancy terminations) [http://dsi.com/prescribing-informationportlet/].

Clin Res Cardiol (2016) 105:117–126
DOI 10.1007/s00392-015-0893-5

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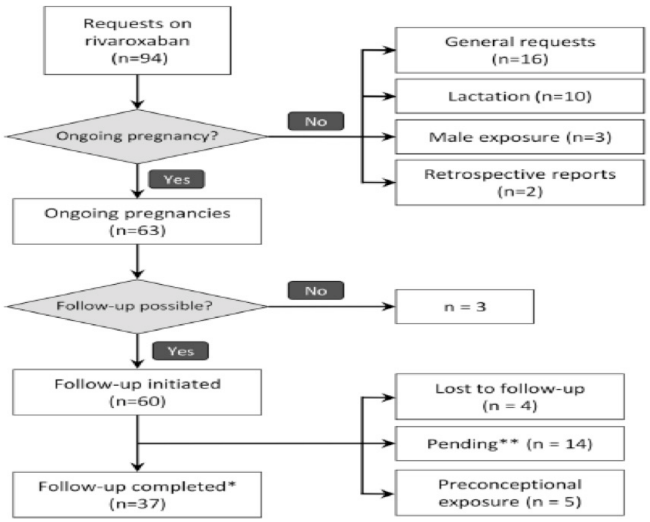
ORIGINAL PAPER

Pregnancy outcome after exposure to the novel oral anticoagulant rivaroxaban in women at suspected risk for thromboembolic events: a case series from the German Embryotox Pharmacovigilance Centre

M. Hoeltzenbein[1,2] · E. Beck[1,2] · K. Meixner[1,2] · C. Schaefer[1,2] · R. Kreutz[1,2]

Ottobre 2008-Dicembre 2014
63 gravidanze esposte a rivaroxaban;
37 gravidanze seguite prospetticamente



6 aborti spontanei
8 IVG
23 nati vivi
1 malformazione grave (precedente s. malformativa in assenza di esposizione al rivaroxaban)

Table 3 DOAC patient selection criteria

Criteria for DOAC use	Comment(s)
Patient preference for and willingness to take DOAC	Patients should be presented will all therapeutic options and their respective perceived advantages and disadvantages (See Table 2)
No contraindication to DOAC therapy	E.g. pregnancy, breastfeeding, mechanical heart valve
Adequate organ function	Clinicians should regularly monitor renal function, particularly for DOACs with greater reliance on renal elimination (see Tables 5, 6 and 12) and, if there are other factors that may increase DOAC exposure (e.g. age, unavoidable use of concomitant p-gp/CYP3A4 inhibitors). Avoid in moderate or severe hepatic dysfunction
No significant drug–drug interactions	See Tables 13 and 14 for detailed guidance
	Patients taking *any* anticoagulant with antiplatelet agents or NSAIDs have a significantly higher risk of bleeding. To minimize bleeding, avoid these drug combinations when possible
No significant disease state interactions	VTE patients with a history of GI bleeding or at risk for GI bleeding may be better candidates for warfarin, apixaban, or edoxaban, as there may be a higher risk of bleeding or GI adverse effects with dabigatran and rivaroxaban
Highly likely to be adherent with DOAC therapy and follow-up plan	See Table 4 for further details
Confirmed ability to obtain DOAC on a longitudinal basis from a financial, insurance coverage and retail availability standpoint	The drug costs of DOACs may be prohibitive for some patients, as compared with generic warfarin plus laboratory monitoring
	There are patient assistance programs available via the pharmaceutical companies, and this should be arranged prior to prescribing

Burnett AE, J Thromb Thrombolysis 2016

LABORATORY SCREENING

Italian Working Group on Thrombophilia

October 2004

- AT heparin cofactor
- PC (functional assay)
- PS (immunologic assay)
- APC-resistance (and/or FV Leiden)
- PT 20210A
- Fasting homocysteine
- LAC and aPL

Routinary search for other polymorphisms in factor V, factor II, and MTHFR (as well as in other genes) is discouraged .

Altri polimorfismi NON UTILI per uno screening trombofilico

- Factor V H1299R
- Factor VII
- Factor XIII V34L
- Beta Fbg -455GA
- Plt Ag HPA1 a/b
- MTHFR C677T
- MTHFR A1298C

- ApoLp B-100 R3500Q
- ApoE (e2, e3, e4)
- Beta-thromboglobulin
- PAI 4G/5G
- .....

WWW.SIGU.NET.IT, febbraio 2015

" ...Pratiche a rischio di inappropriatezza..."

Should be more selective ?

- Despite biological plausibility from
- Association between thrombosis, thrombophilia and placental damage
- Benefit in only some groups in some studies treated with antithrombotics eg LDA and Preeclampsia
- PMC have heterogeneous causes, so should we focus on more homogeneous groups such as women with thrombophilia or start earlier to influence placentation?

So where does this take us?

- Association and biological plausibility for coagulation mechanisms underlying PMPC
- No consistent or clear benefit from antithrombotic intervention
- But PMC are complex in origin
  - Multigenic factors- Maternal and Fetal
- Phenotype and Environment
  - Obesity and smoking
- Classification by outcome rather than cause

LMWH and adverse pregnancy outcome: Are we missing something?

- Benefits may be limited to particular phenotypes or genotypes
- Specific thrombophilias and their interaction with disease
- Thrombotic damage such as placental infarction
- Are there biomarkers or phenotypes to guide treatment?

Arch Gynecol Obstet
DOI 10.1007/s00404-016-4185-8

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GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE

Modulation of factors involved in placental haemostasis and angiogenesis by low-molecular-weight-heparins

Elvira Grandone[1] · Elena Chinni[1] · Michela Villani[1] · Natale Sciannamè[2] · Giovanni L. Tiscia[1] · Giovanni Favuzzi[1] · Filomena Cappucci[1] · Francesco Petruzzelli[2] · Maurizio Margaglione[3]

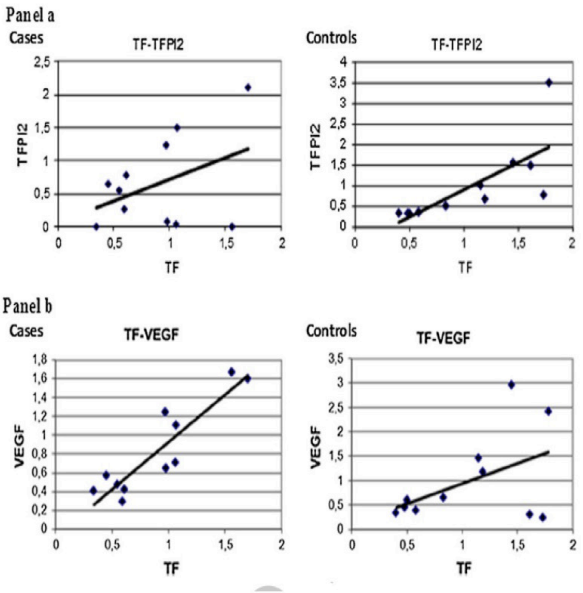


Fig. 1 Relationship between TF-TFPI2 and TF-VEGF in placentae from cases and controls. Direct relationship between TF and TFPI3 (a) and TF and VEGF (b) in placentae from cases (thrombophilic women treated with LMWHs) snd controls

Obstetric antiphospholipid syndrome: early variations of angiogenic factors are associated with adverse outcomes. *The NOH-ANGIO observational study.*

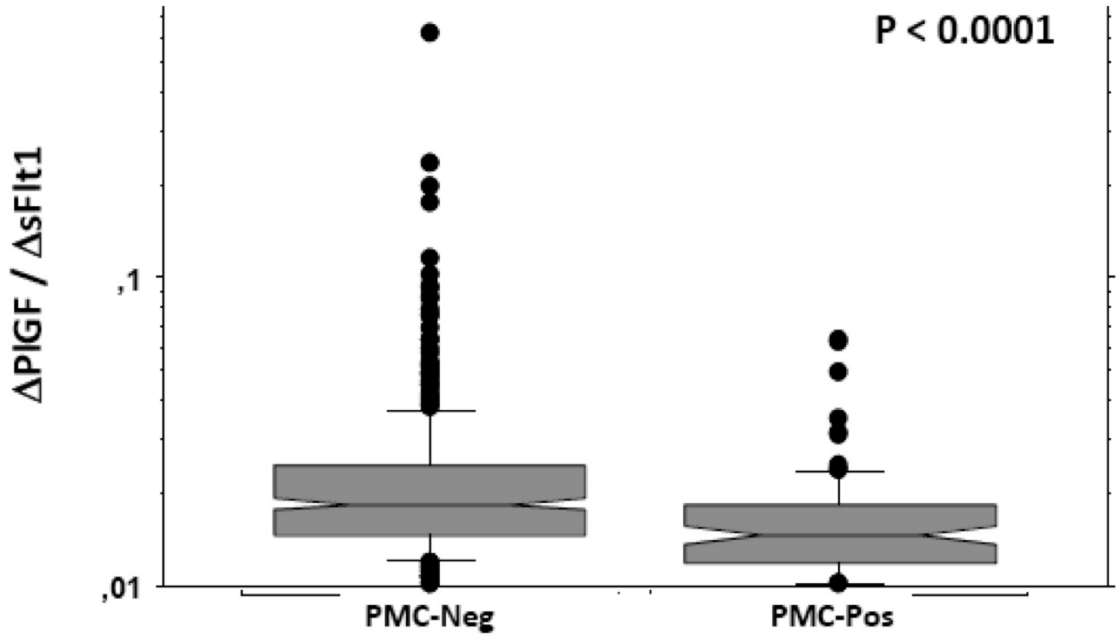
Éva Cochery-Nouvellon, Érick Mercier, Sylvie Bouvier, Géraldine Lissalde-Lavigne, Jean-Pierre Balducchi, Jean-Philippe Galanaud, Isabelle Quéré, Antonia Perez-Martin, Eve Mousty, Vincent Letouzey and Jean-Christophe Gris.

513 obstetric antiphospholipid syndromes with 3 consecutive spontaneous foetal losss before the 10th week of gestation or one fetal loss at or beyond the 10th week.

Proangiogenic factor placenta growth factor and of the antiangiogenic factor soluble fms-like tyrosine kinase-1 on the eve and on the 4th day of the low-molecular weight heparin-low dose aspirin treatment. Both markers are increased in following pregnancies

The ratio between placenta growth factor increase and soluble fms-like tyrosine kinase-1 was a summary variable whose best cut-off values (1.944.10-2) had **high negative predictive values** for placenta-mediated complications

Fig. 2. Variations of PlGF plasma concentrations (ΔPlGF), of sFlt1 plasma concentrations (ΔsFlt1) and of the ΔPlGF : Δ sFlt1 ratio (ΔPlGF / ΔsFlt1) associated with the beginning of the low molecular weight heparin – low dose aspirin treatment in obstetrical APS women who further on developed (PMC-Pos) or did not developed (PMC-Neg) placenta-mediated complications.



Cochery-Nouvellon E, et al Haematologica, 2017, in press

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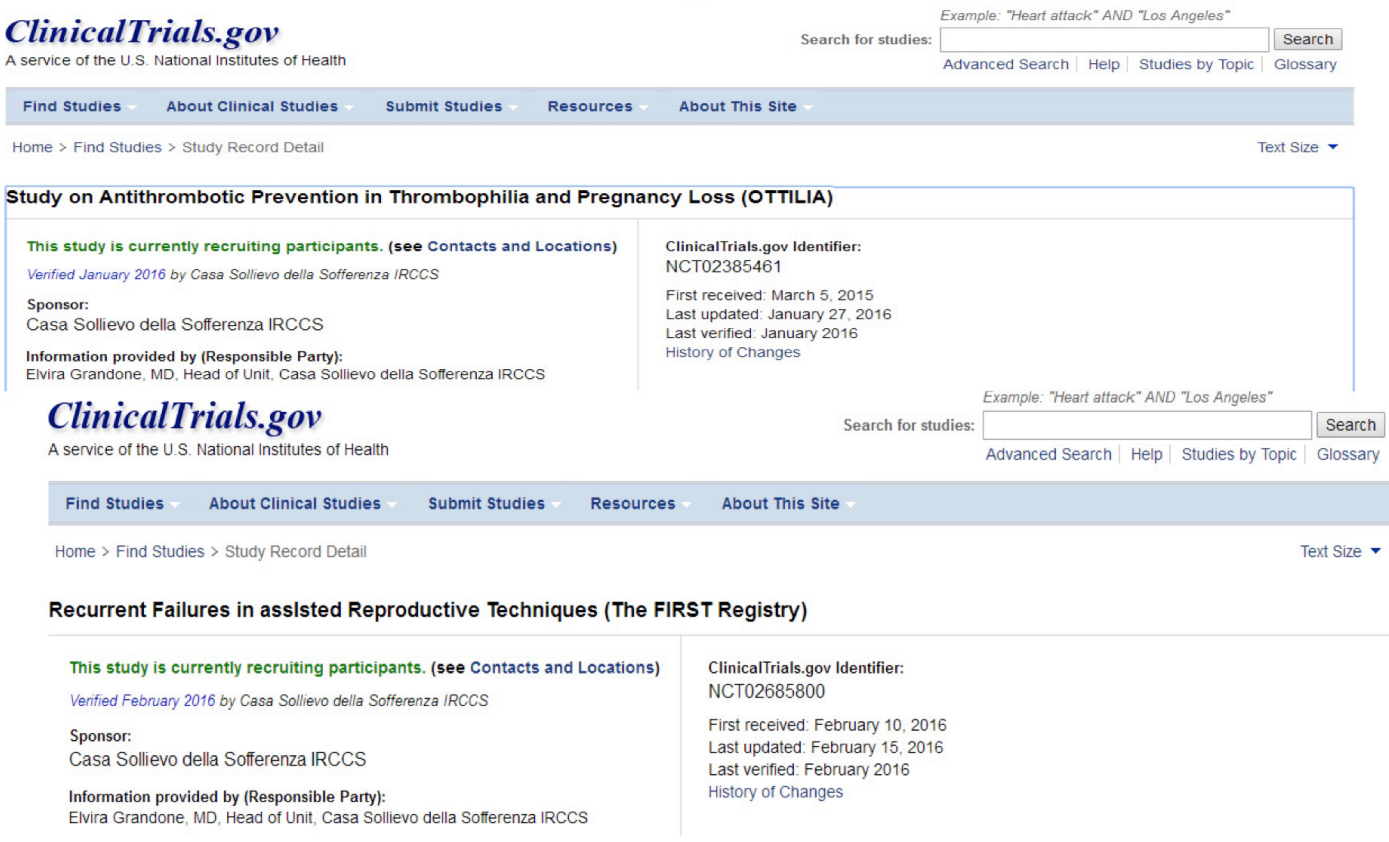

L' indice del progresso di una civiltà è dato dalla considerazione che questa civiltà ha per la donna.

E il modo migliore per valutare questa considerazione è l' attenzione che la società stessa ha per la sua maternità.

Howard Haggard

Devils, Drugs and Doctors, 1913