



**Karolinska  
Institutet**

**Institutionen för kliniska vetenskaper, Danderyds sjukhus**

# Effects of in vitro fertilization on thrombosis and haemostasis and the relationship between infertility and cardiovascular disease

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Aulan, Danderyds sjukhus

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av

**Eli Westerlund**

Leg läkare

*Huvudhandledare:*

Professor Peter Henriksson  
Karolinska Institutet  
Institutionen för kliniska vetenskaper,  
Danderyds sjukhus

*Bihandledare:*

Docent Håkan Wallén  
Karolinska Institutet  
Institutionen för kliniska vetenskaper,  
Danderyds sjukhus

Medicine doktor Aleksandra Antovic  
Karolinska Institutet  
Institutionen för kliniska vetenskaper,  
Danderyds Sjukhus

Professor Outi Hovatta  
Karolinska Institutet  
Institutionen för klinisk vetenskap,  
intervention och teknologi

*Fakultetsopponent:*

Professor Per Morten Sandset  
Universitetet i Oslo  
Institutt for klinisk medisin

*Betygsnämnd:*

Professor Angelica Lindén Hirschberg  
Karolinska Institutet  
Institutionen för kvinnors och barns hälsa

Docent Anders Sjölander  
Umeå Universitet  
Institutionen för folkhälsa och klinisk medicin

Professor Thomas Renné  
Karolinska Institutet  
Institutionen för molekylär medicin och  
kirurgi

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# ABSTRACT

**Background:** Infertility afflicts more than 10% of all couples worldwide. In vitro fertilization (IVF) is now performed at an ever increasing rate. There is scarce information concerning the associations between cardiovascular disease (CVD), venous thromboembolism (VTE) and infertility.

**Aims:** To assess the incidence of pulmonary embolism (PE) and VTE in pregnancy after IVF. To investigate whether there is an association of CVD and infertility. To study effects of IVF on global and individual markers of haemostasis.

**Methods and Results:** We studied all women who had given birth to a child after IVF (n=23,498) between 1990 and 2008 and individually matched women by age and calendar year (n=116,960). Information from the Swedish Medical Birth Register was linked to the Swedish National Patient Register in a cross-sectional study. The incidence of VTE was found to be increased during all pregnancy after IVF compared to pregnancy after natural conception. During the first trimester the risk was increased fourfold for VTE and sevenfold for PE.

We also studied the two groups after delivery until occurrence of hypertension, stroke, coronary heart disease, diabetes mellitus or until end of follow-up (average follow-up time eight years). Both univariable and multivariable analyses showed a higher incidence of hypertension after IVF pregnancy compared to control. There was a tendency towards a higher incidence of stroke, whereas the incidence of coronary heart disease and diabetes did not differ.

Furthermore we studied 31 women undergoing IVF at maximal downregulation (DR) and during high-level stimulation (HLS) of oestradiol synthesis. Antigen levels and activities of both von Willebrand factor (VWF) and ADAMTS13 in plasma were determined at DR and at HLS. Haemostasis was also assessed with 1) the calibrated automated thrombogram (CAT; measures thrombin generation), 2) overall haemostasis potential (OHP; measures fibrin formation and degradation) and 3) fibrin gel permeability measurements (assesses fibrin network characteristics). The increments in oestradiol during IVF were paralleled by an increase in VWF antigen and activity respectively a decrease in circulating ADAMTS13 antigen and activity. We found both an increased thrombin generation and fibrin formation from DR to HLS, whereas fibrin gel permeability did not change.

**Conclusion:** IVF pregnancy is associated with an increased risk of PE and VTE, in particular during the first trimester. The risk of PE is low in absolute terms but because the condition is a leading cause of maternal mortality and clinical suspicion is critical for diagnosis, an awareness of this risk is important. The mechanistic studies identified procoagulable changes in haemostasis during the IVF procedure.

Hypertension was more prevalent after IVF pregnancy. This association of CVD and infertility suggests that infertility and CVD could share common pathophysiological mechanisms.