No evidence that assisted reproduction increases the risk of thrombosis: a Danish National cohort study

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BACKGROUND: Case reports have reported venous and arterial thromboses in women undergoing assisted reproduction. No large systematic studies on the risk of thrombosis have been published. The objective of our study was to investigate whether the risk of thrombosis is increased in women undergoing assisted reproduction.

METHODS: A national register-based cohort study was conducted on all women undergoing IVF or ICSI treatment in Denmark from 1994 to 2005. Data were obtained from the National Patient Registry and the IVF Registry. Women with prior malignant or cardiovascular disease were excluded. Thrombosis occurring within the first 6 and 12 months after assisted reproduction was considered potentially related to the treatment. Thromboses during pregnancy as well as the pregnancy-related diagnoses were excluded from the statistical analysis. The incidence rates of venous and arterial thromboses were compared with previously published estimates of the risk of thrombosis among young Danish women.

RESULTS: We analyzed 30,884 Danish women undergoing 75,141 treatments from 1994 to 2005. The mean age of the women at first treatment was 32.3 years. The delivery rate per cycle was 22%. The incidence rate ratio, with 95% confidence interval (CI), of venous thrombosis within 6 months was 0.95 (CI: 0.38–1.95). The incidence rate ratio of arterial thrombosis within 6 months was 0.36 (CI: 0.04–1.30).

CONCLUSIONS: Our study showed no evidence that assisted reproduction increases the risk of thrombosis.

Key words: assisted reproduction / ovarian hyperstimulation syndrome / thrombosis

Introduction

Several case reports on venous and arterial thromboses in women undergoing assisted reproductive technologies (ARTs) have been published (Chan and Ginsberg, 2006; Chan and Dixon, 2008; Chan, 2009). ART has been considered to increase the risk of thrombosis, similar to that seen during pregnancy (Andersen et al., 1998; Bremme, 2003). Venous thrombosis in relation to ART has been reported at unusual localizations, such as in the upper extremities, the neck and intra-cranially (Chan and Ginsberg, 2006; Chan and Dixon, 2008; Chan, 2009; Vloeberghs et al., 2009; Metwally and Ledger, 2011), whereas the most common arterial event has been reported to be ischemic stroke (Chan, 2009; Vloeberghs et al., 2009). Nearly all thromboses have been reported to occur after ovulation induction in connection with IVF (Chan, 2009). A considerable number of women undergo ART annually. In European countries, the percentage of live born infants conceived by ART ranged from 1 to 4.1% in 2006; the highest numbers originating from Denmark (Nelson and Greer, 2008; de Mouzon et al., 2010). To date, however, no large systematic studies of the risk of thrombosis in relation to ART have been published.

In the present study, we focus on IVF and ICSI. Women undergoing IVF and ICSI are given hormonal drugs to promote the development of multiple oocytes in the ovaries. The medical ovarian stimulation induces supra-physiological endogenous levels of estradiol, though not as high as during pregnancy (Speroff and Fritz, 2005; Nelson and Greer, 2008; Chan, 2009; Nelson, 2009). Pro-coagulant changes, in terms of increased coagulation factors, decreased natural anticoagulant activity and reduced fibrinolytic activity, are found coincidentally with the increased level of estradiol (Stirling et al., 1984; Nelson and Greer, 2008). This hypercoagulability is similar to changes seen in coagulation during pregnancy (Stirling et al., 1984; Nelson and Greer, 2008; Vloeberghs et al., 2009), and is considered to be triggered by the augmented estradiol levels (Stirling et al., 1984; Nelson and Greer, 2008; Vloeberghs et al., 2009).
Ovarian hyperstimulation syndrome (OHSS) is a well-known iatrogenic complication of IVF/ICSI occurring in the luteal phase or in early pregnancy (Vloeberghs et al., 2009). In OHSS, the endogenous estradiol can approximate pregnancy levels, and OHSS has been reported to increase the risk of thrombosis in relation to IVF/ICSI even further (Speroff and Fritz, 2005; Chan, 2009). In Europe, 1.2% of all treatment cycles are complicated by OHSS (de Mouzon et al., 2010).

The drug human chorionic gonadotrophin (hCG), which induces ovulation in IVF/ICSI, exaggerates the pro-thrombotic changes already present during ovarian stimulation (Nelson, 2009), and hCG levels have been shown to be associated with the development of OHSS (Vloeberghs et al., 2009).

On the basis of previous case reports, we hypothesised that women undergoing IVF/ICSI show a higher incidence rate of thrombosis as compared with young women in general. The aim of the present study was to investigate whether IVF/ICSI itself increases the risk of venous and arterial thromboses.

**Methods**

**Population and registers**

This was a register-based, historical cohort study. Since 1994, all IVF and ICSI treatments in Denmark in both private and public clinics have been reported to the National IVF Register (IVF register). All women, who received IVF and ICSI treatments at public or private fertility clinics in Denmark from 1994 to 2005, were identified. Women fertilized by frozen embryo replacement were not included because the procedure does not involve medical ovarian stimulation. We excluded all treatments involving egg donation because the information in the registry did not distinguish unambiguously between women donating and women receiving eggs. Women with prior malignant disease or previous thrombosis were excluded. From the IVF register we obtained cycle-specific information on maternal age, cycle number and treatment duration, presence of OHSS, occurrence of pregnancy, abortions and deliveries.

Using the unique Danish civil registration number, we linked data obtained from the IVF register to information from the National Patient Registry, a nationwide administrative database containing information on discharges from all Danish hospitals. Diagnosis codes for venous and arterial thromboses as well as selected comorbidity diagnoses were taken for our study population from the National Patient Registry from 1994 to 2009. The International Classification of Diseases, 10th revision (ICD-10) diagnosis codes on venous thrombosis were I26 and I80.1–I82.9, and ICD-10 codes on arterial thrombosis were I21, I22, I63–I66, I74, G45 and G46.

**References**

Two national studies on venous and arterial thromboses in young Danish women were used as references to our study population. The reference study on venous thrombosis by Lidegaard et al. (2009) included women who were aged 15–49 years, had no former malignant or cardiovascular disease and were not pregnant. Data on the same ICD-10 codes on thrombosis were taken from the National Patient Registry in the same time period as in our study. Among women not using oral contraception, the rate of venous thrombosis was 3.0 per 10 000 woman-years, and we used that as a reference rate. The age distribution of the IVF/ICSI women was different from that of the reference population, but when applying the age-specific incidence rates in the reference population to the age distribution of the IVF/ICSI women, the adjusted incidence estimate was very close to the unadjusted estimate.

The paper by Lidegaard (1998) on arterial thrombosis included women aged 15–44 years. The incidence of arterial thrombosis, as recorded in the National Patient Registry, was 2.8 per 10 000 years when standardized to the age distribution of our study population. The paper did not include a separate estimate for non-users of oral contraceptives, but we assumed it to be somewhat lower, and we used an incidence rate of 2.25 per 10 000 as a reference rate.

**Statistical analysis**

Using the starting date of hormonal treatment with follicular stimulating hormone (FSH) as the reference date, we calculated the time until a thrombosis, censoring the time at risk at the start of a new treatment cycle, achieved pregnancy or 31 December 2009, whichever came first. Achieved pregnancy was calculated as the birth date of the child minus 250 days or, in the case of abortion, the date of abortion minus 15 days. When a thrombotic event had been recorded in a woman, any of her following IVF/ICSI cycles were excluded from the analysis. Thromboses during pregnancy were excluded from the statistical analysis.

Incidence rates of venous and arterial thromboses in our population were calculated, and compared with reference rates by incidence rate ratios within the first 6 and 12 months of a treatment cycle (Lidegaard,

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

**Figure 2** Cumulative incidence of arterial thrombosis (AT) for the first three years after IVF or ICSI, compared to the incidence in the reference population.
Incidence rates and incidence rate ratios were estimated with the exact Poisson confidence intervals. We also made graphical comparisons of the observed and expected cumulative incidences within 3 years, using the Kaplan–Meier estimate (Figs 1 and 2). Descriptive data are presented as mean and standard deviation if data are normally distributed. If not normally distributed, descriptive data are presented as median with 10th and 90th percentiles. The statistical software Stata® (StataCorp), version 11.2 was used for all statistical analysis. *p*-values < 0.05 were considered statistically significant, and we used 95% confidence intervals (CIs).

The study was approved by the Danish Data Protection Agency. The study needed not to be notified in the ethical committee according to the Danish Committee Legislation, as it was an entirely register-based study.

**Results**

We included 31 098 women and 75 598 IVF/ICSI treatments. Among these, malignant disease was recorded in 135 women and a thrombotic event in 79 women prior to the first treatment cycle. These women were excluded, and the final data set for analysis consisted of 75 141 IVF/ICSI treatments among 30 884 women. The average number of IVF/ICSI treatments per woman was 2.4. The mean maternal age at first IVF/ICSI treatment was 32.3 years. The delivery rate per cycle was 22%, which is in good accordance with previously published delivery rates for IVF- and ICSI treatments in Denmark (de Mouzon et al., 2010). Characteristics of the IVF/ICSI cycles and the pregnancies achieved after IVF/ICSI are shown in Table I.

In Table II, the observed incidence rates within 6 and 12 months after IVF/ICSI are compared with the reference rates. The incidence rate ratios, both for venous and arterial thromboses, were not significantly different from 1. Figures 1 and 2 show Kaplan–Meier plots of the cumulated incidence for the first 3 years after IVF/ICSI, alongside the corresponding reference rates. There was no evidence of an increased incidence during the first months after IVF/ICSI, but the incidence of venous thrombosis seemed to increase in the years after IVF/ICSI.

OHSS within 3 months after treatment was recorded in 1% of all IVF/ICSI cycles. However, OHSS was not present concurrently at any of the thromboses within 12 months after IVF/ICSI. Prior and present morbidity in the women undergoing IVF/ICSI is described in Table III.

**Discussion**

In women undergoing ART, we found similar incidences of thrombosis as reported in the reference populations (Lidegaard, 1998; Lidegaard et al., 2009). Thus, the hypothesis that IVF/ICSI is associated with an increased risk of venous thrombosis was not supported.

As anticipated, we found that most thrombotic events in relation to IVF/ICSI were venous (Chan, 2009; Vloeberghs et al., 2009), though fewer than we expected. Venous thrombosis may be under-reported in general, since not all venous thromboses prompt admission to hospital and thereby a diagnosis registered in the National Patient Registry. Also, there may be false-positive diagnoses as documented by Severinsen et al. (2010). However, the information about the reference population came from the same source and so the comparison is unbiased. Venous events predominate in the female population at
The role of thrombophilia in thrombosis in relation to fertility treatment is unknown, and thrombophilia has been reported with great variation (Nelson and Greer, 2006; Chan, 2009). In our study, we found that 0.01% of the IVF/ICSI women were diagnosed with an inherited thrombophilia. However, we cannot make any conclusion on the possible influence of thrombophilia on the risk of thrombosis in IVF/ICSI.

### Strength and limitations of the study

The large sample size and systematic approach of our study is a major strength. The IVF registry can be considered complete, with cycle-specific information reported by the staff at the fertility clinics. The fact that we may have missed some cases of egg donation does not introduce bias in the comparisons. Concerning the outcome, the comparison with previous large cohort studies in young Danish women using the same registry and the same diagnoses, is also a major strength, and although we had to make some assumptions concerning the reference rate for arterial thrombosis, it could not affect conclusions substantially.

Despite the large sample size, the number of thrombotic events was small. This affects the power of the study, and we cannot rule out that IVF/ICSI has some influence on the incidence of venous thrombosis. However, estimated from the confidence intervals, any additional risk of venous thrombosis can hardly be >3 per 10,000 years at risk, or 1.5 per 10,000 treatments. For arterial thrombosis, any extra risk can hardly be >1 per 10,000 treatments. We conclude that the extra risk, if present at all, is small, and much smaller than the risk associated with pregnancy (Andersen et al., 1998).

We had no information on FSH dose. Furthermore, our register data did not include information on life style factors, such as smoking, obesity, long distance flights, immobilization and sedentary life style. Therefore, we were not able to adjust for these potential confounders. It is possible that women who strive to become pregnant are more concerned with lifestyle and healthy habits, and that might help reducing the risk of thrombosis.

During the latest years of follow-up in our study, there has been an increasing awareness of the issue of IVF/ICSI and thrombosis. We did not obtain information on medical prescriptions for our IVF/ICSI population. Therefore, we cannot rule out that some women considered being at an increased risk of thrombosis prior to initiation of IVF/ICSI might have received prophylaxis with an anticoagulation therapy during IVF/ICSI. However, from our clinical experience, this number is considered very small.

In conclusion, IVF/ICSI treatments do not seem to increase the risk of venous or arterial thrombosis per se. Future studies should attempt to identify potential specific subgroups at high risk of thrombosis among IVF/ICSI patients in order to target the use of prophylactic anticoagulation therapy.

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### Authors’ roles

A.T.H., U.S.K., S.J. and A.M.H. contributed to conception and design of the study and to acquisition of data. S.J. and A.T.H. performed the

### Table III Information on prior morbidity among the 30,884 women included in the study.

<table>
<thead>
<tr>
<th>Morbidity prior to IVF/ICSI</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>115 (0.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>102 (0.3)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>15 (0.1)</td>
</tr>
<tr>
<td>Inherited thrombophilia</td>
<td>30 (0.1)</td>
</tr>
<tr>
<td>Polycystic ovary syndrome</td>
<td>610 (2)</td>
</tr>
</tbody>
</table>

a young age, where the use of oral contraceptives and pregnancy occur, whereas the age-determined increase in the risk of thrombosis is more pronounced with respect to arterial than venous events among females (Lidegaard, 1998). This trend was not different in the IVF/ICSI population, where arterial thrombosis was no more frequent than that in the reference population.

A slightly higher incidence of venous events compared with the reference population was seen in the third year after IVF/ICSI as shown in the Kaplan–Meier plot in Fig. 1. However, we find it unlikely that any effect of IVF/ICSI on the risk of thrombosis should extend more than 1 year. The reason for the later increase in the incidence of venous thrombosis might be that infertile women have a different \( \text{a priori} \) risk of venous thrombosis.

Elevated levels of estradiol confer an increased risk of thrombosis. Decreasing exposure to exogenous estrogens, in the context of hormonal contraceptives, has been shown to decrease the risk of thrombosis (Lidegaard et al., 2009). In the same way, IVF/ICSI implies lower levels of estradiol than seen during pregnancy, and it is therefore plausible that the risk of thrombosis in relation to IVF/ICSI is lower than seen during pregnancy. A recent Danish national cohort study has reported incidence rates per 10,000 pregnancy-years of venous thrombosis from 4 in early pregnancy to 59 in late pregnancy (Virkus et al., 2011).

In contrast to previous case reports and reviews, we excluded thrombosis occurring after pregnancy was achieved, in order to assess the risk associated with IVF/ICSI treatment per se. Pregnancy might be the most important causal factor in these case reports following IVF/ICSI. Pregnancy may explain that thrombosis often occurs within the first weeks after ovulation induction, simultaneously with hormonal changes due to early pregnancy (Chan and Ginsberg, 2006; Chan, 2009). The data available for this study do not allow us to examine whether the pregnancy-associated risk is different for pregnancies occurring with and without assisted reproduction.

Previous studies have suggested that OHSS is associated with an increased risk of thrombosis (Girolami et al., 2007; Chan, 2009; Vlooberghs et al., 2009). OHSS has been reported concurrently with especially arterial thrombosis (Vlooberghs et al., 2009). The incidence of OHSS was low in our study population, and we did not find OHSS present concurrently in any of the thrombotic events. OHSS might be under-diagnosed, since only women with severe OHSS are admitted to hospital, where prophylactic low-molecular weight heparin may be administered. Such information is not available in the register. Therefore, our results can neither confirm nor reject the hypothesis that OHSS increases the risk of thromboembolic disease.
data analysis. A.T.H., U.S.K., S.J. and A.M.H. contributed substantially to data interpretation and to drafting and critically revising the article, and approved the final version to be published.

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**Conflict of interest**

None declared.

**References**


