Venous thromboembolism in relation to in vitro fertilization: an approach to determining the incidence and increase in risk in successful cycles

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Objective: To determine the incidence and the increase in risk of venous thromboembolism (VTE) in relation to IVF and ovarian hyperstimulation syndrome (OHSS) in successful cycles.
Design: Cohort study.
Setting: Population based.
Patient(s): All deliveries (n = 964,532) in Sweden during a 10-year period (1999–2008).
Intervention(s): Comparison of VTEs among those with and without IVF. The National Birth Registry was cross-matched with both the National Discharge Registry and the National IVF Registry. Logistic regression analysis was used to determine odds ratios and 95% confidence intervals.
Main Outcome Measure(s): Risk of first trimester VTE.
Result(s): The incidence of first-trimester VTE in relation to IVF was 0.2%, representing a 10-fold increase as compared with the background population. The 6% to 7% of IVF pregnancies that were complicated by OHSS showed a 100-fold increased risk of VTE, as opposed to the fivefold increased risk seen in the absence of OHSS. The VTEs in conjunction with IVF were diagnosed at a mean gestational age of 62 days; there was no increased risk of VTE related to frozen embryo replacement cycles or IVF after the first trimester.
Conclusion(s): Treating women with OHSS with low-molecular-weight heparin thromboprophylaxis during the first trimester and treating cases at high-risk for OHSS with frozen embryo replacement is likely to lower the risk of VTE. (Fertil Steril® 2012;97:95–100. ©2012 by American Society for Reproductive Medicine.)
Key Words: Venous thromboembolism, ART, IVF, ovarian hyperstimulation syndrome, risk factors, pregnancy

There has been a huge increase in the worldwide use of IVF since the first successful cycle report by Edwards and Steptoe in 1978 (1). In Sweden 13,000 IVF cycles are performed annually, resulting in almost 3,000 newborns per year (2007) (2). Ovarian hyperstimulation syndrome (OHSS), an iatrogenic and potentially fatal IVF complication, occurs as mild forms in up to 33% of all IVF cycles, and 3%–8% of successful IVF cycles are complicated by moderate or severe OHSS (3). The administration of hCG to induce ovulation after ovarian stimulation, or endogenous hCG in conceived pregnancies, is involved in the development of OHSS (4, 5). In conjunction with rapidly increasing E_2 levels, hCG may trigger OHSS in predisposed women. As a consequence of this, there is a fluid shift into third-space causing hemoconcentration. Both of these mechanisms may contribute to a hypercoagulable state, with increased risk of venous thromboembolism (VTE) (5–7).

Despite decades of research, the mechanisms behind OHSS are not fully understood. Venous thromboembolisms in association with IVF have the unusual propensity to be located in the upper extremities and the neck, as compared with their usual occurrence in the left leg (5, 7). The reason for this is not known, but a possible explanation is that an increased amount of peritoneal fluid—with inflammatory properties—is drained through the thoracic duct into the subclavian veins (8). This is reported to down-regulate thrombomodulin and up-regulate tissue factor, locally resulting in an environment with increased risk of VTE in the upper half of the body (9). Another hypothesis proposes that the increased risk might be due to branchial cysts close to the jugular or subclavian veins. In OHSS, these cysts are filled with fluid that

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impairs blood circulation (10). In vitro fertilization cycles are also related to an increased risk of arterial thromboses. These are reported to occur at a mean of 10 days after ET; that is, somewhat earlier than VTEs, which are reported to take place at a mean of 40–42 days after ET (5, 11).

The incidence of VTE in relation to IVF has been reported at approximately 0.1% of treatment cycles (12, 13). According to data from relatively few cases, the VTE risk associated with OHSS is reported to be between 0.8% and 2.4% (14–16). However, there are no reliable data on the incidence or increased risk of VTE in relation to IVF during the first trimester for a large population series.

Our study seeks to estimate the incidence of VTE in relation to IVF with or without the presence of OHSS among women giving birth among 1 million Swedish pregnancies over a 10-year period.

MATERIALS AND METHODS

Virtually all deliveries in Sweden are registered in the Medical Birth Registry (MBR), which comprises prospectively gathered information on the women themselves (personal identification number [PIN], weight, height, parity, and smoking habits), the delivery (diagnoses, number of newborns, gestational age at delivery, procedures, date of delivery, and hospitalization time), and the outcome (Apgar score, fetal weight, and diagnoses). In Sweden, all women who have spent at least one night in hospital as in-patients are registered in the National Discharge Registry (NDR), which contains data regarding PIN, diagnoses, and hospitalization time. The Swedish IVF registry includes the date of ET, type of IVF, and the newborn's date of birth. By using the specific PIN assigned to each Swedish resident and by cross-matching MBR and NDR, it was possible to identify all women giving birth with a diagnosis of VTE in relation to pregnancy and during the first 42 postpartum days in all the pregnancies in Sweden from 1999 to 2008.

The diagnosis codes classified as VTEs (according to the International Classification of Diseases, 10th revision [ICD-10]) were deep venous thrombosis in pregnancy (O223, O228) and postpartum (O871), sinus thrombosis in pregnancy (O225) and postpartum (O873), and obstetric pulmonary embolism (O882), or the corresponding nonpregnant diagnosis numbers I81, I822, I823, I676, I636, I828, I828, and I26*. Ovarian hyperstimulation syndrome was defined as requiring hospitalization as a result of OHSS (N981). In vitro fertilization treatment was dichotomized into fresh IVF/ICSI (intracytoplasmic sperm injection) and frozen embryo replacement (FER) cycles (i.e., cycles with and without ovulation induction). Parity was classified as no prior delivery, one or two prior deliveries (reference), or more than two prior deliveries. Multiple pregnancies were pregnancies with more than one fetus. Smoking was dichotomized into nonsmoking and smoking in early pregnancy (daily smokers).

Most women receiving IVF treatment in Sweden are listed in the IVF registry (2). This allowed us to identify women with VTE as a complication of successful IVF pregnancies. Women who gave birth with an OHSS diagnosis code not included in the IVF registry were included as cases. Because most VTE in relation to IVF occurs in relation to OHSS, one might differentiate between IVF with and without OHSS in assessing the risk of VTE. Venous thromboembolisms occurring during the first trimester were considered as possible complications resulting from the IVF treatment. In addition, all women with OHSS not giving birth during the period studied were cross-matched to the NDR, allowing us to estimate the VTE incidence among those not giving birth.

We anticipated that we might identify approximately 65 VTEs per year among pregnant women in Sweden, of which 20–25 should have occurred in the first trimester of pregnancy (17). We aimed to include 10 years of deliveries (i.e., 200–250 first-trimester VTEs).

For the majority of the VTEs, there was no problem determining in which trimester a VTE occurred. However, the ICD-10 codes are less specific than the ICD-9 codes. As birth approached, ICD-10 code O882 obstetric emboli could either have occurred ante- or postpartum. We did not have permission from the Research Committee on Ethics to further access individual medical records. In cases of uncertainty, women who were hospitalized on either the day before or the day of delivery were classified as postpartum if their hospitalization lasted more than 3 days. Because the focus of our research was IVF-related VTEs in the first trimester, this did not pose a problem. Before we received MBR and NDR registry files from the National Board of Health and Welfare, all data were rendered anonymous, and each PIN was replaced with a dummy variable for the woman and a dummy number for each newborn. The study was approved by the Regional Ethical Review Board in Stockholm (no. 2009/713).

Power Estimation

The risk of thromboembolic complications during pregnancy is 7 per 10,000 pregnancies, with an equal distribution among the trimesters (17). Thus, the expected incidence of VTE in each trimester was 2.3 per 10,000, resulting in a 99% power to identify a fivefold increase in VTE risk with IVF treatment using a 5% two-sided confidence interval (CI) and a 99% power to identify a fivefold increased risk of VTE related to OHSS requiring hospital care (i.e., moderate to severe OHSS, assuming 10% incidence). The power to identify a doubled risk would be 99% and 48%, respectively.

Statistical Analysis

Bivariate and multiple logistic regression analyses were used to determine the relationship between the outcome variable (the occurrence of a thrombosis during the first trimester) and the explanatory variables (IVF, OHSS, maternal age, multiple pregnancy, body mass index [BMI], and smoking). Variables with P values of $<.1$ were included in the multivariate analysis. Because OHSS is a complication of IVF and therefore not an independent variable, we created a new dummy variable for the multivariate analysis to distinguish between IVF treatment with and without OHSS as a risk factor for VTE: no IVF (reference), IVF without OHSS, and IVF with OHSS (18). In analyzing IVF as a risk factor for first-trimester VTEs, IVF pregnancies were also categorized as fresh IVF cycles (cycles with ovulation

induction) and FER; no IVF (reference), IVF without OHSS, IVF with OHSS, and FER. No significant interactions were found among any of the other explanatory variables. Relative risk was determined by odds ratios (ORs) and 95% CIs. All statistical calculations were performed using SPSS software (Statistical Package for the Social Sciences). A P value $< .05$ was considered statistically significant.

RESULTS

As can be seen in Table 1, women receiving IVF treatment differed from the background population in being older, having a lower BMI, and being less likely to smoke. These women were also characterized by a higher incidence of cesarean deliveries, as compared with the background population. Their singleton newborns weighed less, were born earlier, and were at twice the risk of being small for gestational age than the background population. Cases of multiple pregnancies had similar outcomes between the IVF and control population. There was also a gradual decrease in multiple pregnancies in relation to IVF, from 22% in 1999 to 5% in 2007. However, multiple pregnancies were not at increased risk of first-trimester VTE (OR 1.4, 95% CI 0.5–3.8).

In Table 2 we present the results from our analysis of VTEs in relation to IVF. The risk of antepartum VTE in IVF pregnancies showed an almost threefold increase, as compared with the background non-IVF population. We found the incidence of VTE in the first trimester in women with IVF to be approximately 0.17% (32 of 19,194), which is a 10-fold increase over the background population. After the first trimester, IVF pregnancies did not differ in VTE risk compared with pregnancies in the background population.

In Table 3 we present risk factors for VTE during the first trimester. In the subanalyses of IVF treatments, women with a diagnosis of OHSS were at a 100-fold increased risk of VTE during the first trimester, and women without OHSS at a fivefold increased risk, as compared with the background population. Frozen embryo replacement cycles were not related to an increased risk of VTE. There were no substantial differences in the multivariate analysis. Of the other risk

TABLE 1

Background variables of pregnancies with IVF and in background non-IVF population.

Variable	IVF	Background non-IVF population	*P* value
n (%)	19,194 (2.4)	935,338 (97.6)	
Maternal characteristics			
Maternal age (y), mean (SD)	33.5 (4.0)	30.0 (5.1)	<.001
Smokers	786 (4.1)	83,126 (8.9)	<.001
Missing	1,500 (7.8)	57,123 (6.1)	
BMI (kg/m^2), mean (SD)	21.4 (9.1)	21.7 (8.9)	<.001
Multiple pregnancies	2,426 (12.6)	11,819 (1.3)	<.001
OHSS	1,291 (6.7)		
Maternal age groups (y)			<.001
<20	3 (0.0)	16,577 (1.8)	
20–<30	3,115 (16.2)	412,518 (44.1)	
30–<40	14,825 (77.2)	477,506 (51.1)	
>40	1,251 (6.5)	28,737 (3.1)	
Parity groups			<.001
Nulliparous	13,131 (68.4)	409,716 (43.8)	
1 delivery	4,853 (25.3)	339,452 (36.3)	
2 deliveries	932 (4.9)	129,444 (13.8)	
>2 deliveries	27 (1.4)	56,726 (6.1)	
Mode of delivery			
Spontaneous vaginal delivery	11,843 (63.5)	734,395 (78.5)	<.001
Instrumental vaginal delivery	1,662 (8.9)	57,927 (6.2)	<.001
Cesarean delivery	5,301 (27.6)	143,515 (15.3)	<.001
Newborn characteristics, single delivery, n	16,768	923,519	
Male fetal gender	8,655 (51.6)	475,220 (51.5)	.2
Newborn weight (g), mean (SD)	3,462 (618)	3,554 (568)	<.001
Gestational age (d), mean (SD)	277 (16.8)	278.4 (15.1)	<.001
Preterm delivery	1,265 (7.5)	46,343 (5.0)	<.001
SGA	875 (5.2)	35,905 (3.9)	<.001
Apgar <4	61 (0.4)	2,817 (0.3)	.2
Newborn characteristics, duplex delivery, n	4,921	23,795	
Male fetal gender	2,478 (50.4)	11,971 (50.3)	1.0
Newborn weight (g), mean (SD)	2,534 (664)	2,538 (668)	.7
Gestational age (d), mean (SD)	255.1 (23.1)	254.7 (24.6)	.1
Preterm delivery	2,189 (44.5)	10,441 (43.9)	.4
SGA	1,032 (21.0)	4,720 (19.8)	.07
Apgar <4	33 (0.7)	232 (1.0)	.04

Note: Values are number (percentage) unless otherwise noted. Preterm delivery = <259 days or 37 + 0 weeks; Duplex delivery = more than one newborn; SGA = small for gestational age.

Rova. Venous thromboembolism in relation to IVF. Fertil Steril 2012.

TABLE 2

Venous thromboembolic events (VTE) during pregnancy in relation to IVF and background non-IVF population.

	IVF		Background			
Variable	**Pregnancies**	**Incidence/1,000**	**Non-IVF population**	**Incidence/1,000**	**OR**	**95% CI**
n	19,194		935,338			
VTE						
Trimester 1	32	1.67	160	0.17	9.8	6.7–14.3
Trimester 2	5	0.26	164	0.18	1.5	0.6–3.6
Trimester 3	13	0.68	555	0.59	1.1	0.7–2.0
Unknown trimester	1	0.05	31	0.03	NA	
Total antepartum[a]	51	2.66	910	0.97	2.7	2.1–3.6
VTE postpartum	12	0.63	518	0.55	1.2	0.6–2.0

Note: Incidence/1,000 = incidence per 1,000 ongoing pregnancies. We did not have access to data regarding whether pregnancies were IVF after 2008.
[a] We did not know in what trimester some VTEs occurred.

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factors for VTE during the first trimester, obesity was related to a threefold increased risk. Women aged >40 years were at twice the risk. There were 1,360 cases of OHSS among women who did not give birth. In this group, seven cases were diagnosed with VTE (i.e., VTE incidence was 7/1,360 = 0.5%). We had no data regarding whether these were conceived pregnancies.

The VTE cases related to OHSS occurred after a mean of 60 days in gestational age and 68 days after IVF without diagnosed OHSS (Fig. 1). Approximately 6% to 7% of the IVF pregnancies were complicated by OHSS, and this proportion remained constant throughout the study period.

DISCUSSION

Our findings show the incidence of VTE after IVF treatment to be 0.2%. After OHSS the figure was 1.7% (i.e., close to prior estimations [14–16]). Our finding of a 10-fold increased risk

TABLE 3

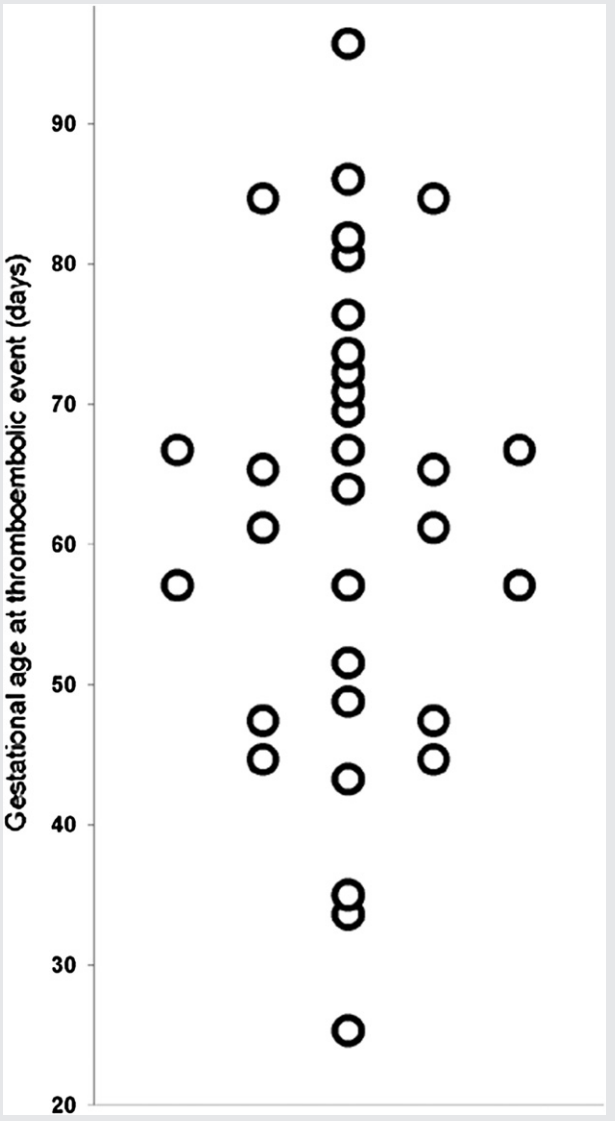
Risk factors for first-trimester VTE.

				Model 1		Model 2	
Risk factor	**Non-VTE pregnancies**	**VTE**	**Incidence/1000**	**OR**	**95% CI**	**OR**	**95% CI**
Categorization 1							
Not IVF	935,178	160	0.2	1.0	Reference		
All IVF	19,162	32	1.7	9.8	6.7–14.3		
Categorization 2							
Not IVF	935,178	160	0.2	1.0	Reference		
All IVF, not OHSS	17,890	13	0.7	4.2	2.4–7.5		
All IVF and OHSS	1,272	19	14.7	87.3	54.1–140.8		
Categorization 3							
Not IVF	935,178	160	0.2	1.0	Reference	1.0	Reference
Fresh IVF, not OHSS[a]	14,520	12	0.8	4.8	2.7–8.7	4.7	2.6–8.4
Fresh IVF and OHSS[a]	1,113	19	16.8	99.7	61.8–161.1	101.0	62.5–163.3
FER cycles	3,529	1	0.3	1.7	0.2–11.8	1.6	0.2–11.3
Maternal age (y)							
<40	924,366	178	0.2	1.0	Reference	1.0	Reference
≥40	29,974	14	0.5	2.4	1.4–4.2	2.1	1.3–3.7
Body mass index (kg/m^2)							
<25	540,802	84	0.2	1.0	Reference	1.0	Reference
≥25 to <30	209,723	40	0.2	1.2	0.8–1.8	1.2	0.8–1.8
≥30	92,689	46	0.5	3.2	2.2–4.6	3.2	2.2–4.6
Unknown	111,126	22	0.2	1.3	0.8–2.0	1.3	0.8–2.1
Multiples and IVF							
Non-IVF, singleton	923,359	160	0.2	1.0	Reference		
Non-IVF, multiple	11,819	0	NA	NA			
IVF, singleton	16,740	28	1.7	9.6	6.4–14.4		
IVF, multiple	2,422	4	1.7	9.5	3.5–25.7		
Smoking							
No	811,836	161	0.2	1.0	Reference		
Yes	83,899	13	0.2	0.8	0.4–1.4		
Unknown	58,605	18	0.3	1.5	1.0–2.5		

Note: Model 1, bivariate analysis; model 2, multivariate analysis.
[a] Incidence of VTE after fresh IVF = 0.9/1,000.

Rova. Venous thromboembolism in relation to IVF. Fertil Steril 2012.

FIGURE 1



Gestational age (in days) at diagnosis of venous thromboembolic event in first trimester among IVF pregnancies.

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of first-trimester VTE and a 2.8-fold increased risk of antepartum VTE almost matches an earlier Norwegian estimate of a fivefold increased risk of antepartum thrombosis (a 4.3- to 6.6-fold increase for singleton and duplex pregnancies) (19). Thus, the 2.8-fold increased risk of VTE in relation to IVF was almost entirely due to the high risk during the first trimester. As compared with the background population, the risk related to fresh IVF in the absence of OHSS increased fivefold and 100-fold in the presence of OHSS in the first trimester. Venous thromboembolisms during IVF treatment in the first trimester occurred at a gestational age of 62 days (or 44–46 days after ET). Thus, the number of days after ET was slightly greater than the previously reported 40–42 days (5, 11). Because we know the great efforts made to avoid OHSS as a complication, we were surprised to find a constant proportion of OHSS (6% to 7%) in relation to IVF. Frozen embryo replacement cycles did not show an increased risk, probably owing to less-frequent/absence of ovulation induction.

Our large population-based sample of almost 1 million pregnancies with prospectively gathered data is an asset of our study. On the other hand, we acknowledge it as a shortcoming that we lack such details as may have been provided by a scrutiny of the medical records involved and documentation of the VTE diagnoses with objective criteria. In addition, women treated for a VTE or OHSS without hospitalization might have been missed. Therefore, we expect that mild and possibly some moderate cases of OHSS were overlooked. Although this will tend to underestimate OHSS as a risk factor, the combined IVF group should be representative. However, if women with upper limb thromboses were less likely to be treated as outpatients, there is the danger of overestimating the risk of VTE in relation to IVF. Another potential problem is overdiagnosis due to our clinical orientation. However, it is an established routine in Sweden to always diagnose VTE objectively, and the cost of the diagnostic measures is absorbed by the Swedish welfare system. Thus, we believe overdiagnosis to be a minor problem and one that will probably be nondifferential (i.e., similar in both groups and not affect the risk estimations). Our results are in agreement with prior studies, and we believe our results to be generalizable to most settings.

We do not have pharmaceutical information on the study subjects (i.e., medication and dosage). The reason that some women with IVF treatment were not included in the IVF registry is presumably because they had IVF done abroad, which is not uncommon. However, we could not exclude the possibility that some cases might have been unregistered. In a registry-based study like ours there is always a possibility of misclassification (i.e., the use of incorrect diagnosis codes).

The total incidence of antepartum VTE was 1.0 in 1,000, which is higher than the Swedish data from 1990 to 1999 (0.64 in 1,000) (17). The reason for this is unknown. However, there is a continuous increase from 1993 to 2008 in the proportion of overweight gravidae, from 20% to 25%, and in obese gravidae from 7% to 12%, explaining at least part of the difference (2). Because women undergoing IVF treatment have cesarean deliveries more often than others, the finding that the risk related to IVF was not increased postpartum might seem paradoxical. However, after having passed a high-risk period without suffering a VTE, the risk is probably lower than average. This can be seen in other situations as well. For example, the use of combined oral contraceptives is related to an increased risk of VTE, but women having a past history of combined oral contraceptive use are at lower risk (20). Similarly, although a first pregnancy is related to an increased risk of VTE, the lowest risk of VTE is after the first and second delivery (17, 20).

Despite the highly significant differences in all outcome variables, apart from Apgar score <4 at 5 minutes, the differences between IVF and background populations are quite small in singleton pregnancies. In multiple pregnancies, there was no difference in outcome between IVF and background pregnancies, with the exception of a slightly lower risk of having a low Apgar score in the IVF group. Thus, the large

differences in newborn outcomes are between singleton and multiple pregnancies, rather than between IVF pregnancies and the background population. The increase in the use of single ET in IVF has resulted in an enormous decrease in the proportion of multiple pregnancies during the study period. Multiple pregnancies are at a significant 2.1- to 2.6-fold increased risk of antepartum VTE (17, 19). However, this did not alter the first-trimester VTE risk in this study.

Clinical Implications

Swedish thromboprophylaxis guidelines are based on a recommendation that low-molecular-weight heparin (LMWH) be prescribed to women with a 5% antepartum (9 months) risk or higher (i.e., the antepartum risk of women with one prior VTE) (21).

On the basis of our findings, the 1.7% VTE risk in first trimester complicated by OHSS suggests that thromboprophylaxis should be extended until the 13th week of gestation. This is slightly longer prophylaxis than the 6 weeks following ET suggested by Nelson, or the 6 weeks after leaving hospital for OHSS proposed by earlier Swedish guidelines (21, 22). Hospitalized women with OHSS are usually scheduled for LMWH thromboprophylaxis, but we do not know dosage or duration if given. A recent prospective follow-up of the Swedish guidelines on women with one prior VTE found an 88% relative risk reduction with normal-dose prophylaxis (i.e., 5,000 U dalteparin once daily or a corresponding dose of other brands) (23). However, a Dutch follow-up of mainly 2,850 U nandroparin daily (half equipotent dose regarding anticoagulation factor X activity) reported disappointing results (24). Those findings indicate that a dose of at least 5,000 U of dalteparin should be used. Future studies are needed to determine the appropriate dosage of LMWH thromboprophylaxis in relation to IVF complicated by OHSS.

We conclude that the incidence of first-trimester VTE in relation to IVF was 0.2%, rising to 1.7% in the case of women with OHSS who received hospitalization. Pregnancies with fresh IVF cycles complicated by OHSS were at a 100-fold increased risk of VTE in the first trimester, as compared with the background population. There was no increase in risk after the first trimester.

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