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Arterial and venous complications after fertility treatment: A French nationwide cohort study

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ABSTRACT

Objectives: To determine whether the risk of thromboembolic complications is higher in women following unsuccessful fertility treatment (FT) and in pregnant women following successful FT, and whether the risk differs according to FT type.

Study design: This is an observational prospective cohort study. All French women aged 18–45 years who received FT between 2013 and 2015 were selected from the French health insurance claim database which registers healthcare consumption for the entire French population. All FT reimbursed over a 28-day period from the date of the first FT were considered to constitute one FT cycle. Each FT cycle was classified according to type: either simple ovulation induction (OI) or ovulation stimulation (OS). All hospitalisations with a diagnosis of venous thromboembolism (VTE), arterial thrombosis (AT) or ovarian hyperstimulation syndrome (OHSS) were identified for the selected women in the French hospital discharge database. Poisson regressions were used to estimate incidence rate ratios (IRR) by comparing i) the incidence of thromboembolic complications (i.e., VTE and AT) and OHSS following unsuccessful FT cycles with the incidence of these two diseases in all non-pregnant women of the same age range (i.e. non-pregnant control group), and ii) incidence of thromboembolic complications and OHSS in women who became pregnant following successful FT with the incidence in women of the same age range with spontaneous (i.e., no FT) pregnancies (i.e., pregnant control group (spontaneous pregnancy)).

Results: During the study period, 277,913 women underwent FT, for a total of 788,007 FT cycles, with 82,821 FT-related pregnancies. Among unsuccessful FT cycles, 75 VTE and 43 AT were observed. OS treatment cycles but not OI were associated with a higher risk of VTE than in reference group (age-adjusted IRR 1.74, 95%CI [1.30–2.34]). Among FT-related pregnancies, 207 VTE and 35 AT were reported. VTE and AT incidence rates during the first trimester were higher after OS treatment cycles than in the pregnant control group (spontaneous pregnancy) after adjusting for age and twin/multiple pregnancies (IRR_{VTE} = 3.29, 95%CI [2.24–4.81]; IRR_{AT} = 2.63, 95%CI [1.06–6.51]).

Conclusion: Monitoring women undergoing FT, especially OS, irrespective of pregnancy status is crucial. The risk of thromboembolic complications in the first trimester for FT-related pregnancies seems to be higher than that for spontaneous pregnancies.

Introduction

Given the increase in childbearing age, the use of fertility treatment (FT) is in constant expansion [1,2]. Medically-assisted reproduction (MAR) treatment comprises various methods, the two most common being simple ovulation induction (OI) with potential natural fertilization, and ovulation stimulation (OS) followed by in-vitro fertilization (IVF) [3].

Thromboembolic complications (including arterial thrombosis (AT) and venous thromboembolism (VTE)) in women using MAR treatment have been reported in many case reports. They may be

Abbreviations: AT, arterial thrombosis; ATC, anatomical therapeutic chemical; CI, confidence intervals; DVT, deep venous thrombosis; FT cycle, fertility treatment cycle; Gn, gonadotropins; GnRH-, GnRH antagonists; GnRH, gonadotropin-releasing hormones; GnRH+, GnRH agonists; HCG, human chorionic gonadotropin; IQR, inter-quartile range; IRR, incidence rate ratio; IVF, in vitro fertilization; MAR, medically assisted reproduction; OHSS, ovarian hyperstimulation syndrome; OI, ovarian induction; OS, ovarian stimulation; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

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related to the development of ovarian hyperstimulation syndrome (OHSS) which induces a hypercoagulable state. However, in the context of FT, thromboembolic complications may also occur without the development of OHSS, and hypercoagulability may be induced by hormonal treatment alone. Given the low incidence of these events among women of childbearing age, very few studies involving an adequate number of cases have been conducted. Three studies showed an excess risk of VTE in women who became pregnant following IVF compared with women with spontaneous pregnancies [4–6]. This risk was particularly high during the first trimester of pregnancy [5,7,8]. Hansen et al., found no evidence of increased AT or VTE risk in the 6 or 12 months following assisted reproduction treatment. To date, most published studies have investigated the risk of VTE following IVF treatment, but data on OI and OS are scarce.

France's national health insurance claim database has recently been made accessible to epidemiologists. This data source, which covers the whole of the French general population, provides exhaustive and nationwide reimbursement data for medical care, treatments and hospitalization.

The objectives of our study were to estimate and compare hospitalised AT and VTE rates following MAR depending on treatment type, and to estimate the risk of both diseases in women during MAR-related pregnancies.

Methods

Data source

Data for each individual were extracted from the French health insurance claim database (Sniiram) which is linked to the French hospital discharge database PMSI (Programme de Médicalisation des Systèmes d'Information). These two national medico-administrative databases now form part of a larger, recently created data system called the French National Health Data System (Systéme National des Données de Santé) [9]. Linkage between Sniiram and PMSI occurs thanks to an individual anonymous number for each beneficiary. The Sniiram covers the entire French population and contains demographic data (age, sex, vital status, area of residence), as well as exhaustive data on all reimbursements for treatments, diagnostic and therapeutic procedures, outpatient medical care and hospital stays with medical diagnoses defined according to ICD-10 codes [10]. The relevance of these data for epidemiology and pharmaco-epidemiology research has been shown elsewhere [11,12].

Study population and follow-up

All women aged 18–45 in France who received pharmacologic FT between the 1st of February 2013 and the 20th of July 2015 were included in the study. Two study populations were considered: women who did not become pregnant in the 50 days following FT (non-pregnant group hereafter) and women who did (pregnant group hereafter).

Control groups

Two control groups were selected: the first comprised all women in France aged 18–45 excluding women who had given birth less than 4 months previously, pregnant women and women who had undergone FT (non-pregnant control group hereafter). The second control group comprised all women in France aged 18–45 who spontaneously (i.e. no FT) became pregnant between the 1st of February 2013 and the 31st of August 2015 (pregnant control group (spontaneous pregnancy) hereafter).

Definition of treatment cycles

Treatments were selected using the Anatomical Therapeutic Chemical (ATC) classification system. All treatments belonging to the following *categories* and having an indication for FT were selected: Clomiphene, Gonadotropin-releasing hormones (GnRH) (comprising both GnRH antagonists (GnRH-) and agonists (GnRH +)), Human Chorionic Gonadotropin (HCG), Gonadotropins (Gn) and other ovulation stimulants.

For each patient, and starting chronologically from the first occurrence of FT found in the database, all FT reimbursed during the subsequent 28 days were considered part of the same FT cycle. All FT reimbursed after the first 28 days were considered to belong to a different FT cycle. Data on the categories and the dosages of treatments prescribed during each treatment cycle were collected. Each treatment cycle was considered to begin on the day of reimbursement for the first treatment of each FT cycle.

Two FT *types* were created depending on the combination of drug categories used. We distinguished between ovarian induction (OI), which is generally followed by natural fertilization, and ovarian stimulation (OS), which is generally followed by IVF. OI treatment cycles were divided into two subgroups: the first included clomiphene only. The second included various drug associations as follows: clomiphene/Gn, clomiphene/hCG, Gn/hCG, and hCG only. OS treatment cycles were also divided into two subgroups. The first included the following: Gn only, Gn/GnRH+, Gn/GnRH+/GnRH-, Gn/GnRH+/hCG, Gn/GnRH-, and Gn/GnRH-/hCG. The second included: GnRH+/GnRH-, GnRH+/GnRH-/hCG, GnRH+/hCG, GnRH- only, and GnRH-/hCG. Treatment cycles with very low prescribed treatment doses (above the 99th percentile) were excluded (n = 1 587, Fig. 1).

Definition of events and pregnancies

We identified all women who had been hospitalized with a primary diagnosis of venous or arterial events using the 10th revision (ICD-10) of the International classification of diseases. The diagnoses codes used for venous events were deep (O223, O871, O879) and superficial (O222, O870) venous thrombosis during pregnancy or puerperium, obstetric pulmonary embolism (O882) and the corresponding non-pregnancy codes (I26, I80, I81, I82). The diagnosis codes used for arterial events including myocardial infarction, stroke, peripheral arterial embolism and transient ischaemic attacks were I21, I22, I23, I24, I63, I74, G45 (except G454) and G46. The code used for ovarian hyperstimulation syndrome (OHSS) was N981.

Pregnancies were defined as a hospital stay where child birth was recorded after 22 weeks of amenorrhea. Pregnancy initiation was computed as the date of child birth minus the gestational age at childbirth plus two weeks.

Events and pregnancies were attributed to the closest preceding FT cycle, with an attribution limit of 90 days after the end of FT for complication-related events and 50 days after the end of FT for pregnancies.

Calculation of person-years

To estimate incidence rates of complication-related events after a treatment cycle among the non-pregnant group, women were considered at risk until the first event occurred (when 'at risk' changed to 'experienced') or the next FT cycle. If a woman did not experience VTE, AT, or OHSS or did not begin another FT cycle, she was considered at risk for 90 days following the FT cycle. For incidence rate estimates in the pregnant group, individuals were considered at risk during pregnancy and during a post-partum

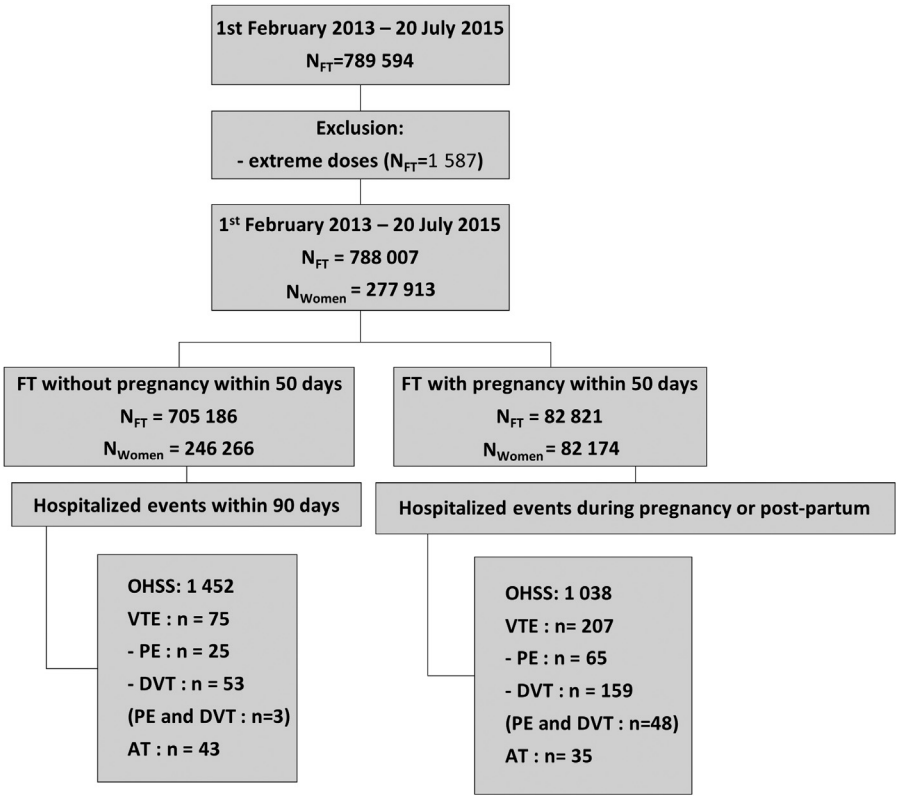

Fig. 1. Flow chart of study population and number of events.
FT = Fertility Treatment cycle; OHSS: ovarian hyperstimulation syndrome; VTE: venous thrombo-embolism; DVT: deep venous thrombosis; PE: pulmonary embolism; AT: arterial thrombosis.

period of 90 days or until the occurrence of an event, whichever came first. Incidence rates were calculated per 10,000 treatment cycles and per 10,000 person-years.

Statistical analysis

VTE and AT incidence rates were calculated according to FT type. For unsuccessful FT cycles, incidence rate ratios (IRR) compared the incidence of VTE and AT in women who had undergone FT with the incidence of these complications in the non-pregnant control group. The same was done for FT-related pregnancies using comparison with the pregnant control group (spontaneous pregnancy). Poisson regression models, adjusted for age as a second order polynomial (to account for the lack of log-linearity), were used to compute IRR comparing the different treatment cycle regimens. To estimate the IRR of complications during pregnancy and the 3-month post-partum period, an additional adjustment for twin/multiple pregnancies was made. A sensitivity analysis was performed to account for the existence of multiple treatment cycles for each woman (whether pregnant or non-pregnant). Since within-woman correlation was close to 0, accounting for it did not change the variance estimates.

Another analysis was performed after excluding individuals with a personal history of VTE or AT in the previous 5 years. Since the results remained unchanged, this factor was not taken into account in the final analysis.

Quantitative variables were reported as means with standard deviation (SD) or median with interquartile range (IQR), depending on the skewness of the distribution. Bivariate comparisons of proportions were made with Chi-squared tests, and bivariate comparisons of means with Student's t-tests. Differences were considered statistically significant with a 5% alpha risk level. Confidence intervals (CI) were reported with a 95% bilateral confidence level. The analysis was performed with SAS software version 9.2.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for the design or implementation of the study. Furthermore, no patients were asked to provide their opinion about the interpretation or writing-up of the results. There are no plans to disseminate the results of the research to study participants or to the relevant patient community.

Results

Study population

The numbers of treatment cycles and individuals at each study stage are reported in a flowchart below (Fig. 1). Between 2013 and 2015, 277,913 women who underwent FT were included in the study, for a total of 788,007 FT cycles. Of these, 705 186 did not lead to pregnancy within 50 days while 82,821 treatment cycles did. The proportion of treatment cycles followed by pregnancy varied from approximately 7% for clomiphene-only OI to approximately 15% for GnRH-based OS (this result does not take into account frozen embryos transferred at a later date). The mean age of those included in the study was 32.4 years (SD 5.7), with women receiving at least one OS treatment being slightly older than those only receiving OI (mean 33.3 vs. 31.5 years). The median number of treatment cycles per woman was 2 (IQR [1–4]).

Table 1
Among unsuccessful FT cycle: Number of FT cycle, individuals and hospitalized events, crude incidence rates per 10,000 treatment cycles and per 10,000 person-years. Among unsuccessful FT cycle.

	All FT cycle	FT cycle type					
		Ovarian Induction (OI)			Ovarian Stimulation (OS)		
		Total OI	Clomiphene	Other OI	Total OS	Gn	GnRH
n							
FT	705 186	451427	206854	243218	253759	245775	7984
individuals	246 266	184848	97305	113851	119974	118768	7335
Ovarian Hyperstimulation syndrome (OHSS)							
n	1 452	269	23	246	1183	1118	65
/10,000 FT	20.6 [19.5-21.7]	6.0 [5.3 - 6.7]	1.1 [0.7 - 1.7]	10.1 [8.9 - 11.5]	46.6 [44.0 - 49.3]	45.5 [42.9 - 48.2]	81.4 [62.9 - 103.7]
/10,000 py	110.4 [104.8-116.2]	32.9 [29.1-37.1]	6.2 [3.9-9.3]	55.5 [48.8-62.9]	237.6 [224.2-251.5]	232.2 [218.8-246.3]	393.6 [303.8-501.7]
Pulmonary Embolism (PE)							
n	25	8	1	7	17	16	1
/10,000 FT	0.4 [0.2-0.5]	0.2 [0.1 - 0.3]	0.0 [0.0 - 0.3]	0.3 [0.1 - 0.6]	0.7 [0.4 - 1.1]	0.7 [0.4 - 1.1]	1.3 [0.0 - 7.0]
/10,000 py	5.7 [4.5-7.1]	3.7 [2.5-5.2]	3.5 [1.9-6.0]	3.8 [2.2-6.1]	9.0 [6.6-12.1]	9.1 [6.6-12.3]	6.1 [0.2-33.7]
Deep Venous Thrombosis (DVT)							
n	53	24	12	12	29	29	0
/10,000 FT	0.8 [0.6-1.0]	0.5 [0.3 - 0.8]	0.6 [0.3 - 1.0]	0.5 [0.3 - 0.9]	1.1 [0.8 - 1.6]	1.2 [0.8 - 1.7]	0.0 [0.0 - 4.6]
/10,000 py	4.0 [3.0-5.3]	2.9 (1.9-4.4]	3.2 [1.7-5.6]	2.7 [1.4-4.7]	5.8 [3.9-8.4]	6.0 [4.0-8.7]	–
All Venous Thrombo-Embolism (VTE)							
n	75	30	13	17	45	44	1
/10,000 FT	1.1 [0.8-1.3]	0.7 [0.4 - 0.9]	0.6 [0.3 - 1.1]	0.7 [0.4 - 1.1]	1.8 [1.3 - 2.4]	1.8 [1.3 - 2.4]	1.3 [0.0 - 7.0]
/10,000 py	1.9 [1.2-2.8]	1.0 [0.4-1.9]	0.3 [0.0-1.5]	1.6 [0.6-3.3]	3.4 [2.0-5.5]	3.3 [1.9-5.4]	6.1 [0.2-33.7]
Arterial Thrombosis (AT)							
n	43	19	9	10	24	24	0
/10,000 FT	0.6 [0.4-0.8]	0.4 [0.3 - 0.7]	0.4 [0.2 - 0.8]	0.4 [0.2 - 0.8]	0.9 [0.6 - 1.4]	1.0 [0.6 - 1.5]	0.0 [0.0 - 4.6]
/10,000 py	3.3 [2.4-4.4]	2.3 [1.4-3.6]	2.4 [1.1-4.6]	2.3 [1.1-4.1]	4.8 [3.1-7.2]	5.0 [3.2-7.4]	–

FT = Fertility Treatment cycle; Gn = Gonadotropin; GnRH = Gonadotropin-releasing hormone (agonists and antagonists); py = person-years.

Complication-related event incidence rates

In total 2490 cases of OHSS, 282 VTE (70 PE, 192 DVT and 20 with both PE and DVT) and 78 AT were observed (Fig. 1). Among unsuccessful fertility treatment cycles (Table 1), the VTE incidence rate per 10,000 person-years was 1.9 [1.2–2.8] (1.0 [0.4–1.9] for OI and 3.4 [2.0–5.5] for OS). The AT incidence rate was 3.3 [2.4–4.4] (2.3 [1.4–3.6] for OI and 4.8 [3.1–7.2] for OS), while the OHSS incidence rate was 110.4 [104.8–116.2] (6.2 [3.9–9.3] for clomiphene-only OI, 55.5 [48.8–62.9] for other OI drug associations and 237.6 [224.2–251.5] for OS)).

The overall VTE incidence rate per 10,000 person-years during FT-related pregnancies and post-partum (Table 2) was 26.4 [22.9–30.2] (21.9 [17.9–26.7] for OI and 32.6 [26.7–39.4] for OS). The AT incidence rate was 4.5 [3.1–6.2] (3.9 [2.3–6.2] for OI and 5.2 [3.0–8.3] for OS) while the OHSS incidence rate was 133.6 [125.6–142.0] (51.0 [44.7–58.0] for OI and 250.3 [233.3–268.2] for OS).

Adjusted incidence rate ratios in women with unsuccessful FT

The age-adjusted IRR for VTE was 1.17 [0.93–1.46] and 0.86 [0.64–1.16] for AT, compared with the control group (Table 3). It differed according to the treatment category with IRR at 0.77 [0.45–1.33] for clomiphene-only OI, 0.79 [0.49–1.27] for other OI drug associations, and 1.76 [1.31–2.37] for OS-Gn. Therefore, a higher risk of VTE was observed in the non-pregnant group who had undergone OS in comparison with the relevant control group, but also compared with those in the non-pregnant group who underwent clomiphene-only OI or other OI drug associations. No significant IRR for AT was found either for those who had undergone OI or OS.

To compute OHSS IRR, the clomiphene-only group was chosen as the reference because very few episodes of OHSS were observed in the general population (chosen as reference population for AT and VTE IRR). After adjusting for age, the IRR for OHSS was 10.28 [6.70–15.76] for other OI drug associations, and 51.17 [33.83–77.40] for OS when compared with clomiphene-only OI.

Adjusted incidence rate ratios in women who became pregnant following FT

The incidence rate of VTE per month of pregnancy and post-partum is shown in Fig. 2 for FT-related and spontaneous pregnancies. The global IRR, adjusted for age and twin/multiple pregnancies, shows higher rates of VTE for FT-related pregnancies during pregnancy and the 3-month post-partum time period (global IRR = 1.16 [1.01–1.34]) with respect to the control group. Analyses by treatment type found higher incidence rates for OS treatment based on Gn (IRR = 1.32 [1.08–1.62]) (Table 4).

Analyses by trimester after adjustment for age and twin/multiple pregnancies showed higher IRR for VTE during the first (IRR = 1.75 [1.23–2.49]) and the third (IRR = 1.30 [1.02–1.66]) trimester when considering both treatment types (Table 4). However, analysis by treatment type showed higher rates of VTE and AT during the first trimester among pregnant women with OS treatment cycles only (i.e., not OI) than in women who became pregnant spontaneously (IRR VTE = 3.29, 95%CI [2.24–4.81]; IRR AT = 2.63, 95%CI [1.06–6.51]).), particularly after OS-Gn treatment cycles (VTE IRR = 3.21 [2.16–4.75] and IRR = 2.75 [1.11–6.81]).

Discussion

Main results

This study estimated incidence rates for hospitalizations for VTE, AT and OHSS in the population of women undergoing FT in France. The risk of VTE increased after OS but not after OI, in both unsuccessful FT treatment cycles and FT-related pregnancies. A

Table 2
Among successful treatment cycle: Number of treatment cycle, individuals and hospitalized events, crude incidence rates per 10,000 treatment cycles and per 10,000 person-years. Among successful FT cycle.

	All FT cycle	FT cycle type					
		Ovarian Induction (OI)			Ovarian Stimulation (OS)		
		Total OI	Clomiphene	Other OI	Total OS	Gn	GnRH
N FT	82 821	48 011	17 420	30 591	34 810	25 916	8 894
N Women	82 174	47704	17338	30 366	34637	25793	8874
Ovarian Hyperstimulation syndrome (OHSS)							
n	1038	232	33	199	806	538	268
/10,000 FT	125.3 [117.9-133.1]	48.3 [42.3 - 54.9]	18.9 [13.0 - 26.6]	65.7 [56.9 - 75.5]	231.5 [216.0 - 247.9]	207.6 [190.6 - 225.7]	301.3 [266.8 - 339.0]
/10,000 py	133.6 [125.6-142.0]	51.0 [44.7-58.0]	19.9 [13.7-28.0]	68.9 [59.6-79.1]	250.3 [233.3-268.2]	250.2 [232.8-268.5]	253.9 [175.8-354.8]
Pulmonary embolism (PE)							
n	65	36	12	24	29	22	7
/10,000 FT	7.8 [6.1-10.0]	7.5 [5.3 - 10.4]	6.9 [3.6 - 12.0]	7.9 [5.1 - 11.8]	8.3 [5.6 - 12.0]	8.5 [5.3 - 12.8]	7.9 [3.2 - 16.2]
/10,000 py	8.3 [6.4-10.5]	7.9 [5.5-10.9]	7.2 [3.7-12.6]	8.3 [5.3-12.3]	8.8 [5.9-12.7]	8.6 [5.6-12.5]	14.6 [1.8-52.8]
Deep Venous Thrombosis (DVT)							
n	159	71	23	48	88	69	19
/10,000 FT	19.2 [16.3-22.4]	14.8 [11.6 - 18.6]	13.2 [8.4 - 19.8]	15.8 [11.7 - 21.0]	25.3 [20.3 - 31.1]	26.6 [20.7 - 33.7]	21.4 [12.9 - 33.3]
/10,000 py	20.3 [17.2-23.7]	15.6 [12.2-19.6]	13.9 [8.8-20.8]	16.5 [12.2-21.9]	26.8 [21.5-33.0]	26.0 [20.7-32.3]	43.9 [16.1-95.6]
All Venous Thrombo-Embolism (VTE)							
n	207	100	33	67	107	85	22
/10,000 FT	25.0 [21.7-28.6]	20.8 [17.0 - 25.3]	18.9 [13.0 - 26.6]	22.1 [17.1 - 28.1]	30.7 [25.2 - 37.1]	32.8 [26.2 - 40.5]	24.7 [15.5 - 37.4]
/10,000 py	26.4 (22.9-30.2]	21.9 [17.8-26.7]	19.9 [13.7-28.0]	23.1 [17.9-29.3]	32.6 [26.7-39.4]	32.1 [26.1-39.0]	43.9 [16.1-95.6]
Arterial Thrombosis (AT)							
n	35	18	7	11	17	11	6
/10,000 FT	4.2 [2.9-5.9]	3.7 [2.2 - 5.9]	4.0 [1.6 - 8.3]	3.6 [1.8 - 6.5]	4.9 [2.8 - 7.8]	4.2 [2.1 - 7.6]	6.7 [2.5 - 14.7]
/10,000 py	4.5 (3.1-6.2]	3.9 [2.3-6.2]	4.2 [1.7-8.7]	3.8 [1.9-6.8]	5.2 [3.0-8.3]	5.1 [2.9-8.2]	7.3 [0.2-40.7]

FT = fertility treatment cycle; Gn = Gonadotropin; GnRH = Gonadotropin-releasing hormone (agonists and antagonists); py = person-years.

Table 3
Age-adjusted IRR by treatment cycle type among unsuccessful treatment cycle.

90 days outcome	Reference group	Total IRR	IRR by treatment cycle type			
			Ovarian Induction (OI)		Ovarian Stimulation (OS)	
			Clomiphene only	Other OI	Gn	GnRH
OHSS	Clomiphene only	–	1	10.28 [6.70-15.76]	44.82 [26.64-67.79]	76.90 [47.78-123.79]
VTE	all women aged 18-45 without MAR treatment	1.17 [0.93-1.46]	0.77 [0.45-1.33]	0.79 [0.49-1.27]	**1.76 [1.31-2.37]**	1.16 [0.16-8.26]
AT	all women aged 18-45 without MAR treatment	0.86 [0.64-1.16]	0.70 [0.36-1.35]	0.60 [0.32-1.12]	1.21 [0.81-1.81]	–

OHSS: ovarian hyperstimulation syndrome; VTE: venous thrombo-embolism; AT: arterial thrombosis; OI = ovarian induction; OS = ovarian stimulation; Gn = Gonadotropin; GnRH = Gonadotropin-releasing hormone (agonists and antagonists).

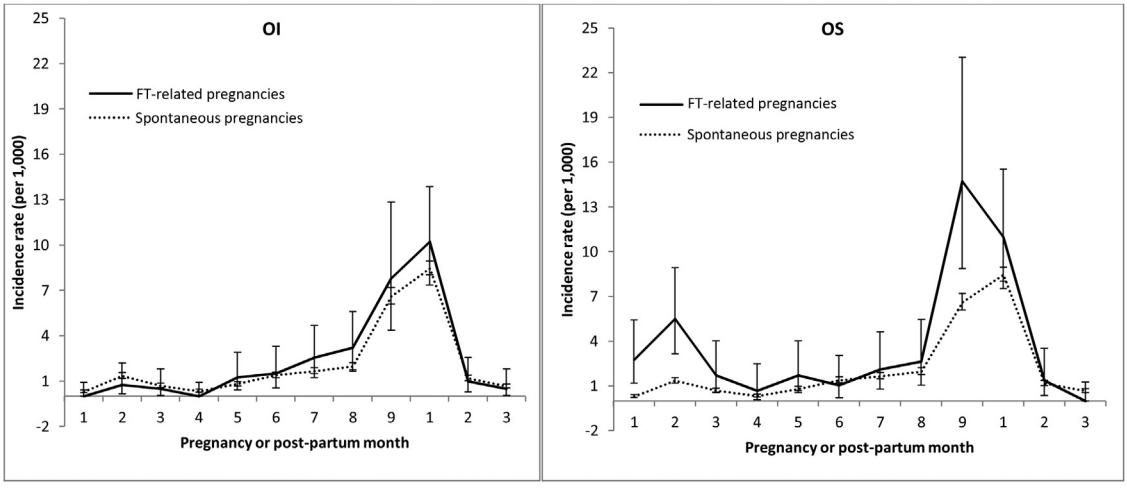

Fig. 2. Crude incidence rate of VTE per 1000 person-years during pregnancy and post-partum by treatment group.
VTE: Venous Thromboembolism; OI: Ovarian induction; OS: Ovarian Stimulation.

Table 4
Cardiovascular IRR[a] between MAR-related pregnancies and spontaneous pregnancies.

90 days outcome	Total IRR	IRR by treatment cycle type			
		Ovarian Induction (OI)		Ovarian Stimulation (OS)	
		Clomiphene only	Other OI	Gn	GnRH
VTE					
Total	**1.16 [1.01-1.34]**	0.99 [0.70-1.40]	1.04 [0.82-1.33]	**1.32 [1.08-1.62]**	1.66 [0.74-3.70]
T1	**1.75 [1.23-2.49]**	0.28 [0.04-1.98]	0.57 [0.21-1.53]	**3.21 [2.16-4.75]**	**4.99 [1.24-20.05]**
T2	1.01 [0.65-1.56]	0.77 [0.25-2.42]	1.06 [0.53-2.14]	1.11 [0.59-2.08]	–
T3	**1.30 [1.02-1.66]**	1.17 [0.66-2.07]	1.29 [0.87-1.92]	1.29 [0.89-1.86]	2.86 [0.92-8.89]
PP	0.99 [0.79-1.24]	1.09 [0.68-1.77]	0.99 [0.69-1.42]	0.96 [0.69-1.35]	0.58 [0.08-4.10]
AT					
Total	1.05 [0.74-1.48]	1.04 [0.76-1.41]	0.93 [0.51-1.69]	1.08 [0.65-1.79]	1.50 [0.21-10.74]
T1	1.46 [0.64-3.36]	1.38 [0.19-9.90]	–	**2.75 [1.11-6.81]**	–
T2	1.30 [0.52-3.22]	2.93 [0.72-11.97]	0.74 [0.10-5.32]	1.17 [0.29-4.79]	–
T3	1.45 [0.78-2.68]	0.72 [0.10-5.14]	1.47 [0.55-3.98]	1.52 [0.62-3.70]	–
PP	0.73 [0.42-1.27]	0.95 [0.30-2.95]	0.95 [0.42-2.14]	0.50 [0.19-1.36]	–

T1-T3: pregnancy trimesters; PP: post-partum; OI: ovarian induction; OS: ovarian stimulation; OHSS: ovarian hyperstimulation syndrome; VTE: venous thrombo-embolism; DVT: deep venous thrombosis; PE: pulmonary embolism; AT: arterial thrombosis.
[a] IRR adjusted for multiple pregnancies, age.

non-significant increase in the risk of AT was observed in women with unsuccessful treatment cycles following OS. During OS-related pregnancy, we observed an increased risk of VTE during the first and third trimesters and an increased risk of AT during the first trimester.

The main strength of our study is the use of exhaustive and nationwide data regarding FT delivery and associated hospitalized complications [9]. To our knowledge, this study provides, for the first time, an estimation of the incidence rates of hospitalizations for OHSS, VTE and AT after clomiphene-only OI. While an increased VTE risk has already been reported following OS, few studies have investigated OI. Most OI treatments are performed outside fertility centers and thus are not included in traditional studies. Our study included the entire French female population benefiting from FT, using data from fertility centers and private ambulatory medicine settings, specialists and general practitioners. The results are therefore representative of the overall French situation. However, FT varies between countries, and generalizations must account for the relative use of OI and OS in each country [1]. Another important strength of our study is that we included both unsuccessful treatment cycles and FT-related pregnancy.

The increased risk of VTE in unsuccessful treatment cycles, particularly in women undergoing OS in our study has not been reported previously. A large Danish cohort study based on a national register of women undergoing IVF, failed to show any association between assisted reproduction and the risk of AT and VTE [13]. However, despite the large sample size, the number of thrombosis-related events in that study remained low and consequently, the authors could not rule out the possibility that IVF had some influence on VTE incidence.

Our result suggesting higher VTE incidence during the first trimester in pregnant women undergoing OS, was in line with other studies [4,7,8,14]. A recent review showed that the antepartum risk of VTE after IVF was twice as high as that in a control population. According to the authors, this was due to a 5- to 10-fold increased risk of VTE after OHSS [14]. Indeed, the increased risk of VTE is linked to that of OHSS, which in turn is brought by IVF [15,16]. Chan and Dixon reported OHSS in 95% of cases of arterial thrombosis and in 70% of cases of venous thrombosis after IVF [17]. The most likely hypothesis to explain the increased risk of arterial and venous thrombosis in patients with OHSS is the activation of coagulation associated with immobilization due to pain, increased abdominal pressure and compression of retroperitoneal vessels by the ovaries. In our study, the proportion of arterial and venous thrombosis cases following OHSS was lower than that of Chan and Dixon. This could be explained by the inclusion of hospitalized OHSS only. Nevertheless, OHSS is not necessarily a prerequisite for the development of thrombosis. The rapid and marked increase of endogenous estradiol levels induced by OS treatment could lead to a pro-thrombotic state and thrombotic complications in susceptible women [18].

In our study, the risk of VTE was also increased during the third trimester in women who became pregnant after FT. A different Danish study to that described above reported a similar result in a register-based study after IVF both in singleton and twin/multiple pregnancies [4]. Causal mechanisms brought on by FT and provoking VTE may differ between the first and third trimesters [18]. During the third trimester and around the time of birth, individual factors or characteristics of the pregnancy might be involved more than FT, for example obesity. In our analyses, we adjusted for age and twin/multiple pregnancies but increased risk of VTE in the third trimester may also have been related to higher rates of caesarean sections and pregnancy complications [5] as well as to health factors causing both infertility and VTE [19].

In our study, the incidence rate of AT was higher after OS treatment during the first trimester of pregnancy. While some case reports of AT in pregnant women following FT exist [18], large epidemiological studies are scarce. It must be noted that although the sample size of our study was large, the number of cases of AT remained low.

The present study confirmed the higher risk of VTE in women undergoing FT and particularly OS treatment, even for unsuccessful treatment cycles. Preventing thrombosis therefore requires the identification of women at risk and the adaptation of MAR treatment protocols to the individual in order to avoid severe OHSS. Close collaboration between gynecologists and obstetricians, hematologists and vascular physicians is essential in order to determine the level of individual risk, as well as the timing, duration and dosage of anticoagulant therapy. Increased attention should also be paid to determine, depending on the risk profile of the individual, whether she should receive Gn or GnRH during OS, since the risk of thromboembolic complications appears to differ between both treatment categories. Finally, monitoring women who become pregnant after FT is necessary, particularly during the first trimester, even for those undergoing OI.

Higher risks of OHSS and AT are reported for FT treatment cycles containing hCG in the literature. We could not explore this hypothesis here because of the large variety of treatment cycles observed in our cohort. More specifically, hCG was prescribed at various dosages and associated with various drugs. We did not have the statistical power to explore the specific effects of each drug especially when combined with others. Furthermore, drug

and dosage choice are probably at least partially influenced by known VTE risk factors causing indication bias (family history of venous or arterial events, body mass index) whose data were not available in the database and may have resulted in lower than expected complication-related event incidence rates for some at-risk treatment cycle categories. There was therefore a non-negligible risk of drawing inaccurate conclusions because of confounders.

Limitations

Our study has several limitations in regard to the identification of complications and risk factors. While most PE and AT result in hospitalization, only the most severe cases of DVT and OHSS are hospitalized, resulting in a probable underestimation of DVT and OHSS incidence in our study. Moreover, to identify VTE we used ICD-10 diagnostic codes recorded in hospital databases. Those codes showed good positive predictive value for both PE and DVT. Sensitivity was high for PE but not for DVT [20,21]. Ascertainment bias may have existed for women receiving OS as they were monitored more closely, owing to a greater probability of being diagnosed with OHSS and other complications such as VTE or AT, compared with women receiving other types of FT (e.g., OI). The presence of inherited and acquired thrombophilia may also increase the risk of thromboembolic complications. Some patients already diagnosed with thrombophilia were probably receiving thromboprophylaxis during FT, which may also have affected the results. However, data on patients' thrombophilic status is not recorded in France's medical databases.

Other study limitations regard the lack of information about individuals and about FT delivery in our databases. With respect to the former, women undergoing fertility treatment are at higher risk of thromboembolic events for many reasons including older age, obesity, chronic diseases, higher rates of nulliparity, hypertension, preeclampsia and cesarean deliveries. Data for these specific variables were not available in the databases and this may have introduced a bias. With respect to information about FT delivery, the Sniiram database only contains information on treatments reimbursed by the French health insurance system. Since all FT treatments are eligible for reimbursement, it is safe to assume that all FT drugs sold are recorded in the database. Nevertheless, only the date when the drug was sold was available in the database. We had no information on the date the drug was administered or whether it was administered at all.

Furthermore, miscarriage before 22 weeks of amenorrhea was not considered as pregnancy in our study (data not available). Therefore, pregnancy-related thromboembolic events were missed if the pregnancy terminated before 22 gestational weeks. The proportion of early or late miscarriages is higher in the presence of thrombophilias, and therefore, some cases of thromboembolic complications may have been missed.

Finally, despite the very large study sample, the incidence of AT was low. Accordingly, it is difficult to make statistical comparisons between the different types of FT.

Conclusion

In this study, fertility treatment (FT), particularly OS treatments, were associated with an increased risk of VTE in both unsuccessful and successful FT cycles. OS treatments were also associated with an increased risk of both VTE and AT during the first trimester of pregnancy, with an additional VTE risk during the last trimester. Therefore, this study highlights the importance of detecting women with high vascular risk before medically assisted reproduction treatment, and the need to closely follow these women once they undergo this treatment, especially when it leads to pregnancy, and most particularly when this is the result of OI.

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Conflicts of interest

All authors completed the ICMJE uniform disclosure form and declare the following: no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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