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PREGNANCY AFTER COMBINED ORAL CONTRACEPTIVE-ASSOCIATED VENOUS THROMBOEMBOLISM: AN INTERNATIONAL RETROSPECTIVE STUDY OF OUTCOMES

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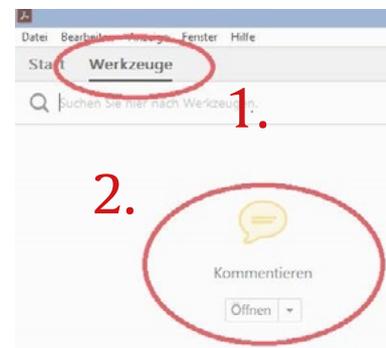
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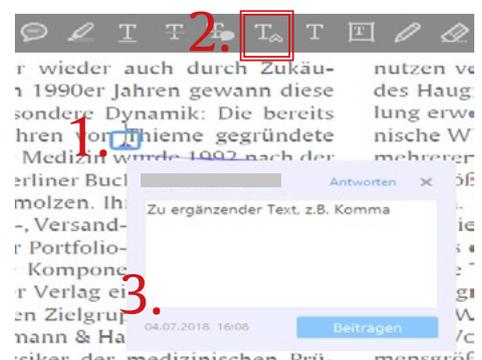
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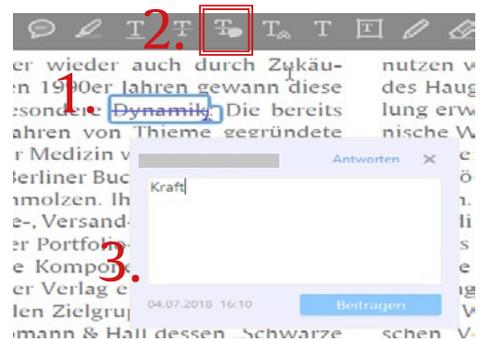
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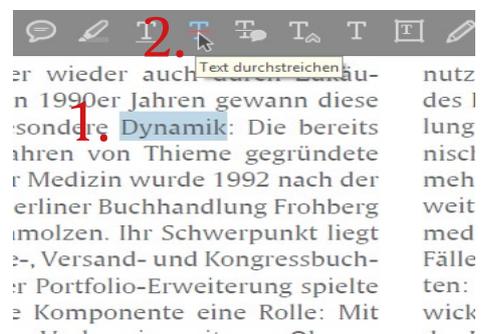
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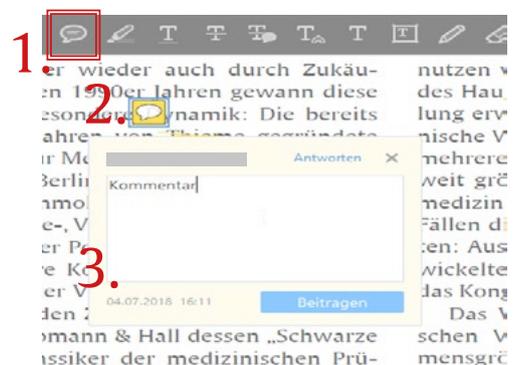
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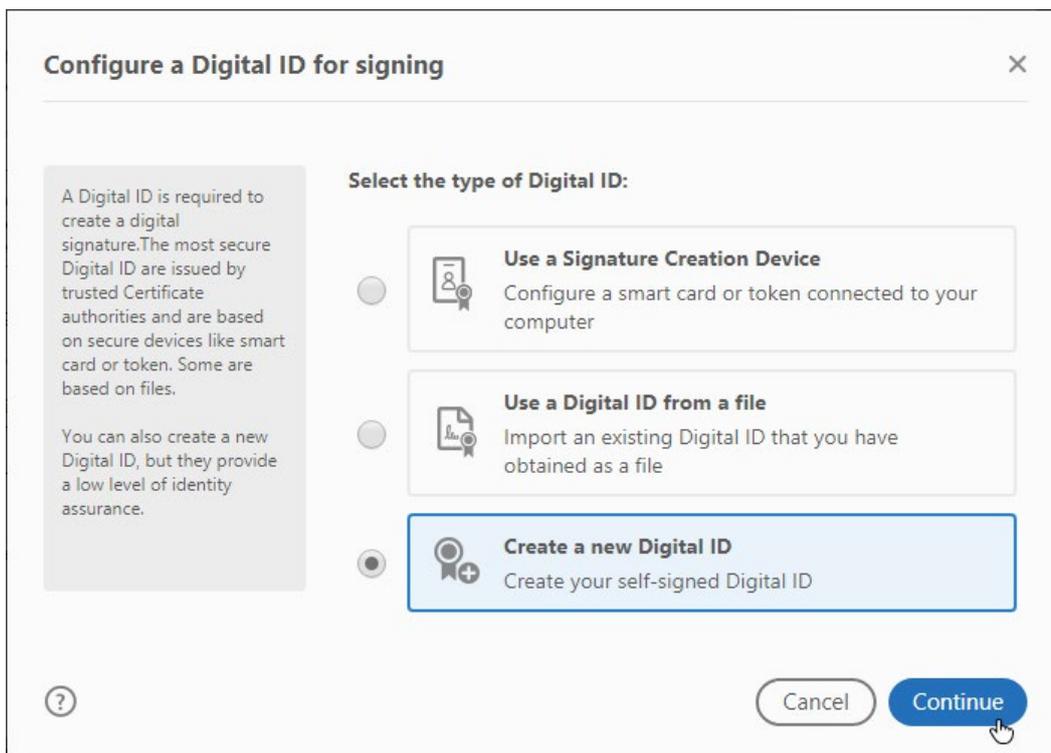
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Pregnancy after Combined Oral Contraceptive-Associated Venous Thromboembolism: An International Retrospective Study of Outcomes

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Thromb Haemost 2022;00:1–15.

Abstract

Background Few data are available on thrombotic outcomes during pregnancy and puerperium occurring after an initial provoked venous thromboembolic (VTE) event.

Objectives To describe thrombotic outcomes during pregnancy after a first combined oral contraceptive (COC)-associated VTE and the factors associated with recurrence.

Methods This was an international multicentric retrospective study on patients referred for thrombophilia screening from January 1, 2010 to January 1, 2021 following a first COC-associated VTE, including women with neither inherited thrombophilia nor antiphospholipid antibodies and focusing on those who had a subsequent pregnancy under the same thromboprophylaxis treatment. Thrombotic recurrences during pregnancy and puerperium as well as risk factors for recurrence were analyzed.

Results We included 2,145 pregnant women. A total of 88 thrombotic events, 58 antenatal and 29 postnatal, occurred, mostly during the first trimester of pregnancy and the first 2 weeks of puerperium. Incidence rates were 49.6 (37–62) per 1,000 patient-years during pregnancy and 118.7 (78–159) per 1,000 patient-years during puerperium. Focusing on pulmonary embolism, incidence rates were 1.68 (1–4) per 1,000 patient-years during pregnancy and 65.5 (35–97) per 1,000 patient-years during puerperium.

Keywords

- ▶ combined oral contraceptives
- ▶ venous thrombosis
- ▶ pregnancy
- ▶ recurrence
- ▶ prognosis

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Risk factors for antenatal recurrences were maternal hypercholesterolemia and birth of a very small-for-gestational-age neonate. A risk factor for postnatal recurrence was the incidence of preeclampsia.

Conclusion Our multicentric retrospective data show significant rates of VTE recurrence during pregnancy and puerperium in women with a previous VTE event associated with COC, despite a unique low-molecular-weight heparin-based thromboprophylaxis. These results may provide benchmarks and valuable information for designing future randomized controlled trials.

Introduction

Venous thromboembolism (VTE), deep vein thrombosis (DVT) and/or pulmonary embolism (PE), is a rare event in women of childbearing age, affecting 2 to 10 per 10,000 persons per year.¹ Exogenous sex steroids, mainly combined oral contraceptives (COCs) containing both synthetic estrogen and progestogen, remain the most common risk factor for VTE in women at fertile age.^{2,3} COCs increase the relative risk of VTE by three to six times and the magnitude of risk depends on the progestogen type and estrogen doses used.^{4,5} Women who have their first VTE while taking oestrogens have a low risk of recurrent VTE after stopping anticoagulation^{6–8} and might not benefit from extended anticoagulant therapy.

Pregnancy and puerperium are the second clinical chronological situations which increase the risk of VTE events in a young woman's life.^{9–11} They are classically associated with a high risk of VTE recurrence in the few available published data.^{12–18} Guidelines recommend antepartum and postpartum thromboprophylaxis for women with a personal history of estrogen-related VTE,^{19,20} despite insufficient available evidence on which to base the recommendations²¹ and modalities for thromboprophylaxis.

We report the thrombotic outcomes during pregnancy and puerperium of 2,145 French and Russian women with a first VTE associated with COC intake, observed over the period 2010 to 2020, negative for constitutive thrombophilia and antiphospholipid antibodies, and treated by the same low-molecular-weight heparin (LMWH)-based thromboprophylaxis.

Methods

Study Design

COC-PREG is an international, multicentric, retrospective, observational study including women selected among consecutive outpatients referred to hematologists, or to gynecologists and obstetricians, for thrombophilia screening after VTE. Three centers participated: Nîmes University Hospital, France; the I.M. Sechenov First Moscow State Medical University, Moscow, and the Altai State Medical University, Barnaul, Russian Federation.

Study Population

Briefly, we screened the medical files of patients referred to our teams, diagnosed with an objectively confirmed first VTE

associated with COC intake, from January 1, 2010 to January 1, 2021 (11 years), and applied common selection criteria for all three centers (► Fig. 1). Suspected DVT was considered confirmed if there was evidence of a positive conclusion using whole-leg compression ultrasound and suspected PE using a perfusion lung scan or helical computed tomography scan. Distal DVT was defined as infrapopliteal DVT without proximal DVT or PE, proximal DVT as popliteal, femoral, or iliac vein DVT. In cases where PE complicated DVT, PE was considered to be the main event. VTE was considered as being associated with COC intake and women exposed to the thrombogenic risk of exogenous synthetic oestrogens if they were taking them when diagnosed with VTE. COCs were classified as second generation (G2; progestins: levonorgestrel and norethisterone), third generation (G3; norgestimate, desogestrel, gestodene, and cyproterone acetate), and fourth generation (G4; drospirenone, nomegestrol acetate, or dienogest).

We excluded women in the postpartum period (up to 12 weeks after delivery), women aged over 45 years, and women with an active cancer or newly diagnosed cancer (within 6 months after VTE diagnosis).

Thrombophilia screening was performed after ceasing anticoagulant treatment and included tests for antithrombin, protein C, protein S, *F5* rs6025 and *F2* rs1799963 polymorphisms, and criteria for antiphospholipid antibodies (aPLAbs). These aPLAbs were tested according to the guidelines of the International Society on Thrombosis and Haemostasis (ISTH),^{22,23} namely, lupus anticoagulant and the solid-phase aPLAbs anticardiolipin immunoglobulin G (IgG) and IgM antibodies and anti-β₂-glycoprotein I IgG and IgM antibodies using commercially available kits from Orgentec Diagnostika GmbH, Mainz, Germany, at the three centers. Women with antithrombin, protein C, or protein S deficiency, or positive for the *F5* rs6025 or *F2* rs1799963 polymorphism, or with transient or persistent positive antiphospholipid antibodies were excluded from the study. We excluded all women with positive thrombophilia testing because we generally do not manage them similarly during pregnancy in the three participating centers, and because we could not agree on a similar prophylactic approach before starting this work.

We finally collated the medical files of all women with an initial COC-associated VTE, who thereafter had a pregnancy during the observation period, whose pregnancy was

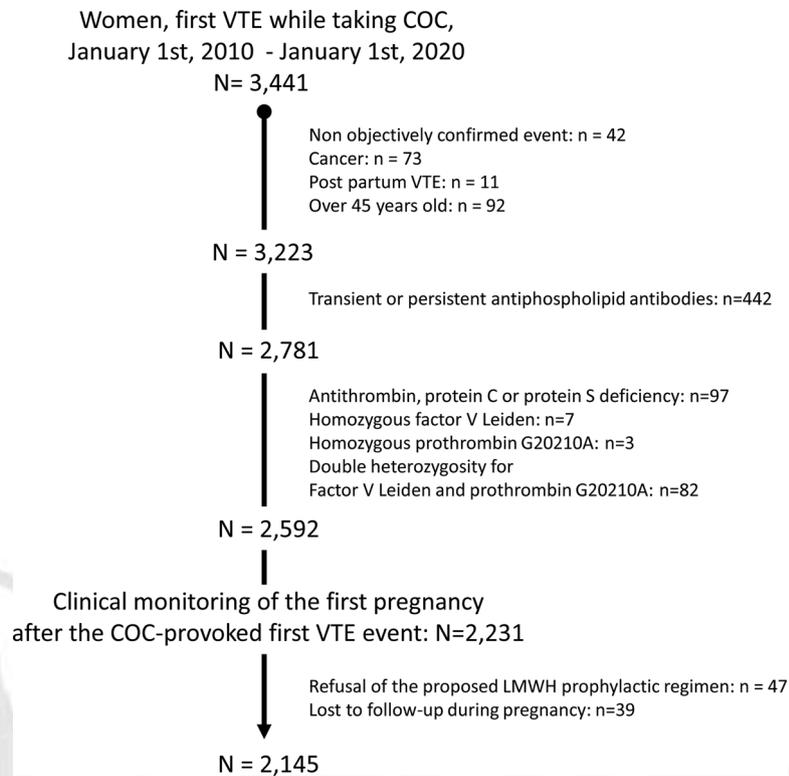


Fig. 1 Flow diagram showing selection of medical files for the retrospective analysis.

followed within the three centers and who accepted to begin the proposed LMWH-based thromboprophylaxis after the positive pregnancy test.

Thromboprophylactic Treatment during Pregnancy

This regimen was common between the three centers. Two LMWH brands were used: Enoxaparin sodium (E), Sanofi, France and Nadroparin calcium (N), Aspen Notre-Dame-de-Bondeville, France. Treatments were adapted to the women's body mass index (BMI): <math><20 \text{ kg}\cdot\text{m}^{-2}</math>: E 20 mg, N 19,00 anti-Xa units; <math><30 \text{ kg}\cdot\text{m}^{-2}</math>: E 40 mg, N 3,800 anti-Xa units; <math><35 \text{ kg}\cdot\text{m}^{-2}</math>: E 60 mg, N 5,700 anti-Xa units; $>35 \text{ kg}\cdot\text{m}^{-2}$: E 80 mg, N 7,600 anti-Xa units. LMWH was given subcutaneously once a day throughout the whole pregnancy and from weeks 4 to 6 postpartum, but twice a day during the first 3 weeks of puerperium when thrombotic risk is at its highest.⁹

Women with hypercholesterolemia or hypertriglyceridemia did not receive any lipid-lowering drugs, including statins during follow-up.

The COC-APS study was approved by the internal review boards of all three participating centers. In accordance with the legislation on medical research, we obtained oral informed consent from all patients.

Follow-Up Arrangements during Pregnancy

The general recommendation in this population of at-risk women with a strong desire for an uncomplicated first pregnancy was to perform an early pregnancy test within 7 days of a late period. Women were systematically evalu-

ated as outpatients, just after their positive pregnancy test, to prescribe thromboprophylaxis and give them recommendations.

They were systematically informed about symptoms evoking a new VTE or arterial thrombosis and sensitized to hemorrhagic manifestations. Patients were advised to contact their involved obstetrician/hematologist within the recruiting center if they had any symptoms of thrombosis or hemorrhage at any time.

Patients with varicose veins were systematically encouraged to wear appropriate elastic compression stockings. However, adhesion was poor and it was difficult to control whether this recommendation was respected. We thus did not collect this variable.

All recurrences of DVT and PE were confirmed according to the ISTH criteria.²⁴ Any other thrombotic events were recorded. Major bleeding events were defined according to the Control of Anticoagulation Subcommittee of the ISTH²⁵: fatal bleeding and/or symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of $20 \text{ g}\cdot\text{L}^{-1}$ or more, or leading to transfusion of 2 or more units of packed red cells. Postpartum hemorrhage was defined according to the World Health Organization's definition as blood loss >500 mL for both vaginal and caesarean section deliveries,²⁶ but blood loss was not systematically measured and quantified.

Data Extracted from Medical Files

Demographic characteristics, clinical data, diagnostic test results, and treatments were finally collected from the medical files. These included parameters potentially or really associated with the risk of VTE during pregnancy and puerperium.

The following data were obtained when the women were seen for thromboprophylaxis prescription after their positive pregnancy test: age, type of COC-associated initial VTE event, time elapsed between VTE and pregnancy, pregnancy after assisted conception techniques, quantitative D-dimer plasma concentrations (categorized as high if $>500 \mu\text{g.L}^{-1}$), HERDOO2 score categorized as high if ≥ 2 ,²⁷ BMI (BMI with obesity defined as values $>30 \text{ kg.m}^{-2}$), family history of VTE in a first degree relative, family history of atherothrombosis, active smoking, varicose veins, hypercholesterolemia (fasting cholesterol above 5.2 mM), and hypertriglyceridemia (fasting triglycerides above 1.7 mM).

The following variables were collected during regular pregnancy follow-up: the starting date and duration of thromboprophylaxis, general pregnancy characteristics (techniques, twinning, hospitalization during pregnancy, ...), non-pregnancy-specific risk factors for VTE (trauma, surgery, infectious disease, inflammatory disease flare, immobilization defined as strict confinement to bed for at least 3 days, ...), pregnancy-specific complications (gestational diabetes, intrahepatic cholestasis of pregnancy, pregnancy demise: from early embryonic loss to intrauterine fetal death, placental diseases: as a whole, then by type and severity), mode of delivery, type of analgesia, gestational age and sex-adjusted neonate weight (percentiles), and neonate and maternal admission to an intensive care unit (ICU). All pregnancy-related complications were defined as previously described.^{28,29}

Outcomes

The primary outcome of this retrospective observational study was the occurrence of symptomatic thrombosis, defined as VTE recurrence and any thrombotic arterial event. The secondary outcomes were VTE recurrence according to initial VTE subtype (distal DVT, proximal DVT, PE) and major bleeding.

All outcomes were discussed and judged collegially among the main investigators of the three centers by electronic communication means (J.-C. G., V.B., M.N.).

Statistical Analysis

There was no a priori study size calculation. The study was only based on our possibilities of recruitment and selection of medical files corresponding to the chosen criteria.

We minimized the amount of missing data by establishing an initial consensus between the three centers, planning to carefully collect the essential information prone to describing the risk of VTE during regular pregnancy follow-up visits.

Quantitative data are given as means, [standard deviation], (range), and qualitative data as numbers (%).

The follow-up period was defined including pregnancy and the first 6 weeks of puerperium. For patients lost to

follow-up, the last evaluation date was considered as the follow-up period.

Incidence rates of thrombosis were calculated as the number of thrombotic events over the number of person-years of pregnancy and puerperium follow-up, defined as up to the end of the first 6 weeks postpartum.

We tested the association between potential risk factors and VTE recurrence. As ante- and postpartum risk factors for VTE naturally differ markedly,^{30,31} we performed two separate analyses for VTE events diagnosed during pregnancy and for VTE events diagnosed during puerperium. To study exposure to late pregnancy risk factors and as no patients with pregnancy loss before 20 weeks of pregnancy had any recurrence, we only included women with an ongoing pregnancy at 20 weeks.¹⁸ We performed a univariate logistic regression analysis and crude odds ratios were reported with their two-sided 95% confidence intervals ($_{95\%}\text{CIs}$). Variables with a *p*-value of less than 0.15 were included in multivariate logistic regression models and adjusted odds ratios (aORs) were computed.

Statistical analyses were performed using StatView-Windows software v.5.0 (SAS Institute Inc., Cary, North Carolina, United States) and XLSTAT software v.2015.4.01.20116 (Addinsoft S.A.R.L., Paris, France).

Results

Patient Characteristics

The selected medical files described 2,145 women, whose prepregnancy characteristics are described in **Table 1**. None of the women included were taking any antithrombotic therapy before pregnancy. Missing values were very limited. Mean age was 31.9 years, the predominant type of initial VTE event was distal DVT in 63.8% of patients, and PE was the rarest (17.6% of cases). Additional triggering risk factors for VTE were positive in 48.9% of the patients, the most frequent being prolonged bed rest at least 3 days, cast immobilization, and a systemic infectious syndrome. Obesity was evidenced in 22% of the cases, varicose veins in 22.4%, and active smoking in 31.4%. There was an underlying chronic systemic inflammatory disease in 5.9% and a history of VTE in at least one first-degree relative in 21.9%. A high HERDOO2 score, ≥ 2 , evaluated despite non-unprovoked initial VTE events, was found in 23.7% of the women.

The initial VTE event was treated by 5 to 10 days of a subcutaneously injected, weight-adjusted, therapeutic dose LMWH followed by a vitamin K antagonist, target international normalized ratio: 2.5 (2–3). The mean duration of anticoagulation was 3 months (range: 3–6 months). The mean time between VTE and pregnancy was 14.3 months (range: 9.4–20.2), and the mean time between the end of anticoagulation and pregnancy was 11.3 months (range: 6.4–14.2 months).

For 2,104 patients, LMWH was begun within 1 week of a positive pregnancy test. For the remaining 41 women, LMWH was not initiated due to a very early pregnancy loss. Cutaneous intolerance was observed in 47 patients and led to a successful switch to another LMWH in 46

Table 1 Characteristics^{Q2} of the 2,145 women whose pregnancies were under study

Q2

Variable (missing values: n)	
Country of residence	
France	394 (18.4)
Russia	1,751 (81.6)
COC-associated initial VTE event	
Distal DVT	1,367 (63.8)
Proximal DVT	401 (18.6)
Pulmonary embolism	377 (17.6)
COC type	
Second generation	1,718 (80.1)
Third generation	416 (19.4)
Fourth generation	11 (0.5)
Additional risk factors for VTE	
Negative	1,096 (51.1)
Positive (<i>more than one is possible</i>)	1,049 (48.9)
Local trauma	129 (6.0)
Cast immobilization	317 (14.8)
Recent surgery	185 (8.6)
Prolonged bed rest	332 (15.5)
Systemic infectious syndrome	236 (11.0)
Systemic inflammatory flare-up	64 (3.0)
Long-haul flight	47 (2.2)
Time elapsed between VTE and pregnancy, mo	14.3 [2.84] (9.4–20.2)
Age, y	31.9 [3.56] (18–41)
Age > 35 y	223 (10.4)
BMI, kg.m ⁻²	26.4 [4.16] (16.9–37.3)
BMI: categories	
Underweight (<18.5 kg.m ⁻²)	14 (0.7)
Normal	1,244 (56.0)
Overweight (>25 kg.m ⁻² and ≤30 kg.m ⁻²)	415 (19.3)
Obesity (>30 kg.m ⁻²)	472 (22.0)
Class I obesity, ≤35 kg.m ⁻²	388 (18.1)
Class II obesity, >35 kg.m ⁻²	84 (3.9)
HERDOO2 score ≥2 (19)	509 (23.7)
Active smoker: yes	673 (31.4)
Varicose veins: yes	480 (22.4)
Arterial hypertension: yes (11)	152 (7.1)
Hypercholesterolemia: yes (32)	205 (9.6)
Hypertriglyceridemia: yes (27)	184 (8.6)
Diabetes mellitus: yes	48 (2.2)
Dysthyroidism: yes (24)	199 (0.3)
Systemic inflammatory disease: yes (9)	127 (5.9)
Family history of VTE, first degree relatives (17)	470 (21.9)
Family history of atherothrombosis, first degree relatives (41)	375 (17.5)

(Continued)

Table 1 (Continued)

Variable (missing values: n)	
ABO blood group (3)	
A	971 (45.4)
O	918 (42.8)
B	181 (8.4)
AB	72 (3.4)

Abbreviations: BMI, body mass index; COC, combined oral contraceptive; DVT, deep vein thrombosis; VTE, venous thromboembolism. Note: Quantitative data are given as means [SD] (range) and qualitative data as numbers (%).

women. One patient remained symptomatic and was given 2.5 mg of fondaparinux per day, then 5 mg daily during the first 3 weeks of puerperium. No LMWH cessation was due to a medical decision, but 49 patients stopped their LMWH treatment prematurely, 6 during pregnancy and 43 in the early postpartum period.

The 2,145 medical files covered a total observational period cumulating in 1,433.22 pregnancy-postpartum woman-years, 1,188.96 pregnant woman-years, and 244.26 postpartum woman-years. No deaths occurred during this period and only 39 patients were lost to follow-up during pregnancy.

Primary Outcome

A total of 88 thrombotic events occurred: 83 DVTs (53 distal DVTs, 30 proximal DVTs) and 18 PEs (13 of which were associated with a proximal DVT). All recurrences were diagnosed in patients actively taking their LMWH treatment and having an ongoing pregnancy at 20 weeks of pregnancy. Additional, nonpregnancy-related risk factors for VTE were positive in only 9 of the 88 patients: local trauma in 3, cast immobilization for a sprained ankle in 4, systemic infectious disease (pyelonephritis) in 2.

Among the 83 DVT recurrences, 53 were ipsilateral to the initial event. VTE recurrences occurred during pregnancy in 59 cases (including 2 PEs) and during puerperium in 29 cases

(including 16 PEs). The distribution of VTE events within pregnancy and puerperium is described in ►Table 2. Even those women who had a very early recurrence had received at least one LMWH injection. Most VTE recurrences occurred during the first trimester of pregnancy (41/59) or during the first 2 weeks of puerperium (24/29). DVT recurrences such as proximal DVT and PE were mainly observed during puerperium.

This globally corresponded to 61.4 thrombotic events per 1,000 patient-years ($_{95\%CI}$: 46–70), i.e., 1 event per 16.3 patient-years: 49.6 (37–62) per 1,000 patient-years during pregnancy and 118.7 (78–159) per 1,000 patient-years during puerperium, the annual recurrence incidence rate thus being 2.4 times higher among postpartum women than in pregnant women. Regarding PE, the incidence rate was 12.56 (7–18) per 1,000 patient-years, i.e., 1 event per 79.6 patient-years: 1.68 (1–4) per 1,000 patient-years during pregnancy and 65.5 (35–97) per 1,000 patient-years during puerperium (39 times higher than during pregnancy).

No arterial thrombotic events were reported during pregnancy or puerperium in these women.

Secondary Outcomes

Initial VTE types were not associated with different risks of VTE recurrence: 54 recurrences occurred in the 1,367 women with an initial distal DVT (3.95%), 18 in the 401 women

Table 2 Distribution of venous thromboembolic (VTE) events during pregnancy (months, M) and puerperium (weeks, W)

Pregnancy										
M1	M2	M3	M4	M5	M6	M6	M8	M9	Total	
VTE	7	16	18	2	5	4	2	3	2	59
Proximal DVT	1	0	1	0	2	1	1	2	2	10
Distal DVT	6	16	17	2	3	3	1	1	0	49
PE	0	2	0	0	0	0	0	0	0	2
Puerperium										
W1	W2	W3	W4	W5	W6	Total				
VTE	14	10	1	3	1	0	29			
Proximal DVT	10	7	1	2	0	0	20			
Distal DVT	0	2	0	1	1	0	4			
PE	9	4	1	2	0	0	16			

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 3 Characteristics of the 2,145 pregnancies included in the study

Variable (missing values: n)	
Assisted conception techniques	41 (1.9)
Ovary hyperstimulation syndrome	1
Gemellar pregnancy	54 (2.5)
Pregnancy loss	
Embryonic loss before week 10	394 (18.4)
Fetal death before week 20	153 (7.1)
Stillbirth	113 (5.3)
Ongoing pregnancies at week 20	1,598 (74.5)
Hospitalization during pregnancy	417 (19.4)
Placental diseases ^a	390 (24.4)
Preeclampsia	235 (14.7)
Severe preeclampsia	185 (11.6)
Early-onset preeclampsia < 34 weeks	154 (9.6)
Eclampsia	48 (3.0)
HELLP syndrome	61 (3.8)
Placental abruption	51 (3.2)
Small-for-gestational-age (SGA) neonate	303 (19)
Severe SGA, <3rd percentile	110 (6.9)
With intrauterine fetal death	20 (1.3)
Gestational diabetes	137 (6.4)
Urinary tract infection (38)	69 (3.2)
Strict confinement to bed, more than 3 days (13)	279 (13.0)
Term at delivery ^a	36.8 [4] (20–41)
Prematurity	476 (29.8)
Prematurity < 34 weeks	281 (17.6)
Prematurity < 30 weeks	122 (7.6)
Induction of labor ^a (21)	515 (32.2)
Caesarean section ^a	393 (24.6)
Gestational-age and sex-adjusted neonate weight, percentiles ^a	39.8 [19.1] (1–93)
Neonate admission to intensive care unit (ICU) ^a	204 (12.8)
Length of stay in ICU, d	4.7 [10.9] (2–23)
Maternal admission to ICU	147 (6.9)
Length of stay in ICU, d	2.5 [1.1] (2–6)
LMWH-mediated thromboprophylaxis:	
No injection, due to very early pregnancy loss	41
At least one injection	2,104
Within 1 week of positive pregnancy test	2,104
Beginning of thromboprophylaxis, weeks of pregnancy	4 [0.5] (3–6)
Switch to the other LMWH for cutaneous manifestations	37 (1.8)
LMWH-induced thrombocytopenia	0
Premature cessation, medical decision	0
Premature cessation, patient will	49 (2.3)
During pregnancy	6 (0.3)
During puerperium	43 (2.0)

Note: Quantitative data are given as means [SD] (range) and qualitative data as numbers (%).

^aBy reference to ongoing pregnancies at week 20.

with initial proximal DVT (4.49%), and 16 in the 377 women with initial PE (4.24%) ($p = 0.87$). There was also no difference in the risk of VTE recurrence diagnosed as PE ($p = 0.60$).

Major bleeding occurred in 38 women (1.77%), all with a severe primary postpartum hemorrhage defined with blood loss estimated as more than 1,000 mL. Postpartum hemorrhage developed in 90 cases (4.20%).

Effect of Putative Risk Factors on Thrombosis Recurrence

The characteristics of pregnancies are described in ► **Table 3**. A significant amount of pregnancy losses/fetal deaths occurred, with three-quarters of pregnancies evolving at 20 weeks. These pregnancies were included in the analyses of risk factors for antenatal, then postnatal, VTE recurrence. The incidence of placental diseases was also far from being negligible.

Risk Factors for VTE Recurrence during Pregnancy

Univariate Analysis

The patient's country of origin, clinical type of initial VTE, and COC generation were not significantly associated with the risk of VTE recurrence. One maternal variable (hypercholesterolemia) and five neonate variables—severe small-for-gestational age (neonate weight lower than the third percentile value of the gestational age- and sex-adjusted weight), neonate admission to ICU, neonatal mortality (days 0 to 27 postpartum), late neonatal mortality (days 7 to 27), and perinatal mortality (pregnancy week 23 to day 27 postpartum)—were associated with VTE recurrence during pregnancy. The five neonate variables were highly dependent on each other (Chi-squared test: $p < 0.0001$) (► **Table 4**).

Multivariate Analysis

Among the neonate variables significant after univariate analysis but found dependent on each other, only severe small-for-gestational age was entered into the multivariate analysis to avoid collinearity. Among the covariates with a p -value of less than 0.15 after the univariate analysis, only BMI (continuous variable), family history of atherothrombosis, type of COC, time between VTE and pregnancy, and smoking were entered into the model for adjustment purposes. Maternal hypercholesterolemia and birth of a very small-for-gestational-age neonate were finally found to be independently associated with VTE recurrence during pregnancy.

Risk Factors for VTE Recurrence during Puerperium

Univariate Analysis

Here also, the patient's country of origin, clinical type of initial VTE, and COC generation were not significantly associated with the risk of VTE recurrence. Six maternal variables—occurrence of any placental disease, preeclampsia, severe preeclampsia, early-onset preeclampsia, maternal admission to the ICU (these five variables being highly dependent on each other, Chi-squared test: $p < 0.0001$), hypercholesterolemia—and six neonate variables—gestational age- and sex-

adjusted weight (percentiles), small-for-gestational-age (lower than the 10th percentile), very small-for-gestational-age (lower than the third percentile), neonate admission to ICU, neonatal mortality (during days 0 to 27 postpartum), late neonatal mortality (day 7 to day 27) (six variables being highly dependent on each other, $p < 0.0001$)—were associated with VTE recurrence during puerperium. The five maternal variables related to placental diseases (occurrence of any placental disease, preeclampsia, severe preeclampsia, early-onset preeclampsia, maternal admission to the ICU) and the six neonate variables related to low intrauterine growth and secondary prognosis (gestational age- and sex-adjusted weight, small-for-gestational-age, very small-for-gestational-age, neonate admission to ICU, neonatal mortality, and late neonatal mortality) were also highly dependent on each other (► **Table 5**).

Multivariate Analysis

Among the maternal and neonate variables significant after the univariate analysis but found dependent on each other, only the occurrence of preeclampsia was entered into the multivariate analysis to avoid collinearity. Among covariates with a p -value of less than 0.15 after the univariate analysis, only family history of VTE and postpartum hemorrhage were finally entered into the model for adjustment purposes and strict confinement to bed for more than 3 days and the occurrence of preeclampsia were highly dependent on each other ($p < 0.0001$). The occurrence of preeclampsia was finally found to be independently associated with VTE recurrence during puerperium.

Other Pregnancy-Related Observed Outcomes

Moving to pregnancy-related, nonthrombotic outcomes, we observed a significant rate of pregnancy losses before 20 weeks (394 embryonic losses and 153 fetal deaths: 25.5% of all the pregnancies) and also 5.3% of all pregnancies ending in a stillbirth. Focusing on ongoing pregnancies at week 20, we also observed a high rate of placental diseases (24.4%), preeclampsia being the main disease (14.7%), with a premature birth in 29.8% of the cases (► **Table 3**).

Discussion

Our multicentric retrospective data on a large number of cases show significant rates of VTE recurrence during pregnancy and puerperium in women with a previous VTE event associated with COC intake despite the same, BMI-indexed, LMWH-based thromboprophylaxis. Compared with the estimated pooled incidence of pregnancy/puerperium-related VTE (1.2 per 1,000 deliveries),³² our overall incidence rate, in a high-risk population receiving prophylaxis, was still over 50 times higher. Most VTE recurrences were diagnosed during the first trimester of pregnancy and within the first 2 weeks of puerperium. Incidence rates were 2.4 times higher during puerperium, despite doubling LMWH dosages during the first 3 weeks of the postpartum period. The overwhelming relative risk of PE during puerperium compared with pregnancy suggests, despite a low absolute risk,

Table 4 Risk factors for antenatal VTE recurrence, first in a monovariate analysis (crude odds ratios: cOR) then through multivariate models (adjusted OR: aOR)

Variable	cOR (95%CI)	p	aOR (95%CI)	p
Country: Russia	1.167 (0.649–2.096)	0.61		
ABO group				
A	1			
B	1.245 (0.609–2.547)	0.55		
AB	0.654 (0.154–2.783)	0.57		
O	0.911 (0.573–1.448)	0.69		
Family history of VTE	1.206 (0.733–1.984)	0.46		
Family history of atherothrombosis	0.511 (0.244–1.071)	0.075	0.550 (0.261–1.158)	0.116
Time between VTE and pregnancy, mo	1.059 (0.981–1.143)	0.139	1.066 (0.986–1.152)	0.108
Initial VTE event				
Distal DVT	1			
Proximal DVT	1.202 (0.694–2.085)	0.51		
Pulmonary embolism	1.085 (0.611–1.926)	0.78		
COC type				
Second generation	1			
Third generation	0.583 (0.306–1.111)	0.101	0.607 (0.317–1.162)	0.132
Fourth generation	2.263 (0.275–18.635)	0.45		
Age, y	0.972 (0.916–1.032)	0.36		
Age > 35 y	0.724 (0.329–1.594)	0.42		
D-dimers, $\mu\text{g.L}^{-1}$	1.001 (0.999–1.002)	0.49		
> 500 $\mu\text{g.L}^{-1}$	1.125 (0.652–1.941)	0.67		
BMI, kg.m^{-2}	0.960 (0.910–1.012)	0.129	0.965 (0.915–1.018)	0.196
> 25 kg.m^{-2}	0.684 (0.387–1.207)	0.189		
BMI category				
Normal	1			
Underweight	No VTE case			
Overweight	0.670 (0.369–1.218)	0.189		
Obesity class I	0.552 (0.286–1.066)	0.077		
Obesity, class II	0.911 (0.321–2.591)	0.86		
HERDOO2 score ≥ 2	1.126 (0.690–1.838)	0.63		
Varicose	0.867 (0.515–1.460)	0.59		
Smoking	1.493 (0.961–2.320)	0.075	1.499 (0.959–2.342)	0.0758
Arterial hypertension	0.759 (0.302–1.911)	0.56		
Systemic inflammatory disease	0.985 (0.389–2.493)	0.98		
Dysthyroidism	0.979 (0.463–2.066)	0.96		
Diabetes	1.110 (0.261–4.713)	0.89		
Gestational diabetes	No VTE case			
Hypercholesterolemia	2.641 (1.527–4.565)	0.0005	2.519 (1.441–4.404)	0.0012
Hypertriglyceridemia	0.614 (0.245–1.539)	0.30		
Assisted reproduction techniques	No VTE			
Gemellar pregnancy	1.367 (0.414–4.520)	0.61		
Urinary tract infection	1.917 (0.742–4.953)	0.179		
Strict confinement to bed, more than 3 days	1.146 (0.735–1.787)	0.55		

(Continued)

Table 4 (Continued)

Variable	cOR (95%CI)	p	aOR (95%CI)	p
Intrahepatic cholestasis of pregnancy	0.608 (0.082–4.525)	0.63		
Hospitalization during pregnancy	1.054 (0.637–1.747)	0.84		
Stillbirth	0.959 (0.409–2.249)	0.92		
Mortality, 24 weeks delivery	1.116 (0.474–2.625)	0.80		
Placental diseases				
Any	1.172 (0.723–1.901)	0.52		
Preeclampsia	1.103 (0.612–1.988)	0.74		
Severe preeclampsia	1.097 (0.572–2.104)	0.78		
Early-onset preeclampsia, <34 weeks	1.210 (0.611–2.394)	0.58		
Eclampsia	0.740 (0.177–3.100)	0.68		
HELLP syndrome	0.884 (0.271–2.878)	0.84		
Placental abruption	1.482 (0.522–4.212)	0.46		
Small-for-gestational-age (SGA) neonate	1.353 (0.815–2.246)	0.24		
SGA neonate, <3rd percentile	2.257 (1.187–4.291)	0.0130	2.245 (1.167–4.317)	0.0154
Induction of labor	1.215 (0.777–1.901)	0.39		
Delivery: Caesarean section	1.231 (0.764–1.986)	0.39		
Pregnancy term, wk	1.017 (0.961–1.076)	0.57		
Prematurity	0.932 (0.579–1.500)	0.77		
< 34 wk	0.881 (0.490–1.583)	0.67		
< 30 wk	0.562 (0.202–1.559)	0.27		
Neonate weight, adjusted percentiles	0.992 (0.981–1.003)	0.167		
Postpartum hemorrhage (PPH)	1.242 (0.527–2.929)	0.62		
Severe PPH	0.458 (0.062–3.375)	0.44		
Maternal admission to ICU	1.285 (0.650–2.540)	0.47		
Neonate admission to ICU	1.858 (1.078–3.202)	0.0257		
Neonatal mortality, D0–D27	2.825 (1.397–5.713)	0.0038		
Early, D0–D6	1.473 (0.444–4.890)	0.53		
Late, D7–D27	4.226 (1.801–9.918)	0.0009		
Perinatal mortality, week 23–D27	1.894 (1.075–3.337)	0.0271		

Abbreviations: 95%CI: 95% confidence interval; BMI, body mass index; COC, combined oral contraceptive; DVT, deep vein thrombosis; ICU, intensive care unit; VTE, venous thromboembolism.

Note: The final model is adjusted for all variables with $p < 0.15$ in the univariate models chosen to avoid collinearity.

the need for a marked improvement in prophylaxis during this crucial period. This also suggests that, in the very special circumstances that follow childbirth and its maternal fallout, the prevention of VTE based on LMWHs could have inhomogeneous efficacy: greater on nonembolic DVTs than on embolic DVTs.

One recent French prospective observational study of VTE recurrences during pregnancy following a first VTE,¹⁸ on 189 women, including 68% after an event provoked by estrogen-containing contraceptives and 32% with inherited thrombophilia, on heterogeneous thromboprophylactic treatment, found VTE recurrence rates apparently higher than ours, but in fact with CIs that overlap ours, both before and after delivery. In terms of absolute numbers, most of their recurrences were during the postpartum period, whereas most of

the ones we observed occurred during pregnancy. This could be the consequence of increasing our LMWH dosages during the first 3 weeks after delivery, but this requires a randomized controlled trial conducted according to the rules of the art.

The significant rate of VTE recurrences that we observed during the first trimester of pregnancy in a subgroup of treated women, also observed by others,¹⁸ as late pregnancy is more risky than early pregnancy in nontreated women from the general population,^{33,34} deserves comments and induces speculations. Identifying this subgroup for specific prophylactic developments is a strategic objective. Early pregnancy is not yet associated with intra-pelvic compression of the venous lower limb vessels due to enlargement of the uterus and fetal engagement. On the other hand, early

Table 5 Risk factors for postnatal VTE recurrence, first in a monivariate analysis (crude odds ratios: cOR) then through multivariate models (adjusted OR: aOR)

Variable	cOR (95%CI)	p	aOR (95%CI)	p
Country: Russia	1.379 (0.476–3.996)	0.55		
ABO group				
A	1			
B	0.785 (0.175–3.521)	0.75		
AB	1.032 (0.132–8.046)	0.98		
O	1.067 (0.491–2.319)	0.87		
Family history of VTE	1.904 (0.877–4.135)	0.104	1.963 (0.900–4.279)	0.0899
Family history of atherothrombosis	0.590 (0.177–1.965)	0.39		
Time between VTE and pregnancy, months	1.064 (0.933–1.213)	0.36		
Initial VTE event				
Distal DVT	1			
Proximal DVT	1.519 (0.658–3.508)	0.33		
Pulmonary embolism	0.385 (0.089–1.665)	0.21		
COC type				
Second generation	1			
Third generation	1.628 (0.714–3.713)	0.25		
Fourth generation	No VTE case			
Age, years	1.053 (0.950–1.167)	0.33		
Age > 35 years	0.967 (0.289–3.230)	0.96		
D-dimers, $\mu\text{g.L}^{-1}$	0.999 (0.995–1.002)	0.47		
> 500 $\mu\text{g.L}^{-1}$	0.348 (0.082–1.473)	0.155		
BMI, kg.m^{-2}	0.986 (0.903–1.077)	0.76		
> 25 kg.m^{-2}	0.693 (0.262–1.830)	0.46		
BMI category				
Normal	1			
Underweight	No VTE case			
Overweight	0.941 (0.370–2.393)	0.90		
Obesity class I	0.658 (0.221–1.961)	0.45		
Obesity, class II	0.747 (0.098–5.687)	0.78		
HERDOO2 score ≥ 2	0.509 (0.176–1.473)	0.21		
Varicose	0.504 (0.174–1.457)	0.21		
Smoking	1.018 (0.460–2.252)	0.97		
Arterial hypertension	0.450 (0.061–3.340)	0.44		
Systemic inflammatory disease	0.584 (0.079–4.345)	0.60		
Dysthyroidism	1.566 (0.537–4.564)	0.41		
Diabetes	1.704 (0.225–12.93)	0.60		
Gestational diabetes	No VTE case			
Hypercholesterolemia	2.679 (1.072–6.694)	0.0350		
Hypertriglyceridemia	0.364 (0.049–2.695)	0.32		
Assisted reproduction techniques	No VTE			
Gemellar pregnancy	1.383 (0.183–10.44)	0.75		
Urinary tract infection	2.357 (0.544–10.21)	0.25		
Strict confinement to bed, more than 3 days	1.782 (0.854–3.721)	0.124		

(Continued)

Table 5 (Continued)

Variable	cOR (95%CI)	p	aOR (95%CI)	p
Intrahepatic cholestasis of pregnancy	No VTE			
Hospitalization during pregnancy	1.514 (0.683–3.355)	0.31		
Stillbirth	0.971 (0.228–4.14)	0.97		
Stillbirth, 24 weeks delivery	1.130 (0.264–4.825)	0.87		
Placental diseases				
Any	2.296 (1.044–4.663)	0.0382		
Preeclampsia	2.625 (1.180–5.839)	0.0180	2.519 (1.120–5.663)	0.0254
Severe preeclampsia	2.443 (1.028–5.830)	0.0430		
Early-onset preeclampsia, <34 wk	3.133 (1.302–7.537)	0.0108		
Eclampsia	1.1A37 (0.151–8.537)	0.90		
HELLP syndrome	0.894 (0.120–6.687)	0.91		
Placental abruption	2.306 (0.533–9.984)	0.26		
Small-for-gestational age (SGA) neonate	2.637 (1.232–5.646)	0.0125		
SGA neonate, <3rd percentile	2.978 (1.112–7.976)	0.0299		
Induction of labor	0.957 (0.432–2.117)	0.91		
Delivery: Caesarean section	1.633 (0.753–3.544)	0.21		
Pregnancy term, wk	0.967 (0.891–1.050)	0.42		
Prematurity	1.236 (0.570–2.679)	0.59		
< 34 wk	1.773 (0.777–4.047)	0.17		
< 30 wk	1.361 (0.406–4.564)	0.62		
Neonate weight, adjusted percentiles	0.975 (0.957–0.993)	0.0077		
Postpartum hemorrhage (PPH)	2.716 (0.924–7.985)	0.069	2.362 (0.790–7.059)	0.124
Severe PPH	1.422 (0.188–10.73)	0.73		
Maternal admission to ICU	3.189 (1.338–7.600)	0.0089		
Neonate admission to ICU	3.178 (1.417–7.130)	0.0050		
Neonatal mortality, D0–D27	3.626 (1.222–10.76)	0.0202		
Early, D0–D6	1.528 (0.202–11.57)	0.68		
Late, D7–D27	5.796 (1.659–20.25)	0.0059		
Perinatal mortality, week 23–D27	2.223 (0.892–5.543)	0.0865		

Abbreviations: 95%CI: 95% confidence interval; BMI, body mass index; COC, combined oral contraceptive; DVT, deep vein thrombosis; ICU, intensive care unit; VTE, venous thromboembolism.

Note: The final model is adjusted for all variables with $p < 0.15$ in the univariate models chosen to avoid collinearity.

pregnancy in these women who had venous thrombosis under synthetic estrogen treatment is associated with increasing hormonal impregnation. We can therefore imagine that it is a subgroup of women whose hemostasis and vessel biology are particularly sensitive and modifiable by the hormonal storm of pregnancy. This deserves to be investigated.

We were surprised to find maternal hypercholesterolemia associated with the risk of VTE recurrence during pregnancy. In fact, after multivariate analysis, this was associated with a lower mean risk value in Russian women (aOR: 2.446, 95%CI: 1.326–4.513, $p = 0.0042$) than in French women (aOR: 4.253, 95%CI: 1.015–17.81, $p = 0.0476$). This may be the consequence and impact of different lifestyles between the two countries,

the weight of socio-economic conditions, and the related food and drinking habits on women's health, a difference that may be accentuated by the Mediterranean origin of the participating French women. However, this was impossible to evaluate in our study. One recent case-control study in Serbia found that hypercholesterolemia doubled the likelihood of developing DVT.³⁵ Low birth weight was also associated with the risk of VTE recurrence during pregnancy. To the best of our knowledge, this has been previously evidenced for postnatal VTE³⁶ but lesser so for antenatal VTE. One practical limiting factor is that this predictor cannot be evaluated early in pregnancy, which therefore prevents its use for adjusting prophylaxis. However, it does suggest that an underlying factor involved in fetal development also

modulates the maternal venous thrombotic risk, without being able to extrapolate from its fetal or maternal or mixed origin, and is not controlled by prophylactic dosages of LMWH. Preeclampsia has been associated with the risk of VTE during the postpartum period, in line with previous evidence in untreated women.^{30,31} Preeclampsia is known to have strong deleterious consequences on maternal systemic vascular biology,³⁷ with endothelial dysfunction and damage, specifically in the form of barrier disruption and impaired vasodilatory capacity, platelet activation, and oxidative stress, which may precipitate its thrombogenic capacity.

Our study has strong limitations. It is a retrospective study of medical files, thus with a low level of evidence. Although we were able to compare our practices and harmonize them as far as possible before the observation period, with frequent exchanges between centers during the whole observation period, the study operations, data collected, data entry, and data quality assurance had not been rigorously planned in advance. Any of these areas may be compromised when relying on data that have already been collected. The absence of strong professional human resources dedicated to academic clinical research in the two participating Russian centers is indeed a limiting factor. Women had been informed about symptoms evoking new thrombosis and had to contact their physician in the event of such symptoms. However, the outcomes were based on symptoms and confirmed by objective methods thus a misclassification bias seems unlikely. The physicians involved were highly aware of thrombosis with no significant limitations regarding access to objective diagnostic methods. An observer bias is thus unlikely. A recall bias is also unlikely because the outcomes were major ones and their spontaneous evolution leads to major clinical consequences if the symptoms are disregarded.

Our study also has certain strengths. It was an international multicentric study performed over a significant period of time and our network was able to recruit a large number of patients, allowing us to collect a good number of cases. The three centers are used to harmonizing their practices due to regular institutional exchanges and they all manage their patients in the same way. Outcomes were discussed collegially using electronic communication resources for all files, as were any questions or uncertainties about cases which occurred during follow-up. We believe that the number of symptomatic vascular events that occurred in patients, but not registered in our collaborators' medical files, is minimal or nonexistent.

Finally, the study population is composed of nonthrombophilic women who have developed a thrombotic event during the use of estrogen–progestogen therapy: since pregnancy “mimics” the same hormonal scenario, it is necessary to program prospective randomized studies that take into account an “early” initiation of heparin prophylaxis in these women and pharmacological dosages more appropriate to prevent thromboembolic recurrence, as data highlight that “standard” heparin prophylaxis may not be sufficient to prevent recurrence of thromboembolic events in pregnancy.

We feel that these observational data may provide benchmarks and valuable information for future randomized controlled trials aimed at the prevention of VTE recurrence during pregnancy and postpartum.

What is known about this topic?

- Provoked venous thromboembolic (VTE) events, including combined oral contraceptive (COC)-induced events, globally have a low recurrence risk.
- Few data are available on thrombotic outcomes during pregnancy and puerperium after an initial COC-provoked VTE.

What does this paper add?

- In women receiving a LMWH-based thromboprophylaxis, the VTE recurrence rate during pregnancy and puerperium was 61.4 (46–70) per 1,000 patient-years.
- The recurrence rate was 49.6 (37–62) per 1,000 patient-years during pregnancy and 118.7 (78–159) per 1,000 patient-years during puerperium.
- Recurrence risks were high despite body mass index-adjusted LMWH dosages and its doubling during the first 3 weeks of puerperium.

Author Contributions

J.-C.G. conceived the study. J.-C.G., V.B., J.K., A.M., and M.N. designed the study. J.-C.G., C.B., S.B., E.N., J.L., A.P.-M., E.M., M.N., J.K., V.B., and A.M. performed the research. J.-C.G., M.N., and J.K. performed the statistical analysis. All authors contributed to data analysis and writing of the paper.

Ethical Approval

This study was approved by Nîmes University Hospital's Institutional Review Board (IRB) and ethics committee, Ivan Sechenov University's IRB in Moscow, and Altai State Medical University's IRB in Barnaul, and performed in accordance with the policy on bioethics and human biological samples of French and Russian laws on clinical research and in accordance with the 1996 revised version of the 1975 Helsinki Declaration. All women had given their informed consent to participate.

Data Availability Statement

The dataset supporting the conclusions of this article is available in the Clinical Data Repository of Nîmes University Hospital, Place du Pr. Robert Debré, 30029 Nîmes cedex 9, France, and may be obtained by directly contacting the corresponding author.

Patient Consent

All participating authors have granted permission for publication.

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Conflict of Interest

None declared.

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