Venous thromboembolism during pregnancy, postpartum or during contraceptive use

Findings from the RIETE Registry

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Summary

Venous thromboembolism (VTE) is a leading cause of maternal death during pregnancy or postpartum, and in women using hormonal contraceptives. However, important issues concerning its natural history and therapy remain unsolved, and most of the protocols for treatment of VTE in this patient population are based on data extrapolated from other populations. RIETE is an ongoing registry of consecutive patients with objectively confirmed, symptomatic, acute VTE. We examined the clinical characteristics and three-month outcome of all enrolled women with pregnancy, postpartum or using hormonal contraceptives. As of December 2008, 173 pregnant women, 135 postpartum, and 798 contraceptive users were enrolled. Of these, 438 (40%) presented with pulmonary embolism (PE) and 668 with deep-vein thrombosis (DVT). Most women with acute PE had dyspnea (72%) or chest pain (75%), but only 2.0% had hypoxaemia. During the three-month study period, five women (0.45%; 95% CI: 0.17–1.00) died (3 had fatal PE), 13 (1.18%; 95% CI: 0.66–1.95) had VTE recurrences, and seven (0.63%; 95% CI: 0.28–1.25) major bleeding. Two of the three women with fatal PE died during the first few hours after arriving at the emergency ward, with no time to start any therapy. The outcome of pregnant or postpartum women with VTE is similar to that in contraceptive users, even though the treatment is different. The non-specific nature of PE signs may have caused some delay in PE diagnosis.

Keywords

Pregnancy, postpartum, contraceptives, venous thromboembolism

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Introduction

Venous thromboembolism (VTE) is a leading cause of maternal death during pregnancy or postpartum, and can cause significant morbidity (1–3). Current guidelines from the American College of Chest Physicians (ACCP) recommend that patients with VTE be treated initially with heparin, followed by long-term treatment with anti-vitamin K (AVK) drugs (4). However, there is still uncertainty about the balance between the efficacy and safety of anticoagulant therapy in pregnant or postpartum women with VTE, since they are often excluded from randomised clinical trials of antithrombotic therapy. Consequently, most of the protocols for treatment of VTE in this patient population are based on data extrapolated from other populations.

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) initiative is an ongoing, multicenter, international (Spain, France, Italy, Israel and Brazil) observational registry, designed to gather data on the clinical characteristics, treatment patterns and outcome in consecutive patients with symptomatic, objectively confirmed, acute VTE (5–8). In this analysis, we examined the clinical characteristics, treatment details and three-month outcome of all enrolled women with pregnancy, postpartum or using hormonal contraceptives.

Methods

Patient entry criteria

Consecutive patients with symptomatic, acute deep venous thrombosis (DVT) or pulmonary embolism (PE), confirmed by

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objective tests (contrast venography or ultrasonography for suspected DVT; pulmonary angiography, lung scintigraphy, or helical computed tomography [CT] scan for suspected PE), were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial or if they would not be available for follow-up. All patients provided oral consent to their participation in the registry, according to the requirements of the ethics committee within each hospital. Patients were managed according to the clinical practice of each participating hospital and were not subject to any predetermined intervention.

Study variables and definitions

Of all women enrolled in RIETE were selected three subgroups: those with pregnancy, postpartum (defined as the two-month period after delivery) and those using hormonal contraceptives. The following parameters are recorded in RIETE: baseline characteristics; clinical status including any coexisting or underlying conditions; risk factors for VTE (i.e. recent immobility, recent surgery or prior VTE); the type and dose of treatment received upon VTE diagnosis; and the clinical outcome during at least the first three months. Immobilised patients were defined in this analysis as non-surgical patients who had been immobilised (i.e. total bed rest with bathroom privileges) for ≥4 days in the two-month period prior to VTE diagnosis. Surgical patients were defined as those who had undergone surgery in the two months prior to VTE diagnosis. Active cancer was defined as newly diagnosed cancer or when receiving anti-neoplastic treatment of any type (i.e. surgery, chemotherapy, radiotherapy, hormonal, support therapy, or combined treatments). Recent bleeding was considered in those patients suffering major bleeding <30 days prior to VTE. Bleeding complications were classified as 'major' if they were overt and were either associated with a decrease in the haemoglobin level of 2.0 g/dl (20 g/l) or more, required a transfusion of two units of blood or more, or were retroperitoneal or intracranial.

Data collection and monitoring

The attending physicians ensure that eligible patients were consecutively enrolled. Data are recorded on to a computer-based case report form at each participating hospital and submitted to a centralised coordinating center through a secure website. Patient identities remain confidential because they are identified by a unique number assigned by the study coordinating center, which is responsible for all data management. Encryption of data is used to enhance confidentiality and security. Data quality is regularly monitored and documented electronically to detect inconsistencies or errors, which are resolved by the local coordinators. Data quality is also monitored by periodic visits to participating hospitals, by contract research organisations, who compare the medical records with the data in the web. A data audit is performed at periodic intervals.

Statistical analysis

All variables were calculated as absolute numbers and proportions, and then compared with the Student's t-test or Chi^2 test in case of quantitative or qualitative variables. These analyses were completed with the Statistical Package for Social Sciences (SPSS) program (version 15.0. for Windows, 2006 SPSS Inc. Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

Role of the funding source

The RIETE registry is an independent registry, partially supported by Sanofi-Aventis in Spain, and by Bayer-Schering-Pharma outside Spain. There is no payment per patient recruitment.

Results

As of December 2008, 25,066 consecutive patients with symptomatic, acute VTE were enrolled in RIETE. Of 2,816 women aged <55 years, 173 (6.1%) were pregnant, 135 (4.8%) postpartum, and 798 (28%) were using hormonal contraceptives. Thus, the study includes 1,106 women, aged 14 to 55 years (mean, 32 years). VTE had developed during the first trimester in 67 (39%) pregnant women, during the second in 31 (18%), and during the third in 75 (43%). The most commonly used contraceptives were: antiandrogenic (cyproterone or drospirenone) 191; third generation (gestodene or desogestrel) 149; second generation (norgestimate or levonorgestrel) 63; vaginal rings (etonorgestrel) 18; transdermic (norelgestromine) 11; intramuscular (medroxiprogesterone) seven; unknown 359.

Most women (97%) in the three subgroups had no co-morbid diseases (i.e. chronic lung disease, heart disease or renal insufficiency), many (65%) had no additional risk factors for VTE. The only exception was postpartum women, many of whom had recent surgery (cesarean section), as shown in ▶Table 1. In all, 438 women (40%) presented with PE, 668 with DVT. Most (78%) pregnant women presented with DVT, while DVT and PE were more balanced in the other subgroups (Table 1). Thrombophilia tests were performed in 58% of women, 47% of whom tested positive with no significant differences between groups. Low-molecular-weight heparin (LMWH) was the most common drug used for initial therapy (Table 1). Most pregnant women (90%) received long-term therapy with LMWH, but 85% of women in the other subgroups were treated with AVK drugs. Mean daily doses of LMWH used for long-term therapy were similar in all three subgroups.

Most women with acute PE presented with dyspnea (72%) or chest pain (75%), but only 18% had arterial PO_2 levels <60 mm Hg; 2.0% had Sat O_2 levels <90% (▶Table 2). Interestingly, most (79%) also had hypocapnia (PCO_2 levels <35 mm Hg). In all, 51% of women had a normal electrocardiogram, 52% a normal chest

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Table 1: Clinical characteristics of the patients.

	Pregnancy	Postpartum	Contraceptives
Patients, N	173	135	798
Clinical characteristics			
Mean age (years ± SD)	31 ± 6	32 ± 7	32 ± 9
Body weight (kg ± SD)	69 ± 13	71 ± 14	69 ± 15
Underlying diseases			
Chronic lung disease	2 (1.2%)	0	18 (2.3%)
Chronic heart failure	1 (0.6%)	0	1 (0.1%)
Abnormal creatinine levels	2 (5.7%)	0	4 (0.5%)
Risk factors for VTE			
Surgery	7 (4.0%)	81 (60%)‡	61 (7.6%)
Immobility ≥4 days	23 (13%)	24 (18%)	124 (16%)
Cancer	0	2 (1.5%)	10 (1.3%)
Recent travel	4 (2.3%)	0	44 (5.5%)†
None of the above	133 (80%)	39 (29%)‡	552 (70%)
Prior VTE	21 (12%)	12 (8.9%)	27 (3.4%)‡
VTE characteristics			
Clinically overt PE	38 (22%)‡	50 (37%)	350 (44%)
Thrombophilia testing			
Patients tested	96 (55%)	71 (53%)	479 (59%)
Positive testing	55 (57%)	42 (59%)	209 (44%)†
Protein C deficiency	2 (2.1%)	4 (5.6%)	6 (1.3%)
Protein S deficiency	5 (5.2%)	5 (7.0%)	18 (3.8%)
Antithrombin deficiency	6 (6.3%)	1 (1.4%)	6 (1.3%)
Factor V Leiden	19 (20%)	7 (9.9%)	61 (13%)
Prothrombin gene mutation	16 (17%)	9 (13%)	52 (11%)
Antiphospholipid syndrome	4 (4.2%)	10 (14%)	21 (4.4%)
Initial therapy			
Unfractionated heparin	16 (9.2%)	13 (9.7%)	84 (11%)
LMWH	154 (89%)	119 (88%)	693 (87%)
Mean LMWH dose (IU/kg/day)	187 ± 51	181 ± 34	185 ± 37
Thrombolytics	2 (1.2%)	0	12 (1.5%)
Inferior vena cava filter	8 (4.6%)	8 (5.9%)	13 (1.6%)
Long-term therapy			
Anti-vitamin K drugs	36 (21%)‡	92 (68%)	697 (87%)
LMWH	133 (78%)‡	39 (29%)	81 (10%)
Mean LMWH dose (IU/kg/day)	173 ± 59	171 ± 44	180 ± 40
3-month outcome			
Recurrent PE	2 (1.2%)	1 (0.7%)	3 (0.4%)
Recurrent DVT	0	2 (1.5%)	5 (0.6%)
Recurrent VTE	2 (1.2%)	3 (2.2%)	8 (1.0%)
Major bleeding	3 (1.7%)	1 (0.7%)	3 (0.4%)
Fatal PE	0	1 (0.7%)	2 (0.3%)
Overall death	0	1 (0.7%)	4 (0.5%)

Comparisons between groups: * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$. VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin.

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Table 2: Clinical characteristics and diagnostic details of the 438 women presenting with acute pulmonary embolism.

	Pregnancy	Postpartum	Contraceptives
Signs and symptoms	38	50	350
Dyspnea	33 (87%)*	38 (78%)	244 (70%)
Chest pain	23 (61%)*	38 (76%)	267 (78%)
Haemoptysis	1 (2.6%)	3 (6.1%)	34 (10%)
Syncope	5 (13%)	3 (6.0%)	40 (12%)
Systolic blood pressure <100 mm Hg	5 (13%)	2 (4.0%)	33 (9.4%)
Heart rate >100 beats per minute	11 (29%)	18 (36%)	127 (36%)
Arterial blood gases			
$SatO_2$ levels, N	35	35	238
Mean $SatO_2$ levels (%)	93 ± 7.7	96 ± 3.2	95 ± 3.6
Sat O_2 levels <90%	1 (2.9%)	1 (2.9%)	4 (1.7%)
PO_2 levels, N	28	35	229
Mean PO_2 levels (mm Hg)	89 ± 25	87 ± 30	78 ± 20
PO_2 <60 mm Hg	2 (7.1%)	5 (14%)	45 (20%)
PCO_2 levels, N	28	35	229
Mean PCO_2 levels (mm Hg)	31 ± 2.6	33 ± 5.2	33 ± 1.2
PCO_2 <35 mm Hg	28 (100%)†	24 (69%)	180 (79%)
Chest-X ray findings	36	49	342
Normal	15 (69%)	24 (56%)	190 (59%)
Cardiomegaly	1 (4.5%)	3 (7.3%)	10 (3.2%)
Pleural effusion	5 (23%)	15 (36%)	66 (21%)
Infiltrate	2 (9.1%)	6 (14%)	49 (16%)
Lung infarction	3 (14%)	4 (9.8%)	41 (13%)
Atelectasis	2 (9.1%)	3 (7.3%)	11 (3.5%)
Vascular redistribution	0	1 (2.4%)	12 (3.8%)
Electrocardiography	38	48	336
Normal	23 (61%)	28 (58%)	183 (52%)
Right bundle branch block	7 (18%)	2 (4.2%)	34 (9.7%)
$S_1Q_3T_3$ pattern	7 (18%)	6 (13%)	71 (20%)
Negative T wave	9 (24%)	9 (19%)	58 (17%)
Ventilation-perfusion lung scan	13	19	139
High-probability	10 (77%)	12 (63%)	113 (81%)
Helical CT-scan,	21	39	256
High-probability	19 (90%)	33 (85%)‡	249 (97%)
Angiography	1	1	13
Echocardiography	21	17	129

Comparisons between groups: * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.

X-ray. Helical CT-scan was the most common test to confirm the diagnosis of PE: it was done in 72% of women, being positive in 95% (Table 2). Ventilation-perfusion lung scan was performed in 39% of women, 79% of whom had a high-probability scan. Echocardiography was performed in 167 patients (15%).

During the three-month study period, five women (0.45%; 95% CI: 0.17–1.00) died, 13 (1.18%; 95% CI: 0.66–1.95) had VTE recurrences, and seven (0.63%; 95% CI: 0.28–1.25) had major bleeding. Three of the five women who died had fatal PE, one died of cancer, one died at home of unknown reason. Two of the three women with fatal PE died during the first few hours after arriving at the emergency ward, with no time to start any therapy. The third patient died on the third day of admission, while on unfractionated heparin (UFH) therapy. Their ages were: 28, 29 and 48 years, and they had no co-morbidities (i.e. cancer, chronic lung disease, heart failure, or renal insufficiciency). In addition, six women had recurrent (non-fatal) PE, seven recurrent DVT, and seven had major bleeding (Table 1).

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Six patients developed recurrent PE during the study period: two pregnant women receiving long-term LMWH therapy (days 49 and 83), one postpartum on LMWH therapy (day 3), and three contraceptive users on long-term AVK therapy (days 27, 30 and 57). Seven women had recurrent DVT: two during initial therapy, five during long-term therapy (4 with AVK). Seven further women had major bleeding: three during initial therapy (2 were treated with unfractionated heparin, 1 with LMWH), four during long-term therapy. Four patients developed thrombocytopenia (none had associated-symptoms).

Discussion

Our data, obtained from a large cohort of young women with acute VTE, reveal that only a minority (2.0%) of those presenting with PE had Sat O_2 levels <90%. This was probably due to hyperventilation, since most of them also had low PCO_2 levels. This is an important finding because the absence of hypoxaemia in young patients with dyspnea or chest pain may induce some delay in the diagnosis of PE. Indeed, three women died of PE. It represents only 0.27% of the overall series, but any death in a young person is always a catastrophe. None of these three women had associated comorbidities, and probably they would not have died if they had not developed VTE. Two of them died shortly after arriving to the emergency ward, allowing minimal time for effective therapy to be administered. Thus, we hypothesise that the non-specific nature of the presenting signs and symptoms in this subgroup of young women with acute PE may have caused a certain delay in diagnosis and starting therapy.

During follow-up, the 1.2% incidence of VTE recurrences and the 0.6% rate of major bleeding complications compare favorably with those in other subgroups of patients with VTE, in line with available retrospective and prospective data (5, 9–13). This is also an important finding because pregnant or postpartum women are often excluded from randomised clinical trials of antithrombotic therapy. This better outcome may be attributed to their younger age or the less frequent occurrence of co-existing, underlying conditions. Current guidelines from the ACCP recommend the use of LMWH throughout pregnancy (14), but data regarding the optimal dose for long-term therapy, or the need to modify LMWH doses through pregnancy remain poorly documented (11, 15–17). In our series, despite a wide range of LMWH doses there were few bleeding complications or VTE recurrences, thus suggesting that few dose adjustments are required.

The clinical presentation of the VTE event varied, with a higher percentage of contraceptive users presenting with clinically overt PE (44%), and a lower percentage (22%) in pregnant women. These findings have already been reported (6), and may reflect real differences or difficulties in the diagnosis of PE during pregnancy. Another interesting finding was the absence of additional risk factors for VTE in most pregnant women (80%) or contraceptive users (70%). One in every two women tested positive for thrombophilia, thus confirming that it is a major risk factor in young women under a hormonal challenge such as contraceptive use or pregnancy. Whether previous knowledge of a thrombophilic condition might result in different management or primary prevention is still an open question.

Most (72%) women with PE underwent helical CT-scan to confirm the diagnosis. CT-pulmonary scans deliver a minimum radiation dose of 2.0 rad (20 mGy) to the breasts of an average-sized woman, and may be associated with an increased risk of breast cancer (18). Certainly, ventilation-perfusion lung scan is less accurate, particularly in patients with abnormal chest X-ray, but in the setting of young women with a normal chest radiograph and no history of cardiopulmonary disease, ventilation-perfusion scan should probably be considered the test of choice. Alternatively, the use of thin-layered bismuth garments to reduce the radiation dose would also be helpful (19).

The RIETE registry provides data on the treatment of VTE in a real-world situation with an unselected patient population, in contrast to the rigorously controlled conditions of randomised clinical studies. It can, therefore, provide insights into the natural history of VTE in young women. It can also help to identify practices for providing treatment to patients, and factors associated with better or worse patient outcomes. However, as an observational study, RIETE is not designed to answer questions regarding the relative efficacy and safety of different modalities of therapy. Data from the registry are hypothesis-generating and provide feedback from real-world clinical situations which may be of help when designing new randomised clinical studies.

In summary, our findings confirm that the outcome of pregnant or postpartum women with VTE is similar to that in contraceptive users, even though the treatment is different. But our most striking finding was the unusual presentation of PE in this patient population, with a minority of women experiencing hypoxaemia. Whether or not it might have induced to unexpected death remains a matter for speculation.

What is known about this topic?

- Venous thromboembolism (VTE) is a leading cause of maternal death during pregnancy or postpartum, and in women taking hormonal contraceptives.

What does this paper add?

- Our findings confirm that the outcome of pregnant or postpartum women with VTE is similar to that in contraceptive users, even though the treatment is different.
- Only a minority of women presenting with acute pulmonary embolism experienced hypoxaemia.

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