Acute Pulmonary Embolism in Women: Focus on Estrogen Therapy as a Predisposing Factor

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Abstract- Acute pulmonary embolism (APE) is a potentially fatal disorder. The literature shows that estrogen therapy is correlated with an increase in mortality and morbidity. Accordingly, the purpose of the present study was to investigate the prevalence and prognostic significance of the recent history of estrogen therapy in women with APE. This study was conducted on female patients admitted to our hospital between January 2008 and January 2016. A total of 276 patients (mean age=62.66±08 y) with confirmed APE were divided into groups with and without recent estrogen therapy. The relationships between estrogen and clinical findings, risk factors, imaging findings, and in-hospital mortality were analyzed. Among the 276 women with APE at presentation, 37 (13.4%) patients had a recent history of estrogen therapy. The estrogen group had a lower frequency of hypertension (21.6% vs49.8%; *P*< .001), immobilization of at least 3 days (16.2% vs 33.5%; *P*= .035), and pleural effusion (0% vs16.7%; *P*= .007) than the group without recent estrogen use. Among the 276 patients, the rate of 1 year's mortality was 15.8% for the group without recent estrogen therapy. No death occurred in the estrogen group. Older age, tachycardia, tachypnea, malignancy, and lack of obesity were the predictors of 1 year's mortality. Among the patients with APE in our study, 13.4% had a history of recent estrogen therapy. No death occurred during the 1-year follow-up of these patients.

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Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and acute pulmonary embolism (APE), occurs in 1 to 2 persons per 1000 individuals per year (1).

APE is a potentially fatal disorder (2) and represents a potentially life-threatening condition that covers a broad spectrum of clinical severity (3).

The predisposing factors of VTE are recent surgery, lower extremity trauma, history of immobilization or prolonged hospitalization/bed rest, obesity, prior episode(s) of VTE, malignancy, use of oral contraceptives, prior hormone replacement therapy, pregnancy, postpartum status, and stroke (4-6). Estrogen is a primary component of several contraceptive regimens commonly prescribed (7). These contraceptives increase the risk of blood clotting substantially, which can ultimately lead to DVT and APE (8). Estrogen plus progestin is associated with a doubled risk of venous thrombosis and increased risks allied to age, overweight or obesity, and factor V Leiden (9). Furthermore, estrogen alone or combined with continuous hormone therapy increases the risk of VTE (10).

To best of our knowledge, the present study is the first investigation on women with APE to specifically assess

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the effects of drugs containing estrogen on clinical testing and mortality rates in Iran. To fill these gaps of knowledge, the purpose of the present study was to investigate the prevalence and prognostic significance of recent history of estrogen therapy in women with APE.

Materials and Methods

Patient enrollment

The present study was conducted in Tehran Heart Center (Tehran, Iran) known as a tertiary care hospital. We prospectively studied 276 consecutive female patients with a diagnosis of APE admitted to our hospital between January 2008 and January 2016.

Patients who developed APE during their hospitalization were not included. The APE diagnosis was confirmed via pulmonary spiral computed tomography scans, angiography, or ventilation perfusion scans. The study was conducted in conformity with the Declaration of Helsinki and was approved by the institutional local ethics committee of Tehran University of Medical Sciences.

Transthoracic 2D and Doppler echocardiographic examinations were performed within 48 hours of admission by experienced operators. All the quantifications were performed in accordance with recommendations of the American Society of Echocardiography Committee (Rudski *et al.*, 2010). Right ventricular (RV) dysfunction was defined as RV diameter to the left ventricular diameter ratio equal to or more than 1in echocardiography or pulmonary computed tomography angiography.

The history of recent estrogen therapy was supposed to be positive if any drug containing estrogen was used within one week of symptom onset even in a single dose.

Complete data on baseline clinical, hemodynamic, and laboratory findings were obtained using face-to-face interviews and the patients' medical records. The patients were treated by the physicians who gave care for the patients according to the guidelines and not influenced by the protocol of this study (11).

Follow-up

All the patients were followed up either by means of clinical examination in outpatient clinics or telephone contacts with their relatives. The follow-up duration was one year after admission. Mortality was defined as death occurring as a result of all causes.

Statistical analysis

The continuous variables are expressed as means±standard deviations or medians (ranges or interquartile ranges), and they were compared using the Student *t*-test or the Mann-Whitney *U*-test, as appropriate. The discrete variables are expressed as frequencies and percentages, and they were compared using the χ^2 test or the Fisher exact test, as required. A *P* less than 0.05 was considered statistically significant. The statistical analyses were conducted using SPSS software, version 17 (SPSS Inc, Chicago, IL).

The Cox, proportional hazards model, was used to evaluate the adjusted and unadjusted associations between estrogen and one year's mortality, and the effects were reported using hazard ratios (HRs) with 95% confidence intervals (CIs).

Results

The study population consisted of 276 female patients at a mean age of 62.66±16.08 years. They had a mean systolic blood pressure of 130.7±22.78 mmHg and a mean respiratory rate of 24.64±6.99 respiration/minute. The risk factors giving rise to APE were immobility for more than 3 days in 86 (31.2%) patients, diabetes mellitus in 55 (19.9%), hypertension in 127 (46%), obesity in 108 (31.2%), malignancy in 18 (6.6%), and recent surgery in 35 (12.7%). On presentation, from 270 (97.8%) patients, 247 (89.5%) had dyspnea and 23 (8.3%) had syncope.

The patients were divided into two groups: a group without recent estrogen therapy and a group with recent estrogen use. The group with recent estrogen use comprised 37 (13.4%) patients.

The group with recent estrogen therapy had been using several types of estrogen therapy. Of the 37 patients, 25 (67.5%) had recently used low-dose drugs, 2 (5.4%) high-dose drugs, and 2 (5.4%) Yasmin drugs. However, 8 (21.6%) patients either did not know the precise type of estrogen therapy which they used, or the information was not reported in their medical file.

Age was significantly different between the two groups ($P< .001$). As is shown in Table 1, no significant differences for systolic blood pressure, heart rate, respiratory rate, dyspnea, and syncope were found between the groups with and without recent estrogen use.

As is depicted in Table 1, the patients with recent estrogen therapy had a lower frequency of hypertension (21.6% vs49.8%; $P< .001$) and immobilization more than three days (16.2% vs. 33.5%; $P= .035$) than the group without recent estrogen use. In addition, the other risk factors were not significantly different between the two groups.

Other signs and electrocardiographic findings did not

significantly differ between the groups (Table 1). The patients without recent estrogen use had a higher frequency of complete right bundle branch block (RBBB), incomplete RBBB, T-wave inversion in the anterior leads (S_1 Q_3 T_3), and RV dysfunction than the patients with estrogen therapy (Table 1).

The patients were followed up for one year. Thirty-eight patients died, and the mortality rate was 13.7% for the 276 patients during the follow-up course. The rate of 1 year's mortality was 15.8% for the group without recent estrogen use and 0 for the group with recent estrogen therapy (Table 1).

Table 1. Admission and Demographic Characteristics of the patient with and without recent estrogen (n = 276)

Parameters		Total (n=276)	Without recent estrogen n=239 (86.6%)	With recent estrogen n=37 (13.4%)	*P*
Age (years)		62.66±16.08	65.82±14.622	42.19±8.51	< .001
SBP (mm Hg)		130.7 ± 22.78	130.99±35.52	128.73 ±17.4	.575
HR (beats/min),		101.9± 30.71	101.68±21.63	103.59±13.4	.466
RR (respiration/min)		24.64 ± 6.99	24.85±7.07	23.37 ± 6.4	.281
Clinical Symptoms and signs, n (%)	**Dyspnea**	247 (89.5)	211 (88.3)	36 (79.3)	.146
	Syncope	23 (8.3)	21 (8.8)	2 (5.4)	.75
Past Medical history, n (%)	**DM**	55 (19.9)	50 (20.9)	5 (13.5)	.294
	Hypertension	127 (46)	119 (49.8)	8 (21.6)	< .001
	Immobilization ≥ 3 days	86 (31.2)	80 (33.5)	6 (16.2)	.035
	Obesity	108 (39.1)	93 (38.9)	15 (14.5)	.85
	Malignancy	18 (6.5)	18 (7.5)	0	.144
	Recent surgery	35 (12.7)	34 (14.2)	1 (2.7)	.61
ECG findings, n (%)	**Complete RBBB**	13 (4.7)	13 (5.4)	0	
	Incomplete RBBB	13 (4.7)	12 (5)	1 (2.7)	.507
	T wave inversion in anterior leads	105 (38)	92 (38.5)	13 (35.1)	.695
	S1 Q3 T3	79 (28.6)	71 (29.7)	8 (21.6)	.311
Imagine findings studies, n (%)	**Pulmonary Infraction**	35 (12.7)	30 (12.6)	5 (13.5)	.795
	Segmental Pulmonary Embolism	37 (13.4)	32 (13.4)	5 (13.5)	1
	Pleural Effusion	40 (14.5)	40 (16.7)	0 (0)	.007
Echocardiographic Findings, n (%)	**RV dysfunction**	186 (27.4)	162 (67.8)	24 (64.9)	.725
	Mortality 1 year, n (%)	38 (13.7)	38 (15.8)	0	--

Continuous variables are presented as mean± standard deviation (SD)
SBP, systolic blood pressure; HR, heart rate; RR, respiratory rate; DM, Diabetes Mellitus; ECG, electrocardiography; RBBB, right bundle branch block; RV, right ventricle

Table 2 demonstrates the predictors of the long-term mortality of APE. The predictors of long-term mortality showed that age (HR: 1.022, CI: 0.992±1.053%; *P*= .008), heart rate (HR: 1.03, CI: 1.008±1.053%; *P*= .003), respiratory rate (HR: 1.033, CI: 0.967±1.104%; *P*= .029), obesity (HR: 0.369, CI: 0.169 - 0.805%; *P*= .012), and malignancy (HR: 3.106, CI: 1.207-7.981%; *P*= .019) were the independent correlates of the occurrence of long-term mortality in the patients with APE.

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Table 2. Predictors of one-year mortality of acute pulmonary embolism (APE)

Parameters		Survived	One year Mortality	HR (95% CI%)	*P*
Age		61.78±16.25	66.74±11.06	1.022 (0.992±1.053)	.008
SBP, mm Hg		131.4 ± 23.26	125.74±19.39	0.977 (0.954 ±1)	.143
HR, beats/min		100.4± 19.61	111±23.78	1.03 (1.008 ± 1.053)	.003
RR (respiration/min)		24.19 ± 6.31	27.34±10.21	1.033 (0.967 ± 1.104)	.029
Symptoms on presentation, n (%)	**Dyspnea**	210(89.4)	35 (92.1)	1.509 (0.464 – 4.91)	.494
	Syncope	20 (8.5)	3 (7.9)	0.928 (0.285 - 3.016)	.901
Medical History	**DM**	46 (19.6)	9 (23.7)	1.274 (0.603 - 2.692)	.526
	Hypertension	104 (44.3)	22 (57.9)	1.532 (0.804 - 2.917)	.195
	Immobilization ≥ 3 days	73 (31.1)	12 (31.63)	1.012 (0.511 - 2.006)	.097
	Obesity	99 (42.1)	8 (21.1)	0.369 (0.169 – 0.805)	.012
	Malignancy	11 (4.7)	5 (13.2)	3.106 (1.209 -7.981)	.0019
	Surgery	28 (11.9)	7 (18.4)	1.573 (0.693 – 3.572)	.279
ECG findings, n (%)	**Complete RBBB**	11 (4.7)	1 (2.6)	0.554 (0.076 – 4.052)	.561
	Incomplete RBBB	9 (3.8)	4 (10.5)	2.503 (0.886 – 7.068)	.083
	T wave inversion in anterior leads	91 (38.7)	14 (36.8)	0.958 (0.495 – 1. 851)	.897
	S1 Q3 T3	68 (28.9)	11 (28.9)	0.988 (0.486 – 1. 977)	.956
Imagine studies	**Segmental Pulmonary Embolism**	35 (14.9)	2 (5.3)	0.332 (0.08 – 1.377)	.129
	Pleural Effusion	34 (14.5)	5 (13.2)	0.967 (0.377 – 2.478)	.944
Echocardiographic Findings, n (%)	**RV dysfunction**	141 (68.5)	23 (60.5)	0.741 (0.387 – 1. 42)	.367

Continuous variables are presented as mean± standard deviation.
CI, confidence interval; HR, hazard ratio; SBP, systolic blood pressure; HR, heart rate; RR, respiratory rate; DM, Diabetes Mellitus; ECG, electrocardiography; RBBB, right bundle branch block; RV, right ventricle

Discussion

In the present study on a cohort of women with APE admitted to Tehran Heart Center, Tehran University of Medical Sciences, a tertiary care teaching hospital, 13.4% of the patients had recent treatment with estrogen, and 86.6% were without recent estrogen use. The overall rate of 1 year's mortality was 13.7%, and none of the patients with recent estrogen therapy died. The predictors of 1 year's mortality were age (HR: 1.022, CI: 0.992±1.053%; *P*= .008), heart rate (HR: 1.03, CI: 1.008±1.053%; *P*= .003), respiratory rate (HR: 1.033, CI: 0.967±1.104%; *P*= .029), obesity (HR: 0.369, CI: 0.169-0.805%; *P*= .012), and malignancy (HR: 3.106, CI: 1.207-7.981%; *P*= .019).

DVT and PE together may be responsible for more than 100000 deaths each year (12). Exposure to estrogen, which is a steroid hormone, can increase the risk of blood clot formation (12). Estrogen plus progestin is associated with a doubled risk of venous thrombosis (9). The absolute risk among women who are of fertile age and use oral contraceptives is fairly low: 2 to 8 persons per 10 000 person-years (13,14). In addition, increased mortality rates are associated with increased age (15-17).

The results of the present study confirmed that an elevation in the heart rate was strongly associated with the mortality rate. Increased heart rates in APE are associated with increased rates of mortality (18). The heart rate represents a quickly available and reliable parameter for patients with APE (18). Measuring the respiratory rate is an easy and reliable method for the assessment of the severity of acute cardiorespiratory and metabolic diseases (19). We found a close association

between the respiratory rate and the mortality rate. In APE, the respiratory rate is an important prognostic parameter as well (20).

Several studies have reported that obesity is a risk factor for APE (21). In a previous study, obesity had the greatest impact on the prevalence of PE in patients aged below 40 years, and the relative risk for PE in obese patients was 5.19 (21). People who are obese are at an increased risk for VTE compared with individuals who are of normal weight (22). Our results revealed that a lower mortality rate was associated with obesity.

We found that malignancy was associated with one year's mortality. Malignancy is a well-known risk factor for APE (23,24), and approximately 1.5% to 2.5% of patients with malignancy undergoing pulmonary vasculature imaging will have incidentally detected APE (25,26). Patients with malignancy have a significantly increased risk for short-term death after the diagnosis of APE, compared with those without malignancy (24,27-33).

The risk for DVT is considered greater with oral than non-oral routes of administration, in agreement with the fact that oral estrogen amplifies the synthesis of thrombotic proteins via the results of a first-pass hepatic metabolism (34). Thus, postmenopausal women who use hormone therapy are at an increased risk. However administration of estrogen containing regimen of minimum dose might be a reasonable choice for postmenopausal females with a good cardiovascular profile (35).

DVT and PE events are related to triggering events such as hospitalization, major surgery, trauma, and prolonged periods of immobility (12). In a previous study, 43% of the patients who died from PE had recent immobilization lasting for a minimum of 4 days (36). The relative risk of VTEin women who take estrogen therapy seems to be even greater if the treated population has pre-existing risk factors for VTEsuch as obesity, immobilization, and fracture (37). Our patients with recent estrogen use had additional risk factors for APE such as immobilization more than 3 days (16.2%), obesity (14.5%), and recent surgery (2.7%).

In the present study, there was no 1 year's mortality among those with estrogen treatment. This might indicate that estrogen therapy as a predisposing factor for APE does not have as many adverse effects as unprovoked APE. However, the lack of mortality in the patients with a recent history of estrogen therapy could be explained by the considerably young age of these patients compared with the other patients (42.19 y vs65.82 y; $P< .001$).

For all the evidence indicating that an increased risk of venous thrombosis is associated with taking hormone replacement therapy, the magnitude of the increased risks diminishes over time (38). The risks of hormone replacement therapy-related VTE and/or PE vary depending on the type of estrogen used, the mode of delivery, and the presence of other predisposing factors. It has been suggested that high-dose estrogen therapy is associated with a greater increased risk of venous thrombosis than low-dose preparations (38). Thrombotic risks are also elevated with high-dose estrogen combined with oral contraceptives relative to standard and low-dose estrogen formulations (39).

One of the limitations in the present study is its small sample size of patients with estrogen compared with the number of patients without recent estrogen use, which may have influenced the results.

Among the female patients diagnosed with APE at Tehran Heart Center, the overall rate of 1 year's mortality was 13.7%. None of our patients with recent estrogen use died during the 1-year follow-up. The patients without recent estrogen therapy were older and had a higher frequency of hypertension, immobilization for at least three days, and pleural effusion than those with recent estrogen use. The predictors of long-term mortality (1 y) were age, heart rate, respiratory rate, and obesity.

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