Pulmonary Hypertension in Patients Using Oral Contraceptives:
A Report of Six Cases

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Six young women who had taken progestational agents for a period of time ranging from six months to five years developed symptoms and signs of pulmonary hypertension. Cardiac catheterization confirmed the presence of severe pulmonary hypertension without evidence of other cardiac or pulmonary abnormalities to explain this phenomenon. Three of the patients had potential predispositions to pulmonary hypertension, including a corrected patent ductus arteriosus with mild pulmonary hypertension in one, collagen vascular disease in a second, and family history of pulmonary hypertension in a third. Three patients had no known predisposing factors. Although the relationship between oral contraceptives and severe pulmonary hypertension is problematic, there have been isolated reports of cases of pulmonary hypertension secondary to oral contraceptive usage. These cases and the possible pathophysiologic mechanisms responsible are discussed.

Idiopathic pulmonary hypertension is a rare and tragic disorder that strikes a young, predominantly female population. Its etiology is obscure and its therapy unsuccessful. Within an eight-month period, we have observed six young women who developed severe pulmonary hypertension while using oral contraceptives. Three of these women had known predisposing causes of pulmonary hypertension; one had had a brother who died at 14 years of age from idiopathic pulmonary hypertension, another had lupus since 12 years of age, and the third patient had mild pulmonary hypertension remaining after closure of a patent ductus arteriosus. The other three cases had no known predisposing cause but developed severe pulmonary hypertension while taking oral contraceptives.

The association of oral contraceptives and pulmonary hypertension may well be fortuitous, but drug-induced pulmonary hypertension does occur in humans.1 Severe pulmonary hypertension has been reported with combined usage of oral contraceptives and aminorex,2 in certain cases of congenital heart disease and oral contraceptive use,3 and with oral contraceptive usage alone.4,5 Moreover, the use of oral contraceptives and the development of intimal vascular lesions in both veins and arteries, including the pulmonary arteries, has been reported.1

CASE REPORTS

The three cases with predisposing conditions favoring the development of pulmonary hypertension are summarized as cases 1 to 3. Cases 4 to 6 represent those patients with pulmonary hypertension receiving oral contraceptives who had no known predisposing factors for the development of pulmonary hypertension.

CASE 1

A white woman, 26 years of age, was admitted to the hospital in July 1972 for evaluation of syncope. The patient enjoyed excellent health until two months prior to admission, at which time she became dyspneic after climbing one flight of stairs. Three weeks before admission, the patient experienced a 30-second syncopal episode while carrying luggage. On the day of admission, while climbing stairs, the patient felt unable to breathe, and her husband noted that her lips had turned blue and her hands were cold. The patient lost consciousness for a few minutes; and when she revived, she was brought to the hospital.

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The patient smoked a pack and a half of cigarettes per day and had taken a contraceptive drug combination containing norlethindrone and mestranol (Norinyl 1+80) for the past two years. There was no history suggesting a connective tissue disorder or thrombophlebitis. The patient had never been pregnant. There was a familial history of digital clubbing. The patient's brother had died at 14 years of age from a connective tissue disorder or thrombophlebitis. The patient had never smoked and had never experienced pulmonary hypertension. Her height was 5 feet 5 inches, and her weight was 120 pounds. Her blood pressure was 114/94 mm Hg, her pulse rate was 100 beats per minute and regular, and her respiratory rate was 18/min.

The patient had been taking a contraceptive drug combination containing norethindrone and mestranol (Ortho-Novum 1+80) for the past two years. There was no history suggesting a connective tissue disorder or thrombophlebitis. The patient had never been pregnant. There was a familial history of digital clubbing. The patient's brother had died at 14 years of age from a connective tissue disorder or thrombophlebitis. The patient had never smoked and had never experienced pulmonary hypertension. Her height was 5 feet 5 inches, and her weight was 120 pounds. Her blood pressure was 114/94 mm Hg, her pulse rate was 100 beats per minute and regular, and her respiratory rate was 18/min.

The patient was a thin woman. Supine blood pressure was 96/70 mm Hg, the pulse rate was 84 beats per minute and regular, and the respiratory rate was 20/min. The lungs were clear to auscultation. There was a prominent jugular a wave but no carotid bruit. A parasternal heave was present over the pulmonic area. The pulmonic sound was accentuated, and there was splitting of a second sound. An S4 was present. The patient's fingernails were clubbed but not cyanotic. There was no evidence of peripheral vascular disease.

The electrocardiogram revealed an axis of +120° with right atrial and right ventricular hypertrophy. A chest radiograph showed right ventricular enlargement and prominence of the pulmonary outflow tract. Results of a hemogram, automated study of blood chemistry (SMA-18), urinalysis, erythrocytic sedimentation rate, and protein electrophoresis were all within normal limits. Arterial blood gas analysis revealed that the pH was 7.528, the arterial carbon dioxide tension (PA CO2) was 25 mm Hg, and the arterial oxygen tension (PA O2) was 72 mm Hg. A lupus-erythematosus preparation and latex fixation test were negative. A pulmonary perfusion scan showed uniform distribution of perfusion. Right cardiac catheterization was performed (Table 1). The patient was advised not to become pregnant, and the use of oral contraceptives was stopped. The patient has been followed-up for three years and has had a basically stable clinical course with continuing dyspnea and syncope.

Case 2

A 25-year-old white woman was admitted to the hospital during December 1972 for evaluation of syncope. The patient described at least three syncopal episodes since April 1972. One episode occurred after she rushed to catch a bus. At the time of admission, the patient could not climb one flight of stairs without stopping on every third step to rest. She noted that when she was short of breath her fingernails turned blue. The patient had been taking a contraceptive drug combination containing norethindrone and mestranol (Ortho-Novum 1+80) intermittently for the past five years and had never been pregnant. She did not smoke and had never experienced thrombophlebitis. The patient was diagnosed as having systemic lupus erythematosus in 1959 and was taking 15 mg of prednisone per day on the day of admission. She had been told that she had a functional heart murmur as a child but believed that it had disappeared.

The patient had been taking a contraceptive drug combination containing norethindrone and mestranol (Ortho-Novum 1+80) for the past two years. There was no history suggesting a connective tissue disorder or thrombophlebitis. The patient had never been pregnant. There was a familial history of digital clubbing. The patient's brother had died at 14 years of age from a connective tissue disorder or thrombophlebitis. The patient had never smoked and had never experienced pulmonary hypertension. Her height was 5 feet 5 inches, and her weight was 120 pounds. Her blood pressure was 114/94 mm Hg, her pulse rate was 100 beats per minute and regular, and her respiratory rate was 18/min. The lungs were clear to auscultation. No jugular a or v waves were noted. There was a palpable second sound in the pulmonic area, and a parasternal lift was present. The second sound was widely split and varied physiologically with respiration. An S4 was present. A grade 3/6 holosystolic murmur that increased with inspiration was best heard in the third intercostal space along the left sternal border. Also, a grade 1/6 systolic ejection murmur was heard in the pulmonic area. The liver was pulsatile, and the spleen was palpated 4 cm below the left costal margin. Pedal edema was absent.

The patient’s electrocardiogram revealed an axis of +130° with right atrial and right ventricular hypertrophy. The chest radiograph showed right ventricular enlargement. The results of a hemogram and an automated study of blood chemistry (SMA-18) were normal, except for a glucose level of 217 mg/100 ml. Arterial blood gas analysis showed a pH of 7.53, a PaCO2 of 26 mm Hg, and a PaO2 of 75 mm Hg. Antinuclear antibody testing showed a 2+ homogeneous fluorescence. The level of the third component of complement was 55 mg/100 ml. The patient sustained a respiratory arrest and died during pulmonary angiographic studies following right cardiac catheterization (Table 1). Autopsy revealed right ventricular hypertrophy with arteriosclerosis of the pulmonary arteries. Intimal hyperplasia and plexiform lesions were present. There was no evidence of mitral valvular disease, septal defects, or small pulmonary emboli. The kidneys were uninvolved. Examination of the leg veins revealed no thrombi.

Case 3

A 23-year-old white woman had had a patent ductus arteriosus ligated when she was nine years old. She was pronounced cured after the operative procedure. At 16 years of age, however, the patient noted mild symptoms of dyspnea on exertion and fatigue and underwent cardiac catheterization. Her pulmonary arterial pressure was 48/20 mm Hg, and her mean right atrial pressure was 3.5 mm Hg. This was believed to represent mild residual pulmonary hypertension due to the patent ductus, and the patient was advised to limit her activities. Over the next six years the patient noticed only mild dyspnea on exertion and shortness of breath. At 22 years of age, she sought medical advice regarding an impending marriage and the possibility of future pregnancies. Physical examination at this time showed the patient to be a petite woman with blood pressure of 130/75 mm Hg and pulse rate of 64 beats per minute. Her respiratory rate was 16/min and not labored. The chest was clear to percussion and auscultation. The neck veins were not distended. There was a

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<th>Pulmonary Arterial Blood Pressure, mm Hg</th>
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Table 1—Cardiac Catheterization Data
A 26-year-old black woman was admitted to the hospital in September 1972 for evaluation of shortness of breath. Two or three months prior to admission, the patient began noticing fatigue and dyspnea while performing ordinary household chores. She had taken a contraceptive drug combination containing norethindrone and ethynylestradiol (Ovral) for five years and had one full-term pregnancy without complications. The patient gave no history suggestive of thromboembolic episodes or of a connective tissue disorder. She had never fainted.

Upon examination the patient’s blood pressure was 120/85 mm Hg, the pulse rate was 80 beats per minute, and the respiration rate was 20/min. The lungs were clear to auscultation. Prominent a waves were present at 30°. Carotid bruits were absent. A left parasternal heave was present, and the second heart sound was easily palpable in the pulmonic area. An S4 was heard. The second heart sound was widely split and varied physiologically with respiration.

The electrocardiogram demonstrated an axis of +120° with right atrial and right ventricular hypertrophy. The chest radiograph revealed right ventricular enlargement with prominence of the pulmonary outflow tract. Findings from a hemogram and an automated study of blood chemistry (SM-A18) and the erythrocytic sedimentation rate were within normal limits. The results of tests for connective tissue disorders were all negative. Arterial blood gas analysis showed pH of 7.45, PaCO₂ of 30 mm Hg, and PaO₂ of 96 mm Hg. The patient underwent right cardiac catheterization (Table 1), which documented pulmonary hypertension. She was then discharged and advised to discontinue her oral contraceptive usage and to avoid pregnancy.

Case 5

A 30-year-old white woman experienced her first syncopal episode while running, three years prior to admission. At that time the patient also noted the onset of mild shortness of breath and tachycardia. These symptoms remained stable until three months prior to admission, when the patient experienced her second syncopal episode while climbing stairs. She first began to take a contraceptive drug combination containing norethindrone acetate and ethynylestradiol (Norlestrin) four years prior to admission; and for the past three years, she had received maintenance therapy with sequential oral contraceptives, including mestranol and a drug combination containing mestranol plus chloramphenicol acetate (Sequen), and then ethynylestradiol and another drug combination containing ethynylestradiol plus dimethisterone (Oracen). The patient had smoked approximately one-half pack of cigarettes per day for 12 years but had discontinued smoking six months prior to admission. She had had two successful full-term pregnancies without complications. There was no history of thromboembolic phenomena or connective tissue disorder.

Physical examination revealed a healthy-appearing woman. The patient’s blood pressure was 115/75 mm Hg, and the pulse rate was 60 beats per minute and regular. The respiration rate was 14/min and not labored. The chest was clear to auscultation. There was a palpable second heart sound in the left intercostal space. The second heart sound was split normally, and the pulmonary component was louder than the aortic component. There was an ejection click audible at the upper left sternal border, followed by a grade 2/6 systolic murmur localized to the second left intercostal space. The jugular venous pressure was not elevated. There was no hepatomegaly, cyanosis, clubbing, or peripheral edema. An electrocardiogram showed right axis deviation of +150°, and a vectorcardiogram was suggestive of right ventricular hypertrophy. A chest radiograph showed promi-
A 29-year-old black woman had been entirely well all of her life. Four years prior to admission, the patient experienced her first syncopal episode while running to her car. Three years prior to admission, she noted the onset of dyspnea associated with dizziness on exertion after climbing two flights of stairs. About the same time, she also noted ankle swelling and the onset of a chronic nonproductive cough. Over the past three years, the patient had noted multiple episodes of near syncopal symptoms and frank syncopal episodes on at least three other occasions. Seven months prior to admission at Stanford University Hospital, the patient underwent cardiac catheterization at another institution, at which time the pulmonary arterial pressures measured 113/57 mm Hg and pulmonary arterial wedge pressures were normal. A left-to-right shunt could not be documented, and pulmonary angiographic studies failed to reveal any evidence of pulmonary emboli or infarct. The pulmonary vascular resistance was measured at approximately ten times normal levels. The patient was treated with phlebotomy, digitalis, diuretics, and anticoagulant therapy, with some decrease in weight and no change in her symptoms. Three weeks prior to admission, the patient noted the onset of precordial chest pain and came to Stanford University Hospital. Five years prior to admission, the patient began to take a contraceptive drug combination containing norethynodrel and mestranol (Enovid-E), and she continued to take this for two years. There was no history of smoking or family history of pulmonary disease, and there were no symptoms of collagen vascular disease.

Physical examination on admission showed the blood pressure to be 105/80 mm Hg, and the pulse rate was 90 beats per minute and regular. The respiration rate was 24/min and somewhat labored. The chest was clear to auscultation. Findings from physical examination were compatible with severe pulmonary hypertension, tricuspid insufficiency, and right axis deviation of +120°. A chest radiograph revealed right ventricular hypertrophy and right axis deviation of +120°. A chest radiograph revealed right ventricular enlargement and prominence of the pulmonary arterial segments. Pulmonary function tests disclosed a PaO₂ of 61 mm Hg (94.1% saturation), with normal volumes and normal flow rates. An echocardiogram showed a decreased diastolic motion of the anterior leaflet of the mitral valve and excessive echoes occurring in the left atrium and in the region of the mitral annulus. Because of the question of a left atrial mass, the patient underwent cardiac catheterization with a transseptal approach. The pulmonary arterial pressure was 98/57 mm Hg, with a mean pulmonary arterial wedge pressure of 9 mm Hg. Pulmonary vascular resistance was markedly elevated, and the cardiac index was 0.5 L/min/sq m. Breathing 100 percent oxygen, the aortic blood saturation rose from 83 percent to 96 percent, and the pulmonary arterial saturation rose from 23 percent to 35 percent. There was no evidence of a shunt. Left atrial angiogram failed to reveal any abnormality in the left atrium, although there was some thickening of the anterior leaflet of the mitral valve. On the day after cardiac catheterization, the patient sustained cardiopulmonary arrest from which she could not be resuscitated. At postmortem examination the heart was enlarged, and there was right ventricular hypertrophy. The pulmonary artery showed diffuse atherosclerotic changes, and there was no evidence of pulmonary emboli or infarction. Microscopically, the small muscular pulmonary arteries showed a marked medial hypertrophy, and larger elastic arteries showed focal intimal atheromata. There was evidence of extensive, chronic passive congestion of the liver. No thrombi were found in the veins of the leg.

**DISCUSSION**

Within an eight-month period, we have observed six women with severe pulmonary hypertension who had been receiving oral contraceptives from six months to five years prior to their proven severe pulmonary hypertension. Three of these patients had predisposing causes for the development of pulmonary hypertension (family history in one, lupus in a second, and mild pulmonary hypertension residual from a corrected patent ductus arteriosus in the third). Although it is possible that the relationship between pulmonary hypertension and oral contraceptives in these six patients is fortuitous, there are several lines of evidence that suggest the relationship is not merely due to chance.

Drug-induced pulmonary hypertension has been demonstrated. An anorectic agent, aminorex fumarate, widely used in central Europe, was shown to produce severe pulmonary hypertension. Rivier and associates,2,5 in reviewing 35 cases of pulmonary hypertension, found two patients who were taking both oral contraceptives and aminorex fumarate. Rivier et al.24 believed that the effects of taking both drugs might be additive, because two other patients with pulmonary hypertension in their series of cases were taking only oral contraceptives; and these investigators therefore inferred that gestational agents alone could produce pulmonary hypertension, and thus, enhance the effects of aminorex fumarate.

Oakley and Somerville5 reported three patients with left-to-right shunts, two with congenital septal defects, and one with a patent ductus arteriosus, who developed shunt reversal and severe pulmonary hypertension six months to two years following the inception of oral contraceptive therapy. These cases closely resemble our case 3. One patient died, and autopsy revealed profound intimal proliferation without evidence of thromboembolic phenomena.

The mechanism by which oral contraceptives might produce severe pulmonary hypertension is not known. Although it is possible that the severe pulmonary hypertension may be secondary to wide-
spread multiple small pulmonary emboli, this hypothesis seems unlikely. Severe systemic pulmonary hypertension is rarely the result of embolization. In the autopsy cases of Oakley and Sommerville, as well as in our three cases with autopsies, there was no evidence of thromboembolic phenomena in either lungs or leg veins. The lesion noted in the pulmonary arterial tree of our cases was severe intimal proliferation with marked atherosclerosis. No emboli were recognized. In the three patients who survived in our study, lung scans or pulmonary arteriograms, or both, failed to show any evidence of pulmonary emboli. During the course of follow-up of the three survivors, there were no acute episodes suggesting emboli. The survivors either remained stable or showed increasing symptoms compatible with pulmonary hypertension and right-sided heart failure. Because of the mortality associated with cardiac catheterization in two of our patients and the lack of symptomatic improvement in the survivors, we did not catheterize these patients to see whether some of the pulmonary hypertension might have regressed with cessation of oral contraceptive therapy. However, the data from the series of Rivier et al and of Oakley and Sommerville and our experiences suggest that this is unlikely.

Irey and Norris have reported 16 women who developed intimal vascular lesions while under the influence of female reproductive steroids. Five were pregnant, four were postpartum, and seven were taking oral contraceptives. The intimal vascular lesions were widespread in this group of patients and included both arterial and venous sites, with areas of narrowing and occlusion found in pulmonary, coronary, mesenteric, and renal arteries in some cases, as well as mesenteric, hepatic, and other venous sites in others. Five of the 16 patients had lesions in the pulmonary arteries which were associated with marked intimal vascular proliferation believed to be mainly fibroplastic in origin. There was no evidence of a primary thrombotic etiology. One pregnant woman and one of the patients taking oral contraceptives had a clinical course compatible with pulmonary hypertension and cor pulmonale. It has been noted previously that pregnancy may have a markedly adverse effect on pulmonary hypertension, but whether hormonal or circulatory factors are responsible has not been established. Two of the patients receiving oral contraceptives that were reported by Irey and Norris had severe vascular lesions demonstrated within the pulmonary artery. One patient had received oral contraceptives for two months and the other for four years. A control group of patients who were neither pregnant nor receiving oral contraceptives failed to show similar proliferative intimal lesions.

Our six cases, as well as previously isolated case reports, are compatible with the hypothesis that oral contraceptives can produce vascular intimal proliferation within the pulmonary arterial branches, leading to severe pulmonary hypertension and cor pulmonale. The autopsy data, clinical course, lung scan, and arteriographic results are inconsistent with a primary thromboembolic etiology. Furthermore, three of our cases, the two cases of combined amenorrhea and oral contraceptive reported by Rivier et al and the three cases of Oakley and Sommerville suggest that the development of pulmonary hypertension with oral contraceptive usage may be enhanced by predisposing causes, such as collagen vascular disease, family history of pulmonary hypertension, or congenital heart disease. On the other hand, some data suggest that an abnormal response to female reproductive steroid administration may occur without known predisposing causes. Further epidemiologic studies will be required to document this relationship, but it seems reasonable at this time to avoid the use of oral contraceptives in those conditions known to be associated with either pulmonary hypertension or intimal vascular lesions.

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