Pulmonary Artery Stenosis Associated with Ductus Arteriosus Following Maternal Rubella

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The most frequent cardiovascular anomaly following maternal rubella is patent ductus arteriosus. The majority of patients with typical signs of patent ductus arteriosus are treated surgically without special diagnostic studies such as cardiac catheterization and angiocardiography. In these individuals residual systolic murmurs may persist and are often attributed to mild pulmonary valvular stenosis. In many of these cases mild valvular pulmonic stenosis has been demonstrated by cardiac catheterization.

Other cardiac malformations have been associated with maternal rubella during the first trimester of pregnancy, but stenosis of the main pulmonary artery or its branches has been only recently described by Rowe. He studied offspring of mothers who had contracted rubella during an epidemic in New Zealand and found a high incidence of varying degrees of pulmonary artery stenoses. In 11 cases of stenoses of the pulmonary artery, only three had an associated patent ductus arteriosus. His report confirmed the previous implication of maternal rubella as a cause of pulmonary stenoses. A history of maternal rubella has occasionally been noted in other series of patients with stenoses of the pulmonary arteries.

The purpose of this report is to present findings in nine patients with pulmonary artery stenoses associated with patent ductus arteriosus. In seven, a definite history of maternal rubella during the first trimester was present. Of the remaining two, one was deaf and the other had a cataract, suggestive evidence of rubella syndrome.

Material and Methods

All nine patients were referred for evaluation of their cardiac status because of a heart murmur first noted in infancy. One (case 9) presented with symptoms of left heart failure. Seven were female, two male, and all are living (table 1). In seven, rubella was diagnosed in the first trimester of pregnancy. In two, no such illness was documented, but a cataract in one and deafness in the other provided indirect evidence of the rubella syndrome.

The usual methods of clinical evaluation were employed, and cardiac catheterization and selective angiocardiography were performed in all.

The diagnosis of pulmonary artery stenosis was made at cardiac catheterization and confirmed by angiocardiography. Biplane selective angiocardiography from the right ventricle or main pulmonary artery was performed in six cases, cineangiocardiography in three instances, and an aortogram in one case (case 9). In three instances in which oxygen saturation data were not conclusive, a small patent ductus arteriosus was diagnosed angiographically. In five patients, the ductus arteriosus was divided, and in one case (case 1) the pulmonary artery stenosis was confirmed during the operation. A surgical correction of the latter lesion was carried out 2½ years later. Postoperative cardiac catheterizations were performed in two patients (cases 1 and 8).

Results

Table 1 contains the pertinent clinical features and cardiovascular lesions of all patients. In addition, case 1 is reported in detail (see Appendix) because of its severity and several

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* We are indebted to Dr. C. K. Liu, Harbor General Hospital, Torrance, California, for permitting us to report case 9.
features of special interest. Their birth dates fell between the months of September and March. Five were born in the same year and two in the same month of the same year. The average birth weight in eight cases in whom this fact was known was 5 lbs., 7 ozs. This low weight is in agreement with the values reported by others. In four infants, associated cataracts with microphthalmus were present, bilateral in one and unilateral in three. Deafness, not associated with cataracts, was moderately severe in one case and extremely severe in the other, resulting in deaf mutism.

Growth and development in the first year of life were slow in five patients, three of whom had large left-to-right shunts. Of three patients with large left-to-right shunts, two infants had rapid respirations while the third, a 27-year-old deaf mute, had exertional dyspnea and orthopnea.

**Physical Findings**

An overactive right ventricular impulse was present in five children. In two there was a biventricular lift, and in the remaining two no abnormal precordial impulse was felt. A systolic thrill was felt at the upper left sternal border in four cases, and in one the thrill was at the lower precordium, probably due to an associated ventricular septal defect. In two the thrill disappeared after division of the ductus arteriosus.

The second heart sound was variable both in intensity and degree of splitting. It was narrowly split in the majority of cases with a slightly accentuated pulmonary component. In the two patients who showed bilateral severe pulmonary artery stenosis, the second pulmonic sound was not as accentuated as one might expect with the degree of main pulmonary artery hypertension.

Continuous murmurs were present in four patients and disappeared after division of the ductus arteriosus. After operation systolic ejection murmurs of varying intensity were present at the pulmonary area in three patients, and a loud holosystolic murmur at the lower left sternal border was heard in the patient with the associated ventricular septal defect. The remaining five patients had only systolic murmurs of blowing quality with maximal intensity at the second and third left intercostal spaces, well transmitted to the right or left anterior chest and axillary area.

**Table 1**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>History of rubella</th>
<th>Birth date</th>
<th>Birth weight (Kg.)</th>
<th>Cataract</th>
<th>Deafness</th>
<th>Anatomic diagnosis</th>
<th>Pulmonary artery stenosis Site</th>
<th>Degree</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>+</td>
<td>3/59</td>
<td>2.070</td>
<td>+</td>
<td>0</td>
<td>Bilateral</td>
<td>Severe</td>
<td></td>
<td>PDA * (divided)</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>+</td>
<td>12/60</td>
<td>3.740</td>
<td>0</td>
<td>0</td>
<td>Bilateral</td>
<td>Severe</td>
<td></td>
<td>PDA, mild PVS</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>+</td>
<td>10/59</td>
<td>2.720</td>
<td>0</td>
<td>0</td>
<td>Bilateral</td>
<td>Moderate</td>
<td></td>
<td>PDA, mild PVS</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>+</td>
<td>9/59</td>
<td>2.100</td>
<td></td>
<td>0</td>
<td>Bilateral</td>
<td>Moderate</td>
<td></td>
<td>PDA (divided)</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>+</td>
<td>12/60</td>
<td>2.490</td>
<td>+</td>
<td>0</td>
<td>Bilateral</td>
<td>Moderate</td>
<td></td>
<td>PDA, mild PVS</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>0</td>
<td>3/59</td>
<td>3.460</td>
<td>+</td>
<td>0</td>
<td>Unilateral</td>
<td>Mild</td>
<td></td>
<td>PDA</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>+</td>
<td>12/62</td>
<td>2.610</td>
<td>+</td>
<td>0</td>
<td>Unilateral</td>
<td>Moderate</td>
<td></td>
<td>PDA (divided)</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>0</td>
<td>1/59</td>
<td>2.350</td>
<td>0</td>
<td>+</td>
<td>Unilateral</td>
<td>Moderate</td>
<td></td>
<td>PDA (divided), mild PVS</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>+</td>
<td>12/34</td>
<td></td>
<td></td>
<td>0</td>
<td>Unilateral</td>
<td>Mild</td>
<td></td>
<td>PDA (divided)</td>
</tr>
</tbody>
</table>

* PDA, patent ductus arteriosus.
† PVS, pulmonary valvular stenosis.
‡ VSD, ventricular septal defect.
Case 9 had ventricular extrasystoles, diastolic gallop, and orthopnea with crepitant rales over both lung fields posteriorly. Bounding peripheral pulses were present in only three cases.

Roentgenologic Findings

In three cases there was no detectable cardiomegaly and the pulmonary vascular markings were within normal limits. Slight to moderate cardiomegaly was noted in four cases. Two had normal, one moderate, and one marked increase in pulmonary vascularity. In two cases there was marked cardiomegaly and marked increase in pulmonary vascular markings. Only two patients had prominence of the pulmonary artery segment (cases 4 and 9).

Electrocardiography

According to the usual criteria for age,\textsuperscript{16} standard electrocardiograms showed right ventricular hypertrophy in four cases, while one was normal. In three there was biventricular hypertrophy, which in one changed to right ventricular hypertrophy after ductus division. Vectorcardiograms correlated well with the electrocardiographic findings in all seven patients tested. Case 9 showed marked left ventricular and left atrial hypertrophy with occasional ventricular extrasystoles.

Phonocardiography

In seven cases phonocardiograms showed the above described characteristics of heart murmurs and sounds. In case 1 no change in the intensity and character of the murmur was noted after the attempted surgical correction of the pulmonary artery stenosis.

Cardiac Catheterization Studies

The catheterization data are shown in table 2. In case 1 such studies were performed at 7 months, 3 years, and 3½ years of age. The pulmonary artery was entered during the second catheterization but its branches were entered only after the attempted surgical correction of the pulmonary artery stenosis.

In case 2 the left pulmonary artery could not be entered. A left pulmonary vein was entered via a patent foramen ovale and a wedge pressure was obtained. This was similar to the mean arterial pressure of the right pulmonary artery, suggesting the presence of a low pressure in the left pulmonary artery as well. Stenosis of the left pulmonary artery was confirmed by cineangiocardiography.

In case 8 the right pulmonary artery was entered only during the second study 2½ years after division of the ductus arteriosus.

In six patients, the diagnosis of patent ductus arteriosus was made by oxygen satura-

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**Table 2**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age at time of study</th>
<th>RV Pressure (mm. Hg)</th>
<th>LPA Pressure (mm. Hg)</th>
<th>Systemic artery pressure (mm. Hg)</th>
<th>Detection of shunt (Angio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7 mo.</td>
<td>122/8</td>
<td>-</td>
<td>120/70</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>3 yr.</td>
<td>120/10</td>
<td>100/10</td>
<td>110/60</td>
<td>0</td>
</tr>
<tr>
<td>3½ yr.</td>
<td>108/10</td>
<td>108/12</td>
<td>20/12</td>
<td>104/60</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>21 mo.</td>
<td>96/12</td>
<td>80/12</td>
<td>120/0-10</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>3 yr.</td>
<td>80/12</td>
<td>44/12</td>
<td>120/60</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>3 yr.</td>
<td>70/4</td>
<td>64/32</td>
<td>110/56</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>18 mo.</td>
<td>75/7</td>
<td>65/15</td>
<td>107/57</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>4 yr.</td>
<td>28/3</td>
<td>27/4</td>
<td>80/52</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>4 mo.</td>
<td>100/6</td>
<td>86/44</td>
<td>120/60</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>10 mo.</td>
<td>60/5</td>
<td>50/16</td>
<td>105/65</td>
<td>+</td>
</tr>
<tr>
<td>3½ yr.</td>
<td>56/8</td>
<td>40/12</td>
<td>20/10</td>
<td>100/60</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>27 yr.</td>
<td>80/5</td>
<td>80/40</td>
<td>150/40</td>
<td>+</td>
</tr>
</tbody>
</table>

* Zero equals mid-thoracic level.
+ Pressure not obtained.
\( \dagger \) No evidence of shunt.
\( \ddagger \) Pressure taken from left ventricle.

RV, right ventricle; MPA, main pulmonary artery; RPA, right pulmonary artery; LPA, left pulmonary artery.

Circulation, Volume XXIX, April 1964
PULMONARY ARTERY STENOSIS

Case 2. Pressure recording during withdrawal of catheter across pulmonic valve. Note mild systolic pressure gradient and typical low pulmonary artery diastolic pressure of bilateral pulmonary artery stenosis.

In four patients the main pulmonary arterial pulse contour was consistent with stenosis affecting both main branches of the pulmonary artery (figs. 1 and 2). In all other cases the main pulmonary arterial pulse contour was normal (figs. 3 and 4) including one case of bilateral stenosis associated with large patent ductus arteriosus.

Angiocardiography

Angiocardiograms (figs. 5–7) demonstrated the extent and location of the pulmonary artery stenosis in eight cases. The aortogram in case 9 demonstrated a large shunt and a markedly dilated main pulmonary artery with moderate narrowing of the origin of the right pulmonary artery. The distal portion of this branch and the left pulmonary artery were markedly dilated.

In four patients with bilateral stenosis and in one with unilateral stenosis the main pulmonary artery appeared hypoplastic. At operation in case 1 the main pulmonary arterial wall appeared thick and fibrotic and lacked its usual elasticity. In three cases the central narrowing of the major branch extended peripherally over a long segment in a tapering fashion.

Summary of Clinical Evaluation

Bilateral pulmonary artery stenosis was found in five patients. In one of them, main pulmonary artery stenosis was noted as well. Unilateral pulmonary artery stenosis involving the right branch was present in four patients. All patients had associated patent ductus arteriosus with left-to-right shunt of vary-
Case 9. Pressure recording indicates stenosis between the right pulmonary artery (RPA) and the main pulmonary artery (MPA) but no gradient across the pulmonic valve.

Figure 4

Case 1. Selective right ventricular angiocardiogram showing a small main pulmonary artery and severe proximal stenosis of the right pulmonary artery.

Figure 5

ing degree. None had right-to-left shunting. Dilatation of the main pulmonary artery was present in only two patients, each with large ductal shunts, one with bilateral stenoses. In one patient an additional shunt was present (ventricular septal defect).

Mild pulmonary valvular stenosis was present in four patients, and a fifth had a pressure gradient across the pulmonary valve of 38 mm. Hg. The pulmonary arterial obstruction was severe in two patients and moderately severe in two additional cases as judged from the pressure gradients across the stenotic areas and electrocardiographic evidence of right ventricular hypertrophy.

Discussion

Patent ductus arteriosus is the most frequent cardiac defect in individuals born following maternal rubella during the first trimester of pregnancy.1-6 Association of pulmonic stenosis with ductus arteriosus has been reported by several authors.7-9 Heiner and Nadas9 reported a group of six patients with patent ductus arteriosus and pulmonary stenosis. Cardiac catheterization was performed in
PULMONARY ARTERY STENOSIS

of these cases might have had associated pulmonary artery stenoses.

The implication of maternal rubella as a cause of pulmonary artery stenoses was first suggested by Arvidsson et al. Three patients in their series of 11 patients had a history of maternal rubella. In series of patients with pulmonary artery stenoses, four additional cases with a history of maternal rubella have been described. The majority of these patients had multiple peripheral stenoses of the pulmonary arteries. Recently Rowe presented evidence that maternal rubella is a factor in the etiology of pulmonary artery stenoses in a study of 31 infants with congenital heart disease following an epidemic of rubella in New Zealand. Twenty-two had patent ductus arteriosus. In at least seven, pulmonary artery

only four, and in these, the pressure in the branches of the pulmonary artery was not reported. All six had noncardiac anomalies compatible with the rubella syndrome, although a definite history of maternal rubella was present in only two. In these two patients, the diagnosis of coexisting pulmonary stenosis was presumed by the persistence of a loud systolic murmur at the pulmonary area and right ventricular hypertrophy in the electrocardiogram. The same authors state that in some patients with maternal rubella, "... the patent ductus arteriosus was associated with pulmonary vascular obstruction without pulmonary stenosis." The site and extent of the vascular obstruction was not defined. One patient with a patent ductus arteriosus had a "stenotic murmur" in the second right interspace without a gradient across the pulmonary valve. The presence of an aortic stenosis was presumed in this case, and it was pointed out that the presence of a stenotic murmur heard best to the right of the sternum and under the right clavicle in these cases with patent ductus arteriosus must lead to suspicion of aortic stenosis. The present study suggests that some

Figure 6
Case 8. Angiocardiogram demonstrating long stenotic segments of the right pulmonary artery.

Figure 7
Case 4. Angiocardiogram depicting small main pulmonary artery, proximal narrowing of the right pulmonary artery with poststenotic dilatation. Proximal narrowing of the left pulmonary artery is not well shown in this projection.
stenoses were found, of which five had bilateral and two unilateral narrowing of the pulmonary arteries. In addition, four older patients with a history of maternal rubella and bilateral pulmonary artery stenoses were included in his series. Associated patent ductus arteriosus was found in only three cases.

Our series further supports Rowe's findings and suggests that pulmonary artery stenoses with or without other significant associated cardiac anomalies is a frequent malformation accompanying the rubella syndrome. Of 14 patients with ductus arteriosus and history of maternal rubella seen by us, nine have had evidence of bilateral or unilateral pulmonary artery stenoses. These nine constitute our present series. The remaining five have residual systolic murmurs after the division of the ductus. Two have been studied by catheterization, and mild pulmonary valvular stenosis was found. One probably has right pulmonary artery stenosis on the basis of the quality and distribution of the residual murmur, and two were not studied. On the other hand, in seven patients without a history of maternal rubella, who had a residual murmur after ductal division, only one had stenosis of the right pulmonary artery. Six had varying degrees of pulmonary valvular stenosis. In our series and that of Rowe, when the stenosis was unilateral only the right pulmonary artery was involved.

Since details of pregnancy are not provided in the majority of reported cases, the true incidence of pulmonary artery stenosis following maternal rubella cannot be estimated. Of the 89 cases of pulmonary artery stenosis now reported, 24 have definite and four probable rubella etiology.

Rubella epidemics undoubtedly may increase the number of pulmonary artery stenoses, but the resultant arterial anomaly following sporadic cases as in our series does not appear to differ from that arising from epidemics. The clinical findings in pulmonary artery stenoses have been well described, but cardiac catheterization with angiocardiography is essential for establishing the diagnosis and providing information about the extent and location of the arterial lesion. The lesion must be suspected whenever a systolic murmur persists after division of patent ductus arteriosus, especially in patients with maternal rubella. Arterial lesions of moderate severity can be suspected by the intensity and radiation of the murmur to the right chest and axilla, posteriorly and to the left side. Since pulmonic valvular stenosis is so commonly present in these cases, transmission of the murmur to the left axilla is not so helpful in suspecting left pulmonary artery stenosis, especially when the lesion is of mild degree. Soft basal murmurs due to mild degrees of arterial stenosis may be erroneously considered innocent, especially when the electrocardiogram and roentgenogram are normal. Their transmission into both axillary regions, however, will often distinguish them.

When a ductus arteriosus with a continuous murmur is present, coexisting pulmonary artery stenosis may be suspected by the transmission of the systolic component of the murmur into the right infraclavicular and axillary area.

The natural history of these pulmonary arterial lesions is not known. Their pathogenesis may be related to the insult to the vascular tissue of the rubella agent. The extremely fibrotic vessel wall found at operation in case 1 suggests an initial inflammatory reaction with eventual fibrosis.

Central rather than peripheral stenoses were found in our series. Mild stenoses may not affect longevity but in multiple peripheral stenoses, secondary thrombotic changes may contribute to the deterioration of these patients.

The prognosis in patients with moderately severe central stenoses is not known. Lack of parallel growth of the involved areas in a growing child may increase the obstruction and eventually lead to right heart failure. Surgical treatment in severe central stenoses may be of help in these individuals, although in our case the result was not satisfactory. Prognosis in these patients must be guarded in spite of the fact that no fatalities have been reported in childhood.
PULMONARY ARTERY STENOSIS

Summary

Nine patients with pulmonary artery stenosis associated with patent ductus arteriosus following maternal rubella are described.

Five of the patients had bilateral pulmonary artery stenosis and four cases involved only the right pulmonary artery. Mild pulmonary valvular stenosis was present in five and a ventricular septal defect in one.

The persistence of a systolic murmur transmitted to the lateral chest wall, after ligation or division of a patent ductus arteriosus, should arouse suspicion of the presence of pulmonary artery stenosis.

This report supports the recently described implication of maternal rubella as a cause of pulmonary artery stenosis. Careful auscultation in patients with history of maternal rubella may discover the presence of such an arterial anomaly, but cardiac catheterization and angiocardiography are necessary for substantiation of diagnosis.

The natural history of these lesions is not known.

Appendix

Case 1

J.J. was born March 7, 1959, following a “full-term” pregnancy complicated by rubella “during the first six weeks” of gestation. Because of a birth weight of 4 lbs., 9 ozs., she was kept in the hospital for 2 weeks. A heart murmur was first heard at the second week of life and at 6 weeks of age a cataract of the left eye was noted.

At age 7 months, her weight and height were found to be below the third percentile on the Harvard developmental grids. Left microphthalmus, cataract, and nystagmus were present. A grade-II systolic thrill was felt at the lower left sternal border. A grade-IV/VI harsh holosystolic murmur was heard over the entire precordium, maximally at the left sternal border and transmitted widely to the right chest and back. The second sound was obscured by the murmur and splitting was difficult to evaluate. It did not appear accentuated. The electrocardiogram showed right ventricular hypertrophy (right axis: R/S V1 = 25/17, R/S V6 = 16/28).

On October 23, 1959, right heart catheterization and selective angiocardiography were performed. The pulmonary artery was not entered and the right ventricular pressure was markedly elevated (table 2). Patent ductus arteriosus was diagnosed from the angiocardiogram, and she was operated upon 2 days later.

The main pulmonary artery had unusually strong pulsations and the wall appeared thickened. There was a thrill at the distal portion of the vessel at its bifurcation. The thrill and the elevated pressure in the pulmonary artery did not change after ligation of the ductus. There was an abrupt transition and thinning of the walls of the distal pulmonary artery just before the origin of the right and left pulmonary branches but no pulsations in either right or left pulmonary arteries. “Coarctation” of the main pulmonary artery, 2 mm. proximal to the point of bifurcation, was noted. The right and left pulmonary arteries tapered to a diameter of 3 mm. near the coarctation (fig. 5).

She was hospitalized again at the age of 3 years. She was small for her age but well nourished. Her exercise tolerance was mildly decreased, and because of the persistent cardiac murmur and right ventricular hypertrophy, repeat cardiac catheterization was performed (table 2). On this occasion the main pulmonary artery was entered and showed marked hypertension. There was no significant gradient across the pulmonary valve. A cineangiocardiogram revealed a hypoplastic main pulmonary artery and narrowing of the pulmonary arteries.

On July 11, 1962, with use of cardiopulmonary bypass, an attempt was made to repair the coarctation of the main pulmonary artery with an elliptical Dacron patch. “. . . A tremendously thickened pulmonary artery was noted (3 mm. in wall thickness). It appeared to be extremely dense fibrous scar tissue in multiple layers. . . . There was not a membrane present but actually this represented a diffuse narrowing of the whole main pulmonary artery. The pulmonary valve was normal. The orifice of the main pulmonary artery into the left pulmonary artery was markedly restricted (4 mm. in diameter) and to a lesser degree to the right.”* The postoperative course was complicated by intermittent seizures for 4 days, tachycardia and signs of right ventricular failure, which responded to digitalization.

Three months later, examination revealed persistent cardiomegaly and reduced exercise tolerance. She was readmitted on December 16, 1962, for repeat cardiac catheterization (table 2). Both right and left pulmonary arteries were catheterized; the main pulmonary artery pressure was unchanged, and an 80-mm. systolic gradient existed between the main pulmonary artery and its branches.

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Circulation. 1964;29:514-522
doi: 10.1161/01.CIR.29.4.514

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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