Heritable Pulmonary Arterial Hypertension Diagnosed during the Postpartum Period: A Case Report and Literature Review

Postpartum Dönemde Tanı Konulan Kalıtsal Pulmoner Arteriyel Hipertansiyon: Bir Olgu Sunumu ve Literatür Taraması

ABSTRACT
Approximately one-third of bone morphogenic protein receptor-2 (BMPR2) mutation carriers develop pulmonary arterial hypertension (PAH), which indicates that additional risk factors are needed for the manifestation of the disease. It is questionable whether pregnancy is a risk factor for PAH development in these patients. We represent a 30-year-old woman with a heterozygous BMPR2 mutation who was diagnosed with PAH during the postpartum period and reviewed the literature in this report. We also discussed the possible underlying mechanisms that might have resulted in PAH development during pregnancy in BMPR2 mutation carriers.

Keywords: BMPR2 mutation, heritable pulmonary arterial hypertension, pregnancy

CASE REPORT
OLGU SUNUMU

Ayşe Çolak
Zeynep Kumral
Ebru Özpelit
Bahri Akdeniz

Department of Cardiology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye

Corresponding author: Ayşe Çolak
aysecolak1@windowslive.com

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She had exertional dyspnea after delivery but she consulted a doctor when her symptoms were aggravated. At admission, her blood pressure was 102/80 mmHg, pulse rate 102 bpm, and pulse oximetry 98% at room air. Physical examination revealed no signs of heart failure and grade 2 pansystolic murmur at the left sternal border. Electrocardiography indicated normal rhythm with right ventricular hypertrophy. Anti-nuclear antibodies were negative and laboratory examination was in the normal range except for brain natriuretic peptide of 305 pg/mL. Transthoracic echocardiography revealed a D-shape with marked right atrial dilatation and systolic PA pressure of 99 mmHg. The presence of congenital heart defects was ruled out with transesophageal echocardiography. Pulmonary function tests showed no signs of heart failure and grade 2 pansystolic murmur at the left sternal border. Electrocardiography indicated normal rhythm with right ventricular hypertrophy. Anti–nuclear antibodies were negative and laboratory examination was in the normal range except for brain natriuretic peptide of 305 pg/mL. Transthoracic echocardiography revealed a D-shape with marked right atrial and ventricular dilatation and systolic PA pressure of 99 mmHg. The presence of congenital heart defects was ruled out with transesophageal echocardiography. Pulmonary function tests were normal and pulmonary embolism was excluded with both invasive pulmonary angiography and ventilation–perfusion lung scan. Invasive hemodynamics demonstrated precapillary PAH with a mean pulmonary artery pressure (mPAP) of 40 mmHg and pulmonary vascular resistance (PVR) of 14.6 Woods (Table 1). DNA analysis showed a heterozygous BMPR2 gene mutation.

**Table 1. Right Heart Catheterization Data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic pulmonary artery pressure</td>
<td>103 mmHg</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure</td>
<td>40 mmHg</td>
</tr>
<tr>
<td>Diastolic pulmonary artery pressure</td>
<td>66 mmHg</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure</td>
<td>–</td>
</tr>
<tr>
<td>Right ventricular pressure</td>
<td>79/0/5 mmHg</td>
</tr>
<tr>
<td>Left ventricular pressure</td>
<td>115/0/6 mmHg</td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>1 mmHg</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>14.6 WU</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>21.3 WU</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>4.04 L/min</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>2.84 L/min/m²</td>
</tr>
<tr>
<td>Mixed venous oxygen pressure</td>
<td>74%</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS**

BMPR2: Bone morphogenic protein receptor-2
HPAH: Hereditary pulmonary arterial hypertension
mPAP: Mean pulmonary artery pressure
PA: Pulmonary artery
PAH: Pulmonary arterial hypertension
PVR: Pulmonary vascular resistance
5-LO: 5-lipoxygenase

The main pathology in PAH is progressive vasculopathy resulting from multifactorial mechanisms including genetic predisposition, inflammation, impaired angiogenesis, and the effect of sex and sex hormones. Aberrations in the signaling pathways of BMPR2 and transforming growth factor beta exhibit a critical role in PAH development. BMPR2 gene mutations resulted in HPAH in about 30% of mutation carriers. These mutations are uncommon and have incomplete penetrance, which suggests that contributor risk factors are required to cause PAH. Our case report supports that pregnancy might be one of the potential risk factors for PAH development in BMPR2 mutation carriers.

Maternal blood volume expands to maintain the perfusion of vital organs during pregnancy. Normal pre–pregnancy pressures are maintained through a decline in both systemic vascular resistance and PVR. Under normal conditions, PVR decreases and mPAP remains unchanged in pregnant women. However, preexisting data demonstrated that pregnancy might also facilitate PAH in women.

There are two case reports in the literature that demonstrates the initiation of PAH during pregnancy in BMPR2 mutation carriers (Table 2). Limoges et al. were the first authors that described a de–novo diagnosis of PAH during pregnancy in 33-year-old woman with BMPR2 mutation. Their patient had one uncomplicated pregnancy, however, in the second trimester of her second pregnancy, she was diagnosed with PAH. Jaliawala et al. published a second case report. Their patient was 30 years of age and diagnosed with PAH in the third trimester of her first pregnancy. She had a heterozygous BMPR2 mutation and chronic amphetamine usage. They discussed whether chronic amphetamine usage added to the physiological stress of pregnancy in BMPR2 mutation carriers contributes to the development of PAH in their patient. Our patient differs from other cases in that her symptoms started just after delivery and she was diagnosed with PAH in the postpartum period.

The possible underlying mechanisms that might have resulted in PAH development during pregnancy in BMPR2 mutation carriers might be described as follows. First, estrogen and its metabolites have been shown to be related to both the penetrance and the development of HPAH. However, there is an "estrogen paradox" in the literature to describe the discrepancy between female predominance in PAH and the protective influences of estrogens in some animal experiments. It is presumed that estrogen has a protective effect on the healthy endothelium, however, in injured endothelium, estrogen stimulates angioproliferation and increases the risk and the progression of PAH. As pregnancy is associated with elevated levels of estrogens and vascular shear stress in response to increased vascular volume, this might explain the appearance of PAH during the peripartum period in our patient. In addition, in familial PAH, hormone replacement therapy with estrogen and progesterone was also described as a risk factor for PAH, which further supports this hypothesis. Second, it has been shown that asymptomatic patients with...
### Table 2. Summary of All Available Case Reports in the Literature

<table>
<thead>
<tr>
<th>No.</th>
<th>Authors</th>
<th>Year</th>
<th>Age at Diagnosis</th>
<th>Pregnancy Period</th>
<th>BMPR2 Mutation</th>
<th>Genetic Counseling</th>
<th>Cardiac Output</th>
<th>Pulmonary Vascular Resistance</th>
<th>Pregnancy Outcome</th>
<th>Maternal Immune System</th>
<th>BMI</th>
<th>Blood Pressure</th>
<th>Catecholamines</th>
<th>Plasma 5-LO</th>
<th>Resolution of PAH</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Limoges et al. 2015</td>
<td>33</td>
<td>2 trimester</td>
<td>Alive</td>
<td>BMPR2 gene mutation (c.741C&gt;A, p.Tyr247X)</td>
<td>Combined spinal-epidural anesthesia</td>
<td>sPAP: 64 mmHg, mPAP: 42 mmHg, dPAP: 31 mmHg, CO: 3.6 L/min</td>
<td>PVR: 14.6 WU, CI: 2.84 L/min/m²</td>
<td>Alive</td>
<td>Combined spinal-epidural anesthesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[CrossRef]</td>
</tr>
<tr>
<td>2</td>
<td>Jaliawala et al. 2022</td>
<td>30</td>
<td>3 trimester</td>
<td>Alive</td>
<td>BMPR2 gene mutation and chronic exposure to amphetamines</td>
<td>Spinal epidural anesthesia</td>
<td>sPAP: 68 mmHg, mPAP: 28 mmHg, dPAP: 18 mmHg, CO: 3.8 L/min</td>
<td>PVR: 4.6 WU, CI: 2.6 L/min/m²</td>
<td>Alive</td>
<td>Spinal epidural anesthesia</td>
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<td>[CrossRef]</td>
</tr>
<tr>
<td>3</td>
<td>Colak et al. 2023</td>
<td>30</td>
<td>Postpartum</td>
<td>Alive</td>
<td>BMPR2 gene mutation and chronic exposure to amphetamines</td>
<td>Normal delivery</td>
<td>sPAP: 99 mmHg, mPAP: 40 mmHg, dPAP: 66 mmHg, CO: 4.3 L/min</td>
<td>PVR: 2.84 L/min/m²</td>
<td>Alive</td>
<td>Normal delivery</td>
<td></td>
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</table>

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**References**


