

# High-risk pregnancy in a patient with pulmonary arterial hypertension due to congenital heart disease (PAH-CHD) with temporary shunt inversion and deoxygenation

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## Abstract

Atrial septal defect (ASD) is one of the most frequent congenital heart diseases (CHD). Up to 10% of adults with an ASD develop pulmonary arterial hypertension (PAH, PAH-CHD) in their lifetime. Despite improved therapy options, gravidity remains a substantial risk for both maternal and neonatal mortality in PAH-CHD patients.

In our patient, gravidity remained uncomplicated until week 32, under specific monotherapy with tadalafil, before onset of dyspnea and markedly increase of systolic pulmonary arterial pressure (PAP) was observed in echocardiography. Urgent Caesarian delivery was performed without any complications and a healthy baby was born. However, immediately afterwards, the patient desaturated (SpO<sub>2</sub> 65%, PaO<sub>2</sub> 37 mmHg) due to a shunt inversion with now right-to-left shunt through the residual ASD. She was admitted to our intensive care unit and specific PH therapy was escalated to a triple combination of tadalafil, ambrisentan, and iloprost. Hereafter, in a slow process of approximately three weeks, the patient's condition improved to baseline.

This rare case of a young woman with high-risk pregnancy in PAH-CHD highlights the hemodynamic changes and treatment options during pregnancy in these patients and emphasizes the urgency of a close monitoring at specialized GUCH/PAH centers with experience in managing PAH under these circumstances.

## Keywords

atrial septal defect, congenital heart disease, pulmonary arterial hypertension, pregnancy, shunt inversion

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## Introduction

Atrial septal defect (ASD) is one of the most frequent congenital heart diseases (CHD) and accounts for 8–10% of all congenital heart defects.<sup>1</sup> It can easily remain undiagnosed in childhood, as it rarely results in manifest clinical symptoms. Up to 10% of adults with an ASD develop pulmonary arterial hypertension (PAH, PAH-CHD) in their lifetime, which is currently defined as a mean pulmonary artery pressure (mPAP)  $\geq$  25 mmHg, a pulmonary arterial wedge pressure (PAWP)  $<$  15 mmHg as well as a pulmonary vascular resistance (PVR)  $>$  3 Wood units (WU) measured by right heart catheterization (RHC) at rest.<sup>2</sup>

Pregnancy remains associated with a substantially increased risk of mortality in PAH, especially during the peri-/postpartum period, due to hemodynamic stress and bleeding complications. The most common risks for maternal death include acute right ventricular (RV) failure as well as stroke from paradoxical embolism due to intracardiac shunting.<sup>3</sup> Additionally, premature birth and growth retardation is frequently reported in successfully delivered newborns.<sup>4</sup> Therefore, current guidelines advise against

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pregnancy in women with PAH.<sup>5</sup> Nonetheless, despite this recommendation, an increasing number of female patients with PAH(-CHD) have the desire to found a family and become pregnant, posing a demanding challenge in patient care.

Here, we describe a challenging case of a young woman with high-risk pregnancy due to PAH-CHD with temporary right-to-left shunting on atrial level and deoxygenation in the postpartum period.

## Case report

A 29-year-old woman was first diagnosed with PAH in May 2015. She initially presented with progressive dyspnea, World Health Organization (WHO)/New York Heart Association (NYHA) functional class (FC) III, and peripheral edema. Transthoracic echocardiography revealed a significant dilatation of the right-sided cavities with a paradoxical septal movement and a D-shaped left ventricle. RV function was preserved. Laboratory assessments showed a substantial rise of NTproBNP (1188 ng/L, normal range < 97.5 ng/L). Morphological imaging with transesophageal echocardiography in an outside clinic had not provided any evidence of a shunt. After exclusion of several differential diagnoses, RHC was performed also in an external clinic. Hemodynamics exhibited a remarkable precapillary PH with a mPAP of 69 mmHg and PVR of 11.6 WU, so that specific dual combination treatment with tadalafil and ambrisentan was initiated. Under therapy, her clinical status improved significantly to WHO/NYHA FC II. Chemically, NTproBNP reached improved values of 444 ng/L (normal range < 97.5 ng/L).

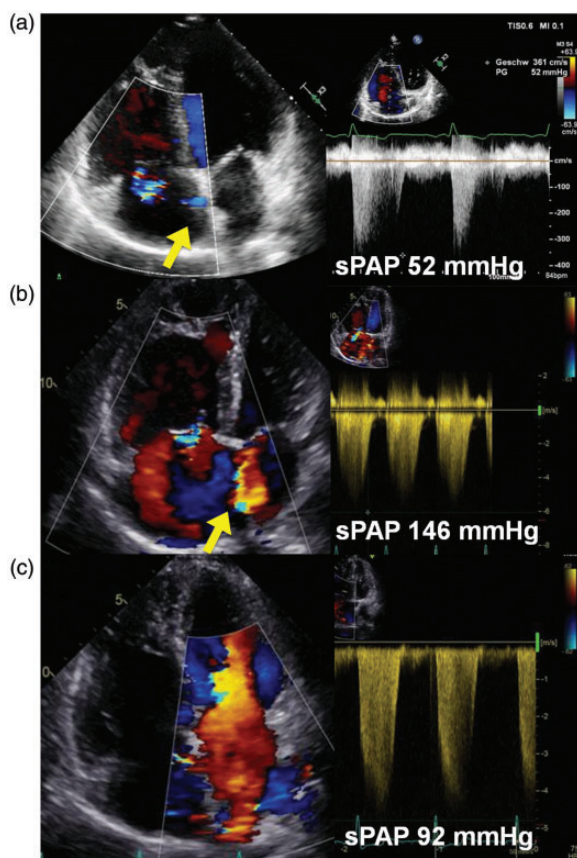
Follow-up RHC five months later in our center demonstrated a marked improvement of pulmonary hemodynamics with a mPAP of 51 mmHg and PVR of 5.7 WU. However, mixed venous oxygen saturation (SvO<sub>2</sub>) was elevated with 82%. Further oxymetry led to the suspicion of a left-to-right shunt at the atrial level (Qp:Qs 1.53). Repeated transesophageal echocardiography confirmed a left-to-right shunt due to a defect in the atrial septum (ASD secundum type, ASD II). After carefully consideration, the patient underwent surgical partial closure of the underlying ASD with a subsequent defect of 5 mm in April 2016, allowing a bidirectional shunt under specific PAH-treatment if required, following the treat-and-repair concept.

Subsequently, after surgery and before pregnancy in March 2017, the patient was in a good clinical condition, with a markedly reduced systolic PAP (sPAP) in echocardiography, normal peripheral saturation (SpO<sub>2</sub> 94%), and a slight left-to-right shunt through the residual ASD under continued dual-specific PAH treatment with tadalafil and ambrisentan (Fig. 1a). During pregnancy, she was closely monitored in our outpatient grown-up congenital heart disease (GUCH/PAH) clinic and discussed in an interdisciplinary, collaborative team for high-risk pregnancies.

As ambrisentan is contraindicated in pregnancy, this medication was immediately stopped after pregnancy was confirmed, leaving the patient on a monotherapy with tadalafil. As the patient did well on combination therapy and hemodynamic changes during pregnancy are expected to worsen PAH, addition of inhaled or parenteral prostanoid therapy was considered but not performed due to resilience of the patient to frequent daily inhalations or a parenteral pump therapy. Instead, the decision was made for close monitoring in our outpatient GUCH/PAH clinic. Pregnancy remained uncomplicated until week 32, under specific monotherapy with tadalafil, before onset of dyspnea and marked increase of sPAP was observed in echocardiography. In accordance with current recommendations, urgent Caesarian delivery was performed under general anesthesia without any complications and a healthy baby was born. After an uneventful period of 72 h, the patient desaturated (SpO<sub>2</sub> 65%, PaO<sub>2</sub> 37 mmHg), presumably due to a shunt inversion with now right-to-left shunt through the residual ASD, which was accompanied by resting dyspnea (Fig. 1b). NTproBNP increased substantially from 489 ng/L to 5421 ng/L. She was admitted to our intensive care unit and targeted PH therapy was escalated to a triple combination of tadalafil (40 mg once daily), ambrisentan (10 mg once daily), and inhaled iloprost (10 µg via Breelib-Inhaler 6–8 times daily). Hereafter, in a slow process of approximately three weeks monitored under intensive care conditions, the patient's condition improved to WHO FC II, normalized peripheral saturation, and again left-to-right shunt, allowing discharge (Fig. 1c). NTproBNP values subsequently decreased to 710 ng/L one month and 485 ng/L two months after delivery, respectively. Currently, she is in good clinical condition with improved sPAP values in TTE (comparable to pre-pregnancy) and is closely monitored in our outpatient GUCH/PAH clinic.

## Discussion

ASD is the most common CHD first diagnosed at adulthood, as patients are often free of clinical symptoms until adolescence or adulthood.<sup>6</sup> In hemodynamically relevant ASD, a closure of the defect is pursued in the absence of relevant PAH (with a marked elevation in PVR above recommended threshold), preferably by catheter intervention if anatomically suited or otherwise surgically.<sup>1</sup> However, guidelines for the evaluation of operability in PAH-CHD do not offer clear cut-off values regarding pulmonary hemodynamics in the preoperative state. Therefore, patients with a PVR in the range of 3–5 WU require individual treatment decisions.<sup>7</sup> Referred to current data, closure of an ASD in an adult patient with persistent or recurrent PAH can be perilous due to the repealed outflow mechanism to systemic circulation and lead to RV failure. Therefore, this may have a worse outcome than adults with an ASD who develop a shunt inversion.<sup>8</sup> In our case, in an interdisciplinary collaborative team with expertise in the area of grown-ups



**Fig. 1.** (a) Transthoracic echocardiography (TTE) before pregnancy. TTE exhibits only moderate dilatation of right heart cavities with improved sPAP and a mild left-to-right shunt through the residual ASD (yellow arrow). (b) Postpartum TTE. TTE demonstrates a substantial increase of sPAP (now supra-systemic) with a right-to-left shunt (shunt inversion, yellow arrow) in comparison to pre-pregnancy. (c) TTE after escalation of specific PAH treatment with tadalafil, ambrisentan, and iloprost. TTE shows a significant decrease of sPAP (sub-systemic) and again left-to-right-shunt through residual ASD.

with CHD, the decision was made for a partial surgical closure of the underlying ASD on the basis of confirmed improvement of pulmonary hemodynamics under dual-targeted PH therapy.

Despite advanced therapies, gravidity still poses a substantial risk for women with PAH(-CHD). Generally, between 1997 and 2007, maternal mortality rates in the range of 17–33% and neonatal mortality rates in the range of 11–13% were reported.<sup>9</sup> Distinct physiological changes lead to an increase of blood volume, cardiac output, red cell mass, and left ventricular mass during pregnancy, whereas blood pressure and systemic vascular resistance decrease – with a nadir in the last trimester of pregnancy.<sup>10,11</sup> Additionally, hormonal changes with increased levels of estrogen and progesterone lead to further vasodilatation.<sup>12</sup> These hemodynamic changes may lead to increased RV stress and to right-to-left shunting. In the absence of a possibility to shunt blood from RA to LA and decrease RV preload, RV failure may finally occur. Here, particularly

related to PAH-CHD, recent data report maternal mortality rates of 36% in Eisenmenger's syndrome.<sup>13</sup>

On the other hand, with improved management and extended therapeutic options, outcome of pregnancies has improved for women with long-term stabilization and nearly normal pulmonary hemodynamics under targeted PAH treatment. Therefore, current data suggest that gravidities may be successfully managed in this highly selected category of patients. In all these cases, likewise in our report, treatment with phosphodiesterase-5-inhibitors, prostanoids, and/or calcium channel blockers was continued during pregnancy. Due to potential embryotoxicity, endothelin receptor antagonists should generally be withdrawn.<sup>14</sup> Women with continued pregnancy and PAH-CHD need to be treated and closely monitored at specialized GUCH/PAH centers with experience in managing PAH under these circumstances. As the risk of right heart failure is particularly high during labor, delivery, the extended postpartum period, and general anesthesia, planned Caesarean sections under regional anesthesia are usually arranged for gestational weeks 32–36 in order to minimize the risk of maternal complications.<sup>3</sup> In our patient, the residual shunt through the partial ASD closure allowed shunt reversal leading to deoxygenation but prevented acute right heart failure with high mortality. As in the present case, postpartum monitoring of women with PAH is essential, as the risk of mortality is a particularly serious threat during the first four weeks after release.<sup>9–11</sup> Especially in this phase, autotransfusion of blood and increase of PVR can lead to right heart failure. As problems and complications are anticipated, one could argue that an even more aggressive approach using upfront parenteral prostanoids (e.g. epoprostenol) with augmented vasodilator potency due to higher effective blood levels should have been warranted. However, this approach is particularly recommended in Eisenmenger's syndrome patients;<sup>5,15,16</sup> and addition of inhaled iloprost led to a substantial improvement of the clinical status in our patient, therefore not necessarily requiring escalation by intravenous application under close surveillance. In addition, the residual shunt may have helped to prevent overt right heart failure. As illustrated in our case, patient compliance and management often complicate best medical treatment, requiring an even closer monitoring and patient education of possible risks. We want to point out that repeated critical evaluation of the therapeutic options is crucial, and any sign of deterioration of clinical status, right heart function, or vital signs should warrant a more aggressive approach.

In our case report, a close interdisciplinary collaboration between GUCH/PAH specialists, gynecologists, and intensive care specialists (“pregnancy heart team,” as requested by the current ESC Guidelines on cardiovascular disease in pregnancy [10]) as well as close monitoring of the patient were essential for the successful management of this high-risk pregnancy in a patient with PAH-CHD, despite the occurrence of severe complications in the peri-/postpartum phase.



### Conflict of interest

Dr. Hohmann reports personal fees from Pfizer, non-financial support from Actelion, non-financial support from MSD, non-financial support from Orion Pharma, outside the submitted work; Dr. Dumitrescu reports personal fees from Actelion, personal fees from Bayer, personal fees from MSD, personal fees from Novartis, grants from Actelion, personal fees from GSK, personal fees from Servier, outside the submitted work; Dr. Gerhardt reports grants and personal fees from Actelion, grants and personal fees from Bayer, grants from Novartis, grants and personal fees from United Therapeutics, personal fees from GSK, outside the submitted work; Dr. Kramer has nothing to disclose; Dr. Rosenkranz reports grants and personal fees from Actelion, grants and personal fees from Bayer, grants and personal fees from Pfizer, grants and personal fees from Novartis, grants and personal fees from United Therapeutics, personal fees from GSK, personal fees from Gilead, personal fees from MSD, outside the submitted work; Dr. Huntgeburth has nothing to disclose.

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