

# Pregnancy in pulmonary arterial hypertension (RCD code: VII-II-1)

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## Abstract

Pulmonary arterial hypertension (PAH) is a progressive disease leading to right ventricular failure and death, if not treated adequately. Pregnancy in women with PAH is associated with significantly high mortality, thus current guidelines strongly recommend, that pregnancy in PAH female patients should be avoided and in the case of pregnancy, termination at early stage is recommended. We present results of a study aimed at assessing maternal and newborn outcomes in gravidas with PAH. Five pregnant females with PAH in the mean age of  $29.6 \pm 8.23$  years were included in the study. In two patients idiopathic PAH (IPAH) and in three PAH due to congenital heart defects and Eisenmenger syndrome were diagnosed. Three patients received PAH-specific therapy (monotherapy) prior to pregnancy. During pregnancy two women received sildenafil, then treprostinil (one started in 33<sup>rd</sup> week of gestation, second few hours before labour). Two patients did not receive PAH specific therapy due to non-availability in Poland at that time and one according to treatment denial. In one case spontaneous abortion at the 8<sup>th</sup> week of pregnancy occurred and one of the patients reported 4 previous miscarriages. Two patients are still alive, one is lost to follow-up and two of them died: one in the postpartum period and the second ca. 18 month after abortion. All newborns survived. Considering the high mortality rate among pregnant women with PAH, pregnancy is strongly contraindicated. If the patient decides to continue pregnancy she should be under medical care in a specialist centre with a multidisciplinary approach and PAH specific treatment should be administered. JRC D 2016; 2 (7): 1–1

**Key words:** rare disease, right ventricular failure, echocardiography, heart catheterization, congenital heart defect, Eisenmenger syndrome, medical therapy, caesarean section

## Background

Pulmonary arterial hypertension (PAH) is a progressive disease leading to right ventricular failure and death, if not treated adequately. It is characterized as a group of disorders leading to progressive obstructive vasculopathy; according to current guidelines diagnosis of PAH can be established when mean pulmonary artery pressure (mPAP), assessed invasively, is higher than 25 mmHg at rest [1,2]. Traditionally PAH was considered to be a disease of young women and the disease with very bad prognosis. The average time from diagnosis to death was estimated at 2.7 years [3]. Currently, PAH quite often affects young women of childbearing age. Sometimes first clinical manifestations of PAH are observed

during pregnancy. Pregnancy in women with PAH is associated with significantly high mortality rate, approximately between 17% and 33%, thus pregnancy in PAH female patients is strongly contraindicated [4]. Physiological changes in the course of pregnancy initially are tolerated quite well, but peri- and postpartum period are critical in these patients. The mortality of newborns is also high, mainly due to prematurity and low birth weight and is estimated at 11–13%. Current guidelines strongly recommend that pregnancy in PAH patients should be avoided and in the case of pregnancy, termination at early stage should be advised.

Recent significant advances in PAH treatment have led to improvement in symptoms, exercise tolerance and survival [2]. Several classes of drugs, including calcium channel inhibitors, prostanoids, endothelin receptor antagonist, phosphodiesterase 5 inhibitors are

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**Table 1. Characteristics of the study group**

Patient	1	2	3	4	5
Diagnosis	IPAH	Common AVC Eisenmenger syndrome	Aorto-pulmonary window Eisenmenger syndrome	IPAH	Patent VSD, surgically closed PDA (age 4) Eisenmenger syndrome
Age	41	32	25	19	31
Number of pregnancies	secundi gravida	primigravida	primigravida	primigravida	pentigravida
PAH specific treatment before pregnancy	none (naïve)	sitaxentan	bosentan	bosentan	none (sitaxentan exposure in the past)
PAH specific treatment during pregnancy	none	none	sildenafil treprostinil (few hours before labour)	sildenafil treprostinil (22 <sup>nd</sup> week)	none
Mode of delivery	spontaneous vaginal labour	spontaneous abortion	caesarean section	caesarean section	caesarean section
Time of delivery	32 week	miscarriage (8 <sup>th</sup> week of gestation)	33 week	37 week	31 week
Outcome	death (26 days after delivery)	death (18 months after abortion)	alive	alive	alive (9 days after delivery)
PAH specific treatment after delivery	none	sitaxentan	bosentan	treprostinil	refused – none (bromocriptine initiated)

PAH – pulmonary arterial hypertension, IPAH – idiopathic pulmonary arterial hypertension, AVC – atrioventricular canal, VSD – ventricular septal defect, PDA – patent ductus arteriosus

widely used. In several reports the use of PAH-specific therapy in pregnant patients with PAH with successful outcomes was described. Thus the aim of our study was to assess maternal and newborn outcome in female patients with PAH in modern treatment era.

## Material and methods

It is a retrospective study analyzing outcome of pregnancy in females with diagnosis of PAH, referred to three centers: Department of Cardiac and Vascular Diseases, Jagiellonian University in Krakow, Department of Cardiology Cardinal Wyszyński Hospital in Lublin and Chair and Department of Cardiology, Medical University of Łódź, Biegański Hospital in years 2006–2015. The diagnosis of PAH was established on the basis of clinical history, physical examination, transthoracic echocardiography and right heart catheterisation (performed routinely before pregnancy). Pregnant patients with other types of pulmonary hypertension were excluded. In all patients demographic data, gestational age at presentation, World Health Organization (WHO) functional class, echocardiographic measurements, PAH-specific therapy, mode of delivery, complications and newborn status were analysed. The characteristics of the analysed group is shown in table 1.

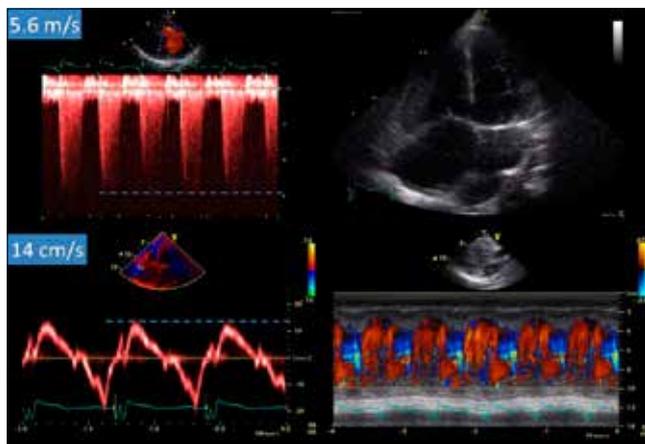
Data are presented as mean and standard deviation (SD) for parametric data. Because of the small number of enrolled patients all analyses are descriptive. Small study group size doesn't allow for in-depth statistical analyses.

## Results

Five pregnant females with PAH were included in the study. The mean age of patients was  $29.25 \pm 9.46$  years. In two patients, idiopathic PAH (IPAH) and in three PAH due to congenital heart defects and Eisenmenger syndrome were diagnosed (Table 1). In four cases PAH was diagnosed before pregnancy, while one patient was newly diagnosed at 24<sup>th</sup> week of gestation. Three patients received PAH-specific therapy (monotherapy) prior to being pregnant: one sitaxentan, two bosentan; one received sitaxentan, but discontinued prior to index pregnancy. In the treated patients endothelin receptor antagonist were withdrawn early, when the pregnancy was discovered. Three patients were primigravidas, one was secundigravida, and one Eisenmenger was pentigravida. At early stage of pregnancy three patients were in WHO functional class III, two in class II. Mean N-terminal pro b-type natriuretic peptide level was  $528 \pm 820.83$  pg/ml. On echocardiography mean right ventricular systolic pressure was estimated at  $103.33 \pm 21.33$  mm Hg, tricuspid annular plane systolic excursion  $15 \pm 2.16$  mm, in one patient pericardial effusion was observed.

Two pregnant women, previously on bosentan monotherapy, received sildenafil after confirming pregnancy. In the course of pregnancy one of them was administered treprostinil subcutaneously, starting from 22<sup>nd</sup> week of gestation with gradually increased doses, because of PAH progression. In the second case treprostinil infusion was started few hours before delivery in case of right heart failure in peripartum period.

Two patients did not receive PAH specific therapy due to non-availability in Poland at that time. In one case spontaneous abortion at the 8<sup>th</sup> week of pregnancy occurred. Remarkably



**Figure 1.** Echocardiography. Widely patent VSD in the Eisenmenger patient in her fifth pregnancy (case 5) with moderately abnormal right ventricle longitudinal function in tissue doppler. Bidirectional equalized VSD flow

pentigravida had a six-months period of sitaxsentan terminated on her request 7 years prior to the index pregnancy. All her previous pregnancies were lost between 22–30 weeks according to history (detailed written reports were not available).

Caesarean section was performed in 3 cases at gestational week 31, 33 and 37 under general anaesthesia, in one case spontaneous vaginal delivery was noted.

Two patients are still alive, two of them died: one in the postpartum period, 26 days after labour due to severe right heart failure (the patient did not received any PAH-specific treatment), second died ca. 18 month after abortion. The pentigravida was lost to follow-up and reluctant to initiate treatment. After delivery and postpartum period in one case bosentan with sildenafil, in second one treprostinil with sildenafil were administered. No newborns deaths were observed. Three children available to follow-up are alive with no congenital defects.

## Discussion

Data regarding the incidence and clinical course of pregnancy in patients with pulmonary arterial hypertension are rare and come from few retrospective analyses.

Weiss et al. investigated 125 cases of pregnant women with PAH (pregnancy over 22 weeks) in the years 1978–1996 [4]. The aetiology of PAH was as follows: Eisenmenger's syndrome – 73 patients, IPAH – 27 patients, other causes leading to PAH – 25 patients. Maternal mortality was 36% among patients with Eisenmenger's syndrome, 30% among patients with IPAH and 56% of patients with other diseases leading to PAH. Three deaths were registered before delivery (in the group with Eisenmenger syndrome), the other deaths occurred up to 35 days after delivery. It has been proven, that the late diagnosis of PAH during pregnancy and too late hospitalization are independent risk factors for mortality. Higher risk of death occurs in nulliparous and is associated with the progression of pulmonary hypertension as well as the delivery by caesarean section.

Results published by Bedard et al. in 2009 are more optimistic [5]. Study group was composed of pregnant women with PAH diagnosis established in the years 1997–2007, before the era of widely available PAH – specific therapy. Bedard et al. showed lower mortality rate in pregnant women compared to previously obtained results, although statistical significance was not obtained. Mortality rate in IPAH was 17%, in PAH in congenital heart diseases 28% and other diseases with PAH 33%. The deaths were observed during the first month after labour and were not found during pregnancy or childbirth. The most common causes of death were refractory right heart failure, cardiogenic shock, ventricular arrhythmias, pulmonary embolism, cerebral congestion, dissection or rupture of the pulmonary artery. Risk factors for mortality were general anaesthesia and pregnancy in nulliparous.

In published studies the survival rate of newborns was about 87–89%. It was found that the infant mortality rate is not related to the aetiology of PAH. About 59 – 85% of premature deliveries were noted and higher incidence of delayed intrauterine growth of foetuses was shown.

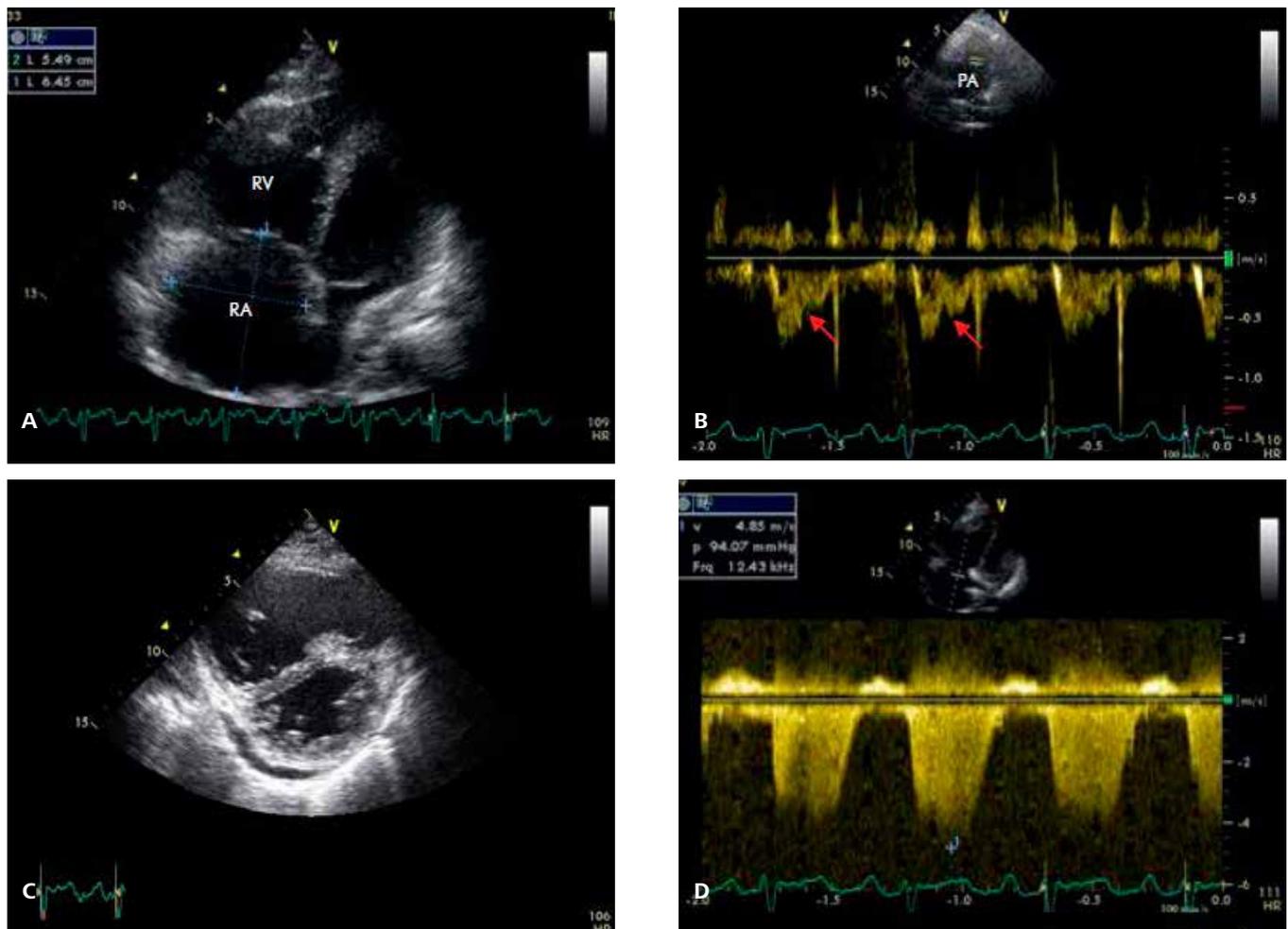
In the study published by Jais et al. survival rate was estimated at 62% [6]. Half of the patients enrolled into the study were responders with nearly normal haemodynamics on calcium channel antagonists therapy and the second half was composed of non-responders, but most of them had well-controlled PAH on specific therapy.

In our study one patient died during post-partum period due to severe refractory right heart failure, two are still alive and one, seen on the day 9 post-delivery refused any follow-up cardiac care. The patient, who died, was naive with PAH diagnosed on 24<sup>th</sup> week of gestation and she received no PAH-specific therapy during pregnancy or post-partum period. This is the first study about pregnancy in PAH patients in Poland.

Usually clinical deterioration during pregnancy is observed between 20 and 24 week of gestation. The most common symptoms include decrease in exercise tolerance, dyspnea, syncope and chest pain. But the most dangerous time is peri- and postpartum period (30 days after delivery). Jais et al. analysed maternal outcome during the year after delivery and showed, that 13% females, who had successful pregnancies, experienced clinical deterioration requiring intensification of PAH therapy, neither was a long-term responder to calcium channel blockers. Remarkably, one of our patients survived four previous pregnancy attempts to finally deliver a healthy baby which seems to be unique in medical literature.

Due to the high mortality pregnancy is absolutely contraindicated in patients with PAH. The use of effective methods of contraception is recommended in women with childbearing potential [7]. Importantly, bosentan therapy decreases the effectiveness of oral contraceptives.

In case of pregnancy in patients with previously diagnosed PAH termination should be advised. Abortion should be performed as soon as possible and no later than on 22<sup>nd</sup> week of gestation. Patients, who decide to continue pregnancy should be supervised in experienced referral centres. Evaluation of clinical status and echocardiography should be performed every 4 weeks. Also regular monitoring of fetal development is required.



**Figure 2.** Echocardiographic signs of PAH in patient 1 in 24<sup>th</sup> week of pregnancy. **A.** Enlargement of right heart chambers. Small left heart cavities. Right atrium: 65 × 55 mm, area 31 cm<sup>2</sup>. **B.** Shortening of the acceleration time to 44 ms, systolic notch (red arrows). **C.** Enlargement of right ventricle and pericardial effusion. **D.** Elevated right ventricular systolic pressure (RVSP ca. 104 mm Hg). RA – right atrium, RV – right ventricle

Due to the high mortality rate of the pregnant females and PAH progression during pregnancy, the early initiation of specific therapy seems to be necessary, despite the absence of strong scientific evidence. It is known, that endothelin receptors antagonists are teratogenic and it's use is absolutely contraindicated in pregnancy.

The mode of delivery is still discussed. Vaginal delivery is associated with less blood loss, less severe hemodynamic changes as well as less dangerous thromboembolic complications and infections [8,9]. It is very important to reduce the pain and shorten the second stage of labour. Delivery by caesarean section is indicated in case of pregnant or fetus deterioration, when pregnancy should be ended immediately. Due to high percentage of premature births, the majority of pregnancies are resolved by caesarean section (approximately 57.9%). Worse outcome was observed in female patients, who underwent caesarean section under general anesthesia, thus regional anesthesia is recommended [10]. General anaesthesia can cause depression of cardiac contractility, increase of pulmonary vascular resistance (positive pressure ventilation) and may result in an increase in pulmonary arterial pressure during laryngoscopy and intubation [11,12].

## Conclusion

The presented case series illustrate several cases of pregnancies in PAH patients in different clinical settings, based on the experience of three reference PAH centers in Poland. According to European Society of Cardiology guidelines [2,10] pregnancy is absolutely contraindicated in patients with PAH. Nowadays pregnancy in patients with PAH should be avoided or terminated at early stage. Thus it is necessary to use effective contraception, even with methods such as the irreversible closure of the fallopian tubes. These methods, in the case of healthy women, are inadmissible in the current legal status in Poland.

Recent studies have shown, that in some selected patients with well controlled PAH and near-normal haemodynamics successful pregnancy and labour in the modern treatment era is possible.

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