

Pulmonary hypertension and pregnancy: The experience of a tertiary institution over 15 years

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ABSTRACT

Background: Pulmonary hypertension (PH) in pregnancy is associated with a high maternal mortality and morbidity and has been found to be as high as 30–56%. **Aim:** To review the management of such patients in a tertiary center over a 15 year period, as the current literature consists of a few case reports, a few small case series and 2 meta-analyses. **Materials and Methods:** A review of all patients admitted to our institution for management of PH in pregnancy between 1994 and February 2009 was undertaken. Cases were identified from the high-risk pregnancy database within the department of anesthesia and from the hospital medical records. Severity of PH, type of PH, NYHA functional status at presentation and delivery, mode of delivery, peripartum monitoring and APGAR scores were noted. Patients were reviewed by a multidisciplinary team and management planned accordingly. **Results:** 19 eligible patients were identified. Patients who were significantly sick due to their PH were aggressively managed during pregnancy. Overall there was an improvement in NYHA functional status at the time of delivery. Epidural analgesia and anesthesia for labor and operatively delivery seem to be the ideal choice. **Conclusion:** Multidisciplinary approach is a key to the successful management of these patients. Secondary PH results in higher morbidity and mortality, in particular, older the age higher the maternal morbidity and mortality.

Key words: Anesthesia; pregnancy; pulmonary hypertension

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INTRODUCTION

Pulmonary hypertension (PH) is an increase of blood pressure in the pulmonary artery, pulmonary vein, or pulmonary capillaries, leading to shortness of breath, dizziness, fainting, and other symptoms, all of which are exacerbated by exertion. PH in pregnancy carries a 25–56% maternal mortality rate with a mixture of intrapartum and postpartum deaths.^[1–3] The published literature contains no large prospective studies comparing outcomes with regard to the relevant clinical questions. There is no consensus on the gold standard management of PH in parturient with regards to timing of delivery, choice of delivery technique and anesthetic choice. The current literature consists of a few case reports, a few small case series (<15) and 2 meta-analyses.

This article describes the experiences and outcomes of 19 deliveries occurring over a 15-year period at a tertiary center for obstetrics, cardiology and neonatology. The organization has a high-risk obstetric service making use of these and other specialty services as required.

MATERIALS AND METHODS

A review of all patients admitted to our institution for management of PH in pregnancy between 1994 and February 2009 was undertaken. Institutional ethics approval was obtained for the study. Cases were identified from the high-risk pregnancy database within the department of anesthesia and from the hospital medical records. Maternal admissions with coded co-morbidities of PH, primary PH and secondary PH were identified. Demographic data were recorded. Severity of PH were based

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on systolic pulmonary artery pressure (sPAP) estimation on transthoracic echocardiogram (TTE) and classified as mild (30–40 mmHg), moderate (40–70 mmHg) or severe (>70 mmHg). Other parameters noted were the type of PH (primary or secondary), New York Heart Association (NYHA) functional status at presentation, NYHA at delivery, timing of delivery (weeks), mode of delivery, peripartum monitoring used for anesthetic management, oxytocin dose given, APGAR scores at 1 and 5 min and birth weight [Table 1].

All patients with PH were seen in the high-risk obstetrics clinic at 25 weeks, except for one patient who presented in late pregnancy. Patients were jointly reviewed by obstetricians, cardiologists, intensive care physicians and anesthetists. A standard and emergency medical management plan was developed for each patient, including details of the proposed delivery methods, timing and medical therapy required in the peripartum period.

RESULTS

Twenty-two cases were identified. Two had PH diagnosed on TTE in the setting of acute reversible pulmonary pathology. In both cases, subsequent TTE confirmed reversion to normal sPAP prior to delivery and these patients were excluded from this review. A further patient had pulmonary stenosis with elevated right ventricular systolic pressures but no pulmonary vascular hypertension and was therefore also excluded. Of the remaining 19 cases, two were second pregnancies and considered as separate events [Table 1]. Six of these had severe, 11 had moderate, and two had mild PH at presentation [Table 1]. One of these mothers presented in extremis with cardiac failure in late pregnancy with no antenatal care. Emergency cesarean section was undertaken. Both mother and baby died in the days following delivery. Neonatal outcomes are detailed by etiology in Table 2.

Major morbidity was classified as cardiac, respiratory or renal failure, and occurred in four of the remaining 18 patients. The morbidity was all in mothers with more significant disease, which also had a greater effect on the fetus [Table 3]. The most common morbidity was cardiac failure, occurring in three patients with severe PH secondary to mitral stenosis. These patients were initially managed with medical therapy but subsequently required percutaneous mitral valvuloplasty. All mothers achieved significant reductions in sPAP postvalvuloplasty prior to delivery. There were no infant or maternal deaths in these

patients. In our series, severity of PH and morbidity also appeared to increase with maternal age as shown in Table 4. Mode of delivery and anesthetic technique in relation to the severity of PH is shown in Table 5.

At presentation, five out of 19 patients had NYHA functional status I, seven were NYHA II, one patient met criteria for NYHA III and six patients were classified as NYHA IV. At the time of delivery, there was an overall improvement in functional status: Eight were NYHA I, six were NYHA II, two were NYHA III, and three were NYHA IV.

DISCUSSION

Clinical classification of PH has been updated in 2008 and divided into five groups by world health organization. Broadly, pulmonary arterial hypertension (Group 1), pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis (Group 1'), PH due to left heart disease (Group 2), PH due to lung diseases and/or hypoxia (Group 3), Chronic thromboembolic PH (Group 4), and PH with unclear and/or multifactorial mechanisms (Group 5).^[4] However, many of the articles quoted have been published prior to this new classification, and we have used the term primary PH (idiopathic under new classification) and secondary PH in this article. Mortality in pregnant women with PH is high, with rates quoted as 30% for primary PH, 36% for Eisenmenger's syndrome and 50% for secondary PH.^[1] However, a systematic outcome review of PH in pregnancy was compared between 2-time periods, 1978–1996 and 1997–2007. Results showed a significant decline in maternal mortality from 38% to 25% during the period 1997–2007 suggesting advanced therapies and a multidisciplinary approach may have produced better outcomes.^[3] Our series has a mortality rate of 5%, with the only death being of a patient who died following delivery from cardiac failure due to fulminant and previously unrecognized PH, having undergone no antenatal assessment or care. Current recommendations for management of PH in pregnancy include termination of pregnancy if diagnosed early^[1] or utilizing a controlled interventional approach with early nebulized prostanoid therapy and early elective cesarean section under regional anesthesia.^[2] Other recommended therapies for peripartum management of PH include sildenafil and nitric oxide.^[3]

Disease severity

Functional classification has been found to have a high correlation with prognosis in pregnant patients

Table 1: Age, gravidity, cause and severity of PH, NYHA class, timing and mode of delivery, monitors used and neonatal outcomes

Case number	Age (G) (P)	Gravidity (G)	Cause of PH	NYHA presentation	NYHA at delivery	PH grade at presentation	Timing of delivery (weeks)	Mode of delivery	Peripartum monitors	Oxytocin dose	Apgar score 1 min	Neonatal outcome Weight (g)	
1	32	G2P1	Secundum ASD	I	I	Moderate	38	Elective LUSCS	Arterial catheter	2.5	7	9	3265
2	25	G3P2	MV and coarctation repair	I	I	Moderate	38	Unassisted NVD	Arterial catheter PAC	5	9	9	3040
3	37	G2P1	ASD, VSD, Eisenmenger's	IV	IV	Severe	35	Emergency LUSCS	Arterial catheter	10	9	9	1950
4	32	G7P3	TR	II	II	Mild	36	Unassisted NVD	Arterial catheter PAC	5	8	9	2792
5	39	G10P7	TR	III-IV	III	Severe	37	Unassisted NVD	Arterial catheter CVC	2.5	8	9	3540
6	29	G2P1	Mixed rheumatic MV disease	II	I	Moderate	39	Elective LUSCS	Arterial catheter	2.5	8	10	3810
7	30	G3P2	Mixed rheumatic MV disease	IV	II	Moderate	38	Unassisted NVD	Noninvasive	5	8	9	2875
8	33	G1P0	Mixed rheumatic MV disease	IV	I	Moderate	40	Instrumented VD	Noninvasive	10	9	10	3715
9	37	G3P2	Mixed rheumatic MV disease	III	III	Mild	35	Elective LUSCS	Arterial catheter TOE	5	3	5	2484
10	30	G1P0	PPH	II	II	Severe	34	Elective LUSCS	Arterial catheter PAC	0.8	4	8	1748
11a	31	G3P1	VSD	II	II	Moderate	31	Elective LUSCS	Arterial catheter PAC	4.5	9	10	2885
lib	32	G4P2	VSD	II	II	Severe	32	Elective LUSCS	Arterial catheter PAC	10	7	8	N/A
12a	25	G3P1	Rheumatic mitral stenosis	II	I	Severe	25	Unassisted NVD	Arterial catheter PAC	N/A	8	9	2875
12b	34	G4P2	Rheumatic mitral stenosis	IV	IV	Severe	34	Emergency LUSCS	Arterial catheter PAC	N/A	N/A	N/A	N/A
13	26	G1P0	Mixed rheumatic MV disease and AI	I	I	Moderate	26	Elective LUSCS	Arterial catheter PAC	2	9	9	2713
14	30	G3P2	Mixed rheumatic MV disease	IV	IV	Moderate	30	Emergency LUSCS	Arterial catheter	5	7	9	2610
15	27	G1P0	Corrected TOF, severe PR, moderate TR	II	II	Moderate	27	Instrumented VD	Noninvasive	2.5	9	9	2900
16	36	G3P2	Mixed rheumatic MV disease	I	I	Moderate	36	Unassisted NVD	Noninvasive	10	9	9	3130
17	37	G2P1	PPH	I	I	Moderate	37	Elective LUSCS	Noninvasive	10	3	7	3030

NYHA: New York Heart Association, PH: Pulmonary hypertension, PPH: Primary pulmonary hypertension, MV: Mitral valve, TR: Tricuspid regurgitation, ASD: Atrial septal defect, VSD: Ventricular septal defect, TOF: Tetralogy of fallot, PR: Pulmonary regurgitation, LUSCS: Lower uterine segment cesarean section, NVD: Normal vaginal delivery, VD: Vaginal delivery, PAC: Pulmonary artery catheter, CVC: Central venous catheter, TOE: Transesophageal echocardiogram, N/A: Not available

Table 2: Neonatal outcomes in relation to etiology

	Mean maternal age	Means PAP	Mean 1-min APGAR	Major morbidity	GA/RA	Vag/LUSCS	Mean birth weight
Primary PH: 2	34.5	87	6	50	1/1	1/1	2644
CHD: 4	31.75	67.5	8.5	25	2/2	1/3	1934
Secondary PH: 13	31.23	60.38	6.77	23	2/11	6/7	2795
Mean	31.68	64.68	7.05	32	5/14	8/11	2598

PAP: Pulmonary artery pressure, GA: General anesthesia, RA: Regional anesthesia, LUSCS: Lower uterine segment cesarean section, PH: Pulmonary hypertension, CHD: Congenital heart disease

Table 3: Neonatal outcomes in relation to severity of PH

sPAP	Median neonatal 1 min APGAR	Mean birth weight
Mild PH (sPAP <40)	8	3098.33
Moderate PH (sPAP 40-70)	8	2973.33
Severe PH (sPAP >70)	6	2222.70

PH: Pulmonary hypertension, sPAP: Systolic pulmonary artery pressure

with PH and with mitral valve disease,^[5-8] and it is the patients' exercise tolerance that primarily directs clinical management. Many patients with severe disease cope well in their day to day lives and report little in the way of symptoms. When they do complain, symptoms are often nonspecific. Of greatest concern is progressive breathlessness or extreme, but general tiredness, which are often attributed to the pregnant state by both patients and their carers. In our series, there was poor correlation in severity of PH and NYHA status, that is, patients with NYHA IV were not always severe PH, likewise NYHA I patients did not necessarily confer mild PH.

In this series, TTE was used to confirm PH. Although cardiac catheterization remains the gold standard for diagnosis of PH, except in pregnancy, it carries a 1–5% risk of serious complication,^[9] which may be increased in the critically ill obstetric patient.^[10] Conflicting reports exist as to the accuracy of TTE in estimating PAP in pregnancy. A retrospective review found that TTE overestimates PAP in pregnancy.^[9] This overestimation was found to be greater in patients with structural cardiac defects.^[9] Conversely, a prospective study where TTE and pulmonary artery catheter (PAC) measurements were done simultaneously found no difference between the two measurements.^[10] The severity of PH on TTE and clinical condition of the patient directed the obstetric and anesthetic decisions. Our patients were monitored with TTE for progression in severity of PH and assessment of right heart function. The decision to use TTE for clinical management,

rather than the NYHA status, is based in a belief that TTE changes will predate functional decline. This hypothesis forms the basis of our management but is yet to be tested in pregnancy. TTE assessments need to be made in the knowledge that cardiac output (CO) and pulmonary resistance determine PAPs. Hence, in pregnancy with increasing CO, we may see an increase in the pressure but the underlying resistance may not have changed.

One of our patients with moderate PH on TTE who denied symptoms underwent exercise echocardiography during the first trimester of her pregnancy. Ventricular function was in the low normal range at rest, but exercise-induced marked hypokinesia, without any symptoms. At 32 weeks, her resting pulmonary pressures were noted to be in the severe range, hence delivery was thought prudent. She went on to have an uneventful cesarean section under GA and recovery. Exercise echocardiography may be a useful way of “stress testing” pregnant women with PH to assess their reserve and direct delivery timing.

Disease etiology

The underlying etiology identifies patients at the highest risk of acute cardiac decompensation during pregnancy. The existing body of literature suggests that secondary PH has the highest risk of mortality^[11] and that PH secondary to mitral valve stenosis poses a high risk of acute pulmonary edema as the pregnancy progresses. Mortality is 1% for NYHA classes II and I and increases to 5% for NYHA classes III and IV.^[5-7] In the presence of atrial fibrillation, the mortality increases to 14–15%.^[6,7] There is a higher fetal and neonatal complication rate in women with a history of cardiac events or symptoms prior to pregnancy.^[6,7] The risk is greatest near term and in the peripartum period.^[5,6] Intensive medical management of patients with developing heart failure is successful in stabilizing most symptomatic patients^[7,12] and allows many to continue the pregnancy to term and improves maternal condition for delivery.^[12] Percutaneous mitral valvuloplasty should be considered if cardiac performance deteriorates.^[13]

Table 4: Relation of maternal age, severity of PH and maternal morbidity

Maternal age	Mild PH	Moderate PH	Severe PH	Maternal morbidity	Median neonatal 1-min APGAR	sPAP
20-25	0	1	1	1/2	8.5	73
26-30	0	5	1	0/6	7.5	59.17
31-35	1	3	2	1/6	8	62.16
36-40	1	2	2	3/5	6.4	71

PH: Pulmonary hypertension, sPAP: Systolic pulmonary artery pressure

Table 5: Mode of delivery and anesthetic technique in relation to severity of PH

	Vaginal delivery	Emergency LUSCS	Elective LUSCS	GA	RA
Mild PH	1	0	1	1	1
Moderate PH	5	1	5	0	11
Severe PH	2	2	2	4	2

PH: Pulmonary hypertension, GA: General anesthesia, RA: Regional anesthesia; LUSCS: Lower uterine segment cesarean section

Eight patients in this series had significant rheumatic mitral stenosis, one of whom had two pregnancies. Four of these required medical management in order to stabilize symptoms, in the form of diuretics, digitalis, anticoagulation and nifedipine. Three of these four patients then underwent mitral valvuloplasty and had immediate improvement in symptoms. One was discharged at 31 weeks and represented in spontaneous labor at 40 weeks. She went on to have an uncomplicated delivery. A second had a more complicated course suffering pericardial tamponade during the procedure, which was successfully drained with a pericardial catheter. After a few days of improvement in her symptoms, she developed rapid atrial fibrillation and subsequently underwent urgent cesarean section. The last presented with two pregnancies, had the valvotomy during the first and uneventfully delivered vaginally 12 weeks after the procedure. During her second pregnancy, she presented at 36 weeks with pneumonia and acute pulmonary edema, threatened respiratory arrest that necessitated emergency cesarean section. She subsequently made a good recovery. Nitric Oxide was used in one patient who then received sildenafil in the postoperative period.

Timing and mode of delivery

Patient management aims at supporting pregnancy for as long as possible toward term for a normal vaginal delivery. Cesarean section may have the potential for greater hemodynamic instability due to blood loss and pain. Operative delivery has been found to be an independent risk factor for maternal mortality in patients with secondary PH and a potential risk factor

for all patients.^[1] The optimal mode of delivery remains controversial; however, a recent paper suggested that a planned cesarean section at 34 weeks under regional anesthesia was their preferred approach.^[14] At our institution, if patients remained well, the pregnancy was allowed to continue, albeit with frequent review with vaginal delivery as the preferred mode. However, Cesarean section was not an infrequent occurrence often due to obstetric indications, emergency presentations and failure of medical management. Any sign of breathlessness or generalized tiredness would prompt hospital admission and delivery if symptoms did not resolve with bed rest and medical management. Additionally, signs of right heart failure would necessitate urgent cesarean section. In this series, 8 vaginal deliveries were achieved. Those with moderate to severe disease labored in the intensive care unit (two patients) or coronary care (two patients) with both a midwife and intensive care nurse in attendance. This facilitated both obstetric care and intensive monitoring of the hemodynamic parameters of the mothers. The first 72 h postpartum appears to be the time of greatest risk, when the hemodynamic changes reach their peak, with most maternal deaths occurring early after delivery.^[1,11,15,16] It is, therefore, important that these patients remain in a monitored environment after delivery, where they can be observed intensively and have appropriate intervention should the need arise.

One emergency and two elective cesarean sections were performed for obstetric indications (breech, previous cesarean). Two emergency cesarean sections were performed for acute heart failure. Five cesarean sections were performed due to concern about the mother's cardiac condition. It has been suggested that vaginal delivery is better tolerated than cesarean delivery by pregnant women with PH^[11,17] or it may be that the women allowed to labor have less severe disease and, therefore, better outcomes.

Labor analgesia

For labor, epidural analgesia is the preferred option. It is titratable and minimizes the hemodynamic effects

of pain. All patients who had vaginal deliveries had pain relief with epidural analgesia without any complications. Theoretically, the systemic vasodilatation produced by the sympathetic block may induce hypotension in the patient with a limited or fixed return to the left atrium, but this has not been a problem in our series of laboring woman, probably due to the slow onset of the block allowing compensation. There were no complications related to the use of epidural analgesia in this series.

Cesarean section and anesthetic choice

This decision was dictated by the managing anesthetist based on the severity of PH. The ability of the patient to lie flat may often be the deciding factor between a regional and general anesthesia (GA) for cesarean section. In this series, 5 out of 10 cesarean sections were performed under epidural anesthesia. Five patients underwent cesarean section under GA. In one, regional anesthesia was contraindicated due to anticoagulation and maternal hemodynamic instability. In another two, maternal instability precluded regional anesthesia. In one case, GA was administered to better control the use of nitric oxide that was deemed necessary due to severe disease. In all cases, good neonatal and maternal outcomes were achieved.

General anesthetic technique

This varied with anesthetist, but the commonest practice was to use a small dose of midazolam to allay the anxiety associated with placement of invasive lines, cognizant of the fact that sedation may worsen pulmonary vascular resistance. Preoxygenation was administered via facemask. Induction was achieved using 3–5 mcg/kg of fentanyl to provide stable hemodynamics and good modification of the hemodynamic response to laryngoscopy supplemented with judicious doses of propofol as required. Standard inhalational anesthetic technique, with O₂ in air and isoflurane or sevoflurane, was used for maintenance.

Maintenance of ideal homeostasis is important. Temperature, acid-base balance, oxygenation and carbon dioxide levels should all be maintained within the normal range and deviation can have quite profound effects on the pulmonary pressure. A large alveolar-arterial CO₂ gradient was often observed, and a blood gas should be checked early on and ventilation adjusted accordingly.

One patient undergoing GA received inhaled nitric oxide intraoperatively. This improved both the hemodynamics

and the blood gases. Nebulized prostacyclin is now available in our institution and has the advantage of being much easier to use while still being effective. It is categorized as B3: Drugs, which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

However, Kiely *et al.* reported use of prastanoid therapy without harmful effects to the fetus.^[14] Prostacyclin derivatives, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors have been approved for use in PH. However, these agents are not approved for the treatment of PH associated with sickle cell disease due to inadequate data to support their efficacy.^[18] It is often necessary to support the systemic circulation whilst using nitric oxide and in this case noradrenalin was used and found it to be effective. Adrenaline also has been reported to be useful, although we are concerned about the potential for tachycardia.

Use of oxytocin

Bolus doses of oxytocin cause hypotension via systemic vasodilatation, and this effect is exaggerated in the anaesthetized patient. This can exacerbate PH by reducing right coronary blood flow leading to right ventricular failure and a low output state that is not responsive to volume or inotropic support. Although induction or augmentation of labor with low-dose oxytocin is considered safe, there have been reports of exacerbation of primary PH at low infusion rates.^[17,19] Ergometrine and prostaglandin F₂ alpha cause pulmonary vasoconstriction and therefore contraindicated in PH.^[19]

In this series, six patients underwent augmentation of labor with low dose intravenous (IV) oxytocin. A bolus of oxytocin was given in all but two cases (both the same patient), in doses ranging from 0.8 units to 10 units IV. The one patient in our series who received 10 units of oxytocin was the one who underwent cesarean section prior to the diagnosis of severe PH. This dose was the routine practice at the time. There were no adverse hemodynamic effects documented in the other patients, which may be due to the smaller doses given and the longer administration times.

Monitors

In the literature, the use of PAC is controversial with little evidence of an improvement in outcome. Nonetheless, they are often used because they offer parameters on which clinical decisions are made in a group of patients in whom assessment can be difficult. In particular, the use of pulmonary vasodilating drugs requires quantified parameters to guide their use. In our institution, we use PAC catheters for those with severe disease, as estimated on TTE or determined from the symptomatology.

The reasons for our use of pulmonary artery catheter:

- Transthoracic echocardiogram may overestimate the degree of PH in the pregnant patient.^[9] In our series, 8 peripartum PAC were used. In 4 of these patients measured PAP were lower than estimated, which helped simplify subsequent management. Three of these patients underwent subsequent uneventful vaginal delivery, with no significant change in the hemodynamics
- We have found that the central venous pressure (CVP) and CO are the useful parameters to plan hemodynamic decisions. The measured PAP is indicative of disease severity; however, they are CO dependent. We found that CVP and CO are the most useful combination of measures for clinical management. A rise in CVP and reduction in CO reflect deterioration in right ventricular function, which can manifest as a drop in pulmonary pressures. If PAP was being considered in isolation of the CVP and CO, this could be misinterpreted as an improvement in the patient's condition rather than the harbinger of right heart failure. There are risks involved in PAC insertion (arrhythmia, pulmonary artery rupture) but the benefit of monitoring all three parameters, (CO, CVP and PAP) in determining the timing of interventions and management is invaluable in our experience. In future CVP and noninvasive CO methods may reduce the use of the PAC. Transesophageal echocardiogram was used in one patient to guide intraoperative management and is obviously a modality that we will use more into the future.

CONCLUSION

Pulmonary hypertension is a rare and serious condition in pregnancy with a tendency to rapid deterioration in severe cases. Early recognition and medical management is helpful and can direct obstetric and anesthetic management. Multidisciplinary management

and planning are essential. TTE is diagnostic and gives us information for risk stratification. It is also a monitor of right heart function, and the use of exercise testing may have some outcome predictive value. Mild PH appears to be low-risk; however, monitoring with TTE is essential should the disease progress or they become symptomatic. Epidural analgesia and anesthesia for labor and operative delivery seems to be an acceptable choice. General anesthetic is safe and is the management of choice in the emergent or unstable cases. PAC is invasive, however, provides useful and accurate information if the correct CVP and CO are assessed. The risks versus benefit of PAC should be considered before insertion, and newer noninvasive or semi-invasive modalities may now be more appropriate. Secondary PH results in higher morbidity and mortality, in particular, older the age higher the maternal morbidity and mortality.

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