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Pregnancy and pulmonary hypertension

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Pulmonary hypertension during pregnancy is associated with considerable risks of maternal mortality and morbidity. Our systematic review of the literature on the use of targeted treatments for pulmonary arterial hypertension during pregnancy indicates a considerable decrease of mortality since a previous review in 1998 (16% *v* 38%), and a further non-significant decrease in mortality since the latest review in 2009 (16% *v* 25%). In addition to the use of targeted treatments, the timely institution of these treatments, and early planned delivery, may contribute to better outcome. Furthermore, research suggests that women with mild pulmonary hypertension or favourable functional class may have a better prognosis, but there is yet no proof of decreased mortality among these women. Despite an improved prognosis, pregnancy is contra-indicated in women with pulmonary hypertension and, when pregnancy occurs, termination should be considered. When pregnancy continues, management by a multidisciplinary team in a specialist centre is indicated.

Introduction

Pulmonary hypertension is a rare disease with different causes. Despite improvements in treatment options, it still carries a grave prognosis, with significant morbidity and mortality. The haemodynamic changes of pregnancy are not well tolerated in women with pulmonary hypertension. Mortality has

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been described in up to 50% of women with pulmonary hypertension [1]. Prognosis has improved in recent years, but pregnancy is still contraindicated in women with pulmonary hypertension [2,3]. In this chapter, we provide a brief overview of the diagnosis, classification and pathophysiology of pulmonary hypertension. We also review modern treatment options and available published research on pregnancy in women with pulmonary hypertension. Our specific aims are to establish what factors determine prognosis of pregnant women with pulmonary hypertension. We systematically reviewed the literature describing the outcome of pregnancy in women treated with targeted pulmonary hypertension treatments.

Definition, classification and pathology of pulmonary hypertension

Pulmonary hypertension is defined as an increase in mean pulmonary arterial pressure (mPAP) 25 mm Hg or over at rest as assessed by right heart catheterisation [4]. At the fourth World Symposium on Pulmonary Hypertension in Dana Point (2008), a clinical classification of pulmonary hypertension was agreed upon (Table 1), and this has now been incorporated into the European Guidelines [4]. Haemodynamically, pulmonary hypertension associated with left heart disease (group 2) can be characterised as post-capillary pulmonary hypertension, with a pulmonary capillary wedge pressure greater than 15 mm Hg. All other groups (groups 1,3,4,5) are defined as pre-capillary pulmonary hypertension; in these conditions, pulmonary capillary wedge pressure is 15 mm Hg or less. In people with pulmonary hypertension, cardiac output can be normal or reduced. It is useful to realise that pulmonary hypertension comprises all peoples with increased mPAP 25 mm Hg or over at rest, whereas the term pulmonary arterial hypertension (PAH) is reserved for the clinical condition of group 1 pulmonary hypertension (Table 1).

The pathophysiology differs between clinical groups. In group 1 (PAH), the distal pulmonary arteries show intimal proliferation, medial hypertrophy, inflammatory and thrombotic lesions, as well as complex plexiform lesions. Pulmonary veins are only affected in group 1'. The increase in pulmonary vascular resistance (PVR) is the result of multiple contributing factors. These include vasoconstriction resulting from an imbalance of vasodilator and vasoconstrictor substances associated with endothelial dysfunction, as well as inflammation, proliferation, and thrombosis. In group 2 (pulmonary hypertension caused by left heart disease), the backward transmission of the elevated left atrial pressure leads to an increase in capillary wedge pressure and mPAP. The pulmonary veins are enlarged and thickened, interstitial oedema is observed, and intimal fibrosis and medial hypertrophy may occur.

Table 1
Clinical classification of pulmonary hypertension.

1. Pulmonary arterial hypertension
   - 1.1.Idiopathic
   - 1.2. Heritable (i.e. BMPR2, ALK1)
   - 1.3. Drugs and toxins induced (i.e. fenfluramine, amphetamine)
   - 1.4. Associated with
     - Connective tissue diseases,
     - HIV infection
     - Portal hypertension
     - Congenital heart disease (Eisenmenger syndrome, or associated with moderate systemic to pulmonary shunts, small shunts or corrected congenital heart disease)
     - Schistosomiasis
     - Chronic haemolytic anaemia
   - 1.5 Persistent pulmonary hypertension of the newborn
   - 1′ Pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis
2. Pulmonary hypertension due to left heart disease
(systolic or diastolic dysfunction, valvular disease)
3. Pulmonary hypertension due to lung diseases and/or hypoxia
(i.e. chronic obstructive pulmonary disease, interstitial lung diseases, mixed restrictive/obstructive pulmonary disease, high altitude, and others)
4. Chronic thrombo-embolic pulmonary hypertension
5. Pulmonary hypertension with unclear, multifactorial mechanisms, or both
(i.e. haematological disorders, systemic disorders, metabolic disorders and others)

When the mPAP is disproportionally elevated compared with the capillary wedge pressure (increased transpulmonary gradient) the PVR will also be increased. Reversible vasoconstrictive or fixed obstructive pulmonary hypertension can be present. Group 3 (pulmonary hypertension caused by lung diseases and hypoxia) is characterised by vasoconstriction reactive to hypoxia, as well as by inflammation, whereas toxic effects of smoke and mechanical effects (emphysema) may play a role. A loss of capillaries occurs and medial hypertrophy and obstruction of distal arteries caused by intimal proliferation are also seen.

Group 4 (chronic thrombo-embolic pulmonary hypertension) is characterised by organised thrombi leading to pulmonary arterial stenosis or occlusion. Coagulation abnormalities may play a role in the pathogenesis of thormbo-embolic pulmonary hypertension. Local thrombosis can occur. In non-obstructed areas, abnormalities indistinguishable from the lesions found in PAH are found.

Group 5 is a heterogeneous group, and the pathobiology and physiology is not well defined [4].

Haemodynamic and haemostatic changes in pregnant women with pulmonary hypertension

Early in pregnancy, plasma volume starts to increase and, by the end of the second trimester, an increase in plasma volume of 40% volume is achieved. Red blood cell mass increases by 20–30%. Systemic vascular resistance decreases. As a result of these changes, cardiac output increases. In normal pregnancy, this is achieved mainly by an increase in stroke volume in the first and second trimester, whereas, later in pregnancy, heart rate also increases and contributes to the increase in cardiac output. During delivery and postpartum, there is a further increase in cardiac output and blood volume, caused by pain, anxiety, and volume shifts, including autotransfusion during uterine contractions [2]. In healthy women, the pulmonary circulation adapts to the increases in blood volume and cardiac output by pulmonary vasodilatation, preventing pulmonary pressures rising during pregnancy. In women with pulmonary hypertension, the pulmonary circulation is unable to cope with these haemodynamic changes as a result of pulmonary vascular remodelling. Therefore, pulmonary pressures will rise when cardiac output increases. Moreover, the right ventricle may not be able to sufficiently increase cardiac output, and dyspnoea, heart failure, and syncope may occur. Pulmonary hypertension is not uncommonly a new diagnosis during pregnancy, as the haemodynamic burden of pregnancy can provoke symptoms that were previously not present. In women with Eisenmenger syndrome, the combination of a fixed pulmonary vascular resistance and decrease in systemic vascular resistance leads to increased right-to-left shunt and hypoxia [5].

Pregnancy is a hypercoagulable state owing to increased platelet aggregation, increased concentrations of fibrinogen and clotting factors, and impairment of venous return by the enlarged uterus. This may result in enhancement of pulmonary vascular thrombosis, as well as peripheral venous thrombosis with risk of pulmonary embolism, further aggravating or causing pulmonary hypertension during pregnancy. Women with Eisenmenger syndrome, who have an intra-cardiac right-to-left shunt, are at increased risk of paradoxical emboli during pregnancy. These women frequently have a prothrombotic state, and are also at increased risk of bleeding.

Maternal pregnancy outcome

Despite the well-recognized risk of pregnancy, pulmonary hypertension could not be identified as a predictor of maternal outcome in two large studies on pregnancy outcome in women with heart disease [6,7]. This can be explained by the low prevalence of pulmonary hypertension in these two studies, which were carried out in western countries. Pulmonary hypertension is a rare condition in women of fertile age and, with the diagnosis, women are generally advised against pregnancy. In a Korean study on pregnancy in women with congenital heart disease, pulmonary hypertension was an independent predictor of maternal as well as of offspring outcome [8]. Pulmonary hypertension predicted the occurrence of heart failure during pregnancy in the European Registry on Pregnancy and Cardiac Disease [9].

Two previous systematic reviews described the outcome of pregnant women with pulmonary hypertension. The first review covered the years 1978–1996 and described 125 pregnancies. Maternal mortality was observed in 38% of these pregnancies and was 30% in primary pulmonary hypertension,

36% in Eisenmenger syndrome, and 56% in other causes of pulmonary hypertension [1]. The second review was published in 2009, covered the years 1997–2007, and included 73 pregnancies. Maternal mortality was 25%, which was significantly lower than in the previous era ($P = 0.047$). Women with idiopathic PAH had a mortality of 17%, mortality in women with pulmonary hypertension related to congenital heart disease was 28%, and, in women with other causes of pulmonary hypertension, it was 33% [3]. Most deaths occurred after delivery in both reviews. Causes of death were right ventricular failure, sudden death, and pulmonary thrombo-embolism. Independent predictors of maternal mortality were late diagnosis and late hospital admission in the early era. In the systematic review covering the years 1997–2007, maternal mortality was higher in primips and in women who delivered by caesarean section under general anaesthesia. Importantly, pulmonary artery pressure was not a predictor of outcome in both reviews. New York Heart Association (NYHA) functional class and the use of advanced pulmonary hypertension treatments (which was reported in 73% in the last review) were also not found to predict maternal outcome.

In many studies of pregnant women with underlying heart disease, NYHA class is, however, an established predictor of pregnancy outcome [6–10].

Two studies describing a total of 54 pregnancies have been published since the last review, which specifically focus on the severity of pulmonary hypertension, functional class, and their relationship to maternal outcome (Table 2) [11,12]. Women with mild pulmonary hypertension (systolic pulmonary artery pressure (sPAP) less than 50 mm HG or mPAP less than 40 mm Hg) had less increase in pulmonary arterial pressure during pregnancy, were more often in NYHA class I or II in early pregnancy ($P < 0.0001$), and deteriorated less often in NYHA class ($P < 0.0001$). A few people with mild PAH deteriorated from NYHA class II to class III/IV. Maternal mortality was surprisingly low in these two studies, with only two deaths in 54 women (4%). Both deaths were in women with severe pulmonary hypertension. Terminations and miscarriages are excluded from this analysis. In both studies, women with severe pulmonary hypertension delivered earlier than women with mild pulmonary hypertension, with the decision to deliver based on clinical or haemodynamic deterioration. These planned early deliveries may have contributed to the good outcome. Advanced treatments (e.g. prostacyclin analogues, phosphodiesterase inhibitors, and endothelin receptor antagonists [ERA]) were not available for the women in these two studies.

In a recent Chinese study of 30 pregnancies, maternal mortality was reported in 17%. In this study, only a few women were treated with targeted pulmonary hypertension treatments [13].

In another recent study describing 20 pregnancies and six terminations, a poor maternal outcome (death or transplantation) occurred in four out of the 20 pregnancies (20%) [14]. Women who died or

Table 2
New York Heart Association class, pulmonary pressures and time of delivery during pregnancy in two recent studies [11,12].

	Mild pulmonary hypertension	Severe pulmonary hypertension	
NYHA early to late in pregnancy	$n = 26$	$n = 28$	
I – I	19 (73%)	3 (11%)	
I – II	3 (12%)	–	
II – II	2 (8%)	–	
II – III/IV	2 (8%)	21 (75%)	
III – III/IV	–	4 (14%)	
sPAP (mm Hg) [11]	$n = 10$	$n = 14$	
Early pregnancy	39.3 ± 6.6	68.2 ± 11.1	
Late pregnancy	47.2 ± 9.2	95.8 ± 18.5	
sPAP (mm Hg) [12]	$n = 16$	$n = 14$	
Early pregnancy	40.4 ± 3.6	63.1 ± 7.6	
Late pregnancy	41.7 ± 4.1	71.6 ± 7.9	
Time of delivery (weeks)			
Katsuragi et al. [11]	$n = 10$	$n = 14$	
	36.4 ± 4.0	31.4 ± 2.8	$P < 0.005$
Subbaiah et al. [12]	$n = 16$	$n = 14$	
	37.3 ± 1.1	34.8 ± 1.7	$P < 0.05$

NYHA, New York Heart Association; sPAP, systolic pulmonary artery pressure.

required transplantation ($n = 4$) had higher mPAP than women who survived and delivered healthy babies ($n = 16$) (mPAP 71 ± 5 *v* 36 ± 15 mm Hg). Of note, all women that were responders to calcium channel blocker therapy ($n = 8$) had successful pregnancies. These women had near normal pulmonary pressures with calcium channel blocker therapy (mPAP 30 ± 6 mm Hg), and treatment was continued throughout pregnancy. Several other women used advanced pulmonary hypertension treatments [14].

In summary, these four recent studies seem to confirm an improved prognosis of pregnancy in women with pulmonary hypertension. In these studies, prognosis seems better in women with mild pulmonary hypertension, especially when they are in NYHA class I or when they have well-controlled pulmonary hypertension with calcium blocker therapy.

Outcome of termination of pregnancy and miscarriage has rarely been described. A recent prospective study of 26 pregnancies in women with pulmonary hypertension included six induced abortions, mainly in women with severe pulmonary hypertension. No complications occurred [14]. Another study included three miscarriages at 6–12 weeks of pregnancy; maternal outcome in these women was good [15].

Current therapeutic strategies in pulmonary hypertension

Therapeutic strategies in non-pregnant women vary with the clinical classification. Anticoagulation therapy is usually prescribed in women with idiopathic and inheritable PAH and PAH associated with anorexigens. It may also be considered in group 1.4 PAH depending on the underlying disease. In women with portal hypertension or Eisenmenger syndrome, the risk of bleeding is often elevated (e.g. oesophageal varices and haemoptysis), and the use of anticoagulation therapy is therefore controversial. Anticoagulation therapy is indicated lifelong in chronic thrombo-embolic pulmonary hypertension (group 4) [4]. When there is an established indication for anticoagulation therapy outside pregnancy, anticoagulation should be maintained during pregnancy [2]. Vitamin K antagonists are placenta-permeable, and are associated with embryopathy with a risk of fetal malformations in the order of 6% (dose-dependent) when used in the first trimester, whereas an additional risk of fetal intracranial bleeding occurs throughout pregnancy [16,17]. Low molecular weight and unfractionated heparin do not cross the placenta, and therefore can be used during pregnancy. They should be monitored and dosed according to factor anti-Xa levels or activated thromboplastin time (APTT), as dose requirements change considerably during pregnancy [2].

Diuretics are recommended in women with pulmonary hypertension when clinical signs of heart failure are present. During pregnancy, the widest experience is with furosemide and hydrochlorothiazide. Both cross the placenta but are probably not fetotoxic, although data in humans are limited. They may cause placental hypoperfusion and oligohydramnios. Spironolactone should be avoided because it is associated with anti-androgenic effects in male animal fetuses [2].

Current specific treatments for people with pulmonary hypertension include calcium channel blockers, ERA, phosphodiesterase inhibitors, and prostanoids. Calcium channel blockers are mainly reserved for women in group 1 (PAH) who show a positive response to vasoreactive testing. For non-responders, they are contra-indicated. Furthermore, they are not advised in Eisenmenger syndrome. Vasoreactivity is determined by exposure to nitric oxide, prostanoids, or adenosine during right heart catheterization. The most widely used calcium channel blocking agents in PAH are nifedipine and diltiazem. During pregnancy, nifedipine is routinely used to treat preterm labour and pre-eclampsia, and seems not to be associated with fetotoxicity when used in the second and third trimester of pregnancy. It is fetotoxic in animals, and human data on its use in the first trimester are scarce. It is tocolytic, and may cause placental hypoperfusion owing to hypotension. Diltiazem is fetotoxic in animals, and no controlled studies in humans have been conducted. A retrospective review, however, did not reveal important risks for the fetus. Both drugs should only be used in pregnant women when the benefit clearly outweighs the risk. It should also be borne in mind that higher dosages of these drugs are used in the treatment of pulmonary hypertension compared with other indications. Given the high maternal risk of pregnancy in women with pulmonary hypertension, however, these drugs, if possible, should be continued when there is an indication outside pregnancy. Endothelin receptor antagonists have a strong vasodilating and antiproliferative effect by blocking the effect of endothelin-1. The oral ERAs currently in use are bosentan and ambrisentan. They have shown to be beneficial by improving

exercise capacity and functional class in PAH group 1. Their use in pregnancy is contra-indicated, however, as serious teratogenicity has been seen in animals. They may also decrease the efficacy of hormonal contraceptives, and it is advised that two different methods of contraception are used to ensure that pregnancy does not occur. Phosphodiesterase-5-inhibitors lead to a prolonged vasodilatory effect of nitric oxide in pulmonary arteries. Phosphodiesterase-5-inhibitors affect pulmonary vascular tone and also have favourable effects on the myocardium, as they may block adrenergic, hypertrophic, and pro-apoptotic signalling. These oral medications have proven efficacy in increasing exercise tolerance, improving functional class, and delaying clinical worsening in PAH group 1. Sildenafil and tadalafil are the current agents in use. Sildenafil was not fetotoxic in animal studies, even at high doses, but human data are scarce. Tadalafil also seemed to be safe in animal studies. Prostacyclin derivatives are pulmonary and systemic vasodilators, and inhibit platelet aggregation. Epoprostenol needs to be administered as a continuous intravenous infusion, whereas treprostinil can also be given subcutaneously or as inhalation therapy. Iloprost is another agent that is administered by inhalation. The short half-life and the route and frequency of administration, is a disadvantage of these medications. When they are discontinued, for example because of failure of an infusion pump, severe rebound pulmonary hypertension can occur, especially with epoprostenol. Epoprostenol and iloprost are used in peoples with functional class III or IV. Treprostinil is also used in functional class II. Clinical benefits of prostacyclin derivates include improvement in mortality, exercise capacity, and functional class. Epoprostenol and treprostinil did not show fetotoxicity or teratogenicity in animal studies, but human controlled studies are not available. Iloprost is fetotoxic in animals, and human data are scarce. On the basis of these data, when prostacyclin derivates are indicated during pregnancy, theoretically epoprostenol and treprostinil are favoured over iloprost [2,4,5].

Systematic review of targeted pulmonary hypertension treatment and pregnancy outcome

We carried out a systematic review of the literature to analyse the outcome of pregnancy in women with pulmonary hypertension who had been treated with targeted pulmonary hypertension treatments (calcium channel blockers, nitric oxide, prostacyclin derivates, ERA, or phosphodiesterase inhibitors).

Methods

We reviewed the published studies on the treatment of women with pulmonary arterial hypertension during pregnancy using the guidelines of the PRISMA-statement protocol (available at www.prisma-statement.org). The inclusion procedure is shown in Fig. 1. We carried out an extensive *MedLine* public database search for literature concerning pulmonary (arterial) hypertension and pregnancy, as described in Fig. 1. We limited the publication dates from 1 January 1998 up to the date last searched 19 September 2013 to minimise inclusion of obsolete treatments. The filters 'Humans', 'Female', 'Adolescent: 13–18 years', 'Adult: 19 + years', 'Adult: 19–44 years' (to include only patients of fertile age) were activated. On the basis of the reviewers' language skills, only articles written in Dutch, English and German were included. Duplicates were removed, and articles identified through other resources (i.e. cross-referencing) were added. Articles were screened according to abstract and title. Studies not addressing pulmonary hypertension in pregnant women were excluded. Subsequently the remaining full-text articles were screened and included or excluded (Fig. 1). Reasons for exclusion were inadequate end points, review article or comment without original cases, no targeted pulmonary hypertension treatment, article not available, or inconsistent data. Additionally, four publications were excluded because of insufficient individual patient data to allow analysis; these publications have been discussed separately [11–14]. Publication bias and selective reporting within studies could not be minimised. We excluded miscarriages and pregnancy terminations. To allow comparison with previous reviews, we classified individuals as idiopathic PAH (IPAH) (when no specific cause could be identified), pulmonary hypertension associated with congenital heart disease, including Eisenmenger syndrome (CHD-PAH) or pulmonary hypertension with other causes (oPH) (e.g. pulmonary hypertension associated with connective tissue disease, medication, human immunodeficiency virus, and chronic pulmonary thrombo-embolism) [1,3]. Pulmonary hypertension group 2 and 3 were not included as

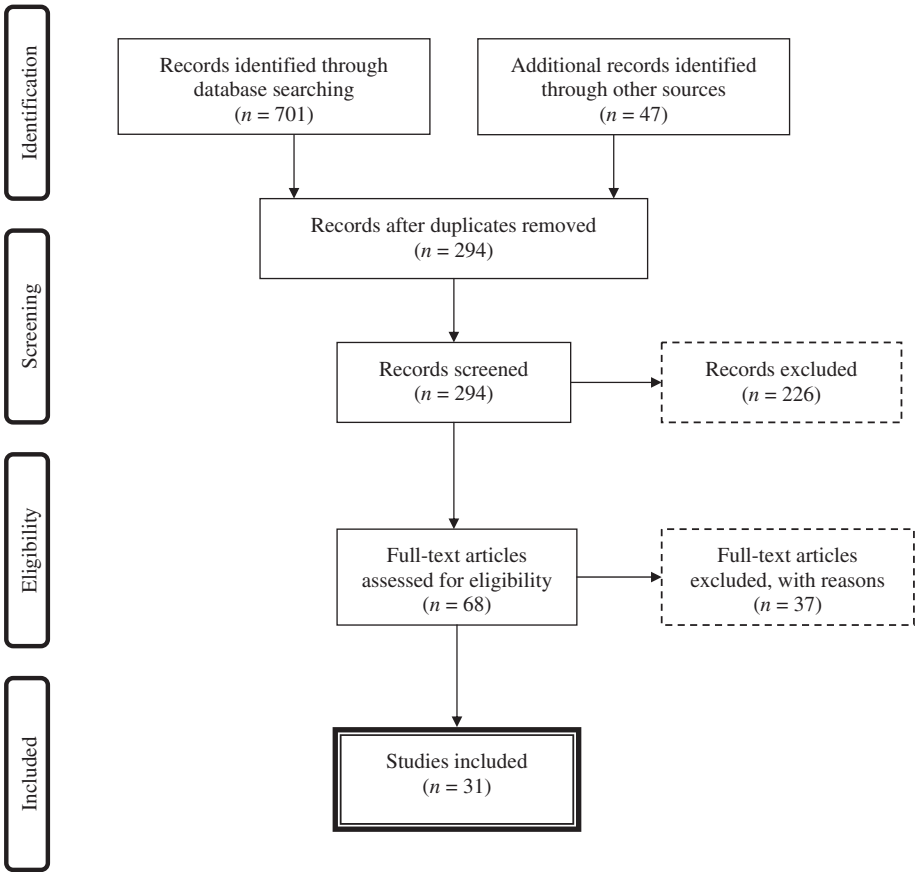

Fig. 1. Inclusion and exclusion of publications for systematic review on pregnancy in women using targeted pulmonary hypertension pregnancies. *MedLine* public database search for literature concerning pulmonary (arterial) hypertension and pregnancy included the following Mesh terms: ('Pulmonary arterial hypertension' (supplementary concept) AND 'Pregnancy'[Mesh]) AND 'Therapeutics'[Mesh] and 'Hypertension, Pulmonary'[Mesh] AND 'Pregnancy'[Mesh]) AND 'Therapeutics'[Mesh], and full text search. Additionally, a full text search was conducted on treatment for pulmonary (arterial) hypertension in pregnancy: 'Pulmonary hypertension' AND 'pregnancy' AND 'treatment'; 'Pulmonary hypertension' AND 'pregnancy' AND 'therapy'; 'Pulmonary arterial hypertension' AND 'pregnancy' AND 'therapy'; 'Pulmonary arterial hypertension' AND 'pregnancy' AND 'treatment'. Furthermore, a full text search was conducted specifically for the use of prostacyclin derivates, endothelin receptor antagonists, phosphodiesterase-5-inhibitors, and calcium antagonists during pregnancy in women with pulmonary (arterial) hypertension (i.e. 'Pulmonary arterial hypertension' AND 'pregnancy' AND 'prostacyclin'); 'Pulmonary hypertension' AND 'pregnancy' AND 'prostacyclin'.

PAH-specific treatment is not indicated for these forms of pulmonary hypertension. We collected data on cause of pulmonary hypertension, sPAP, mPAP, medication including targeted pulmonary hypertension medication, start of pulmonary hypertension medication (weeks of pregnancy), time of delivery, mode of delivery, functional class, maternal, and fetal death. For comparison with outcomes of previous reviews, Fisher's exact test was used. P-values were two-sided and a p-value of less than 0.05 was considered significant.

Results

We included 31 studies with 77 parturients who were treated with targeted pulmonary hypertension treatments [15,18–48]. Mortality occurred in 12 women (16%). In the IPAH group ($n = 32$), three women (9%) died, in the CHD-PAH group ($n = 30$) seven women (23%) died, and mortality in the oPH group ($n = 15$) was 13% ($n = 2$). Details of the women that died are provided in Table 3. Most deaths

Table 3
Women who died during pregnancy.

Patient study	Aetiology presentation	sPAP mm Hg	Pulmonary hypertension treatment start	Delivery weeks, mode	Death (details)	Fetal outcome
Patient 1: Curry et al., 2012 [15]	CHD Pre-pregnancy	104	Iloprost postpartum	26, caesarean section	15 days postpartum	Survived; birthweight 620 g
Patient 2: Curry et al., 2012 [15]	CHD Pre-pregnancy	60	Diltiazem pre-pregnancy	36, caesarean section	Delivery (SVT at oxytocin)	Survived; birthweight 2570 g
Patient 3: Easterling et al., 1999 [19]	IPAH 28 weeks	75	Prostacyclin	–	8 h after diagnosis	Died *in utero* with mother
Patient 4: Goodwin et al., 1999 [22]	CHD 36 weeks	90	Nitric oxide inhalation 36 weeks	36, vaginal	5 days postpartum	Survived; birthweight 2640 g
Patient 5: Lust et al., 1999 [25]	CHD 26 weeks	85	Nitric oxide inhalation; delivery prostacyclin 2 weeks postpartum	34, vaginal	3 weeks postpartum	Survived; birthweight 1823 g
Patient 6: Duarte 2013 [28]	CHD –	126	Epoprostenol Week 27	28, caesarean section	6 weeks postpartum	Survived –
Patient 7: Kiely et al., 2010 [42]	IPAH 9 weeks	150	Iloprost intravenous week 14, inhalation week 34	34, caesarean section	4 weeks postpartum, stopped medication	Survived; birthweight 1580 g
Patient 8: Monnery et al., 2001 [43]	IPAH 28 weeks	100	Nitric oxide, inhalation delivery post-partum inhalation/intravenous iloprost	32, caesarean section	2 weeks postpartum	Survived –
Patient 9: McMillan 2002 [44]	oPH 16 weeks	32 (during pregnancy 80)	Nitric oxide inhalation; Delivery	31, caesarean section	<1 day postpartum	Survived; birthweight 1500 g
Patient 10: McMillan et al., 2002 [44]	oPH 7 weeks	55	Nitric oxide inhalation, prostacyclin intravenous; both at delivery	32, caesarean section	<1 day postpartum	Died; birthweight 1860 g
Patient 11: Rosengarten et al., 2012 [47]	CHD	–	Epoprostenol intravenous sildenafil; start unknown[a]	34, caesarean section	<2 weeks postpartum	Survived –
Patient 12: Rosengarten et al., 2012 [47]	CHD	mPAP 50	Iloprost inhalation, sildenafil; start unknown[a]	34, caesarean section	<2 weeks postpartum	Survived –

[a] Medication was started during pregnancy and not at delivery; CHD, congenital heart disease; IPAH, idiopathic pulmonary hypertension; mPAP, mean pulmonary arterial pressure; oPH, other cause of pulmonary hypertension; sPAP, systolic pulmonary artery pressure; SVT, supraventricular tachycardia.

occurred postpartum ($n = 10$, 83%). Two deaths were at 28 weeks of pregnancy and during delivery. Causes of death were known in 10 women, in seven of them right ventricular failure was involved, one woman died of sepsis, one died suddenly at home, and one died during delivery owing to intractable tachycardia after a bolus of oxytocin. Offspring death occurred only in three pregnancies (4%), and, in two of those pregnancies, the mother also died. Comparison with the review of Weiss showed a significant decrease in total mortality from 38% to 16%; $P = 0.0005$ [1]. Mortality decreased significantly in patients with oPH but, in the subgroups with CHD-PAH and IPAH, the decrease in mortality was not significant. No significant differences were reported in mortality compared with the review of Bedard et al. [49], but there was significant overlap in inclusion (Table 4). Calcium channel blockers were used in 13 women and were the only targeted treatment in five of these women. Prostacyclin derivates were the most common used targeted medication ($n = 61$). Sildenafil was given in 26 women and nitric oxide inhalation therapy in 10 women. Bosentan was used before pregnancy and discontinued in three women, two women continued this medication throughout pregnancy, and nine women started with

Table 4
Mortality in women with pulmonary hypertension: comparison of three reviews.

	Weiss et al. [1] (1978–1996)	Bedard et al. [3] (1997–2007)	Current systematic review (1998–2013)
Total mortality	48/125 (38%)	18/73 (25%)	12/77 (16%)
Mortality, IPAH	8/27 (30%)	5/29 (17%)	3/32 (9%)
Mortality, CHD-PAH	26/73 (36%)	8/29 (28%)	7/30 (23%)
Mortality, oPH	14/25 (56%)	5/15 (33%)	2/15 (13%)

CHD-PAH, pulmonary arterial hypertension associated with congenital heart disease; IPAH, idiopathic pulmonary arterial hypertension; oPH, other cause of pulmonary hypertension.

bosentan after pregnancy. More than one targeted pulmonary hypertension therapy was used in 30 women (39%). In 65 pregnancies (83%), anticoagulation therapy was given, most often low molecular weight heparin. Thirteen women were only receiving targeted pulmonary hypertension therapies during their deliveries, postpartum, or both. Six of these women died (46%), compared with 9% in the group of women in which targeted pulmonary hypertension therapy was started at least a week before their deliveries ($P = 0.017$). One of the six women that died and had received targeted therapy only at delivery or postpartum, presented at delivery, and could therefore not have received earlier treatment. In 70 women, the severity of pulmonary hypertension was reported, 16 women had mild pulmonary hypertension (mPAP $\leq$ 35 mm Hg or [when mPAP was unknown] sPAP $\leq$ 50 mm Hg), and 54 women had severe pulmonary hypertension. One of the women with mild pulmonary hypertension died (6%), and 10 women with severe pulmonary hypertension died (19%) (non-significant).

Conclusions

Our data confirm an ongoing decrease in maternal mortality in all subgroups of pregnant women with pulmonary hypertension. Despite this decrease, mortality remains high and is especially high postpartum. Interestingly, mortality has also decreased in those women not receiving targeted pulmonary hypertension therapies. Recent studies reporting the outcome of pregnant women with pulmonary hypertension in countries in which advanced pulmonary hypertension therapies were not available, also documented lower mortality than in previous years [11–13]. Early planned delivery may have contributed to improved outcome in these studies. Initiation of targeted pulmonary hypertension therapy well before delivery seemed to contribute to favourable outcome in our review. Although on average women with mild pulmonary hypertension have less increase in pulmonary pressures during pregnancy compared with women with severe pulmonary hypertension. Some studies reported that women with mild pulmonary hypertension did better than women with severe pulmonary hypertension, mortality was not significantly reduced in women with mild pulmonary hypertension in our review. Offspring mortality seems to be related to maternal mortality.

Management of reproductive issues in women with pulmonary hypertension

Although mortality has decreased over time, it is still high, and it is difficult to identify women who have a lower risk. Therefore, in line with current guidelines, all women with established pulmonary hypertension should be advised against pregnancy [2]. This also implies that girls and women must be informed about safe and effective contraception [50]. Barrier methods such as condoms, diaphragms, and cervical caps, give protection against sexual transmittable diseases, and do not have health risks, but their high failure rate with typical use (15–30%) makes them an inappropriate contraceptive for women with pulmonary hypertension. Combined contraceptives containing both oestrogen and progestogen (e.g. oral, vaginal ring [Nuvaring], and transdermal patch) are contra-indicated in women with pulmonary hypertension because of their association with thrombo-embolic complications. The progesterone only pill (desogestrel 0.075 mg) is effective but requires excellent compliance. The etonogestrel-releasing subdermal implant is one of the most effective contraceptives available. Bruising at implantation can occur in women taking anticoagulant therapy, but is rarely serious short-term discontinuation of anticoagulation may be considered.

Three-monthly medroxyprogesterone-acetate intramuscular injections are also effective and safe for women with pulmonary hypertension, though bruising can also be a problem. All progestogen-only contraceptives have the disadvantage of irregular vaginal blood loss. Intra-uterine devices have a low failure rate. Their main disadvantages are heavy bleeding (copper spiral) or irregular bleeding (levonorgestrel-releasing device), and the risk of a vaginal reaction at insertion, which may be poorly tolerated in women with pulmonary hypertension, especially in women with Eisenmenger syndrome. Implantation should therefore take place in a hospital setting [5,50].

Endothelin receptor antagonists reduce the effectiveness of oral contraceptives; therefore, use of an additional contraceptive method is advised.

When women with pulmonary hypertension become pregnant, termination of pregnancy is recommended [2]. As termination is in itself associated with considerable risks in these women, it needs to be carried out in a tertiary centre, with involvement of an experienced multidisciplinary team (e.g. pulmonary hypertension specialist as well as an anaesthetist and gynaecologist).

When a woman chooses to continue the pregnancy, it is mandatory that she is immediately referred to an expert pulmonary hypertension centre, and is treated by a multidisciplinary team starting early in pregnancy. The team should comprise pulmonary hypertension specialists as well as a cardiologist, obstetrician, and cardiac anaesthetist who have experience in treating cardiac high-risk pregnancies [2,5,51]. Oxygen therapy has no proven benefit on pregnancy outcome, but should be applied when hypoxaemia is observed. Restriction of physical activity is advisable. Anticoagulation therapy is given on an individual basis: when it is indicated outside pregnancy it should be continued, but when there is bleeding risk (e.g. Eisenmenger syndrome with risk of haemoptysis, esophageal varices) the risk may outweigh the benefit. Vitamin K antagonists can be replaced by low molecular weight heparin with monitoring of anti Xa levels, especially in the first trimester and the last month of pregnancy. Heart failure is treated with diuretics. Iron deficiency should be treated, but, in women with Eisenmenger syndrome, caution is required. Iron depletion may result in these patients in microcytosis which increases blood viscosity; therefore, iron deficiency should be treated with judicious iron supplementation to maintain erythrocyte mean corpuscular volume. Targeted pulmonary hypertension therapies used before pregnancy should be continued, but it is usually recommended that ERAs, which are teratogenic, are stopped and replaced by other medications (usually prostacyclin or sildenafil) [52]. The European Guidelines do, however, advise that ERA may be continued after counselling the woman about their possible teratogenic effects [2]. On the basis of current published research, it is not possible to give strong recommendations about the optimal timing to start pulmonary hypertension targeted therapies in women who have not previously used them. In many reports, medications were commenced at the end of the second trimester or during the third trimester. The literature strongly suggests, however, that use of these treatments only during delivery and postpartum is associated with worse outcome than if they were started early. We, therefore, recommend initiating these medications preferably at least 3 months before delivery, but earlier when clinically indicated, as optimal treatment effect may only be reached after a 3-month period. Good results have been described both with inhaled and intravenous prostacyclin, and also with sildenafil. It is important that medication is continued postpartum for a prolonged period, because maternal deaths can occur several months after delivery. The postpartum medication can include ERAs, but again this should be individualized on the basis of pulmonary pressures and clinical status.

Research gives us reason to believe that a planned early delivery at 32–34 weeks, before any clinical deterioration, is an important contributor to good outcome [11,12,42]. Later delivery (34–37 weeks) may be possible in completely stable women who have mild pulmonary hypertension without further elevation of pulmonary pressures during pregnancy. Vaginal delivery is not contraindicated; however, early delivery often necessitates a caesarean section in many cases. In the review of Bedard et al. [3] general anaesthesia was associated with worse outcome than epidural or spinal anesthesia. This may be because women receiving general anaesthesia had more severe disease, but negative effects of general anaesthesia include an increase in pulmonary pressures and cardiodepression [3]. Probably expert application of epidural or a combination of epidural and spinal anaesthesia is the best option for these women. During delivery, monitoring of haemodynamics (e.g. heart rate, blood pressure, oxygen saturation) is required, but the benefit of invasive monitoring of pulmonary artery pressures is debatable.

After delivery, the woman should be observed and treated in a critical care unit for several days and remain hospitalised for at least 2 weeks. After discharge, frequent clinical and echocardiographic evaluation is advised, as the months after delivery are a period with increased risk of maternal death [2,5,51,53].

Practice points

- Pulmonary hypertension in pregnant women is associated with high mortality and morbidity, despite significant improvement in prognosis in the past 2 decades.
- Women with pulmonary hypertension should be advised against pregnancy.
- When women with pulmonary hypertension are pregnant and choose to continue their pregnancy, management by a multidisciplinary team in an expert centre is mandatory.
- Early institution of targeted PAH therapy and early planned delivery may contribute to improved outcome.
- Women with mild pulmonary hypertension or favourable functional class may have a better prognosis, but as no proof of lower mortality is yet available, they should still be advised against pregnancy.

Research agenda

- Multicentre research to confirm value of early start of targeted PAH therapy and investigate the value of combination of phosphodiesterase inhibitors and prostacyclin analogues.

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