Policy Directive

Women and Babies: Persistent Pulmonary Hypertension of the Newborn (PPHN)

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Functional Sub-Group: Clinical Governance

Summary: Babies with persistent pulmonary hypertension will undergo early diagnosis and appropriate management

National Standard: Standard 1: Governance for safety and quality in Health service organisations
                     Standard 9: Recognising and responding to clinical deterioration in acute health care

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Approved by: General Manager
             RPA Women and Babies Service Improvement Committee

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Persistent Pulmonary Hypertension of the Newborn

CONTENTS

1. Introduction

2. Policy Statement

3. Principles/Guidelines
   3.1 Definitions 3
   3.2 Incidence 4
   3.3 Risk Factors 4
   3.4 Pathophysiology 4
   3.5 Clinical diagnosis 5
   3.6 Echocardiographic diagnosis 5
   3.7 Interventions 6
   3.8 Outcomes 12


5. Key points 14

6. References 14
Persistent Pulmonary Hypertension of the Newborn

1. Introduction

The risks addressed by this policy:

Potential serious morbidity and mortality associated with lack of recognition of PPHN

The aims / expected outcome of this policy

Persistent pulmonary hypertension will be recognised early, diagnosed and appropriately managed

2. Policy Statement

The goal of this policy is to identify babies with pulmonary hypertension and to commence therapy immediately and appropriately. The therapeutic goal should be to avoid hypoxia.

3. Guidelines

3.1 Definition:

During fetal life, the placenta serves as the organ of gas exchange. Blood flow in the pulmonary circulation remains highly restricted by hypoxic pulmonary vasoconstriction of the small pulmonary arteries. This is reversed at birth due to the sudden increase in lung oxygenation when the newborn takes their first breath. The first few breaths induce a rapid decrease in pulmonary vascular resistance and an increase in pulmonary vascular flow with lung expansion.1

Classically, PPHN is defined as the failure of the normal postnatal fall in pulmonary vascular resistance which leads to the persistence of right to left shunts across the fetal channels (ductus arteriosus and foramen ovale) and resultant hypoxia.2 This is a simplified view of what is a complex condition and in many babies the major shunt is occurring at an intrapulmonary level.2 It is important to think of PPHN as primary or secondary.3

- **Primary PPHN** is the form of PPHN which most closely fits the classical definition, typically presenting soon after birth with hypoxaemia in a baby with clinically and radiologically normal lungs.3 This condition is probably due to a primary dysfunction in the pulmonary endothelial vasodilating mechanisms.4
• **Secondary PPHN** is PPHN which is secondary to a disease in the parenchyma of the lungs. This is over-diagnosed and while most babies with lung disease will have pulmonary artery pressures above normal, only the sickest (oxygenation index >25 in term babies or >15 in preterm babies) will consistently have pulmonary pressures close to or above systemic pressures. In these babies the pulmonary vasoconstriction is probably secondary to hypoxia, acidosis and high ventilatory pressures.

3.2 Incidence:

PPHN is an uncommon condition and mainly affects term or post-term babies; however, may be present in the preterm infant. The incidence reported in the UK ranges from 0.4 – 0.68/1000 live births. In a study in 12 major North American Centres, the incidence is reported as 1.9/1000.

3.3 Risk Factors:

• **Primary PPHN** is usually idiopathic in origin. It is often associated with a variety of complications of pregnancy including maternal diabetes, maternal hypertension, obesity and post maturity. It has also been described in association with polycythaemia, fetal anaemia and premature ductal closure.

• **Secondary PPHN**
  
  o **Respiratory:** Meconium aspiration, respiratory distress syndrome, Transient Tachyypnea of the Newborn (TTN), pneumonia, bronchopulmonary dysplasia, congenital diaphragmatic hernia, capillary alveolar dysplasia, surfactant deficiency, pulmonary interstitial lymphangiectasia
  
  o **Non-Respiratory:** Sepsis, Hypoxic Ischaemic Encephalopathy, drugs (Selective Serotonin Reuptake Inhibitors (SSRIs)), Vein of Galen,

3.4 Pathophysiology:

The pathophysiology of PPHN is complex and related to the causes of increased pulmonary vascular resistance in the perinatal period. Some of the factors include

1. Vasoconstriction
2. Pulmonary vascular remodelling
3. Pulmonary vascular hypoplasia
4. Obstruction
5. Pulmonary parenchymal pathology
6. Iatrogenic factors
7. Right ventricular myocardial dysfunction
3.5 Clinical Diagnosis:

- Primary PPHN presents in the early postnatal period as cyanosis where the level of hypoxia is disproportionate to the degree of respiratory distress. The clinical presentation closely mimics that of cyanotic congenital heart disease. There may be differential cyanosis between upper and lower body, clinically and on blood gases. The lung fields are often clear or minimally opacified on X-ray. The degree of hypoxia is variable and the pCO₂ is normal or sometimes low.
- Secondary PPHN presents primarily as respiratory distress, often with respiratory failure and the need for high ventilator pressures and increasing oxygen requirements. The CXR is mostly abnormal, in keeping with the underlying respiratory condition.

Infants with PPHN may have a prominent precordial impulse, loud second heart sound, a systolic parasternal murmur due to tricuspid incompetence and a large cardiac shadow on chest x-ray.

3.6 Echocardiographic diagnosis: 

This allows accurate diagnosis of PPHN and should be done as soon as practical in the clinical course. The benefits of echocardiography include the following:

- The ability to exclude congenital heart disease.
- The ability to define the pulmonary artery pressure using tricuspid incompetence or ductal shunt velocities.
- Define the presence, degree and direction of shunt through the ductus arteriosus and foramen ovale. These shunts are often less than is assumed, firstly because pulmonary pressures are subsystemic and secondly because both fetal channels particularly the ductus close early in the course of the disease.⁴
- Define the ventricular outputs. These are commonly very low in the early course.⁴ Sehgal⁸ et al demonstrated global myocardial dysfunction in infants with pulmonary hypertension with low right and left ventricular outputs in the majority of babies. Left ventricular output < 100ml/kg/min indicates a high risk of mortality.⁴¹

On point of care cardiac ultrasound the following are indicative of pulmonary hypertension:

- Pulmonary pressures equivalent or greater than systemic pressures measured on the TR jet using continuous wave doppler⁴³
- Pulmonary Artery Time to peak velocity to Rv ejection time ratio < 0.2
- Reduced LPA velocity – low velocities are predictive of good response to iNO
- The direction and velocity of the ductal shunt – a right to left shunt for more than 30% of the cardiac cycle indicates that Pulmonary Artery Pressure (PAP) is higher than systemic pressure. ⁴²
3.7 Interventions:

The aim of treatment is to maintain normal arterial oxygen levels and normal oxygen delivery to the organs of the body. The two most potent natural pulmonary vasodilators are oxygen and lung inflation.

3.7.1. Oxygen

This will help to maintain arterial oxygen levels and will act as a pulmonary vasodilator. However animal data would suggest that optimal pulmonary vasodilation occurs with a $p_{aO_2}$ around 100mmHg; however it does depend on whether there is an associated acidosis. No benefit is likely from higher levels of inspired oxygen which may also contribute to secondary lung injury. Therefore maintain saturations in the normal range (95-100%), aiming to maintain $p_{aO_2}$ between 60-100 mmHg in term infants.

3.7.2. Conventional ventilation

This is the mainstay of respiratory support; the principles will be much as described for ventilation of preterm babies but with the following differences.

- Muscle relaxants should be reserved for newborns where there is difficulty establishing adequate ventilation despite good sedation.
- To maintain normal blood gases it is sometimes necessary to achieve higher than usual tidal volumes (up to 6mls/kg). Oxygenation is often very sensitive to small reductions in minute volume such as can occur with retained secretions or handling.
- Aim to maintain normal $p_{CO_2}$ in the range 35 to 40 mmHg, $p_{CO_2}$ lower than this may cause cerebral vasoconstriction. Hypercarbia leads to pulmonary vasoconstriction and should be avoided.

3.7.3. High Frequency Oscillatory Ventilation (HFOV):

A review of randomised studies comparing HFOV with conventional ventilation in babies with severe hypoxic respiratory failure has shown no differences in mortality, chronic lung disease or air leak. In a proportion of babies HFOV allowed for better oxygenation by allowing better lung inflation and "alveolar recruitment". In babies with secondary PPHN and underlying lung parenchymal disease HFOV improves oxygenation and reduces right to left extrapulmonary shunting due to aggressive lung recruitment. HFOV should not be started without senior consultation and supervision.

3.7.4. Inotropes:

The role of inotropes in PPHN is poorly substantiated. Low ventricular outputs are common in these babies however it is not clear that this is due to primary pump failure. Observational studies here and elsewhere have suggested that low output may reflect the right ventricle struggling with a high afterload to get blood through the lungs, which in turn causes a low left ventricular output. In animal studies, dopamine has similar vasoconstrictor activity on the pulmonary as on the systemic vasculature, so at an empirical level, dobutamine is the
preferred inotrope starting at 10 µ/kg/min. Noradrenalin improves oxygenation in infants with PPHN through a decrease in pulmonary systemic artery pressure ratio and improved cardiac performance.  

<table>
<thead>
<tr>
<th>Inotrope</th>
<th>Effects</th>
<th>Dosage</th>
<th>Unwanted Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>Improves cardiac output</td>
<td>2.5-20µg/kg/min</td>
<td></td>
</tr>
<tr>
<td>(first line)</td>
<td>Little peripheral vascular effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenalin</td>
<td>Improves cardiac output through inotropic effect</td>
<td>0.05-1µg/kg/min</td>
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<td>(second line)</td>
<td>Increases BP (α effect)</td>
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</tr>
<tr>
<td>Noradrenalin</td>
<td>Improves cardiac output through inotropic effect</td>
<td>0.05-1µg/kg/min</td>
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<tr>
<td>(second line)</td>
<td>Increases BP (α effect)</td>
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<tr>
<td></td>
<td>Improvement in pulmonary blood flow secondary to the release of endothelial nitric oxide</td>
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</tr>
<tr>
<td>Dopamine</td>
<td>Increases myoccardial contractility, BP and cardiac output</td>
<td>1-20µg/kg/min</td>
<td>Increase in systemic and pulmonary pressure at high doses</td>
</tr>
<tr>
<td>(third line)</td>
<td>Increased systemic vascular resistance</td>
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### 3.7.5. Vasodilators:

**A. Nitric oxide (NO)**

- Nitric oxide (NO) is a naturally occurring vasodilator which is present in the vascular endothelium of all the tissues of the body. At a cellular level it works by activating guanylate cyclase leading to an increase in the production of cyclic GMP which in turn relaxes vascular smooth muscle. It is rapidly inactivated in the blood stream with production of methaemoglobin and inorganic nitrates and nitrites. Due to these properties, when it is given by inhalation (iNO) it dilates the pulmonary blood vessels in ventilated lung, reducing pulmonary vascular resistance, increasing pulmonary blood flow and improving ventilation
perfusion mismatch without having any significant effect on the systemic vasculature. It is the vasodilator of choice in term babies with persistent pulmonary hypertension.

- It has a rapid onset of action, typically within minutes. The safety and efficacy of iNO for PPHN in term infants has been studied through randomised controlled trials and demonstrates that:
  - iNO significantly improves oxygenation. 15-21
  - iNO significantly reduces the need for rescue with ECMO. 16,17
  - The use of iNO in PPHN does not reduce mortality, length of hospitalisation, chronic lung disease or alter neurodevelopmental outcomes

- The role of iNO in preterm babies is inconclusive. The Cochrane review by Barrington & Finer included 9 trials which were categorized into: early rescue, early prophylactic and late therapy groups. iNO used as rescue therapy in the very ill preterm infant was ineffective and if used early for RDS does not improve survival; however was not harmful (no increase in neurodevelopmental disability or IVH). There is some evidence to suggest that later use of iNO to prevent BPD may be useful however, more studies need to be done. 34

- Prescribing Nitric Oxide
  - iNO is registered with the Australian Therapeutic Goods Administration (TGA). It needs to be prescribed on the medication chart. Start and stop times as well as dosage changes must be charted accurate
- **Indications for iNO in term and preterm babies**

<table>
<thead>
<tr>
<th>Term infants</th>
<th>Preterm infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxic respiratory failure with paO2 &lt; 60mmHg or sats &lt;90% despite maximal respiratory support and FiO2&gt;80%</td>
<td>Hypoxic respiratory failure with paO2&lt;50mmHg or sats &lt;90% despite maximal respiratory support and FiO2&gt;80% with echocardiographic evidence of pulmonary hypertension and low cardiac output</td>
</tr>
<tr>
<td>A ventilated baby with FiO2&gt;50% with echocardiographic evidence of pulmonary hypertension +/- low cardiac output</td>
<td></td>
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</table>

  - Observational studies have demonstrated that preterm infants with respiratory failure born after prolonged rupture of membranes with oligohydramnios benefit from the early use of iNO. 33,35

- **Contra-indications**
  - Major Cardiac anomalies
  - Lethal congenital anomalies

  iNO should not be routinely used in infants with congenital diaphragmatic hernia. 46 Previous studies demonstrated that there was an increase in the need for ECMO without a reduction in the mortality in the babies on iNO.

- **Dosage**
  - Term babies start at 10ppm increasing to 20ppm depending on the response.
  - Preterm infants start at 5ppm and increase to 10ppm depending on response.
  - There is no consistent evidence of a dose response effect with iNO and therefore attempts should be made to reduce the dose to the minimal effective dose. If a trial of increased dose does not have any benefit in oxygenation or haemodynamics then reduce the dose.
Complications
- Methaemoglobinaemia
  - iNO can cause methaemoglobinaemia although unlikely at a dose of 20ppm. Preterm infants are more susceptible because of relatively low levels of the enzyme methaemoglobin reductase. Methaemoglobin levels should be checked every 24 hours (≤20ppm); every 12 hours if on higher doses. All infants should be monitored (MetHb monitor). If levels > 5 % iNO should be reduced or stopped.

Weaning
- There is little evidence to guide the best method of weaning iNO. The aim should be to deliver the minimum dose compatible with normal oxygenation and haemodynamics
  - In term babies there is an advantage in maintaining a low dose of NO (1-2ppm) while oxygen and ventilator pressures are weaned, especially if there is echocardiographic evidence of raised pulmonary artery pressures.
  - FiO2 should be increased prior to discontinuation of iNO therapy
  - In preterm infants wean as quickly as possible

iNO delivery system
- At RPA we use the iNOmax DSIR (Ikaria) nitric oxide delivery set up

B. Sildenafil
- Sildenafil is a phosphodiesterase 5 inhibitor which results in vasodilation by selectively reducing pulmonary vascular resistance. Sildenafil is safe and easy to administer; it is available in an IV and oral preparation and is relatively inexpensive. Enteral administration and gastro-intestinal absorption may be impaired in critically ill patients. A pilot study of intravenous sildenafil demonstrated that it was well tolerated with improved oxygenation in some infants. A randomised control trial evaluating the efficacy of intravenous sildenafil is currently underway.
- There is a lack of evidence to support sildenafil use in persistent pulmonary hypertension in preterm infants.
- Consider Sildenafil in the following circumstances
  - Proven severe PPHN not responding to adequate ventilation and iNO (limited observational data suggests additional benefit)
  - Failed attempt to wean iNO
o Dosage
  ▪ 0.5-2mg/kg/dose 6 hourly

C. Milrinone
  o Milrinone causes pulmonary vasodilation by inhibiting phosphodiesterase 3. Milirone is reported to decrease rebound pulmonary hypertension when iNO is ceased. It has inotropic effects and is also effective in reducing the afterload by improving right sided cardiac output. Milrinone led to better oxygenation and improvement in pulmonary and systemic haemodynamics in patients with suboptimal response to iNO. The safety and efficacy has not been confirmed in a RCT and therefore it is not routinely used at RPAH.

D. Magnesium Sulphate
  o There is insufficient evidence to support its use in PPHN.

E. Bosentan
  o Bosentan is an orally active dual endothelin receptor antagonist which reduces Peripheral Vascular Resistance (PVR) and pulmonary arterial pressure in pulmonary hypertension in adults. A recent randomised controlled trial demonstrated that bosentan was superior to placebo (p<0.0001) as an adjuvant therapy of PPHN in neonates. All the trials have been done in low-income settings where iNO and ECMO are not readily available. Bosentan is not used at RPAH.

3.7.6. Extracorporeal membrane oxygenation (ECMO)

Since the introduction of iNO and HFOV, together with surfactant, the need for ECMO in PPHN has declined considerably. However the UK collaborative trial showed a significant reduction in mortality with ECMO treatment in babies with an oxygenation index >40. In babies with an OI >40 despite iNO and HFOV, transfer to a paediatric intensive care for ECMO should be considered. All potential referrals should be discussed with the Paediatric Intensivist at SCH or The Children’s Hospital Westmead.

Selection Criteria
  1. Respiratory failure
  2. OI > 40 for 4 hours (OI=(MAP x FiO2 x 100)/PaO2)

Exclusion Criteria (Absolute)
  1. < 2.5kg for V-V ECMO and < 1.8kg for V-A ECMO
  2. Major intracranial haemorrhage (Grade 3 or 4)
3. Severe neurologic injury
4. Lethal malformation

Exclusion Criteria (Relative)\textsuperscript{43}
1. < 34 weeks gestation
2. Mechanical ventilation > 14 days
3. Uncontrolled coagulopathy
4. Grade 1/2 IVH
5. Overwhelming sepsis
6. Syndrome with poor prognosis
7. Congenital diaphragmatic hernia with pre-ductal sats < 90% during resuscitation or stabilisation
8. Malignancy

Acidosis, prematurity and profound hypoxemia are independently associated with an increased mortality. \textsuperscript{29}

3.8 Outcomes

Persistent pulmonary hypertension of the newborn has a 10-20\% mortality. Survivors have significant morbidities including cognitive delays, hearing loss and risk of rehospitalisation. \textsuperscript{30,31} The use of iNO in PPHN did not alter neurodevelopmental and social/emotional/behavioural outcomes compared with infants who were not exposed to iNO \textsuperscript{32}
4. Management of Pulmonary Hypertension of the Newborn

Clinically suspected PPHN

Point of care cardiac ultrasound
- Confirm PPHN
- Exclude congenital cardiac disease
- Define SVC, RVO and LVO flows

Adequately oxygenate and ventilate – conventional ventilation/HFOV
- Maintain normal saturations (95-100%); PaO₂ 60-100mmHg
- PaCO₂ normal range

Add inotropes if hypotensive, pulmonary pressures are significantly suprasystemic or low systemic blood flow*
- First line – dobutamine
- Second line – adrenalin/noradrenalin
- Third line – dopamine

Add pulmonary vasodilator if ongoing hypoxic respiratory failure
- Inhaled NO

Consider ECMO if OI^ remains > 40 despite HFOV, iNO and Sildenafil

*RVO and LVO < 150mls/kg/min; SVC< 50mls/kg/min

^Oxygenation Index = (FiO₂ x Mean Airway pressure)/ PaO₂
5. **Key points**

| Optimal alveolar recruitment should be established prior to initiation of iNO therapy | Level of evidence 1b  
|---|---|---|---|
| Nitric oxide (NO) is the vasodilator of choice in term babies | Strength of recommendation A  
| Intravenous sildenafil is well tolerated and improves oxygenation in PPHN | Level of evidence 1b  
| ECMO should be considered in babies who fail to respond to HFOV and NO | Strength of recommendation A  

6. **References**

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