PERINATAL ISSUES IN ARPKD
A BRIEF OVERVIEW

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The Major Issues

- Normal and abnormal lung development in utero
- Some basic science that may be applicable
- Predictability prenatally and postnatally
- Therapeutic interventions for pulmonary issues both prenatally and postnatally
- Renal insufficiency and its implications
Normal Lung Development

- Embryonal
- Pseudoglandular
- Canalicular
- Saccular
- Alveolar
Lung Development Phases: Human & Mouse

I. Embryonic
   Mouse: E 9–12
   Human: Wk 3–7

II. Pseudoglandular
    E 12–15
    Wk 5–17

III. Canalicular
     E 15–17
     Wk 16–26

IV. Saccular
    E 17–Birth
    Wk 26–36

V. Alveolar
   Birth–PN20
   Wk 36–3 years
Normal Lung Development

- About 75% of bronchial branching occurs between 10 and 14 weeks.
- The subsequent canalicular phase consists of widening of airways, lengthening, flattening of the surface. During this phase, mechanical factors play an important role.
- These mechanical factors include the pressure of secreted lung fluid and stretching by fetal breathing.
Lung Development

- After the pseudoglandular stage, fetal urine contributes significantly to amniotic volume
- All future airway branches made
- Therefore, lack of urine should effect post airway branch development, not airway branch number
- Models seem to suggest an early defect in lung development
Throughout pregnancy, developing lungs secrete liquid into the designated air spaces (a chloride-dependent transport)

Cleared by fetal breathing and lung peristalsis

Tracheal occlusion causes increased lung growth—a treatment that MIGHT ameliorate lung insufficiency in diaphragmatic herniae

Suggests that lung liquid dynamics important in pulmonary hypoplasia
But

A transgenic mouse model of renal agenesis (knockout of a laminin binding site) demonstrates decreased pulmonary growth BEFORE there would be significant renal development.

Suggests, at least in some cases, defects in renal development cause pulmonary changes because the renal defect either prevents a growth factor from being made or interferes with its function.

The implication of this is that mechanical explanations alone cannot predict the magnitude of lung hypoplasia.
Only 10% of cardiac output goes thru pulmonary vessels \textit{utero}

Vascular tone (resistance) increases as term approaches

Multiple systems work to keep high pulmonary resistance:

- leukotrienes (vasoconstrictor)
- low prostacyclin (vasodilator)
- low nitric oxide (vasodilator)
- innate ability to oppose vasodilation
Vascular Transition

- At birth, rapid increase in pulmonary blood flow, reduced pulmonary vascular resistance, clearance of pulmonary fluid
- Primary mechanism for vasodilation is production of nitric oxide (NO) and other arachidonic acid metabolites
- Nitric oxide production increases dramatically at birth. Lung cell expression of endothelial nitric oxide synthase and its target, soluble guanylate synthase increase in late gestation.
Vascular Transition

- Ultimately, increased NO production and sGC lead to increased cyclic guanosine monophosphate (cGMP) in vessel smooth muscle which produces vasodilation by decreasing intracellular calcium.

- There are also endogenous inhibitors of NO activity (ADMA or asymmetric dimethyl arginine) which may play a role in utero in keeping eNOS low.
Vascular Transition

- Prostacyclin pathway also involved in vasodilation
- Cyclooxygenase (COX) is rate limiting enzyme that generates prostacyclin from arachidonic acid. COX-1 is upregulated during late gestation
- This leads to increase prostacyclin which interacts with adenylate cyclase to increase intracellular cyclic adenosine monophosphate (cAMP) which leads to vasorelaxation
3 different signals cause transition mechanical lung distention decrease carbon dioxide increase in oxygen tension

Oxygen stimulates both eNOS and COX-1 causing increase in NO and prostacyclin

Oxygen also stimulates release of ATP from RBCs which increases eNOS and COX-1
Can We Predict Pulmonary Hypoplasia?

- Definition complex: size, lung weight/body weight, radial alveolar count, DNA content
- Fetal MRI can, to some extent, quantify lung volume and lung to head ratio as well as lung signal intensity (decreased intensity seen in hypoplastic lungs)
- That said, the data is not perfect—sensitivity to detect hypoplasia is ~80-90%
Can We Predict Pulmonary Hypoplasia?

- Postnatal predictability of survival and/or pulmonary disability is impossible to predict from the literature.
- Published series report many differing etiologies, amount of amniotic fluid, radiologic parameters and types of therapies.
- The use of techniques commonly now used for diaphragmatic hernia management may be applicable.
- The development of severe recurrent bilateral pneumothoraces usually precludes survival.
Can We Intervene Prenatally?

- There is little solid information on prenatal intervention for ARPKD
- Most are studies of shunt procedures for other renal anomalies or are about amnioinfusion for premature rupture of the membranes
- For now, prenatal intervention must be said to be unproven
Postnatal Intervention

Gentle ventilation
  low peak pressure
  low end expiratory pressure
  short inspiratory time
  high rate
High frequency ventilation
  Oscillator
  Jet
Postnatal Intervention

Both HFOV & Jet
Small tidal volumes
Extremely high rates: 400-600 bpm
Method of gas exchange very complex but both with low mean airway pressure
No useful data on use in pulmonary hypoplasia
Comparison with diaphragmatic hernia
Postnatal Intervention

Nevertheless…………………………

Seems to work in some cases of pulmonary hypoplasia

Risks????

Worse air leak

Compromised venous return

Effects on brain blood flow
Postnatal Intervention

- Nitric oxide (NOT laughing gas!!)
  - Inhaled gas—primarily acts on pulmonary vessels
  - Administration is fairly simple
  - Binds tightly to hemoglobin limiting exposure to other organs
  - Try when Oxygenation Index > 25 (OI= (mean airway pressure x FiO2)/post ductal PaO2)
  - Short term toxicity minimal
  - Unanswered questions concerning central nervous system toxicity
  - No data for pulmonary hypoplasia
Postnatal Interventions

- Sildenafil—since inhaled NO works primarily by activation of soluble guanylate cyclase and cyclic GMP-dependent protein kinase investigators looked to other ways to increase cGMP.

- Inhibition of cGMP-metabolizing PDE5 (phosphodiesterase5) may increase cGMP concentrations and cause pulmonary vasodilation
Postnatal Interventions

- Sildenafil is a PDE5 inhibitor
  Available as an oral medicine and now IV
  May be useful for “maintenance” therapy
- Milrinone inhibits PDE3, the phosphodiesterase that metabolizes cAMP. Since cAMP also stimulates vasodilation this may be additive to inhaled NO
- Prostaglandin I\(_2\) increases cAMP and may be useful in an inhaled form. Similarly, inhaled PGE\(_2\) may improve oxygenation
- Scavengers of reactive oxygen species, such as superoxide dismutase, may also improve oxygenation
- Bosentan, nonselective oral endothelin receptor antagonist reverses endothelin-induced smooth muscle constriction
A myriad of potential therapies for inadequate lung blood flow
None, unfortunately, have been proven to overcome the effects of an inadequate number of lung vessels
This is an area that will require multicentered trials in order to prove the efficacy of any of these treatments
In the mean time, clinicians are likely to try many of these without definite proof of value
We do not know all the side effects
The management of renal insufficiency is, unfortunately, well known to neonatologists. Usually due to perinatal asphyxia or congenital heart disease. A trial of dialysis (ultrafiltration or peritoneal) is well tolerated. In-dwelling catheters for intravenous nutrition allows for careful titration of protein and mineral intake.
Renal Insufficiency

- The major complexity is deciding whether poor renal function is due to perinatal events or underlying renal insufficiency.
- If the problem is perinatal in origin, are other organs, especially the central nervous system similarly damaged?
- Which leads to........decisions, decisions
The Hard Choices From a Neonatologist’s Perspective

- Prenatal counseling
  My goal is to help families make decisions that they are comfortable with
  No right answer
  Which outcome could they least live with?
  Delivery room decisions
  Trials of treatment
  Deciding on a methodology for stopping
  Palliative care is care
Thank you and I would love to answer your questions. I hope I have clarified both the forest and the trees.