Fetal Physiology and the Transition to Extrauterine Life

Sarah Morton, MD, PhD and
Fellow, Harvard Neonatal-Perinatal Medicine Training Program, Boston, MA

Dara Brodsky, MD
Assistant Professor of Pediatrics, Harvard Medical School, Associate Director of the NICU, Beth Israel Deaconess Medical Center, Boston, MA

Sarah Morton: Sarah.morton@childrens.harvard.edu; Dara Brodsky: dbrodsky@bidmc.harvard.edu

Abstract

The physiology of the fetus is fundamentally different from the neonate with both structural and functional distinctions. The fetus is well-adapted to the relatively hypoxemic intrauterine environment. The transition from intra- to extrauterine life requires rapid, complex and well-orchestrated steps to ensure neonatal survival. This chapter explains intrauterine physiology that allows the fetus to survive and then reviews the physiologic changes that occur during the transition to extrauterine life. Asphyxia fundamentally alters the physiology of transition and necessitates a thoughtful approach in the management of affected neonates.

Keywords
fetal physiology; intrauterine circulation; transition from intrauterine to extrauterine life; transition physiology

Introduction

The physiology of the fetus is fundamentally different from the neonate with both structural and functional distinctions. The transition from intra- to extrauterine life requires rapid, complex and well-orchestrated steps to ensure neonatal survival. It is critical that neonatal care providers have a clear understanding of fetal and normal transitional physiology so that they can recognize deviations from typical physiology and appropriately manage these scenarios. Asphyxia fundamentally alters the physiology of transition and necessitates a thoughtful approach in the management of affected neonates.
Fetal Physiology

Cardiac Development

The human fetal circulation begins when the heart first beats at approximately 22 days of gestation. Gas exchange is initially provided by both the yolk sac and the placenta until the placenta becomes dominant at 10 weeks’ gestation. Because oxygenated maternal blood mixes with poorly oxygenated blood within the free-flowing placental space, the oxygen content of blood provided to the fetus is lower than the maternal uterine arterial blood, causing the fetus to live in a relatively hypoxemic environment. As the fetal lungs do not contribute to intrauterine oxygenation, there are several intrauterine shunts designed to direct blood away from the fetal lungs. Unique aspects of the fetal circulation (and other organ systems) are summarized in Table 1.

Our initial knowledge about the human fetal circulation was obtained from data in fetal sheep. Recently, ultrasonography and magnetic resonance imaging (MRI) during human gestation have provided new detailed information about fetal blood flow in human fetuses (schematic shown in Figure 1). A comprehensive summary of the quantitative assessment of the human fetal circulation was recently published.

In brief, starting at the level of the placenta, the well-oxygenated blood from branches of the maternal uterine artery flows freely into the placental space in funnel-shaped spurts. Oxygen is then transferred across a concentration gradient from the placental space into vessels within multiple villi that line the fetal side of the placenta. These villi contain capillaries that merge and form the umbilical vein (UV). Umbilical venous blood has an oxygen saturation of 70% to 80%, which is the highest oxygen saturation in the fetal circulation (Figure 2). As the umbilical vein enters the fetus, it splits at the level of the liver with some blood perfusing the hepatic circulation and the remainder entering into the ductus venosus.

The direction of flow of the intrauterine circulation helps to maximize oxygen delivery to the developing brain and heart. Although blood from the ductus venosus and inferior vena cava (IVC) merges near the fetal heart, blood from each vessel is directed separately within the heart. Poorly oxygenated blood from the IVC enters the right atrium (RA), merges with the poorly oxygenated superior vena caval (SVC) blood, and is preferentially directed into the right ventricle (RV). A small portion of the RV output goes to the lungs via the pulmonary arteries, while the remaining flow is shunted across the ductus arteriosus to the descending aorta. This blood flow in the descending aorta, with an oxygen saturation of 60%, perfuses the abdominal organs and lower body before returning to the low-resistance placenta.

In contrast, better oxygenated blood from the ductus venosus is preferentially directed from the RA across the foramen ovale to the left atrium (LA). This right-to-left shunt accounts for approximately 25% of the total cardiac output. This shunted blood then mixes with a small amount of blood from the pulmonary veins before entering the ascending aorta to supply the carotid and coronary arteries. As most of the source of this blood originated from the better
oxygenated ductal venous blood, the brain and heart receive blood with an oxygen saturation of approximately 65%, slightly higher than the 60% in the postductal aorta.

In addition to the unique cardiac circulation, there are also differences in cardiac function in the fetus compared to the neonate. For example, the inotropic ability of the fetal and neonatal heart is not identical. The contractility of the immature heart is decreased because of lower myofibrillar content per tissue volume. In addition, the relative immaturity of the calcium regulatory mechanism renders the fetal heart intolerant of low calcium levels.

In general, the fetus has a limited ability to adjust cardiac output. In utero, the heart functions at the peak of the Frank-Starling ventricular function curve with increases in preload having a minimal impact on cardiac output. Fetal cardiac output is primarily increased by modulation of the heart rate with fetal tachycardia leading to an increase in cardiac output and fetal bradycardia corresponding to a lower ventricular output. However, this mechanism is not ideal as sympathetic regulation of cardiac function is reduced, with both a decreased number of β-adrenoreceptors and decreased sympathetic innervation.

**Pulmonary Development**

Lung development occurs in two phases: growth followed by maturation. The lung bud septates from the foregut during the first trimester; following, lobar buds subdivide and form bronchopulmonary segments. The gas-exchanging portions of the airway are formed during the canalicular phase that occurs during the second trimester. Alveolar ductal development starts at 24 weeks’ gestation, and septation of the air sacs begins at 36 weeks’ gestation. During both phases of development, distal pulmonary epithelial cells actively secrete a chloride-rich fluid into the bronchial tree. This results in the accumulation of fluid within the fetal airways. Compared to postnatal lungs, the fetus’ lungs are hyperexpanded.

Elevated intrapulmonary vascular pressures as a result of fluid distension contribute to increased pulmonary vascular resistance. The presence of this airway fluid is critical for stimulating lung development. This is supported by data in fetal lambs showing that tracheal ligation, which prevents lung fluid from escaping, leads to faster pulmonary growth and development.

Fetal lung fluid contains components that change over the course of gestation. Prior to birth, the content of fetal lung fluid is altered because of the increased expression of surfactant lipoproteins by type II pneumocytes in response to increasing cortisol levels at the end of the third trimester. These lipoproteins function to lower surface tension in the lungs, allowing for inflation at lower pressures.

As the fetal airways and lung parenchyma develop, so does the pulmonary vasculature. The development of the pulmonary circulation starts by 34 days’ gestation in the human fetus. Advances in fetal magnetic resonance imaging (MRI) have allowed more precise examination of the relative blood flow in the human fetus, and recent evidence suggests that pulmonary blood flow increases with gestational age from an initial low of 10% to almost 50% of the combined ventricular output by term gestation.
Because of preferential shunting of deoxygenated blood into the right ventricle, blood reaching the intrauterine pulmonary circulation has an oxygenation saturation of approximately 55%. Fetal hypoxemia decreases pulmonary blood flow, which in turn suppresses the production of nitric oxide and prostaglandin I$_2$\textsuperscript{15}. This results in an elevated pulmonary vascular resistance at baseline. Any additional fetal hypoxemia as a result of maternal or placental issues leads to lowering of the oxygen delivered to the pulmonary circulation, which increases pulmonary vascular resistance further and activates hypoxia inducible factor-1, triggering vascular remodeling\textsuperscript{16,17}.

Much like the cardiovascular system, there are both structural and functional changes of the fetal lungs during gestation. Fetal breathing starts at 10 weeks’ gestation and is associated with rapid eye movement sleep. It is inhibited by hypoxemia and stimulated by hyperoxemia\textsuperscript{18}. Such breathing movements are important to pulmonary development, as cessation of fetal breathing via phrenectomy in fetal sheep leads to pulmonary hypoplasia\textsuperscript{19}.

**Endocrine development**

Cortisol production increases from 30 to 36 weeks’ gestation, and a second peak occurs before spontaneous labor at term gestational age\textsuperscript{18}. Elevated cortisol levels lead to activation of thyroid hormone, maturation of hepatic glucose metabolism enzymes, and improved maintenance of euglycemia after delivery. Cortisol levels are lower in the setting of preterm delivery or Cesarean section without labor, and increased with chorioamnionitis.

**Hematologic development**

Between 2 and 3 weeks’ gestation, the yolk sac initiates fetal erythropoiesis. From 5 weeks’ gestation to 6 months’ gestation, the liver becomes the primary site of erythropoiesis, followed by the bone marrow thereafter. Relative hypoxemia induces hypoxia-inducible factor-1, which stimulates the fetal kidneys to produce erythropoietin, driving red blood cell production and thereby improving oxygenation of the fetus by increasing the oxygen carrying capacity.

Another mechanism by which the fetus compensates for the relative hypoxemic environment, is by depending on fetal hemoglobin. This unique hemoglobin has a high oxygen affinity, creating a leftward shift in the oxyhemoglobin curve that increases oxygen uptake at the lower oxygenated placental vascular bed. However, given the resultant higher affinity, less oxygen will be offloaded to capillary beds in tissues unless local factors modify the oxygen affinity of fetal hemoglobin. For example, fetal acidosis augments delivery of oxygen to tissues by decreasing the affinity of fetal hemoglobin for oxygen.

**Transition**

Transition to extrauterine life is characterized by changes in circulatory pathways, initiation of ventilation and oxygenation via the lungs instead of the placenta, and many changes in metabolism. These changes are summarized in Table 2.
Cardiovascular changes

With the first postnatal breath, the pulmonary vascular resistance decreases dramatically. This is caused by a combination of increased oxygen exposure as well as ventilation itself\textsuperscript{20}. When the umbilical cord is clamped, the low-resistance vascular bed of the placenta is disconnected, leading to an increase in the newborn’s systemic vascular resistance. The pressure within the LA then increases because of the increased distal aortic pressure and the greater amount of blood returning to the LA from the lungs. With the left atrial pressure being greater than the right atrial pressure, the flap across the foramen ovale closes.

Most term infants have a reversal of flow across the ductus arteriosus with left-to-right flow occurring within 10 minutes after birth, resulting in greater pulmonary blood flow\textsuperscript{21,22}. Serial ultrasonography has demonstrated doubling of LV output and a concomitant increase in stroke volume in the first hour after delivery\textsuperscript{23}. During the circulatory transition from fetal to neonatal physiology, systemic vascular resistance (SVR) has a larger influence on blood pressure than blood flow\textsuperscript{24}. The increase in SVR leads to a rapid and transient increase in cerebral blood flow. Increased oxygenation and decreased blood flow leads to closure of the fetal cardiac shunts, as summarized in Table 3. Oxygenation of the ductus arteriosus further leads to increased calcium channel activity resulting in functional closure. Smooth muscle cells of the ductus arteriosus respond to increased oxygen with inhibition of potassium channel activity, also causing ductal constriction\textsuperscript{25}.

These events are affected by many factors at birth, including the timing of umbilical cord clamping. Clamping of the umbilical vein prior to the onset of ventilation removes the primary source of in utero left-sided venous return from the ductus venosus (i.e., ductus venosus → RA → PFO → LA → LV). This occurs before an increase in pulmonary blood flow, resulting in a period of decreased left ventricular preload and decreased cardiac output that persists until ventilation is established\textsuperscript{26}. Delaying cord clamping until the onset of ventilation can prevent this decrease in cardiac output\textsuperscript{27}. Theoretically, the umbilical arteries should vasoconstrict before the umbilical vein closes, leading to net blood flow towards the infant. However, in practice this has not always been observed and may depend on the difference in height between the placenta and the infant.

Our understanding of the nuanced cardiovascular changes that occur at birth has been advanced by new, non-invasive method for assessing local perfusion and oxygenation. Near-infrared spectroscopy (NIRS) is a noninvasive monitoring technique that can be used to measure tissue oxygenation index and calculate peripheral blood flow and peripheral oxygen delivery. Using NIRS to measure cerebral oxygen saturation, term infants experience an increase in cerebral perfusion in the first few minutes of life, corresponding to an increase in blood oxygen content\textsuperscript{28}. This increased oxygenation happens faster in the brain than in other tissues\textsuperscript{29}. Interestingly, cerebral oxygen saturation is both higher and less variable than abdominal tissue oxygen saturation in preterm infants over the first weeks of life\textsuperscript{30}.

Pulmonary changes

Significant pulmonary changes are triggered at the onset of labor. Surfactant is a mixture of lipids and proteins that reduces the surface tension within airways by forming a monolayer
at the liquid-air interface. Surfactant secretion into the fetal lungs is stimulated by labor. Alveolar stretch as a result of initiation of ventilation further increases the secretion of surfactant. These polar molecules function to lower surface tension in the lungs, allowing for inflation at lower pressures.

Clearance of fetal lung fluid also begins before birth, is augmented by labor, and is mostly completed by 2 hours of age. There are multiple mechanisms that assist with this process. During spontaneous labor and immediately after birth, the respiratory epithelium changes from active fluid secretion (with active chloride transport into the intraluminal space) to active fluid absorption (with active sodium transport into the interstitium). The sodium-mediated active absorption process is believed to be initiated even before labor with regulation by increased cortisol and thyroid hormone levels. Beta-receptor agonist stimulation promotes this respiratory epithelium transition during spontaneous labor. Increased oxygenation after birth helps to maintain the expression of these sodium-mediated channels. In a rabbit model, fetal airway liquid has also been shown to be cleared postnatally by increases in the trans-epithelial pressure gradient during inspiration that functions to drive fluid into tissues to where it can be removed by the pulmonary microcirculation and lymphatic vessels. Effective clearance of fetal lung fluid decreases pulmonary vascular resistance, and the increased intravascular fluid volume leads to an increase in the plasma volume during the first few hours of age.

After birth, infants must establish breathing patterns more regular than those of the fetus. Most term and preterm infants will breathe spontaneously unless they have severe hypoxemia, which represses the initiation of breathing. Gas exchange is stabilized by 2 minutes in most babies after vaginal delivery and improvement in heart rate is the best clinical indicator of successful ventilation. Preterm infants have lower lung volumes relative to body weight compared to term infants, and have delayed clearance of fetal lung fluid because of decreased sodium resorption. Infants with transient tachypnea of the newborn or surfactant deficiency also have decreased sodium resorption.

As ventilation is initiated, a positive ratio of inspiratory to expiratory volumes results in a functional residual capacity (FRC). Preterm infants with lower amounts of surfactant have a lower baseline FRC. Positive end-expiratory pressure can help preterm infants to establish a more uniform FRC. Continuous positive airway pressure can help preterm infants adapt by triggering production and secretion of surfactant.

An observational study of term infants found that oxygen saturation did not reach 90% until an average of 8 minutes after birth in healthy newborns breathing room air, and the post-ductal saturations remained on average 8% lower than pre-ductal saturations for the first 15 minutes of age. Oxygenation has many effects, including relaxation of pulmonary vascular smooth muscle, which is mediated in part by increased cGMP-dependent protein kinase activity.

With the onset of respiration, there are significant changes in pulmonary blood flow. The closure of cardiac shunts changes the circulatory system from a fetal configuration with parallel output from the right and left ventricles contributing to a total cardiac output of 450
mL/kg/min, to a neonatal system where each ventricle has a cardiac output of 400 mL/kg/min. As a result of this increase in right-sided output, pulmonary blood flow increases to 100% in the newborn. Increased pulmonary blood flow causes sheer stress, which in turn reduces pulmonary vascular resistance via increased nitric oxide production. Pulmonary arterial pressure reaches half systemic arterial pressure by 24 hours of age, attaining adult levels by 2 weeks in most typical infants. Experimental paradigms that allow ventilation without oxygenation show a blunted drop in pulmonary vascular resistance compared to ventilation with the appropriate physiologic increase in oxygen. Endogenous vasoactive agents and their effects are summarized in Table 4.

**Hematologic changes**

After birth, the production of fetal hemoglobin decreases and there is a concomitant increase in hemoglobin β chain production such that normal levels of adult hemoglobin are achieved by 4 to 6 months of age. Exposure to the increased oxygenation of the extrauterine environment leads to decreased erythropoietin, leading to lower rates of erythropoiesis in the neonate (nadir approximately 1 month) compared to the fetus.

**Metabolic changes**

Glucose and amino acids are actively transported to the fetus across the placenta, a process that is stopped by separation from the placental circulation. Generally, smaller mammals have higher metabolic rates. However, the fetus has a low metabolic rate despite a small size, with a metabolic rate similar to that of the pregnant woman. After delivery, there is a progressive increase in metabolic rate, which occurs more slowly in preterm infants.

Mitochondrial density increases as the metabolic rate increases.

To maintain blood glucose after separation from the placental circulation, the newborn experiences a surge in catecholamine and glucagon levels and a decrease in insulin amounts. Gluconeogenesis and glycogenolysis in the liver ensures stable blood glucose until oral intake volumes improve over the first few days after birth. Ketone bodies and lactate provide additional energy for the brain, with hepatic ketogenesis increasing after the first 12 hours of age.

As with pulmonary changes, many hormonal changes necessary for successful transition to extra-uterine life are initiated during the fetal period. Cortisol levels begin to rise at 30 weeks’ gestation and peak just following delivery. The combined action of cortisol and thyroid hormone activates sodium channel activity that drives resorption of lung fluid. Stressful deliveries, or Cesarean delivery without labor, can uncover a relative adrenal insufficiency in infants who do not produce an adequate response to the physiologic challenge.

Norepinephrine, epinephrine and dopamine are released from the neonatal adrenal medulla and other sympathetic nervous system tissues. The importance of catecholamines in adaptation to extrauterine life has been demonstrated using a lamb model. Neonatal lambs who had an adrenalectomy at term had markedly lower levels of epinephrine and norepinephrine, which resulted in lower blood pressures. Birth leads to increased
production and release of catecholamines, renin-angiotensin and vasopressin. These are important for the increase in cardiac output that occurs postnatally, as well as increases in plasma glucose and free fatty acids. Preterm neonates have a slower rise in catecholamine levels but plateau at serum concentrations higher than those found in term infants. Interestingly, compared to the fetus, term neonates have lower thresholds of catecholamine concentrations necessary to produce changes in blood pressure, serum glucose, and free fatty acids, which are necessary for the transition to the extra-uterine environment.

**Temperature regulation**

At birth, infants emerge covered in liquid, resulting in potential heat loss via evaporation. If newborns are not held skin-to-skin or wrapped in a warm blanket, hypothermia can ensue because of conduction, convection and radiant heat losses. Relative to older children, neonates have a higher body surface area, limited capacity to generate heat via shivering, and decreased subcutaneous fat for insulation. Brown adipose tissue lipolysis triggered by norepinephrine can generate heat, and peripheral vasoconstriction can minimize heat loss. Thyroid hormones surge after birth, possibly in response to the relatively cold extrauterine environment.

**Summary**

The transition from intrauterine to extrauterine life requires a rapid adaptation of multiple organ systems. Separation from the placental circulation results in increased systemic vascular resistance, while initiation of ventilation lowers pulmonary vascular resistance. These combined factors, with the associated increased oxygenation, result in closures of the foramen ovale, ductus arteriosus, and ductus venosus. A successful transition also requires increased metabolic and endocrine activities to support blood pressure and blood glucose levels. Precise orchestration of these complex physiologic events is necessary to avoid disease relating to birth asphyxia, or failures of the cardiovascular, respiratory or other organ systems.

**References**

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Key Points

1. The intrauterine circulation diverts blood away from the fetal lungs via 2 right-to-left shunts: ductus venosus blood is diverted through the foramen oval into the left atrium and the majority of the right ventricular output is shunted via the ductus into the descending aorta.

2. The accumulation of fetal lung fluid within the fetal airways is critical for fetal lung development.

3. The transition to extraterine life is characterized by changes in circulatory pathways, initiation of ventilation and oxygenation via the lungs, and many changes in metabolism.
Figure 1. Fetal circulation

This schematic summarizes the fetal circulation. The placenta provides oxygen and nutrients to the fetus via the umbilical vein (UV). The UV splits at the level of the liver with some blood perfusing the hepatic circulation and the remainder entering the ductus venosus. While most of the blood from the ductus venosus is directed across the foramen ovale to the left atrium, the inferior and superior vena caval blood preferentially enters the right atrium. Right ventricular output is directed across the patent ductus arteriosus into the descending aorta while left ventricular output provides blood flow to the preductal vessels supplying the brain, coronary arteries, and upper body. Intrauterine pulmonary blood flow is initially limited because of high pulmonary vascular resistance and the right-to-left shunting across the patent foramen ovale and patent ductus arteriosus.
Blood within the umbilical vein has the highest oxygen saturation (70% to 80%, estimated pO2=32–35 torr) compared with the rest of the fetal circulation. Because of the preferential shunting of ductus venosus blood into the left atrium, and the poorly oxygenated inferior and superior vena caval blood (40% to 45%, estimated pO2=12–14) preferentially entering the right atrium, the left side of the heart has a slightly higher oxygen saturation (65%, estimated pO2=26–28 torr) compared with the right side of the heart (55%, estimated pO2=20–22 torr). As a result, the left ventricular output to the brain, coronary arteries, and the upper body, has a slightly higher oxygen saturation/oxygen content compared with the lower body, which is mostly provided by the right ventricular output.
### Table 1

**Unique Characteristics of Fetal Physiology**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right-to-left shunts</td>
<td>Foramen ovale, Patent ductus arteriosus, Relative hypoxic environment&lt;br&gt; Differential blood flow with ductus venosus flow providing most of left side of heart and IVC/SVC providing most of right ventricular output; leads to differential in oxygenation in pre- and post-ductal aortic vessels&lt;br&gt; High-resistance, low-flow pulmonary circulation&lt;br&gt; Limited ability to regulate cardiac output (mostly via changes in heart rate)&lt;br&gt; Pulmonary epithelial cells actively secrete chloride leading to accumulation of fluid within fetal airways&lt;br&gt; Fetal erythropoiesis occurs in liver until 3rd trimester when transitions to bone marrow&lt;br&gt; Fetal hemoglobin, allowing for oxygen uptake in the lower oxygenated placental vascular bed</td>
</tr>
</tbody>
</table>
**Table 2**

Important Physiologic Changes During Transition to Extrauterine Life

<table>
<thead>
<tr>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Increased systemic vascular resistance with separation from the low-resistance placental vasculature</td>
</tr>
<tr>
<td>Closure of right-to-left shunts</td>
</tr>
<tr>
<td>- Foramen ovale (closes when left atrial pressure greater than right atrial pressure)</td>
</tr>
<tr>
<td>- Ductus arteriosus (left-to-right flow within minutes of ventilation, then closure over days)</td>
</tr>
<tr>
<td>Rapid lowering of pulmonary vascular resistance with onset of ventilation</td>
</tr>
<tr>
<td>Clearance of fluid from airways via active sodium absorption and changes in airway pressure due to ventilation</td>
</tr>
<tr>
<td>Increased metabolic rate leading to higher glucose needs</td>
</tr>
<tr>
<td>Increased catecholamine levels to support blood pressure</td>
</tr>
</tbody>
</table>
## Table 3

Postnatal Mechanisms of Cardiac Shunt Closure

<table>
<thead>
<tr>
<th>Physiologic Trigger</th>
<th>Effect</th>
<th>Vessel Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased oxygenation</td>
<td>Constriction</td>
<td>Umbilical artery, Ductus arteriosus</td>
</tr>
<tr>
<td></td>
<td>Dilation</td>
<td>Pulmonary artery</td>
</tr>
<tr>
<td>Decreased blood flow</td>
<td>Constriction</td>
<td>Umbilical vein, Ductus venosus</td>
</tr>
</tbody>
</table>
### Table 4
Intrauterine and Postnatal Modulation of Pulmonary Vascular Resistance

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Synthetic Enzyme</th>
<th>Effect on PVR</th>
<th>Downstream Targets</th>
<th>Activity Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>NOS; upregulated by sheer stress</td>
<td>Decrease</td>
<td>Soluble guanylate cyclase generates cGMP; cGMP activates PKG</td>
<td>Expressed early in first trimester; endothelial NOS and neuronal NOS decrease at term while inducible NOS increases</td>
</tr>
<tr>
<td>PG12</td>
<td>COX-1</td>
<td>Decrease</td>
<td>Adenylyl cyclase generates cAMP</td>
<td>Synthesis starts in third trimester and increases after delivery</td>
</tr>
<tr>
<td>Bradykinin</td>
<td></td>
<td>Decrease</td>
<td>Increases NO, EDRF</td>
<td></td>
</tr>
<tr>
<td>PDE5</td>
<td></td>
<td>Increase</td>
<td>Counteracts NO by degrading cGMP</td>
<td>Increased activity in fetus compared to neonate</td>
</tr>
<tr>
<td>Endothelin</td>
<td>Pulmonary endothelium</td>
<td>Increase</td>
<td>Calcium: increases SR release and muscle sensitivity</td>
<td>Increasing levels in second and third trimester, then decreases after birth</td>
</tr>
<tr>
<td>Platelet activating factor</td>
<td>PLA2, made in response to hypoxia</td>
<td>Increase</td>
<td>Increased calcium release</td>
<td>Higher in fetus than newborn</td>
</tr>
<tr>
<td>Reactive oxygen species</td>
<td>Mitochondria; upregulated by hypoxia; inactivated by SOD and catalase</td>
<td>Increase</td>
<td>Inhibit NO</td>
<td>Catalase expression increases through gestation until 3 months postnatal47</td>
</tr>
</tbody>
</table>

Early in the first trimester, NOS is expressed and stimulates vasodilation48. PDE5, which counteracts the downstream effects of nitric oxide, has increased activity in the fetus compared to the neonate. PG12 synthesis, which lowers PVR, starts in the third trimester in lamb models as a result of an increase in COX-1 expression49. Endothelin, produced by the pulmonary endothelium at increasing levels during the second and third trimester and then decreases following delivery, leads to increased PVR via increased calcium flux and sensitivity in vascular smooth muscle cells in fetal pigs. PVR=pulmonary vascular resistance; NO=nitric oxide; NOS=nitric oxide synthase; PKG=protein kinase G; PG12=prostaglandin I2; COX=cyclooxygenase; PDE5=phosphodiesterase 5; SR=sarcoplasmic reticulum; PLA2=phospholipase A2; SOD=superoxide dismutase.