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# Physiology of Transition from intrauterine to Extrauterine Life

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## Summary

The transition from a fetus to a newborn is the most complex adaptation that occurs in human experience. Lung adaptation requires the coordinated clearance of fetal lung fluid, surfactant secretion, and the onset of consistent breathing. With the removal of the low-pressure placenta, the cardiovascular response requires striking changes in blood flow, pressures and pulmonary vasodilation. The newborn must also quickly control its energy metabolism and thermoregulation. The primary mediators that both prepare the fetus for birth and support the multi-organ transition are cortisol and catecholamine. Abnormalities in adaptation are frequently found following preterm birth or delivery by cesarean section at term, and many of these infants will need delivery room resuscitation to assist in this transition.

### Keywords

Corticosteroids; catecholamines; lung function; cardiovascular; cesarean section

## A. Overview

The transition from a fetus to a newborn is the most complex physiologic adaptation that occurs in human experience. Prior to medicalization of delivery, the transition had to occur quickly for survival of the newborn. All organ systems are involved at some level, but the major immediate adaptations are the establishment of air breathing concurrently with changes in pressures and flows within the cardiovascular system. Other essential adaptations are striking changes in endocrine function, substrate metabolism, and thermogenesis (Box 1). Hospital based deliveries increase the difficulties for transition for many fetuses because of the frequent use of Cesarean sections, deliveries prior to the onset of labor, rapid clamping of the cord, and the anesthetics and analgesics associated with these hospital deliveries. The net result is the frequent need to assist the newborn with the birth transition. Preterm deliveries cause particular difficulties for transition and expose the preterm infant to lung injury from mechanical ventilation. These components of the fetal to neonatal transition will be reviewed for preterm and term deliveries.



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**Box 1**

**Essential components for a normal neonatal transition**

- Clearance of fetal lung fluid
- Surfactant secretion, and breathing
- Transition of fetal to neonatal circulation
- Decrease in pulmonary vascular resistance and increased pulmonary blood flow
- Endocrine support of the transition

## B. Endocrine adaptions to Birth

### 1. Cortisol

Cortisol is the major regulatory hormone for terminal maturation of the fetus and for neonatal adaption at birth (1). The “cortisol surge” is initiated with the switch from maternal-transplacental derived corticosteroids to the ability of the fetal adrenal to synthesize and release cortisol under fetal hypothalamic control. Fetal cortisol levels in the human are low (5–10ug/ml) relative to normal cortisol levels until about 30 weeks gestation. Cortisol levels progressively increase to about 20ug/ml by about 36 weeks gestation and increase further to about 45ug/ml prior to labor at term. Cortisol increases further during labor to peak at high levels of about 200ug/ml several hours after term delivery. The increase in fetal cortisol throughout late gestation supports multiple physiologic changes that facilitate normal neonatal adaption. For example over the final weeks of gestation, the conversion of $T_4$ to $T_3$ increases, catecholamine release by the adrenal and other chromaffin tissues increases, glucose metabolic pathways in the liver mature, gut digestive capacity increases (enzyme induction), β-adrenergic receptor density increases in many tissues including the heart and the lungs, and the surfactant system in the lungs is induced to mature (2). Cortisol in association with increasing thyroid hormones activates the sodium pump that clears fetal lung fluid at birth. These cortisol-modulated changes are normally a progressive process of preparation for birth as the cortisol levels rise prior to birth then peak soon after delivery. This normal increase in cortisol supports an integrated transition following birth (Box 2) Cesarean section without labor at term blunts the postnatal rise in cortisol, and the cortisol responses to preterm birth also are attenuated because of unresponsiveness and immaturity of the adrenal gland (3). A particularly stressful delivery can uncover a “functional” adrenal insufficiency if the adrenal gland cannot respond to the increased stress. The very preterm infant may have low cortisol levels around birth with symptoms such as low blood pressure that are responsive to cortisol treatment. In contrast antenatal exposure to chorioamnionitis may increase fetal cortisol levels prior to delivery (4).

**Box 2**

**Some effects of cortisol on factors contributing to a normal fetal to newborn transition**

- Lung maturation – anatomy and surfactant
- Clearance of fetal lung fluid
- Increased β receptor density
- Gut functional maturation
- Maturation of thyroid axis

- Regulate catecholamine release
- Control energy substrate metabolism

## 2. Catecholamines

Despite the enthusiasm of clinicians to use catecholamines infusions to increase the blood pressure of very preterm infants following birth, the normal physiology of endogenous catecholamines during and after birth are not reviewed in recent neonatology text books. The term human fetus can release catecholamines (norepinephrine, epinephrine, and dopamine) from adrenal medullary and other sympathetic tissues in response to fetal stresses of various sorts, as evaluated by catecholamine values in cord blood (5). The preterm fetus has higher cord catecholamine levels than the term fetus, and cesarean delivery is associated with lower cord catecholamine levels. The details of the catecholamine responses to term and preterm labor and delivery were characterized elegantly by Padbury and colleagues in a series of reports beginning in the 1980s. Using catheterized fetal sheep that were transitioned through delivery, they demonstrated that norepinephrine and epinephrine increase to high levels within minutes of term delivery and cord clamping (6). In contrast the catecholamines increased more slowly following preterm delivery but to levels that were about 3 fold higher for norepinephrine and 5 fold higher for epinephrine than after term delivery. (Fig 1) The lower increases in catecholamines in the term newborn were associated with larger increases in plasma glucose and free fatty acids than in the preterm. Careful measurement of thresholds for responses of fetal sheep to epinephrine and norepinephrine infusion demonstrated that the term fetus had lower thresholds and greater responses for blood pressure, glucose, and free fatty acid increases than did the preterm fetuses (7). The catecholamine increases at delivery resulted primarily from adrenal release as adrenalectomy ablated the increase in epinephrine and norepinephrine and blunted blood pressure, glucose and fatty acids increases and pulmonary adaption (8). The fetus is in part protected from the cardiovascular and metabolic effects of stress mediated catecholamine release because the placenta increases catecholamine clearance (9).

These studies demonstrate the importance of a large catecholamine release as a normal response to the birth process for fetal adaption. The catecholamine surge is primarily responsible for the increase in blood pressure following birth, adaption of energy metabolism with support of the primary substrates for metabolism after birth – glucose and fatty acids, and for initiating thermogenesis from brown fat. The preterm secretes more catecholamines because the organ systems are less responsive – higher concentration thresholds for response and lower responses. Cesarean section of the unlabored fetus depresses catecholamine release. Catecholamine release at birth can be viewed as the “gas” that drives the adaptive responses. However, fetal exposure to cortisol is the “carburetor” that is the potent regulator of the responses of the newborn to catecholamines. Antenatal corticosteroid treatments decrease catecholamine levels in preterm infants compared with unexposed infants (10). Cortisol treatments of fetal sheep also greatly decrease the postnatal increase in both norepinephrine and epinephrine (11) (Fig 2). Nevertheless, the animals had better cardiovascular and metabolic adaptation to preterm birth. These studies demonstrate the importance of both cortisol and catecholamines to adaptations to birth.

Other vasoactive substances such as angiotensin II and renin also increase greatly at birth in association with increases in blood pressure (12). The net effect is the normal exposure of the newborn to very high levels of multiple vasoactive substances to support adaption. The basic physiology of these agents was described over 20 years ago in animal models with confirmation in term and moderately preterm infants. Much of this work could be profitably repeated for extremely low birth weight infants to better understand how their

catecholamines responses to preterm birth may be dysregulated and to better target therapies. For example, Ezaki and colleagues recently reported that very low birth weight infants with severe hypotension had a decreased conversion of dopamine to norepinephrine (13).

### 3. Thyroid Hormones

The thyroid axis matures in late gestation in parallel to the increase in cortisol with increased thyroid simulating hormone (TSH), $T_3$ and $T_4$ levels, and decreased rT3 levels as term approaches (14). Following term birth, TSH quickly peaks and decreases, and $T_3$ and $T_4$ increase in response primarily to the increased cortisol, to cord clamping and to the cold stimulus of birth. Acute ablation of thyroid function at birth did not greatly alter thermogenesis or cardiovascular adaptation in experimental animals. However, inhibition of thyroid function more chronically prior to birth did interfere with postnatal cardiovascular adaptation and thermogenesis in newborn lambs (15). These results demonstrate a supportive and preparative role for thyroid hormones for birth rather than as acute modulators of endocrine adaptation to birth. For example, fetal infusions of T3 and cortisol can activate the $Na^+$, $K^+$, ATPase that helps clear fetal lung fluid after birth (16). Term infants with congenital hypothyroidism generally do not have abnormalities of early neonatal adaptation that are evident in the controlled environment of hospital deliveries. Very preterm infants have a blunted thyroid functional transition from fetal to newborn life with very low levels of plasma $T_3$ and $T_4$ relative to term infants. The effects of the depressed thyroid function on the early postnatal transition in the preterm are unclear but probably contribute to the depressed adaptive behavior of the preterm.

## C. Metabolic Adaptations

### 1. Energy Metabolism

Fetal energy needs are supported primarily by the transplacental transfer of glucose to the fetus (17). Although the fetal liver is capable of gluconeogenesis from early gestation, gluconeogenesis is minimal during normal fetal homeostasis. Rather as term approaches glucose and other substrates are being stored as glycogen and fat in anticipation of birth in the high insulin and low glycogen fetal environment. With delivery and cord clamping, the maternal glucose supply is removed, and plasma glucose levels normally fall over the early hours after birth. The glucose and free fatty acid levels are accompanied by a fall in insulin, and increase in glycogen, the normal glucose homeostatic hormones. However, the large catecholamine release and increase in cortisol are probably the major acute regulators of plasma glucose and free fatty acid levels in the immediate newborn period. For example, adrenalectomy of the fetal sheep who received cortisol replacement blunts and delays the post-delivery increase in plasma free fatty acids and results in persistent hypoglycemia (8) (Fig. 1). Fetal treatments with cortisol decrease the catecholamine surge at birth, but increase both plasma glucose, and free fatty acids relative to control animals (11) (Fig. 2). Therefore, the metabolic adaptations to birth are regulated by acute changes in insulin and glucogen, but also by catecholamines and cortisol in term infants.

Cortisol and catecholamine responses to preterm birth are dysregulated with less cortisol and more catecholamine release. The preterm also has minimal glycogen and fat stores (17). Therefore, the availability of energy substrates during the birth transition will be severely challenging for the preterm. This aspect of adaptation in the immediate newborn period is treated routinely with glucose infusion to prevent hypoglycemia. However, the integrated effects of the endocrine abnormalities and responses to glucose infusions have not been well described in extremely low birth weight infants.

### 2. Thermoregulation

Fetal body temperature is about 0.5°C above the maternal temperature. Although the fetus produces heat from metabolism, that heat is effectively dissipated across the placenta and fetal membranes. At birth the sympathetic release resulting from the redundant stimuli of increased oxygenation, ventilation, cord occlusion and a cold stimulus to the skin activates thermogenesis by brown adipose tissue (18). This thermogenic response potential has developed during late gestation by an increase in brown adipose tissue around the kidney and in the intrascapular areas of the back to become about 1% of fetal weight at term (19). Brown adipose tissue generates heat by uncoupling oxidative metabolism from ATP synthesis in the mitochondria, with the release of heat (18). This uncoupling is mediated by the mitochondrial membrane protein uncoupling protein 1 (UCP1) which is activated by norepinephrine released by the sympathetic innervation of brown adipose tissue. UCP1 levels increase in the brown adipose tissue during late gestation in response to a local conversion of $T_4$ to $T_3$ and to induction of UCP1 synthesis in response to the increasing cortisol levels in the fetal plasma as term approaches. Thus the same hormones that modulate the fetal preparation for birth and the transition period are central to thermogenesis by brown adipose tissue. The term infant also can generate some heat by shivering thermogenesis, which is an increase in non-purposeful skeletal muscle activity signaled by cutaneous nerve endings via central motor neurons. Shivering thermogenesis seems to be of secondary importance to the newborn human. The preterm human is at a major disadvantage for thermoregulation following birth as brown adipose tissue has not developed in quantity or response potential for a cold stress.

## D. Cardiovascular Adaptations

Profound changes in the cardiovascular system occur after delivery in response to removal of the low resistance placenta as the source of fetal gas exchange and nutrition. Much of our knowledge regarding cardiovascular adaptation after birth is based on studies in animals, particularly the sheep. The major changes are an increase in the cardiac output and transition of fetal circulation to an adult type of circulation. Increased cardiac output is required to provide for increases in basal metabolism, work of breathing, and thermogenesis. In the close-to-term fetus, the combined ventricular output is about 450 mL/kg/min, with the right ventricular output accounting for 2/3rd of the cardiac output and the left ventricle ejecting 1/3rd of the cardiac output (20). Soon after birth, the circulation changes from “parallel” to “series”, where the right ventricular output equals the left ventricular output. The cardiac output nearly doubles after birth to about 400 mL/kg/min (for the right and the left ventricle). This marked increase in cardiac output parallels closely the rise in oxygen consumption. The organs experiencing increased blood flow after birth are the lungs, heart, kidney and the gastrointestinal tract (21). Although the precise mechanisms mediating increased cardiac output after birth are not known, the increase in cortisol and vasoactive hormones, that include catecholamines, the rennin-angiotensin system, vasopressin and thyroid hormone contribute to support of blood pressure and cardiovascular function (20).

In the fetus, the relatively well-oxygenated blood from the placenta is delivered via the umbilical cord and ductus venous. This ductus venous blood enters the right atrium from the inferior vena cava and is directed preferentially to the left atrium by the foramen ovule and subsequently delivered preferentially to the brain and the coronary circulation by the fetal left ventricle. The right ventricle is the predominant ventricle in the fetus, and most of the right ventricular output goes to the descending aorta via the ductus arteriosus since very little blood enters the pulmonary circulation. With birth and removal of the low resistance placenta, blood flow increases to the pulmonary circulation. Shortly after birth functional closure of ductus arteriosus begins. The mechanisms contributing to the high pulmonary vascular resistance in the fetal lung are primarily the low oxygen tension and low pulmonary

blood flow which suppresses the synthesis and release of nitric oxide (NO) and prostaglandin $I_2$ from the pulmonary endothelium (22). Fetal exposure to hypoxia will increase the already high pulmonary vascular resistance and hyperoxia will decrease pulmonary vascular resistance and increase fetal pulmonary blood flow (23). Experimentally, ventilation of the fetal lung without changing oxygenation will decrease pulmonary vascular resistance and increase pulmonary blood flow by 400%. With delivery, ventilation, and oxygenation, NO and $PGI_2$ increase with a rapid fall in pulmonary vascular resistance. The use of supplemental oxygen for the initiation of ventilation will cause pulmonary vascular resistance to decrease more rapidly with the resultant more rapid increase in pulmonary blood flow (24). However, there is no benefit in systemic oxygenation, and the pulmonary vessels subsequently become more refractory to dilation by NO or acetylcholine.

The cardiovascular transition at birth also is modulated by corticosteroids. Exposure of fetal sheep to betamethasone increased fetal pulmonary blood flow but did not alter postnatal pulmonary vasodilation in preterm sheep (25). Heart function after preterm birth is improved by antenatal exposure to corticosteroids (7). The fetal and newborn blood pressures increase, as does cardiac output and left ventricular contractibility. These effects are partially explained by an increase in beta-receptor signaling to an increase in cyclic AMP. Similarly adrenalectomy ablates the increase in blood pressure that normally occurs at birth (8) (Fig. 2). Thus, although there are specific mediators such as NO and $PGI_2$ that facilitate cardiovascular transition, the consistent theme is that the same mediators – corticosteroids and catecholines also facilitate this transition.

The normal oxygen saturation of fetal blood in the left atrium is about 65% (26). During labor the human fetus tolerates oxygen saturations as low as 30% without developing acidosis (27). After birth, the pre-ductal saturation in normal term infants gradually increases to about 90% at 5 minutes of age (28). This knowledge is important to avoid unnecessary administration of supplemental oxygen during resuscitation.

## E. Lung Adaptations

### 1. Fetal Lung Fluid

The most essential adaptation to birth is the initiation of breathing, but the airspaces of the fetal lung are filled with fetal lung fluid. What is fetal lung fluid and how is it cleared from the airspaces? Fetal lung fluid is secreted by the airway epithelium as a filtrate of the interstitial fluid of the lung by the active transport of chloride (29). Consequently the chloride content of fetal lung fluid is high and protein content is very low. The production rate is high, although direct measurements are not available for the human fetus. The volume of lung fluid of the fetal sheep increases from mid gestation and the secretion rate increases to about 4ml/kg/hr by late gestation (30). Production and maintenance of the normal volume of fetal lung fluid is essential for normal lung growth. The electrochemical gradient for the production of fetal lung fluid is substantial and can over-distend the airspaces. This behavior of the production of fetal lung fluid is used to advantage to obstruct the trachea, which will distend the hypoplastic lungs of fetuses with diaphragmatic hernia.

In experiments with fetal rabbits and sheep, Bland and colleagues demonstrated that fetal lung fluid production decreased prior to the onset of labor, and the volume of lung fluid in the airspaces decreased from about 25 ml/kg to 18 ml/kg (31). The fetal lung fluid volume decreased further with labor such that the airways contained about 10 ml/kg at delivery. Harding and Hooper measured an airspace fluid volume of about 50 ml/kg in fetal sheep at term and without labor, which is about twice the functional residual capacity of the newborn term lamb after adaptation to air breathing (30).

The endocrine adaptations that begin before delivery are critical to fluid clearance. Cortisol, thyroid hormones and catecholamines all increase and shut down the active chloride mediated secretion of fetal lung fluid and activate the basal $Na^+$, $K^+$, ATPase of type II cells on the airway epithelium. Sodium in fetal lung fluid enters the apical surfaces of type II cells and is pumped into the interstitium with water and other electrolytes following passively, thus removing fluid from the airways. In preterm fetal sheep, infusion of cortisol and $T_3$ will activate the sodium pump, which normally occurs at term(16). The components of fetal lung fluid then are cleared directly into the vasculature or via lymphatics from the lung interstitium over many hours.

This clearance of a large volume of airspace fluid is remarkably efficient normally. The essential contribution of activation of $Na^+$ transport was demonstrated by respiratory distress in animals from amiloride inhibition of the $Na^+$, $K^+$, and ATPase. Mice with defective $Na^+$ transporters will die following delivery because of failure to clear fetal lung fluid (32). The frequent clinical scenario where retained lung fluid contributes to poor respiratory adaptation is the operative delivery of infants who were not in labor. These infants do not increase their oxygen saturations as quickly as vaginally delivered term infants (28), and there is an increased incidence of transient tachypnea of the newborn and other respiratory morbidities (29)(Table 1). In experimental studies in sheep, the increased volume of fetal lung fluid interferes with respiratory adaptation, and vaginal delivery facilitates adaptation relative to operative delivery at equivalent volumes of fetal lung fluid (33).

Transient tachypnea of the newborn is most frequent in late preterm infants. This syndrome is thought to directly result from ineffective clearance of fetal lung fluid because of inadequate $Na^+$ transport, either because of decreased numbers of transporters or lack of activation (34). Preterm infants also have decreased $Na^+$ transport, and late preterm infants with transient tachypnea of the newborn have low amounts of surfactant (35). Thus, the infant with transient tachypnea of the newborn has immaturity of $Na^+$ transport and a tendency for surfactant deficiency while the infant with RDS has more severe surfactant deficiency that also includes immature $Na^+$ transport. These two diseases probably are, in fact, a continuum of these two abnormalities from mild to severe.

A hypothetical calculation may help the clinician to understand why lung fluid can compromise neonatal adaptation. If the 3 kg term infant has about 30 ml/kg of fetal lung fluid in the airspaces at Cesarean delivery without labor and that infant is intubated, then no fluid can passively drain from the lungs. Assuming that the blood volume of this infant is 80 ml/kg and the hematocrit is 50 %, then the plasma volume is 40ml/kg. The fetal lung fluid will move from the airspace to the lung interstitium initially interfering with lung mechanics and gas exchange. This fluid then will be transferred to the plasma, which if this occurred acutely would expand plasma volume from 40 ml/kg to 70 ml/kg. This transfer occurs over hours in reality. Nevertheless, the fetal lung fluid volume that must be accommodated during neonatal adaptation is added stress for the newborn.

## 2. Breathing at Birth

The essential component to neonatal adaptation to birth is the maintenance of adequate respiratory effort. The stimuli changing the fetal breathing pattern virtually instantaneously to continuous breathing remain incompletely defined and probably are redundant as are the stimuli for other adaptations to birth. Most of the information about fetal breathing and it's transition after birth is from quite old studies using fetal sheep models, with some verification in the human fetus (36). The fetal state in utero can be classified into REM sleep and quiet sleep with no clear periods of wakefulness. During REM sleep, the fetus has irregular breathing activity characterized by long inspiratory and expiratory times with movement of variable volumes of fetal lung fluid (mixed with amniotic fluid) into and out of

the lung. Fetal breathing, swallowing and licking activities are confined to REM sleep, with minimal movements during quiet sleep. Fetal hypoxia abolishes fetal breathing while high fetal $PO_2$ values stimulate fetal breathing. With birth, the fetal sheep will not breathe consistently until the cord is clamped. This observation has generated the hypothesis that breathing is suppressed by a placentally derived substance except in the REM state. Fetal sheep given prostaglandin $E_2$ infusions stop breathing, and treatment with prostaglandin synthetase inhibitors such as indomethacin cause continuous fetal breathing (37). The net effect is that the normal fetal to neonatal transition results in the rapid onset of vigorous breathing because of the combined stimuli of cord clamping (and the probable removal of rapidly catabolized prostaglandins that suppress breathing), diffuse tactile and cold stimuli that act centrally, and changes in $PCO_2$ and $PO_2$ levels in the blood. The newborn will not initiate breathing if hypoxia is severe. Remarkably, in the absence of hypoxia, virtually all term infants will effectively initiate breathing. The majority of very preterm infants also will successfully initiate breathing if given opportunity (38).

## 3. Surfactant and Lung Adaptation

The adequate development of the fetal lung to support gas exchange is the essential adaptation in preparation for birth. During the last third of gestation the fetal lung septates into about 4 million distal saccules (respiratory bronchioles and alveolar ducts) derived from the 17 generations of airways by about 32 weeks and then further separates to form alveoli (39). In parallel the lung parenchymal tissue mass decreases relative to body weight such that the potential gas volume of the airways and alveoli increase greatly. Concurrently from about 22 weeks gestational age surfactant lipid and the lipophilic proteins SP-B and SP-C begin to be synthesized and aggregated into lamellar bodies in the maturing type II cells (40). The lamellar bodies are the storage and secretory packets for the essential biophysically active components of surfactant. As the lung matures, more and more of the lamellar bodies are released into fetal lung fluid and subsequently mix with amniotic fluid or are swallowed. By term type II cells in the fetal lung contain much more surfactant than does the adult lung, and this large pool of surfactant is poised for release prior to and at delivery.

As delivery approaches, fetal lung fluid secretion ceases (see above) and fetal lung fluid volume may decrease. Simultaneously, surfactant is secreted into the fetal lung fluid with labor, which will increase the surfactant concentration in the fetal lung fluid(41). The presumed mediators of this secretion are the increases in catecholamines that stimulate Beta-receptors. Purinergic agonists such as ATP may also promote this pre-delivery secretion. Subsequently the initiation of ventilation following birth causes alveolar stretch and therefore deformations of type II cells, another secretion signal. The large increase in catecholamines following delivery probably further stimulates surfactant secretion. In term animals shortly after birth, the alveolar pool size of surfactant is about 100 mg/kg. This value is 5 to 20 fold higher than the amount of surfactant in the alveoli of healthy adult animals or humans. Although no measurements are available for the term human, a similar value is likely based on the amount of surfactant present in amniotic fluid at term. Thus the term fetus is assured of having adequate surfactant for the transition to air breathing (42). The high surfactant pool size decreases to adult levels over the first week of life in animal models. Following operative delivery of preterm lambs, a stable surfactant pool of alveolar surfactant is achieved in about 3 hours despite no labor (43). Although there has been no surfactant secretion prior to delivery, the endocrine and lung stretch effects allow the unlabored fetal lung to quickly adapt to air breathing. The secretory events concurrent with birth do not appreciably deplete surfactant stores in type II cells because surfactant synthesis and packaging into lamellar bodies continues and the surfactant that has been secreted also is recycled back into type II cells for secretion as needed (44).

The preterm lung has several disadvantages for transition to air breathing. The structurally immature lung has less potential lung gas volume relative to body weight and metabolic needs, and secretion of fetal lung fluid may not cease prior to and after delivery, which will delay clearance of fetal lung fluid. Further, the amount of surfactant stored in type II cells is low, and thus less surfactant can be secreted in response to birth. The result is a lower concentration of surfactant to form a surface film and stabilize the lung. Surprisingly many preterm lungs can adapt, perhaps with a bit of help from continuous positive airway pressure. The small alveolar surfactant pool size need not be more than about 5 mg/kg for the preterm lamb supported by continuous positive airway pressure (45). This result illustrates that the term infant has large excesses of surfactant to assure a successful transition to air breathing.

## 4. Injury of the Preterm Lung

The transition from a fetus to a newborn requires the initiation of breathing, clearance of fluid from airways, and ventilation of the distal airspaces. Normal newborns inflate their lungs at birth by generating large negative pressure breaths, which pull the lung fluid from the airways into the distal airspaces. The infant continues to clear lung fluid with subsequent inflations (46, 47). Spontaneously breathing newborn rabbits quickly move fluid from their airways to the alveoli and subsequently into the interstitium at birth, with 50% of lung aeration occurring with the first three breaths. They use an increased inspiratory volume to expiratory volume ratio to achieve functional residual capacity (FRC)(47). The majority of the clearance of fetal lung fluid occurs during inspiration, with a return of lung fluid into airways during expiration when PEEP is not used(47). In newborn preterm rabbits, the use of PEEP during initiation of ventilation facilitates the development of FRC and surfactant treatment creates more uniformed distribution of FRC (48, 49)

Many preterm or asphyxiated term infants do not have adequate spontaneous respirations at birth and require positive pressure ventilation. Premature infants have immature lungs that are more difficult to ventilate due to inadequate surfactant to decrease surface tension and maintain FRC. The airways in the preterm lung stretch with positive pressure ventilation and the decreased surfactant pools contribute to non-uniform expansion of the lung with areas of focal over- distension and atelectasis (50, 51). The initial ventilation of the preterm lung will occur before much of the endogenous surfactant is secreted and surfactant therapy cannot practically be given before the initiation of ventilation. The movement of fluid at the air interface across epithelial cells generates high surface forces that distort the cells and injure the epithelium of the small airways, a feature prominent in infants in the lungs of infants who have died of RDS (52, 53). CPAP or PEEP should minimize the movement of fluid in the airways, and surfactant will lower the pressure required to move fluid into the small airways and decrease the injury from fluid movement (48, 54). As few as six large tidal volume breaths at birth can eliminate the surfactant treatment in responses of preterm sheep because of acute lung injury (55). In preterm sheep models, we demonstrated that airway stretch occurs during initiation of ventilation and initial injury is localized primarily to the bronchi and bronchioles (53). Acute phase response genes involved in inflammation, angiogenesis, vascular remodeling, and apoptosis were activated within the lung, and immunologically active proteins (HSP70, HSP60) were released by the airway epithelium into the airspace fluid (56).

As with preterm sheep, ventilated very low birth weight (VLBW) infants have increased pro-inflammatory cytokines (IL-8, IL-1β, IL-6, and MCP-1) in tracheal aspirates soon after birth, which correlate with an increased risk of BPD (57). Ventilation of preterm infants with respiratory distress increased plasma levels of IL-1β, IL-8 and TNF-α and decreased levels of the anti-inflammatory cytokine IL-10 (58). We previously demonstrated that regardless of the tidal volume or PEEP used, initiation of ventilation in fluid-filled,

surfactant deficient preterm lambs is injurious (56, 59). Small increases in the endogenous surfactant pool size can increase the uniformity of lung expansion and thus decrease focal injury (60). The preterm lung is likely at risk for small and large airway injury from initiation of ventilation during resuscitation.

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### Key Points

1. The transition from fetal to extrauterine life is the summation of multiple rapid organ adaptations that often have redundant mediators.
2. The primary mediators that both prepare the fetus for birth and support the multi-organ transitions are cortisol and catecholamines.
3. Lung adaptation requires the coordinated clearance of fetal lung fluid, surfactant secretion, and the onset of consistent breathing.
4. Cardiovascular transition requires striking changes in blood flow, pressures and pulmonary vasodilation.
5. Abnormalities in adaptation are frequent following preterm birth or delivery by cesarean section at term.

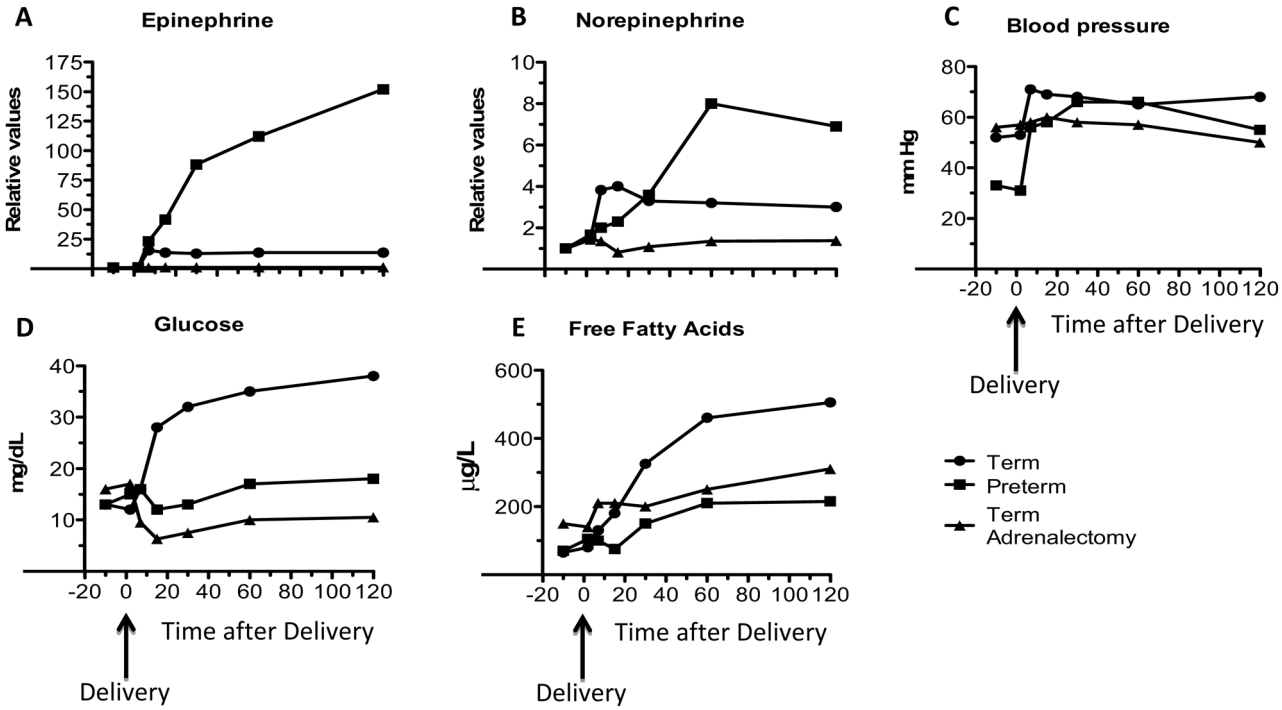


**Figure 1.**

Catecholamine response to delivery of term lambs, preterm lambs and term lambs following adrenalectomy. Fetal term (145±2 day gestation) and preterm (130±1 day gestation) lambs were delivered at 0 time following fetal catheter placement. The adrenalectomy lambs had adrenal glands removed at 138±1 days and received continuous cortisol supplemental until delivery at 142 days gestation. Epinephrine and norepinephrine values are expressed relative to the values measured 10 min prior to delivery. A. Epinephrine increased about 12 fold over the -10 min value for the term lambs, and this increase was ablated by adrenalectomy. The increase in epinephrine was much larger for the preterm lambs. B. There was a similar pattern for the norepinephrine responses. C. Blood pressure increased in term and preterm animals but not in term adrenalectomized animals. D, E. Glucose and free fatty acids in blood increased more for term than preterm lambs with minimal increases following adrenalectomy. Data from Padbury *et al* (6, 8).

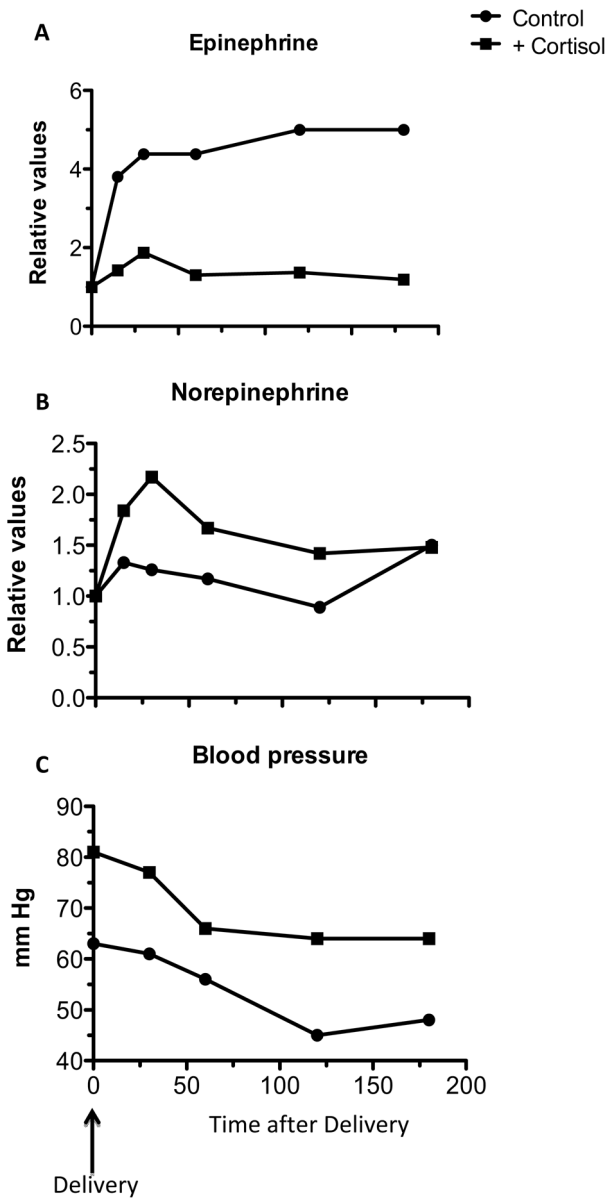


**Figure 2.**

Antenatal cortisol alters postnatal catecholamine secretion and blood pressure responses to delivery in preterm lambs. Fetal sheep had vascular catheters placed at 122–125 days gestation, and the fetuses were randomized to a 60 hr cortisol or vehicle infusion at 128 days gestation. The fetuses were delivered and supported on mechanical ventilation. During transition, epinephrine (A) and norepinephrine (B) increased more in control lambs than in cortisol-exposed lambs. Nevertheless, blood pressure (c) was higher in the cortisol-exposed newborns than the control animals. Data from Stein *et al* (11).

**Table 1**

respiratory morbidities are increased by Cesarean section deliveries without labor relative to vaginal births after a previous Cesarean section.[†]

| | Cesarean Section | Vaginal Birth |
|---|---|---|
| Number | 15212 | 8336 |
| Respiratory Distress Syndrome | 2.1% | 1.4%[*] |
| Transient tachypnea | 4.1% | 1.9%[*] |
| Oxygen therapy | 4.4% | 2.5%[*] |
| Mechanical ventilation | 1.3% | 0.8%[*] |

[*] $p < 0.001$ vs. Cesarean section,

[†] Data from Jain L and Eaton D. C. (29)