Transition from fetus to neonate

Amit Gupta
Anshuman Paria

Abstract

This article provides an overview of the key physiological changes that take place as the fetus transtitions to neonatal life. It provides and an overview of fetal transition with a focus on respiratory and cardiovascular changes.

Keywords Catecholamines; cortisol; CPAP; ductus arteriosus; lung fluid; pulmonary blood flow; surfactant; transition

Introduction

Fetal transition is a dynamic process with profound changes in physiology involving all systems. The key change is the establishment of breathing which is accompanied by concurrent changes in pulmonary flow as the fetus starts an independent existence. Striking adaptive changes are needed to navigate this challenging phase safely and expeditiously, and sick and preterm babies may need prompt medical help to ensure successful transition.

Respiratory transition

The transition from fetal to neonatal life requires fluid-filled lungs to be aerated, followed by initiation of pulmonary gas exchange as well as the conversion of fetal circulation into the adult form. Complex changes to fetal physiology happen within minutes of birth.[1] The vast majority of infants make this transition without any clinical intervention with fewer than 10% of babies requiring some form of support and <1 % needing extensive resuscitation (e.g. chest compression).[1]

Respiratory transition includes three main events: clearance of lung fluid; initiation of breathing; and surfactant production and distribution. Infants born preterm pose additional challenges related to size and end organ immaturity.

Clearance of lung fluid

In utero, the airways are filled with liquid that is secreted by the fetal lung, which then effuses through the trachea. Fetal lung growth and airway development are stimulated by lung distension. This is of clinical relevance as conditions that lead to inadequate fetal lung fluid production (as in renal agenesis) or long-standing loss of amniotic fluid (long-standing premature rupture of membrane in extreme preterm babies) will lead to decreased amount of fetal lung fluid, resulting in pulmonary hypoplasia. In congenital diaphragmatic hernia, lung growth can be increased by blocking the egress of lung fluid through trachea.

During fetal life, the lung epithelium is in a secretory mode, mainly caused by active secretion of chloride ions. At birth, there is an urgent need for the newborn to clear this liquid rapidly in order to allow air entry and trigger the onset of gas exchange.

Both mechanical and cellular mechanisms are required to achieve rapid elimination of this lung fluid. Recent literature has identified three different mechanisms to be responsible for clearance of this fluid:[2]

1. Uterine contractions during labour play a vital role by increasing the fetal abdominal pressure and forcing the fetal diaphragm upwards resulting in an increase in airway pressure. This increase in pressure results clearance of lung fluid via the trachea.
2. The change in maternal fetal hormonal milieu associated with impending delivery, including an upsurge in hormonal concentrations of glucocorticoids and adrenaline, the latter being further increased by the labour. Adrenaline stimulates the Na^+ reabsorption mechanism from the airways via activation of epithelial apical sodium channels. Once sodium is in the epithelial cells, it is actively pumped out into the interstitium by Na–K-ATPase pump. Chorine ions and water passively follow Na^+ into the interstitium. The high osmolarity of the interstitial fluid may play a part as well. Increased availability of oxygen at birth potentiates the process, promoting further lung fluid clearance.
3. Most importantly perhaps, recent studies have shown that rapid clearance of large volume of lung fluid is initiated by an increase in transpulmonary (i.e. across the airway wall) pressure generated during inspiration or lung inflation. This pressure provides a hydrostatic pressure gradient that drives the intra-alveolar liquid to move from the airways and into the surrounding interstitial tissue. This movement has been observed in rabbit models to be as fast as 35 ml/kg/h, a rate much higher than possible by epithelial Na channels. Once this fluid has been pushed into the interstitial compartment, the pressure in that compartment remains increased for at least 4–6 hours and then gradually comes down, drained by pulmonary vasculature (mainly) as well as lymphatics (approximately 15%).[2]

High compliance of the chest wall plays two important roles in this transition. It allows for the pressure from uterine contractions to be transferred to the thoracic cavity, resulting in partial clearance of fluid from airways, and it helps to accommodate the rapidly shifting fluid into the pulmonary interstitium.

The increased incidence of transient tachypnoea of newborn in babies born to mothers who did not undergo rigour of labour (i.e. elective caesarean section) is due to a combination of decreased antenatal (lack of uterine contraction) and postnatal fluid clearance (lack of catecholamine induced upregulation of Na^+/K^+/ATPase pumps).

Surfactant

Surfactant plays an important role in lung inflation by counteracting the surface tension, and thereby preventing the alveoli from collapsing. The absence of sufficient surfactant leads to

Amit Gupta ***MD FRCPCH*** *is a Consultant Neonatologist at Oxford University Hospitals NHS Trust, Oxford, UK. Conflicts of interest: none declared.*

Anshuman Paria ***MRCPCH MD DM (Neonatology)*** *is a Locum Consultant in Neonatology at East Lancashire Hospitals NHS Trust, UK. Conflicts of interest: none declared.*

neonatal respiratory distress syndrome (NRDS) characterized by widespread collapse and diffuse atelectasis of the lung, with plain X-ray showing small volume 'whiteout' lungs in its severest form.

The incidence and severity of RDS are inversely proportional to the gestational age of the baby. Type II pneumocytes within the lungs start producing surfactant at 22 weeks of gestation and the surfactant pool increases in size with gestational maturity. This is exemplified by the fact that surfactant pool in preterm babies with RDS is approximately 5 mg/kg compared with term neonates who have a pool of 100 mg/kg. Surfactant present in preterm babies also has proportionally lower quantities of phosphatidylglycerol and surfactant proteins.[3]

Surfactant production by type 2 pneumocytes is induced by antenatal corticosteroids. Antenatal steroids in preterm babies also improve the lung mechanics-improving the overall lung volume and compliance, allowing a better gas exchange. Antenatal steroids also induce pulmonary beta receptors. Catecholamines released during labour act through these receptors and stimulate the release of surfactants as well upregulates epithelial Na^+ channels, important for absorption of lung fluid after birth.[4] Of particular clinical importance is the fact that surfactant production is increased by both exogenous and endogenous steroids. Chorioamnionitis can lead to surfactant synthesis, hence these babies may have lower severity of respiratory distress syndrome, however, the presence of inflammation puts them at a higher risk of Chronic lung disease.

Initiation of breathing

During fetal life, the fetus breathes episodically, mainly during REM sleep phase.[4] The stimuli for initiation of spontaneous breathing are ill-defined and are thought to be due to a combination of the removal of placenta-derived rapidly catabolized prostaglandins as a result of cord clamping, a drop in ambient temperature, a rise in PCO_2 and a catecholamine surge.[5] Unless severely hypoxic, the fetus moves into a pattern of regular spontaneous breathing soon after birth.

The initial breaths in spontaneously breathing newborns generate very high inspiratory (mean = −52, maximum up to −105 cmH_2O) and expiratory (mean = +71 cm) pressures with the average inspiratory tidal volume of approximately 40 ml. To generate the lung volumes seen in stable term newborn, they often employ expiratory braking, which is attempted exhalation against partially closed glottis. Expiratory braking is also used during initial cry to aid lung recruitment.[5]

Fetal oxygenation

Fetal oxygen saturations are approximately 70%, and drops even further during labour. However, this is sufficient for the fetus, owing to presence of fetal haemoglobin with high oxygen affinity and relatively low in utero oxygen consumption. The low intrauterine requirement of oxygen is due to the fact the fetus does not need to spend energy to maintain thermoregulation as well the reduced activity of various organs, such as lungs, gut and kidney. Saturations rise rapidly after birth, to reach 80–90% by 5 minutes of life.

Clinical relevance

Application of positive end expiratory pressure (PEEP) assists by providing an opposing pressure within the airspaces which counterbalances the high interstitial tissue pressure, preventing fluid re-accumulating in the airways in the absence of PEEP. In babies, unstressed by labour such as those born by caesarean section as well as those preterm babies where adrenaline mediated sodium transport is minimally effective, there is relatively more fluid in the airway which needs to be moved into the interstitium during initial inspiratory breaths. The clearing of this extra fluid would need higher inspiratory pressures; however, this in turn may result in an increased amount of interstitial fluid, forming perivascular cuffs and fluid in the fissures. This increases the likelihood of the fluid reentering the airways during the expiratory phase. CPAP provides continuous positive pressure in both phases of breathing and this forms the basis of its effectiveness in the treatment of infants with transient tachypnoea of newborn.

Apart from having a smaller surfactant pool, the lungs in preterm infants are more immature with fewer air spaces as compared to overall lung volume. Prompt administration of appropriate level of delivery room CPAP can not only prevent the collapse of alveoli but also prevents interstitial lung fluid from reentering the alveolar cavity. Endocrine changes following the birth of the unlaboured fetus (catecholamine release) as well distension of alveolar cavity causing stretch-induced deformations of type 2 pneumocytes, leads to the release of surfactants. This now forms a thin but functional layer of surfactant over alveolar surface, which stabilizes the lung volume in conjunction with CPAP.[6]

The lungs of preterm infants are fragile and are prone to injury if over distended. Six large volume breaths may be sufficient to cause lung injury. The role of the use of surfactant is well established. However, recent evidence supports the use of CPAP in the first instance in spontaneously breathing preterm infants. Several recent trials using either CPAP alone or a combination of brief intubation and surfactant installation followed by CPAP have shown benefit in reducing long-term lung disease.[7] Meta-analyses have also shown that for every 25 babies treated with CPAP in delivery room vs. intubation, one additional newborn would survive to 36 weeks without bronchopulmonary dysplasia.[7]

Cardiovascular transition

Lung aeration plays a pivotal role in initiating the complex cascade of events in cardiovascular physiology that are vital to a smooth transition.

Fetal circulation

In fetal life, the ventricles of the fetal heart pump in parallel as the right and left ventricle both contribute predominantly to the systemic circulation. However, soon after birth, owing to changes described below, right ventricle starts pumping into pulmonary circulation, which drain into left atrium and this blood gets pumped into the systemic circulation by the left ventricle, thus completing a series circulation.

In fetal life, pulmonary vascular resistance (PVR) of the fluid-filled lung field is high and pulmonary blood flow is only 10% of

this combined ventricular output. Most of the right ventricular output (~90%) flows pass through the ductus arteriosus (an embryonic connection between the pulmonary artery and aorta) into the aorta, contributing to systemic blood flow. The low resistance placental circulation at least receives 30–50% of combined ventricular output and contributes in similar proportion to the venous return to right side of the fetal heart through the umbilical vein. The oxygenated umbilical venous (highest oxygen concentration in fetal circulation) blood flows through the ductus venosus (a fetal connection between the umbilical vein and IVC), passes up the IVC and into the right atrium. The oxygenated blood from the ductus venosus undergoes minimal mixing in the IVC and streams preferentially (owing to differential velocities) through the foramen ovale (embryological opening between RA and LA) to directly enter the left atrium (LA). This serves two purposes: it provides a left-sided preload, and it results in pre ductal cerebral circulation to be preferentially more oxygenated as compared with the post ductal arteries. After birth, the initiation of pulmonary gas exchange triggers a significant decrease in PVR and increase in pulmonary blood flow (PBF).

In fetal life there are four important shunts: placenta, ductus venous, foramen ovale and ductus arteriosus. As soon as the cord is clamped; the systemic resistance is increased as the low resistance placenta is removed. Functional closure of ductus venosus (DV) occurs soon after birth, while structural closure requires longer, about 3–7 days in a term baby. This anatomical patency of DV is key for successful umbilical venous catheterization during first week of life.

Once the cord is clamped, the foramen ovale still remains an opening within the atrial septum covered by a flap valve. Functional closure is brought about soon after birth as the pulmonary vascular resistance decreases to allow more blood in the LA through the pulmonary veins. The increased pressure in the LA closes the flap valve and impedes any flow of blood from the right to left side of the atria.

The ductus arteriosus (DA) is the last of these embryological shunts and often remains patent in preterm babies postnatally. However, in term babies, DA closes functionally within 10–15 hours of birth, mainly as a response to postnatal increase in saturation (PaO_2 25 mmHg in fetal life to 50 mmHg in postnatal life). This oxygen responsiveness of ductal tissue is related to gestational age of the newborn, with ductal smooth muscle in preterm less likely to respond to this increase in oxygen saturation. Preterm babies have higher levels of circulating PGE2 and NO,[15] vital to maintain ductal patency. In term babies, this PGE2 is metabolized by the lung itself, something that premature lungs cannot achieve. Even when there is constriction in the much less muscular walled preterm duct, the medial layer of the ductus does not undergo enough constriction related hypoxia to cause anatomical closure, hence allowing for future reopening.[8]

Functional changes

Animal models suggest that aeration of lungs is the main trigger for an increase in pulmonary blood flow (PBF) showing an increase in PBF by 400% in the absence of any increase in oxygenation.[9] Recent phase contrast X-ray studies have also demonstrated that regional lung aeration can trigger a global increase in PBF resulting in improved left sided cardiac output even in presence of partially aerated lung.[10]

Pulmonary venous flow is the source of LA filling in postnatal life. Clamping of umbilical cord increases systemic vascular resistance (by removal of low resistance placental bed) instantaneously. The flow through the ductus arteriosus is from right to left in fetal life, is bidirectional in immediate postnatal period, and becomes increasingly left to right as PVR falls.

There are differences in how term and preterm infants adapt in the postnatal period. In term babies, the transition from the in-utero parallel circulation to the postnatal series circulation (as the vascular shunts close) is much smoother in contrast to their preterm counterparts. Postnatally, the LA preload increases with decreasing PVR and HR increases initially due to increased catecholamines in the circulation. BP is well maintained with circulating cortisol and catecholamines.

Cardiac output nearly doubles in the immediate postnatal period in term babies, but gradually returns to lower levels within the first 24 hours. This increment in cardiac output in the preterm baby is slower, increasing over first 3–4 days. Pulmonary vascular resistance drops in response to increased oxygenation immediately and then plateaus until 6–8 weeks of postnatal age, when there is further drop of pulmonary pressure. Failure of pulmonary pressures to drop postnatally may cause persistent pulmonary hypertension in the newborn.

Systemic vascular resistance (SVR) may be variable in very premature neonates. High SVR may compromise cardiac contractility and impede systemic blood flow, whereas low SVR may lead to systemic hypotension. Low SVR can be due to poor vasomotor tone, immature neuroendocrinal control mechanism, or due to dysregulated NO (nitric oxide) production. A subset of ELBW babies may maintain BP in normal range with low systemic perfusion (high SVR reducing blood flow to all organs other than brain, heart and adrenal – a stage of compensated shock), while others with low BP have been thought to be in state of uncompensated shock. Tissue perfusion and tissue oxygenation are impaired in a state of very high SVR and high BP (reducing organ perfusion) or in a state of very low BP with low SVR (low perfusion pressure). Low SVC flow (a surrogate for systemic blood flow) is present in large proportion of very preterm newborns.[11] Low SVC flow during the early hours has been associated with higher grade Intraventricular haemorrhage.

The fetal myocardium

The fetal myocardium has fewer contractile elements than in later postnatal life (only 30% compared with 60% in adults), a higher aqueous content, an increased reliance on extracellular calcium and a slower release of calcium from the fetal myocardial contractile tissue. The fetal myocardium is also relatively more sensitive to hypoxia (in utero saturation below 30% results in metabolic acidosis), but relatively more resistant to acidosis. In the first 2 weeks of life in ELBW, the transitional myocardial contractility is resistant to drop in pH until 7.02. In fact, the acidosis results in increased myocardial contractility and drop in SVR, leading to improved tissue perfusion. Overzealous correction of acidosis may not increase myocardial contractility in these babies during the first 14 days of life.[12]

Clinical relevance

Delaying the clamping of the umbilical cord until ventilation has been established has a physiologically sound basis. It allows for aeration-induced pulmonary vasodilatation and improvement of pulmonary venous flow, and avoids a sudden drop in LA preload associated with immediate clamping of umbilical vessels (as blood from umbilical vein flowing through PFO into LA stops).

In preterm infants, the immature myocardium is incapable of improving on the baseline cardiac contractility when challenged. Instead, it responds to increased afterload by a decrease in myocardial contractility. Increase in cardiac output may initially be mainly dependent on a higher increase in heart rate as the very preterm ventricles are also stiffer at birth.

Since flow through ductus arteriosus can be at least 50% of the left ventricular output in very preterm babies, this forms a short circuit where a portion of left ventricular output returns to heart via the DA, through the pulmonary circulation to the left atrium via the pulmonary veins. This can potentially result in pulmonary over-circulation and cardiac overload.

In preterm infants, correlation between BP and systemic blood flow appears to be weak. There is, however, evidence suggesting that low SVC flow initially may be associated with an increased risk of IVH. SVC flow is lower in first 5 days, then gradually increases from 5 hours onwards through the first 2–3 days. IVH tends to happen when the blood flow is normalized after initial period of hypo-perfusion. Delayed cord clamping (DCC) is associated with significantly higher SVC flow and may attenuate this hypo-perfusion-reperfusion phenomenon. This may explain its beneficial effects on reducing the incidence of severe IVH.[11,12]

Owing to the challenges faced by preterm myocardium (increased afterload with a large duct) in the initial few hours of life, addition of vasoconstrictive agents like dopamine to aid sagging mean blood pressure can pose additional problems. Addition of dobutamine (a beta agonist) appears to be more physiological in this scenario.

Endocrine adaptions at birth

Cortisol

Cortisol remains one of the most important hormones in the background of any successful transition from fetus to newborn. A 'cortisol surge' is initiated with the switch from dependence on maternal-derived corticosteroids to the phase where fetal adrenal glands start synthesizing and releasing cortisol under fetal hypothalamic control. Fetal cortisol levels increase gradually with increasing gestation, reaching high levels at term gestation, increasing even further during labour and peaking just after birth.

Cortisol is responsible for some physiological changes relevant to successful transition such as: (i) conversion of T4 to T3; (ii) increasing catecholamine secretion; (iii) increasing the β-adrenergic receptor density in heart and lungs; (iv) maturation of pulmonary surfactants; and (v) maturation of glucose metabolism in the liver. Other than the effects of lung maturation (by increasing collagen and elastin, thinning of alveolar septae, and increasing surfactant production) and aiding lung fluid resorption through catecholamine and T3, cortisol also has beneficial effects on maturation of gut and renal function.

Hypotension in extremely premature newborn is often responsive to cortisol as they are born with very low levels of this key hormone.[13]

Thyroxine

The thyroid hormones increase gradually with increased gestation. Cold stress, cord clamping and increased cortisol levels at birth results in an acute and short lasting rise in TSH and sustained higher levels of T3 and T4.[5]

Cortisol acts along with thyroid hormones to activate the sodium pump that clears fluid from alveoli, an action of key importance to aeration of the lung. Thyroid hormones play a supportive role and prepare the fetus for transition, but unlike catecholamine do not play an active role to modulate adaptation to birth acutely, as evident in the fact that term babies with congenital hypothyroidism often have uncomplicated transition at birth.

Catecholamines

Catecholamines are responsible for most of the acute adaptations that mark the smooth transition to postnatal life. Catecholamine levels are high at birth and this catecholamine surge is primarily responsible for the increase in BP in early postnatal life, for the postnatal changes in energy metabolism resulting in higher glucose and fatty acid levels and for thermogenesis from brown fat. This rise in catecholamine levels is faster in term babies compared with preterm babies, but overall levels are lower. However, although preterm babies have higher catecholamine levels, their physiological responses to these levels are lower than that in term babies as their organ systems are less responsive.[14]

Preterm babies demonstrate a picture of dysregulated endocrinal homeostasis, with higher levels of catecholamines and low levels of cortisol. Preterm infants whose mothers are exposed to antenatal corticosteroids have better adaptation as demonstrated by higher blood pressures and better metabolic transition at birth.

Thermoregulation

Fetal body temperature in utero is maintained 0.5°C higher than the maternal temperature. Once born, babies are exposed to cooler environmental temperatures. This, along with other stimuli present at birth, leads to norepinephrine-mediated thermogenesis by using brown adipose tissue (present around the kidney and in the infrascapular areas in term neonates). Norepinephrine achieves thermogenesis by facilitating uncoupling of oxidative metabolism from ATP synthesis in brown adipose tissue. Thyroid hormones and to some extent cortisol play an important background role in this process. As compared to term neonates, thermoregulation is a bigger challenge in preterm as the brown adipose tissue present lacks in both quantities as well as in maturation of response mechanism to cold stress at birth.[5]

Hypothermia is a proven cause of mortality at birth. For every 1°C drop in admission temperature, odds of dying increase by 28%.[15] Current resuscitation guidelines recommend maintaining delivery room temperature at 26°C, use of polyethylene wrap or bag at birth in newborn infants <28 weeks as well as judicious use of exothermic mattress.[1]

Energy and metabolism

Nearing term, the fetus is in an anabolic state, aided by high insulin and low glucagon levels, and starts preparing from independent existence by increasing the glycogen and fat store. Ketone bodies are also produced in increasing quantities. At birth, the continuous infusion of sugar through the placenta is abruptly stopped, and the ensuing hypoglycemia leads to increase in glucagon, cortisol, and catecholamines in blood. Gluconeogenesis, lipolysis and glycogenolysis are kickstarter and ketone bodies are utilized. Preterm infants have limited stores and are at risk for developing hypoglycaemia if a supply of glucose is not established early. Considering the complexities and magnitude of changes needed, It is indeed surprising that most fetuses manage this complex transition with relative ease. ◆

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