**Fetal Physiology and the Transition to Extrauterine Life**

INTRODUCTION

There are significant structural and functional differences between the physiology of the fetus and the neonate. To ensure the survival of the neonate, the shift from intrauterine to extrauterine life involves quick, intricate, and well-planned steps. To spot abnormalities from regular physiology and handle these situations, neonatal care practitioners must have a thorough understanding of fetal and normal transitional physiology. Neonatal patients who have experienced asphyxia must be managed carefully since it fundamentally affects the physiology of transition.

FETAL PHYSIOLOGY

Cardiac Development

At around 22 days gestation, the heart starts to beat, signaling the start of the human fetal circulation. Up to 10 weeks of gestation, both the yolk sac and the placenta share primary responsibility for gas exchange. The oxygen content of blood supplied to the fetus is lower than that of mother uterine arterial blood, resulting in the fetus living in a somewhat hypoxemic environment. This is because oxygenated maternal blood mixes with poorly oxygenated blood within the free-flowing placental region. There are a number of intrauterine shunts created to divert blood away from the fetal lungs because the fetal lungs do not contribute to intrauterine oxygenation.

In a nutshell, well-oxygenated blood from uterine artery branches of the mother freely flows into the placental space in funnel-shaped spurts beginning at the level of the placenta. Then, veins within many villi that line the fetal side of the placenta receive oxygen via a concentration gradient from the placental space. The capillaries in these villi combine to form the umbilical vein (UV). The highest oxygen saturation in fetal circulation is seen in the umbilical venous blood, which has an oxygen saturation of 70% to 80%². At the level of the liver, where the umbilical vein enters the fetus, it separates, sending some blood to the hepatic circulation and the rest to the ductus venosus¹.

The intrauterine circulation's direction of flow contributes to maximizing oxygen delivery to the developing heart and brain. Although blood from the inferior vena cava (IVC) and ductus venosus (DV) combines close to the fetal heart, each vessel's blood is guided differently within the heart. IVC blood that has low oxygen levels enters the right atrium (RA), mixes with inferior vena cava (SVC) blood that also has low oxygen levels, and is then preferentially guided into the right ventricle (RV). The pulmonary arteries carry a tiny percentage of the RV output to the lungs, while the remainder flow is diverted across the ductus arteriosus to the descending aorta. An oxygen saturation of 60% in this blood flow in the descending aorta perfuses the lower body and abdominal organs before returning to the low resistance placenta.³

The ductus venosus, which provides better oxygenation, is instead preferentially directed from the RA over the foramen ovale to the left atrium (LA). Approximately 25% of the overall cardiac output is accounted for by this right-to-left shunt. In order to supply the carotid and coronary arteries, this shunted blood subsequently combines with a little volume of blood from the pulmonary veins before entering the ascending aorta. Since the majority of this blood comes from the better oxygenated ductal venous blood, the brain and heart receive blood with an oxygen saturation of roughly 65%, somewhat higher than the 60% in the post ductal aorta.²

The fetus's capacity to regulate cardiac output is generally constrained. Increases in preload have only a small effect on cardiac output when the heart is functioning in utero, when it is at the crest of the Frank-Starling ventricular function curve. Fetal tachycardia causes a rise in cardiac output, while fetal bradycardia causes a decrease in ventricular output, which is how fetal cardiac output is predominantly raised. This technique, however, is not optimal because it results in lessened sympathetic innervation and less sympathetic regulation of heart function.

Pulmonary Development

Growth and maturation are the two phases of lung development. In the first trimester, the lobar buds split to create bronchopulmonary segments after the lung bud septates from the foregut. During the canalicular phase of the second trimester, the parts of the airway that exchange gases are produced. At 24 weeks' gestation, alveolar duct development begins, and at 36 weeks' gestation, the air sacs start to septate. Distal pulmonary epithelial cells actively discharge a chloride-rich fluid into the bronchial tree throughout both phases of development10. As a result, fluid builds up inside the fetal airways. The lungs of the fetus are hyperexpanded in comparison to postnatal lungs.¹°

Increased pulmonary vascular resistance is a result of elevated intrapulmonary vascular pressures brought on by fluid distension. This airway fluid's presence is essential for promoting lung growth. Data from fetal lambs support this, demonstrating how tracheal ligation, which stops lung fluid from escaping, causes a higher rate of pulmonary growth and development.¹

Over the course of pregnancy, several components in the fetal lung fluid alter. Due to type II pneumocytes' enhanced expression of surfactant lipoproteins in response to rising cortisol levels near the end of the third trimester, the composition of the fetal lung fluid is changed before delivery. By reducing the surface tension in the lungs, these lipoproteins allow for inflation at lower pressures.

The fetal pulmonary vasculature develops along with the fetal airways and lung tissue. The pulmonary circulation begins to develop in the human baby during 34 days gestation. Recent research 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. This finding is consistent with advances in fetal magnetic resonance imaging (MRI), which have made it possible to examine the relative blood flow in the human fetus with greater precision.

Blood reaching the intrauterine pulmonary circulation has an oxygen saturation level of roughly 55% due to preferential shunting of deoxygenated blood into the right ventricle. Nitric oxide and prostaglandin I215 production are suppressed as a result of fetal hypoxemia's reduced pulmonary blood flow. As a result, the baseline pulmonary vascular resistance is increased. Any further fetal hypoxemia brought on by maternal or placental problems lowers the amount of oxygen delivered to the pulmonary circulation, increasing pulmonary vascular resistance and activating hypoxia inducible factor-1, which in turn brings about vascular remodeling.³

The fetal lungs undergo morphological and functional changes during gestation, much like the cardiovascular system does. Beginning at 10 weeks gestation, rapid eye movement sleep is accompanied by fetal respiration. Hyperoxia stimulates it whereas hypoxia inhibits it. As phrenectomy in fetal sheep causes pulmonary hypoplasia, such breathing movements are crucial to the development of the lungs.

Endocrine development

From 30 to 36 weeks' gestation, cortisol production rises, and a second peak happens just before spontaneous delivery at term gestational age18. Increased cortisol levels result in the thyroid hormone being activated, the hepatic glucose metabolism enzymes maturing, and better euglycemic control following delivery. In cases of premature delivery or C-sections without labor, cortisol levels are decreased; in cases of chorioamnionitis, they are elevated.

Hematologic development

Fetal erythropoiesis begins in the yolk sac during weeks two and three of gestation. The liver replaces the bone marrow as the principal site of erythropoiesis between 5 weeks and 6 months of gestation. The production of erythropoietin by the fetal kidneys is stimulated by relative hypoxia-inducible factor-1, which also increases the oxygen carrying capacity of red blood cells and thus improves fetal oxygenation.

Fetal hemoglobin is another method the fetus uses to make up for the relatively hypoxemic environment. Due to the high oxygen affinity of this particular hemoglobin, the oxyhemoglobin curve is shifted to the left, increasing oxygen intake at the lower oxygenated placental vascular bed. If local conditions do not change the oxygen affinity of fetal hemoglobin, the oxygen offload to capillary beds in tissues will be reduced as a result of the greater affinity. For instance, prenatal acidosis increases oxygen supply to tissues by lowering fetal hemoglobin's affinity for oxygen.

Transition

Alterations in circulatory pathways, beginning of ventilation and oxygenation via the lungs instead of the placenta, and other metabolic changes are characteristics of the transition to extrauterine life.

Cardiovascular changes

The pulmonary vascular resistance dramatically lowers with the first postpartum breath. This is brought on by both increased oxygen exposure and ventilation itself. When the umbilical cord is clamped, the placenta's low-resistance vascular bed is cut off, increasing the newborn's systemic vascular resistance. Due to the elevated distal aortic pressure and more blood flowing back into the LA from the lungs, the pressure inside the LA then rises. The flap over the foramen ovale shuts when the pressure in the left atrium is higher than that in the right atrium.

Most term babies experience a left-to-right flow reversal through the ductus arteriosus within the first 10 minutes of life, which increases pulmonary blood flow. In the first hour following birth, serial ultrasonography has shown a doubling of LV output and a concurrent increase in stroke volume. Systemic vascular resistance (SVR) affects blood pressure more than blood flow during the circulatory transition from fetal to neonatal physiology. A quick and temporary increase in cerebral blood flow results from an increase in SVR. The fetal cardiac shunts close as a result of increased oxygenation and reduced blood flow. Increasing calcium channel activity as a result of ductus arteriosus oxygenation also causes functional closure. Increased oxygen levels cause potassium channel activity in the smooth muscle cells of the ductus arteriosus to be inhibited, which also results in ductal constriction.

Numerous birth-related factors, such as the moment the umbilical cord is clamped, influence these events. The principal source of in utero left-sided venous return from the ductus venosus (i.e., ductus venosus RA PFO LA LV) is eliminated by clamping the umbilical vein before the start of ventilation. As a result, there is a period of lower left ventricular preload and decreased cardiac output that lasts until ventilation is established. This happens prior to an increase in pulmonary blood flow. This decline in cardiac output can be avoided by delaying cord clamping until the start of breathing. The umbilical arteries are supposed to vasoconstrict before the umbilical vein closes, resulting in net blood flow to the baby. As a result of the placenta's and the baby's different heights, this hasn't always been observed in practice.

A brand-new, non-invasive technique for determining local perfusion and oxygenation has increased our understanding of the subtle circulatory alterations that take place before delivery. The tissue oxygenation index can be determined using near-infrared spectroscopy (NIRS), which can also be used to determine peripheral blood flow and oxygen delivery. Term newborns exhibit a rise in cerebral perfusion in the first few minutes of life, which is correlated with an increase in blood oxygen content, according to NIRS measurements of cerebral oxygen saturation. The brain experiences this increased oxygenation more quickly than other tissues. Intriguingly, throughout the first several weeks of life, brain oxygen saturation is higher and less variable than abdominal tissue oxygen saturation in preterm newborns.

Pulmonary changes

At the start of labor, significant pulmonary alterations are initiated. By producing a monolayer at the liquid-air interface, surfactant, a combination of lipids and proteins, lowers the surface tension in airways. Labor promotes surfactant secretion into the fetal lungs. Alveolar stretching brought on by the start of breathing further boosts surfactant secretion. The lungs' surface tension is reduced by these polar molecules, enabling inflation at lower pressures.

The elimination of fetal lung fluid also starts prior to birth, is accelerated by labor, and is largely finished by the time the baby is two hours old. Various mechanisms support this process in various ways. The respiratory epithelium switches from active fluid secretion (with active chloride transport into the intraluminal space) to active fluid absorption during spontaneous labor and right after birth (with active sodium transport into the interstitium). It is thought that the sodium-mediated active absorption process begins even before labor and is controlled by elevated cortisol and thyroid hormone levels. During spontaneous labor, activation of the beta-receptor agonist stimulates this respiratory epithelium shift. Following birth, increased oxygenation aids in preserving the expression of these sodium-mediated channels. Increases in the trans-epithelial pressure gradient during inspiration, which pushes fluid into tissues where it may be evacuated by the pulmonary microcirculation and lymphatic vessels32, have also been demonstrated to clear embryonic airway fluids postnatally in a rabbit model. Effective fetal lung fluid clearance lowers pulmonary vascular resistance, and during the first few hours after birth, the increased intravascular fluid volume causes an increase in plasma volume.

Infants must develop breathing patterns after birth that are more regular than those of the fetus. With the exception of those who have severe hypoxemia, which inhibits the start of breathing, most term and preterm infants will breathe on their own. After vaginal delivery, gas exchange stabilizes in the majority of newborns within two minutes, and the strongest clinical indicator of effective breathing is an increase in heart rate. In comparison to term babies, preterm babies have reduced lung volumes per unit of body weight and delayed fetal lung fluid clearance due to lower sodium absorption. Decreased sodium absorption is also present in newborns with transitory tachypnea of the newborn or surfactant insufficiency.

A functional residual capacity develops as soon as breathing is started when the inspiratory to expiratory volume ratio is positive (FRC). The baseline FRC is lower in preterm newborns with lower surfactant levels. A more uniform FRC can be established in preterm newborns with the aid of positive end-expiratory pressure. By inducing the creation and secretion of surfactant, continuous positive airway pressure can aid premature newborns in adapting.

According to an observational study of term infants, in healthy newborns breathing room air, oxygen saturation did not reach 90% until an average of 8 minutes after birth. For the first 15 minutes after birth, post ductal saturations were on average 8% lower than preductal saturations. The relaxation of pulmonary vascular smooth muscle, which is a result of oxygenation, is mediated in part by an increase in cGMP-dependent protein kinase activity.

Pulmonary blood flow undergoes major alterations with the start of respiration. When cardiac shunts are closed, the circulatory system is transformed from fetal to neonatal, with each ventricle having a cardiac output of 400 mL/kg/min instead of the fetal configuration's parallel output from the right and left ventricles contributing to a total cardiac output of 450 mL/kg/min18. This rise in right-sided output causes the newborn's pulmonary blood flow to reach 100%. By increasing the synthesis of nitric oxide, higher pulmonary blood flow reduces pulmonary vascular resistance.

By 24 hours of age, the pulmonary arterial pressure is equal to half the systemic arterial pressure, and by 2 weeks, it approaches adult values in the majority of typical newborns. When compared to ventilation with the proper physiologic rise in oxygen, experimental paradigms that permit ventilation without oxygenation demonstrate a slowed decline in pulmonary vascular resistance.

Hematologic changes

Fetal hemoglobin production declines after delivery, and hemoglobin chain production rises concurrently, so that by 4 to 6 months of age, normal amounts of adult hemoglobin are reached. In comparison to the fetus, the neonate experiences lower rates of erythropoiesis (nadir at around one month) due to decreased erythropoietin caused by exposure to the extrauterine environment's enhanced oxygenation.

Metabolic changes

Separation from the placental circulation halts the active transfer of glucose and amino acids to the fetus across the placenta42. Smaller mammals typically have higher metabolic rates. Despite its small size, the fetus has a low metabolic rate that is comparable to that of a pregnant woman. After delivery, there is a gradual rise in metabolic rate; in preterm infants, this rise happens more slowly. The density of mitochondria grows as metabolic rate grows.

The infant experiences an increase in catecholamine and glucagon levels and a drop in insulin levels in order to maintain blood glucose after being released from the placental circulation. As oral intake amounts increase over the first few days after birth, gluconeogenesis and glycogenolysis in the liver maintain steady blood glucose levels. Additional energy for the brain is provided by ketone bodies and lactate, with hepatic ketogenesis increasing after the first 12 hours of life.

Many hormonal changes required for a smooth transition to extra-uterine life start during the fetal period, similar to pulmonary alterations. At 30 weeks gestation, cortisol levels start to climb and reach their peak right after delivery. Cortisol and thyroid hormone work together to activate sodium channel activity, which promotes the resorption of lung fluid. Infants who do not respond adequately to the physiologic challenge may have a relative adrenal insufficiency, which can be discovered during stressful deliveries or Cesarean sections without labor.

In addition to other sympathetic nervous system components, the newborn adrenal medulla releases norepinephrine, epinephrine, and dopamine. The use of a lamb model has been used to illustrate the significance of catecholamines in the adaptation to extrauterine life. Neonatal lambs with adrenalectomy at term had significantly lower epinephrine and norepinephrine concentrations, which led to decreased blood pressure. Renin-angiotensin, catecholamine, and vasopressin production and release are all boosted during pregnancy and childbirth. These play a crucial role in the postnatal increase in cardiac output, plasma glucose levels, and free fatty acid levels. While catecholamine levels in preterm neonates rise more slowly than those in term newborns, they plateau at higher serum levels. The transfer from the uterine milieu to the extra-uterine environment requires changes in blood pressure, serum glucose, and free fatty acids, all of which are interestingly lower in term neonates than in the fetus.

Temperature Regulation

Infants are born drenched in liquid, which could cause evaporation to lose heat. Hypothermia can develop in neonates if they are not held skin-to-skin or covered in a warm blanket due to conduction, convection, and radiation heat losses. Neonates have a larger body surface area than older kids have, less ability to shiver to create heat, and less subcutaneous fat to act as insulation. Norepinephrine-induced brown adipose tissue lipolysis can produce heat, while peripheral vasoconstriction can reduce heat loss. After birth, thyroid hormones increase, probably in reaction to the extrauterine environment's comparatively cold climate.

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