Review

Birth brain injury: etiology and prevention—
Part II: The premature child and cesarean section deliveries

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Abstract

The physiological transition from placental life support to neonatal independence incurs massive changes in anatomy and physiology. Placental respiration is maintained until the lungs are functioning and cord closure is finalized only after an optimal blood volume is provided by placental transfusion (PT). Premature cord clamping can incur major injury.

The circumstances of premature birth and Cesarean section birth increase the risk of major blood loss from premature cord clamping. The smaller the preemie, the larger the portion of feto-placental blood volume is in the placenta, and larger amounts of PT are required to establish function of the preemie's lungs and other vital organs during transition from placental life support. The germinal matrix is extremely active metabolically providing neurons for growth of the cerebral cortex and is extremely vulnerable to ischemic damage resulting from inadequate PT.

At cesarean birth, especially if it is elective and the uterus is not contracting, the factors that effect PT (uterine contraction and gravity) are absent, and they may be reversed. If the neonate is held above the mother's abdomen, blood may flow down the vein into the placenta that is further distended in the flaccid uterus by the arteries; the result is massive blood loss. The resultant hypovolemic shock may be compounded by persistent fetal circulation and multi-organ dysfunction, retraction respiration and brain infarction.

1. Introduction

The risk of a preterm infant developing cerebral palsy is nearly 40 times that of a term infant [1]. The cesarean section child is five times more prone to die from respiratory disorders than the child born vaginally [2]. Until recently, these two birth categories have been routinely subjected to immediate cord clamping. (ICC) A thorough knowledge of normal (physiological) cord closure is needed to comprehend the full effects of ICC. When the cord closes naturally, massive changes occur in anatomy and physiology [3, 4]. The placental life support system—respiration, alimentation, fluid balance and excretion—is phased out and its functions are transferred to the newly activated life support organs of the newborn.

At birth, immediately after the child enters the atmosphere, these events occur:

1. The "cold crying reflex." All mammals are born wet. Dry air cools the wet skin. This stimulates inspiration and crying/breathing.
2. Lung aeration dilates pulmonary arterioles. In the fetus, these vessels are constricted, limiting pulmonary blood flow to a fraction of the cardiac output. Breathing spills pulmonary artery blood flow through the lungs to the left atrium (See Fig. 3) [5].
3. The "cold pressor reflex" increases systemic blood pressure and reverses ductus arteriosus flow, increasing pulmonary flow.
4. Massive placental transfusion augments the pulmonary and systemic circulations.

5. Increased pulmonary blood flow "erects" alveoli—the "Jaykka" effect [6, 7].
6. Pulmonary blood flow closes the foramen ovale. The foramen ovale is a flap-valve that closes when the left atrial pressure exceeds the right. (Fig. 3)
7. Oxygenated blood flow closes umbilical arteries.
8. Oxygenated blood flow closes the ductus arteriosus [8].
9. Increased venous pressure reflexively closes all the umbilical vessels in the abdomen and the ductus venosus [4].

**2. Normal fetal/neonatal transition: placental transfusion**.

Figure 1 illustrates the hemodynamics of these changes [4]. Placental blood is forced into the child by uterine contraction (Figure 2) or by gravity. With a strong contraction, high uterine pressure infuses over 100mls in 30 seconds (Figs. 1 and 2) and distends the inferior vena cava, the heart and lungs. If the child has not breathed, this massive inflow of blood may, of itself, erect and aerate the alveoli [6].

If the umbilical arteries are patent, blood may be pumped back into the placenta during uterine diastole and reverse flow may occur in the umbilical vein [4]. However, once pulmonary respiration is established, the umbilical arteries narrow and close; [8] sphincters acting like pressure valves on the umbilical vessels in the abdomen regulate subsequent placental transfusion. Transfusion proceeds in a "step-wise" manner [4] with each uterine contraction, and no blood is lost during uterine diastole until an optimal blood volume is achieved.

Figure 1 is unusual in that the child lived on placental respiration for nearly ten minutes before crying—in a warm blanket there is little "cold-stimulus" for crying. At most births the

child cries immediately and the vessels close physiologically within five minutes. If the child is held well below the level of the placenta, gravity generated placental transfusion may be very rapid and completed in a period of 40 seconds [9].
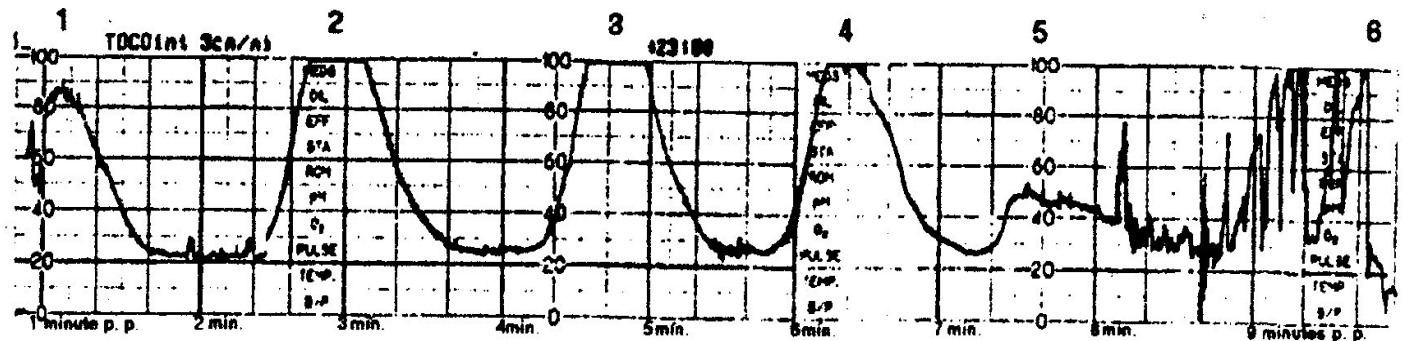
Figure 1. Weight changes in baby lying at level of vulva, with cord pulsating for 19 minutes. Note weight changes induced by uterine contractions and relaxation. (Reprinted with permission from Elsevier. Gunther M. The transfer of blood between the baby and the placenta in the minutes after birth. The Lancet, 1957;359:1278.)
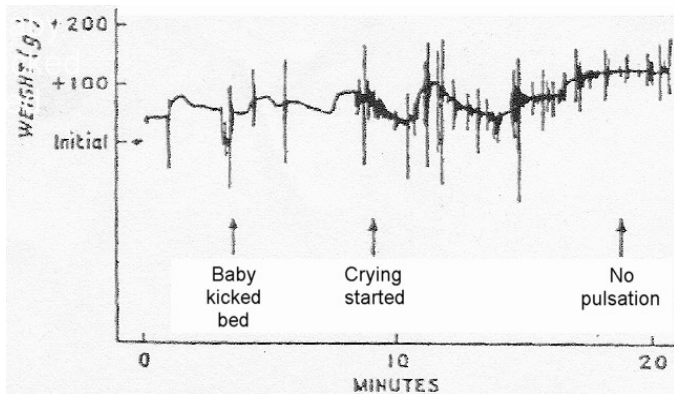
During physiological cord closure, the fetal circulation system is converted to the adult circulation; valve and vessel closures isolate the right heart from the left heart. The entire cardiac output is diverted through the lungs and the systemic circulation changes from partial oxygen saturation to full saturation; the systemic blood pressure rises [3]. The large blood volume increase from placental transfusion ensures adequate perfusion and function of the neonatal heart, lungs, brain, gut, liver, kidneys, respiratory muscles and skin.

Other fluid balance changes occur after cord closure. The higher blood pressure forces fluid into the interstitial space resulting in hemo-concentration. The resultant higher colloid osmotic pressure (COP) absorbs amniotic fluid from the lungs and prevents pulmonary edema. Excess tissue fluid and adequate blood volume result in early diuresis in the physiological newborn.

Cord clamping before these changes have been completed, and especially ICC, disrupts physiology and may prevent anatomical changes; major pathology may result [2,10]. The preemie and the cesarean section child are especially prone to injury.

3. Preemies 27–33 weeks gestation

The smaller the preemie, the larger is the relative size of the placenta and the blood volume contained in it. All life support organs are in an earlier stage of growth and development and the plasma colloid osmotic pressure (COP) (albumin concentration) is lower than in the term child. COP and placental capillary hydrostatic pressure regulate fluid balance at the placental interface and the low fetal preemie blood pressure requires a correspondingly low COP. After birth, the lungs replace the placental interface, and the function of plasma COP then is to keep the alveoli dry. The term child can attain a high COP readily with minor hemo-concentration; the preemie must hemo-concentrate much more to achieve the same COP, and must have a correspondingly larger placental transfusion to avoid eventual hypovolemia.

ICC separates the preemie from a very large portion of the feto-placental blood volume and causes sudden, massive disruption of its circulatory system [3]. In the preemie, ICC almost always produces hypovolemia, respiratory distress syndrome (RDS), crepitations (pulmonary edema) and retraction respiration; without active management, the ICC preemie will often die.

Without the term baby's layer of insulating blubber and with decreased tissue metabolism from hypovolemia, the ICC preemie cannot maintain its body temperature; incubation is required. Positive alveolar pressure respiration is needed to prevent pulmonary edema and retraction respiration [11]. Too weak to suckle, many ICC preemies require a feeding tube. Despite management, RDS often progresses to hyaline membrane disease (HMD) and permanent lung damage; the germinal matrix of the preemie's brain is particularly susceptible to hypovolemic/ischemic infarction [12].

Figure 2. Umbilical/placental venous pressure recorded in mms. of Hg. with a catheter inserted in the vein after cutting and clamping the cord 45 seconds after delivery. The first contraction is about one minute post partum (1) as the uterus closes round the placenta. Successive contractions (2 & 3) generate pressures of over 100 mms. of Hg. until the placenta is separated during contraction (4). A fifth contraction pushes the placenta through the lower segment into the vagina (5) followed by sharp peaks of pressure due to maternal effort which eventually expels the placenta from the vulva. (6) This third stage of labor followed a spontaneous term labor and delivery. No medication was used. (Fetal and Neonatal Physiology, Polin RA, Fox ww, eds. W. B. Saunders Co., 1992)

4. Hyaline membrane disease (HMD)

HMD is diagnostic for RDS, otherwise known as shock lung. It can occur at any age in hypovolemic shock, but most frequently develops in preemies and cesarean section babies. ICC produces HMD in foals [14] and primates [15], and HMD can be induced in newborn puppies and rabbits by removal of blood volume. [14] Deficient perfusion of lung tissue in hypovolemic shock produces gradual infarction of lung tissue. As alveolar cells die, a sero-sanguinous exudate coats the alveolar walls; at autopsy, the cut surface of the HMD lung resembles cut liver. If the child survives, the areas of HMD result in permanent lung scarring.

The reader should note that perfusion of lung tissue is from the bronchial arteries that originate from the aorta. The fetal lungs grow and develop on this blood supply and until the lungs are aerated, very little blood flows though the pulmonary circuit. It is systemic hypotension/hypovolemic shock that creates deficient perfusion of lung tissue. Pulmonary arterial blood flows through the lungs, it does not "supply" the lungs. The bronchial arteries are the lungs' blood supply. The mesenteric arteries are the blood supply of the gut; necrotizing enterocolitis (infarction) occurs similarly in hypovolemic shock.

Surfactant is supposedly a major factor in "lung maturity." Surfactant lowers surface tension and thus lessens the tendency of alveoli to collapse. It appears in the lungs after 37 weeks gestation. RDS/HMD results from hypovolemia at any age regardless of the presence or absence of surfactant in the lungs. Surfactant does not cure RDS, and its absence does not cause RDS. A preemie at 34 weeks gestation with no surfactant and with a normal placental transfusion can have perfectly "mature" normal lungs.

5. Germinal matrix infarction: intra-ventricular hemorrhage (IVH)

The germinal matrix (GM) in the preemie is an area of intense mitotic activity, generating neuroblasts that migrate peripherally to form the cerebral cortex [12]. Lying next to the lateral ventricles, it is very vascular in keeping with the very high rate of metabolism. Its function in building the cerebral cortex is finished by the 36th week of gestation and the area becomes relatively inactive metabolically thereafter.

Because of intense metabolism, the GM is extremely prone to infarction if brain perfusion decreases—as in hypovolemic shock—and because of the vascularity, the infarct rapidly becomes hemorrhagic with bleeding into the ventricle. (IVH) If the child survives, the infarcted tissue is eventually absorbed and the extent of the local damage may be assessed by the amount of enlargement of the ventricle. With local damage combined with the loss of cortical neurons, neurological impairment of these IVH preemies is often severe [1].

Before birth, the blood perfusing the GM is not saturated with oxygen. On MRI, the IVH lesion is visualized as an infarct. Suarez [13] noted that 95% of IVH cases also had RDS – shock lung. Inadequate perfusion of the GM is the obvious cause of IVH, not hypoxia.

6. Prevention of IVH and HMD in preemies

In 1993, Kinmond et al. published a double blind, controlled, random study on preemies 27 – 33 weeks gestation. [16] The control group had ICC and no gravity drainage of placental blood. The other group was lowered 20 cms below the vulva and clamping was delayed for a period of 30 seconds. (DCC)

1. The DCC group needed ZERO blood transfusions, the ICC group 23 ml/Kg.
2. DCC group averaged 3 days of supplemental oxygen; 10 days for the ICC group.
3. Three ICC infants developed chronic lung disease (HMD) versus NONE of the DCC group.
4. Two infants from each group sustained IVH; however, the ICC infants developed enlarged ventricles (loss of brain tissue); the DCC infants did not.

Kinmond comments, "We did not time the onset of respiration in relation to cord clamping, but many infants in the regulated (DCC) group were already crying."

Kinmond's DCC group did **not** receive a physiological placental transfusion with reflexive transition from fetal to adult circulation; they were subjected to 30 seconds of gravity-generated transfusion followed by sudden disruption of the placental circulation. Even so, this partial placental transfusion resulted in a dramatic decrease in morbidity.

Eleven years later, in 2004, the Cochrane report [17] reviewed seven randomized controlled trials on 297 preterm babies and concluded that delayed clamping for a period of 60 to 120 seconds reduces the need for blood transfusion and reduces the risk of IVH. An extensive educational and review article on cord clamping [18] advises, "Wait a minute" before clamping the preemie's cord.

An ethical question arises herein: "randomized controlled" trials means that legal informed consent [19] was obtained from the parents of DCC AND ICC preemies in these trials. Were these parents adequately and legally informed of the results of Kinmond's study prior to the birth of their preterm child? If they had been, the trial would be neither random nor controlled; any rational parent would have insisted on Kinmond's method and forbidden ICC. Any rational physician would have concurred. What is the current medico-legal status of an ICC preemie recorded in the Cochrane review that developed IVH, cerebral palsy and received a blood transfusion?

Since 1994, steroid use prior to delivery has reduced the severity of RDS in preemies [20,21]. Long-term use of steroids results in growth retardation and use after delivery does not relieve RDS. The beneficial effects of steroids appears to result from constriction of placental blood vessels, and use before delivery shifts blood volume to the fetus that is then born with some placental transfusion. Kinmond produced superior results without steroid side effects by delaying cord clamping and using gravity assisted placental transfusion.

All these reports indicate that most, if not all of the pathology that is now considered to be intrinsic with "prematurity" is in fact due to blood loss produced by a cord clamp. A study of preemies delivered with cord and placenta intact and sent to the

NICU without cord clamping would settle the issue quickly. Such a study has never been attempted.

The germinal matrix is perhaps the most critical part of the developing human brain, and the most fragile. Its integrity depends on a copious and uninterrupted flow of blood. In Kinmond's and other similar studies, some placental transfusion is shown to be very beneficial in ensuring that perfusion; however, in these studies the child is still subjected to sudden removal of 30% of the venous return to the heart, and sudden reduction of 30% of the cardiac output. Hemo-dynamic adjustment to this cord-clamp trauma may interfere with continuous GM perfusion.

In the event of premature birth, the only way to guarantee continuous copious perfusion of the germinal matrix is to allow the natural and gradual transition from placental life support to the neonate's own life support organs. Non-use of the cord clamp during delivery ensures gradual perinatal transition and should eliminate most of the neurological damage that currently occurs in preemies.

7. The cesarean section neonate

In general, cesarean section is a very safe method of treating and avoiding maternal and neonatal complications. However, the c-section mode of delivery increases the risk of neonatal blood loss by impeding placental transfusion.

At elective c-section, the uterus is seldom contracting, and thus does not generate placental transfusion. The child is usually delivered onto the thighs of the mother, above the level of the placenta, and gravity forces blood backwards through the umbilical vein (it has no valves) into the placenta in the flaccid uterus. The pulsating umbilical arteries also contribute to engorgement of the placenta. Cord clamping that is delayed for 30 or 60 seconds in this situation can result in much more blood loss than immediate clamping incurs; what appeared to be a very normal child at the moment of birth may reach the resuscitation table 60 seconds later cord-clamped, apneic and in hypovolemic shock. NeoReview's advice [18] to "wait a minute," like a little learning, may be a dangerous thing.

The vaginally delivered child may receive some placental transfusion from the uterine contraction that delivers the child, and during labor there is usually some loss of amniotic fluid resulting in some cord compression, less than occurs in oligohydramnios. The resultant increased umbilical venous pressure leads to some hemo-concentration with increase in COP; this helps to prevent pulmonary edema after birth. The elective cesarean child is not subjected to these changes and is more likely to have a lower COP, and is more prone to develop pulmonary edema.

Fifty years ago, hyaline membrane disease (HMD) and the "pulmonary syndrome" were well-recognized hazards of c-section. Landau [22] effectively removed these hazards in a series of 87 consecutive sections by delivering child, cord and placenta intact, and hanging up the placenta like an IV, permitting full placental transfusion to occur. No child so treated developed HMD or RDS.

Yet in 2001, the risk of respiratory diseases in elective sections including fatal cases (reported in ACOG's "Green Journal") was five times higher than in vaginal deliveries. [2] Lan-

dau's method of prevention did not appear in the list of references [10].

The most lethal of the elective cesarean hypovolemic complications is persistent fetal circulation, also referred to as persistent pulmonary hypertension. (PPH) [2] The ICC c-section child may not receive enough blood volume at birth to open the pulmonary circulation and hence to close the foramen ovale. It then never achieves enough oxygenation of left ventricular blood to effect closure of the ductus arteriosus [8] or the umbilical arteries (that are already clamped). Despite ventilation and some relaxation of pulmonary arterioles, the right ventricle augments the left (hypertensively) in maintaining systemic circulation through the ductus arteriosus, bypassing the lungs. The fetal circulation persists.

Mortality in these cases is high and life-saving extracorporeal oxygenation may be tried. Levine [2] mentions aggressive use of oxygen desaturations. The rational treatment would appear to be massive blood transfusion until pulmonary congestion occurs, forcing closure of the foramen ovale. Rational prevention involves normal placental transfusion and non-use of the cord clamp [10].

Occasionally, a C-section, hypovolemic child will progress through RDS and retraction respiration to HIE and cerebral palsy, completely analogous to the cord-compressed neonate. (See Part 1) More frequently, the RDS will be controlled by positive alveolar pressure, oxygen and IVs and the child will be discharged anemic, on an iron supplement, without any hint of brain damage having occurred. However, if the five-minute Apgar score was six or less, [23] there is a risk of brain damage.

To avoid all of the above, the Landau technique [22] may be used at c-section. Otherwise, resuscitation, or more properly **transition** of the c-section neonate should be accomplished on the operating table [3]. The child must have ventilation well established (color pink) before any thought of cord closure is attempted. After airway clearing, a cold wet sponge applied briefly to the buttocks or the abdomen will start the "cold crying reflex." Intravenous oxytocin will stimulate contraction of the uterus around the placenta to effect placental transfusion. Lowering the child over the edge of the operating table can induce placental transfusion by gravity. The neonatologist should be at the operating table, not the resuscitation table, managing placental transfusion and observing ventilation and oxygenation. The objective of these procedures is a five-minute Apgar score of ten or more; in that case, there is no risk of brain damage.

8. Discussion

As in HIE and CP in the cord compressed neonate, brain damage in the preemie and the c-section neonates is the result of hypovolemia and deficient tissue perfusion, not hypoxia / asphyxia. The brain damage is grossly detectable on MRI and in the case of IVH, with ultrasonography. Prevention of these lesions requires continuous copious perfusion of the brain during transition from placental life support to the child's own life support systems; the only certain method of achieving continuous perfusion after birth is not clamping the umbilical cord.

The recently advocated "half measures" that allow some placental transfusion—clamping after a minute or two—[17,18]

may improve, but will not eliminate the problem for preemies or section babies, and if the preemie is delivered by cesarean section, it may be impossible to obtain gravity drainage and effect significant placental transfusion within minutes. A major impediment to management improvement is the perinatal professions' indoctrination with the concepts that placental transfusion is essentially harmful and pathogenic, and that preemies are intrinsically disabled with "immature" organs.

Most neonatologists have never seen a child delivered without the use of a cord clamp; Gunther's and Landau's [4,22] papers are the only ones not using cord clamps. Kinmond's preemies that had placental transfusion and cried soon after birth can hardly have had immature lungs despite having no surfactant – they did not develop HMD, and if they could cry, (many cried) they probably could suckle. They also probably could maintain a normal body temperature if wrapped in suitable insulation such as a rabbit skin [24].

The inclusion of a nursery rhyme in this multi-referenced review of "scientific medical research" is deliberate. The maximum size of a Baby Bunting, capable of being wrapped in a rabbit skin, is about 1,500 grams; thus the rhyme almost certainly refers to a preemie. There is no mention of a cord clamp and no indication of the outcome of being insulated with a rabbit skin; however, the survival of the ditty over centuries would tend to indicate successful, warm survival for Baby Buntings. When this fanciful speculation is placed in juxtaposition with the meticulous, scientifically documented outcomes of the entire peer reviewed references to premature birth, a major fallacy appears.

Despite all scientific claims of "control, random and double blind" objectivity, [16-18] there is no reference in any study to the physiological norm, the physiological control; every preemie in every study had its cord clamped. What happens when the cord isn't clamped? Without an objective answer to that question, the value or hazard of any cord clamp at any time is also fanciful speculation. It is quite probable that Baby Bunting's cord was not clamped and that it closed naturally, physiologically [25]. Thus all the peer-reviewed, premature-birth references have no answer for the nursery rhyme's speculation, and they probably have as much scientific significance as the nursery rhyme. They may have much less.

In regards to the peer-reviewed, cord-clamping literature, what would a massive cohort of physiological deliveries without cord clamps show? Currently the indications are that Baby Buntings (no cord clamps) would be healthy and that cord clamps should hardly ever be used.

On reviewing the physiological process, even after arterial closure (no pulsation) venous placental transfusion may occur [4]. Given a continuous process of hemo-concentration, fluid balance and hemo-dynamic adjustment after birth, even with the placenta separated from the uterus and delivered, it would seem appropriate to place the placenta in a position relative to the child that allows for some gravity assisted transfusion (that is controlled reflexively by the child) while other "resuscitation" measures are taken care of. Optimal placental transfusion also entails optimal endowment with circulating stem cells and other blood born factors that have contributed to human survival prior to the invention of the cord clamp.

In the term neonate, hypothermia is a symptom of hypovolemic shock, and hypothermia is not infrequently seen in the immediately clamped newborn. Measuring blood pressure and urine output will confirm the diagnosis. Blood transfusion corrects the hypovolemia and the hypothermia; placental transfusion prevents both. In the preemie, hypothermia is unlikely to occur while blood is circulating through the attached, warm placenta during transition. After transition and after placental transfusion with natural cord closure, hypothermia is unlikely to occur inside a rabbit skin or its equivalent.

The kangaroo "Joey" is an animal pseudo paradigm for the preemie—it is delivered routinely in the very premature state, almost embryonic, clamps its own cord, crawls into the warm pouch (incubator) and latches on to a nipple "feeding tube," breathing with very mature lungs (Fig. 4). The human mother has substituted a rabbit skin for the missing marsupial pouch, and if the human nipple fails, a substitute for the long nipple is available; but has the 24-26-week human preemie lost normal lung function and the ability to close the umbilical cord correctly? It would be surprising if these basic survival functions (that are closely inter-dependent) had been discarded [11].

Unfortunately, brain dysfunction in preemies and c-section neonates is not limited to visible brain lesions that are detectable radiologically. Preemies, especially very low birth weight preemies, have higher rates of mental retardation, neuro-behavioral dysfunction and poor school performance, [1] and a disproportionate number of autistic children are delivered by c-section [26,27]. The etiology of these later dysfunctions and deficiencies in apparently "normal" neonates will be addressed in Part 3.

9. Conclusion

During physiological childbirth, without any extrinsic interference, the newborn reflexively switches from placental life support to its own organs of life support. This transition entails a large transfusion of placental blood into the child, that blood being utilized to initiate and establish function in the lungs, brain, gut, kidneys, liver, respiratory muscles and the skin. The heart and great vessels are anatomically altered to change the fetal circulation to the adult. Placental respiration is maintained until pulmonary respiration is established and the child begins atmospheric life with a blood volume that is optimal for survival. The umbilical vessels then close reflexively. There is no evidence that this process cannot occur in preterm infants.

Clamping the umbilical cord during the above transition process may result in serious injury, with disruption of anatomy and physiology. Using current cord-clamping methods, the premature child and the cesarean section child continue to be exposed to birth-brain damage and other injuries resulting from hypovolemia

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Figure 3. Diagrammatic representation of umbilical, hepatic and pulmonary circulation in the newborn lamb related to placental transfusion in the third stage of labor (Adapted from Rudolph & Rudolph in Polin & Fox, eds. Fetal and Neonatal Physiology. Philadelphia: WB Saunders Co., 1992.) F.O. Foramen Ovale, I.V.C. Inferior Vena Cava, L.A. Left Atrium, L.V. Left Ventricle, R.A. Right Atrium, R.V. Right Ventricle, D.V. Ductus Venosus, L.H.V, R.H.V., Left and Right Hepatic Veins, L.P.V., R.P.V., Left and right PortalVeins, U.A. Umbilical Arteries, U.V. Umbilical Vein
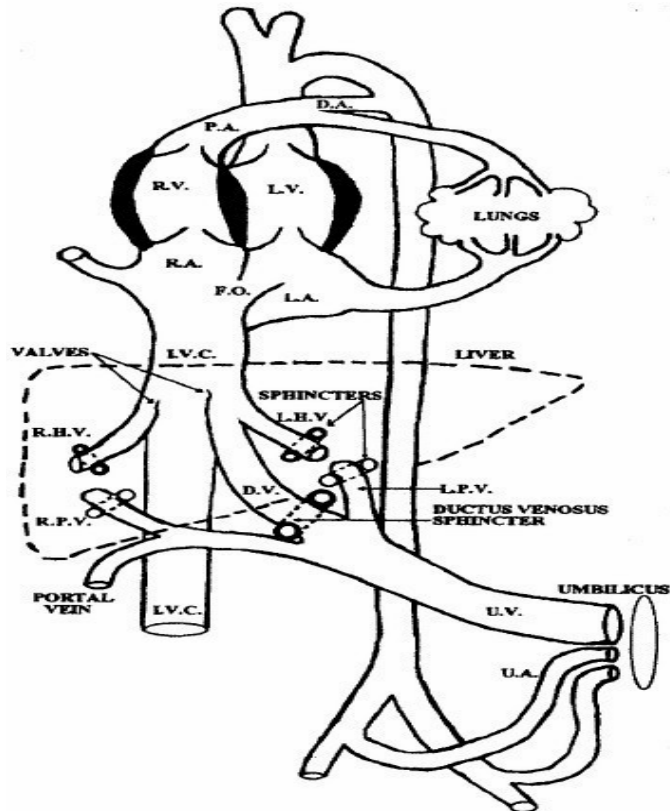

Figure 4. Kangaroo in premature state ("Joey nursing in pouch"— Reprinted with permission from Mitsuaki Iwago, Minden. www.mindenpictures.com)