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Disertační práce

The importance of tissue oxygenation changes in monochorionic twins for predicting severe neonatal morbidity

Význam změn tkáňové oxygenace u monochoriálních dvojčat v predikci závažné neonatální morbidity

MUDr. Peter Korček

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Školitel: Prof. MUDr. Zbyněk Straňák, PhD, MBA

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Contents 1
Abstract 3
Abstrakt 4
1. Introduction and Overview 5
1.1. Preterm Newborns 5
1.1.1. Neonatal Morbidity 5
1.1.2. Preterm Birth 6
1.1.3. Multiple Pregnancy 7
1.2. Circulation 12
1.2.1. Postnatal Adaptation 12
1.2.2. Blood Pressure 14
1.2.3. Myocardial Dysfunction 15
1.2.4. Autonomic Dysfunction 16
1.2.5. Clinical Assessment 17
1.2.6. End-organ Perfusion 17
1.3. Near-infrared Spectroscopy 20
1.3.1. Technology 20
1.3.2. Neonatal Application 21
1.3.3. Normative Values 22
1.3.4. Interventions 24
1.3.5. Potential Side Effects 25
2. Project Goals 27
2.1. Hypotheses 27
3. Material and Methods 28
3.1. Subjects 28
3.2. Cerebral Oxygenation 28
3.3. Definition of Morbidities 29
3.4. Statistical Analysis 29
4. Results 30
4.1. Descriptive Statistics 30
4.2. Neonatal Outcome 39
4.3. Cerebral Oxygenation 40
5. Discussion 49
5.1. Perinatal Brain Injury 49

5.2. Cerebral Oxygenation……51
5.2.1. Cerebral Blood Flow……51
5.2.2. Cerebral Autoregulation……...52
5.2.3. Cerebral Oxygen Delivery……... 54
5.2.4. Cerebral Hypoxia……54
5.2.5. Cerebral Oxygenation and Brain Injury……...55
5.2.6. Cerebral Oxygenation and Systemic Circulation…… 56
5.2.7. Cerebral Oxygenation – Summary……...57
5.3. Cerebral Oxygenation and Multiple Birth……...58
5.3.1. Recipient Twins ……...58
5.3.2. Donor Twins ……... 58
5.3.3. Fetal Growth Restriction ……59
5.3.4. No Fetal Compromise ……59
5.3.5. Study Limitations ……60
6. Conclusions ……. 61
7. References ……62
8. List of abbreviations ……... 74
9. Supplements ……..... 76

Abstract

Despite improvements in perinatal outcome in recent decades, multiple pregnancies are associated with increased risk of complications including preterm birth, fetal growth restriction (FGR) and twin-twin transfusion syndrome (TTTS). Fetal circulatory disturbances and immature cerebral vasculature increase the risk for serious perinatal injury and adverse neurodevelopmental outcome in multiple births. Cerebral oxygenation ($crSO_2$) monitoring using near-infrared spectroscopy (NIRS) is increasingly used in high-risk infants. However, limited data are available in twin preterm infants with respect to cerebral tissue perfusion.

The aim of this project was to measure $crSO_2$ using NIRS in preterm monochorionic and dichorionic twins during the first 72 hours of life and find out correlation between underlying fetal conditions and $crSO_2$ development. We divided the study population into 4 subgroups based on major fetal pathology: donor (1) and recipient (2) monochorionic twins (with TTTS), selective FGR infants (3) and twins without fetal compromise (4). We observed significant variation in $crSO_2$ among the subgroups using mixed model analysis. The recipient twins exhibited the lowest $crSO_2$ throughout the study period, whereas the FGR and donor twins presented with the highest values. Nevertheless, we found no statistically significant differences in neonatal mortality and morbidity among subgroups.

In conclusion, we were able to reveal significant correlation between $crSO_2$ values postnatally and underlying fetal pathology in monochorionic and dichorionic preterm twins. The presented $crSO_2$ patterns in these infants provide some insight into altered cerebral hemodynamics that stems from the fetal complications. The cerebral tissue oxygenation changes may contribute to adverse neurodevelopmental outcome in multiple births.

Key words: preterm newborns, monochorionic twins, cerebral oxygenation

Abstrakt

Přestože došlo ke zlepšení perinatální péče v posledních desetiletích, jsou vícečetná těhotenství asociovaná se zvýšeným rizikem komplikací, jako např. předčasný porod, fetální růstová restrikce (fetal growth restriction - FGR) a transfuzní syndrom (twin-twin transfusion syndrome - TTTS). Intrauterinní cirkulační nestabilita a nezralá mozková vaskulatura významně přispívají k riziku vážného perinatálního poškození a zhoršeného neurologického vývoje dětí z vícečetných gravidit. Měření cerebrální oxygenace ($crSO_2$) pomocí metody Near-Infrared Specotroscopy (NIRS) se používá stále častěji u rizikových novorozenců. I přes rozšířenost metody však existují omezená data s ohledem na nezralá dvojčata a jejich cerebrální tkáňovou perfuzi.

Cílem práce bylo analyzovat $crSO_2$ pomocí metody NIRS u nezralých monochoriálních a bichoriálních dvojčat v prvních 72 hodinách života a objasnit korelaci mezi fetálními komplikacemi a postnatálním vývojem $crSO_2$. Na základě dominantních fetálních komplikací jsme rozdělili studijní populaci na 4 skupiny: donoři (1) a recipienti (2) z monochoriální gravidity s TTTS, novorozenci s FGR (3) a novorozenci bez významné fetální komplikace (4). Použitím analýzy smíšeného modelu jsme zjistili signifikantní rozdíly v $crSO_2$ mezi jednotlivými skupinami. Ve skupině recipientů byly zaznamenány nejnižší hodnoty $crSO_2$ v průběhu zkoumaného období, naproti tomu donoři a novorozenci s růstovou restrikcí měli hodnoty $crSO_2$ nejvyšší. Nebyly však nalezeny statisticky významné rozdíly v mortalitě a morbiditě mezi sledovanými skupinami.

V předložené práci demonstrujeme signifikantní korelaci mezi postnatální cerebrální oxygenací a fetálními komplikacemi u nezralých dětí z monochoriálních a bichoriálních gravidit. Prezentované výsledky objasňují u těchto novorozenců alterovanou cerebrální hemodynamiku, která reflektuje vznik a vývoj specifických fetálních komplikací. Změny v cerebrální oxygenaci mohou u dětí z mnohočetných gravidit přispívat ke zhoršenému neuropsychickému vývoji.

Klíčová slova: nezralí novorozenci, monochoriální dvojčata, cerebrální oxygenace

1. Introduction and Overview

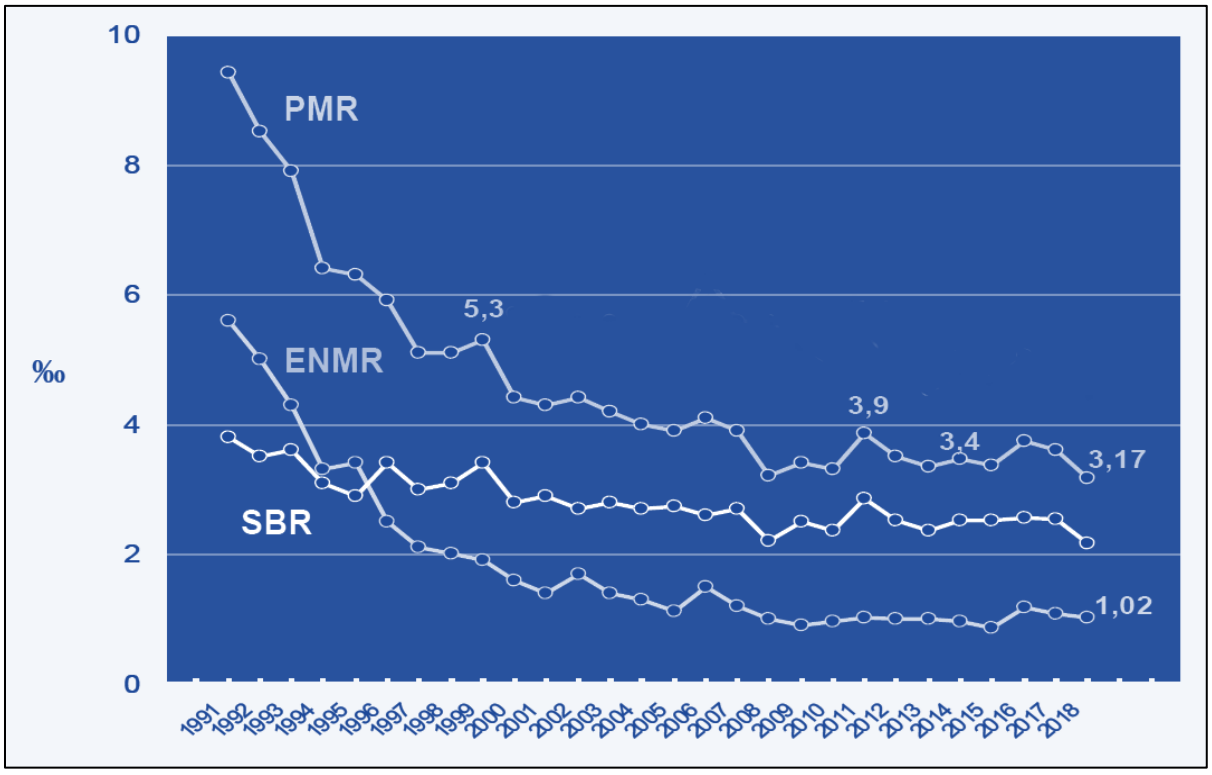
1.1. Preterm Newborns

1.1.1. Neonatal Morbidity

Premature birth is defined as any birth before 37 completed weeks of gestation and it has been estimated to account for up to 10 % of all births.[1] Preterm birth is a substantial cause of neonatal and pediatric morbidity and mortality.[2] Prematurity is the single most important cause of death in the first month of life and prematurity remains a global health problem due to the associated learning and motor disabilities and sensory impairment.[1,2]

Over the last decades, improvements in neonatal intensive care have led to decreased mortality of preterm population. The centralization of care for high-risk pregnancies, delaying preterm birth in order to administer corticosteroids for fetal lung maturation, better-quality ventilation and circulation support, and exogenous surfactant administration significantly aided to improving survival of preterm newborns (**Figure 1**).[3]

Figure 1. Development of Perinatal mortality (PMR), Stillbirth (SBR) and Early neonatal mortality (ENMR) rates in Czech Republic.



Henceforth, the focus has shifted from reducing mortality to reducing short-term and long-term morbidity. The leading cause of moderate to severe neurodevelopmental impairment in preterm infants is brain injury – peri/intraventricular hemorrhage (PIVH), periventricular leukomalacia (PVL) and hypoxic-ischemic encephalopathy (HIE).[1-3] Consequently, the neurological pathologies lead to adverse outcomes, including cerebral palsy (CP), cognitive disabilities, sensory deficits and epilepsy.[1-3]

In addition, major neonatal morbidities can further aggravate neurodevelopmental outcome through ventilation and circulation instability, particularly during the early postnatal period.[3] The most important ones are respiratory distress syndrome (RDS), pulmonary hemorrhage, hemodynamically significant patent ductus arteriosus (PDA), hypotension, early onset sepsis (EOS) and necrotizing enterocolitis (NEC).[3,4]

Despite improvements in perinatal care, the rate of neurodevelopmental impairment remains significant. Contributing negative factors include extreme prematurity (< 28 weeks of gestation), very low birth weight (birth weight (BW) < 1500 grams), multiple pregnancy, fetal growth restriction (FGR) and antenatal or postnatal hemodynamic disturbances.[3-5]

1.1.2. Preterm Birth

Common signs of impending preterm birth include abdominal or back pain, premature rupture of membranes or cervical dilatation. Subsequent preterm labor (induced or spontaneous) constitutes of frequent and potent uterine contractions accompanied by cervical dilatation and effacement.[1,2]

The specific cause of premature birth is often not identified. However, known risk factors of preterm delivery include complicated obstetric history (previous premature birth, multiple miscarriages or abortions), infection (chorioamnionitis), in vitro fertilization, congenital anomalies (uterus, placenta) or chronic conditions (diabetes mellitus, maternal hypertension, obesity/anorexia, cigarette smoking, drug abuse).[1-3]

Last but not least, multiple pregnancy is a known major risk factor for premature delivery.[6,7]

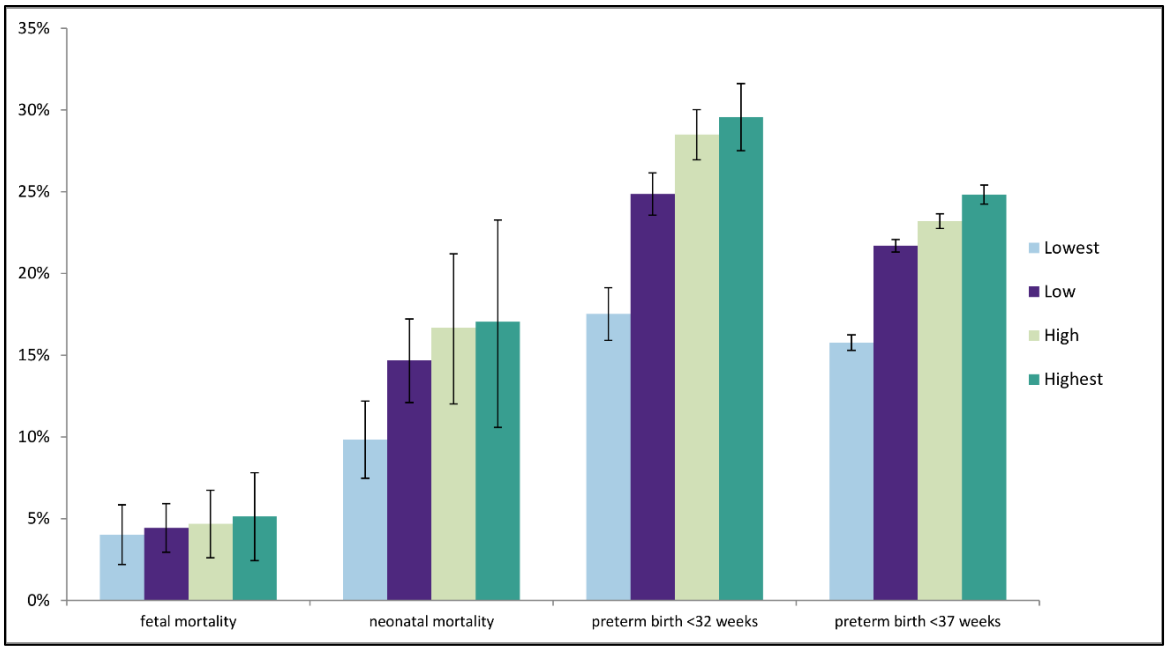
1.1.3. Multiple Pregnancy

The proportion of multiple pregnancies out of all pregnancies is expanding. The rise can be explained by the increasing maternal age at childbirth as well as the use of assisted reproduction.[8]

Multiple pregnancies carry higher risks of stillbirth and adverse fetal outcomes.[6,7] When compared with singletons, newborns from multiple pregnancies have substantially higher rates of preterm birth, perinatal morbidity and mortality and adverse long-term neurodevelopmental outcome.[6-8]

In 2010, the median preterm birth rate for singletons was 5.6% and for multiples 53.4%, while rates for very preterm birth (< 32 weeks) were 0.7% and 8.8%, respectively. The estimated pooled risk ratio for fetal death among multiple births compared with singletons was 2.4 (95% CI 1.5 – 3.6). The median neonatal mortality rate for singletons was 1.8 (per 1000 live births) compared to 14.6 among the multiples. Overview of populations risks for adverse outcomes among countries with variable multiple birth rates is shown in **Figure 2**.[8]

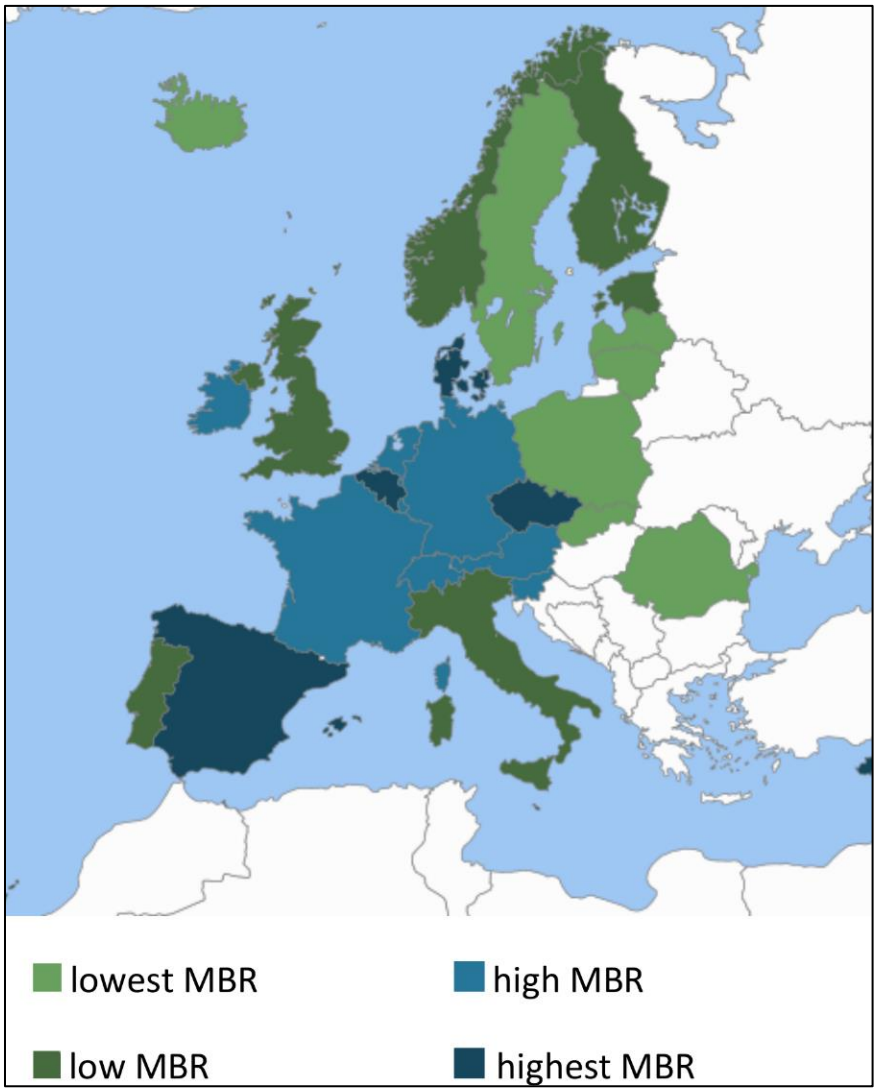
Figure 2. The population risks of fetal and neonatal mortality, preterm and very preterm birth attributable to multiple pregnancy in 4 groups of European countries defined by their Multiple birth rates (MBR). Lowest MBR group (< 15 multiple births per 1000 women having live or stillbirths); Low MBR group (15.0 – 16.9 per 1000); High MBR group (17.0 – 18.9 per 1000); Highest MBR group (≥ 19.0 per 1000).



Twins are by far the most common form of multiple births. The median multiple and twinning rate in Europe (2010) was 17.1 and 16.8 births per 1000 women, respectively. Individual rates in European countries vary widely, however, no clear geographical pattern was observed in the distribution.[8]

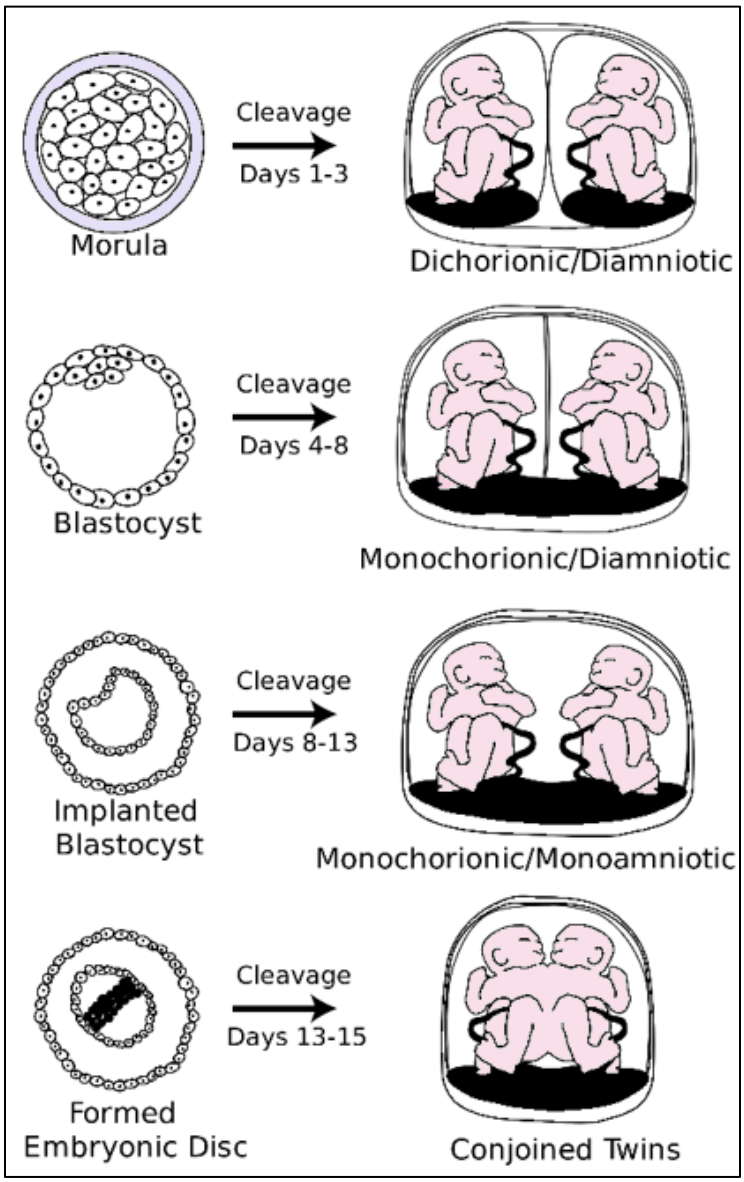
Importantly, Czech Republic has had one of the highest multiple and twinning rates among European countries - 21.1 multiple births and 21.0 twin births per 1000 women having live or stillbirths (**Figure 3**).[8]

Figure 3. Variation in Multiple birth rates (MBR) across Europe. Lowest MBR group (< 15 multiple births per 1000 women having live or stillbirths); Low MBR group (15.0 – 16.9 per 1000); High MBR group (17.0 – 18.9 per 1000); Highest MBR group (≥ 19.0 per 1000).



Twins can exist in the uterus in a number of ways: dichorionic-diamniotic (DCDA), monochorionic-diamniotic (MCDA) and rarely monochorionic-monoamniotic twins.[6,7] These multiple pregnancies are associated with increased risk of complications including preterm birth, FGR, twin–twin transfusion syndrome (TTTS) and congenital abnormalities (**Figure 4**).[6,7]

Figure 4. Various types of chorionicity and amniosity in monozygotic twins based on the time of fertilized egg division.

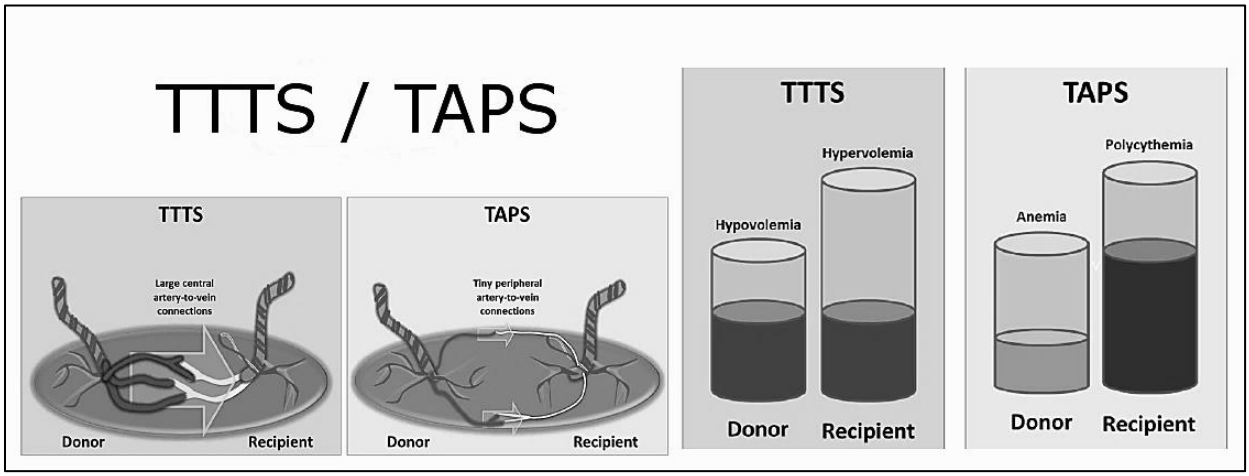


Monochorionic twin pregnancies can suffer from TTTS, specific complication due to pathological anastomoses in the shared placenta leading to unbalanced blood flow through arterio-venous anastomoses between twins.[7,9] This condition causes hypervolemia, higher afterload through increased vascular resistance, hypertrophic cardiomyopathy and finally cardiac failure in the recipient twin.[10,11]

In contrast, the donor twin is hypovolemic, has low cardiac output (CO), tissue hypoperfusion and activated renin-angiotensin-aldosterone axis. TTTS occurs at a frequency of 10–15 % in MCDA twin pregnancies, and the majority of these cases are diagnosed during the second trimester (**Figure 5**).[10,11]

Twin anemia–polycythemia sequence (TAPS) (5%) is a rare form of TTTS, which is characterized by the presence of large intertwin hemoglobin (Hb) difference without signs of twin oligo-polyhydramnios sequence (chronic transfusion through small one-way anastomoses).[7,12]

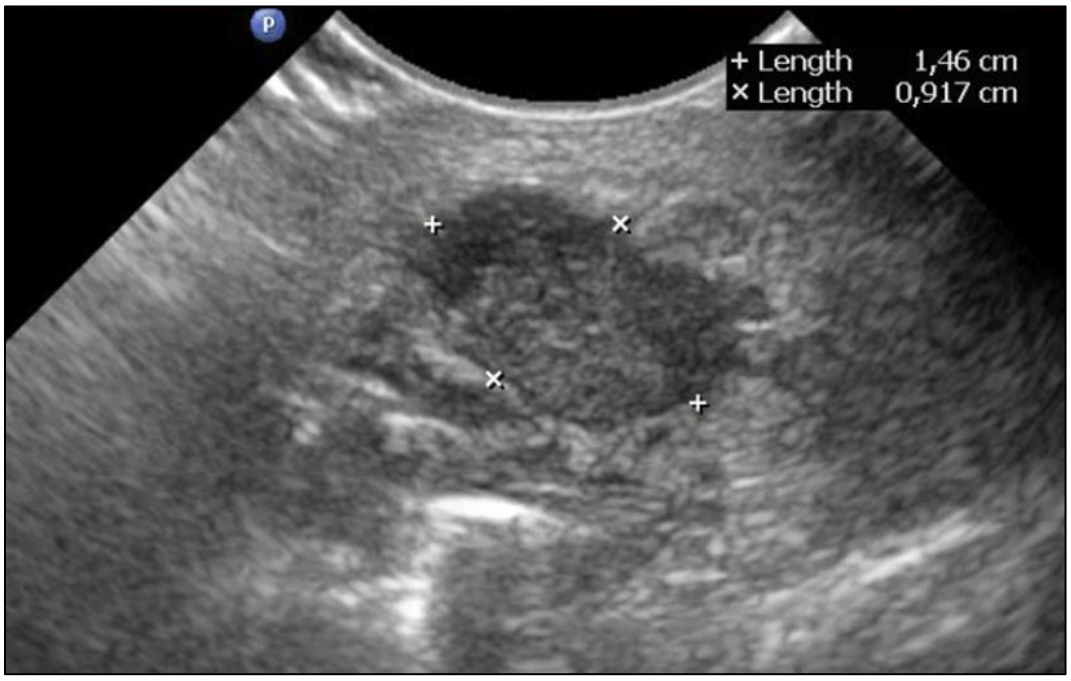
Figure 5. Complications of monochorionic diamniotic twin pregnancy. TTTS = twin-twin transfusion syndrome; TAPS = twin anemia-polycythemia sequence.



Alternatively, selective FGR (occurring in 12-25%) can occur in either monochorionic or dichorionic twin pregnancies and represents uneven placental distribution between twins.[10,11] Placental insufficiency can lead to “brain-sparing” effect - cardiovascular adaptation of the fetus to maintain adequate cerebral perfusion.[13]

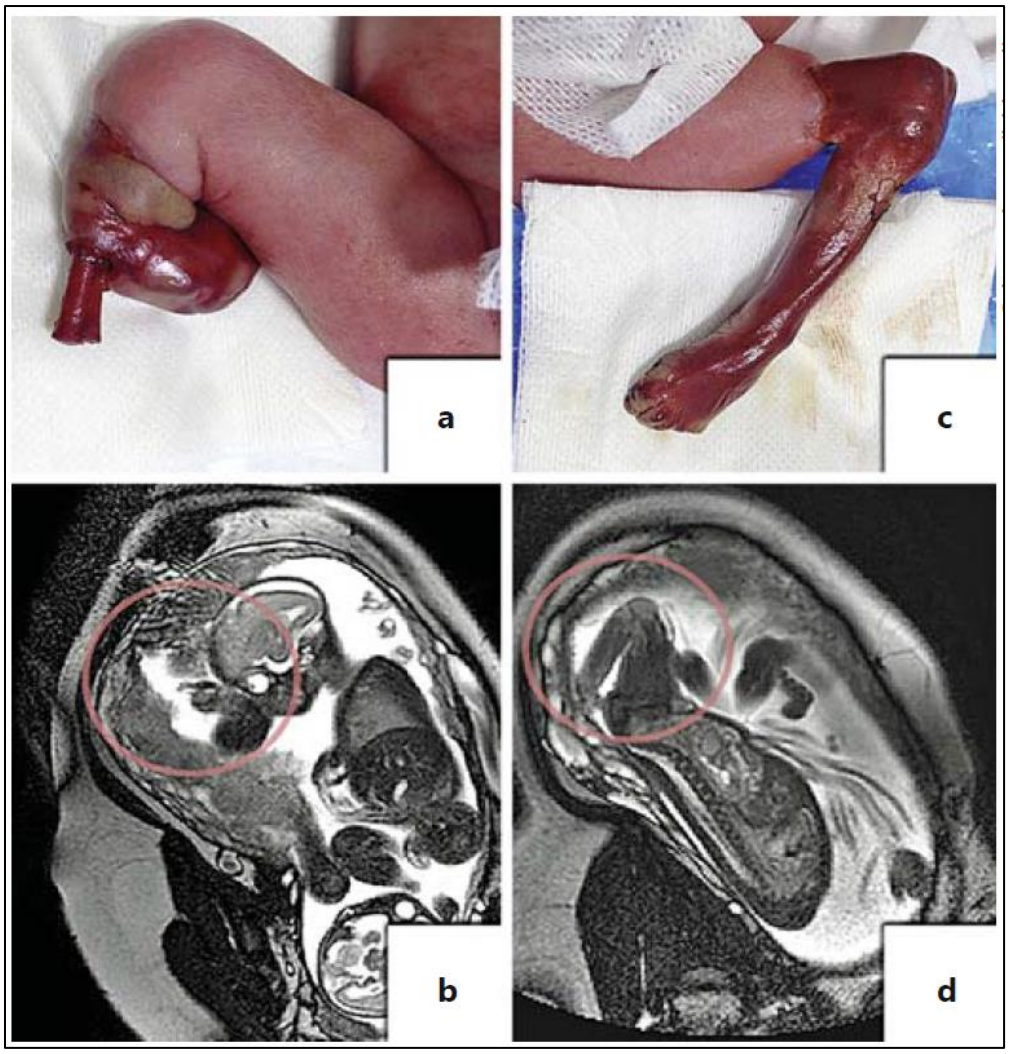
Furthermore, monochorionic twin pregnancy increases the risk for hemodynamic compromise, which can lead to prenatal and postnatal organ complications. Importantly, the adverse effects of dysfunctional circulation exist even in the absence of the twin-twin transfusion syndrome. Fetal distress and hemodynamic compromise can increase susceptibility to infection (submandibular sialadenitis) or thromboembolic complications (limb ischemia) (**Figure 6, 7**).

Figure 6. Submandibular sialadenitis on the ultrasound scan in a preterm newborn from monochorionic twin pregnancy.



Neurodevelopmental outcome remains the most challenging issue in multiple births.[14,15] Fetal circulatory disturbances and immature vasculature (particularly in the germinal matrix and periventricular white matter) increase the risk for perinatal brain injury and adverse neurodevelopmental outcome.[16,17] Multiple risk factors can further aggravate the cerebral perfusion and brain development – myocardial dysfunction, decreased CO, systemic hypotension and cerebral blood flow (CBF) fluctuations.[18]

Figure 7. Prenatally acquired multiple limb ischemia in a very low birth weight monochorionic twin. Clinical findings (a, c) and antenatal magnetic resonance imaging (b, d).

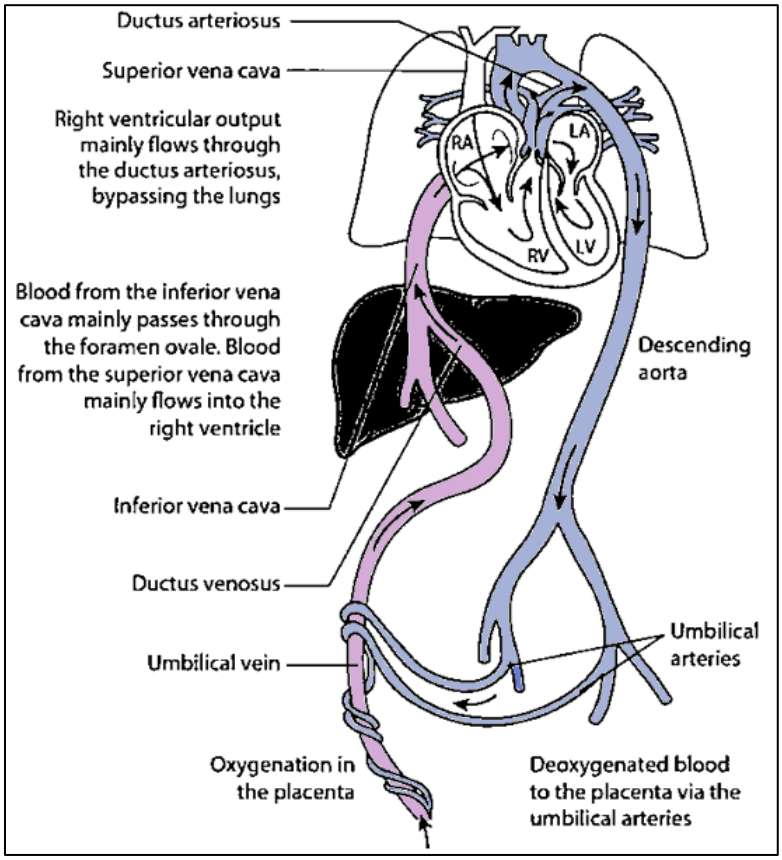


1.2. Circulation

1.2.1. Postnatal Adaptation

Neonatal adaptation is a complex process that involves multiple adaptive changes within several organ systems. For successful transition from intrauterine to extrauterine environment, relatively rapid conversion to air breathing and blood flow changes (especially in pulmonary vascular system) must occur simultaneously (**Figure 8**).[19]

Figure 8. Fetal circulation.



Adequate blood volume is necessary to facilitate adaptive processes and ensure sufficient oxygen transport and organ/tissue perfusion.[19] Placental transfusion may be considered in order to enhance arterial oxygen content, increasing CO, and improving oxygen delivery.[20] It involves a shift of placental blood to the neonate immediately after delivery and may be achieved in two different ways: delayed cord clamping and umbilical cord milking. These techniques can help

to achieve a greater blood volume at birth (increase of up to 10–15 mL/kg), which may be significant especially in very low birth weight (VLBW) infants.[19,20]

1.2.2. Blood Pressure

Hypotension in the early postnatal period is a common diagnosis within preterm population and has been statistically associated with adverse short-term and long-term outcomes.[21] There are a number of compensatory responses that occur to maintain perfusion and oxygen delivery to the most vital organs, which include peripheral vasoconstriction to maintain blood pressure (BP).[22]

Progression to the uncompensated phase is characterized by signs of poor perfusion accompanied with low BP, ultimately leading to the irreversible stage if therapy is not introduced. Untreated hypotension results in low end-organ blood flow, including impaired CBF, cerebral ischemia and brain injury.[21,22]

Consequently, many clinicians rely on absolute BP values to guide intervention.[23,24] Blood pressure reference ranges are often based on BW, gestational age (GA) and postnatal age criteria. The most common criterion states that the mean arterial BP (MABP) in mmHg should be maintained above the GA in weeks.[25,26]

However, several studies have shown a poor relationship between this criterion and the incidence of PIVH in preterm infants.[27] The possible explanation is that the end-organ blood flow depends not only on the absolute BP values, but also on its components – cardiac output and peripheral vascular resistance.[28] Hence, there is little correlation between systemic blood flow and BP in preterm infants and very low systemic perfusion can occur with normal, low or high BP.[27,28]

There were several studies pointing out that hypotension is not closely related to superior vena cava (SVC) blood flow, an indirect measure of systemic blood flow.[29] Others have shown a poor relationship between BP and CO indices including left (LVO) and right ventricular output (RVO).[30,31]

Therefore, preterm infants with lower than average BP often have no biochemical or clinical signs of shock, may have normal systemic blood flow, sufficient tissue oxygen delivery and possibly do not require treatment ("permissive hypotension").[32]

The etiology of hypotension (however defined) in the first 72 hours of life is multifactorial. Among the many variables are myocardial dysfunction, abnormal vasoregulation, PDA influence, severe RDS, EOS, hypovolemia and relative adrenal insufficiency.[28]

In terms of hypotension treatment, excessive intervention in preterm infants may be unnecessary, or harmful.[33] Analysis of a large neonatal database has demonstrated that treatment of hypotension was associated with an increase in serious brain injury.[34]

The most common approach to treatment is to give one or more fluid boluses followed by administration of dopamine, epinephrine or norepinephrine (**Table 1**).[33-35] However, we have to bear in mind structural and functional immaturity of preterm myocardium and autonomic system.

Table 1. Overview of the most common inotropic and vasopressor drugs used in neonatal intensive care unit and their relationship to receptor types.

Drug	$Alpha_1$	$Alpha_2$	$Beta_1$	$Beta_2$	Dopamine-R
Dopamine	+	0	++	++	+++
Dobutamine	0	0	+	+++	++
Adrenaline	++	++	+++	+++	0
Noradrenaline	+++	+++	++	+	0

1.2.3. Myocardial Dysfunction

There are significant differences in myocardial structure and function between preterm infant, term infant and adult.[36] These differences affect myocardial contractility and the myocardial response to changes in both preload and afterload.[37] There is a lack of sarcoplasmic reticulum, poorly formed T-tubule system and the myofibrils are shorter.

The newborn myocardium contains much more fibrous non-contractile tissue and has reduced sympathetic innervation. Regardless of these limitations, the neonatal myocardium is very functional.[36,37]

Nevertheless, there is a limited ability to increase CO in response to drugs and an elevated sensitivity to increased afterload which may lead to a decrease in CO.[38] If afterload is increased sufficiently, CO may fall despite a positive inotropic intervention.[38]

These developmental disadvantages coupled with pathological conditions during early postnatal adaptation (hypoxemia, sepsis, hypotension) can lead to considerable myocardial dysfunction.[36-38]

1.2.4. Autonomic Dysfunction

At birth, there are limited α-receptors and little sympathetic innervation of the myocardium of the term infant.[39] In contrast, the density of β-adrenoceptors, which is low at ages equivalent to extreme preterm delivery, appears to increase during the third trimester.[39]

The hemodynamic effects resulting from stimulation of these receptors are minor, due to the aforementioned limited functional reserve of neonatal myocardium.

In the developing peripheral vasculature, there is abundance of active α1-receptors in comparison to scarcity of β2-receptors. Thus, vasoconstriction from α1-adrenoceptor stimulation can cause marked increases in systemic vascular resistance.

Owing to unbalanced stimulation of myocardium and peripheral vasculature, the increase in afterload leads to a decrease in CO and only a slight increase in BP.[39,40]

Last but not least, dopaminergic receptors mediate vasodilation in the renal and mesenteric circulations. The functional maturation of these receptors in coronary and cerebral circulations remains largely unknown.[41]

1.2.5. Clinical Assessment

Hemodynamic status of a preterm infant can be also assessed using physical (capillary refill time, heart rate, urine output) and biochemical findings (pH, base deficit, and lactate). However, if isolated, none of these parameters is specific in detecting poor perfusion.[42,43]

Capillary refill time values exist for the term neonate, but there is limited data available for the preterm infant.[42] Furthermore, there is a weak association between capillary refill time and systemic blood flow.[43]

Heart rates vary significantly with gestational and postnatal age and can correlate with oxygen consumption.[44] Still, neither absolute heart rate nor trend analysis of heart rate is a clinically useful tool to assess cardiac function.

Urine output is low and variable in the first 24 hours of life. Nevertheless, a good urine output usually signifies overall adequate renal perfusion, thus indicating absence of marked hypotension and systemic hypoperfusion.[32]

Serial lactate values obtained during the first day can predict outcome in preterm infants.[45] Persistent lactate elevation in unstable ventilated newborns is linked to increased mortality.[46] Increased lactate levels (> 5.7 mmol/L) during early postnatal adaptation can be used to determine positive and negative predictive values for a combined adverse outcome (death, severe PIVH or poor neurodevelopmental outcome).[45,46]

Combined clinical and biochemical assessment might be more beneficial in recognizing patients with suboptimal hemodynamic status, however, it does not inform us entirely about the end-organ perfusion.[42,47]

1.2.6. End-organ Perfusion

The principal concern regarding circulatory disturbances is impaired cerebral autoregulation and inadequate cerebral perfusion resulting in brain injury.[28] Understanding end-organ perfusion can be important in relation to the development of PIVH and PVL with consequent adverse neurodevelopmental outcome.[28,48]

Unfortunately, the commonly used variables (peripheral oxygen saturation (SpO_2), MABP, clinical and biochemical parameters) do not provide us with the complete hemodynamic representation.[48,49]

Non-invasive measurements such as targeted neonatal echocardiography (TNE) and near-infrared spectroscopy (NIRS) could help us identify and monitor high-risk infants.[49,50]

In clinical practice, TNE (or functional echocardiography) has become a useful non-invasive, bedside tool that can be used to assess myocardial contractility and adequacy of circulatory status in preterm infants. It provides an objective assessment of cardiac function and output and permits assessment of response to therapeutic interventions (**Figure 9-11**).[50]

In the preterm infant, circulatory shunting complicates the measurement of systemic blood flow. SVC flow measurement provides a shunt-independent assessment of blood flow to the upper body and low SVC blood flow has been associated with adverse outcome.[47,50]

While TNE is frequently used by clinicians to guide their hemodynamic interventions in preterm infants, there is little evidence on improving their outcome.[50] In comparison, NIRS has been utilized to assess the adequacy of cerebral oxygenation in high-risk preterm infants.[18,49]

Figure 9. Functional echocardiography depicting M-mode measurement and fractional shortening that are used to estimate systolic function of the heart.

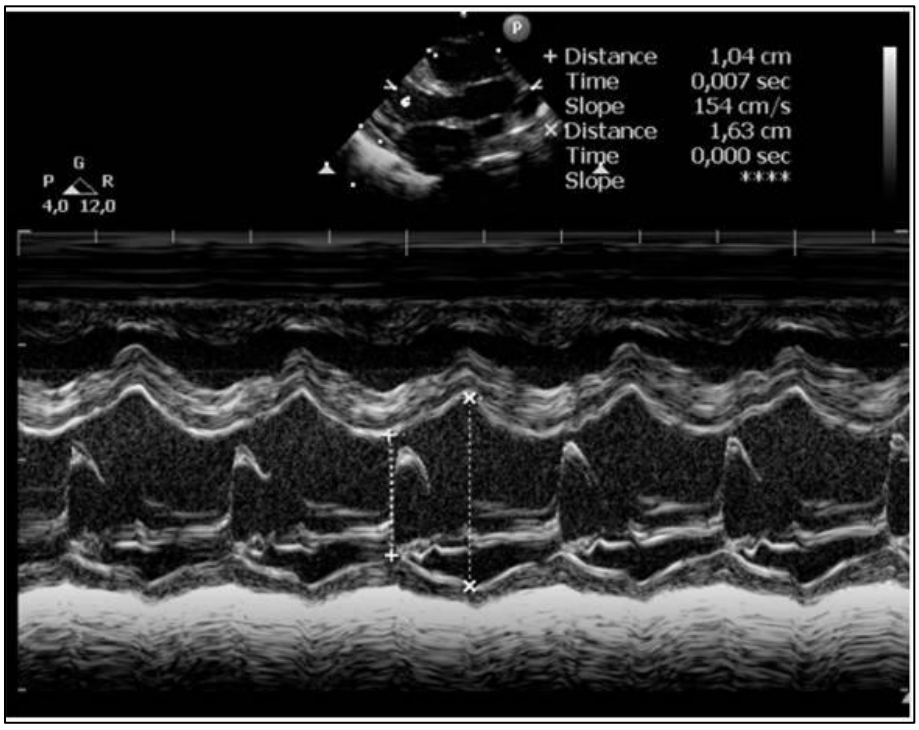


Figure 10. Functional echocardiography depicting superior vena cava (SVC) flow measurement.

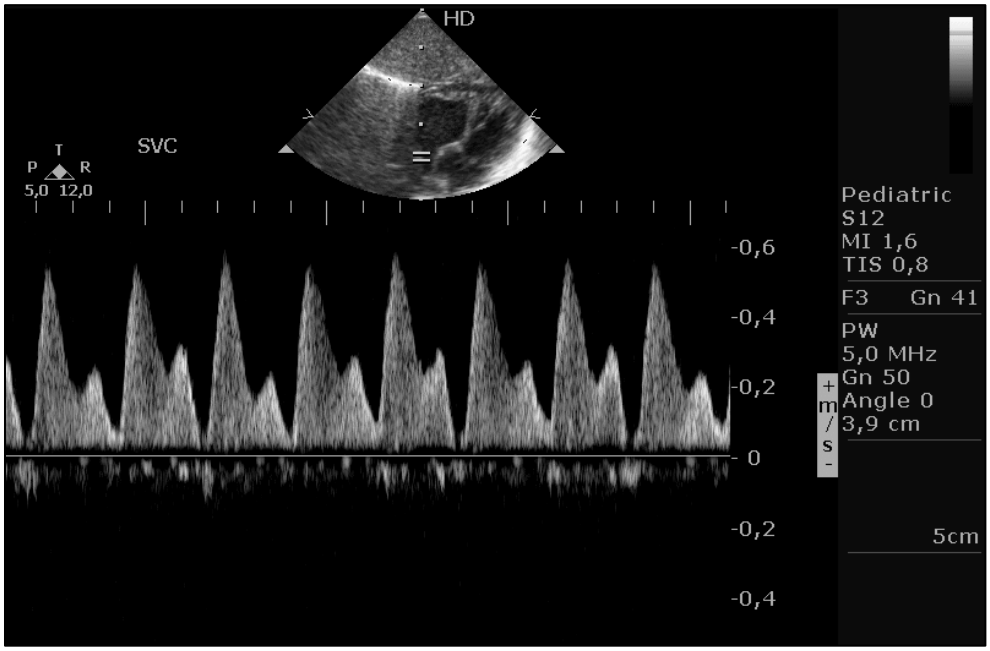
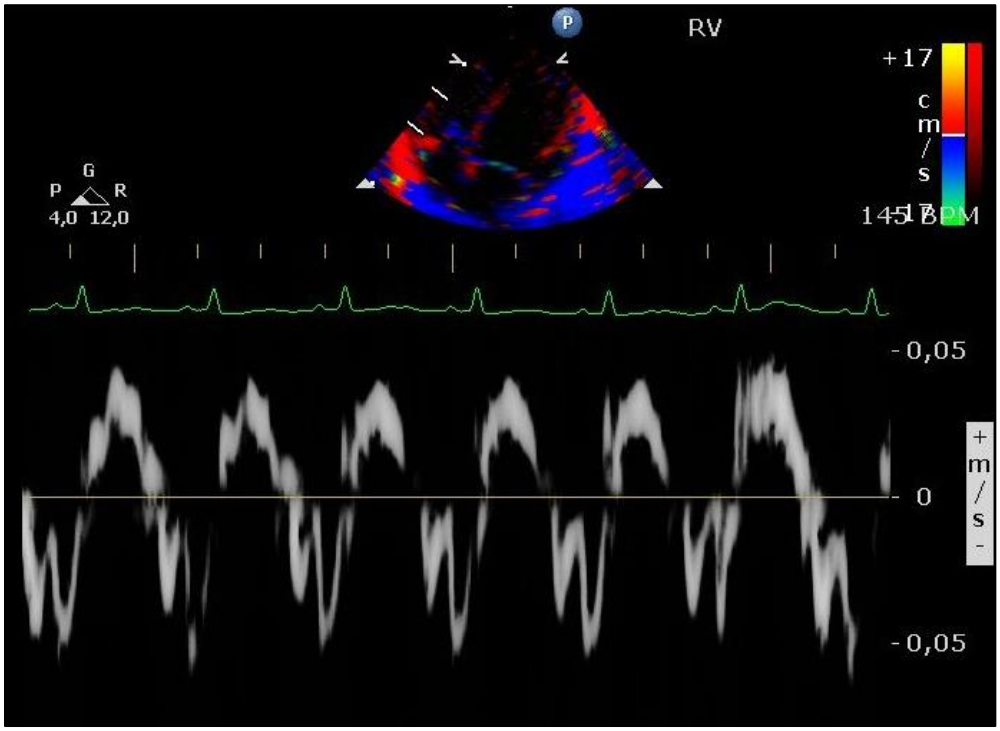


Figure 11. Functional echocardiography depicting tissue Doppler imaging of the right ventricle.



1.3. Near-infrared Spectroscopy

1.3.1. Technology

The concept of NIRS was first published in 1977 and used in neonates in 1985, however, it took almost 40 years to establish the method in neonatology.[51,52] NIRS possesses a number of advantages for modern neonatal care - non-invasive, painless, bed-side, non-ionizing, continuous and portable monitoring of a patient.[48]

From the technological point of view, the actual near-infrared light spectrum goes through most biological tissues. When we assume that all the other tissues remain stable (bone, muscle, skin) than the only changing parameter is the brain blood flow and oxygenation.[49]

In blood there are two chromophores, deoxygenated (dHb) and oxygenated hemoglobin (oxyHb) that can absorb near-infrared light. Both dHb and oxyHb have their peak wavelength-dependent near-infrared spectral absorption (**Figure 12**).[48,49]

Depending on the NIRS devices two to four wavelengths are emitted between 700-850 nm in order to maximize the absorption separation between dHb and oxyHb and to eliminate the wavelength absorption by other molecules. Using the Beer-Lambert law values of oxyHb and dHb can be calculated.[48,49]

However, the difference between the light emitted and the light measured is not only caused by absorption but also by scattering. As we do not know the amount of scattering, absolute values cannot be calculated and therefore multiple detectors are used.

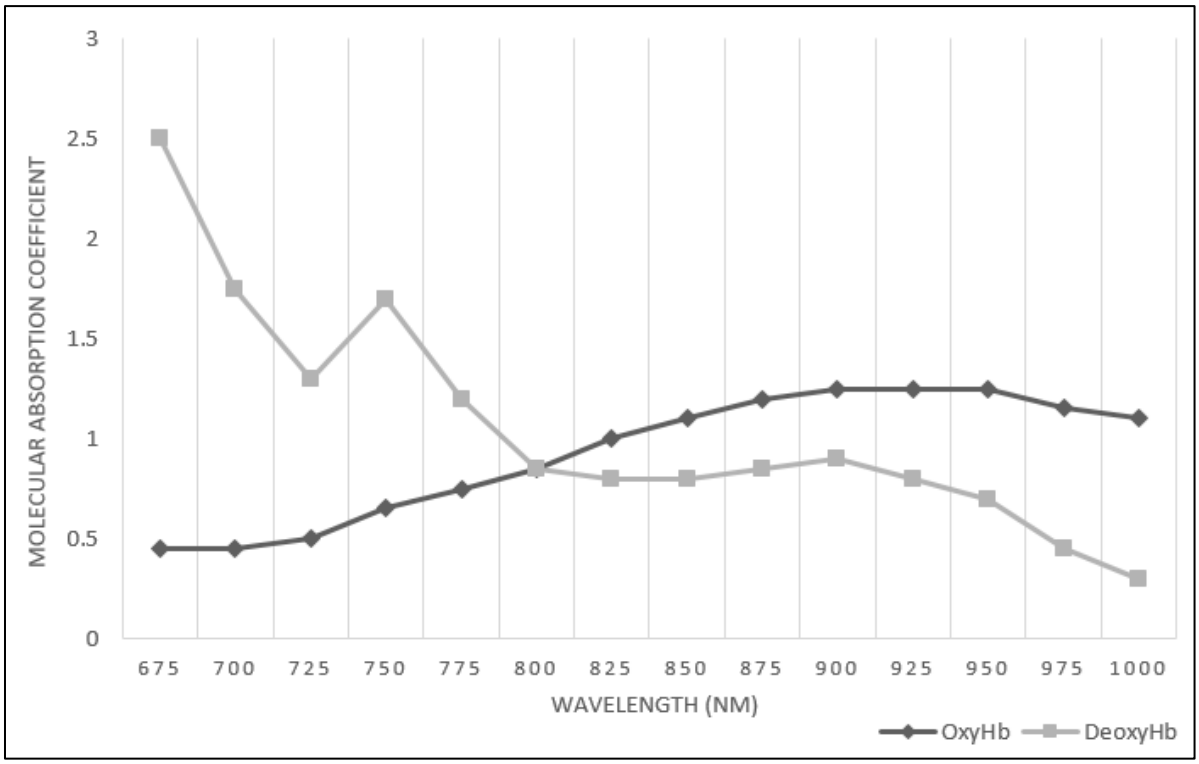
If scattering is assumed to be equal for the different detectors, absolute values can be measured and oxyHb and dHb calculated into ratio-based percentage oxygen saturation using different algorithms and methods.[48,49]

Because of this, the displayed values are relative rather than absolute and are labeled regional/tissue oxygenation, regional/oxygen saturation or rSO_2.

(oxyHb / [oxyHb + dHb]; range 0 - 100%)

As NIRS measures all blood in the brain, it is a mixed saturation value. Nonetheless, because 70-80% of the blood is venous blood it mainly reflects the venous oxygen saturation. NIRS can be used on many somatic sites (renal, splanchnic tissue perfusion), however, the primary area of interest in neonates remains to be central nervous system.[48,49]

Figure 12. Hemoglobin wavelength absorption profile. OxyHb = oxygenated hemoglobin; DeoxyHb = deoxygenated hemoglobin.



1.3.2. Neonatal Application

Soft and thin tissues on relatively large (and often hair-scarce) newborn head serve as relatively penetrable "window" through which the brain can be monitored. Accordingly, the cerebral tissue oxygenation ($crSO_2$) then reflects the regional balance between the oxygen supply and demand for the underlying tissue.[48,49] Cerebral blood volume (CBV), dHb, oxyHb and total Hb changes can also give extra information regarding changes in the blood flow.[18] Cerebral oxygen supply depends on SpO_2, Hb concentration and CBF.[18,48,51] Supposing there are no significant changes in the metabolic rate (hypoglycemia induces CBF increase), SpO_2 and Hb concentration, $crSO_2$ deviations suggest deviations in CBF.[18,48,49]

Finally, fractional cerebral tissue oxygen extraction (FcTOE) can be calculated if SpO_2 is known:

$$\mathbf{FcTOE = ([SpO_2 - crSO_2] / SpO_2; range\ 0 - 1)}$$

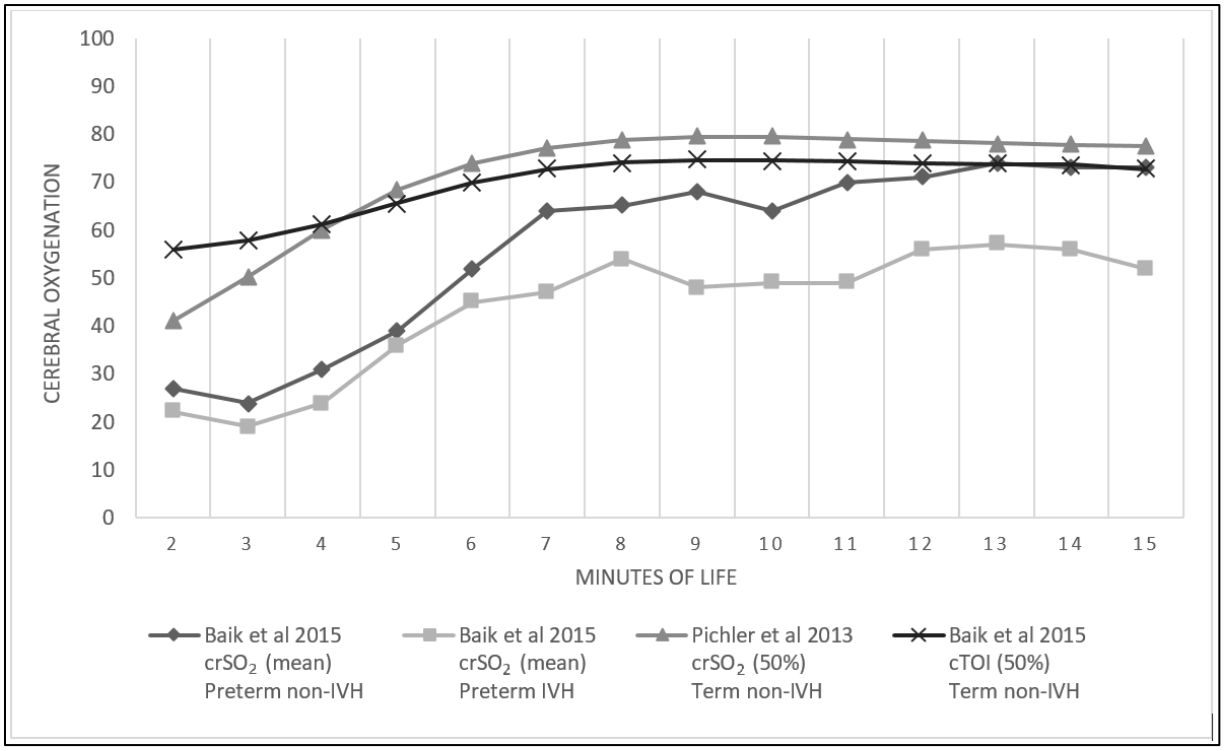
FcTOE is inversely related to CBF (decrease in CBF causes increase in FcTOE) and reflects the balance between cerebral oxygen supply and oxygen consumption.[53] Therefore, FcTOE can be useful to separate cerebral hypoxic hypoxia (lack of oxygen with normal perfusion) from ischemic hypoxia (lack of oxygen due to low perfusion) and high FcTOE was associated with significant neurologic injury in preterm infants in first postnatal days.[18,53]

1.3.3. Normative Values

Baik et al established centiles for tissue oxygenation index (TOI) and FcTOE in term newborns without a need for medical support during the first 15 minutes of life (using NIRO 200NX).[54] Similar findings in term infants were observed by Pichler et al, who used INVOS 5100 NIRS device to measure $crSO_2$.[55] Comparably, preterm infants without PIVH showed lower $crSO_2$ values initially, however, by the 15th minute of life the values reached values of term counterparts. Interestingly, preterm infants who developed PIVH later had significantly lower $crSO_2$ throughout the first 15 minutes of life (**Figure 13**).[54,55]

Fuchs et al showed that $crSO_2$ had risen after birth continuously from 37% (mean) at one minute of age and had reached a steady state in the range of 61-84% roughly seven minutes after birth.[56] Similar findings were observed in studies of term infants, however, after the plateau phase they documented a decrease in cerebral oxygen saturation (increased FcTOE caused by reduced CBF) that could be caused by relatively significant left-to-right duct shunting. This CBF decrease was then followed by a gradual rise over the course of the first postnatal days.[53-55]

Figure 13. Cerebral oxygenation during the first 15 minutes of life in term and preterm infants with and without peri/intraventricular hemorrhage. $crSO_2$ = cerebral oxygenation; cTOI = cerebral tissue oxygenation index; IVH = intraventricular hemorrhage.



A relatively large study on preterm infants < 32 weeks showed that average $crSO_2$ at admission was 65% and rose with higher gestational age (1% per week).[57] $crSO_2$ also peaked at around 36 hours of age and then slowly declined in the first 72 hours. Furthermore, other authors obtained $crSO_2$ values from 439 preterm infants < 32 weeks' gestation in the first three postnatal days and here, $crSO_2$ range was 55–85%. For gestational age of 24 to 27 weeks, the 10th centile was around 55% using the INVOS device with the adult sensor.[53,57]

In the newborn pigs, $crSO_2$ of 55% represents a safety level of cerebral oxygenation, in which the brain maintains physiologic metabolism, including normal concentrations of lactate. However, it takes only 30 minutes of $crSO_2$ < 35% to trigger subcellular damage and several hours to cause neuronal apoptosis.[49]

Finally, differences in $crSO_2$ and both gender and trophic status of preterm infants have also been studied. Cohen et al demonstrated that in the first postnatal days, small-for-gestational age (SGA) infants exhibited slightly increased cerebral oxygenation when compared to non-SGA infants which might be explained by an increased CBF due to intra-uterine "brain-sparing" effect.[58]

1.3.4. Interventions

Endotracheal suctioning seems to negatively affect cerebral hemodynamic status and the magnitude of alteration depends on the mode of suctioning.[59]

Caffeine administration in premature infants showed no significant effect on cerebral oxygenation, although others observed transient decrease in this regard.[60] Ibuprofen did not significantly reduce CBF and cerebral oxygenation.[61]

Red blood cell transfusion can potentially decrease the frequency of $crSO_2$ depressions in infants who had low initial NIRS values before transfusion was given, otherwise relative polycythemia (high hematocrit leading to higher blood viscosity) can reduce CBF and thus be potentially harmful.[58]

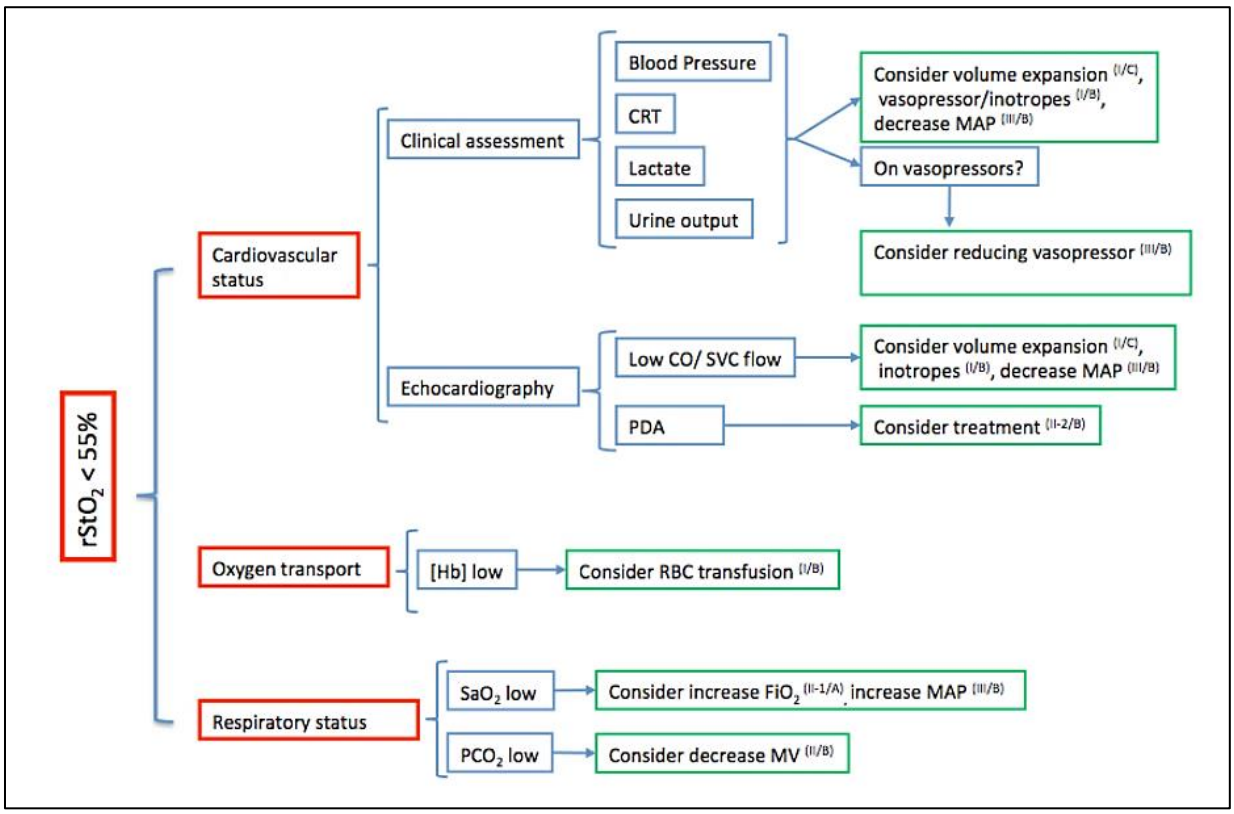
On the contrary, blood sampling from an umbilical arterial catheter was shown to reduce CBV and $crSO_2$ in VLBW infants (the greater the amount of withdrawn blood, the more significant reduction).[62]

In terms of possible interventions based on NIRS values, several studies already used clearly-defined treatment protocols (**Figure 14**).[63]

The recently completed SafeBoosC phase II trial was conducted at eight sites in eight European countries. 166 extremely preterm infants were randomized to visible monitoring of cerebral oxygenation by NIRS combined with an evidence-based treatment guideline (experimental group) versus blinded NIRS and treatment as usual (control group). The trial found that NIRS monitoring in combination with an evidence-based treatment guideline successfully reduced the burden of hypoxia and hyperoxia from 81% to 36%hours during the first three days of life ($p<0.001$). Furthermore, the proportion of severe brain injury assessed by central reading of serial cranial ultrasound was 12.5% in the experimental group versus 23.4% in the control group, RR 0.53 (95% CI: 0.26 to 1.08). Mortality was 14% in the experimental versus 25% in the control group, RR 0.50 (95% CI: 0.29 to 1.00).

The objective of the SafeBoosC-III trial is to investigate the benefit and harms of treatment based on NIRS monitoring compared with treatment as usual. The hypothesis is that treatment based on NIRS monitoring for extremely preterm infants during the first 72 hours of life will result in a reduction in severe brain injury or death at 36 weeks postmenstrual age.

Figure 14. Treatment guideline algorithm for the SafeBoosC-III trial (Safeguarding the Brain of our smallest Children – Multinational randomized phase III clinical trial evaluating treatment based on near-infrared spectroscopy monitoring versus treatment as usual in premature infants). CRT = capillary refill time; MAP = mean airway pressure; CO = cardiac output; SVC = superior vena cava; PDA = patent ductus arteriosus; Hb = hemoglobin; RBC = red blood cell; MV = minute ventilation; $rStO_2$ = cerebral oxygenation.

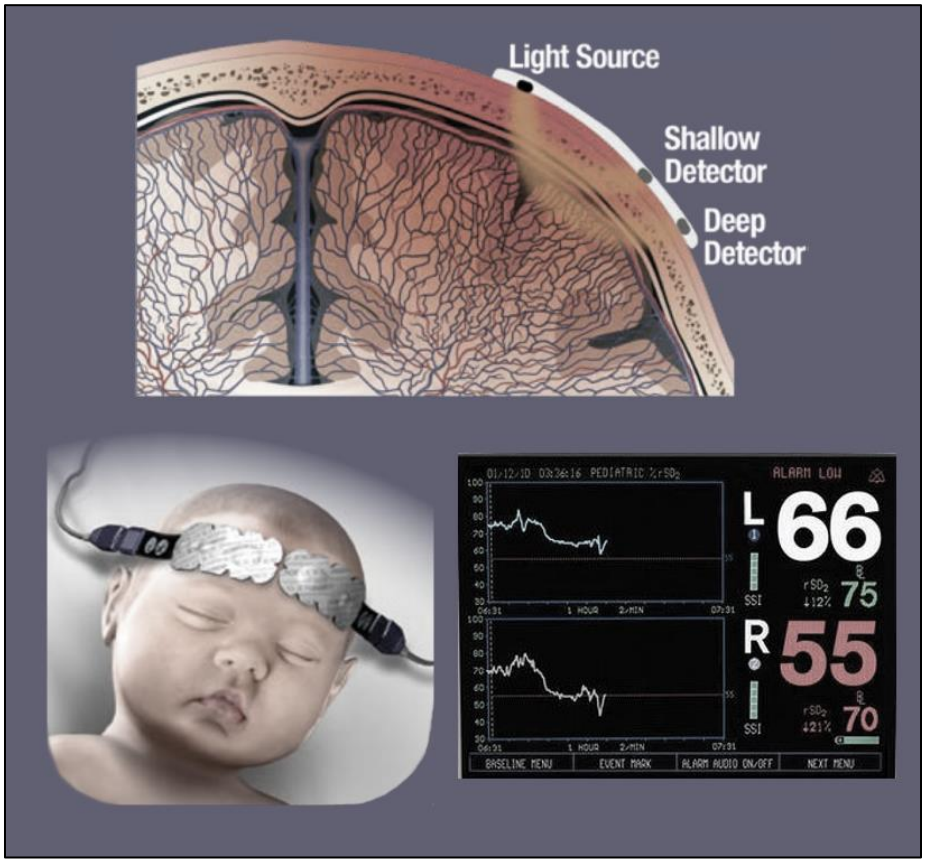


1.3.5. Potential Side Effects

From the patient safety point of view, sensors emanating near-infrared spectrum can cause thermic or pressure injury. However, others observed that NIRS did not generate skin burns even if applied for a longer time period. Besides, certain protective measures (gauze strips) can reduce occurrence of such injuries and the technique was confirmed by NIRS device producers as having no negative impact on NIRS signal (**Figure 15**).[48,49]

Last but not least, cost of NIRS machines should not be forgotten and one has to bear in mind the cost of single use probes as well.[53,64]

Figure 15. Schematic representation of cerebral NIRS application in newborns.



2. Project Goals

The aims of the project were to provide comprehensive literature review of NIRS application in neonatology and to find out possible correlation between cerebral oxygenation and fetal development and hemodynamic complications in preterm monochorionic and dichorionic twins.

2.1. Hypotheses

A. There are no differences in regional cerebral oxygenation between monochorionic and dichorionic twins.

B. There is no discordance in regional cerebral oxygenation among individual twins.

C. The changes in regional cerebral oxygenation can predict adverse outcome (intra/periventricular hemorrhage, periventricular leukomalacia, neurodevelopmental impairment, cerebral palsy).

3. Materials and Methods

3.1. Subjects

The institutional Ethical Committee of Institute for the Care of Mother and Child approved the study under the guidelines of the Helsinki Declaration (reference SOP 15/05/2008). Written informed consent was obtained from parents of all infants enrolled in the study.

Preterm infants from multiple pregnancies < 32 weeks of gestation were enrolled and followed-up in this prospective, observational study. Patients with serious contributing morbidities were excluded: prenatally diagnosed congenital malformations and chromosomal abnormalities, prenatally acquired brain lesion, birth below limit of viability (gestational age < 24+0), need of chest compression at the delivery room and significant skin lesion contraindicating the use of NIRS sensor.

The patient enrollment took place between October 2016 and January 2018 at the Institute for the Care of Mother and Child, Prague.

3.2. Cerebral Oxygenation

Cerebral regional oxygenation was measured with a NIRS monitor (INVOS 5100C, Medtronic, Dublin, Ireland) with sample rate of 1 Hz. Measurements started within 1 hour from birth and lasted up to 72 hours of age. A transducer (INVOS Cerebral Oximetry Infant-Neonatal sensor, Medtronic, Dublin, Ireland) was placed on the frontoparietal side of infant's head.

The method takes advantage of near-infrared spectral absorption by deoxygenated and oxygenated hemoglobin. Using Beer-Lambert law and machine-specific detection algorithms, oxyHb and dHb can be calculated into percentage oxygenation (oxyHb / [oxyHb + dHb]) with range 0-100%. NIRS represents mainly venous oxygen saturation as 70-80 % of cerebral blood is venous blood.

Artifacts in $crSO_2$ were removed manually before results were analyzed. Artifacts were defined as: changes in $crSO_2$ that could not be physiologically explained (e.g. a 30% step change between 2 subsequent data points) or changes that were accompanied by severe distortion in the other parameters suggesting infant movement or handling. Thereafter, $crSO_2$ was averaged for every 1-hour period. No action was taken based on recorded values.

3.3. Definition of Morbidities

Twin-Twin Transfusion Syndrome was defined using the following criteria: a single placenta, same sex, and significant amniotic fluid volume discordance between the two fetuses - with a deep vertical pocket of ≥ 8 cm in the sac of the recipient twin and ≤ 2 cm in the sac of the donor twin. Fetal therapy (selective laser coagulation of placental vessels) was performed accordingly.[65]

Fetal Growth Restriction was diagnosed prenatally by obstetricians using 2D and Doppler measurement of the fetus (abdominal circumference, estimated fetal weight, end-diastolic flow patterns in the umbilical and uterine artery).[66]

Fetal growth restriction was confirmed postnatally using Fenton growth charts.[67] Other neonatal outcomes (respiratory distress syndrome, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis and periventricular leukomalacia) were followed up according to the Vermont Oxford definition.[68]

Blood counts were measured with a Coulter Micro Dif II (Coulter Electronics Ltd., Fullerton, US) in all patients up to 2 hours after admission. Transfusion was indicated according to hemoglobin level (< 120 g/L) and clinical judgment.

3.4. Statistical Analysis

The study group was divided into 4 subgroups based on major fetal pathology: donor (1) and recipient (2) monochorionic twins, FGR infants (3) and newborns without any known fetal pathology (4). Statistical analysis reflected subjects' specificity (twins) using linear mixed model for scale variables and generalized linear model for categorical variables. Patterns of $crSO_2$ were evaluated using mixed model analysis with random effect (pair) and repeated measurement based on covariance structure.

Cerebral oxygenation graph was modelled using estimated marginal mean and standard error. Clinical variables are reported using descriptive statistical methods. All reported *p*-values are two-sided and $p < 0.05$ was considered statistically significant. The analysis was performed with Statistical Package for Social Sciences (SPSS 26.0; SPSS Institute, Chicago, IL, USA).

4. Results

4.1. Descriptive Statistics

Overall, 62 preterm newborns were included. Scale variables and their distributions within the study population and individual subgroups are displayed below (**Figure 16-31).**

Figure 16. Histogram and distribution of gestational age within the study population.

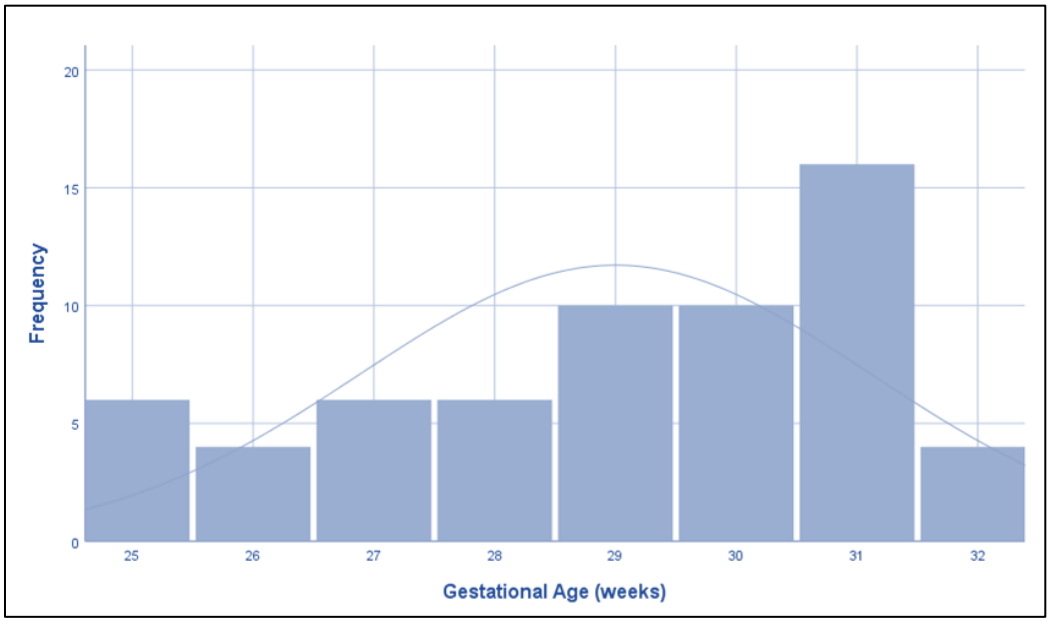


Figure 17. Box plots of gestational age for the study subgroups.

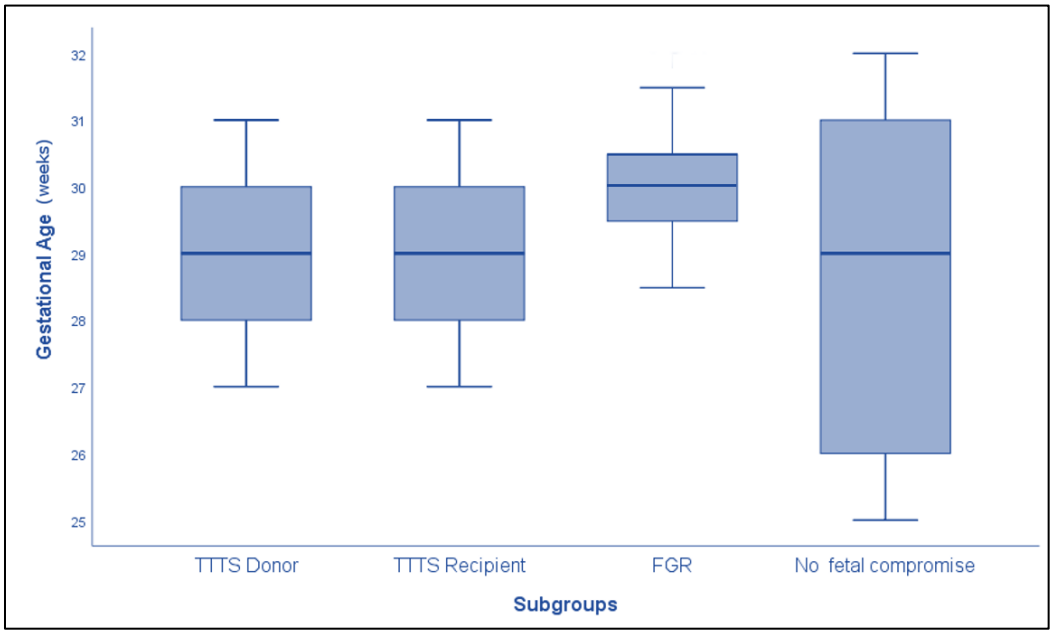


Figure 18. Box plot of birth weight distribution within the study population.

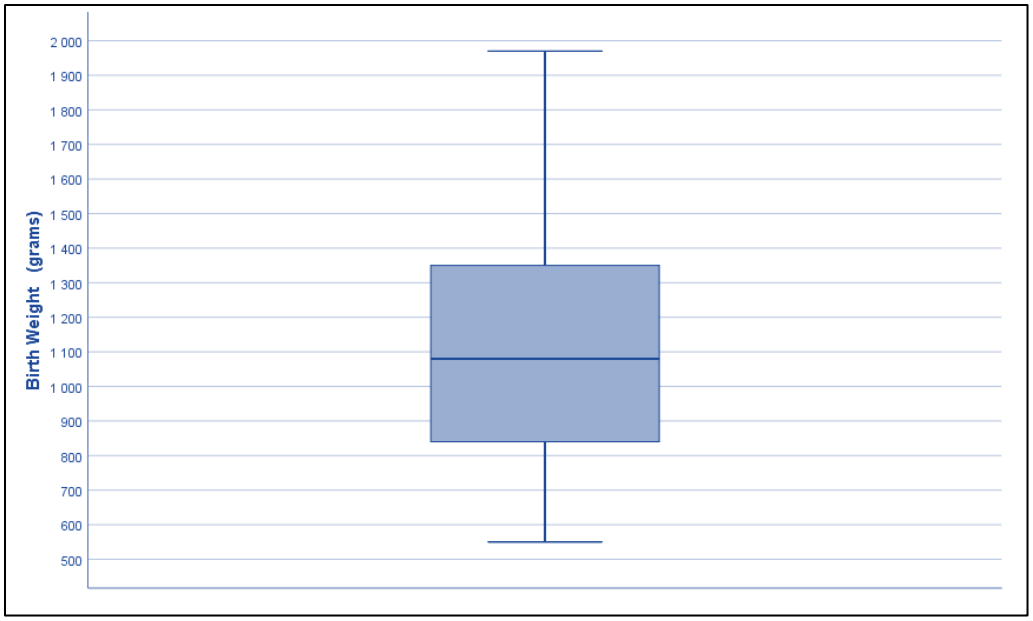


Figure 19. Box plots of birth weight for the study subgroups.

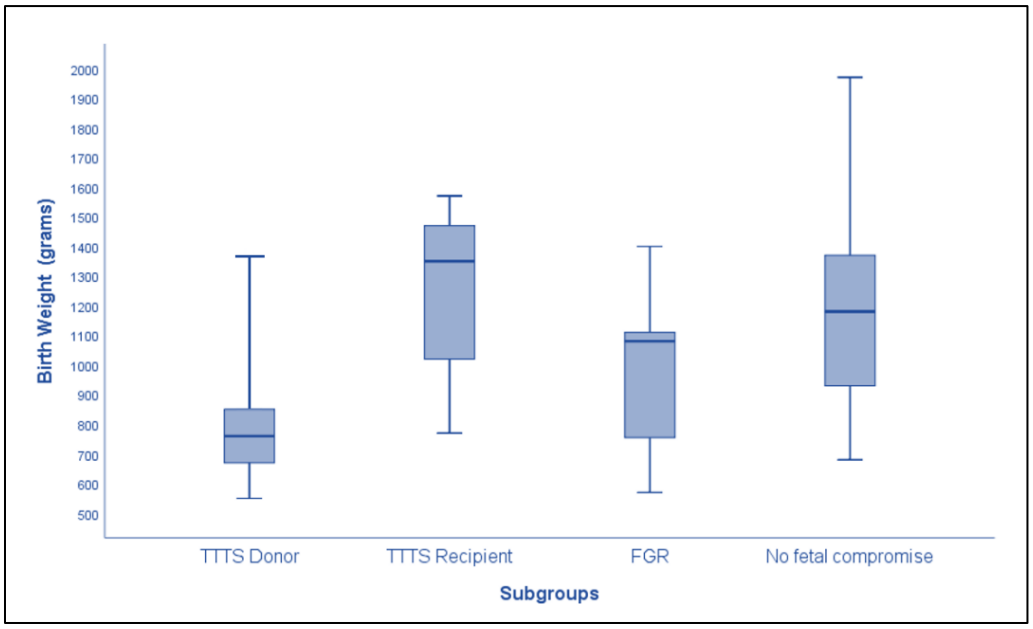


Figure 20. Histogram of APGAR scores at 1 minute of life.

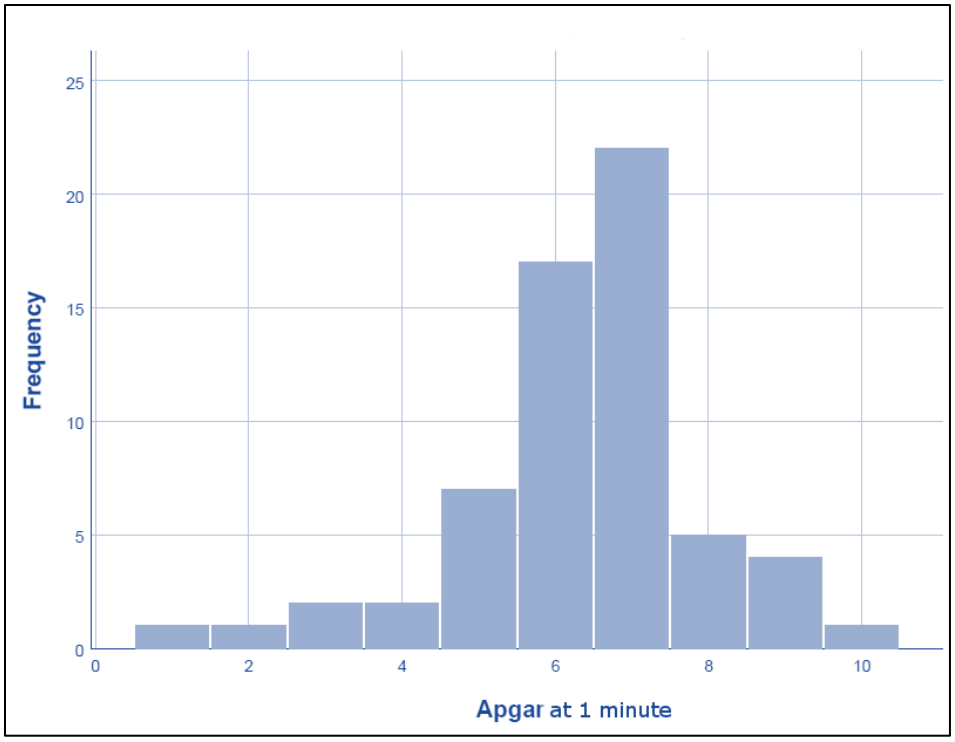


Figure 21. Histogram of APGAR scores at 5 minutes of life.

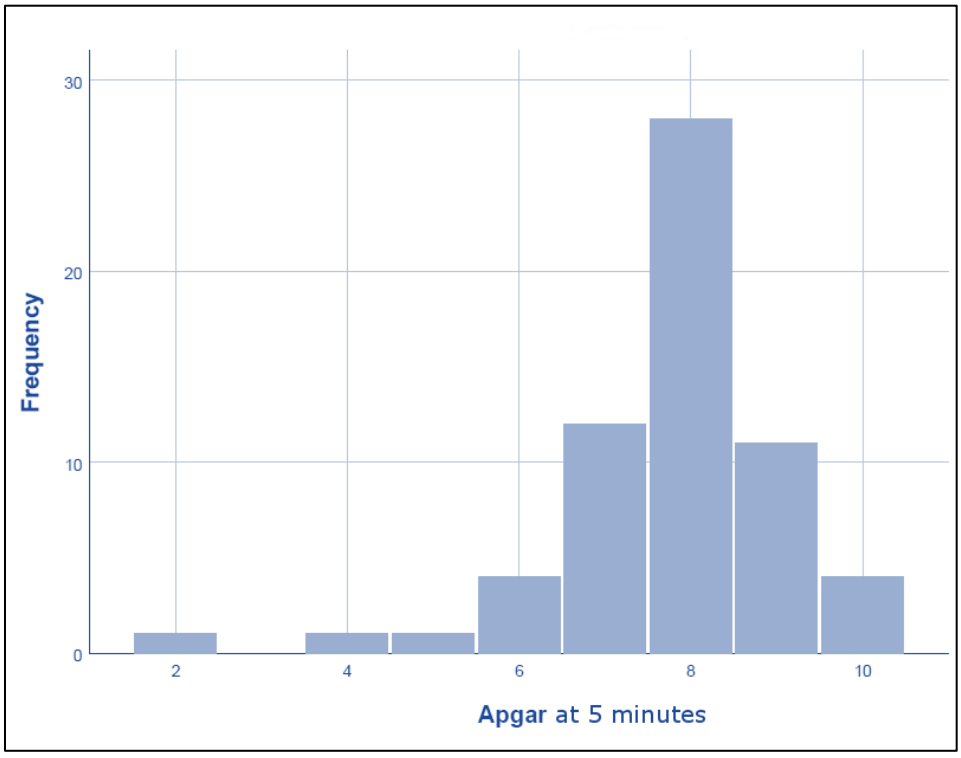


Figure 22. Histogram of hemoglobin (measured in g/L) distribution within the study group.

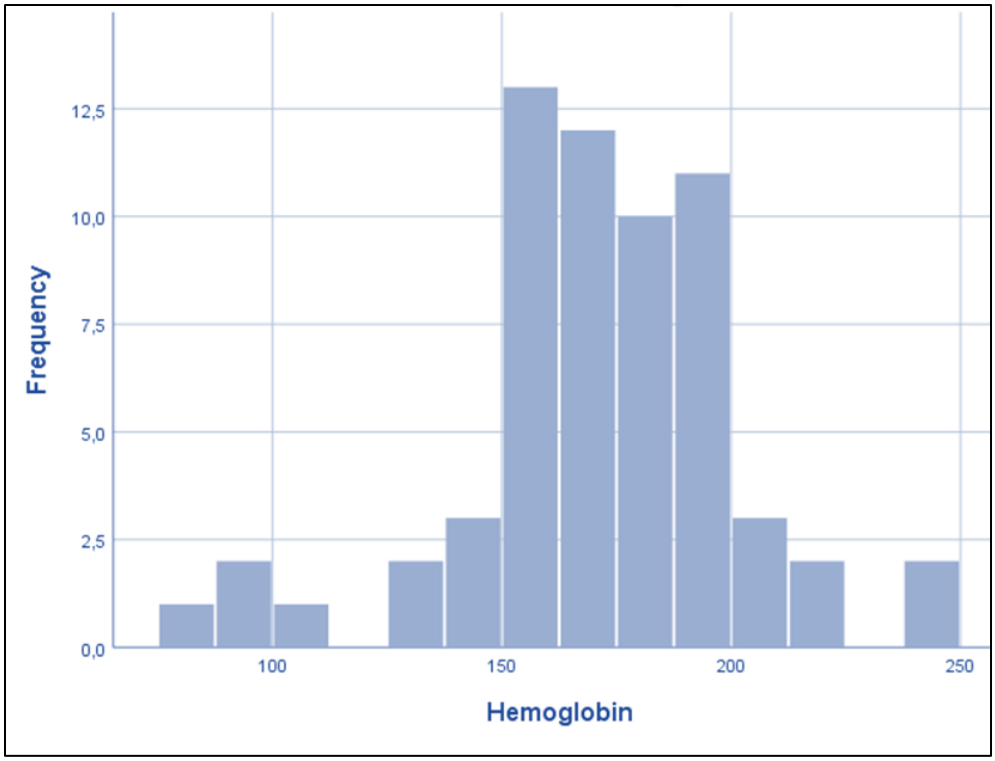


Figure 23. Histogram of hematocrit distribution within the study group.

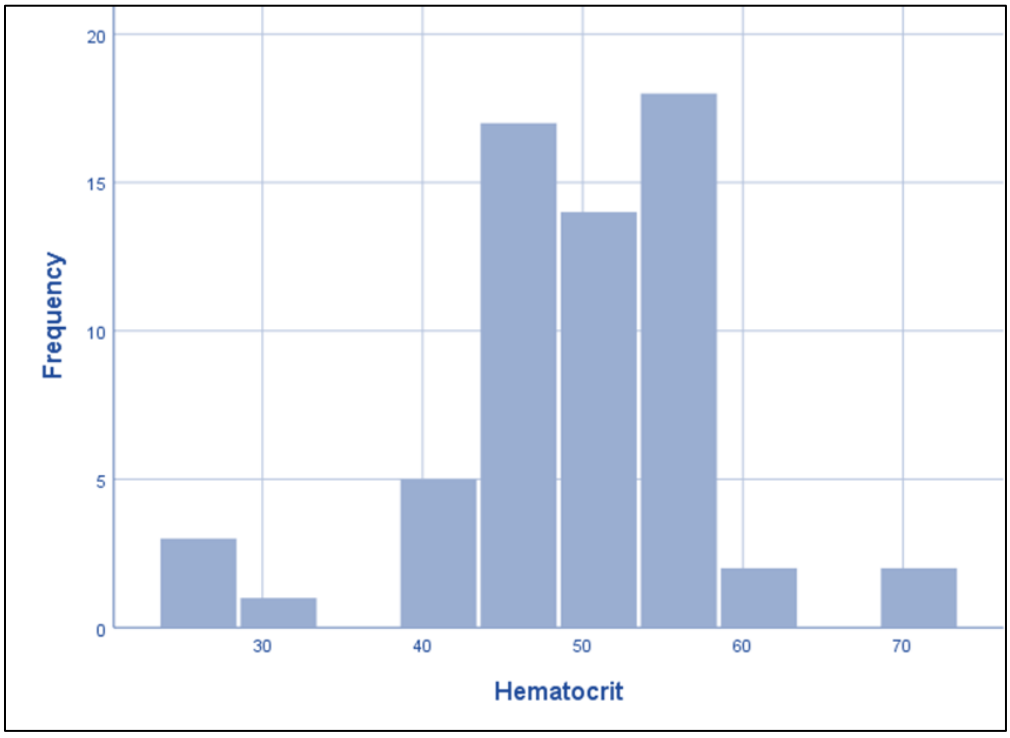


Figure 24. Pie chart of percentual distribution of patients within the subgroups. TTTS = twin-twin transfusion syndrome; FGR = fetal growth restriction.

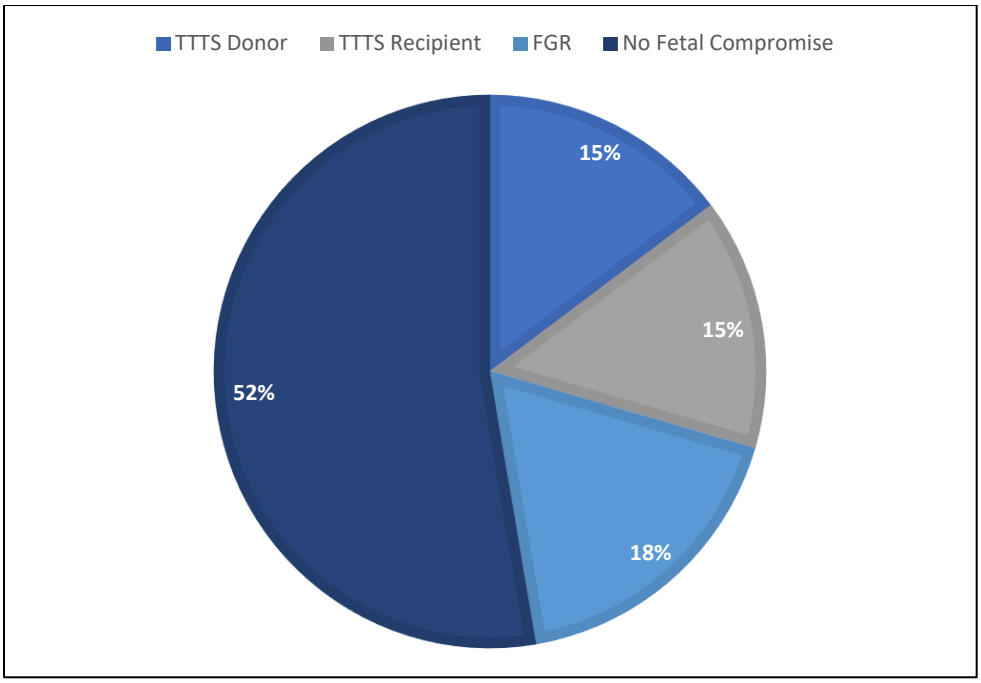


Figure 25. Pie chart of gender distribution within the study group.

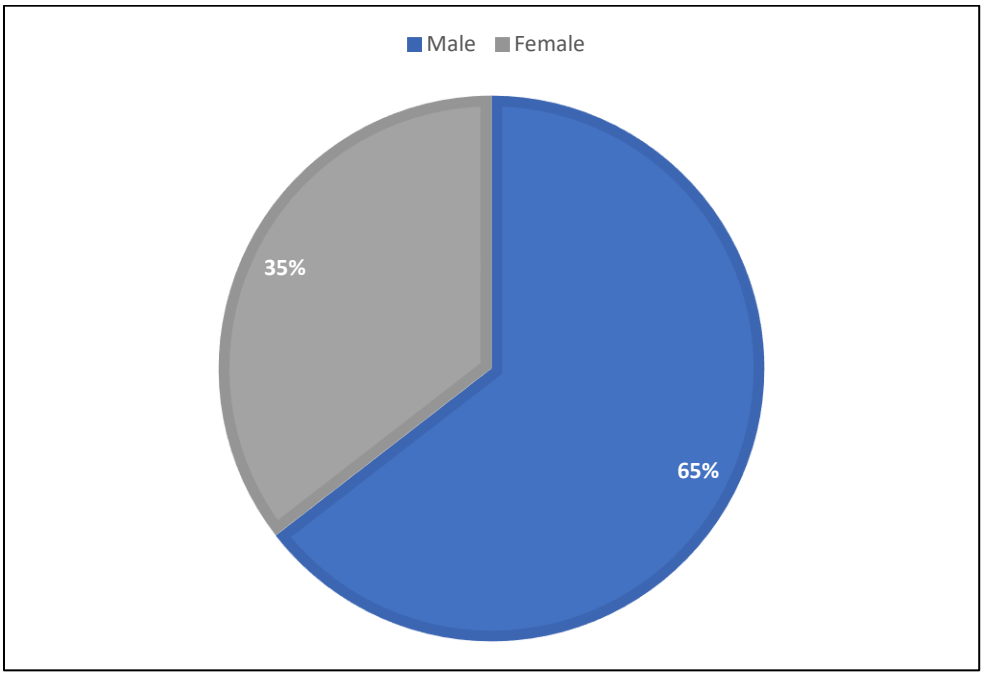


Figure 26. Pie chart of antenatal corticosteroids courses (completed versus incomplete/none) within the study group.

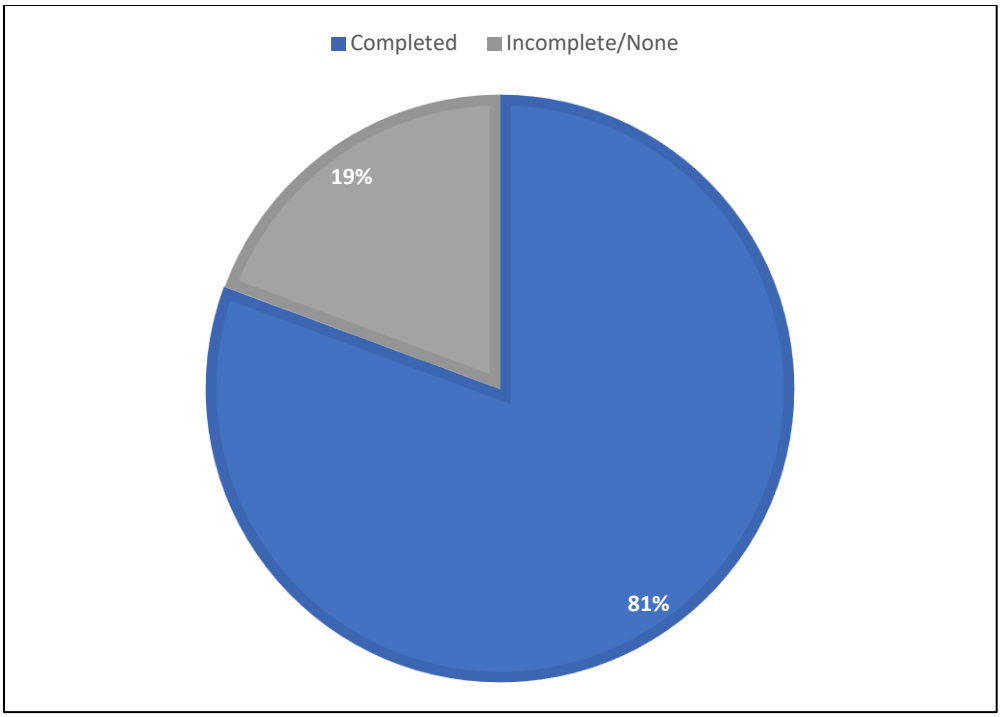


Figure 27. Pie chart of antenatal corticosteroids courses (completed versus incomplete/none) within the study subgroups. TTTS = twin-twin transfusion syndrome; FGR = fetal growth restriction.

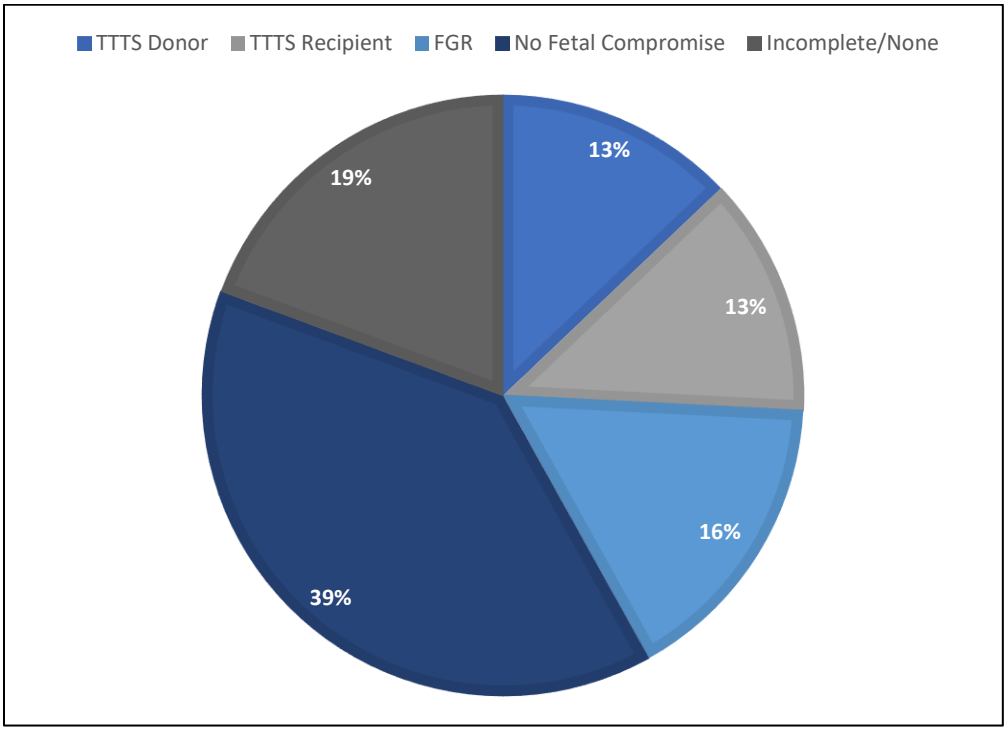


Figure 28. Pie chart of respiratory distress syndrome (RDS) occurrence within the study group.

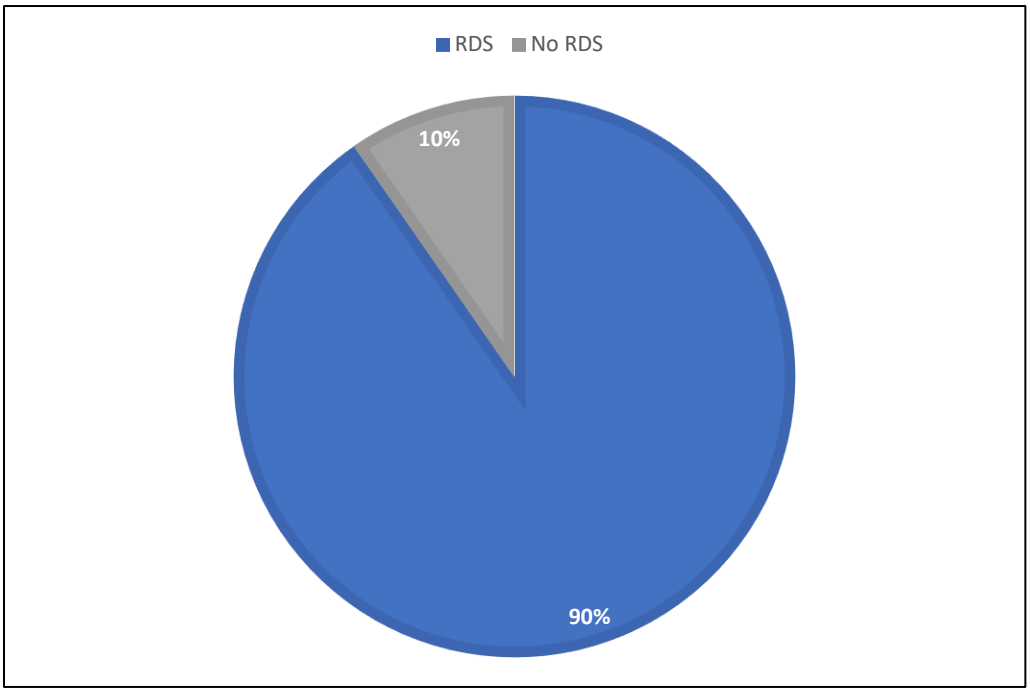


Figure 29. Pie chart of respiratory distress syndrome (RDS) occurrence within the study subgroups. TTTS = twin-twin transfusion syndrome; FGR = fetal growth restriction.

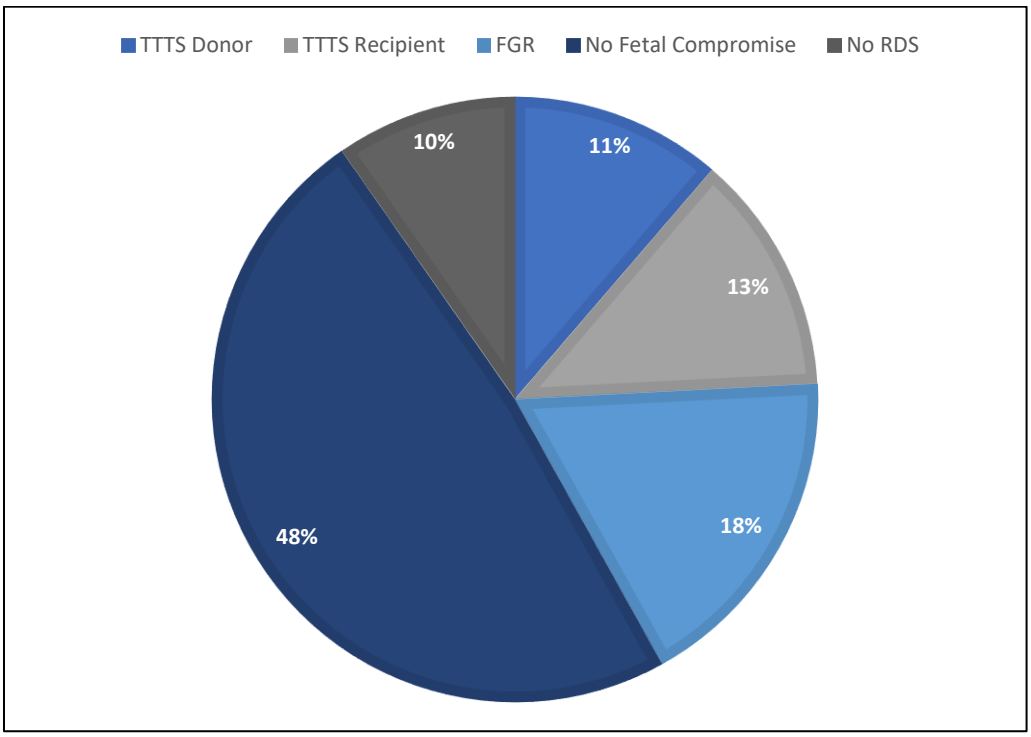


Figure 30. Pie chart of hypotension (requiring intervention) occurrence within the study group.

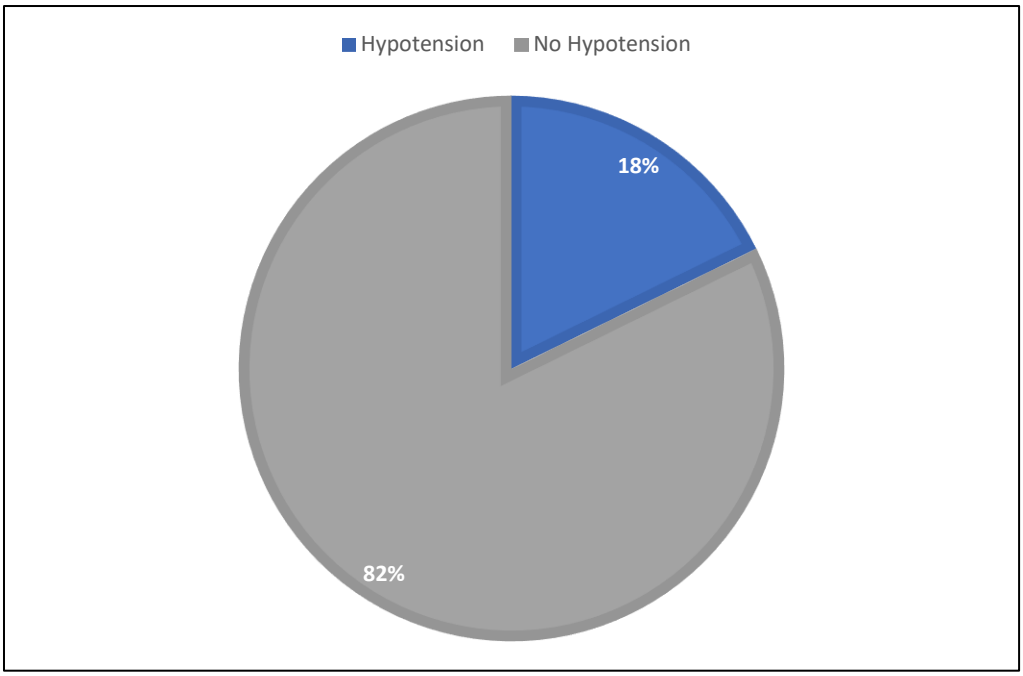
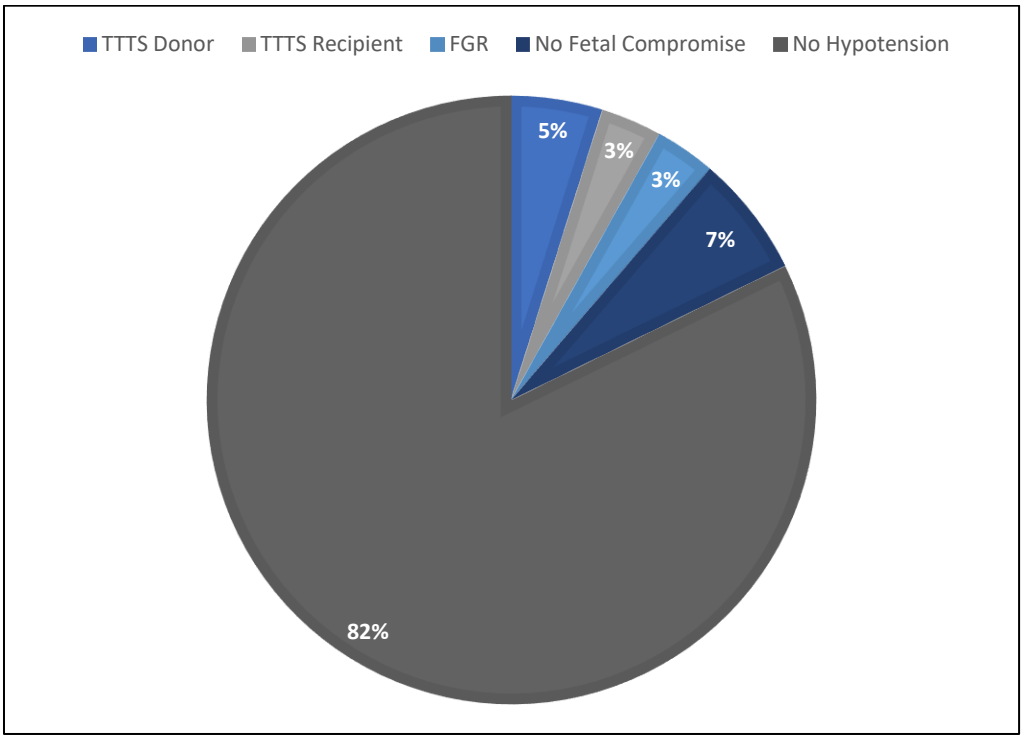


Figure 31. Pie chart of hypotension (requiring intervention) occurrence within the study subgroups. TTTS = twin-twin transfusion syndrome; FGR = fetal growth restriction.



Overall characteristic of the study group and subgroups (including neonatal morbidities and treatment) are displayed in the **Table 2**.

Table 2. Study population and subgroups. Continuous data are presented as mean ± SD. TTTS = twin-twin transfusion syndrome, FGR = fetal growth restriction, MCDA = monochorionic diamniotic, SLCPV = selective laser coagulation of placental vessels, RBCT = red blood cell transfusion, ANS = antenatal corticosteroids, RDS = respiratory distress syndrome, PDA = persistent ductus arteriosus, NEC = necrotizing enterocolitis, EOS = early-onset sepsis, PIVH = peri/intraventricular hemorrhage, PVL = periventricular leukomalacia.

Variable	Study group	Study Subgroups			
		TTTS Donor	TTTS Recipient	FGR	No fetal compromise
Number of patients, no. (% of all infants)	62 (100 %)	9 (15 %)	9 (15 %)	11 (18 %)	33 (52 %)
MCDA twin, no. (%)	38 (61 %)	9 (100 %)	9 (100 %)	7 (64 %)	13 (39 %)
Fetal therapy – SLCPV, no. (%)	4 (7 %)	2 (22 %)	2 (22 %)	0	0
Gestational age, weeks	29.0 ± 2.1	29.0 ± 1.4	29.0 ± 1.4	30.0 ± 1.9	28.7 ± 2.4
Birth weight, grams	1111 ± 322	856 ± 289	1228 ± 288	960 ± 251	1197 ± 314
Hemoglobin at birth, g/L	171 ± 30	161 ± 48	177 ± 45	163 ± 27	174 ± 19
RBCT in the first 72 hours, n (%)	3 (5 %)	2 (22 %)	0	1 (9 %)	0
APGAR, 1 minute	6.4 ± 1.6	5.9 ± 2.1	7.1 ± 1.5	6.7 ± 0.9	6.1 ± 1.6
APGAR, 5 minutes	7.8 ± 1.4	7.0 ± 2.4	8.4 ± 1.1	7.9 ± 0.7	7.7 ± 1.1
C-section delivery, no. (%)	60 (97 %)	9 (100 %)	9 (100 %)	11 (100 %)	31 (94 %)
Male gender, no. (%)	40 (65 %)	6 (67 %)	6 (67 %)	9 (82 %)	19 (58 %)
ANS (completed), no. (%)	50 (81 %)	8 (89 %)	8 (89 %)	10 (91 %)	24 (73 %)
Intubated at delivery suite, no. (%)	5 (8 %)	1 (11 %)	0	0	4 (12 %)

RDS, no. (%)	56 (90 %)	7 (78 %)	8 (89 %)	11 (100 %)	30 (91 %)
Pulmonary hemorrhage, no. (%)	1 (2 %)	1 (11 %)	0	0	0
PDA treated, no. (%)	3 (5 %)	1 (11 %)	0	1 (9 %)	1 (3 %)
Hypotension treated, no. (%)	11 (18 %)	3 (33 %)	2 (22 %)	2 (18 %)	4 (12 %)
Respiratory support at 36 weeks, no. (%)	13 (2 %)	4 (44 %)	2 (22 %)	1 (9 %)	6 (18 %)
NEC, no. (%)	4 (7 %)	1 (11 %)	2 (22 %)	0	1 (3 %)
EOS, no. (%)	6 (10 %)	1 (11 %)	2 (22 %)	0	3 (9 %)
PIVH grade I-II, no. (%)	3 (5 %)	0	0	1 (9 %)	2 (6 %)
PIVH grade III-IV, no. (%)	2 (3 %)	1 (11 %)	0	0	1 (3 %)
PVL, no. (%)	1 (2 %)	1 (11 %)	0	0	0

4.2. Neonatal Outcome

We used linear mixed model with random effect (pair) for analyzing scale variables among the subgroups. We found significant difference in birth weight among the 4 subgroups ($p < 0.001$). No significant differences were found in other scale variables, including admission hemoglobin and hematocrit ($p = 0.501$ and $p = 0.476$, respectively).

For the analysis of categorical variables among the 4 subgroups, we used generalized linear model with random effect (pair). The incidence of severe neonatal morbidities was low among subgroups and did not allow to detect any statistical differences even when we analyzed composite morbidity (hypotension, necrotizing enterocolitis, severe intraventricular hemorrhage (grade 3 and 4) and periventricular leukomalacia; $p = 0.089$). No statistically significant differences were noticed in neonatal mortality.

In addition, no significant differences were found in red blood cell transfusion (RBCT) in the first 72 hours or fetal therapy among the subgroups ($p = 0.337$ and $p = 1.0$, respectively).

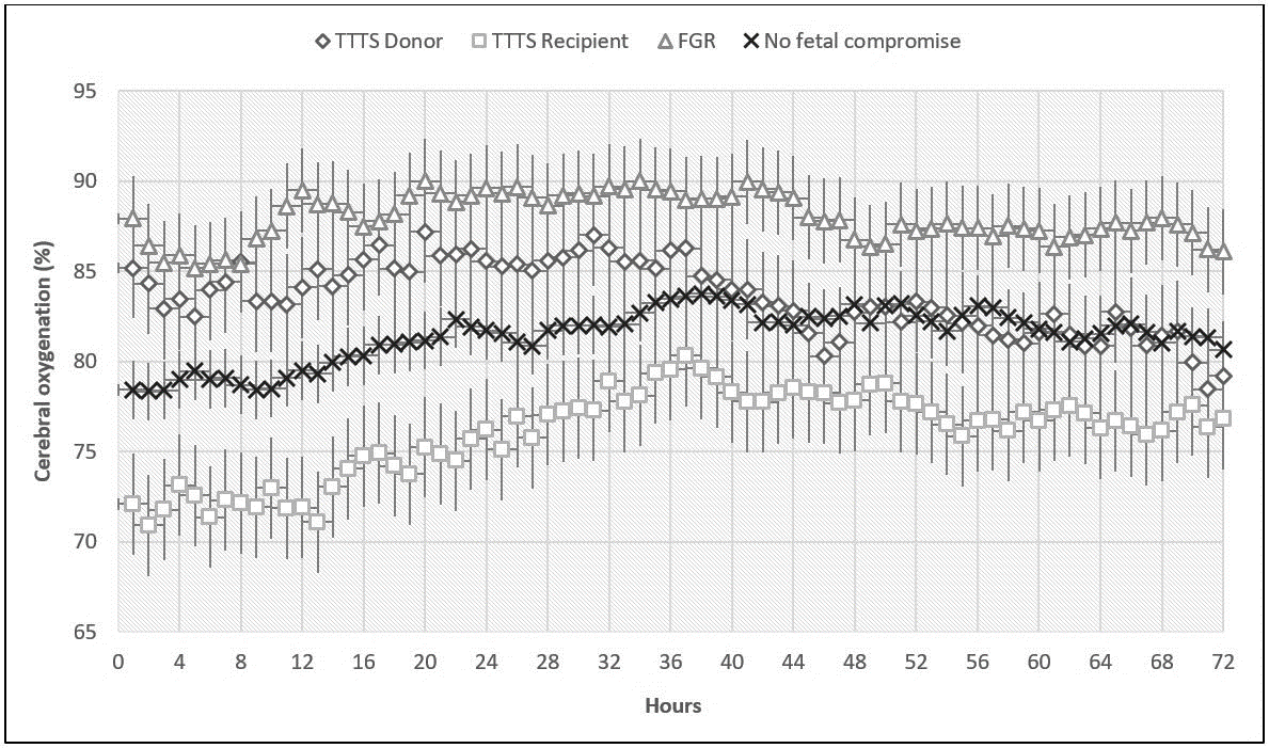
4.3. Cerebral Oxygenation

A total of 4464 1-hour $crSO_2$ averages were used for analysis (**Table 3-6**). The recipient twins exhibited the lowest $crSO_2$ (expressed as mean ± SE) throughout the study period (76±0.3%), whereas the FGR and donor twins presented with the highest values (86±0.3% and 83±0.4% respectively). Newborns without any observed fetal complication (TTTS or FGR) presented with $crSO_2$ of 81±0.2%. Graphical overview of $crSO_2$ development among the subgroups (using estimated marginal mean and standard error) is shown in **Figure 32**.

We observed significant variances in $crSO_2$ over time among the subgroups using mixed model analysis with random effect (pair) and repeated measurement based on covariance structure (type III tests of fixed effects: $p < 0.001$).

Using estimates of fixed effects, significant differences were found between the subgroup with no fetal compromise (reference subgroup) and FGR and recipient infants ($p < 0.001$ and $p = 0.038$, respectively). When analyzing the reference subgroup and donor twins only, the difference was not significant ($p = 0.356$). Moreover, the $crSO_2$ values for donor twins were comparable with the reference subgroup after 36 hours.

Figure 32. Postnatal cerebral oxygenation patterns based on underlying fetal pathology. TTTS = twin-twin transfusion syndrome; FGR = fetal growth restriction.



When Hb was added to the mixed model, the analysis revealed significant correlation between Hb and $crSO_2$ (type III tests of fixed effects: $p < 0.001$) (**Figure 33**). Using mixed model test, there was no significant correlation between RBCT and $crSO_2$ ($p = 0.284$).

Figure 33. Postnatal cerebral oxygenation patterns based on underlying fetal pathology and hemoglobin levels on admission. TTTS = twin-twin transfusion syndrome; FGR = fetal growth restriction.

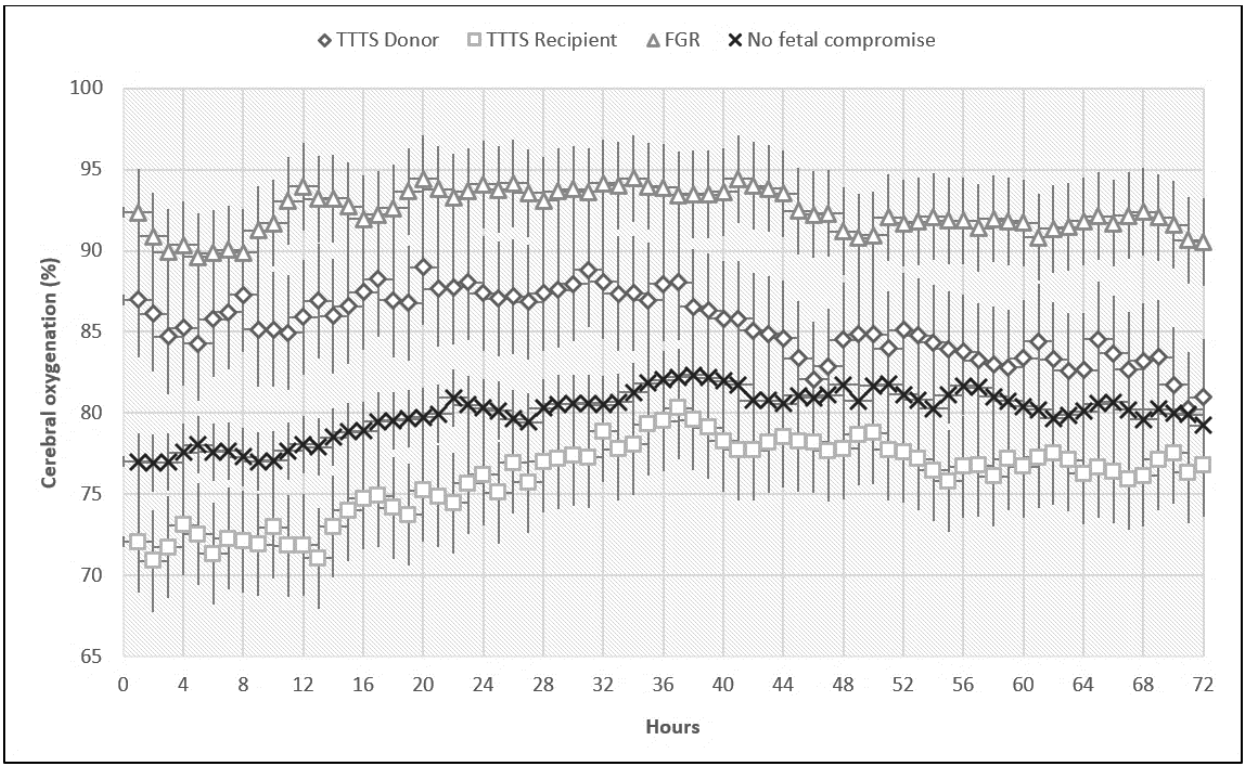


Table 3. Overview of cerebral oxygenation ($crSO_2$) in donor twins (twin-twin transfusion syndrome) during the first 72 hours of life. NIRS data shown as mean and standard error (SE).

Hour of life	Mean $crSO_2$	SE	Low Range	High Range
1	85.20	2.81	82.39	88.00
2	84.32	2.81	81.52	87.13
3	82.94	2.81	80.13	85.74
4	83.46	2.81	80.66	86.27
5	82.48	2.81	79.68	85.29
6	83.98	2.81	81.17	86.78
7	84.42	2.81	81.62	87.23
8	85.50	2.81	82.69	88.31
9	83.34	2.81	80.53	86.15
10	83.35	2.81	80.55	86.16
11	83.16	2.81	80.35	85.96

12	84.11	2.81	81.31	86.92
13	85.12	2.81	82.32	87.93
14	84.18	2.81	81.37	86.99
15	84.80	2.81	82.00	87.61
16	85.65	2.81	82.84	88.46
17	86.46	2.81	83.65	89.26
18	85.16	2.81	82.35	87.97
19	84.98	2.81	82.18	87.79
20	87.18	2.81	84.37	89.99
21	85.87	2.81	83.06	88.68
22	85.96	2.81	83.15	88.77
23	86.26	2.81	83.45	89.06
24	85.58	2.81	82.77	88.38
25	85.26	2.81	82.45	88.07
26	85.38	2.81	82.58	88.19
27	85.04	2.81	82.24	87.85
28	85.60	2.81	82.79	88.40
29	85.78	2.81	82.98	88.59
30	86.17	2.81	83.36	88.98
31	87.02	2.81	84.22	89.83
32	86.30	2.81	83.50	89.11
33	85.55	2.81	82.74	88.36
34	85.60	2.81	82.79	88.41
35	85.14	2.81	82.34	87.95
36	86.16	2.81	83.35	88.96
37	86.27	2.81	83.46	89.08
38	84.75	2.81	81.94	87.56
39	84.52	2.81	81.71	87.33
40	84.01	2.81	81.20	86.82
41	84.01	2.81	81.21	86.82
42	83.30	2.81	80.49	86.11
43	83.09	2.81	80.28	85.90
44	82.80	2.81	80.00	85.61
45	81.59	2.81	78.78	84.39
46	80.30	2.81	77.49	83.10
47	81.07	2.81	78.27	83.88
48	82.72	2.81	79.91	85.53
49	83.06	2.81	80.26	85.87
50	83.05	2.81	80.24	85.85
51	82.19	2.81	79.38	84.99
52	83.31	2.81	80.51	86.12
53	82.99	2.81	80.18	85.80
54	82.56	2.81	79.75	85.36

55	82.14	2.81	79.33	84.95
56	81.97	2.81	79.16	84.78
57	81.45	2.81	78.65	84.26
58	81.23	2.81	78.42	84.04
59	81.01	2.81	78.20	83.82
60	81.60	2.81	78.79	84.41
61	82.63	2.81	79.82	85.43
62	81.51	2.81	78.71	84.32
63	80.83	2.81	78.02	83.63
64	80.85	2.81	78.04	83.65
65	82.77	2.81	79.96	85.57
66	81.87	2.81	79.06	84.68
67	80.89	2.81	78.08	83.69
68	81.42	2.81	78.61	84.23
69	81.66	2.81	78.85	84.47
70	79.95	2.81	77.15	82.76
71	78.46	2.81	75.65	81.26
72	79.20	2.81	76.39	82.00

Table 4. Overview of cerebral oxygenation ($crSO_2$) in recipient twins (twin-twin transfusion syndrome) during the first 72 hours of life. NIRS data shown as mean and standard error (SE).

Hour of life	Mean $crSO_2$	SE	Low Range	High Range
1	72.11	2.81	69.30	74.91
2	70.93	2.81	68.12	73.74
3	71.77	2.81	68.96	74.58
4	73.15	2.81	70.34	75.95
5	72.57	2.81	69.76	75.37
6	71.37	2.81	68.56	74.18
7	72.30	2.81	69.49	75.11
8	72.13	2.81	69.32	74.94
9	71.92	2.81	69.12	74.73
10	72.99	2.81	70.18	75.80
11	71.87	2.81	69.06	74.67
12	71.89	2.81	69.08	74.70
13	71.08	2.81	68.27	73.89
14	73.04	2.81	70.23	75.85
15	74.05	2.81	71.24	76.86
16	74.78	2.81	71.97	77.58
17	74.92	2.81	72.11	77.73
18	74.20	2.81	71.40	77.01
19	73.76	2.81	70.96	76.57
20	75.25	2.81	72.45	78.06

21	74.89	2.81	72.09	77.70
22	74.49	2.81	71.68	77.29
23	75.70	2.81	72.89	78.51
24	76.23	2.81	73.42	79.03
25	75.13	2.81	72.32	77.94
26	76.96	2.81	74.15	79.77
27	75.77	2.81	72.97	78.58
28	77.05	2.81	74.24	79.86
29	77.22	2.81	74.41	80.02
30	77.42	2.81	74.62	80.23
31	77.29	2.81	74.48	80.10
32	78.91	2.81	76.10	81.71
33	77.80	2.81	74.99	80.60
34	78.11	2.81	75.31	80.92
35	79.34	2.81	76.54	82.15
36	79.55	2.81	76.75	82.36
37	80.33	2.81	77.52	83.14
38	79.62	2.81	76.81	82.43
39	79.14	2.81	76.34	81.95
40	78.29	2.81	75.49	81.10
41	77.77	2.81	74.96	80.58
42	77.75	2.81	74.94	80.56
43	78.25	2.81	75.45	81.06
44	78.56	2.81	75.75	81.37
45	78.31	2.81	75.50	81.12
46	78.25	2.81	75.44	81.06
47	77.70	2.81	74.89	80.50
48	77.83	2.81	75.03	80.64
49	78.71	2.81	75.91	81.52
50	78.81	2.81	76.00	81.61
51	77.79	2.81	74.98	80.59
52	77.64	2.81	74.83	80.44
53	77.20	2.81	74.39	80.01
54	76.51	2.81	73.71	79.32
55	75.85	2.81	73.04	78.65
56	76.73	2.81	73.92	79.53
57	76.79	2.81	73.98	79.60
58	76.15	2.81	73.34	78.96
59	77.20	2.81	74.39	80.00
60	76.73	2.81	73.92	79.53
61	77.31	2.81	74.50	80.11
62	77.54	2.81	74.73	80.34
63	77.13	2.81	74.33	79.94

64	76.29	2.81	73.48	79.09
65	76.70	2.81	73.89	79.51
66	76.40	2.81	73.59	79.21
67	75.95	2.81	73.15	78.76
68	76.15	2.81	73.35	78.96
69	77.18	2.81	74.38	79.99
70	77.58	2.81	74.77	80.38
71	76.35	2.81	73.55	79.16
72	76.81	2.81	74.01	79.62

Table 5. Overview of cerebral oxygenation ($crSO_2$) in newborns with fetal growth restriction during the first 72 hours of life. NIRS data shown as mean and standard error (SE).

Hour of life	Mean $crSO_2$	SE	Low Range	High Range
1	87.92	2.35	85.58	90.27
2	86.43	2.35	84.08	88.77
3	85.47	2.35	83.12	87.82
4	85.90	2.35	83.55	88.24
5	85.19	2.35	82.84	87.54
6	85.41	2.35	83.06	87.75
7	85.62	2.35	83.28	87.97
8	85.43	2.35	83.09	87.78
9	86.82	2.35	84.47	89.17
10	87.25	2.35	84.90	89.60
11	88.63	2.35	86.28	90.97
12	89.50	2.35	87.15	91.84
13	88.74	2.35	86.39	91.09
14	88.77	2.35	86.42	91.12
15	88.29	2.35	85.94	90.64
16	87.50	2.35	85.15	89.85
17	87.77	2.35	85.42	90.12
18	88.17	2.35	85.82	90.52
19	89.21	2.35	86.86	91.56
20	89.99	2.35	87.65	92.34
21	89.34	2.35	86.99	91.68
22	88.84	2.35	86.50	91.19
23	89.20	2.35	86.85	91.54
24	89.64	2.35	87.29	91.98
25	89.32	2.35	86.97	91.66
26	89.70	2.35	87.35	92.04
27	89.10	2.35	86.76	91.45
28	88.63	2.35	86.28	90.98
29	89.20	2.35	86.85	91.55

30	89.33	2.35	86.98	91.68
31	89.17	2.35	86.82	91.52
32	89.71	2.35	87.36	92.06
33	89.57	2.35	87.22	91.92
34	90.00	2.35	87.65	92.35
35	89.52	2.35	87.18	91.87
36	89.45	2.35	87.10	91.80
37	88.99	2.35	86.64	91.33
38	89.04	2.35	86.69	91.39
39	89.02	2.35	86.67	91.37
40	89.16	2.35	86.82	91.51
41	89.97	2.35	87.62	92.32
42	89.56	2.35	87.21	91.90
43	89.38	2.35	87.03	91.73
44	89.07	2.35	86.72	91.41
45	88.00	2.35	85.65	90.34
46	87.79	2.35	85.44	90.14
47	87.85	2.35	85.50	90.20
48	86.76	2.35	84.41	89.11
49	86.35	2.35	84.00	88.70
50	86.53	2.35	84.18	88.87
51	87.60	2.35	85.25	89.95
52	87.24	2.35	84.90	89.59
53	87.36	2.35	85.01	89.71
54	87.64	2.35	85.30	89.99
55	87.41	2.35	85.06	89.76
56	87.41	2.35	85.06	89.75
57	86.95	2.35	84.61	89.30
58	87.52	2.35	85.17	89.87
59	87.36	2.35	85.02	89.71
60	87.26	2.35	84.91	89.61
61	86.38	2.35	84.03	88.73
62	86.90	2.35	84.55	89.25
63	87.02	2.35	84.67	89.37
64	87.36	2.35	85.01	89.71
65	87.69	2.35	85.34	90.03
66	87.24	2.35	84.89	89.59
67	87.71	2.35	85.36	90.06
68	87.95	2.35	85.61	90.30
69	87.60	2.35	85.25	89.95
70	87.15	2.35	84.80	89.50
71	86.21	2.35	83.86	88.56
72	86.10	2.35	83.75	88.44

Table 6. Overview of cerebral oxygenation ($crSO_2$) in newborns without fetal compromise during the first 72 hours of life. NIRS data shown as mean and standard error (SE).

Hour of life	Mean $crSO_2$	SE	Low Range	High Range
1	78.42	1.61	76.81	80.03
2	78.35	1.61	76.74	79.96
3	78.40	1.61	76.78	80.01
4	78.99	1.61	77.38	80.60
5	79.46	1.61	77.85	81.07
6	79.01	1.61	77.40	80.62
7	79.08	1.61	77.47	80.69
8	78.71	1.61	77.10	80.33
9	78.43	1.61	76.82	80.04
10	78.50	1.61	76.89	80.11
11	79.09	1.61	77.48	80.70
12	79.49	1.61	77.88	81.10
13	79.32	1.61	77.71	80.93
14	79.93	1.61	78.32	81.54
15	80.25	1.61	78.64	81.87
16	80.32	1.61	78.71	81.94
17	80.91	1.61	79.29	82.52
18	80.95	1.61	79.34	82.56
19	81.06	1.61	79.45	82.67
20	81.17	1.61	79.56	82.78
21	81.38	1.61	79.76	82.99
22	82.35	1.61	80.74	83.97
23	81.93	1.61	80.32	83.55
24	81.72	1.61	80.11	83.34
25	81.58	1.61	79.96	83.19
26	81.07	1.61	79.46	82.69
27	80.87	1.61	79.25	82.48
28	81.72	1.61	80.11	83.34
29	81.97	1.61	80.36	83.59
30	82.00	1.61	80.38	83.61
31	82.03	1.61	80.42	83.64
32	81.91	1.61	80.30	83.52
33	82.08	1.61	80.47	83.69
34	82.70	1.61	81.09	84.31
35	83.27	1.61	81.66	84.88
36	83.47	1.61	81.86	85.08
37	83.62	1.61	82.01	85.23
38	83.77	1.61	82.16	85.39
39	83.60	1.61	81.99	85.21
40	83.40	1.61	81.78	85.01

41	83.17	1.61	81.56	84.78
42	82.18	1.61	80.57	83.79
43	82.19	1.61	80.58	83.80
44	82.00	1.61	80.39	83.62
45	82.49	1.61	80.88	84.10
46	82.38	1.61	80.76	83.99
47	82.53	1.61	80.92	84.14
48	83.16	1.61	81.55	84.77
49	82.15	1.61	80.53	83.76
50	83.10	1.61	81.48	84.71
51	83.19	1.61	81.58	84.80
52	82.56	1.61	80.95	84.17
53	82.23	1.61	80.62	83.84
54	81.68	1.61	80.07	83.29
55	82.54	1.61	80.93	84.15
56	83.09	1.61	81.48	84.70
57	83.01	1.61	81.39	84.62
58	82.43	1.61	80.82	84.04
59	82.18	1.61	80.56	83.79
60	81.82	1.61	80.21	83.43
61	81.62	1.61	80.01	83.23
62	81.09	1.61	79.48	82.71
63	81.29	1.61	79.68	82.90
64	81.54	1.61	79.92	83.15
65	81.98	1.61	80.37	83.59
66	82.08	1.61	80.46	83.69
67	81.63	1.61	80.01	83.24
68	81.04	1.61	79.43	82.65
69	81.66	1.61	80.05	83.27
70	81.39	1.61	79.78	83.01
71	81.33	1.61	79.72	82.94
72	80.66	1.61	79.05	82.27

5. Discussion

5.1. Perinatal Brain Injury

The central nervous system of extremely preterm infants is highly susceptible to perinatal injuries due to the presence of immature vasculature in the germinal matrix and periventricular white matter.[69]

Furthermore, the sensitivity of cerebral tissue to hypoxia-ischemia stems from already low baseline CBF and high oxygen consumption with increased oxygen extraction.[70,71] In addition, myocardial dysfunction, decreased CO and systemic hypoperfusion, commonly observed in the first postnatal days, can further aggravate the situation.[72]

The incidence of severe PIVH and PVL is an inverse function of gestational age with extremely preterm infants being affected the most.[73,74] These morbidities significantly correlate with neurodevelopmental impairment and majority of PIVH events occur during the first postnatal days (**Figure 34**).[72-74]

Perinatal brain injuries disrupt the coordinated growth of the whole brain, leading to diffuse deficits in cognitive function in survivors.[74,75] Structural abnormalities of the VLBW infant's brain persist into late childhood and adolescence and correlate with neuropsychological abnormalities (inattention, hyperactivity, anxiety, socio-emotional problems). Furthermore, severe PIVH and PVL are associated with the development of CP (**Figure 35**).[74,75]

The multifactorial development of PIVH/PVL can be associated with cerebral oxygenation fluctuations, systemic inflammation and impaired regional as well as systemic hemodynamic status.[70-73] A typical example can be seen in reperfusion injury that may precede PIVH/PVL. With myocardial function improving over the course of the first postnatal days, the initially low CBF can turn to relative cerebral hyperperfusion.[76,77]

Figure 34. Coronary view on the cranial ultrasound depicting intraventricular hemorrhage grade 3 (extensive hemorrhage with distension or dilatation of the lateral ventricles).

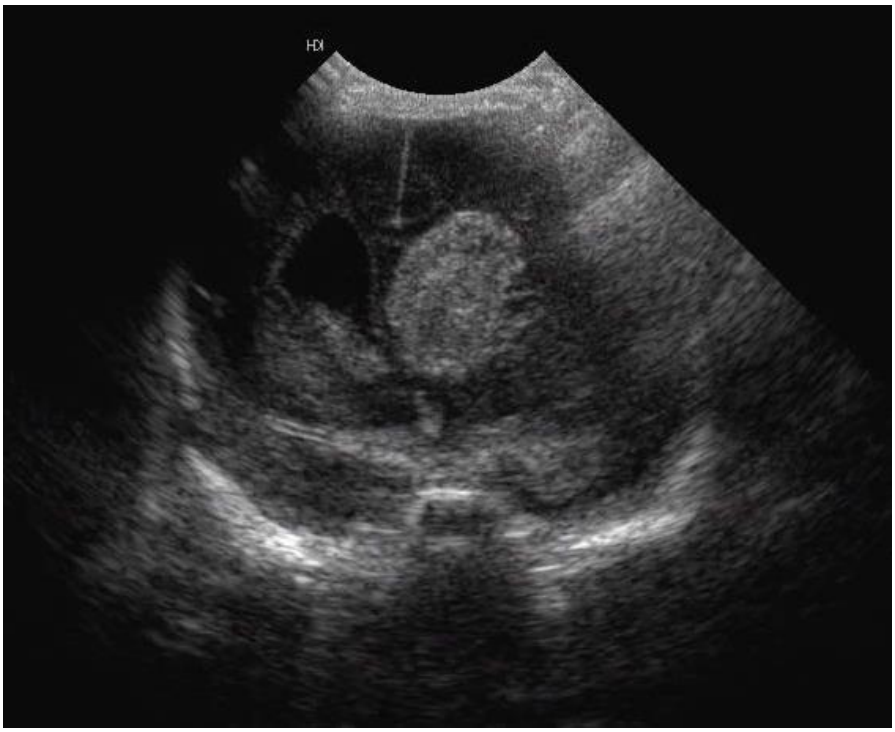
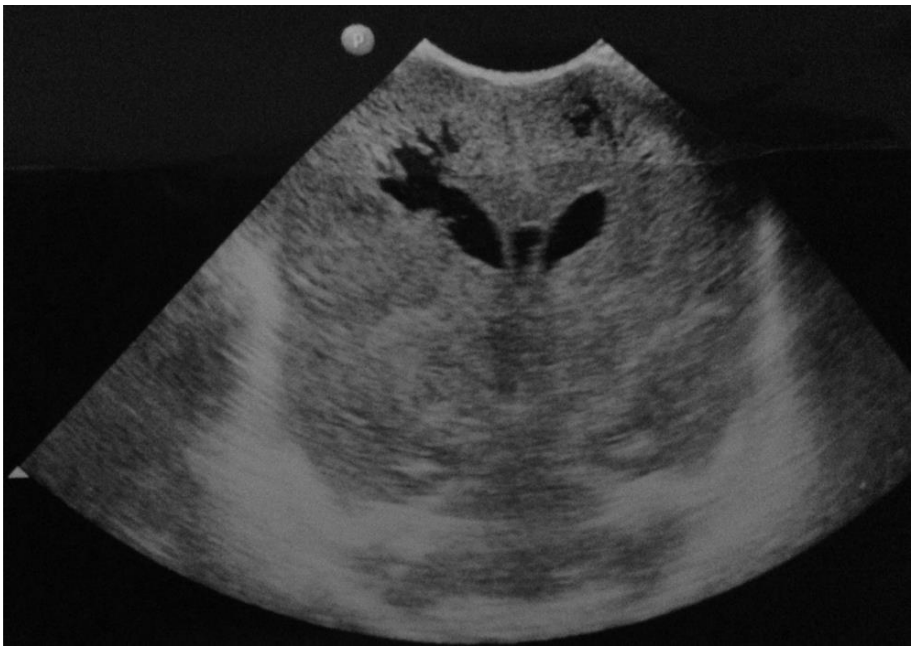


Figure 35. Coronary view on the cranial ultrasound depicting periventricular leukomalacia (white matter injury adjacent to lateral ventricles).



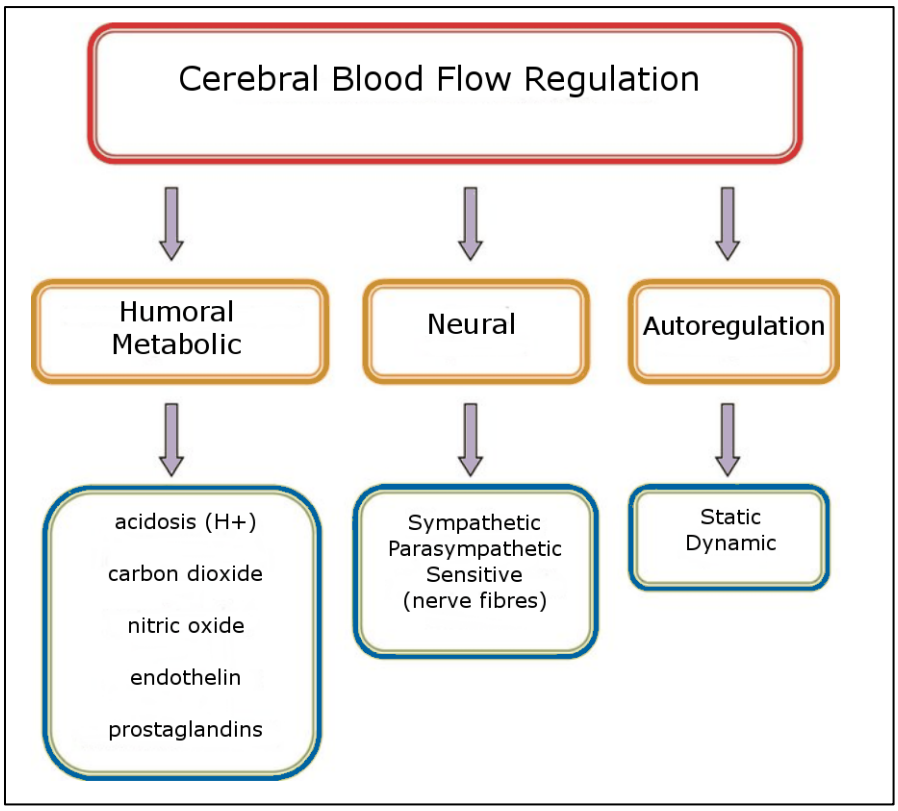
5.2. Cerebral Oxygenation

5.2.1. Cerebral Blood Flow

Cerebral oxygenation status depends on interaction between cerebral blood flow and oxygen delivery and consumption. Cerebral blood flow is determined by cardiac output (heart rate x stroke volume) and cerebral vascular resistance (CVR).[78] As a dynamic network, cerebral vasoregulation reacts to systemic and local factors in order maintain adequate oxygen and substrate delivery.[78,79]

Due to the essential role of central nervous system, local regulation (autoregulation) is principal and include metabolic, humoral and myogenic factors (**Figure 36**).[80]

Figure 36. Overview of cerebral blood flow regulation.



Among these, metabolic factors control the cerebral vasculature the most and induce dilatation of the vessels in a response to hypercapnia, acidosis and hypoxia.[78-80] On the contrary, hyperoxia and hypocapnia cause cerebral vasoconstriction. Humoral factors include vasoactive

agents produced by the endothelium such as prostaglandins (PGE_2), nitric oxide (dilatation) and endothelin (constriction).[78-80]

Preterm infants have relatively low global baseline CBF (approximately 20 ml/100g/min) in comparison to older children.[81] However, CBF is redistributed at birth in favour of cerebral cortex due to the increasing metabolic needs and oxygen consumption.[78,81] Apart from these changes, preterm infants experience also cardiovascular fluctuations (myocardial and autonomic dysfunction, hypotension requiring treatment) that can put strain on immature cerebral autoregulation.[78-81]

5.2.2. Cerebral Autoregulation

Cerebral autoregulation (CAR) concept (maintenance of constant CBF despite blood pressure changes within a certain range) represents one of the key aspects of cerebral hemodynamics in a preterm newborn.[82,83]

Cerebral autoregulation can be dysfunctional or completely absent (a decrease in MABP causes a decrease in CBF) in critically ill preterm infants and may be associated with increased mortality and brain injury through various pathophysiological mechanisms – hypoperfusion with hypoxic-ischemic injury, cerebral perfusion fluctuation, hyperperfusion (causing hyperoxia and peroxidation) or reperfusion injury.[71-73,83]

Particularly oxidative stress is strongly associated with white matter injury as oligodendrocytes (axon myelination) exhibit unique vulnerability to oxygen reactive species.[84] This causes arrest in oligodendrocyte maturation and is followed by a myelination failure of neuronal axons. The resulting reduced neuronal connectivity and brain volume are important predictors of neurodevelopmental outcome in preterm infants.[76,77,84]

However, many preterm infants on intensive care units are able to maintain adequate cerebral perfusion at MABP in the range 23 to 40 mmHg or borderline MABP.[85,86] Analogously, borderline MABP does not correlate with lower $crSO_2$ or with worse neurodevelopmental outcome.[87] Furthermore, prolonged and significant hypocapnia (decreasing CBF) associates with later development of PVL (**Figure 37, 38**).[88]

Figure 37. Cerebral blood flow autoregulation.

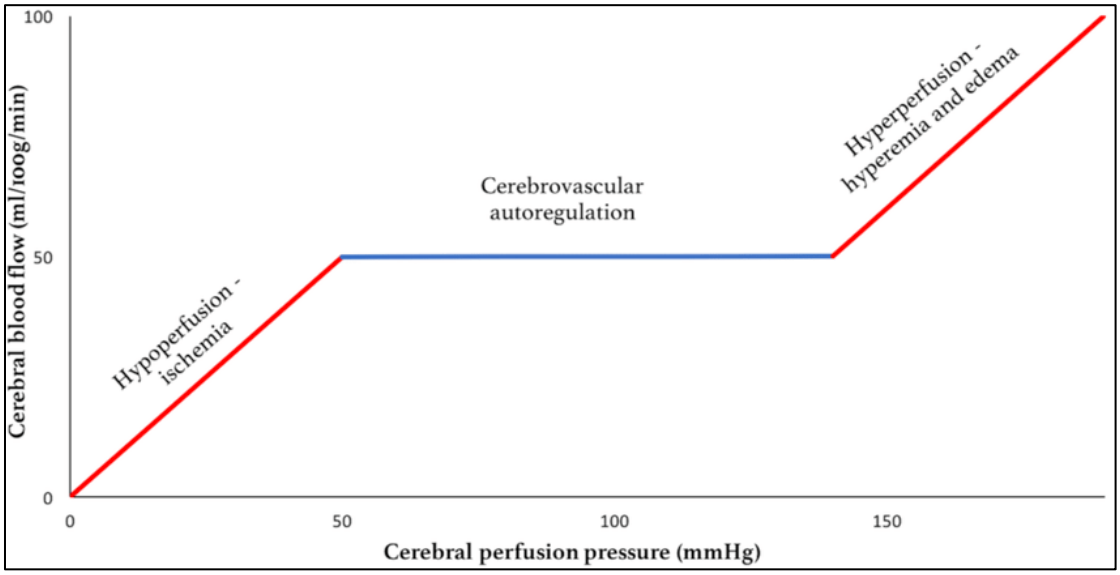
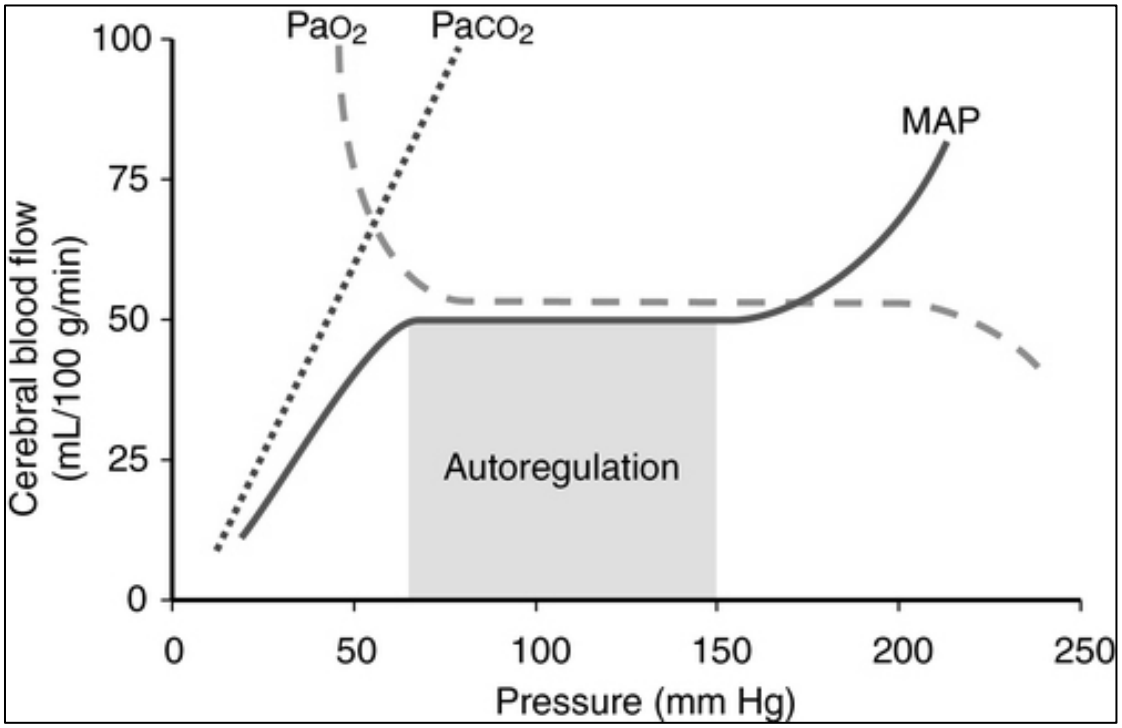


Figure 38. Cerebral blood flow autoregulation and its relationship to partial pressures of oxygen and carbon dioxide.



5.2.3. Cerebral Oxygen Delivery

Cerebral tissue oxygen delivery is another aspect of cerebral oxygenation status and depends on arterial oxygen content and CBF. Furthermore, cerebral metabolic rate of oxygen (cMRO) establishes a balance between cerebral metabolic requirements (consumption) and oxygen delivery.[89]

In order to maintain stable cMRO, the brain can either increase CBF or extract more oxygen from the blood. The principal adaptive mechanism is an increase in CBF, resulting in increased oxygen delivery.[89,90]

Apart from the CBF, changes in SaO_2 and Hb may also disturb the balance between oxygen delivery and cMRO, causing perinatal brain injury through cerebral hypoxia.[81,90]

5.2.4. Cerebral Hypoxia

Based on the leading pathophysiology, cerebral hypoxia can be of three different categories: hypoxic hypoxia (partial pressure of oxygen = pO_2), anemic hypoxia (Hb) or ischemic hypoxia (CBF).

Hypoxic hypoxia is caused by low pO_2 and is the most common form of hypoxia. As a response to the decrease in oxygen content, increased CBF and FcTOE maintain adequate cerebral oxygenation. Due to immaturity of these adaptive mechanisms, preterm newborns are more susceptible to cerebral injury resulting from this type of hypoxia.[91]

Anemic hypoxia is caused by a decrease in Hb concentration or number of red blood cells. It can also be caused by reduced ability of Hb to bind oxygen. As previously stated, CBF and FcTOE increase to meet the metabolic requirements of cerebral tissue. However, anemic hypoxia is relatively rare and there were also reports of a decrease in cMRO (decreased metabolic requirements) in case of severe anemia.[92]

Ischemic hypoxia reflects a decrease in CBF that is unable to maintain adequate brain perfusion and oxygenation. CBF is a function of CO (mainly determined by heart rate) and CVR (mainly determined by regional hemodynamic regulations – pCO_2).[93,94]

5.2.5. Cerebral Oxygenation and Brain Injury

Alderliesten et al observed higher $crSO_2$ (and lower FcTOE) values prior to the development of severe PIVH suggesting cerebral hyperperfusion.[73] Others found similar findings and elevated CBF (higher $crSO_2$) was observed also during and after the injury process indicating prolonged hyperoxygenation status in infants with PIVH.[71]

Hypercapnia (present especially during reperfusion phase) was also detected more often in the affected newborns, a finding known to be associated with an increased risk of PIVH.[72,77] Because pCO_2 is a potent CBF regulator, increasing severity of hypercapnia is associated with progressive CBF increase and later on attenuation of CBF autoregulation.[70,72,77]

Alternatively, many studies observed decreased $crSO_2$ during transition period in newborns who later developed PIVH.[70,73] Increased FcTOE in VLBW newborns can identify those at increased risk for significant sonographic brain injury (PIVH grade 2-3 and/or intraparenchymal lesions) or death.[95] Additionally, Cerbo et al found correlation between time spent with $crSO_2 \leq 40$ % and brain injury or early mortality.[96]

Intrauterine inflammation is often associated with increased risk of PIVH in preterm infants and increased cerebral metabolic load (increased FcTOE) imposed by chorioamnionitis could explain the subsequent hypoxic-ischemic brain injury.[97]

Low CBF in the first postnatal day was found to be associated with PIVH even after gradual increase in CBF during the second or third postnatal days.[71,72] The reason could be that PIVH patients have lower stroke volume and left ventricular output initially. These parameters gradually normalize (improving myocardial performance) just before the PIVH occurs, suggesting hypoperfusion-reperfusion brain injury.[72,77]

These observations support the finding that both high and low $crSO_2$ (during the first postnatal day) can be associated with adverse neurodevelopmental outcome of preterm infants at 2-3 years of age.[98] Several studies also concluded that over the first two weeks of life, low $crSO_2$ for prolonged periods of time was associated with poorer cognitive outcomes.[69,76,98]

5.2.6. Cerebral Oxygenation and Systemic Circulation

Cerbo et al found out that $crSO_2 \leq 40$ % (representing CBF) and SVC flow < 40 ml/kg/minute (representing systemic blood flow) independently increase mortality in preterm infants < 30 weeks' gestation.[96] Equally, $crSO_2$ correlated well with SVC flow and LVO in preterm infants in the first days of life.[56] These findings can be explained by initial myocardial dysfunction that can contribute to decreased CO and this is then translated into relatively low cerebral perfusion (particularly if CAR is impaired). Over time, myocardium recovers and as the left ventricular stroke volume and CO improve, cerebral hypoperfusion-reperfusion injury can occur.[72,99]

Contributing factor can be also seen in relative sensitivity of certain newborns to a sudden increase in afterload after delivery (removal of low-pressure placental circulation).[77,100] Owing to unbalanced stimulation of myocardium and peripheral vasculature (autonomic dysfunction), the increase in afterload leads to a decrease in CO and only a minor increase in BP.[58,100]

To alleviate the negative impact of these transitions, preterm newborns may benefit from interventions increasing preload, thus stabilizing cardiac function.[100] This can be one of the reasons placental transfusion (delayed cord clamping or umbilical cord milking) is associated with a lower incidence of PIVH/PVL.[100,101]

Also, diastolic dysfunction (although gradually improving in VLBW infants in the first postnatal days) can reduce initial cardiac preload.[102] However, active interventions to improve low systemic blood flow or diastolic function in the early postnatal period did not alter the outcome of preterm infants.[103]

Patent ductus arteriosus has been frequently associated with most neonatal morbidities, including PIVH/PVL.[104] One of the possible explanations is that the gradual increase in left ventricular output could be down-regulated by significant left-to-right shunting, thus reducing CBF.[58,77] Preterm infants with low SVC flow have a larger PDA than those with normal SVC flow during the first 12 hours after birth (and not afterwards).[58,77] The presence of PIVH itself can theoretically induce an inflammatory response that keeps the duct open (sepsis-like event).[73] Although hemodynamic status of PDA depends mostly on definition and clinical picture, ductal diameter has been shown to possess the strongest association to cerebral oxygenation (low $crSO_2$ can indicate significant PDA).[105]

N-terminal probrain natriuretic peptide (NT-proBNP), a cardiac marker, was observed to increase as the diameter of the ductus arteriosus increases and some authors demonstrated an inverse relationship between NT-proBNP and $crSO_2$.[99] Other authors demonstrated that even a clinically significant PDA does not affect $crSO_2$ (and FcTOE) while Lemmers et al observed decreased $crSO_2$ in infants with hemodynamically significant PDA.[106,107]

Regarding interventions, dopamine was suggested to cause direct cerebral vasoconstriction in some preterm infants, which can thwart CAR even further on the background of systemic hypotension that initiated inotrope administration.[108] Volume therapy led to a statistically significant, but clinically irrelevant, rise in MABP without a concomitant change in FcTOE.[109]

5.2.7. Cerebral Oxygenation – Summary

Neurologic morbidities determining the neurodevelopmental outcome are significantly associated with systemic and regional hemodynamic disturbances in preterm infants.[72,95] NIRS evaluates cerebral oxygenation that can offer a more complete picture about end organ perfusion.[69,77]

In this regard, NIRS monitoring seems to be reasonable in newborns with numerous significant risks for neurologic injury and adverse neurodevelopment – multiple birth, prematurity and antenatal or perinatal circulatory disturbances.

5.3. Cerebral Oxygenation and Multiple Birth

Twin-twin transfusion syndrome and fetal growth restriction represent the most common and severe complications in multiple pregnancy.[7,10,13] These conditions are associated with hemodynamic turbulences that may disturb cerebral tissue oxygenation postnatally.[11,13]

5.3.1. Recipient Twins

We observed the lowest $crSO_2$ in recipient twins throughout the study period. The main contributing factor might be substantial hypertrophic cardiomyopathy causing reduction in myocardial compliance and leading to outflow obstruction and poorer CO.[110,111] These changes can decrease cerebral blood flow and oxygenation.[112]

Cerebral vasoconstriction and ischemia mediated through endothelin ET_A receptors are also involved.[113] Targeted neonatal echocardiography (TNE) confirmed hypertrophic cardiomyopathy in all our enrolled recipients.

Furthermore, polycythemia (leading to higher blood viscosity) can reduce cerebral blood flow and $crSO_2$.[11] Recipient twins displayed the highest Hb values at birth among the subgroups and this relative polycythemia-hyperviscosity significantly correlated with lower $crSO_2$ within the subgroup.

5.3.2. Donor Twins

In contrast, the mean $crSO_2$ in donor twins was significantly higher. Donor twins suffer from absolute hypovolemia which results in the redistribution of blood flow.[11,111] Renal hypoperfusion activates the renin-angiotensin system that causes increased vascular resistance with smooth muscle hypertrophy.[11,110] These changes can lead to secondary placental dysfunction and fetal growth restriction.[114]

Due to pathological anastomoses, donor twins commonly develop anemia that can augment the established hyperdynamic circulation.[115] As a consequence, cerebral blood flow increases to maintain adequate tissue oxygenation.

5.3.3. Fetal Growth Restriction

Although FGR infants exhibited high $crSO_2$ values similar to donor twins, we hypothesize different pathophysiological mechanisms in this subgroup. Primary placental insufficiency and subsequent chronic fetal hypoxia induce adaptive CO redistribution to favour essential organs, including the brain - the "brain sparing" effect.[116]

Furthermore, animal models showed an increase in cerebral capillaries size as a reaction to hypoxic environment.[117,118] Cohen et al demonstrated the effect persistence during postnatal adaptation which could explain higher cerebral blood flow and $crSO_2$.[58]

Furthermore, severe hypoglycemia is commonly observed in these infants, and this can also cause a significant increase in the cerebral blood flow.[69,90]

5.3.4. No Fetal Compromise

In the subgroup of newborns without fetal compromise, $crSO_2$ gradually improved over the first 36 hours and then stabilized thereafter.

This is in accordance with available literature as relatively large study on preterm infants < 32 weeks showed that average $crSO_2$ at admission was 65%, peaked at around 36 hours of age and then slowly declined in the first 72 hours.[57] Another study presented $crSO_2$ values from 439 infants < 32 weeks gestation in the first three days of life and the resulting $crSO_2$ range was 55–85%.[119]

There is a number of reasons for this pattern. During the first days of life, preterm infants demonstrate generally low baseline cerebral blood flow and higher oxygen consumption with increased oxygen extraction in preterm infants.[71,72]

In addition, myocardial dysfunction with decreased CO and systemic hypoperfusion can contribute to lower $crSO_2$ during this period. As myocardial performance improves (ventricular stroke volume and CO increase), $crSO_2$ gradually increases and stabilizes.[72,77]

5.3.5. Study Limitations

Despite varied $crSO_2$ patterns, we did not find significant difference in morbidity or mortality among the subgroups. This could be explained by a small overall number of patients, as well as relatively low number of infants within the subgroups.

Furthermore, $crSO_2$ did not reach critical levels even in the recipient twins who presented with the lowest values. In one study of preterm infants < 30 weeks gestation, increased mortality was observed if $crSO_2$ dropped below 40%.[96]

Animal studies revealed that $crSO_2$ of 55% represents a safety level or cerebral oxygenation, in which brain maintains physiologic metabolism and only it took 30 minutes of $crSO_2$ < 35% to initiate subcellular damage and several hours to cause neuronal apoptosis.[76,83]

Last but not least, we did not analyze correlation between $crSO_2$ and other variables (i.e. SpO_2, blood pressure, acid base parameters, ventilatory setting and TNE) that would provide a more complete picture of cerebral and systemic hemodynamics.

6. Conclusions

Postnatal cerebral oxygenation among monochorionic and dichorionic preterm twins correlates significantly with the underlying fetal pathology. The presented $crSO_2$ patterns could provide some insight into altered cerebral hemodynamics that stems from the underlying fetal pathology. Early detection of altered cerebral tissue oxygenation may decrease the risk of cerebral impairment and adverse neurodevelopmental outcome in this population.

A. We observed significant differences in regional cerebral oxygenation between monochorionic and dichorionic twins.

B. We revealed statistically significant discordance in regional cerebral oxygenation among individual twins.

C. Despite varied $crSO_2$ patterns, we did not find significant difference in morbidity (intra/periventricular hemorrhage, periventricular leukomalacia) or mortality among the subgroups. This could be explained by a small overall number of patients, as well as relatively low number of infants within the subgroups. Furthermore, $crSO_2$ did not reach critical levels even in the recipient twins who presented with the lowest values.

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8. List of Abbreviations

BP	blood pressure
BW	birth weight
CAR	cerebral autoregulation
CBF	cerebral blood flow
CBV	cerebral blood volume
cMRO	cerebral metabolic rate of oxygen
CO	cardiac output
CP	cerebral palsy
$crSO_2$	cerebral tissue oxygenation
CVR	cerebral vascular resistance
DCDA	dichorionic diamniotic
dHb	deoxygenated hemoglobin
EOS	early onset sepsis
FcTOE	fractional cerebral tissue oxygen extraction
FGR	fetal growth restriction
GA	gestational age
Hb	hemoglobin
HIE	hypoxic-ischemic encephalopathy
LVO	left ventricular output
MABP	mean arterial blood pressure
MCDA	monochorionic diamniotic
NEC	necrotizing enterocolitis
NIRS	near-infrared spectroscopy
NT-proBNP	N-terminal probrain natriuretic peptide
oxyHb	oxygenated hemoglobin
pCO_2	partial pressure of carbon dioxide
PDA	patent ductus arteriosus
PIVH	peri/intraventricular haemorrhage
pO_2	partial pressure of oxygen
PVL	periventricular leukomalacia
RDS	respiratory distress syndrome
rSO_2	regional tissue oxygenation

RBCT	red blood cell transfusion
RVO	right ventricular output
SGA	small for gestational age
SaO_2	arterial oxygen saturation
SpO_2	peripheral oxygen saturation (pulse oximetry)
SVC	superior vena cava
TAPS	twin-anemia polycythemia sequence
TNE	targeted neonatal echocardiography
TOI	tissue oxygenation index
TTTS	twin-twin transfusion syndrome
VLBW	very low birth weight

9. Supplements

Published Articles

A. **Korček P**, Širc J, Straňák Z. Cerebral oxygenation reflects fetal development in preterm monochorionic and dichorionic twins. Early Human Development 2020; 144: 105025. *[First Author; Impact Factor 2.2]*

B. **Korček P**, Straňák Z, Širc J, Naulaers G. The role of near-infrared spectroscopy monitoring in preterm infants, Journal of Perinatology (Nature America) 2017; 37: 1070-1077. *[First Author; Impact Factor 2.1]*

C. Straňák Z, Feyereislová S, **Korček P**, Dempsey E. Placental transfusion and cardiovascular instability in the preterm infant. Frontiers in Pediatrics 2018; 6: 39. *[Corresponding Author; Impact Factor 2.4]*

D. Straňák Z, **Korček P**, Hympánová L, Kynčl M, Krofta L. Prenatally acquired multiple limb ischemia in a very low birth weight monochorionic twin. Fetal Diagnosis and Therapy 2017; 41: 237-238. *[Corresponding Author; Impact Factor 2.0]*

E. **Korček P**, Straňák Z. Fetal distress and circulatory disturbance in monochorionic twins: possible risk factors for sialadenitis? International Journal of Pediatric Otorhinolaryngology 2015; 79: 2476-2478. *[First Author; Impact Factor 1.2]*

F. Korčeková Z, **Korček P**, Čunát V, Staníčková Z, Zemanová P, Straňák Z. Tibial speed of sound changes in preterm infants during the first year of life. Bone 2020; 132: 115191. *[Corresponding Author; Impact Factor 4.5]*

G. Straňák Z, Feyereisl J, **Korček P**, Feyereislová S, Krofta L. Procalcitonin is more likely to be released by the fetus rather than placental tissue during chorioamnionitis. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2016; 160: 499-502. *[Corresponding Author; Impact Factor 1.1]*

H. **Korček P**, Straňák Z, Čunát V. Congenital Lactobacillus Blood Stream Infection in Extremely Preterm Twins. Indian J Pediatr 2016; 83: 1027. *[First Author; Impact Factor 1.1]*

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Cerebral oxygenation reflects fetal development in preterm monochorionic and dichorionic twins

Peter Korček*, Jan Širc, Zbyněk Straňák

Institute for the Care of Mother and Child - Neonatology, Podolské nábřeží 157/36, Prague 14700, Czech Republic
3rd Faculty of Medicine - Charles University, Ruská 2411/87, Prague 10000, Czech Republic

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ABSTRACT

Background: Cerebral oxygenation ($crSO_2$) monitoring is increasingly used in high-risk infants. Monochorionic twins suffer from specific fetal pathologies that can affect cerebral hemodynamics. Limited data are available on $crSO_2$ and blood flow patterns in this population after birth.

Objective: To evaluate $crSO_2$ changes in preterm monochorionic and dichorionic twins during the first 72 h of life.

Methods: Near-infrared spectroscopy was used to measure $crSO_2$ in 62 infants from 31 twin pregnancies < 32 weeks of gestation. The study group was divided into 4 subgroups: donor (1) and recipient (2) monochorionic twins (with twin-twin transfusion syndrome), fetal growth restriction (FGR) infants (3) and twins without fetal compromise (4).

Results: There was significant difference in birth weight ($p < 0.001$) among 4 subgroups. We observed significant variation in $crSO_2$ among the subgroups using mixed model analysis ($p < 0.001$). The recipient twins exhibited the lowest $crSO_2$ (mean ± SE) throughout the study period (76 ± 0.3%), whereas the FGR and donor twins presented with the highest values (86 ± 0.3% and 83 ± 0.4% respectively). We found no statistically significant differences in neonatal mortality and morbidity among subgroups.

Conclusion: Our study revealed significant correlation between $crSO_2$ values postnatally and underlying fetal pathology in monochorionic and dichorionic preterm twins.

1. Introduction

Despite improvements in perinatal outcomes in recent decades, multiple pregnancies are associated with increased risks of complications including preterm birth, fetal growth restriction (FGR), twin–twin transfusion syndrome (TTTS) and congenital abnormalities [1,2]. There are three ways twins can exist in the uterus: dichorionic-diamniotic, monochorionic-diamniotic and rarely monochorionic-monoamniotic twins [1,2].

Monochorionic twin pregnancies can suffer from TTTS, specific complication due to pathological anastomoses in the shared placenta leading to unbalanced blood flow through arterio-venous anastomoses between twins [2,3]. This condition causes hypervolemia, higher afterload through increased vascular resistance, hypertrophic cardiomyopathy and finally cardiac failure in the recipient twin [4,5]. In contrast, the donor twin is hypovolemic, has low cardiac output, tissue hypoperfusion and activated renin-angiotensin-aldosterone axis [4,5].

Alternatively, selective FGR can occur in either monochorionic or dichorionic twin pregnancies and represents uneven placental distribution between twins [4,5]. Placental insufficiency can lead to "brain-sparing" effect - cardiovascular adaptation of the fetus to maintain adequate cerebral perfusion [6].

Neurodevelopmental outcome remains the most challenging issue in multiple birth. Fetal circulatory disturbances and immature vasculature, specifically in the germinal matrix and periventricular white matter, increase the risk for serious perinatal events and worse neurodevelopmental outcome [7–10]. Multiple risk factors can further aggravate the brain development - low baseline cerebral blood flow, high oxygen extraction, myocardial dysfunction, decreased cardiac output and systemic hypotension [11–13].

Accurate measurement of circulatory dysfunction, including cerebral tissue oxygenation ($crSO_2$) is useful in early postnatal period [14,15]. Near-infrared spectroscopy (NIRS) becomes commonly used in critically ill infants and offers non-invasive monitoring of organ perfusion [11,16]. However, limited data are available in twin preterm infants with respect to cerebral tissue perfusion.

* Corresponding author at: Institute for the Care of Mother and Child - Neonatology, Podolské nábřeží 157, Prague 14700, Czech Republic.
E-mail address: peterkorcek.upmd@gmail.com (P. Korček).

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The aim of this prospective, observational study was to measure $crSO_2$ using NIRS in preterm monochorionic and dichorionic twins during the first 72 h of life and find out correlation between underlying fetal conditions and $crSO_2$ development.

2. Materials and methods

2.1. Subjects

The institutional Ethical Committee of Institute for the Care of Mother and Child approved the study under the guidelines of the Helsinki Declaration (reference SOP 15/05/2008). Written informed consent was obtained from parents of all infants enrolled in the study. Preterm infants from multiple pregnancies < 32 weeks of gestation were enrolled and followed-up in this prospective, observational study. Patients with serious contributing morbidities were excluded: prenatally diagnosed congenital malformations and chromosomal abnormalities, prenatally acquired brain lesion, birth below limit of viability (gestational age < 24 + 0), need of chest compression at the delivery room and significant skin lesion contraindicating the use of NIRS sensor. The patient enrollment took place between October 2016 and January 2018 at the Institute for the Care of Mother and Child, Prague.

2.2. NIRS

Cerebral regional oxygenation was measured with a NIRS monitor (INVOS 5100C, Medtronic, Dublin, Ireland) with sample rate of 1 Hz. Measurements started within 1 h from birth and lasted up to 72 h of age. A transducer (INVOS Cerebral Oximetry Infant-Neonatal sensor, Medtronic, Dublin, Ireland) was placed on the frontoparietal side of infant's head. The method takes advantage of near-infrared spectral absorption by deoxygenated (dHb) and oxygenated (oxyHb) hemoglobin. Using Beer-Lambert law and machine-specific detection algorithms, oxyHb and dHb can be calculated into percentage oxygenation (oxyHb / [oxyHb + dHb]) with range 0–100%. NIRS represents mainly venous oxygen saturation as 70–80% of cerebral blood is venous blood [13]. Artifacts in $crSO_2$ were removed manually before results were analyzed. Artifacts were defined as: changes in $crSO_2$ that could not be physiologically explained (e.g. a 30% step change between 2 subsequent data points) or changes that were accompanied by severe distortion in the other parameters suggesting infant movement or handling. Thereafter, $crSO_2$ was averaged for every 1-hour period. No action was taken based on recorded values.

2.3. Definition of morbidities

Twin-Twin Transfusion Syndrome was defined using the following criteria: a single placenta, same sex, and significant amniotic fluid volume discordance between the two fetuses - with a deep vertical pocket of ≥ 8 cm in the sac of the recipient twin and ≤ 2 cm in the sac of the donor twin. Fetal therapy (selective laser coagulation of placental vessels) was performed accordingly [17]. Fetal Growth Restriction was diagnosed prenatally by obstetricians using 2D and Doppler measurement of the fetus (abdominal circumference, estimated fetal weight, end-diastolic flow patterns in the umbilical and uterine artery) [18].

Fetal growth restriction was confirmed postnatally using Fenton growth charts [19]. Other neonatal outcomes (respiratory distress syndrome, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis and periventricular leukomalacia) were followed up according to the Vermont Oxford definition [20]. Blood counts were measured with a Coulter Micro Dif II (Coulter Electronics Ltd., Fullerton, US) in all patients up to 2 h after admission. Transfusion was indicated according to hemoglobin (Hb) level (< 120 g/L) and clinical judgment.

2.4. Statistical analysis

The study group was divided into 4 subgroups based on major fetal pathology: donor (1) and recipient (2) monochorionic twins, FGR infants (3) and newborns without any known fetal pathology (4). Statistical analysis reflected subjects' specificity (twins) using linear mixed model for scale variables and generalized linear model for categorical variables. Patterns of $crSO_2$ were evaluated using mixed model analysis with random effect (pair) and repeated measurement based on covariance structure. Cerebral oxygenation graph was modelled using estimated marginal mean and standard error. Clinical variables are reported using descriptive statistical methods. All reported p-values are two-sided and $p < 0.05$ was considered statistically significant. The analysis was performed with Statistical Package for Social Sciences (SPSS 26.0; SPSS Institute, Chicago, IL, USA).

3. Results

3.1. Neonatal outcome

Overall, 62 preterm newborns were included. Characteristics of the study group and subgroups are expressed in Table 1. The incidence of severe neonatal morbidities was low among subgroups and did not allow to detect any statistical differences even when we analyzed composite morbidity (hypotension, necrotizing enterocolitis, intraventricular hemorrhage and periventricular leukomalacia; $p = 0.089$). We found significant difference in birth weight ($p < 0.001$) among the 4 subgroups. No statistically significant differences were noticed in neonatal mortality. No significant differences were found in Hb after admission and red blood cell transfusion (RBCT) in the first 72 h among the subgroups ($p = 0.501$ and $p = 0.337$, respectively).

3.2. Cerebral oxygenation measurement

A total of 4464 1-hour $crSO_2$ averages were used for analysis. The recipient twins exhibited the lowest $crSO_2$ (expressed as mean ± SE) throughout the study period (76 ± 0.3%), whereas the FGR and donor twins presented with the highest values (86 ± 0.3% and 83 ± 0.4% respectively). Newborns without any observed fetal complication (TTTS or FGR) presented with $crSO_2$ of 81 ± 0.2%. Graphical overview of $crSO_2$ development among the subgroups (using estimated marginal mean and standard error) is shown in Fig. 1. We observed significant variances in $crSO_2$ over time among the subgroups using mixed model analysis with random effect (pair) and repeated measurement based on covariance structure (type III tests of fixed effects: $p < 0.001$). Using estimates of fixed effects, significant differences were found between the subgroup with no fetal compromise (reference subgroup) and FGR and recipient infants ($p < 0.001$ and $p = 0.038$, respectively). When analyzing the reference subgroup and donor twins only, the difference was not significant ($p = 0.356$). Moreover, the $crSO_2$ values for donor twins were comparable with the reference subgroup after 36 h. When Hb was added to the mixed model, the analysis revealed significant correlation between Hb and $crSO_2$ (type III tests of fixed effects: $p < 0.001$). Using mixed model test, there was no significant correlation between RBCT and $crSO_2$ ($p = 0.284$).

4. Discussion

TTTS and FGR represent the most common and severe complications in multiple pregnancies [2,4,6]. Involved fetuses suffer from hemodynamic disturbances that may affect cerebral oxygenation and tissue perfusion postnatally [5,6]. Our study demonstrates the important role of fetal underlying conditions on postnatal cerebral tissue perfusion.

We observed the lowest $crSO_2$ in recipient twins throughout the

Table 1
Study population and subgroups.

Variable	Study group	Study subgroups			
		TTTS Donor	TTTS Recipient	FGR	No fetal compromise
Number of patients, no. (% of all infants)	62 (100%)	9 (15%)	9 (15%)	11 (18%)	33 (52%)
MCDA twin, no. (%)	38 (61%)	9 (100%)	9 (100%)	7 (64%)	13 (39%)
Fetal therapy – SLCPV, no. (%)	4 (7%)	2 (22%)	2 (22%)	0	0
Gestational age, weeks	29.0 ± 2.1	29.0 ± 1.4	29.0 ± 1.4	30.0 ± 1.9	28.7 ± 2.4
Birth weight, grams	1111 ± 322	856 ± 289	1228 ± 288	960 ± 251	1197 ± 314
Hemoglobin at birth, g/L	171 ± 30	161 ± 48	177 ± 45	163 ± 27	174 ± 19
RBCT in the first 72 h, n (%)	3 (5%)	2 (22%)	0	1 (9%)	0
APGAR, 1 min	6.4 ± 1.6	5.9 ± 2.1	7.1 ± 1.5	6.7 ± 0.9	6.1 ± 1.6
APGAR, 5 min	7.8 ± 1.4	7.0 ± 2.4	8.4 ± 1.1	7.9 ± 0.7	7.7 ± 1.1
C-section delivery, no. (%)	60 (97%)	9 (100%)	9 (100%)	11 (100%)	31 (94%)
Male gender, no. (%)	40 (65%)	6 (67%)	6 (67%)	9 (82%)	19 (58%)
ANS (completed), no. (%)	50 (87%)	8 (89%)	8 (89%)	10 (91%)	24 (73%)
Intubated at delivery suite, no. (%)	5 (8%)	1 (11%)	0	0	4 (12%)
RDS, no. (%)	56 (90%)	7 (78%)	8 (89%)	11 (100%)	30 (91%)
Pulmonary hemorrhage, no. (%)	1 (2%)	1 (11%)	0	0	0
PDA treated, no. (%)	3 (5%)	1 (11%)	0	1 (9%)	1 (3%)
Hypotension treated, no. (%)	11 (18%)	3 (33%)	2 (22%)	2 (18%)	4 (12%)
Respiratory support at 36 weeks, no. (%)	13 (2%)	4 (44%)	2 (22%)	1 (9%)	6 (18%)
NEC, no. (%)	4 (7%)	1 (11%)	2 (22%)	0	1 (3%)
EOS, no. (%)	6 (10%)	1 (11%)	2 (22%)	0	3 (9%)
PIVH grade I–II, no. (%)	3 (5%)	0	0	1 (9%)	2 (6%)
PIVH grade III–IV, no. (%)	2 (3%)	1 (11%)	0	0	1 (3%)
PVL, no. (%)	1 (2%)	1 (11%)	0	0	0

Continuous data are presented as mean ± SD. TTTS = twin-twin transfusion syndrome, FGR = fetal growth restriction, MCDA = monochorionic diamniotic, SLCPV = selective laser coagulation of placental vessels, RBCT = red blood cell transfusion, ANS = antenatal corticosteroids, RDS = respiratory distress syndrome, PDA = persistent ductus arteriosus, NEC = necrotizing enterocolitis, EOS = early-onset sepsis, PIVH = peri/intraventricular hemorrhage, PVL = periventricular leukomalacia.

study period. The main contributing factor might be substantial hypertrophic cardiomyopathy causing reduction in myocardial compliance and leading to outflow obstruction and poorer cardiac output [21–23]. These changes can decrease cerebral blood flow and oxygenation. Cerebral vasoconstriction and ischemia mediated through endothelin ET_A receptors are also involved [24]. Targeted neonatal echocardiography (TNE) confirmed hypertrophic cardiomyopathy in all our enrolled recipients (TNE was not part of the analysis). Furthermore, polycythemia (leading to higher blood viscosity) can reduce cerebral blood flow and $crSO_2$ [15]. Recipient twins displayed the highest Hb values at birth among the subgroups and this relative polycythemia-hyperviscosity significantly correlated with lower $crSO_2$ within the subgroup.

In contrast, the mean $crSO_2$ in donor twins was significantly higher. Donor twins suffer from absolute hypovolemia which results in the redistribution of blood flow [5,22]. Renal hypoperfusion activates the renin-angiotensin system that causes increased vascular resistance with smooth muscle hypertrophy [5,21]. These changes can lead to secondary placental dysfunction and fetal growth restriction [25]. Due to pathological anastomoses, donor twins commonly develop anemia that

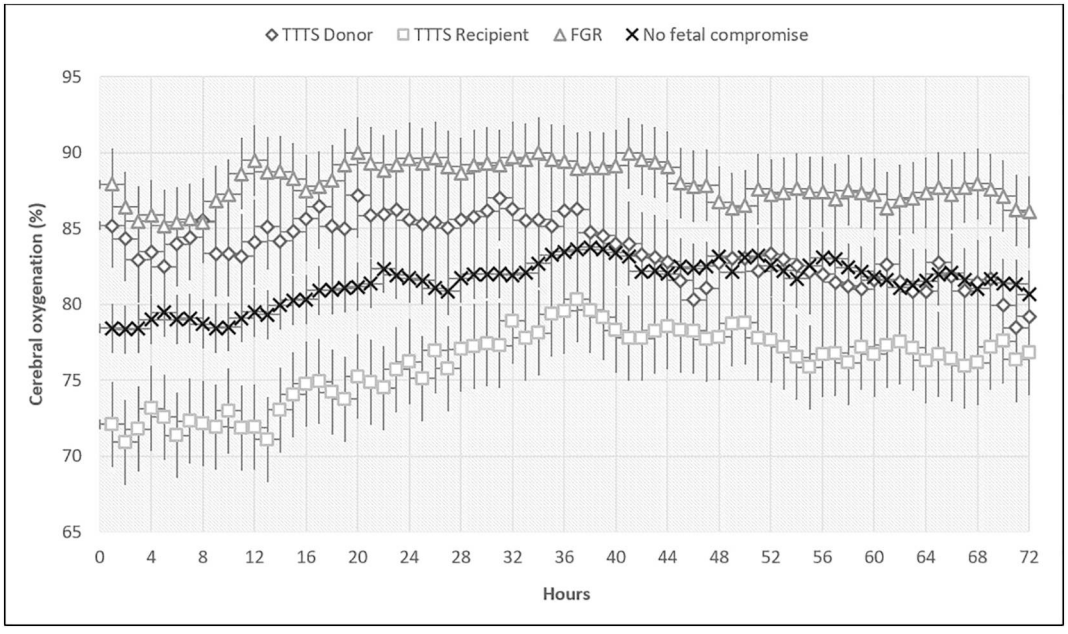

Fig. 1. Postnatal cerebral oxygenation patterns based on underlying fetal pathology. TTTS = twin-twin transfusion syndrome; FGR = fetal growth restriction.

can augment the established hyperdynamic circulation [26]. As a consequence, cerebral blood flow increases to maintain adequate tissue oxygenation.

Although FGR infants exhibited high $crSO_2$ values similar to donor twins, we hypothesize different pathophysiological mechanisms in this subgroup. Primary placental insufficiency and subsequent chronic fetal hypoxia induce adaptive cardiac output redistribution to favour essential organs, including the brain - the "brain sparing" effect [27]. Furthermore, animal models showed an increase in cerebral capillaries size as a reaction to hypoxic environment [28,29]. Cohen et al. demonstrated the effect persistence during postnatal adaptation which could explain higher cerebral blood flow and $crSO_2$ [30]. Furthermore, severe hypoglycemia is commonly observed in these infants, and this can also cause a significant increase in the cerebral blood flow [11,14]. There was no specific monitoring of the glucose levels as part of this study.

In the subgroup of newborns without fetal compromise, $crSO_2$ gradually improved over the first 36 h and then stabilized thereafter. This is in accordance with available literature as relatively large study on preterm infants < 32 weeks showed that average $crSO_2$ at admission was 65%, peaked at around 36 h of age and then slowly declined in the first 72 h [31]. Furthermore, other authors obtained $crSO_2$ values from 439 infants < 32 weeks gestation in the first three days of life and the resulting $crSO_2$ range was 55–85% [32,33]. There are a number of reasons for this pattern. During the first days of life, preterm infants demonstrate generally low baseline cerebral blood flow and higher oxygen consumption with increased oxygen extraction in preterm infants [12,34]. In addition, myocardial dysfunction with decreased cardiac output and systemic hypoperfusion can contribute to lower $crSO_2$ during this period [12]. As myocardial performance improves (ventricular stroke volume and cardiac output increase), $crSO_2$ gradually increases and stabilizes [12].

Despite varied $crSO_2$ patterns, we did not find significant difference in morbidity or mortality among the subgroups. This could be explained by a small overall number of patients, as well as relatively low number of infants within the subgroups. Furthermore, $crSO_2$ did not reach critical levels even in the recipient twins who presented with the lowest values. In one study of preterm infants < 30 weeks gestation, increased mortality was observed if $crSO_2$ dropped below 40% [35]. Animal studies revealed that $crSO_2$ of 55% represents a safety level or cerebral oxygenation, in which brain maintains physiologic metabolism and only it took 30 min of $crSO_2$ < 35% to initiate subcellular damage and several hours to cause neuronal apoptosis [32,36]. Nevertheless, TTTS or FGR infants do suffer from increased morbidity and mortality and there exists a correlation between $crSO_2$ and later neurodevelopment [7,37,38].

The presented $crSO_2$ patterns in these infants could provide some insight into altered cerebral hemodynamics that stems from the underlying fetal pathology.

4.1. Limitations

We did not analyze correlation between $crSO_2$ and other variables (i.e. SpO_2, blood pressure, acid base parameters, ventilatory setting and TNE) that would provide a more complete picture of cerebral and systemic hemodynamics.

4.2. Conclusions

Postnatal cerebral oxygenation among monochorionic and dichorionic preterm twins correlates significantly with the underlying fetal pathology. Early detection of altered cerebral tissue oxygenation may decrease the risk of cerebral impairment and worsened neurodevelopmental outcome.

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CRediT authorship contribution statement

Peter Korček: Conceptualization, Methodology, Funding acquisition, Formal analysis, Writing - original draft, Writing - review & editing.**Jan Širc:**Funding acquisition, Writing - original draft, Writing - review & editing.**Zbyněk Straňák:**Formal analysis, Writing - original draft, Supervision, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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STATE-OF-THE-ART

The role of near-infrared spectroscopy monitoring in preterm infants

P Korček[1,2], Z Straňák[1,2], J Širc[1,2] and G Naulaers[3]

Neurological morbidities such as peri/intraventricular hemorrhage and periventricular leukomalacia largely determine the neurodevelopmental outcome of vulnerable preterm infants and our aim should be to minimize their occurrence or severity. Bed-side neuromonitoring could provide valuable pieces of information about possible hemodynamic disturbances that are significantly associated with neurological morbidities and increased mortality. Near-infrared spectroscopy offers evaluation of regional cerebral oxygenation, which in conjunction with other non-invasive methods may give us a more complete picture about end-organ perfusion. This monitoring tool could help us fully understand the pathophysiology of severe neurological morbidities and guide our management in order to reduce their incidence.

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INTRODUCTION

The central nervous system of extremely preterm infants is highly susceptible to perinatal injuries due to the presence of immature vasculature in the germinal matrix and periventricular white matter.[1] Furthermore, the sensitivity of cerebral tissue to hypoxia–ischemia[2] stems from already low baseline cerebral blood flow (CBF) and high oxygen consumption with increased oxygen extraction.[3,4] In addition, myocardial dysfunction, decreased cardiac output and systemic hypoperfusion, commonly observed in the first postnatal days, can aggravate the situation even further.[4] Owing to these vulnerabilities, it is perhaps not surprising that the events occurring during the perinatal transition and postnatal adaptation (intrapartum complications, impaired hemodynamic and respiratory adaptation, medical interventions) may have significant short- and long-term impact on the maturing nervous system.[3,5,6]

Specifically, the incidence of severe peri-intraventricular hemorrhage (PIVH) and periventricular leukomalacia (PVL) is an inverse function of gestational age with extremely preterm infants being affected the most.[5,7] These morbidities significantly correlate with neurodevelopmental impairment and majority of PIVH events occur during the first postnatal days.[4,5,7] As already mentioned, the multifactorial development of PIVH/PVL can be associated with impaired regional as well as systemic hemodynamic status.[2–6] A typical example can be seen in reperfusion injury that may precede PIVH/PVL. With myocardial function improving over the course of the first postnatal days, the initially low CBF can turn to relative cerebral hyperperfusion.[3,4,6,8,9]

Understanding end-organ perfusion can be important in relation to the development of PIVH and PVL.[1,2,8,10] Nevertheless, the commonly used variables (like peripheral oxygen saturation (SpO_2), mean arterial blood pressure (MABP), heart rate do not provide us with the whole hemodynamic picture and certain parameters such as cardiac output or superior vena cava (SVC) flow can be difficult to obtain.[1,2,8,10,11] Non-invasive measurements such as targeted neonatal echocardiography and near-infrared spectroscopy (NIRS) could help us identify and monitor high-risk infants.[5,12,13] Although targeted neonatal echocardiography is frequently used by clinicians to guide their hemodynamic interventions in preterm infants, there is little evidence on improving their outcome.[13] NIRS could give us valuable clues about regional oxygen saturation that adds extra piece of information about the cerebral tissue perfusion.[10–12]

THEORETICAL AND PRACTICAL BACKGROUND

NIRS technology

The concept of NIRS was first published in 1977[14] and used in neonates in 1985;[15] however, after almost 40 years of existence, its day-to-day clinical usage in preterm neonates remains controversial and not entirely supported.[10] The situation is even more puzzling given the tremendous advantages of the method in nowadays neonatal units—non-invasive, painless, bed-side, non-ionizing, continuous and portable monitoring of a patient.[10–12] From the technological point of view, the actual near-infrared light spectrum goes through most biological tissues. When we assume that all the other tissues remain stable (bone, muscle, skin), then the only changing parameter is the brain blood flow and oxygenation. In blood, there are two chromophores, deoxygenated and oxygenated hemoglobin (dHb and oxyHb, respectively), which absorb near-infrared light. Both dHb and oxyHb have their peak wavelength-dependent near-infrared spectral absorption. Depending on the NIRS devices two to four wavelengths are emitted between 700 and 850 nm in order to maximize the absorption separation between dHb and oxyHb and to eliminate the wavelength absorption by other molecules.[10–12] Using the Beer–Lambert law, values of oxyHb and dHb can be calculated. However, the difference between the light emitted and the light

[1]Institute for the Care of Mother and Child, Fetal Medicine Center, Prague, Czech Republic; [2]Third Faculty of Medicine, Prague, Czech Republic and [3]Department of Development and Regeneration, Katholieke Universiteit Leuven, Leuven, Belgium. Correspondence: Professor Z Straňák, Institute for the Care of Mother and Child, Fetal Medicine Center, Podolské nábřeží 157, Prague, 14700, Czech Republic.
E-mail: z.stranak@seznam.cz
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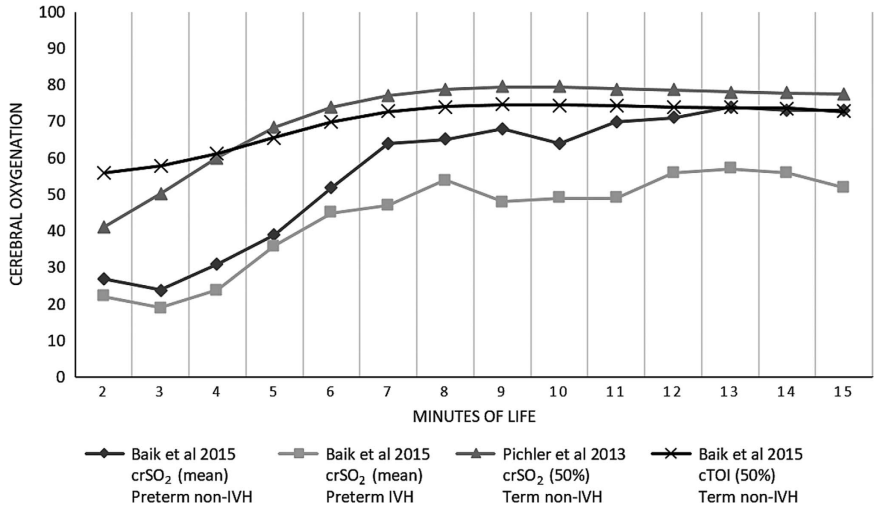

Figure 1. Cerebral oxygenation dynamics in the first 15 min of life in term and preterm infants, with and without intraventricular hemorrhage (IVH). Oxygenation was measured either by INVOS 5100 (cerebral hemoglobin oxygen saturation ($crSO_2$)) or NIRO 200NX (cerebral tissue oxygenation index (cTOI)).

measured is not only caused by absorption but also by scattering. As we do not know the amount of scattering, absolute values cannot be calculated and therefore multiple detectors are used. If scattering is assumed to be equal for the different detectors, absolute values can be measured and oxyHb and dHb can be calculated into ratio-based percentage oxygen saturation (oxyHb/(oxyHb+dHb); range 0 to 100%) using different algorithms and methods.[1,12] Because of this, the displayed values are relative rather than absolute and are labeled regional/tissue oxygenation, regional/oxygen saturation or rSO_2 (analogous to SpO_2).[12] As NIRS measures all blood in the brain, it is a mixed saturation value. Nonetheless, because 70% to 80% of the blood is venous blood it mainly reflects the venous oxygen saturation.[10–12] NIRS can be used on many somatic sites (renal, splanchnic tissue perfusion); however, the primary area of interest in neonates remains to be central nervous system.

Neonatal application and pathophysiology

Concerning neonatal application, soft and thin tissues on relatively large (and often hair-scarce) newborn head serve as relatively penetrable 'window' through which the brain can be monitored. Accordingly, the cerebral Hb oxygen saturation ($crSO_2$) then reflects the regional balance between the oxygen supply and demand for the underlying tissue.[10–12] Cerebral blood volume, dHb, oxyHb and total Hb changes can also give extra information regarding changes in the blood flow; however, we will not discuss them in this article mainly because they can only be measured by specific NIRS instruments and are very prone to movement.[4,9] Cerebral oxygen supply depends on SpO_2, Hb concentration and CBF.[2] Supposing there are no significant changes in the metabolic rate (hypoglycemia induces CBF increase), SpO_2 and Hb concentration, $crSO_2$ deviations suggest deviations in CBF (function of peripheral vascular resistance and cardiac output).[1,2,4,9,16,17] Finally, cerebral fractional tissue oxygen extraction (cFTOE) can be calculated if SaO_2 is known (($SaO_2 - crSO_2$)/SaO_2). This variable is inversely related to CBF (decrease in CBF causes increase in cFTOE) and reflects the balance between cerebral oxygen supply and oxygen consumption.[18,19] Therefore, cFTOE can prove useful to separate cerebral hypoxic hypoxia (lack of oxygen with normal perfusion) from ischemic hypoxia (lack of oxygen coming with low perfusion)[3] and high cFTOE can be associated with significant neurological injury in preterm infants in first postnatal days.[4,6] As an indirect measurement of cerebral perfusion, NIRS has always excited neonatologists and researchers, who conducted a large number of studies in both term and preterm infants.[10,11]

Normative values

Many observational studies attempted to establish percentile charts for $crSO_2$ in the first postnatal days. Baik *et al.*[20] established centiles for tissue oxygenation index and cFTOE in term newborns without a need for medical support during the first 15 min of life (using NIRO 200NX). Similar findings in term infants were observed by Pichler *et al.*,[21] who used INVOS 5100 NIRS device to measure $crSO_2$. Comparably, preterm infants without PIVH showed lower $crSO_2$ values initially; however, by the fifteenth minute of life the values reached values of term counterparts.[2] Interestingly, preterm infants who developed PIVH later had significantly lower $crSO_2$ throughout the first 15 min of life (Figure 1).[2,20,21] Fuchs *et al.*[22] showed that $crSO_2$ had risen after birth continuously from 37% (mean) at 1 min of age and had reached a steady state in the range of 61% to 84% roughly 7 min after birth. Similar findings were observed by Noori *et al.*[9] in term infants. However, in this study, after the plateau phase of $crSO_2$ they documented a decrease in cerebral oxygen saturation (increased cFTOE caused by reduced CBF) that could be caused by relatively significant left-to-right duct shunting. This CBF decrease was then followed by a gradual rise over the course of the first postnatal days. A relatively large study on preterm infants < 32 weeks showed that average $crSO_2$ at admission was 65% and rose with higher gestational age (1% per week). $crSO_2$ also peaked at around 36 h of age and then slowly declined in the first 72 h.[23] Furthermore, other authors obtained $crSO_2$ values from 439 preterm infants < 32 weeks gestation in the first 3 postnatal days and here $crSO_2$ range was 55% to 85%. For gestational age of 24 to 27 weeks, the 10th centile was around 55% using the INVOS device with the adult sensor.[8,10] Perhaps not surprisingly, in the newborn pigs, $crSO_2$ of 55% represents a safety level of cerebral oxygenation, in which the brain maintains physiological metabolism, including normal concentrations of lactate. However, it takes only 30 min of $crSO_2 < 35\%$ to trigger subcellular damage and several hours to cause neuronal apoptosis.[8,12] Finally, differences in $crSO_2$ and both gender and trophic status of preterm infants have also been studied. Cohen *et al.*[17] demonstrated that, in the first postnatal days, small-for-gestational age (SGA) infants exhibited slightly

increased cerebral oxygenation when compared with non-small-for-gestational age infants that might be explained by an increased CBF due to intrauterine 'brain-sparing' effect.

Medications and interventions

Impact of various interventions (including medication administration) on cerebral oxygen saturation was also investigated. For example, endotracheal suctioning seems to negatively affect cerebral hemodynamic status[24] and the magnitude of alteration depends on the mode of suctioning.[25] Caffeine administration in premature infants showed no significant effect on cerebral oxygenation,[26] although others observed transient decrease in this regard.[27] Also, the automated adjustment of inspired oxygen has no significant effect on $crSO_2$ despite minimizing the frequency of hypoxemic episodes.[28] Isolated bradycardia has the lowest impact on $crSO_2$ while a combination of initial desaturation followed by bradycardia has the highest.[29] Ibuprofen did not significantly reduce CBF and cerebral oxygenation.[30] Inappropriate and aggressive ventilation with high mean airway pressures increases pulmonary vascular resistance, reduces pulmonary blood flow and left ventricular output and decreases SVC flow, which correlates with decreased $crSO_2$.[9,31] Interestingly, red blood cell transfusion can potentially decrease the frequency of $crSO_2$ depressions in infants who had low initial NIRS values before transfusion was given, otherwise relative polycythemia (high hematocrit leading to higher blood viscosity) can reduce CBF and thus be potentially harmful.[10,17] On the contrary, blood sampling from an umbilical arterial catheter was shown to reduce cerebral blood volume and $crSO_2$ in very low birth weight infants (the greater the amount of withdrawn blood, the more significant reduction).[32]

Intervention trials

Although the number of experimental and observational NIRS studies prevails, several interventional studies have been conducted or are underway. The COSGOD (cerebral oxygenation to guide supplemental oxygen) trial showed that the burden of cerebral hypoxia during the first 15 min of life can be reduced if NIRS-monitored $crSO_2$ is added to the 'standard' SpO_2 to guide respiratory and supplemental oxygen support.[33] Similarly, SafeBoosC-II trial reported reduced burden of cerebral hypoxia in extremely preterm infants during the first 3 postnatal days if cerebral oxygenation monitoring was implemented and guidelines for interventions based on $crSO_2$ were provided.[34] Other trials (TOHOP (treatment of hypotension of prematurity), AHIP (avoiding hypotension in preterm neonates)) are still ongoing and they will try to investigate the MABP–$crSO_2$ association and the ability of preterm neonates to maintain cerebral autoregulation during hypotension or to find out the importance of $crSO_2$ monitoring in relation to minimizing the frequency of hypotensive events and the usage of inotropes. The HIP (management of hypotension in preterm infants) trial investigates coherence between $crSO_2$ (INVOS 5100 NIRS device) and MABP in hypotensive infants < 28 weeks gestation treated with either placebo or dopamine.[35]

Routine NIRS monitoring

Despite numerous neonatal studies, NIRS has not been implemented into the standard postnatal monitoring. SpO_2, MABP, heart rate and Hb are preferred variables, although they do not provide detailed picture of adequate end-organ/tissue perfusion and alert us only indirectly to discrepancy in the oxygen supply (regional blood flow and volume) and oxygen consumption (metabolic rate).[2,8,10] These variables (particularly SpO_2 and heart rate measured by pulse oximetry) are used during neonatal resuscitation and often we depend on them to avoid hypoxia or hyperoxia, although they are less than ideal under certain circumstances. On the contrary, NIRS-measured $crSO_2$ does not have some restrictions pulse oximetry possesses (for example, dependency on blood flow pulsations).[22] Therefore, NIRS monitoring during neonatal transition for adjusting therapy in well-indicated intensive care patients could prevent later development of cerebral complications.[2]

DETECTION OF BRAIN INJURY USING NIRS

Cerebral autoregulation

As mentioned above, significant neurological morbidities (PIVH/PVL) in preterm infants can strongly correlate with their later neurodevelopmental outcome and monitoring cerebral oxygen saturation can help us identify infants most vulnerable to severe brain injury.[3,5,11,21,36] Cerebral autoregulation (CAR) concept (CBF–MABP relationship with constant CBF for blood pressure changes within a certain range) represents one of the key aspects of cerebral hemodynamics in a preterm newborn.[1,5,18,37] CAR can be dysfunctional or completely absent (a decrease in MABP causes a decrease in CBF) in critically ill preterm infants and may be associated with increased mortality and brain injury through various pathophysiological mechanisms—hypoperfusion with hypoxic–ischemic injury,[3,6,8–10,37] cerebral perfusion fluctuation,[5,6,8,12,37] hyperperfusion[1,5,36,37] (causing hyperoxia[8] and peroxidation[8,10]) or reperfusion injury.[4,9] Particularly oxidative stress is strongly associated with white matter injury as oligodendrocytes (axon myelination) exhibit unique vulnerability to oxygen reactive species.[31] On the contrary, many preterm infants on intensive care units are able to maintain adequate cerebral perfusion at MABP in the range 23 to 40 mm Hg[38] or borderline MABP.[19] Analogously, borderline MABP does not correlate with lower $crSO_2$ or with worse neurodevelopmental outcome.[39] Furthermore, the association between hypocapnia (that can negatively alter the CBF) and PVL developed later on is well recognized.[40] Being an indicator of cerebral perfusion, NIRS-measured $crSO_2$ changes (and cFTOE or tissue oxygenation index) have been repeatedly studied in relation to the development of severe forms of PIVH/PVL.

NIRS and PIVH

Alderliesten *et al.*[5] observed higher $crSO_2$ (and lower cFTOE) values prior to the development of severe PIVH, suggesting cerebral hyperperfusion. Others found similar findings and elevated CBF (higher $crSO_2$) was observed also during and after the injury process, indicating prolonged hyperoxygenation status in infants with PIVH.[3] Hypercapnia (present especially during reperfusion phase) was also detected more often in the affected newborns, a finding known to be associated with an increased risk of PIVH.[4,9] Because PCO_2 is a potent CBF regulator, increasing severity of hypercapnia is associated with progressive CBF increase and ultimately attenuation of CBF autoregulation.[2,4,9]

However, many studies observed decreased $crSO_2$ during transition period[2,5] in newborns who later developed PIVH. Correspondingly, increased cFTOE in VLBW newborns can identify those at increased risk for significant sonographic brain injury (PIVH II–III and/or intraparenchymal lesions) or death.[3,41] Intriguingly, lower $crSO_2$ values occurred irrespective of the grade of PIVH.[42] Additionally, Cerbo *et al.*[6] found correlation between time spent with $crSO_2 \leqslant 40\%$ and brain injury or early mortality.

Intrauterine inflammation is often associated with increased risk of PIVH in preterm infants and increased cerebral metabolic load (increased cFTOE) imposed by chorioamnionitis could explain the subsequent hypoxic–ischemic brain injury.[42] Low CBF in the first postnatal day was found to be associated with PIVH even after gradual increase in CBF during the second or third postnatal days.[3,4] The reason could be that PIVH patients have lower stroke

Table 1. Overview of the recent studies concerning NIRS application in neonatal population

Leading author	*Journal*	*NIRS device*	*Number of patients*	*GA/BW*	*Measured parameters*	*Duration of NIRS measurement*	*Conclusions*
Alderliesten	Journal of Pediatrics 2013	INVOS 5100	30	⩽32	$crSO_2$, cFTOE, MABP, MABP-rSO_2 correlation	First 72 h	$crSO_2$ and cFTOE suggest cerebral hyperperfusion in infants with severe PIVH MABP–$crSO_2$ correlation indicates more blood pressure-passive brain perfusion in infants with PIVH
Alderliesten	Journal of Pediatrics 2014	INVOS 5100	66	⩽32	$crSO_2$, SpO_2, cFTOE, MABP, BSID III	First 72 h	MABP less than GA (in weeks) was not associated with lower $crSO_2$ or with lower neurodevelopmental outcome scores Regardless of MABP, low $crSO_2$ was associated with worse neurodevelopmental outcome.
Baik	ADC-FNE 2015	INVOS 5100	24	< 32	$crSO_2$, HR, SpO_2	First 15 min	IVH group showed significantly lower $crSO_2$ values during the immediate transition. There was no difference concerning SpO_2 and HR between IVH and non-IVH group of infants.
Baik	Neonatology 2015	NIRO 200NX	140	Term (mean 39)	TOI, cFTOE, SpO_2, HR	First 15 min	The reference ranges and centile charts of cTOI measured with the NIRO 200NX and cFTOE calculated out of cTOI and SpO_2 in neonates during the immediate neonatal transition (uncomplicated term infants).
Balegar	Journal of Pediatrics 2014	NIRO 200	71	⩽30	TOI, SpO_2	First 72 h	Elevated cFTOE values are associated with increased risk of early poor outcome in very preterm infants (PIVH II–IV, death).
Binder-Heschl	JMFNM 2016	INVOS 5100	46	< 37 (mean 33)	$crSO_2$, SpO_2, cFTOE, MABP	24 h (started within 6 h after birth)	Mild short-term hypotensive episodes in preterm infants did not affect $crSO_2$ Cerebral autoregulation is maintained in case of borderline hypotension and may protect infants from cerebral injury (mostly non-invasive MABP measurements in the study).
Binder-Heschl	Acta Pediatrica 2015	INVOS 5100	35	< 37 (mean 33)	$crSO_2$, SpO_2, cFTOE, pro-BNP	24 h (started within 6 h after birth)	$crSO_2$ is influenced by cardiac function, in addition to oxygen consumption, arterial oxygen saturation and vascular resistance, and this can be measured by NT-proBNP.
Cerbo	Neonatology 2015	INVOS 5100	60	< 30	$crSO_2$, cFTOE, SVC flow	First 48 h	$crSO_2 \leqslant 40\%$ and SVC flow < 40 ml kg^{-1} min^{-1} independently increase the risk of death. The trend in cFTOE supports the ischemic–hypoperfusion hypothesis as a mechanism for cerebral damage.
Cohen	ADC-FNE 2016	INVOS 5100	204	Median 30	$crSO_2$, SpO_2, cFTOE	First 72 h	Growth restriction and gender influence cerebral oxygenation and oxygen extraction in preterm neonates throughout the first 3 days of life.
Costa	Journal of Pediatrics 2015	NIRO 200NX	60	⩽32 (median 26)	TOI, SpO_2, HR, MABP	Measured in range of 5–228 h	Significant deviation below optimal MABP was observed in infants who died Deviation of MABP above optimal level was observed in infants who developed more severe IVH.
Dix	ADC-FNE 2016	INVOS 5100	380	< 32	$crSO_2$, PDA	First 72 h+1 h before ECHO (days 2, 4, 6)	Ductal diameter is the only echocardiographic parameter significantly related to cerebral oxygenation over time. Low cerebral oxygenation may be suggestive of a hsPDA.
Eriksen	Acta Pediatrica 2014	NIRO 300	60	⩽32	$crSO_2$, MABP	2–3 h $crSO_2$ measurement in the first 24 h	Dopamine therapy was associated with decreased cerebral autoregulation in preterm infants. We were unable to determine whether dopamine directly impaired cerebral autoregulation or was merely an indicator of illness.
Fuchs	Journal of Perinatology 2012	Foresight	51	< 1500 g	crSO2, SpO_2, cFTOE, HR	First 10 min	Cerebral tissue oxygen saturation monitoring is feasible during neonatal resuscitation of VLBW infants within the first minutes of life. Increasing $crSO_2$ in resuscitated infants in the first 10 min of life.
Kooi	Neonatology 2013	INVOS 5100	14	< 30	$crSO_2$, SpO_2, cFTOE, MABP	$crSO_2$ before and after volume administration	Cerebral perfusion does not improve in preterm infants with signs of poor perfusion following volume expansion In these infants, either CAR is present or volume expansion is inadequate to affect cFTOE.
Laan	Neonatology 2016	INVOS 5100	49	< 32	$crSO_2$, SpO_2, cFTOE, PDA parameters	1 h $crSO_2$ before/after ECHO	In preterm infants with clinical signs of an hsPDA within 2 weeks after birth, cerebral oxygen saturation and extraction are not affected by an hsPDA or by retrograde diastolic blood flow in the descending aorta.

Table 1. (Continued)

Leading author	*Journal*	*NIRS device*	*Number of patients*	*GA/BW*	*Measured parameters*	*Duration of NIRS measurement*	*Conclusions*
Mintzer	Journal of Pediatrics 2015	INVOS 5100	15	< 1250 g	$crSO_2$	First 10 days	UA blood sampling is associated with significant $crSO_2$ decrements with increased variability over clinically significant intervals.
Noori	Journal of Pediatrics 2014	INVOS 5100	22	< 28	$crSO_2$, cFTOE, cardiac function	4–76 h	Cardiac function and CBF remain stable in very preterm neonates who do not develop PIVH during the first 3 postnatal days—infants who develop PIVH have lower systemic perfusion and CBF followed by an increase in these variables preceding the development of PIVH.
Pichler	Journal of Pediatrics 2016	INVOS 5100	60	< 34	$crSO_2$, SpO_2, HR	First 15 min	Reduction of burden of cerebral hypoxia during immediate transition and resuscitation after birth is feasible by $crSO_2$ monitoring to guide respiratory and supplemental oxygen support (COSGOD trial).
Pichler	Journal of Pediatrics 2013	INVOS 5100	381	35–39	$crSO_2$, SpO_2, cFTOE, HR	First 15 min	The reference ranges of $crSO_2$ and cFTOE in neonates requiring no medical support during transition immediately after birth (only 27 preterm infants included).
Pichler	JMFNM 2016	INVOS 5100	76	Mean 32	$crSO_2$, SpO_2, cFTOE	First 15 min	Delayed cord clamping (60 s) was associated with lower initial $crSO_2$ and higher cFTOE and lower initial Apgar-score and heart rate compared with early cord clamping (< 30 s).
Schmid	Neonatology 2015	Foresight	16	⩽30 (mean 26)	$crSO_2$, SpO_2, HR	16 h (measured in range of 7–58 days)	Isolated bradycardia had the lowest impact on cerebral desaturation and combined events had the highest. Most infants preserved cerebral oxygenation >60% during events.
Stark	ADC-FNE 2016	NIRO 200	83	⩽30	$crSO_2$, total internal carotid blood flow	30 min $crSO_2$ measurement (days 1 and 3)	The increased cerebral metabolic load imposed by the presence of inflammation results in a higher risk of critical hypoxic ischemia in the preterm with increased susceptibility to significant PIVH.
Verhagen	Clinical Neurophysiology 2014	INVOS 5100	25	< 32	$crSO_2$, SpO_2, cFTOE, MABP	24 h (in the first 72 h of life)	A statistically significant negative correlation between MABP and FTOE using NIRS, suggesting the absence of cerebral autoregulation in almost half of the preterm infants studied.
Verhagen	DMCN 2015	INVOS 5100	67	< 32	$crSO_2$, SpO_2, cFTOE, BSID III	2 h on days 1–5, 8 and 15	Cerebral oxygen saturation during the first 2 weeks after birth is associated with neurodevelopmental outcome of preterm infants at 2–3 years. High and low $crSO_2$ on day 1 were associated with poorer neurodevelopmental outcome.
Waitz	Journal of Pediatrics 2015	Foresight	15	⩽28 (mean 25)	$crSO_2$, SpO_2	24 h (measured in range of 19–74 days)	Automated FiO_2 control in preterm infants with frequent SpO_2 fluctuations significantly increased the time within the SpO_2 target range and reduced the incidence of prolonged hypoxemic events compared with manual FiO_2 adjustment but did not significantly affect cerebral tissue oxygenation.

Abbreviations: ADC-FNE, Archives of Disease in Childhood – Fetal and Neonatal Edition; BSID III, Bayley Scales of Infant Development, Third edition; BW, birth weight; CAR, cerebrovascular autoregulation;CBF, cerebral blood flow; cFTOE, cerebral fractional tissue oxygen extraction; COSGOD, cerebral oxygenation to guide supplemental oxygen; $crSO_2$, cerebral hemoglobin oxygen saturation; cTOI, cerebral tissue oxygenation index; DMCN, Developmental Medicine and Child Neurology; ECHO, echocardiographic evaluation; GA, gestational age; HR, heart rate; hsPDA, hemodynamically significant patent ductus arteriosus; IVH, intraventricular hemorrhage; JMFNM, Journal of Maternal-Fetal and Neonatal Medicine; MABP, mean arterial blood pressure; NIRS, near-infrared spectroscopy; NT-proBNP, N-terminal pro-brain natriuretic peptide; PIVH, peri-intraventricular hemorrhage; SpO_2, arterial oxygenation; SVC, superior vena cava; TOI, tissue oxygenation index; UA, umbilical arterial; VLBW, very low birth weight.

volume and left ventricular output initially. These parameters gradually normalize (improving myocardial performance) just before the PIVH occurs, suggesting hypoperfusion–reperfusion brain injury.[4,9] These observations support the finding that both high and low $crSO_2$ (during the first postnatal day) can be associated with adverse neurodevelopmental outcome of preterm infants at 2–3 years of age. The researchers also concluded that over the first 2 weeks of life, low $crSO_2$ for prolonged periods of time was associated with poorer cognitive outcomes.[36]

It is noteworthy that PIVH infants in many aforementioned studies experienced more intensive treatment (inotropes, pharmacological duct closure, mechanical ventilation), which in combination with observed blood pressure-passive cerebral perfusion can cause fluctuations in CBF and we have to factor in also the direct effect of treatment modalities on cerebral perfusion.[3,5,9,42]

NIRS and systemic circulation

Despite obvious interlink between dysfunctional cerebral hemodynamics and adverse neurological outcome in preterm infants, certain studies imply circulatory disturbances to be at the beginning of the whole process.[4,9,16] It seems that rather both systems are involved in determining the adverse outcome of patients (brain injury/death). For example, Cerbo *et al.*[6] reported that $crSO_2 \leqslant 40\%$ (representing CBF) and SVC flow < 40 ml kg^{-1} min^{-1} (representing systemic blood flow) independently increase mortality in preterm infants < 30 weeks gestation. Equally, $crSO_2$ correlated well with SVC flow and left ventricular cardiac output in preterm infants in the first days of life.[22] These findings can be explained by initial myocardial dysfunction that can contribute to decreased cardiac output and this is then translated into relatively low cerebral perfusion (particularly if CAR is impaired). Over time, myocardium recovers (several hours to days), and as the left ventricular stroke volume and cardiac output improve, cerebral hypoperfusion–reperfusion injury can occur.[4,16,17] A contributing factor is the relative sensitivity of certain newborns to a sudden increase in afterload after delivery (removal of low-pressure placental circulation).[9,16] To alleviate the negative impact of these transitions, preterm newborns may benefit from interventions that increase preload, thus stabilizing cardiac function.[9,43] This can be one of the reasons passive or active placental transfusion are associated with a lower incidence of PIVH/PVL.[43,44] However, a recent study found that delayed cord clamping was linked to lower $crSO_2$ values during the immediate postnatal transition.[45] Also, diastolic dysfunction (although gradually improving in VLBW infants in the first postnatal days) can reduce initial cardiac preload.[9,46] Unfortunately, active interventions to improve low systemic blood flow or diastolic function in the early postnatal period did not bring the desired outcomes.[47]

Expectedly, myocardial dysfunction probably cannot account for all aspects of hemodynamic disturbance and subsequent brain injury. Patent ductus arteriosus (PDA) has been frequently associated with most neonatal morbidities, including PIVH/PVL.[48] One of the possible explanations is that the gradual increase in left ventricular output could be downregulated by significant left-to-right shunting, thus reducing CBF (preterm infants with low SVC flow have a larger PDA than those with normal SVC flow during the first 12 h after birth but not afterward).[9,17] The presence of PIVH itself can theoretically induce an inflammatory response that keeps the duct open (sepsis-like event).[5] Although hemodynamic status of PDA depends mostly on definition and clinical picture, ductal diameter has been shown to possess the strongest association with cerebral oxygenation (low $crSO_2$ can indicate significant PDA).[49] Indeed, the cardiac marker N-terminal pro-brain natriuretic peptide (NT-proBNP) was observed to increase as the diameter of the ductus arteriosus increases and some authors demonstrated an inverse relationship between NT-proBNP and $crSO_2$.[16] Other authors demonstrated that even a clinically significant PDA does not affect $crSO_2$ (and cFTOE)[50] while Lemmers *et al.*[51] observed decreased $crSO_2$ in infants with hemodynamically significant PDA. These controversial conclusions probably result from varied methodology of presented studies (including heterogeneous group of infants) and possible influence of concomitant pharmacological interventions ('sick' infants tend to be more hypotensive and are treated more aggressively for PDA).[50–52] Regarding interventions, dopamine was suggested to cause direct cerebral vasoconstriction (alpha receptors) in some preterm infants, which can thwart CAR even further on the background of systemic hypotension that initiated inotrope administration.[52] Furthermore, volume therapy led to a statistically significant, but clinically irrelevant, rise in MABP without a concomitant change in cFTOE.[53] Table 1 summarizes the aforementioned NIRS studies conducted in the recent years (Table 1).

POTENTIAL SIDE EFFECTS OF NIRS

Unfortunately, cerebral oximetry has potential disadvantages that may be responsible for reduced use in in routine clinical settings. From the point of view of patients' safety, sensors emanating near-infrared spectrum may cause thermic or pressure injury.[8,10] However, others observed that NIRS did not cause skin burns even if applied for a longer time periods.[11] Certain protective measures (gauze strips) can reduce occurrence of such injuries and this technique was confirmed by NIRS device producers as having no negative impact on NIRS signal.[32] Perhaps most importantly, cerebral oxygenation value can be difficult to grasp and manipulate in terms of routine bed-side clinical usage.[1,8,10,12] Coupled with wide-ranging 'normal' $crSO_2$ values (when compared with SpO_2, for example), NIRS makes decisions based on single values rather difficult.[8–12,20,22] The observed variability stems from different NIRS machines using different algorithms and probes, which were used in the studies with various methodologies and diverse neonatal populations. However, even $crSO_2$ variability using the same probe with the same machine (suboptimal reproducibility) appears to be significant.[1,8,12] Besides the technical issues, it is well known that the venous saturation varies between patients as shown in measurements of the jugular venous saturation. We are used to interpret arterial saturations, which represent rather small interindividual changes, but venous saturation changes are much wider. One would need to tackle not only interpatient but also intrapatient variability, when a slight shift in sensor placement can give different readings on the same patient.[11,12] Last but not least, the cost of NIRS machines is significant and one has to bear in mind the cost of the single-use probes as well.[10]

CONCLUSION

Neurological morbidities determining the neurodevelopmental outcome are significantly associated with systemic and regional hemodynamic disturbances in preterm infants. NIRS evaluates cerebral oxygenation offering a more complete picture of end-organ perfusion. Furthermore, it could help us fully understand the pathophysiology of severe neurological morbidities and possibly guide our management in order to reduce their incidence and/or severity. In this regard, NIRS seems to be reasonable in newborns with significant risks for neurological injury—extreme prematurity, chorioamnionitis, severe respiratory distress syndrome or circulatory disturbances. Owing to past research and intervention trials, NIRS application in high-risk preterm infants seems to have better utility than ever before. Unfortunately, these infants also display the greatest vulnerability to potentially harmful side effects. Therefore, we should try to increase measurement precision (newer algorithms, sensor placement), reduce harmfulness (selective patient measurement) and establish

reference values in the most preterm infants to fully implement routine NIRS monitoring.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

PK, ZS and JS: substantial contributions to design, acquisition, analysis, and interpretation of the data. GN: drafted and reviewed the article for important intellectual content.

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Placental Transfusion and Cardiovascular Instability in the Preterm Infant

Zbyněk Straňák[1,2], Simona Feyereislová[1,2], Peter Korček[1,2] and Eugene Dempsey[3,4]*

[1] Third Faculty of Medicine, Charles University, Prague, Czechia, [2] Institute for the Care of Mother and Child, Prague, Czechia, [3] Department of Paediatrics and Child Health, Neonatal Intensive Care Unit, University College Cork, Cork, Ireland, [4] INFANT Centre, University College Cork, Cork, Ireland

Postnatal adaptation in preterm newborn comprises complex physiological processes that involve significant changes in the circulatory and respiratory system. Increasing hemoglobin level and blood volume following placental transfusion may be of importance in enhancing arterial oxygen content, increasing cardiac output, and improving oxygen delivery. The European consensus on resuscitation of preterm infants recommends delayed cord clamping (DCC) for at least 60 s to promote placenta–fetal transfusion in uncompromised neonates. Recently, published meta-analyses suggest that DCC is associated with fewer infants requiring transfusions for anemia, a lower incidence of intraventricular hemorrhage, and lower risk for necrotizing enterocolitis. Umbilical cord milking (UCM) has the potential to avoid some disadvantages associated with DCC including the increased risk of hypothermia or delay in commencing manual ventilation. UCM represents an active form of blood transfer from placenta to neonate and may have some advantages over DCC. Moreover, both methods are associated with improvement in hemodynamic parameters and blood pressure within first hours after delivery compared to immediate cord clamping. Placental transfusion appears to be beneficial for the preterm uncompromised infant. Further studies are needed to evaluate simultaneous placental transfusion with resuscitation of deteriorating neonates. It would be of great interest for future research to investigate advantages of this approach further and to assess its impact on neonatal outcomes, particularly in extremely preterm infants.

Keywords: birth transition, placental transfusion, hypotension, neonatal outcome, very low birth weight

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Karel Allegaert,
University Hospitals Leuven, Belgium

****Correspondence:***
Peter Korček
peterkorcek.upmd@gmail.com

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INTRODUCTION

Neonatal adaptation is a complex physiological process that involves numerous adaptive changes within several organ systems. In order to achieve this, an almost immediate transition to air breathing with intricate pressure changes as well as changes of blood flow in circulatory system must occur simultaneously, especially enhanced pulmonary blood flow. Adequate blood volume is necessary to facilitate these adaptive processes and ensure sufficient oxygen transport and organ/tissue perfusion.

Abbreviations: BP, blood pressure; CI, confidence interval; DCC, delayed cord clamping; ELBW, extremely low birth weight; GA, gestational age; ICC, immediate cord clamping; IVH, intraventricular hemorrhage; LV, left ventricle; MABP, mean arterial blood pressure; MCA, middle cerebral artery; PDA, patent ductus arteriosus; SVC, superior vena cava; SVCF, superior vena cava flow; RR, risk ratio; RVO, right ventricular output; UCM, umbilical cord milking; VLBW, very low birth weight.

Increasing fetal hemoglobin (Hb) by placental transfusion may be considered a method in enhancing arterial oxygen content, increasing cardiac output, and improving oxygen delivery. It involves a shift of placental blood to the neonate within a limited amount of time immediately after delivery and may be achieved in two different ways: delayed cord clamping (DCC) and umbilical cord milking (UCM) (1–3).

These enhanced placental transfusion techniques can help to achieve a greater blood volume at birth (increase of up to 10–15 mL/kg), which may be significant especially in very low birth weight infants. Most of the blood volume (50–70%) is transferred within the first minute of life and can form up to 15% of overall blood volume of the neonate. Milking the cord four times provides a comparable amount of placental–fetal blood being transferred as performing DCC for at least 30 s (3, 4).

Recommendations with regards to the handling of umbilical cord have changed significantly over the last decades. The 2015 ILCOR and ERC guidelines advocate DCC (for at least 1 min) in uncompromised term and preterm infants. However, the authors advise that placental transfusion should be discontinued in infants who are not breathing, so that resuscitation measures are not delayed. The European consensus on resuscitation of the preterm infant recommends DCC (if possible) for at least 60 s to promote placental–fetal transfusion. Cord milking is considered a reasonable alternative if DCC is not possible (5–7).

The aim of this review is to present the recently published data with regards to different methods of placental transfusion, to compare and emphasize their impact in postnatal adaptation with particular emphasis on measures of cardiovascular stability in the first days of life in preterm infants.

RATIONALE FOR PLACENTAL TRANSFUSION

In optimal circumstances, appropriate aeration of the lungs, as achieved by spontaneous breathing, leads to increased pulmonary blood flow with a consequent increase in preload of the left ventricle (LV) and hence increased cerebral blood flow (8–10). However, after removing low resistance placental circulation by immediate cord clamping (ICC), there is a sudden increase in systemic arterial resistance of the neonate, which leads to increased afterload of the LV, as well as decreased preload of the right side of the heart (8–10). Furthermore, immaturity of myocardium in preterm infants means that they are vulnerable to rapid hemodynamic changes that can cause fluctuations in organ/tissue perfusion (3). In particular, the central nervous system appears to be most vulnerable to such changes, as cerebral autoregulation in preterm infants can be often impaired or absent in the immediate transitional period (11, 12).

In cases where cord clamping precedes onset of spontaneous ventilation, decreasing ventricular preload and ventricular output could potentially result in a decrease in cerebral blood flow. Low and altered cerebral blood flow has been associated with intraventricular hemorrhage (IVH). Thus, maintaining cerebral blood flow is an important component in reducing the incidence of severe IVH (8–10). In this respect, a published study using Near InfraRed Spectroscopy as well as several meta-analyses on this topic have shown that an adequate placental transfusion by DCC or UCM may increase cerebral blood flow during postnatal adaptation of the newborn and may help reduce IVH occurrence (10).

In addition, apart from lower rates of IVH, other benefits of enhanced placental transfusion in preterm neonates and newborns with extremely low birth weight have already been reported: higher Hb levels, reduced number of needed blood transfusions, lower risk for necrotizing enterocolitis, and higher mean blood pressure (BP) after birth (13, 14). Data relating to short-term hemodynamic variables are discussed in greater detail below.

PLACENTAL TRANSFUSION: HEMODYNAMIC EFFECTS

A number of studies highlight the potential cardiovascular benefits of placental transfusion in preterm infants. These include effects on mean BP, administration of volume and inotropes and other objective hemodynamic assessment methods [e.g., superior vena cava (SVC) blood flow, right ventricle output]. The studies are outlined in **Table 1** and discussed in greater detail below (10, 12–21). We have grouped the studies as placental transfusion (either DCC or UCM) compared to ICC and then a comparison of alternative placental transfusion strategies, focusing primarily on markers of cardiovascular stability.

COMPARISON 1: DCC COMPARED TO ICC

A previous meta-analysis of 15 studies examined 738 infants born before 37 weeks of gestation, having either DCC or UCM compared to ICC and found no significant differences in a number of outcome variables including Apgar scores, extent of resuscitation, incidence of hypothermia, polycythemia, and various pulmonary outcomes (ventilatory support, oxygen dependence). However, the following benefits were noted: DCC was associated with fewer infants requiring blood transfusions [risk ratio (RR) 0.61, 95% confidence interval (CI) 0.46–0.81], less IVH (ultrasound diagnosis of all grades: RR 0.59, 95% CI = 0.41–0.85), lower risk for necrotizing enterocolitis (RR 0.62, 95% CI = 0.43–0.90), and a lesser need for inotropic support (RR 0.42, 95% CI = 0.23–0.77) (22). However, there were only four studies reporting incidence and treatment of hypotension. The mean arterial blood pressure (MABP) was significantly higher in those allocated to DCC. Two studies (13, 23) present data at birth (97 infants, MD 3.52, 95% CI 0.60–6.45) and two other studies (10, 24) at age 4 h (111 infants, MD 2.49, 95% CI 0.26–4.72).

A number of more recent studies comparing DCC with ICC have reported BP data. Backes et al. found that infants who received DCC, as compared to those with ICC, had a higher BP within the first 24 h of life (mean difference of 4.13 mmHg, 95% CI 2.0 to 6.2, $P < 0.01$) and infants in the ICC group received significantly more treatment for hypotension (ICC 45% vs DCC 12%, $P < 0.01$). Interestingly, there was a trend toward lower rates of severe IVH, particularly for the most preterm infants (22–24 weeks of gestation) (12).

TABLE 1 | Overview of randomized controlled trials regarding the methods of placental transfusion and their impact on hemodynamics in preterm infants.

Leading author (journal and year)	Reference	Placental transfusion	Number of patients	Gestational age	Hemodynamic background	Conclusions
Baenziger (Pediatrics 2007)	(10)	Delayed cord clamping (DCC) (60–90 s) vs immediate cord clamping (ICC)	39	30 (mean)	Cerebral blood volume was not different between two groups at the age of 4 and 24 h, and mean cerebral tissue oxygenation was higher in the DCC group at the age of 4 (4.4%) and 24 h (3.2%)	Delayed cord clamping improves cerebral oxygenation in preterm infants in the first 24 h. Mean arterial blood pressure (MABP) was higher in the DCC group at 4 h of age, but not at 24 h
Backes (Journal of Perinatology 2016)	(12)	DCC (30–45 s) vs ICC (<10 s)	40	22–27	Higher MABP in the first 24 h (4.13 mmHg difference) and significantly lower frequency of hypotension treatment were observed in the DCC group	DCC appears safe, feasible, and offers hematological and circulatory advantages No statistically significant differences were found in severe neonatal morbidities except for lower incidence of severe intraventricular hemorrhage (IVH) in the DCC group
Kugelman (American Journal of Perinatology 2007)	(13)	DCC (30–45 s) vs ICC (5–10 s)	65	<35	The DCC group tended to have higher initial diastolic blood pressure (BP) and higher hematocrit. Very low birth weight (VLBW) infants with DCC tended to have higher MABP and needed less mechanical ventilation and surfactant administration	DCC seems to be safe and may be beneficial (from ventilation and circulation point of view) when compared with ICC in premature infants
Sommers (Pediatrics 2012)	(14)	DCC vs ICC	51	<32 (24–31)	Higher superior vena cava flow (SVCF) over the study period and greater right ventricular output (RVO) at 48 h of life in the DCC group were observed. No difference in other parameters (middle cerebral artery velocity, left ventricle shortening fraction, patent ductus arteriosus (PDA), MABP) were described	DCC in preterm infants is associated with potentially beneficial hemodynamic changes over the first days of life
Katheria (Journal of Pediatrics 2014)	(15)	Umbilical cord milking (UCM) vs ICC	60	<32	Systemic blood flow (SVCF, RVO) in the first 6 and 30 h of life was higher in the UCM group	Greater systemic blood flow was demonstrated with UCM in preterm neonates The UCM group also had fewer days on oxygen therapy and less frequent use of oxygen at 36 weeks of corrected postmenstrual age
Ibrahim (Journal of Perinatology 2000)	(16)	DCC (20 s) vs ICC	32	24–28	Higher MABP at 4 h of life and lower need of albumin transfusion to stabilize blood pressure and increase tissue perfusion in the first 24 h were recorded in the DCC group	DCC significantly reduced the requirement for albumin transfusion. DCC also increased the initial hematocrit, hemoglobin levels, and MABP. The risks for PDA/IVH were similar in both groups
Katheria (Pediatrics 2015)	(17)	DCC (45–60 s) vs UCM	197	<32 (23–31)	Systemic blood flow (SVCF, RVO) in the first 12 h was higher in the UCM group. MABP over the first 15 h and urine output in the first 24 h were higher in the UCM group	UCM provides greater placental transfusion when compared to DCC, especially in preterm infants born by cesarean delivery. Risk for any IVH was lower in the UCM group. Other neonatal morbidities were similar
March (Journal of Perinatology 2013)	(18)	UCM vs ICC	75	24–28	Initial systolic and diastolic BPs were higher in the UCM group (difference of 2.5 mmHg for systolic and 1 mmHg for diastolic pressure). Differences were not statistically significant	Infants in the UCM group were significantly less likely to develop any IVH (incidence of 25% in the UCM group vs 51% in the ICC group). However, the incidence of severe IVH was similar in both groups

(*Continued*)

TABLE 1 | Continued

Leading author (journal and year)	Reference	Placental transfusion	Number of patients	Gestational age	Hemodynamic background	Conclusions
Oh (Journal of Perinatology 2011)	(19)	DCC (30–45 s) vs ICC (<10 s)	33	24–28	No difference observed between groups in hourly MABP in the first 12 h of life	DCC offers effective placento–fetal transfusion in VLBW infants—trend toward higher hematocrit in the first 6 weeks of life. However, no statistically significant differences in neonatal morbidities between groups were demonstrated
Mercer (Journal of Pediatrics 2016)	(20)	DCC (30–45 s) vs ICC (<10 s)	202	<32	No difference in the admission MABP between groups	There were no differences in rates of IVH; however, the DCC group had better motor performance at 18–22 months of corrected age (Bayley Scales of Infant Development third Edition)
Popat (Journal of Pediatrics 2016)	(21)	DCC (≥60 s) vs ICC (<10 s)	266	<30	No difference between groups in SVCF measurement; however, the DCC group had lower RVO. Rates of treated hypotension, PDA size, and its treatment were similar	DCC had no effect on systemic blood flow in preterm infants measured as SVCF in the first 24 h

Another study addressing various hemodynamic outcomes included over 200 patients. There was no significant difference between groups in the mean BP values and the lowest SVC flow [ICC 71.4 mL/kg/min (SD 28.1) vs DCC 70.2 mL/kg/min (SD 26.9); $P = 0.7$]. The group with DCC also had lower right ventricular output (RVO) (−21.9 mL/kg/min, 95% CI −39.0, −4.7; $P = 0.01$). Rates of interventions for hypotension did not differ between the groups (21).

Since the abovementioned reviews, the largest randomized trial of DCC compared to ICC has been reported by Australian Placental Transfusion Study Collaborative group (25). The study revealed no significant difference in the primary outcome (death or major morbidity at 36 weeks of gestation) between infants assigned to DCC (37.0%) and those assigned to ICC (37.2%) group (RR 1.00; 95% CI, 0.88–1.13; $P = 0.96$). The mortality was 6.4% in the DCC group, and 9.0% in the ICC group ($P = 0.03$ in unadjusted analyses; $P = 0.39$ after *post hoc* adjustment for multiple secondary outcomes). Limitation of this study was that a considerable percentage (27%) of infants who were randomized to DCC group received ICC instead. The major reason for this was concerns about the infants well being (25). Moreover, similar limitations have been found in another large study, where the reasons included, in addition, implementation issues including miscommunication, concern about the mother, and fetal concern (21).

COMPARISON 2: UCM COMPARED TO ICC

Umbilical cord milking has the potential to avoid some perceived disadvantages of DCC such as potential delay in life saving therapy of the sick neonate and the risk of hypothermia (2). However, the exact description of UCM technique varies between published studies, in particular, in terms of the number of times the stripping of umbilical cord is performed, the definition of the milking speed, and in whether the umbilical cord is cut before or after the cord milking has been performed. The milking speed of 20 cm/2s and the frequency of cord stripping of 3–5 times are most commonly used in published cases.

A recent meta-analysis of 7 clinical trials involving 501 neonates compared UCM to ICC. Five studies included 277 infants born before <33 weeks. This review found that milking the cord was associated with higher Hb levels (mean difference, 20 g/L, 95% CI = 13–27), lower risk of IVH of all grades (RR 0.62, 95% CI = 0.41–0.93), and lower oxygen requirement at 36 weeks postmenstrual age (RR 0.42, 95% CI = 0.21–0.83). There was no statistically significant difference in mortality. When specifically addressing hypotension and its treatment, the authors found no difference in the incidence of hypotension in the first 24 h requiring treatment with volume expanders or support with inotropes between the two groups (11).

Katheria and colleagues randomized 60 neonates to UCM or ICC. They showed improved immediate transition in the delivery room. Neonates randomized to cord milking had a significantly higher mean and diastolic BP at 6 h. Infants in the milking arm had higher SVC flow in the first 6 h (98 ± 27 vs 66 ± 18 mL/kg/min, $P < 0.001$), greater hematocrite at 12 h (46 ± 10 vs 38 ± 7 mg/dL, $P = 0.02$), and were less likely to receive a blood transfusion (9/14 vs 14/14 infants, $P = 0.04$) compared with infants with ICC (15).

Hosono et al. present data on 40 preterm infants who were randomized to UCM or ICC. UCM was associated with higher initial BP values. The initial systolic, diastolic, and mean BPs in the milked group were significantly higher than in the control group ($P < 0.05$). This translated into a greater proportion of infants receiving inotropes in the control arm (26).

Conversely, March et al. found no difference between early systolic pressure values [3.0 (37.0–51.0) vs 40.5 (36.0–46.5), *P*-value 0.32] and diastolic BP values [22.0 (18.0–29.0) vs 21.0 (15.0–28.5) *P*-value 0.68] (18). In what appears to be a pre/post type study, Takami et al. report improved MABP on admission (mmHg) 28 (3.2) vs 35 (4.3) *P*-value <0.05, an improved urine output within 24 h (mL/kg) 1.1 (1.1) vs 1.9 (1.3) *P*-value

<0.05, and less need for volume expansion 58 vs 19% *P*-value <0.05 (27). They also recorded measures of cardiac output and cerebral oxygenation. Both LVCO and SVC flow in the milked group were significantly higher than those in the control group. The TOI in the milked group was significantly higher than in the control group over the first 36 h after birth. However, these findings need to be interpreted in light of potential biases in trial design.

COMPARISON 3: DCC AND UCM

The key methodological differences between DCC and UCM have been highlighted previously. DCC or UCM may not be of equal benefit for all preterm newborns. In neonates born by cesarean delivery, more blood can potentially remain in the placenta at birth due to anesthetic and surgical interventions that interfere with active uterine contractions.

In a two-center trial involving 197 neonates born at less than 32 weeks of gestation, Katheria et al. demonstrated that UCM seems to be a preferential method of placental transfusion in neonates born by cesarean delivery (17). The UCM (4 strippings) group had higher SVC blood flow and RVO measures in the first 12 h of life, a higher Hb level, better body temperature in delivery room, higher BP in the first 15 h, and higher urine output in the first 24 h of life, as compared to the DCC (45–60 s) group. There were no differences between the DCC and UCM groups for neonates born vaginally. There were no differences in cerebral oxygen saturation or cardiac output as measured by impedance (17).

Rabe et al. also compared UCM (4 strippings) and DCC (30 s) in a similar population group (neonates of less than 33 weeks of gestation at birth), but found no difference between the groups in both the admission Hb levels or the number of blood transfusions required in the first 6 weeks of life. This trial, however, comprised of only 58 randomized neonates (31 in DCC and 27 in UCM group), and the mode of delivery was not accounted for (28).

COMPARISON 4: VENTILATION WITH DCC COMPARED TO DCC ALONE

One trial has compared DCC alone to ventilation with DCC. In this trial, Katheria et al. compared 62 infants with DCC alone to 63 infants with ventilation with DCC and found no differences between a large number of early hemodynamic changes (cerebral oxygenation by near-infrared spectroscopy, cardiac output and stroke volume by electrical cardiometry, or SVC flow by functional echocardiography) (29).

SUMMARY OF HAEMODYNAMIC EFFECTS

Recent data demonstrate that DCC or UCM is advantageous over ICC. Despite a number of trials performed to date, the evidence for improved cardiovascular adaptation is somewhat inconsistent. What is clear is that placental transfusion, either as DCC or UCM, compared to ICC is not associated with an adverse effect on BP, the need for volume administration or inotrope use. The majority of studies that report on these outcomes either show no difference or else an improvement in the placental transfusion arm.

Very few trials report on measures of cardiac output and the largest study that presented data on SVC flow and RVO had a high crossover rate from DCC to ICC. This trial found no difference in SVC flow and a reduction in RVO in the ICC group (21). Conversely, milking was associated with an improvement in both SVC flow and RVO, suggesting that UCM may be a better alternative to DCC in cardiovascular adaptation. These questions remain to be answered by future studies.

CARDIOVASCULAR ADAPTATION AND LONG-TERM OUTCOMES

The potential benefit of placental transfusion with regards to neurodevelopmental outcome may be multifactorial. Enhanced cardiovascular adaptation resulting in improved cardiac output and improved cerebral blood flow may play an important role. The potential benefits may result in a reduction in brain injury as evidenced by reduced rates of IVH. In addition to these potential changes, improved blood volume resulting in increased iron content may also be neuroprotective. Furthermore, as cord blood is known to contain hematopoietic stem cells at birth, neonates may possibly benefit from their neuroprotective or even neurorestorative effect (20). Mercer et al. reported on preterm infants of less than 32 weeks of gestation, who received either ICC (in less than 10 s) or DCC (after 30–45 s). While there was no difference in the first recorded mean BP, rates of IVH or late onset sepsis between the groups, the DCC group showed better motor performance at 18–22 months corrected age (Bayley Scales of Infant Development, Third Edition) suggesting other potential mechanisms (20). Long-term follow-up of completed trials and future studies will help to clarify such potential benefits.

A recently published study of 197 infants showed those randomized to UCM had higher language and cognitive scores compared with those randomized to DCC. There was no difference in rates of mild or moderate to severe neurodevelopmental impairment (17).

CONCLUSION

Many questions remain unanswered in relation to placental transfusion and its potential hemodynamic effects. UCM may have advantages over DCC by reducing the incidence of morbidities, the number of needed blood transfusions, and the requirement for supplemental oxygen at 36 weeks postmenstrual age. UCM may be of greater benefit than DCC to neonates born by cesarean section and a significant proportion of preterm neonates tend to be delivered by this method. UCM is more likely to be readily complied with than DCC due to fewer concerns of delaying commencement of care for the preterm neonate, as was evidenced in the recent RCT where 27% of patients assigned to DCC had ICC performed instead for this reason (25).

Reassuringly a recent meta-analysis by Backes et al. show that there seem to be no differences regarding safety measures

observed (5-min Apgar scores, admission temperatures of neonates, incidence of delivery room intubation, peak serum bilirubin levels) when using DCC or UCM (30).

Many of the published clinical studies regarding placental transfusion have excluded neonates with the need for resuscitation at delivery, limiting the generalizability of the findings. Studies that include these patients are hence needed. There are, however, a number of planned and ongoing studies in this area. Some of these studies include short term markers of cardiocerebral adaptation incorporating echocardiography measures and near infrared spectroscopy. One such trial is the PREMOD 2 study (NCT 01866982), which includes detailed assessment of preterm infants of less than 28 weeks gestation in the delivery room and during the first 24 h of life. Infants will receive DCC or UCM and will have measures of cerebral oxygenation and echocardiography performed, which will hopefully provide further insight into the (patho-)physiological changes that are occurring over this time. Additional studies regarding neurodevelopmental outcomes, specifically in preterm neonates having had DCC in comparison to UCM performed would also be of great importance.

AUTHOR CONTRIBUTIONS

ZS, SF, and PK: these authors contributed equally to this work—substantially contributed to the conception of the work, drafted and reviewed the article. SF and PK: analysis and interpretation of presented data. ED: reviewed the article for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Case report

Fetal distress and circulatory disturbance in monochorionic twins: Possible risk factors for sialadenitis?

Peter Korček [a,b], Zbyněk Straňák [a,b,*]

[a] Institute for the Care of Mother and Child, Fetal Medicine Center, Podolské nábřeží 157, 14700 Prague, Czech Republic
[b] Third Faculty of Medicine, Charles University, Ruská 87, 10000 Prague, Czech Republic

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ABSTRACT

Neonatal sialadenitis is a rare condition. The vast majority of cases are caused by *Staphylococcus aureus* with predominant involvement of the parotid gland and need for long-term antimicrobial therapy. We reviewed three distinct cases of submandibular sialadenitis in preterm infants from monochorionic pregnancies. The association with neonatal sialadenitis is unproven. We speculate about the role of fetal distress and circulatory compromise in monochorionic twins as a risk factor in the development of this serious condition.

1. Introduction

Neonatal sialadenitis is an uncommon disease. Most of the reports demonstrate suppurative parotitis caused by *Staphylococcus aureus* with prematurity, dehydration, male gender and oral trauma being the main risk factors [1]. The primary or solitary involvement of the submandibular gland is extremely rare [2]. The authors describe three preterm infants from monochorionic diamniotic pregnancies who developed unilateral submandibular sialadenitis. The possible association between monochorionicity and sialadenitis is discussed.

2. Case reports

2.1. Patient 1

A preterm infant was born at 30 weeks gestation due to selective intrauterine growth restriction. The pregnancy was complicated by twin-to-twin transfusion syndrome (TTTS) and the prenatal ultrasound revealed decreased cerebroplacental ratio multiples of median (CPR MoM-multiples of median show how far the test result deviates from the median) in the small for gestational age twin (Table 1). The TTTS (Quintero Stage 1) did not require intervention. The immediate postnatal period was uneventful. A swollen erythematous mass (2.5 × 2.0 cm) was found in the left submandibular region with clinical signs of infection on the 10th day of life. The laboratory markers for infection were positive except for blood culture. The patient was treated with Oxacillin and Gentamicin for suspected submandibular sialadenitis. There was no purulent discharge in the mouth and the swelling regressed within 1 week. The infant experienced no further complications.

2.2. Patient 2

A preterm infant from monochorionic pregnancy was born at 30 weeks gestation due to the abnormal prenatal ultrasound, which showed decreased CPR MoM. The infant was intubated, received surfactant and remained on ventilatory support for 1 week. On the 7th day of life the newborn developed a swelling in the left submandibular region. The mass was tender on palpation; the infant stopped tolerating the feeds and was crying irritably. The laboratory work-up was positive for infection, the blood culture remained negative and the baby was started on intravenous Oxacillin. Despite the therapy, the mass was enlarging and the ultrasound disclosed abscess formation in the gland (Fig. 1). Because of the complication the infant underwent surgery where incision was made and the suppurative contents drained. A culture obtained during operation was positive for *S. aureus*. Following

* Corresponding author at: Institute for the Care of Mother and Child, Fetal medicine center, Podolské nábřeží 157, 14700 Prague 4, Czech Republic.
Tel.: +420 296 511 806; fax: +420 241 432 572.
E-mail address: z.stranak@seznam.cz (Z. Straňák).

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Table 1
Patients' overview. Prenatal and postnatal parameters.

	Patient 1	Patient 2	Patient 3
Gestational age (weeks)	30+1	30+2	33+4
Birth weight (grams)	960	1360	1940
Arteria cerebri media—pulsatility index[1]	1.10	1.25	1.10
Cerebroplacental ratio[2]	0.60	1.29	1.22
Twin-to-twin transfusion syndrome	Yes	No	No
Sex	Male	Male	Male
Mode of delivery	Cesarean section	Cesarean section	Cesarean section
Congenital anomalies	None	None	Left-sided pes equinus
C-reactive protein (mg/l)	24.50	76.60	7.50
Duration of antibiotic treatment (days)	5	15	5
Surgery	No	Yes	No
Blood culture	Negative	Negative	Positive

[1,2] Fetal ultrasound parameters measured on the day of delivery. For normal ranges see the article by Ebbing et al. [7].

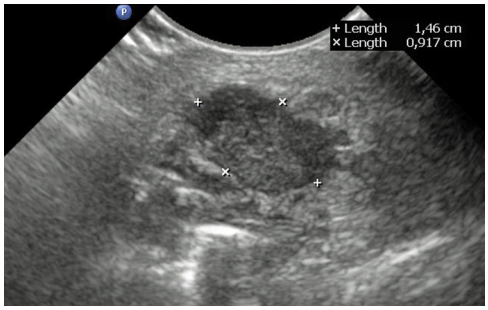

Fig. 1. Multilocular abscess cavity in the submandibular gland on ultrasound scan.

treatment, the neonate recovered without any further complications.

2.3. Patient 3

A preterm infant from monochorionic pregnancy was born at 33 weeks gestation due to preeclampsia and abnormal prenatal ultrasound (decreased CPR MoM). On the 3rd day of life the newborn presented with transient papulopustular rash in the right inguinal and cubital region and *S. aureus* and *hominis* were cultured from the swab. On the 5th day of life, an erythematous swelling developed in the right submandibular area. Clinical and laboratory signs of sepsis were positive. The antibiotic therapy (Ampicillin, Sulbactam) was initiated, followed by Vankomycin due to *S. aureus* in the blood culture. The infant recovered rapidly without any further complications and post-treatment blood culture was negative.

3. Discussion

Unilateral submandibular sialadenitis is a rare finding in newborns. Suggested risk factors include hypostimulation of the salivary glands during prolonged orogastric or nasogastric feeding, bacterial colonization of the oral cavity, prematurity, dehydration and duration of hospitalization in the intensive care unit [2]. Our patients exhibited many features of previously described cases of submandibular sialadenitis. No congenital anomalies were found in the oral cavity and other pathologies in the submandibular region were ruled out. Even though all patients were preterm, none of them suffered from dehydration. One preterm (Patient 3) did not require gastric tube feeding due to his gestational age and birth weight and for the same reasons was not admitted to the intensive care unit. The blood culture was positive for *S. aureus* in one of the patients, while in another one the bacteria were cultured from the purulent material obtained during surgery. However, one patient had negative blood culture and there was no purulent material present for culture. These observations emphasize the multifactorial etiology of the disease [1,2].

Interestingly, all patients were monochorionic twins and this factor has not yet been associated with neonatal sialadenitis. The monochorionicity increases the risk for hemodynamic compromise in the fetuses, which can lead to prenatal and postnatal complications (reversed a-wave ductus venosus, fusion of right and left ventricular inflow, tricuspid and mitral valve regurgitation, increased myocardial performance index, organ complications) [3–5]. Importantly, the adverse hemodynamic findings exist even in the absence of the TTTS [5,6]. In our series, both scenarios occurred (TTTS and non-TTTS pregnancies). Furthermore, all our patients presented with abnormal fetal ultrasound parameters–decreased middle cerebral artery pulsatility index and thus decreased cerebroplacental ratio [7]. These findings associated with the fetal distress and circulatory compromise could increase the susceptibility to infection [8,9]. In contrast, as monochorionic pregnancy suffers from an increased risk of preterm birth with significant morbidity, this fact alone can increase the likelihood of neonatal infection, including sialadenitis [10]. However, we did not experience neonatal sialadenitis prior to the establishment of the fetal medicine center, which started concentrating monochorionic pregnancies.

4. Conclusion

Neonatal sialadenitis is a rare disease with varied clinical course and ongoing infection surveillance is strongly recommended in order to prevent or treat the condition. Furthermore, monochorionic pregnancy with fetal hemodynamic dysregulation could be an additive risk factor in the complex pathophysiology of sialadenitis.

Conflict of interest statement

None.

Acknowledgments

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Prenatally Acquired Multiple Limb Ischemia in a Very Low Birth Weight Monochorionic Twin

Zbyněk Straňák[a, b] Peter Korček[a, b] Lucie Hympánová[a, b] Martin Kynčl[c] Ladislav Krofta[a, b]

[a]Fetal Medicine Centre, Institute for the Care of Mother and Child, [b]Third Faculty of Medicine, Charles University, and [c]Department of Radiology, University Hospital of Motol, Prague, Czech Republic

Key Words
Monochorionic pregnancy · Twin-to-twin transfusion syndrome · Multiple limb ischemia

Abstract
Limb ischemia is an extremely rare event occuring in monochorionic twin pregnancy complicated by twin-to-twin transfusion syndrome (TTTS) and twin anemia polycythemia sequence (TAPS). The authors describe a case of TTTS and TAPS treated successfully using amnioreduction and laser ablation. However, severe ischemia of both lower extremities in the recipient twin developed after the fetal treatment. This serious complication was diagnosed on MRI in utero and confirmed postnatally. Elective amputation of the affected limbs was performed. The etiology of the disease remains unclear despite profound clinical and histopathological examinations; although the role of thromboembolism in monochorionic pregnancy seems to be most likely, this unique case of multiple limb ischemia with distinct macroscopic findings has not yet been described.

Case Report

This is the first report of multiple limb ischemia in monochorionic twins. A fetal MRI revealed multiple limb ischemia. The monochorionic diamniotic twins were referred for twin-to-twin transfusion syndrome (TTTS) at 21 weeks of gestation (grade I according to Quintero). The symptoms of twin anemia polycythemia syndrome (TAPS) developed at 24 weeks of gestation, and fetal therapy was indicated. A fetoscopic guided laser occlusion, using the Solomon technique, was performed, followed by amniodrainage. There was a significant improvement of TAPS and TTTS ultrasound parameters in both twins after the intervention. A targeted MRI revealed no lesion in the twins' fetal nervous system. The pregnancy had to be terminated for preterm uterine contractions at 29 5/7 weeks of gestation by cesarean section. The birth weight for twin A (former recipient) was 1,202 g (hemoglobin 202 g/l, hematocrit 0,599) and 1,250 g (hemoglobin 172 g/l, hematocrit 0,494) for twin B (former donor). The affected twin A exhibited bilateral lower limb deformities where the right lower limb was edematous and cyanotic with a protruding tibia and fibula, whereas the left one was hypoplastic, macerated and necrotic with sharp demarcation of the defect from the rest of the leg (fig. 1). No signs of amniotic bands were seen after the delivery, and the ultrasound scan revealed no thromboembolic complications. Both legs were amputated at the demarcation line and the infant was discharged after 50 days with satisfactorily healed wounds.

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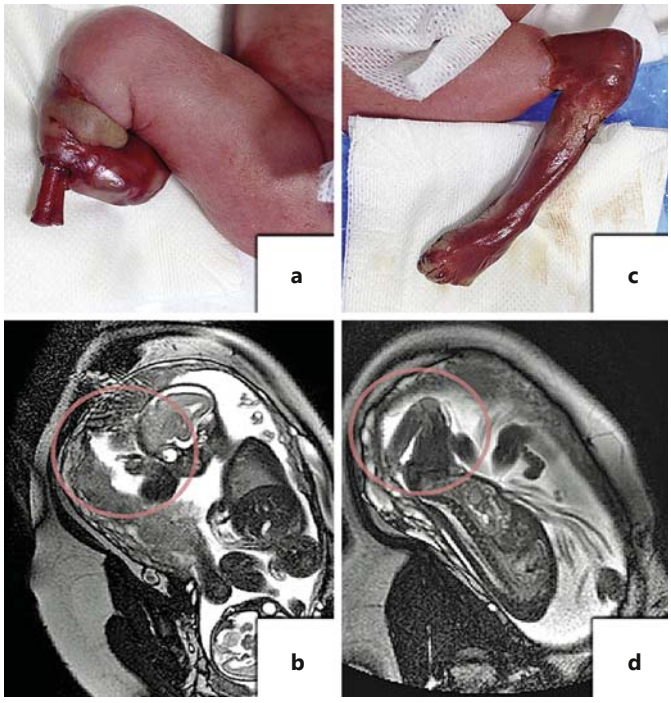
E-Mail karger@karger.com
www.karger.com/fdt

Peter Korček, MD
Institute for the Care of Mother and Child
Podolske Nabrezi 157
CZ–14700 Prague 4 (Czech Republic)
E-Mail peterkorcek.upmd@gmail.com



Color version available online

Fig. 1. Multiple limb ischemia with different macroscopic findings between the right (**a**, **b**) and left (**c**, **d**) lower extremity, documented by fetal MRI (circles) and immediately after birth.

Discussion

Monochorionic twin pregnancy suffers from an increased risk of serious complications for the fetuses and for the mother, especially if TTTS or TAPS is present [1]. The predominant therapeutic intervention is selective laser ablation of the anastomoses, which can improve the survival and the outcome of the surviving twins [2]. There is also an increased risk for vascular limb ischemia which might be independent of the TTTS and fetal therapy [3]. In the cases reviewed, only 1 extremity was affected, and they shared a very similar macroscopic pathology [4].

Our case is unique in that multiple extremities were affected and that the macroscopic findings were different, although previously described. We suggest that the bilateral limb ischemia was caused by the monochorionic pregnancy pathophysiology rather than other complications [5]. The role of laser treatment might be discussed, although given the fact that the procedure was ultrasound guided and performed at an experienced fetal institution, the causation is unlikely. The case makes a point of the importance of thorough ultrasound examination of all organ systems including the extremities (because our antenatal ultrasound scans revealed no abnormality). Furthermore, the MRI was targeted on the presence and degree of white matter injury, which was not diagnosed. Nevertheless, the retrospective analysis of the scan revealed pathologic changes in both lower limbs. A thorough full-scan MRI evaluation can disclose other than CNS abnormalities, including thromboembolic complications.

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Full Length Article

Tibial speed of sound changes in preterm infants during the first year of life

Zuzana Korčeková[a], Peter Korček[a,b,*], Václav Čunát[a], Zuzana Staníčková[a], Patrícia Zemanová[a], Zbyněk Straňák[a,b]

[a] Institute for the care of mother and child - Neonatology, Podolské nábřeží 157/36, Prague 14700, Czech Republic
[b] 3rd Faculty of Medicine, Charles University, Ruská 2411/87, Prague 10000, Czech Republic

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ABSTRACT

Introduction: Metabolic bone disease of prematurity (MBD) frequently affects preterm infants. The accurate diagnosis of the MBD remains a challenging issue despite characteristic clinical, laboratory and imaging features. Recently, non-invasive quantitative ultrasound (QUS) measuring speed of sound (SOS) has been applied to assess bone status. Limited data are available on comparison of QUS among preterm infants.

Objective: To evaluate development of tibial bone SOS values in preterm infants during the first year of life and compare the SOS values among different birth weight categories.

Methods: QUS was used in 153 infants below 34 weeks of gestation. The study group was divided into 3 subgroups based on birth weight (BW): ≤1000 g, 1001–1500 g and > 1500 g. SOS measurement was performed at 6 and 12 months of corrected age (CA).

Results: Overall, we found significant increase in mean tibial SOS between 6 and 12 months of CA (3004 ± 123 vs 3253 ± 109 m/s, $p = 0.001$). There were significant differences in SOS among birth weight categories at 6 months of CA ($p = 0.045$). However, these differences were not statistically significant at 12 months of CA ($p = 0.289$). The infants ≤ 1000 g scored the highest SOS values at both time points.

Conclusions: Tibial SOS significantly increases during infancy in preterm newborns. Significant variation exists in SOS at 6 months, but not at 12 months of corrected age according to BW. Moreover, inverse correlation between BW and SOS indicating better bone status was revealed in extremely low birth weight infants at both 6 or at 12 months of CA.

1. Introduction

Intrauterine bone development occurs mainly during the third trimester through significant (approximately 80%) calcium and phosphate accretion [1,2]. In addition, calcium accretion is exponentially related to gestational age and linearly related to birth weight (BW) [3]. These processes are seriously influenced by preterm delivery and lead to metabolic bone disease (MBD) that can be aggravated by other neonatal morbidities, medication (corticosteroids, diuretics) and nutritional management [4–8]. The incidence of MBD in very low birth weight infants (BW < 1500 g) and extremely low birth weight infants (BW < 1000 g) varies between 16 and 40% [9]. MBD can be diagnosed based on characteristic clinical, laboratory and imaging features [10–12]. Unfortunately, these methods are invasive and inaccurate in some cases [12–15].

Recently, quantitative ultrasound (QUS) has been applied to analyze bone status owing to its numerous advantages for preterm newborns – non-invasive, radiation-free, portable and relatively inexpensive method [2,15,16]. QUS gives information about both quantitative and qualitative aspects - bone density, cortical thickness, elasticity and bone microarchitecture [16]. Commonly used parameter of QUS is speed of sound (SOS).

Previous studies showed that SOS values exhibit certain pattern within the first year of life [2,4]. After birth, there is an initial decrease with nadir around 2–4 months of age, after which catch-up growth occurs with increasing SOS [15,17]. In preterm newborns, the decrease and subsequent catch-up are more significant, however, at 12 months of age, SOS values do not differ significantly between term and preterm infants [2,4]. The pattern can be attributed to changes in cortical bone (92% of bone mass after birth) and postnatal growth of medullar bone (especially in long bones), resulting in physiological decrease in cortical bone thickness [18,19].

As many studies focused on comparing term and preterm population, the aim of this study was to evaluate postnatal changes of tibial SOS in preterm infants only and shed light on postnatal SOS development in different birth weight categories.

* Corresponding author at: Institute for the care of mother and child, Neonatology, Podolské nábřeží 157, Prague 14700, Czech Republic.
E-mail address: peterkorcek.upmd@gmail.com (P. Korček).

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2. Materials and methods

2.1. Subjects

The study was approved by the Review Board and Ethics Committee of Institute for the care of mother and child. Informed consent was documented by the use of a written consent form and signed by the parents of all infants enrolled in the study. Preterm infants < 34 weeks of gestation were enrolled and followed-up in prospective, observational study. The data were collected from October 2016 to August 2018. Patients with serious contributing morbidities were excluded (congenital malformations, chromosomal abnormalities, renal and metabolic disorders).

2.2. QUS measurements of the tibial SOS

The measurement was performed using an appropriate sized probe (CS cortex small probe) with the Sunlight Omnisense 7000S Quantitative Ultrasound scanner (Sunlight Medical Ltd., Israel). This technique allows the measurement of the time taken by the ultrasound signal to travel between transmitters and receivers contained within the probe. These propagation times determine the bone SOS (measured in m/s). SOS increases with an increase in bone density and strength. System quality verification of the Sunlight Omnisense 7000S Quantitative Ultrasound scanner was performed using a phantom before each measurement, provided by the manufacturer.

SOS was measured on tibial bone for all enrolled infants. During measurements, the mid-tibia shaft length was determined by measuring the distance from the knee to the heel – one half of the distance was noted and marked at that point using a medical grade marker. The probe was then aligned along and parallel to the bone and moved around in an arc over the tibia until a reliable estimate of the SOS was obtained. The machine indicated when it had obtained adequate data for each cycle, and a minimum of three cycles were required to generate a measurement. In some infants, it was only possible to obtain an adequate signal when the probe was held stationary at one point on the tibia. The signal was sometimes only obtained after the probe was moved slightly from the measured site. The same probe was used for all measurements. The examination was tolerated well by all the infants.

The measurements were performed at 6 and 12 months of corrected age (range 0 ± 14 days). Small for gestational age infants were defined as having birth weight of < 10th percentile according to Fenton growth charts [20]. Other neonatal outcomes (respiratory distress syndrome, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis, periventricular leukomalacia and bronchopulmonary dysplasia) were followed up according to the Vermont Oxford definition [21].

2.3. Statistical analysis

The study group was analyzed based on birth weight in 3 subgroups (≤1000 g, 1001–1500 g and > 1500 g). Data were expressed as the mean ± standard deviation (SD). Student's *t*-test and paired samples *t*-test were used to compare independent variables as indicated. ANOVA test was used to compare SOS among subgroups at 6 and 12 months of corrected age (CA). $P < 0.05$ was expressed as statistically significant. The analysis was performed with Statistical Package for Social Sciences (SPSS 26.0; SPSS Institute, Chicago, IL, USA).

3. Results

Overall, 153 preterm newborns were included. Characteristic of the study group is shown in Table 1. Mean tibial SOS at 6 months CA (SOS1) and 12 months CA (SOS2) was 3004 ± 123 m/s and 3253 ± 109 m/s, respectively (Fig. 1). Using paired samples test, there was a significant increase in tibial bone SOS between 2 time points (249 ± 136 m/s), with $p = 0.001$. Moreover, when comparing SOS and three BW categories, there was a significant difference ($p = 0.045$) in SOS1 measurements among groups, whereas SOS2 results were not significant ($p = 0.289$) (Table 2). Remarkably, preterm newborns with the lowest birth weight (≤1000 g category) scored the highest SOS at both 6 and 12 months CA. On the contrary, infants with BW > 1500 g had the lowest SOS at both time points (Fig. 2).

Table 1
Demographic data. Continuous data are presented as mean ± SD. ANS = antenatal corticosteroids, RDS = respiratory distress syndrome, CPAP = continuous positive airway pressure, DOL = day of life, BPD = bronchopulmonary dysplasia, RAI = relative adrenal insufficiency, NEC = necrotizing enterocolitis, PDA = persistent ductus arteriosus, PIVH = peri/intraventricular hemorrhage, PVL = periventricular leukomalacia, LOS = late-onset sepsis.

Variable	*N* = 153
Gestational age, weeks	29.6 ± 2.5
Birth weight, grams	1309 ± 440
C-section delivery, no. (%)	123 (80.4%)
Male gender, no. (%)	85 (55.6%)
Small for gestational age, no. (%)	17 (11.1%)
Twin pregnancy, no. (%)	68 (44.4%)
ANS (completed), no. (%)	102 (66.7%)
RDS, no. (%)	128 (83.7%)
CPAP, no. (%)	126 (82.4%)
Invasive ventilation, no. (%)	53 (34.6%)
Oxygen at DOL 28, no. (%)	38 (24.8%)
Respiratory support at 36 weeks, no. (%)	13 (8.5%)
Corticosteroids for BPD, no. (%)	25 (16.3%)
Hydrocortisone for RAI, no. (%)	19 (12.4%)
NEC, no. (%)	2 (1.3%)
PDA > 2 mm (over 72 h), no. (%)	32 (20.9%)
PDA treatment, no. (%)	7 (4.6%)
Hypotension (first 72 h), no. (%)	18 (11.8%)
PIVH grade III-IV, no. (%)	5 (3.3%)
PVL, no. (%)	2 (1.3%)
LOS, no. (%)	16 (10.5%)
Parenteral nutrition, days	8 ± 6.7
Weight at discharge, grams	2224 ± 486
Enteral feeding at discharge – human milk, no. (%)	96 (62.7%)
Oxygen at discharge, no. (%)	9 (5.9%)

4. Discussion

Our results showcase a significant rise in tibial bone SOS in preterm infants between 6 and 12 months CA. This finding is in accordance with other researchers who documented steady increase in SOS after initial decline in both term and preterm infants [2,4,13,15,16].

We found significant differences in SOS values among preterm infants of different birth weight categories (≤1000 g, 1001–1500 g and > 1500 g subgroups) at 6 months CA. Similarly, substantial difference was already perceived between term (higher birth weight) and preterm (lower birth weight) infants [2,16]. These studies also supported our SOS results at 12 months CA when no significant difference among BW subgroups was found [2,16]. This phenomenon is probably influenced by rapid catch-up in SOS in preterm infants following the nadir at approximately 2–4 months of age [3,4,12,14,15].

However, our study shows the highest SOS values at both time points in the “smallest” infants (BW ≤ 1000 g). We revealed the inverse correlation between birth weight and SOS at both 6 and 12 months CA.

There could be a number of reasons for such findings. As the MBD of prematurity develops around 6–16 weeks postnatally, the “smallest” newborns (BW ≤ 1000 g) show signs of the disease already during the hospitalization [9]. Consequently, treatment can be commenced in time [4]. Furthermore, complex physiotherapy (during hospitalization and continuing post-discharge) can reduce the burden of MBD [22]. Finally, these infants have more follow-up visits and specific planned interventions.

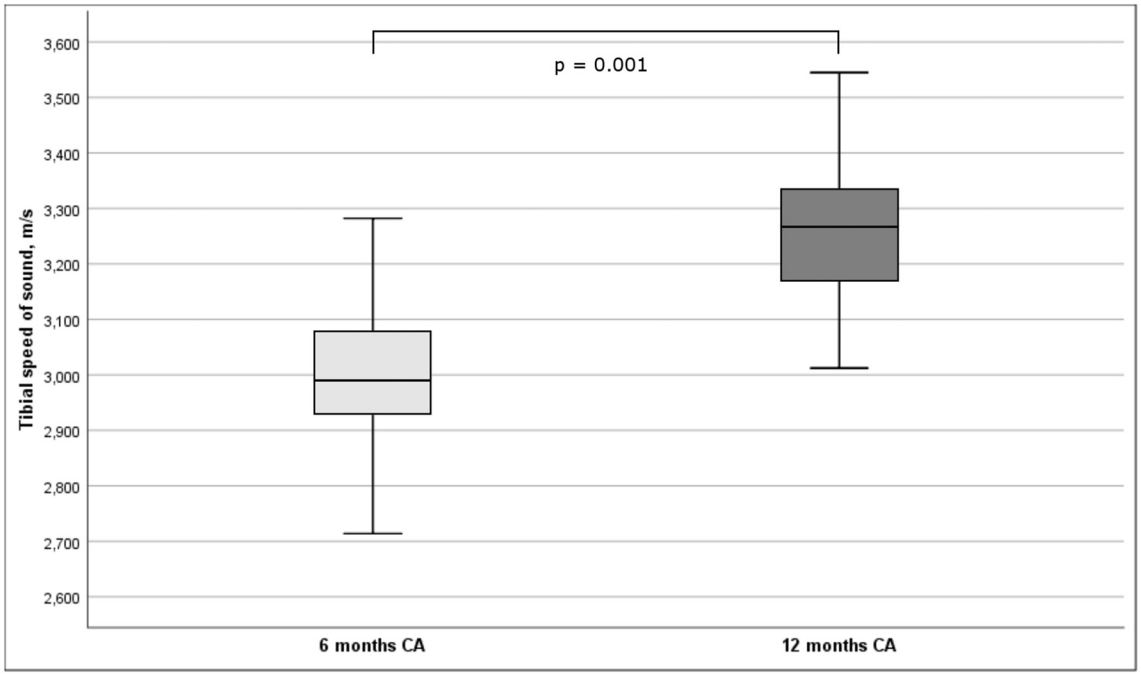

Fig. 1. Tibial speed of sound distribution within the study period. Significant difference between speed of sound at 6 and 12 months of corrected age (CA).

Table 2
Tibial speed of sound among birth weight categories during the first year of life. Continuous data are presented as mean ± SD. CA = corrected age.

Parameter	BW ≤ 1000 g (n = 41)	BW 1001 - 1500 g (n = 72)	BW > 1500 g (n = 40)	ANOVA test
SOS 1, m/s (6 months CA)	3033 ± 105	3009 ± 121	2966 ± 138	p = 0.045
SOS 2, m/s (12 months CA)	3274 ± 110	3251 ± 104	3236 ± 115	p = 0.289

In contrast, preterm infants with higher GA and BW (especially > 1500 g) are usually deemed as a "low-risk" group with shorter duration of hospitalization and less preventive measures [23]. Thus, MBD can develop post-discharge and can be missed due to less complex follow-up of these patients. As a result, the initiation of treatment can be delayed leading to worse bone health status in infants with BW > 1500 g,

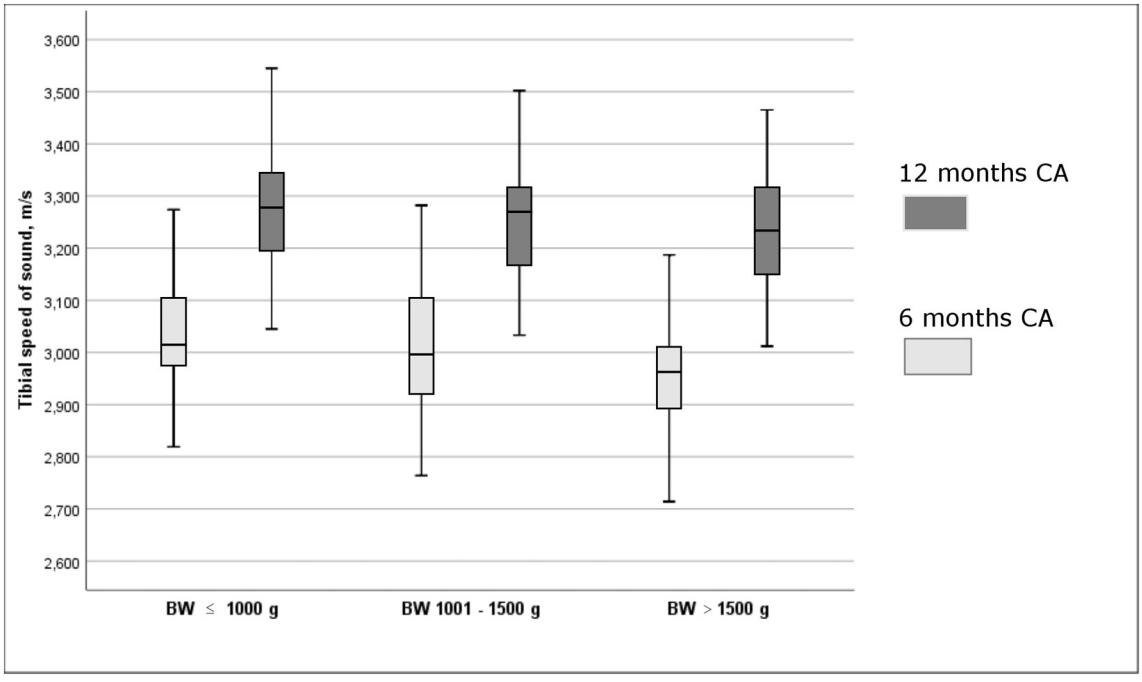

Fig. 2. Relation of tibial speed of sound to birth weight during the first year of life. BW = birth weight; SOS = speed of sound; CA = corrected age.

reflected by SOS values [4,24].

4.1. Limitations

We performed only 2 SOS measurements and the SOS difference between BW groups at 6 months CA was borderline significant ($p = 0.045$). Furthermore, we did not account for other variables, such as enteral supplements affecting bone status, chronic medication and type of enteral feeding.

4.2. Conclusions

Tibial SOS measurement seems to be reliable non-invasive method in the assessment of bone status. The value of SOS correlates with birth weight and varies until 12 months of CA. We suggest the SOS measurement should be performed in all preterm infants with special consideration in infants with BW > 1500 g. Monitoring and accurate diagnosis of MBD are essential throughout follow-up.

Author contributions

Zuzana Korčeková: Conceptualization, Methodology, Data curation, Writing – Original draft preparation, Investigation. *Peter Korček*: Conceptualization, Methodology, Data curation, Writing – Original draft preparation, Formal Analysis. *Václav Čunát*: Data curation. *Zuzana Staníčková*: Investigation. *Patrícia Zemanová*: Investigation. *Zbyněk Straňák*: Writing – Reviewing and Editing, Supervision.

Declaration of competing interest

None.

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Procalcitonin is more likely to be released by the fetus rather than placental tissue during chorioamnionitis

Zbynek Stranak[a,b], Jaroslav Feyereisl[a,b], Peter Korcek[a,b], Simona Feyereislova[a,b], Ladislav Krofta[a,b]

Aims. To analyze the relationship between maternal, cord blood and neonatal procalcitonin (PCT) levels in preterm deliveries with and without histologically proven chorioamnionitis (HCA).
Methods. 91 mother-infant pairs from 24+0 to 33+0 gestational weeks were analyzed. Procalcitonin was measured in all mothers within 24 hours before and subsequently in cord blood and in neonates within the first two hours after delivery. PCT levels were analysed in relationship to HCA and clinical outcome.
Results. HCA was confirmed in 28 cases (31%). We found no differences in PCT values between HCA positive and negative groups in maternal blood (0.1±0.1 vs 0.09±0.09 ng/L, $P = 0.76$). PCT values in cord blood and neonates were significantly higher in the HCA positive compared to HCA negative group (0.23±0.1 vs 1.2±2.7 ng/L, $P < 0.001$ and 0.89±3.4 vs 4.2±9.3 ng/L, $P < 0.0001$ respectively). PCT values in neonates were significantly higher than those of cord blood. Levels were not influenced by the mode of delivery, gestational age or premature rupture of membranes. Chorioamnionitis was more frequently associated with early onset neonatal sepsis (36% in HCA group vs 5% in non HCA group, $P < 0.0001$). Comparison of other clinical data revealed no differences between HCA positive and negative groups.
Conclusion. This study showed higher PCT in cord and neonatal blood in the presence of proven histological chorioamnionitis. The measurement of PCT in mothers' blood is not helpful for diagnosis of HCA. The changes in PCT values shown suggest its production and release by fetal tissue.

Key words: procalcitonin, preterm labor, intra-amniotic infection, early onset sepsis

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[a] *3rd Faculty of Medicine, Charles University in Prague, Czech Republic*
[b] *Institute for the Care of Mother and Child, Prague, Czech Republic*
Corresponding author: Peter Korcek, e-mail: peterkorcek.upmd@gmail.com

INTRODUCTION

Preterm birth represents a serious challenge for perinatal medicine which is reflected in its contribution to over 70% of perinatal mortality in developed countries. In addition, surviving infants frequently suffer from cardiorespiratory problems, mental retardation, cerebral palsy, and vision and hearing impairment[1].

The most common cause of preterm birth is chorioamnionitis which is implicated in the majority of extremely preterm births. Chorioamnionitis is often asymptomatic and clinical signs lack both sensitivity and specificity – over one third of women with these signs do not have histological evidence of placental inflammation as other causes may produce similar clinical features to chorioamnionitis[2,3].

Chorioamnionitis can occur without microbiologically-proven amniotic fluid infection in over half of the cases. However, released endotoxins and exotoxins possibly by bacteria colonizing the choriodecidual space initiate production of inflammatory cytokines provoking the maternal and fetal inflammatory response syndrome[4].

Procalcitonin (PCT) is a peptide pro-hormone of calcitonin, physiologically produced by the thyroid gland. In response to endotoxin and inflammatory cytokines, PCT can be produced by monocytes and other organs[2,5]. In contrast to C-reactive protein (CRP), PCT reflects the onset and resolution of the inflammatory process more accurately. Thus, PCT may be more useful than CRP in the early diagnosis of infection and monitoring of the disease[2,3].

For this reason, PCT plays an important role in the diagnosis of neonatal sepsis despite the fact that it may be elevated in non-infected infants with other complications[2]. PCT is also increased in cord blood of chorioamnionitis-affected newborns. Furthermore, the measurement of PCT in the maternal blood remains controversial in the diagnosis of intra-amniotic infection and chorioamnionitis[5,6].

The aim of our study was to investigate the relationship between histologically proven chorioamnionitis and maternal, umbilical and neonatal PCT levels.

MATERIALS AND METHODS

This retrospective study was approved by the Local Ethics Committee and the Local Committee on Human Research. Inclusion criteria were: preterm delivery at 24+0 to 33+0 weeks of gestation, patients born in our perinatal centre, completed measurements of the inflammatory parameters in the mother within 24 h before de-

livery, completed measurement of procalcitonin (PCT) in the newborn within 2 h after delivery, completed measurement of procalcitonin in the cord blood and completed histological examination of the placenta. Excluded were all patients with incomplete biochemical, haematological and histological investigations, patients with severe congenital anomalies, patients who required resuscitation at the delivery room and patients with unknown outcome. Between January 2005 and December 2014, 91 mother-infant pairs were eligible for the study.

Blood sampling and tests

Blood samples for the assessment of PCT, C-reactive protein (CRP) and white blood count (WBC) were taken from the mother within 24 hours before preterm delivery (venous blood) and subsequently from the newborn within the first two hours after delivery (venous or arterial blood). Cord blood was obtained immediately after delivery from the umbilical vein. Blood counts were measured with a Coulter Micro Dif II (Coulter Electronics Ltd., Fullerton, US) and CRP was measured by turbidimetry (SLT Spectra, Austria). Immunoluminometric assay (Lumitest PCT, Brahms, Germany) was used for PCT analysis. Luminescence was measured automatically in a Berilux Analyser (Behring Diagnostics, Germany).

Clinical and histological chorioamnionitis

Clinical chorioamnionitis was defined using criteria proposed by Gibbs[7]: body temperature ≥ 37.8 °C and a minimum of two other criteria: maternal or fetal tachycardia, uterine tenderness, malodorous vaginal discharge and leucocytosis ≥ 15 000 mm^{-3}. Histologically proven chorioamnionitis was defined by the presence of at least one inflammatory change in the placenta (intervillositis, deciduitis, or villositis), in membranes (amnionitis, deciduitis, or chorioamnionitis), or in the umbilical cord (funiculitis).

Postnatal data

Data were collected from the patient medical records. The definition of early-onset sepsis was based on the criteria proposed by Chiesa[6] (neonates with a positive blood culture and clinical signs of infection and/or neonates with negative blood culture, clinical signs of infection and positive sepsis screen). Other neonatal outcomes (respiratory distress syndrome, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis, periventricular leukomalacia and bronchopulmonary dysplasia) were followed up according to the Vermont-Oxford definition[8].

Statistical analysis

Data are reported using descriptive statistical methods. Univariate analyses were performed using Chi-square, Fisher's exact and Mann-Whitney U tests. All reported *P*-values are two-sided and not adjusted for multiplicity. $P < 0.05$ was considered statistically significant. Data analysis was performed using the IBM SPSS Statistics 23.0.0.0 software (IBM Corp., Armonk, NY).

RESULTS

The study population consisted of 91 mother-infant pairs. The mean gestational age of the study group was 28.9 weeks (range 24 – 33 weeks). Premature preterm rupture of membranes (PPROM) was recorded in 50 cases (55%) with average duration 24 h (range 2 – 136 hrs). No case of clinical chorioamnionitis was found. In contrast, histological chorioamnionitis was confirmed in 28 cases (31%).

Diagnosis of chorioamnionitis from maternal blood

We found no significant differences in procalcitonin values between histologically chorioamnionitis positive and negative groups in maternal blood. The measurement of WBC and CRP was more accurate in detection of subclinical chorioamnionitis. The incidence of chorioamnionitis was not influenced by the PPROM. The results are shown in Table 1.

PCT value in the diagnosis of chorioamnionitis

The measurement of PCT in maternal blood disclosed very low PCT values and there was no difference between "chorioamnionitis" and "no chorioamnionitis" groups. The comparison of PCT level in cord blood revealed the association with chorioamnionitis (no chorioamnionitis: 0,23±0.1 ug/L vs. 1.2±2.7 ug/L in chorioamnionitis group, $P < 0.0001$). PCT values were significantly raised and higher in preterm neonates following pregnancies complicated by chorioamnionitis. The changes of PCT values in maternal, cord and neonatal blood are demonstrated in Fig. 1.

Table 1. Maternal inflammatory parameters in study population and as per study group (no chorioamnionitis versus histologically proven chorioamnionitis).

	Study group (n=91)	No chorioamnionitis group (n=63)	Chorioamnionitis group (n=28)	*P*
WBC count (x1000/uL) mean + (95%CI)	13.8 (13.0-14.6)	13.1 (12.2-14.0)	16.0 (14.6-17.5)	0.001
C-reactive protein (mg/L) mean + (95%CI)	17.5 (11.8-23.2)	8.4 (4.9-11.9)	38.8 (24.0-53.6)	0.0001
Procalcitonin (ug/L) mean + (95%CI)	0.10 (0.07-0.12)	0.1 (0.07-0.13)	0.09 (0.05-0.11)	0.76

Data are presented as means (lower and upper bound 95% Confidence Interval). Statistically significant difference $P<0.05$

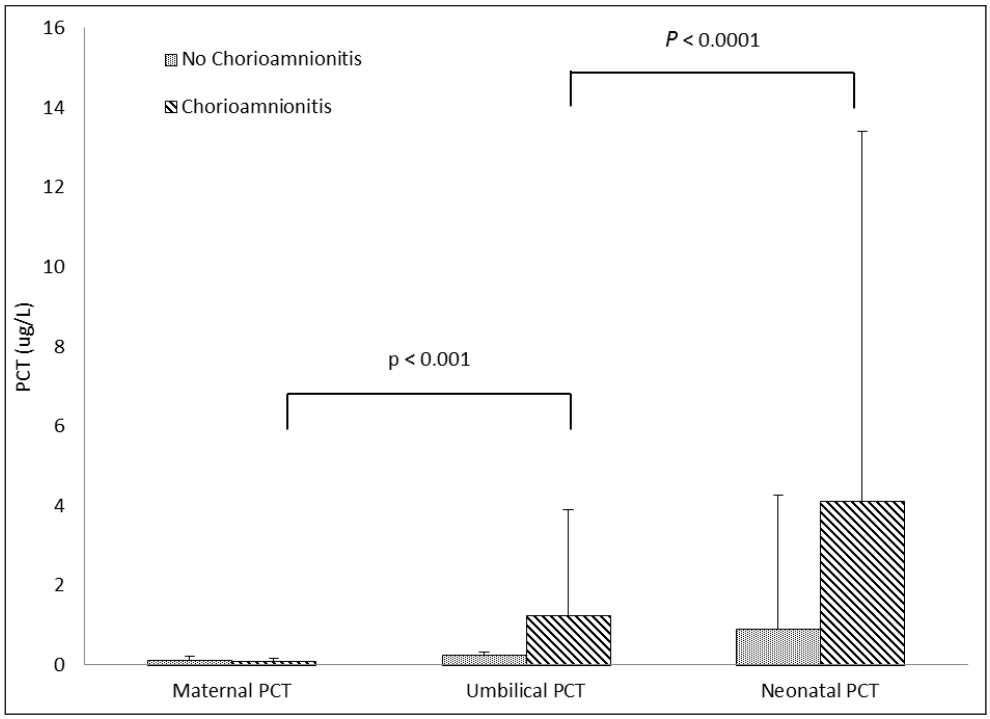

Fig. 1. The changes of PCT values in maternal, cord and neonatal blood. Mean values and positive standard deviations are shown by study group ("no chorioamnionitis" versus "chorioamnionitis"). Statistically significant difference $P < 0.05$.

Chorioamnionitis and neonatal outcome

We found a strong association between chorioamnionitis and the occurrence of early onset sepsis. Preterm infants following chorioamnionitis had delayed postnatal transition and more frequent administration of antibiotics. There were no differences in other neonatal parameters. Neonatal morbidity and mortality are shown in Table 2.

DISCUSSION

Despite the progress in perinatal medicine, histological chorioamnionitis (HCA) remains a leading cause of preterm birth. Rapid diagnosis and management of HCA are essential[9-11]. Unfortunately, clinical signs of HCA and microbiological assessment of the amniotic fluid appear to be unreliable diagnostic critera[2,3].

We investigated the role of procalcitonin (PCT) measurement in diagnosing HCA. Unfortunately, no significant difference in the maternal PCT values was found between the HCA positive and negative group. This finding is in accord with some recently published data showing that measurement of PCT in maternal blood is unreliable in the clinical diagnosis of chorioamnionitis[2]. Despite conflicting evidence, our study showed significant elevation in maternal WBC and CRP in the chorioamnionitis positive group[12,13].

In our study, PCT was elevated in umbilical cord

Table 2. Neonatal outcome in chorioamnionitis positive and chorioamnionitis negative groups. Statistically significant difference $P<0.05$ (expressed between "no chorioamnionitis" and "chorioamnionitis" group).

	Chorioamnionitis (N=28)	No chorioamnionitis (n=63)	*P*
Gestational age (weeks), mean ± SD	28.5 ± 2.5	29.1 ± 2.4	0.35
Birth weight (g), mean ± SD	1188 ± 402	1266 ± 351	0.52
Apgar at 5 minutem mean ± SD (95% CI)	7.9 ± 1.1 (7.5-8.4)	8.5 ± 1.0 (8.2-8.8)	0.01
Respiratory distress syndrome, n (%)	20 (71)	32 (51)	0.12
Early onset sepsis, n (%)	10 (36)	3 (5)	0.0001
Use of antibiotics, n (%)	20 (71)	31 (49)	0.05
Patent ductus arteriosus, n (%)	7 (25)	13 (21)	0.64
Intraventricular haemorrhage grade III and IV, n (%)	3 (10)	3 (5)	0.15
Bronchopulmonary dysplasia, n (%)	7 (25)	10 (16)	0.30
Necrotizing enterocolitis, n (%)	2 (7)	2 (3)	0.39
Periventricular leukomalacia, n (%)	2 (7)	2 (3)	0.39
Survival, n (%)	27 (96)	62 (98)	0.56

blood at the time of delivery in the HCA group. This is in accordance with some published data[2,3]. Howman et al observed a modest increase of inflammatory markers in the maternal and cord blood in pregnancies complicated by histological chorioamnionitis[2]. Su et al found PCT to be a relatively good rule-in and rule-out marker for prediction of neonatal sepsis[3]. One study reported elevated cord blood levels of PCT as an independant risk factor for mortality in preterm populations less than 33 weeks gestation[14].

We confirmed significantly elevated PCT in the infants of mothers with HCA. These newborns also had increased risk for early-onset sepsis and delayed postnatal adaptation. Moreover, there was an insignificant increase in the incidence of respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD). Park et al associated mild to moderate HCA in preterm population with a decrease in RDS. We did not find such association perhaps due to the lack of appropriate number of patients[14,15].

The strength of our study is the measurement of PCT in mother-infant pair which allowed us to evaluate the PCT changes in maternal, placental (umbilical) and neonatal circulation. Serial PCT measurements revealed that PCT values were significantly different and varied according to HCA presence or absence. Undetectable PCT values in maternal circulation in combination with positive PCT values in umbilical cord blood as well as the neonatal circulation support the hypothesis that PCT is produced by fetal tissues as a result of the fetal inflammatory response syndrome during chorioamnionitis[16].

There is an apparent gradual rise of PCT in the particular compartments in mother-infant pairs with histological CHA. Coupled with other laboratory markers of infection, neonatal serial PCT measurements in at-risk infants can be quite a strong predictor of their moribidties, specifically early-onset sepsis[15].

There are several limitations to the study: the relatively small size and unbalanced patient groups (28 mother-infant pairs in CHA-positive group and 63 in CHA-negative group), the data were analysed retrospectively. Maternal PCT values were obtained at various timepoints within 24 hours before delivery, which may have an impact on the comparison of maternal and cord blood values. PCT can also be increased in non-infected infants with other complications (intracranial haemorrhage, respiratory distress syndrome and perinatal asphyxia) (ref.[2]). Furthermore, PCT shows a physiological increase in the first few days of life, which complicates the interpretation of results[3].

CONCLUSION

This study confirmed the helpful role of PCT measurement in cord and neonatal blood in the presence of proven histological chorioamnionitis. The measurement of PCT in mothers' blood does not seem useful in the diagnosis of subclinical chorioamnionitis. More studies are needed to confirm the possible release of PCT from fetus during chorioamnionitis.

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Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

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SCIENTIFIC LETTER

Congenital *Lactobacillus* Blood Stream Infection in Extremely Preterm Twins

Peter Korček[1,2] · **Zbyněk Straňák**[1,2] · **Václav Čunát**[1]

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To the Editor: Lactobacillus spp. blood stream infection is extremely rare in children and is predominantly described in the adult population [1]. Only a few reports exist regarding neonatal *Lactobacillus* infection.

A 31-y-old woman with preterm dichorionic diamniotic twins was admitted due to the rupture of membranes. Tocolytics, antenatal corticosteroids and antibiotics were administered in view of chorioamnionitis (patient history, elevated C-reactive protein). Inflammatory markers escalated despite treatment and failed tocolysis led to cesarean section at 24 + 5 wk gestational age. Both infants suffered from severe respiratory distress syndrome and required prolonged ventilatory support. The infants were started on Penicillin and Gentamicin, however, no serious signs of sepsis were observed and the blood sample at admission revealed no significant elevation of inflammatory markers. Nevertheless, blood cultures were positive for *Lactobacillus spp*. The infants were treated successfully with antibiotics for seven days and post-treatment blood cultures were negative. The infants' outcome was favourable without any serious adverse events.

The main risk factors for *Lactobacillus* infection appear to be immunodeficiency, severe underlying disease, invasive lines or prolonged ineffective antibiotic treatment [1]. Although congenital *Lactobacillus* infection is uncommon and has been reported previously, this complication has not been yet described in extremely preterm twins.

In our case, the twins' blood cultures at admission were positive for *Lactobacillus spp*. Interestingly, the inflammatory response in infants was minimal including the twin A, where histological chorioamnionitis was confirmed. The infection transmission remains unclear as we were unable to cultivate *Lactobacillus spp*. from any other site (neonatal, placental and cervicovaginal swabs). However, the contamination was considered unlikely as blood cultures were obtained by two skilled neonatologists in a tertiary center.

Cultured from blood stream using sterile technique, *Lactobacillus* should be recognized as a serious pathogen regardless of mild clinical and laboratory findings, especially in extremely preterm infants [2, 3]. We can speculate about different outcome in our patients if the optimal antibiotic treatment was not given.

Compliance with Ethical Standards

Conflict of Interest None.

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✉ Zbyněk Straňák
z.stranak@seznam.cz

[1] Fetal Medicine Center, Institute for the Care of Mother and Child, Podolské nábřeží, 157 Prague, Czech Republic

[2] Third Faculty of Medicine, Charles University, Prague, Czech Republic