Thieme

Resuscitation of Term Compromised and Asphyctic Newborns: Better with Intact Umbilical Cord?

Reanimationsmaßnahmen bei einem reifen kompromittierten und asphyktischen Neugeborenen: besser mit intakter Nabelschnur?

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ABSTRACT

The authors hypothesize that particularly severely compromised and asphyctic term infants in need of resuscitation may benefit from delayed umbilical cord clamping (after several minutes). Although evidence is sparse, the underlying pathophysiological mechanisms support this assumption. For this review the authors have analyzed the available research. Based on these data they conclude that it may be unfavorable to immediately clamp the cord of asphyctic newborns (e.g., after shoulder dystocia) although recommended in current guidelines to provide quick neonatological support. Compression of the umbilical cord or thorax obstructs venous flow to the fetus more than arterial flow to the placenta. The fetus is consequently cut off from a supply of oxygenated, venous blood. This may cause not only hypoxemia and consecutive hypoxia during delivery but possibly also hypovolemia. Immediate cord clamping may aggravate the situation of the already compromised newborn, particularly if the cord is cut before the lungs are ventilated. By contrast, delayed cord clamping leads to fetoplacental transfusion of oxygenated venous blood, which may buffer an existing acidosis. Furthermore, it may enhance blood volume by up to 20%, leading to higher levels of various blood components, such as red and white blood cells, thrombocytes, mesenchymal stem cells, immunoglobulins, and iron. In addition, the resulting increase in pulmonary perfusion may compensate for an existing hypoxemia or hypoxia. Early cord clamping before lung perfusion reduces the preload of the left ventricle and hinders the establishment of sufficient circulation. Animal models and clini-

cal trials support this opinion. The authors raise the question whether it would be better to resuscitate compromised newborns with intact umbilical cords. Obstetric and neonatal teams need to work even closer together to improve neonatal outcomes.

ZUSAMMENFASSUNG

Die Autoren stellen die Hypothese auf, dass insbesondere asphyktische, reanimationspflichtige reife Neugeborene nach der Geburt von einer Spätabnabelung (nach mehreren Minuten) profitieren könnten. Dafür sprechen plausible pathophysiologische Zusammenhänge. Die Autoren haben für ihr Review die verfügbaren Studien zusammengetragen. Aufgrund der vorliegenden Daten erscheint es nachteilig, ein asphyktisches Neugeborenes (z. B. nach Schulterdystokie) rasch abzunabeln, obwohl dies in den aktuellen Leitlinien gerade in dieser Situation empfohlen wird. Durch Kompression der Nabelschnur oder des Thorax ist der venöse Rückfluss stärker betroffen als der arterielle Fluss in die Plazenta. Sauerstoffreiches venöses Blut steht so nicht für die Versorgung des Fetus zur Verfügung. Das Neugeborene leidet bei der Geburt oftmals nicht nur unter einer Hypoxämie und konsekutiven Hypoxie, sondern womöglich häufig auch oder vor allem unter einer Hypovolämie. Ein sofortiges Abnabeln, insbesondere wenn diese noch vor Beginn der Atmung stattfindet, könnte die Lage des ohnehin kompromittierten Neugeborenen noch weiter verschärfen. Verzögertes Abnabeln hingegen führt zu einer fetoplazentaren Transfusion sauerstoffreichen venösen Bluts, das eine bestehende Azidose puffern könnte. Zudem wird auf diese Weise das Blutvolumen um bis zu 20% gesteigert, was zu einem Anstieg aller Blutbestandteile führt, z. B. rote und weiße Blutzellen, Thrombozyten, mesenchymale Stammzellen, Immunglobuline, Eisen. Außerdem kommt es zu einer Erhöhung der pulmonalen Perfusion, was zusätzlich zu einem Ausgleich einer bestehenden Hypoxämie oder Hypoxie beitragen könnte. Wird zu früh, vor Eröffnung der Lungenstrombahn, abgenabelt, fehlt dem linken Ventrikel die für einen funtionierenden Kreislauf notwendige Vorlast. Sowohl tierexperimentelle als auch klinische Studien untermauern diese Auffassung. Die Autoren werfen die Frage auf, ob eine Reanimation kompromittierter Neugeborener bei intakter Nabelschnur günstiger sein könnte. Geburtshilfliche und neonatologische Teams sollten noch enger zusammenarbeiten, um eine Verbesserung des neonatologischen Outcomes zu erreichen.

Introduction

Every year, almost one million newborns worldwide die from the consequences of perinatal asphyxia [1]. This makes asphyxia a major cause of global mortality [1, 2]. Neonates who survive asphyxia may develop hypoxic-ischemic encephalopathy which, if severe, can cause serious organ damage which will persist for the rest of their lives [3, 4]. Perinatal asphyxia is usually the result of oxygen deficiency during or immediately prior to delivery [5]. Perinatal asphyxia may be due to placental causes (e.g., acute placental insufficiency due to placental abruption [6] or uterine rupture [6]), umbilical cord occlusion [5–7] (e.g., nuchal cord, umbilical cord knot or umbilical cord compression caused by breech birth) or fetal causes (e.g., thorax compression following shoulder dystocia [5, 7, 8]) and is associated with hypoxia, hypercapnia and acidosis [6]. This adverse event commonly results in an absence of breathing or an insufficient or delayed start of spontaneous breathing after delivery, which exacerbates hypoxia, hypercapnia and acidosis.

This is the primary reason why immediate clamping after delivery became standard practice in Western countries in the second half of the 20th century, as this makes it technically easier to initiate prompt treatment for respiratory insufficiency in a primary care setting equipped with the necessary instruments. This approach was recommended in several studies carried out in small patient groups published in the 1960s and 70s [9, 10], cited in [11], even though large-scale studies were lacking [11]. More recent studies, however, have come to the unambiguous conclusion that delayed cord clamping is beneficial for healthy newborns because it increases hemoglobin levels and iron reserves [12–14]. The neonate receives an additional 40 mg iron after 1 minute and 50 mg iron after 3 minutes through placental transfusion. This provides newborns with iron reserves of 115–125 mg/kg, which prevents iron deficiency in the first 6 months and probably up until the end of the first year of life [11]. If clamping is carried out too early, prior to complete opening of the pulmonary circulation, then the left ventricle misses out on the preloading required for functional circulation. Delayed umbilical cord clamping facilitates the complex transition from fetal to postnatal circulation until the change-over has been completed. For example, if the lungs are still not fully ventilated, as long as the left atrium still receives a limited amount of blood through the pulmonary veins, delayed clamping will ensure that blood still flows through the foramen ovale, allowing sufficient left ventricular preloading to be maintained in an otherwise healthy, non-compromised neonate. It is assumed that delayed clamping accelerates this process (▶ Table 1). Delayed clamping is therefore becoming the standard, and the current AWMF guideline on the care of newborns in maternity hospitals recommends that the umbilical cord of term-born, vaginally delivered newborns should be clamped after 1 to 3 minutes at the earliest [15].

In addition, the transfer of mesenchymal stem cells could also have a beneficial effect [16] by contributing to cellular repair and, in the authors' opinion, could play a beneficial role for neonates particularly in cases with inflammation, organ dysfunction and preterm birth.

Given the fact that different blood components are especially important for these compromised newborns because of the threatening overall clinical picture (limp, non-reactive, bradycardic, possibly even asystolic) [7], it is particularly paradoxical that immediate clamping is generally performed in asphyctic neonates

(e.g., after shoulder dystocia) in order to provide them with primary neonatology care as quickly as possible.

Even the WHO recommends this in their guidelines on the resuscitation of neonates. The consensus for this weak recommendation is based on an absence of evidence about neonates requiring resuscitation. However, the WHO has pointed out that artificial respiration can also be carried out before clamping if the treating physician has sufficient experience [17]. In their current guidelines, the European Resuscitation Council also states that immediate clamping should be carried out when caring for group 3 neonates (poor muscle tone +/− pale, insufficient spontaneous breathing or apnea, heart rate < 60/min or not detectable). But the European Resuscitation Council also reports that equipment is available which would allow neonates to be resuscitated with an intact umbilical cord and that studies have shown that this is feasible, although it is still unclear whether this would be the optimal strategy [18]. But, as in most German hospitals the resuscitation unit is not located in the immediate vicinity of the mother in the labor ward, immediate clamping is almost inevitable.

The authors of this review hypothesize that, given the neonatal adaptation processes, immediate clamping of the umbilical cord of compromised neonates requiring resuscitation could be associated with negative consequences for the newborn. The authors therefore urge physicians to consider whether it would not be better to refrain from immediate clamping, change the immediate postnatal management of neonates in future and review how neonatal care is managed. Term neonates would not require any special equipment nor would neonates who are delivered by cesarean section. In the authors' experience, the initial management steps can be easily carried out without resuscitation measures, as follows: wait-and-see, stimulate, keep warm, evaluate, open the airways, apply mask ventilation, if necessary, optimize mask ventilation. Thorax compression can be started at the umbilical cord, if it is possible or the situation appears to demand it. The prerequisites for this approach are listed in ▶ Table 2.

Material and Methods

For this review, a systematic PubMed search was carried out between 2 March 2021 and 23 May 2021 using the following search terms: "delayed umbilical cord clamping", "delayed umbilical cord clamping" NOT "preterm", "delayed cord clamping", "delayed cord clamping term", "asphyxia" AND "delayed cord clamping". The interactive education platform ClinicalKey of the scientific publisher Elsevier was additionally searched. The search terms used here were: "delayed cord clamping", "umbilical cord clamping" AND "asystole", "umbilical cord clamping" AND "complications", "neonatal asphyxia", "umbilical cord clamping" AND "asphyxia". References listed in the articles were examined to find further relevant publications. The search focused on reviews, human studies (randomized clinical studies, observational studies, case-control studies, case studies and feasibility studies) and animal experiments. All examined sources used for the review are listed in ▶ Table 3.

▶ **Table 1** Risks of immediate cord clamping and discussed potential benefits of delayed cord clamping.

Risks of immediate cord clamping:
Flow of oxygenated blood to the neonate is discontinued
Transfer of placental blood to the infant is reduced
→ hypovolemia, anemia, reduced transfer of stem cells
reduced left ventricular preloading
→ delayed switch from fetal to postnatal circulation

Discussed potential benefits of delayed umbilical cord clamping:
Faster improvement of oxygenation
Faster stabilization of circulation
Fewer blood pressure fluctuations
Less need for transfusions
Improved repair of potential damages through the effect of stem cells

▶ **Table 2** Prerequisites for delayed clamping of perinatally compromised infants and infants with perinatal asphyxia.

- Close cooperation between midwives, obstetricians and pediatricians (neonatologists)
- Primary care resources, particularly to ventilate the neonate, must be available in the labor ward and the operating room during C-section
- Courses of action and responsibilities must be defined and determined

Review

Studies on clamping, particularly in term neonates, are rare, although a number of studies on clamping in preterm infants are now available. Prospective randomized studies of term infants are only available in exceptional cases.

To better understand the pathophysiological interactions, 2 animal experiments in asphyctic sheep carried out in 2020 and 2017, respectively, were also reviewed [19, 20].

The authors also summarize a randomized study from 1988 and a systematic review with a meta-analysis from 2018 in the category "preterm neonates" [21, 22].

To consider the impact of late clamping in compromised term-born neonates, a randomized clinical study from 2019, a randomized clinical feasibility study from 2017, a prospective observational study from 2017, an observational study from 2015, a case report from 2016, a non-randomized feasibility study of a single-center cohort from 2018 and an observational study from 2014 were analyzed and evaluated [23–29]. The authors particularly focused on the randomized clinical study by Andersson et al. which was carried out in a Nepalese hospital [23], as it is one of the few existing clinical studies on this issue. An overview of the publications used is given in ▶ Table 1. The authors found no further studies during their search of the literature which did not support or which disproved the authors' hypothesis.

▶ Table 3 Review of publications comparing immediate vs. delayed clamping when resuscitation is required.

Author and year of publication	Type of study	Number of animals/ participants	Outcome parameters	Results/conclusions
Animal experiments				
Polglase et al., 2020 [19]	Animal experiments in asphyctic asystolic sheep	28[1] (ICC: 12, DCC: 16 [DCC1: 8, DCC10: 8])	Cerebral oxygenation is significantly lower with DCC10 versus ICC between 80 and 320 s after delivery and after 15 min. Mean blood pressure is significantly lower with DCC10 versus ICC between 50 and 160 s after delivery, subsequently no difference; systolic blood pressure is significantly lower with DCC10 vs. ICC between 60 and 180 s after delivery, subsequently no difference. Mean pulmonary blood flow is significantly lower with DCC10 vs. ICC between 50 and 200 s after delivery and after 15 min, even compared to DCC1 between 100 and 200 s ($p < 0.07$). End-diastolic pulmonary blood flow is significantly lower with DCC10 vs. ICC between 30 and 270 s after delivery and after 15 min, even compared to DCC1 between 40 and 260 s.	Significant reduction of post-asphyctic rebound hypertension with DCC10. ICC and DCC1 could result in additional brain damage. It is possible that delayed clamping reduces the damage to the cerebral circulation.
Polglase et al., 2017 [20]	Animal experiment in asphyctic sheep	20[2] (ICC: 7, DCC: 8)	Return to pre-asphyctic blood pressure within a significantly shorter time with ICC vs. DCC (ICC: 83.3 s [SD 32.7 s], DCC: 127.1 s [SD 33.5 s]), $p = 0.037$. Systolic and diastolic pressure in the carotid artery significantly higher with ICC at 70 s after ventilation. Rapid, significant "overshooting" of systemic arterial pressure with ICC after ventilation versus DCC (ICC 2 min after ventilation [68.4 [SD 6,2] vs. 51.4 [SD 1.9] mmHg]). Significantly increased extravasation of proteins in white matter (by 86%) and gray matter (by 47%) with ICC versus DCC (indication of a breakdown of the blood-brain barrier, increased risk of hemorrhage).	DCC protects against post-asphyctic rebound hypertension, less cerebro-vascular damage.
Studies in preterm neonates				
Hofmeyer et al., 1988 [21]	Randomized study	38	Cerebral hemorrhage rate could be decreased from 77% to 35% if clamping is carried out after 1 min at the earliest.	Hypothesis that if immediate clamping is carried out, the increase in arterial pressure could trigger intra- or peri-ventricular bleeding.
Fogarty et al., 2018 [30]	Systematic review and meta-analysis	2834	18 randomized control studies were compared. Result: DCC reduced in-hospital mortality (risk ratio 0.68 [95% CI: 0.52–0.90], risk difference: -0.03 [95% CI: −0.05 – −0.01], $p = 0.005$; number needed to benefit: 33 [95% CI: 20–100]); analysis of subgroups showed that DCC reduces the incidence of low Apgar scores after 1 minute but not after 5 minutes.	High level of evidence that delayed clamping reduces in-hospital mortality of preterm neonates.

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▶ Table 3 Review of publications comparing immediate vs. delayed clamping when resuscitation is required. *(Continued)*

Author and year of publication	Type of study	Number of animals/ participants	Outcome parameters	Results/conclusions
Studies in term neonates				
Andersson et al., 2019 [23]	Randomized clinical study	231 (ICC: 134[3], DCC: 97)	Oxygen saturation is significantly higher with DCC vs. ICC (90.4 % vs. 85.4 % after 10 min [difference of 5 % for CI of 3.5–6.5, $p < 0.001$[5], 83.6 % vs. 76.6 after 5 min [difference of 7 % for CI of 5.3–8.7, $p < 0.001$[5]], 71.7 % vs. 62.4 % after 1 min [difference of 9.1 % for CI of 7.3–11, $p < 0.001$[5]]). Apgar scores significantly higher with DCC vs. ICC (9.4 vs. 9.0 after 10 min [difference of 0.4 for CI of 0.2–0.7, $p = 0.03$[5]], 6.8 vs. 6.5 after 5 min [difference of 0.3 for CI of 0.1–0.5, $p = 0.01$[5]] and 5.1 vs. 4.3 after 1 min [difference of 0.8 for CI of 0.5–1.1, $p \leq 0.001$[5]]). Pulse significantly lower with DCC vs. ICC (105 vs. 116 after 1 min [CI: −11 − −9, $p < 0.001$[5]] and 124 vs. 134 after 5 min [CI: −11 − −8, $p < 0.001$[5]]). Faster onset of breathing with DCC vs. ICC (37 s vs. 45 s, $p < 0,001$[6]). Faster onset of regular breathing with DCC vs. ICC (78 s vs. 98 s, $p < 0.001$[6]).	No safety concerns when resuscitation was carried out with intact umbilical cord. Associated with better recovery compared to routine resuscitation performed after cord clamping. More studies are necessary to verify low transfer of neonates to intensive care units and lower mortality with DCC and for long-term observation of neurological development.
Katheria et al., 2017 [24]	Randomized clinical feasibility study	60 (ICC: 30, DCC: 30)	60 neonates with an intrapartum risk that they would require resuscitation were divided into 2 groups: ICC (30) and DCC (30); 19 in the ICC group were resuscitated (5 with active ventilation, 1 intubation), 13 in the DCC group were resuscitated (2 with active ventilation, 1 intubation). Outcome after 12 h: ▪ higher blood pressure in the DCC group (53 [SD 13] vs. 47 [SD 7] with ICC, $p = 0.02$) ▪ higher StO_2 values in the DCC group (82 [SD 5] vs. 79 [SD 7] in the ICC group, $p = 0.02$) ▪ lower FTOE in the DCC group (0.15 [SD 0.05] vs. 0.18 [SD 0.06] with ICC, $p = 0.03$) Better Apgar scores in DCC group (after 1 min 8 [Q1 9, Q3 9] vs. 8 [Q1 8, Q3 8], after 5 min 9 [Q1 9, Q3 9] vs. 8 [Q1 8, Q3 8]).	Trend to fewer resuscitations in the DCC group.
Lefebvre et al., 2017 [25]	Prospective observational study	40 (ICC: 20, DCC: 20)	pH values in umbilical cord blood after 1 h higher with DCC (7.17 [SD 0.1] vs. 7.08 with ICC [SD 0.2], $p < 0.05$). Plasma lactate levels after 1 h are lower with DCC (3.6 mmol/l [SD 2.3] vs. 6.6 mmol/l [SD 4.3] with ICC, $p < 0.05$). Mean blood pressure after 1 h is significantly higher with DCC (52 mmHg vs. 42 mmHg with ICC). Mean blood pressure with DCC was higher (after 6 h 47 [SD 3.9] vs. 40 [SD 5.6] mmHg and after 12 h 44 [SD 2.9] vs. 39 [SD 3.3] mmHg).	Resuscitation with intact umbilical cord is possible even in infants with congenital diaphragmatic hernia. DCC can support cardiorespiratory transition.
Ersdal et al., 2016 [26]	Observational study	1269 (ICC: 1146, DCC: 98)	All participants in the study were not breathing and required positive pressure ventilation, 18 % in the ICC group and 14 % in the DCC group died or required neonatal intensive care ($p = 0.328$).	According to logistic modelling, there was no association between resuscitation before or after clamping and outcome at 24 hours.

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► **Table 3** Review of publications comparing immediate vs. delayed clamping when resuscitation is required. *(Continued)*

Author and year of publication	Type of study	Number of animals/ participants	Outcome parameters	Results/conclusions
Menticoglou et al., 2016 [27]	Case study	2	In both infants, circulation was only restored after volume resuscitation; both infants died.	Resuscitation was unsuccessful, possibly because of hypovolemic shock; for pathophysiological reasons, the authors recommend delayed cord clamping and early volume resuscitation.
Blank et al., 2018 [28]	Non-randomized feasibility study in a single-center cohort	44[4]	12 infants were resuscitated (8 required strong stimulation, 1 infant required CPAP ventilation, 3 infants received positive pressure ventilation).	Cord clamping of term infants can be carried out when it would be physiologically useful, even if the infant requires resuscitation.
Ersdal et al., 2014 [29]	Observational study	15 563 (ICC: 639, DCC: 12 088)	In 639 cases, clamping was carried out before onset of breathing, 9 of them died or were transferred to the intensive care unit (ICU); In 12 088 clamping was done after the onset of breathing, 38 died or were transferred to the ICU (odds ratio = 4.53; 95% CI: 1.92–9.58, p = 0.0005), 53 cases were not valid.	Risk of transfer to intensive care unit and of death is higher if clamping is carried out before onset of breathing.

[1] 3 sheep were excluded because return of spontaneous circulation (ROSC) was not achieved.

[2] 5 lambs had to be resuscitated immediately after birth and were therefore excluded.

[3] Out of 134, only 65 followed the instructions for the timing of clamping.

[4] 2 infants were clamped earlier because of complications.

[5] calculated with unpaired 2-tailed t-test

[6] calculated with Mann-Whitney U-test

FTOE: fractional [cerebral] tissue oxygen extraction; ICC: immediate cord clamping (clamping before the start of ventilation); DCC: delayed cord clamping (clamping after the onset of ventilation); DCC1 and DCC10: clamping carried out at 1 and 10 minutes, respectively, after ROSC; ROSC: return of spontaneous circulation; SD: standard deviation; StO_2: tissue [muscle] oxygen saturation

Note: For the purposes of clarity, all groups in the different studies are categorized either as ICC or DCC in this overview, even if they are referred to differently in the actual studies.

Animal experiments of late clamping and possible protection against brain damage

There are many publications on neonatal adaption based on animal experiments in sheep. In one experiment carried out in almost term lambs, Polglase et al. [19] compared immediate with delayed clamping in lambs with advanced asphyxia. Fetal asphyxia was induced until cardiac arrest occurred. One group (n = 16) was resuscitated with cardiac massage and ventilated before cord clamping, the other group (n = 12) first underwent cord clamping and was then ventilated. The authors divided the first group again into one group of 8 lambs who were clamped one minute after the return of spontaneous circulation and one group of 8 lambs who were clamped 10 minutes after the return of spontaneous circulation. In the group which was resuscitated before being clamped, asphyxia was induced by clamping the maternal internal iliac artery to interrupt blood flow to the uterus without affecting perfusion of the umbilical cord. In the group which was clamped immediately, asphyxia was induced by clamping the umbilical cord [19].

The results show that it made no difference whether the umbilical cord was clamped before the lungs were ventilated or whether clamping was carried out one minute after the return of spontaneous circulation. However, a significant difference was found if clamping was delayed for 10 minutes after the return of spontaneous circulation. The latter group showed a significant decrease in post-asphyctic rebound hypertension. Cerebral blood flow and cerebral oxygenation were also significantly better (► **Table 1**). The authors also suggested that immediate cord clamping could contribute to additional brain damage whereas the risk could be reduced by delaying cord clamping by 10 minutes [19].

With their experiment the authors confirmed similar results from a previous study published in 2017 [20]: in that study, they had observed significant post-asphyctic rebound tachycardia and hypertension in lambs close to term who were clamped immediately compared to a group of lambs which only underwent cord clamping after ventilation. The results were determined by fitting the lambs with devices to measure blood flow and pressure in the umbilical artery, carotid artery, pulmonary artery, and femoral artery as well as measuring systemic and cerebral oxygenation. The lambs treated with immediate cord clamping had higher rates of brain damage as indicated by reduced expression of blood-brain barrier proteins and increased leakage of cerebrovascular proteins in subcortical white matter (by 86%) and gray matter (by 47%), which points to a breakdown in the blood-brain barrier [20]. The authors concluded that immediate clamping immediately exposed the brain to greater pressure post asphyxia, increasing the risk of cerebrovascular damage. In contrast, in the group which

underwent cord clamping after ventilation, the brain was protected from injury during asphyxia [20].

Late clamping and possible reduction of mortality of preterm neonates

The benefits of late cord clamping for preterm neonates have been known for some time, even though late cord clamping in this group of neonates only came into more general use in the last 5 years. In a small randomized study of 38 pregnant women already published in 1988, Hofmeyr et al. reported that the cerebral hemorrhage rate could be reduced from 77% to 35% if preterm neonates undergo cord clamping one minute after delivery at the earliest [21].

In this context, a systematic review with a meta-analysis published in 2018 by Fogarty et al. offers very informative results [30]. The authors of the study compared the effects on in-hospital mortality of preterm neonates who underwent either early or late cord clamping. For this they used the data obtained from 18 randomized controlled studies, which defined early clamping as < 30 seconds and late clamping as > 30 seconds. According to their data, delayed clamping significantly reduced in-hospital mortality by around one third [30]. The results were also picked up by the German guideline on preterm birth, which recommends that preterm neonates should undergo late cord clamping [22]. The authors of this review believe that no data was available about the impact of longer time periods between delivery and cord clamping (e.g., more than 5 or more than 10 minutes or time periods which are defined based on clinical findings, e.g., spontaneous breathing, breathing rate, pH values, heart rate, collapse of umbilical cord vessels). It is all the more significant that the above-described difference in mortality was still apparent despite the very small difference in the timing of clamping (< 30 seconds vs. > 30 seconds). It is not clear whether this was due to the time it took to perform clamping or to the higher probability that spontaneous breathing would begin after > 30 seconds. The results of the animal experiments of Polglase et al. [19, 20] suggest, however, that a longer delay before carrying out clamping could also reduce perinatal mortality and morbidity in humans.

Nepalese study indicates faster recovery following resuscitation with intact umbilical cord

To date, the authors' search of the literature has found very few studies investigating the outcomes after resuscitation performed with an intact umbilical cord in human neonates born at term. A Swedish-Nepalese randomized clinical study investigated compromised neonates born at term and late preterm neonates (≥ 33 GW [weeks of gestation]) [23]. One group of neonates was resuscitated with an intact umbilical cord (intervention group), the other group was resuscitated following immediate cord clamping (control group). In the intervention group clamping was supposed to occur 180 seconds after delivery at the earliest. All of the infants were born by vaginal delivery. Newborns were recruited into the study by obtaining the consent to participate in the study of 1560 pregnant women admitted to the low risk Maternal and Neonatal Service Center (MNSC). 780 women were randomly allocated into the group whose infants would be clamped immediately after delivery while the other 780 women

were allocated into the group whose infants would be clamped 3 minutes after appearance of the shoulders at the earliest. Out of a total of 1560 neonates, 1329 breathed spontaneously and were therefore excluded from the study. The remaining 231 neonates required resuscitation and were therefore included in the study. 134 of them were in the group which was supposed to undergo delayed clamping and 97 were in the group which was supposed to undergo immediate clamping [23].

The researchers had previously carried out a power analysis which calculated that each group required 99 participants to be able to demonstrate a difference of 2% oxygen saturation (SpO_2) between groups at 10 minutes after the birth (with a statistical power of 80% and a significance of 0.05). The group of neonates who underwent immediate clamping was slightly smaller and only numbered 97 while the group with delayed clamping carried out after 3 minutes was larger (n = 134) [23].

If the birth occurred without complications, the infants were retrospectively excluded from the study. If the infants did not breathe spontaneously, they were stimulated to breathe during the first minute or received positive pressure ventilation. This approach had previously been established in the hospital in the form of a Helping Babies Breathe (HBB) algorithm. Because of the closeness of events, blinding was not possible [23].

Average oxygen saturation at 10 minutes after delivery in the group which underwent late clamping was 5% higher (95% CI: 3.5–6.5) and was therefore significantly higher compared to the group which underwent immediate clamping (90.4% vs. 85.4%, p < 0.001) (▶ **Table 3**). In the late clamping group, only 57 neonates (44%) had an oxygen saturation of < 90% after 10 minutes, whereas the equivalent figure for the immediate clamping group was 93 (100%) (▶ **Fig. 1**). The absolute risk reduction was 56% (95% CI: 48–56%). Average Apgar scores for the late clamping group were also significantly higher (▶ **Table 3** and **Fig. 1**). Moreover, average pulse in the late clamping group after 1 minute and after 5 minutes was lower (▶ **Table 3**). Onset of spontaneous breathing was faster in the neonates of this group (▶ **Table 3**), and mortality prior to discharge from hospital was also lower in the late clamping group (0 vs. 3) (▶ **Fig. 1**) [23].

As the authors themselves admit, the study has several limitations. Because recruitment could only be carried out retrospectively, the groups were not of equal size. Moreover, one of the groups had slightly too few participants to achieve statistical power and significance [23].

Moreover, the interventions, which had been randomly allocated, were often not implemented. Although all of the children in the group in which all neonates were supposed to be clamped immediately were indeed clamped immediately (100%), in the other group where clamping was supposed to have been delayed by 180 seconds, this was only done in 65 (48.6%) neonates. The median time to clamping was 105 seconds (interquartile range: 30–191). The authors themselves voiced their concerns that lower implementation of the specifications affected whether the results could be generalized [23].

When the authors only included those infants in the group of late clamped neonates in which the specifications for clamping had been complied with, the results were similar or even better compared to neonates who had been clamped immediately (oxy-
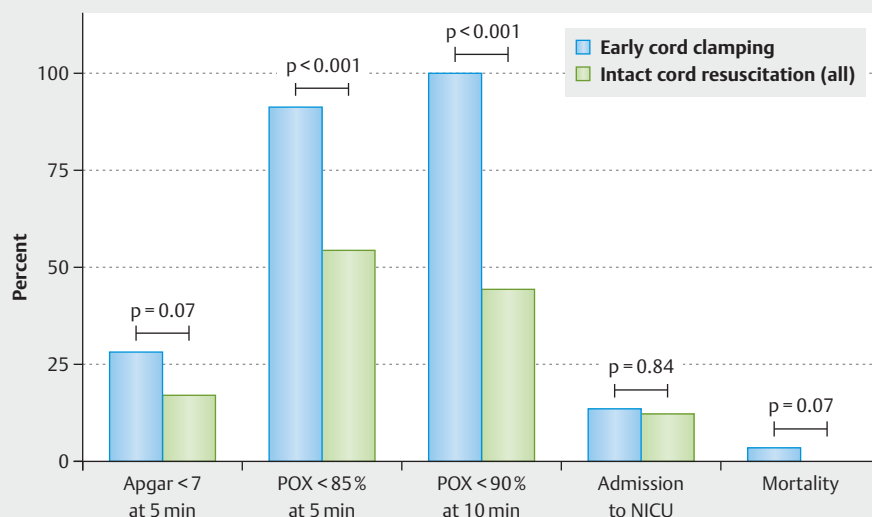
▶ **Fig. 1** Results of the Nepcord III trial [23]. Compromised neonates who underwent immediate cord clamping and were then resuscitated consistently had poorer results compared to neonates resuscitated with an intact umbilical cord. After 5 minutes, neonates in the early clamping group were more likely to have an Apgar score < 7, and oxygen saturation (SpO_2) as measured by pulse oximetry was also lower in this group at 5 and 10 minutes. They were more likely to be require a transfer to the intensive care unit and died more often. P values (p) were calculated using Fisher's exact test. POX = Oxygen saturation.

gen saturation after 10 minutes: 98% vs. 85.4% [95% CI: 11.8–13.3, p < 0.001], after 5 minutes: 91.4% vs. 76.6% [95% CI: 13.6–16, p < 0.001], after 1 minute: 79.8% vs. 62.4% [95% CI: 16.1–18.7, p < 0.001]). The Apgar scores were also better (9.6 vs. 9.0 after 10 minutes [95% CI: 0.2–1.0, p = 0.001], 7.0 vs. 6.6 after 5 minutes [95% CI: 0.2–0.7, p < 0.001], 5.7 vs. 4.3 after 1 minute [95% CI: 1.1–1.6, p < 0.001]) [23].

Another problem facing the authors of this study was that not all interventions were equally serious. For 15% of all participants in the study, suctioning the airways to induce the infants to breathe was sufficient. 32% of the newborns required stimulation to breathe and 53% required a ventilation mask. When only children who required mask ventilation were included in the analysis, the results were similarly unequivocal. Oxygen saturation in the late clamping group was 91.9% vs. 85.1% after 10 minutes (95% CI: 4.4–9.3, p < 0.001), 85.6% vs. 76.1% after 5 minutes (95% CI: 6.9–12.0, p < 0.001), 73.7% vs. 62.6% after 1 minute (95% CI: 8.2–13.9, p < 0.001) [23].

The authors conclude that resuscitation with intact umbilical cord is associated with faster recovery than when resuscitation is carried out after clamping. The authors point out that further studies are necessary to obtain recommendations from organizations such as the International Liaison Committee on Resuscitation (ILCOR) [23].

Possibly less resuscitation and better Apgar scores

A randomized clinical feasibility study (with German involvement) by Katheria et al. [24] has also been carried out. It included 60 newborns who were considered at risk intrapartum of needing resuscitation after delivery (e.g., recurrent fetal decelerations, tachycardia, bradycardia, shoulder dystocia, or ventouse or forceps delivery). The authors of the study categorized stimulation of breathing, administration of oxygen, and active ventilation as resuscitation measures [24].

At delivery, the newborns were randomly allocated into 2 groups. One group (n = 30) was clamped after 1 minute, the other group (n = 30) after 5 minutes. Higher blood pressures, higher StO_2 levels (tissue [muscle] oxygen saturation) and lower FTOE values (cerebral tissue oxygen extraction) after 12 hours of life were detected in the group of late clamped children. Even though the number of required resuscitation measures was low, a trend to fewer resuscitations and better Apgar scores was detected in the late clamping group [24].

In a retrospective observational study, Lefebvre et al. [25] also came to the conclusion that resuscitation with intact umbilical cord can be beneficial. A total of 40 newborns with prenatally diagnosed diaphragmatic hernia were included in the study. In one group (ICC [immediate cord clamping] n = 20) clamping was carried out immediately; in the other group (ICR [intact cord resuscitation], n = 20) clamping was carried out after resuscitation measures had been initiated. After one hour, the newborns in the ICR group had higher pH levels in umbilical cord blood, lower plasma lactate levels and significantly higher blood pressure (▶ **Table 3**). Even after 6 and after 12 hours, blood pressure in the late clamping group was higher. The authors of the study concluded that resuscitation carried out with intact umbilical cord can support the cardiorespiratory transition [25].

In contrast, the observational study by Ersdal et al. [26] found no association between the timing of clamping and the start of breathing or the start of resuscitation measures in terms of outcomes at 24 hours. In a Tanzanian hospital, 19 863 live-born children born between November 2009 and January 2014 were ob-

served. 1269 did not start breathing spontaneously and required positive pressure ventilation. The umbilical cord of 1146 infants was clamped prior to starting resuscitation. Clamping was carried out after resuscitation in 98 infants. 18% of infants in the first group died or required neonatal intensive care; in the second group the figure was 14%. Ersdal et al. used logistic modelling which found no association between resuscitation before or after clamping [26].

In one case study, Menticoglou et al. [27] described 2 cases with shoulder dystocia which was remedied within 5 minutes. Both children were born asystolic, and were immediately clamped and resuscitated in accordance with standard practice, initially without success. Circulation could only be restored following volume resuscitation. However, both children subsequently died. The reason given by authors of the case report for the failure of resuscitation was that the children had suffered a hypovolemic shock. Based on pathophysiological considerations, the authors therefore advocate in similar cases that either cord clamping should be delayed or volume resuscitation should be initiated more quickly [27].

Clamping after onset of breathing

Blank et al. [28] recruited 44 pregnant women (≥ 32nd week of gestation) into a non-randomized feasibility study of a single-center cohort. 23 children were born by cesarean section (8 of which were unplanned), 15 were delivered vaginally (6 with instruments). Clamping was done in accordance with the principle of baby-directed umbilical cord clamping. If the infant was breathing normally, clamping was delayed for at least 2 minutes. If the infant required help to breathe, exhaled carbon dioxide was measured using a CO_2 detector which had been previously placed in the ventilation mask. If a certain level of CO_2 was detected, the attending healthcare professional then waited for a further 60 seconds before clamping the cord. Blank et al. thereby ensured that gas exchange in the lungs had started before the umbilical cord was clamped. In 2 of the 44 cases, the specifications were not complied with because of the occurrence of complications and the infants were clamped earlier. Twelve of the 44 children required resuscitation measures. Eight of these infants required strong stimulation to start spontaneous breathing. One infant required CPAP (continuous positive airway pressure) ventilation, and 3 children were apnoeic and required positive pressure ventilation. The authors of this study concluded that it is possible to determine the physiologically best time to clamp the cord. The best time is after pulmonary gas exchange has started [28].

A large observational study of more than 15 000 newborns in a Tanzanian hospital came to the conclusion that the risk of being transferred to an intensive care unit or of dying was greater if the children were clamped before they started breathing [29].

The results of the cited animal studies and studies of preterm and term neonates are in accord with the current scientific understanding of the physiological processes which occur during neonatal adaption. This highlights the need for further and larger, well-designed studies but also provides a justification for resuscitating asphyctic and/or asystolic infants with depressed cardiac function BEFORE cord clamping. The prerequisite for this is that

any measures carried out in the newborn are performed to a very high standard.

Possible benefits of placental transfusion

An important benefit of late clamping is the placental transfusion of blood which occurs immediately after birth (▶ **Fig. 2**). If the process is straightforward, unilateral transfer of blood through the umbilical cord to the infant will occur at the physiological onset of spontaneous breathing [31]. This is partly the result of uterine contractions around the placenta [31, 32], and partly created by the push-pull effect of the ductus venosus which, in the opinion of the authors of this review, is primarily caused by a lowering of atrioventricular valve levels during systole. Ventilation of the lungs through inspiration also contributes to transfusion [32]. If cord clamping of a healthy newborn is delayed, it will ensure that the infant will receive 87% of the volume of fetoplacental blood. But if clamping is carried out immediately, only 67% of the blood volume will remain in the neonate [31]. Although experience has demonstrated that healthy children cope well with the reduced blood volume, ILCOR (International Liaison Committee on Resuscitation) recommends waiting at least one minute before clamping the cord because of the associated physiological benefits (e.g., better hemoglobin levels) [33]. Although a similar recommendation for neonates requiring resuscitation would make complete sense, no such recommendation has been issued because of the lack of evidence.

Pathophysiological considerations indicate that when asphyctic neonates begin breathing spontaneously after resuscitation, maintaining the connection to the placenta via the umbilical cord is particularly important. This is because, prior to ventilation of the lungs, left ventricle preloading is largely performed by the umbilical cord vein. But if the umbilical vein is clamped before transition to pulmonary gas exchange has occurred, it will result in an abrupt but significant decrease of the preloading volume as the lungs are not sufficiently perfused at this point to compensate for the lack of preloading [34 – 36].

Can the risk of hypovolemia be prevented?

Particularly in asphyctic neonates, placental volume shift may have already occurred during the birth process as a result of complications such as umbilical cord occlusion or thorax compressions (e.g., due to shoulder dystocia, vaginal breech birth or a long second stage of labor) [32]. This effect can be explained by the fact that the muscle layer of umbilical cord arteries which transport oxygen-poor blood from the fetus to the placenta are stronger than that of umbilical cord veins which provide the fetus with oxygen-rich blood. They remain open longer during a compression [32] and also have a higher blood pressure [37], even if the differences in pressure are higher on the fetal side than on the placental side [38]. Consequently, more blood flows out of the fetus than flows into the fetus [7, 32]. Moreover, the authors of this review believe that when thorax compression is present during systole, the heart is unable to develop the full suction effect required for sufficient cardiac preloading. This process also leads inevitably to a volume shift in the direction of the placenta. The authors are of the opinion that these events can lead to fetal and ultimately neonatal hypovolemia. If clamping is then carried out immediately,
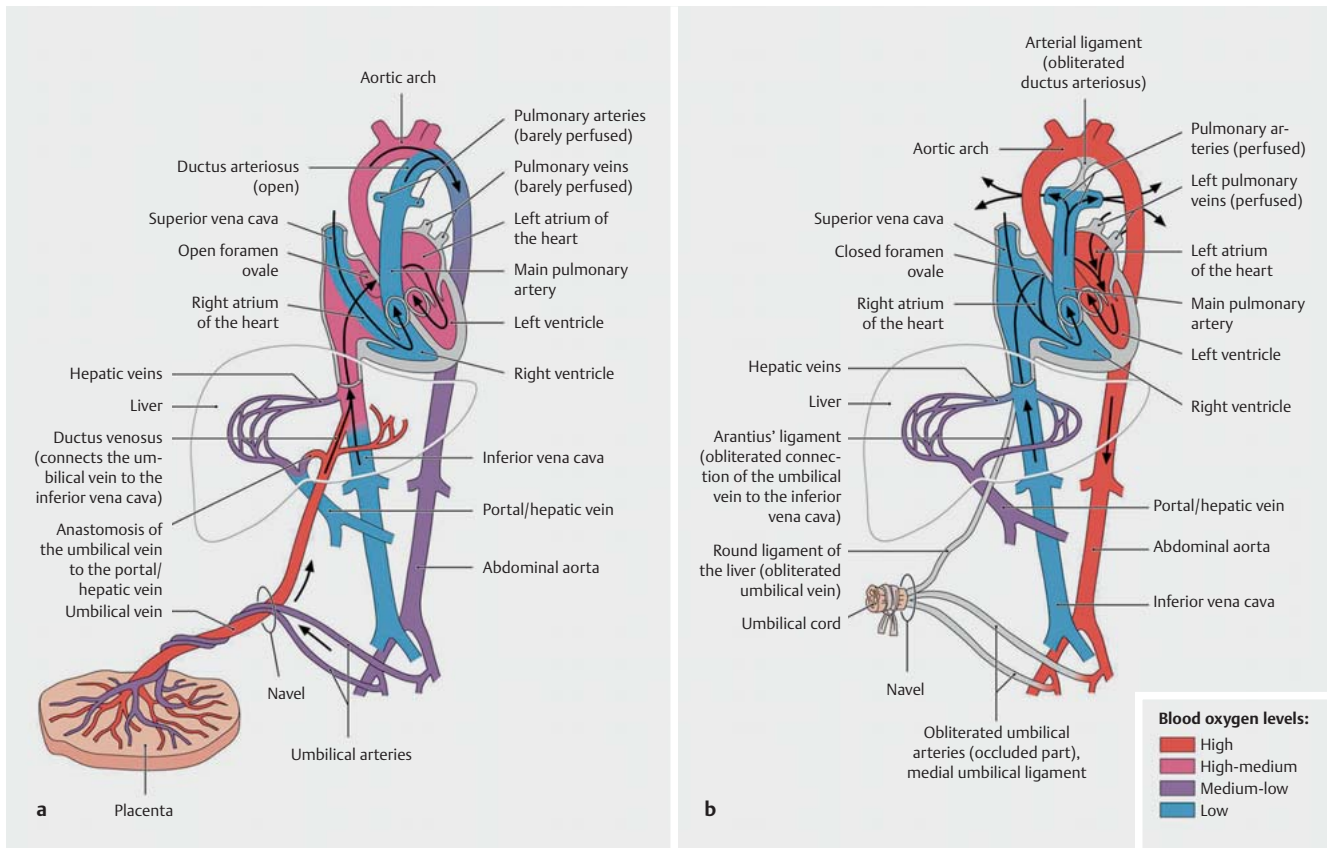
▶ **Fig. 2** Infant blood circulation before (**a**) and after (**b**) birth. Before birth (**a**) most of the left ventricular preload is provided by the placental circulation. Blood flows through the ductus venosus, inferior vena cava and foramen ovale either directly into the left atrium or is pumped into the aorta through the ductus arteriosus. After birth (**b**) placental supply for left ventricular preloading disappears; the pulmonary veins are now responsible for left ventricular preloading (Source: Schünke M, Schulte E, Schumacher U, Voll M, Wesker K. 2.6 Prä- und postnataler Blutkreislauf und die häufigsten angeborenen Herzfehler. In: Schünke M, Schulte E, Schumacher U, Voll M, Wesker K, eds. Prometheus LernAtlas – Innere Organe. 5th ed. Stuttgart: Thieme; 2018).

the logical result is that the hypovolemic state will be maintained or even exacerbated. The infant is unable to use the blood in the placenta to reduce hypovolemia.

To date, the occurrence of hypovolemia in asphyctic neonates has not been clearly evidenced in studies [27]. A few studies on term-born asphyctic neonates provide some indications that late clamping could counteract hypovolemia. Both Katheria et al. [24] and Lefebvre [25] detected higher blood pressure rates in late-clamped infants. The authors of this review know from clinical practice that infants born with asphyxia are more likely to require transfusions because of postpartum anemia. In addition, the pale appearance and lack of muscle tone of these infants indirectly support a presumption of hypovolemia.

Can the risk of hypoxia be reduced?

The occurrence of hypoxia in combination with hypovolemia has a particularly disruptive effect on neonatal adaption. But the authors of this review believe that this scenario is precisely what can occur in the context of the complications described here: the decreased supply of oxygen-rich blood from the placenta initially leads to hypoxemia which, in the authors' experience, can develop

quite quickly. This gives rise to tissue hypoxia, which can ultimately lead to organ damage, particularly of the brain. This condition is aggravated if early clamping of the cord stops the supply of placental blood immediately after the birth and before the onset of spontaneous breathing. This assessment by the authors of this review is supported by the results of the animal experiments of Polglase et al., in which asphyctic, hypotonic term-delivered lambs with bradycardia resuscitated with an intact umbilical cord had more stable cerebral perfusion and fewer cerebrovascular lesions compared to similar animals which were clamped immediately [20], even if it is not clear whether these results can be also transferred to humans. However, the study by Anderson et al. of term-born compromised infants has also shown that oxygen saturation is better if clamping is delayed [23]. In their clinical feasibility study, Katheria et al. found that late-clamped infants had more tissue oxygen: they had higher StO_2 and lower FTOE levels [32]. This permits the conclusion that late clamping could prevent tissue hypoxia.

Does immediate clamping prevent utilization of own resources?

The suspicion that umbilical cord occlusion and/or thorax compression during birth can lead to neonatal hypoxia is also supported by the authors' personal observations in clinical practice: If the expulsion stage is very long, arterial and venous pH values can often differ quite considerably – an indication that the arterial blood is becoming increasingly hypoxemic, hypercapnic and acidotic while the oxygen-rich blood in the umbilical vein is stagnant and cannot be aspirated, i.e., proper circulation is no longer present. The authors are of the opinion that if clamping is carried out too early, it will deprive the infant of the opportunity to use its own resources, i.e., its own oxygenated blood from the placenta, to reduce the acquired hypoxemia and resulting hypoxia.

Clamping that is performed too early can additionally result in large fluctuations in arterial pressure. As peripheral vascular resistance increases immediately, arterial pressure will initially increase [39, 40], cited in [36], but will subsequently drop again because of the drop in cardiac output caused by the cessation of inflow from the umbilical vein [36]. Arterial pressure increases again during lung ventilation (rebound increase) [34]. Polglase et al. were able to show with ovine experiments that the occurrence of post-asphyctic rebound hypertension was significantly lower if clamping was delayed [19].

Resuscitate compromised children while keeping the umbilical cord intact?

Based on the theoretical considerations presented here which are supported by the results of a number of studies, the authors are convinced that depressed, asphyctic and/or asystolic infants should, in principle, be resuscitated between the mother's legs or on her stomach with the umbilical cord remaining intact so that the lungs can be ventilated while the umbilical circulation is still intact. Neonatal care following cesarean section can be carried out in a similar manner at the operating table.

Although the physiological benefits of performing clamping only after the start of breathing appear to be plausible, there is currently no broad-based confirmatory evidence for this. The results of studies of term-born compromised children are contradictory and the total numbers are not big enough to provide robust evidence. But the high quality of the evidence showing reduced in-hospital mortality of late clamped preterm neonates [30] already indicates that comprised neonates born at term could also benefit from delayed clamping. After all, to best of the authors' knowledge, the physiological mechanisms of neonatal adaptation of preterm infants are the same or at least very similar to those occurring in compromised term-born neonates.

There is also no evidence that immediate clamping is the right approach. Immediate clamping has become widely used in practice without it being clear whether it is the right approach or whether it may be the wrong approach and lead to serious consequences.

The mere fact that no study has been able to show any disadvantages associated with delayed clamping speaks for delaying cord clamping. Even if there is as yet no evidence to fully support it, the authors point out that, if adequate neonatal care is avail-able next to the mother, it cannot be assumed that delayed clamping will lead to a deterioration of the infant's condition.

Conclusion

A look at the physiological processes occurring during neonatal adaption makes it clear that up to now, too little attention has been focused on the time point when cord clamping should be carried out. Based on theoretical considerations, the authors are of the opinion that, where possible, clamping should only be done when the infant has already started breathing, its lungs have filled with air, and lung circulation has the necessary blood volume required for perfusion. This is the only way to increase pulmonary blood flow sufficiently to ensure that the heart is supplied with enough blood and avoid hypovolemia.

It is particularly important that late clamping is carried out in situations of asphyxia caused by umbilical cord occlusion, shoulder dystocia, vaginal breech birth or a very long expulsion stage [5–8], as these normally result in reduced return flow through the umbilical veins to the infant which can develop into neonatal hypovolemia and placental hypervolemia [32]. Late clamping particularly facilitates the inflow of oxygen-rich blood from the placenta to the neonate [31] and the authors of this review are of the opinion that this can help mitigate against hypoxemia and the resulting hypoxia and, at least theoretically, reduce the extent of damage (particularly of the brain).

Despite the lack of confirmatory evidence, the authors are of the opinion that the above-described pathophysiological reasons indicate that late clamping of compromised asphyctic neonates offers clear benefits. Documentation of the precise time point of cord clamping, the start of breathing and the outcome, for example after 24 hours, could provide information whether cord clamping after the start of breathing is successful in practice. This should be verified and monitored using perinatal statistics. The benefits of performing clamping after resuscitation urgently need to be confirmed by further studies in human newborns, preferably prospective randomized controlled studies. Only when more evidence is available will organizations such as ILCOR or the WHO issue evidence-based recommendations.

Conflict of Interest

Patrick Stelzl has a part-time job agreement as consultant and speaker and is member of the Steering Committee in concerns of the LION ("Labour Induction Outcomes Network") project for Angusta 25 µg tablets from Norgine Pharma GmbH.
Rath: Lectures for CSL Behring, Nette, Ferring

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