
CURRENT BEST EVIDENCE: A REVIEW OF THE LITERATURE ON UMBILICAL CORD CLAMPING

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ABSTRACT

Immediate clamping of the umbilical cord can reduce the red blood cells an infant receives at birth by more than 50%, resulting in potential short-term and long-term neonatal problems. Cord clamping studies from 1980 to 2001 were reviewed. Five hundred thirty-one term infants in the nine identified randomized and nonrandomized studies experienced late clamping, ranging from 3 minutes to cessation of pulsations, without symptoms of polycythemia or significant hyperbilirubinemia. Higher red blood cell flow to vital organs in the first week was noted, and term infants had less anemia at 2 months and increased duration of early breastfeeding. In seven randomized trials of preterm infants, benefits associated with delayed clamping in these infants included higher hematocrit and hemoglobin levels, blood pressure, and blood volume, with better cardiopulmonary adaptation and fewer days of oxygen and ventilation and fewer transfusions needed. For both term and preterm infants, few, if any, risks were associated with delayed cord clamping. Longitudinal studies of infants with immediate and delayed cord clamping are needed. *J Midwifery Womens Health* 2001;46:402-414 © 2001 by the American College of Nurse-Midwives.

After decades of discussion, debate, and dialogue, there is little agreement about the optimal time to clamp the umbilical cord after birth. Similarly, consensus regarding the potential benefits or harm to the newborn infant that can be attributed to delayed cord clamping is lacking. Clear clinical guidelines based on solid data from research are thus needed.

In a recent survey of members of the American College of Nurse-Midwives, 35% of certified nurse-midwives (CNMs) and certified midwives (CMs) reported that they waited until pulsation stopped to clamp the cord (1), whereas 26% reported that they clamp the umbilical cord before 1 minute. The reason stated for the delay was to promote optimal neonatal transition by providing oxygen, nutrients, and additional blood volume through the pulsating cord; the reasons given for immediate cord clamping were the beliefs that time makes no difference and/or that early cord clamping prevents jaundice and polycythemia. Most midwives offered few references for their beliefs and practices, indicating the lack of evidence-based practice and need

for a current review of the literature. A 1950 survey of physician practices (the only one found) described most doctors as believing that cord clamping time was unimportant, although 24% reported milking the cord (2). Does delayed cord clamping have any benefits for infants? Or, does it cause harm such as neonatal jaundice or polycythemia? What is the evidence?

The purpose of this article is to evaluate the literature on cord-clamping practices published between 1980 and 2001 to provide the best possible foundation for clinical practice. The use of evidence-based research guidelines will allow clinicians to look beyond unsystematic clinical experiences, the pathologic emphasis on neonatal transition, and institutional routines and assist them to interpret the evidence obtained from clinical research (3).

BACKGROUND

Over the last decade there has been a shift in how clinicians and researchers examine clinical questions—from relying on the opinions of experts or authorities (authority-based) to a careful critique of the completed research on the subject of interest. The latter approach, introduced by Dr. Archie Cochrane (4,5), has been labeled “evidence-based medicine” or “evidence-based practice.” Authority-based medicine continues to be an important component of clinical judgment when evidence is lacking and is not to be lightly discarded on the basis of a few studies. However, a careful review of the literature to establish the current best evidence offers the most defensible answers for the clinical questions faced by health professionals, when applied judiciously and conscientiously (6).

Many practices in health care, especially in maternity care, were developed because of expediency, habit, or logic and were not subjected to the rigors of good science. The near abandonment of breastfeeding a few decades ago because of lack of knowledge about its benefits is a prime example.

Immediate clamping of the umbilical cord can reduce the number of red blood cells available to an infant by more than 50% (7) as seen in Figure 1. This practice originated with changes in obstetrics and the development of neonatology and is just now beginning to receive the scientific review worthy of its potential impact on the neonate. Delayed clamping allows time for a transfer of

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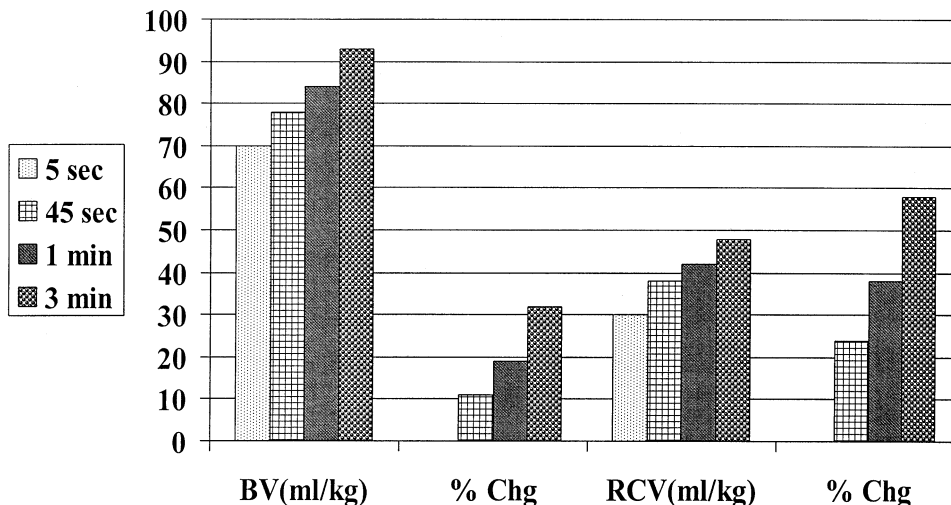


FIGURE 1.

Percent change in blood volume and red cell volume caused by delayed cord clamping. BV = blood volume; RCV = red cell volume. Developed from data in Yao et al, "Distribution of Blood between Infant and Placental after Birth," *The Lancet*, October 25, 1969.

the fetal blood in the placenta to the infant at the time of birth.

As Figure 1 shows, "placental transfusion" can provide the infant with an additional 30% more blood volume and up to 60% more red blood cells, the only oxygen-carrying component in the body (8). Both are lost with immediate cord clamping. What is debated is whether this transfusion is harmful or beneficial.

In the literature, it is common to find a theoretic association postulated between delayed cord clamping and symptomatic polycythemia with increased viscosity, hyperbilirubinemia, and transient tachypnea in term infants, although reference to specific well-designed studies (9–12) is lacking. Benefits, such as less anemia (13,14) and better cardiopulmonary adaption (16,17), are rarely mentioned, except in specialized reports (13–16) and by way of the public media (18).

SELECTION CRITERIA

This article will analyze the potential harms and benefits of delayed cord clamping by use of data obtained from randomized clinical trials and "controlled trials." A study

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done in which treatment groups were not randomized but were said to be indistinguishable before treatment will be considered a "controlled trial."

A literature review on umbilical cord clamping intervals was conducted using guidelines developed from evidence-based health care guidelines (5,19). For this review, only the randomized clinical trials for term (20–23) and preterm infants (24–30) and well-designed controlled trials (31–35) were included in the summaries found in Appendices A and B. Other studies, review articles, expert committee reports, and case studies are referred to as appropriate throughout the text.

SEARCH STRATEGY

The studies reviewed in this article were obtained through a variety of sources. Some references were available through the Cochrane Library, although a complete review has not been undertaken as of this writing. Entering the key words *umbilical cord clamping* in the PubMed Database of the National Library of Medicine revealed in a large number of articles on the subject. These articles yielded many secondary references. The four older review articles provided analyses and references of still older, but not necessarily unimportant, articles (36–39).

TYPES OF INTERVENTION

The primary study intervention examined was delayed clamping of the umbilical cord. In studies of delayed cord clamping for preterm infants, the term "delayed" meant no longer than 30 to 45 seconds (24–30). For term

infants, the “delay” ranges from 3 minutes (22,31–34) to cessation of any pulsations in the cord (20,22,23) or up to 10 minutes (35). The definitions used for “early” cord clamping ranged from immediate (20,21,31–34) to before 1 minute (22,23,35) for term infants. For preterm infants, most studies defined “early” cord clamping as immediate (24,26,29,31); however, for two studies “immediate” implied a 20-second delay (25,27).

Other factors that have a significant impact on placental transfusion were also noted; these include the level at which the infant was held during the delay and the use of oxytocic medications for the mother after delivery. For example, variations range from holding the infant at the introitus or level of the placenta (20,24), to placing the infant on the maternal abdomen (22,23,29,31–33,35), to lowering the infant from 10 to 30 cm below the level of the placenta (20,21,25–28,30). One study identified two placement levels (20).

TYPES OF OUTCOME MEASURES

Outcome measures for all infants are highly diverse, preventing a meaningful meta-analysis at this time. For term infants, they include physiologic variables such as hematocrit and ferritin levels (20,21,23,31–35), bilirubin levels, time of cord separation, breastfeeding rates (22), neonatal jaundice (22,23), and many variables that did not seem to differ between treatment groups. Examination of psychological and developmental variables were secondary efforts in two studies whose purpose was evaluation of the safety of a Leboyer birth (which includes delayed cord clamping) (23,35). These secondary variables included the Brazelton Neonatal Assessment and the mother’s opinion at 8 months postpartum as to whether the birth had influenced the infant’s behavior (23). Studies involving preterm infants looked at the need for transfusions (24,25,30), hematocrit and blood pressures (24,26–30), bilirubin levels (24,30), and days of ventilation and oxygen use (30). The duration of any long-term follow-up of preterm infants was 4 to 6 weeks and included the number of transfusions received between birth and 4 to 6 weeks of life (24,25). All studies included can be found in Appendix A for term infants and Appendix B for preterm infants.

METHODS

Participants were randomly assigned to treatment groups in each of the randomized clinical trials. All “controlled trials” reported that there were no differences in the two groups at the beginning of the studies. Concealment of randomization or “blinding” was not always addressed in cord clamping studies and often is not possible, especially at preterm infants’ births, when the presence of the neonatologist who will care for the infant is essential.

However, the method of evaluating outcome measures after the birth was blinded whenever possible (23). All patients were accounted for at the end of the trials, and most investigators specifically ensured that data were analyzed with subjects in their intended groups. Authors of two of the four randomized trials on term infants stated that they did not enroll parents who had a strong preference for delayed cord clamping (22,23).

DATA ANALYSIS

A careful review of two issues of primary concern was conducted: 1) Is harm done to term or preterm infants by delaying cord clamping? 2) Are there real or potential benefits from delaying clamping for any infants? Alleged harmful effects examined include symptomatic polycythemia and/or increased viscosity (10–12), increased incidence of jaundice and hyperbilirubinemia (11,12), increased transient tachypnea for term babies (12), and any adverse outcome for preterm infants.

DESCRIPTION OF STUDIES

The methodologic quality of the studies included ranged from satisfactory to rigorous. The search strategy revealed no published meta-analyses. One unpublished meta-analysis on preterm infants and cord clamping was found (40), but the results were extremely limited, because the studies differed widely on variables, methods, and conditions. Four randomized clinical trials involving term infants (20–23) and seven with preterm infants as subjects were found (24–30). In addition, there are five well-designed “controlled trials” (without randomization) on term infants from the last decade (31–35). Overviews of the randomized clinical trials and “controlled trials” on cord clamping in term infants from 1980 to 2001 are presented in Appendix A. Current randomized clinical trials involving preterm infants follow in Appendix B. Older studies are cited in the narrative.

One randomized clinical trial offered poorly defined variables, listed no times of cord clamping, and did not state whether the investigator was present for the birth, but it is included because it was only one of four randomized clinical trials with term infants as subjects (21). Four review articles from 1967 to 1982 offer summaries of the research available before their dates of publication (36–39). In addition, three expert opinion articles (15,16,41), two expert committee reports (13,14), and two case studies were found (42,43).

ESSENTIAL PHYSIOLOGIC PARAMETERS

Reasonable evaluation of the benefits or harms related to the timing of cord clamping requires a basic understand-

TABLE 1
Effects of Delayed Umbilical Cord Clamping on Neonatal Systems in the First Hours After Birth

<i>Parameters</i>	<i>Change*</i>	<i>Parameters</i>	<i>Change*</i>
Blood volume/components		Other cardiac effects	
Blood volume (7,36,51)	↑	Heart rate (53,55,63)	=
Red cell mass (7,36,51)	↑	Cardiac size (53)	↑
Plasma volume (7,36,51)	↑	Preejection period (60)	↑↓
Hematocrit (52,53)	=, ↑	Murmurs (53)	↓
Vascular pressures		Renal function	
Pulmonary artery (54,55)	↑	Glomerular filtration rate (56)	↑
Atrial pressure (54)	↑	Urine flow (56)	↑↓
Systolic blood pressure (53)	↑	Urinary sodium excretion (56)	↓
Blood flow		Respiration	
Renal blood flow (56)	↑	Respiratory rate (53,59,61)	↑, ↓
Cutaneous blood flow (57,58)	↑	Lung compliance (61,62)	↓
Systemic/pulmonary resistance (59)	↑	Function residual capacity (61,62)	↓
		Expiratory grunting (63)	↑, ↓

* ↑ = increased; ↓ = decreased; "=" = no change found.

ing of neonatal transitional physiology plus consideration of potential confounding factors. Approximately 110 to 115 mL/kg of blood are in the fetal-placental circulation at any point in time (44). Approximately 40% of the fetal cardiac output goes to the placenta per minute, whereas 8% to 10% goes to the fetus' lungs (45,46). The fetal lung is an organ of excretion producing up to 400 mL of amniotic fluid per day (47). During labor, the production of fluid decreases but does not cease. Thus, at birth, the newborn's lung must make immediate dramatic changes in both function and structure. The lung function must change from a fluid-producing organ in the fetus to one of gas exchange in the neonate. The lung structure must change from the fluid-filled state in the fetus to that of open gas-filled alveoli with excellent capillary circulation (48,49).

These dramatic changes are precipitated by a massive increase in blood flow to the lung—from 8% of the cardiac output in fetal life to 45% immediately after birth (46). The increased blood flow causes the pulmonary capillaries to become erect, thereby pulling open the alveoli and easing the entry of air (48,49). Immediate cord clamping limits access to the blood volume the infant needs to accomplish this huge task, because there is no reservoir within the body from which to draw. See Figure 1.

If the volume of blood in the capillary bed of the placenta is unavailable to the newborn because of early cord clamping, the necessary volume must be drawn from other organs, potentially causing their underperfusion. However, having lost placental support, all other organs must now function independently and need optimal perfusion as they begin vital functions essential for life. When the cord is not clamped, the umbilical circulation ceases when the umbilical arteries close and the cord stops pulsating. The umbilical arteries constrict

spontaneously when oxygen levels in the infant's circulating venous blood rise to more than 36 mmHg, paralleling the changes noted between fetal levels and neonatal levels of oxygen (50).

Table 1 provides an overview of the findings from several well-designed "controlled trials" completed before 1980 that examined the physiologic effect of delayed cord clamping on the newborn's systems in the first few hours of life (51–63). Most of the differences result from increased vasodilation and perfusion and include such findings as higher vascular pressures, higher peripheral temperatures, and increased renal blood flow. Many of these findings have been validated by the results from more recently completed trials.

Confounding Factors in Cord Clamping Studies

Events that occur during labor and birth, as well as measurement factors, may confound the results of research on cord clamping. Four birth-related factors in addition to the timing of cord clamping influence the speed and amount of placental transfusion at birth. They include the level at which the infant is held (64); the type and method of delivery (28,65); uterine contractions during third stage (66); and oxytocic use at birth (67).

Problematic measurement factors in studies include the difficulty in measuring blood volume, inaccuracy of the hematocrit in reflecting blood volume in hypoxic babies, and effects of capillary leak syndrome (16,68). Other factors occurring during labor that might decrease a neonate's blood volume at birth, but are beyond the scope of this article, include hypoxia (69), nuchal cord (42,70), and hypertonic uterine contractions.

Level Infant Is Held. Delaying cord clamping and keeping the infant at the level of the introitus for 45

seconds results in an 11% increase in blood volume, but a 24% increase in oxygen-carrying red blood cells, as shown in Figure 1 (7). Raising the infant significantly (30–60 cm) delays placental transfusion and lowering the infant 30 to 60 cm speeds the transfusion of blood from the placenta from 3 minutes to 1 minute (64).

Vaginal vs. Cesarean Birth. Because infants born by cesarean section tend to have lower blood volumes, the route of delivery must be noted in any study or review. Several authors have documented that placental transfusion occurs more successfully after vaginal birth than after a cesarean delivery (28,65). Narenda et al (28) found increased blood volume with delayed cord clamping at all births, but there was a smaller increase when preterm infants were born by cesarean section than when they were born vaginally.

Uterine Contractions. Uterine contractions after birth hasten the transfer of blood in the placenta to the baby (66). Occurring at regular intervals during third stage, they usually begin between 1 and 3 minutes postpartum (71).

Use of Oxytocic Drugs Immediately Postpartum. There are major differences in the use of oxytocics in the United States and Europe. Mothers in European studies are usually given oxytocic drugs immediately after delivery of the anterior shoulder (22,25) or after birth (17). In contrast, the usual practice in the United States is to wait until the placenta is delivered. The use of oxytocic drugs has been shown to speed up placental transfusion (67) to the infant, making it inappropriate to compare these infants with those whose mothers were not given oxytocic drugs until after the placenta delivered.

Method and Speed of Delivery. One birth practice common in the United States is to deliver the shoulders and body of the infant rapidly after birth of the head. This practice does not allow for the continued placental circulation that occurs while waiting for restitution and the next contraction. Delivering the shoulders and body immediately followed by rapid cord ligation results in significantly less placental transfusion at birth than the infant would receive with a slower, more physiologic birth.

Blood Volume Measurement. Currently, there is no direct, simple, accurate, and rapid way to measure blood volume. Blood volume has been measured by the tagging of one of its elements, such as albumin or red blood cells, with a tracer substance (44). Tagging red blood cells with nonradioactive chromium, or a similar substance, is the most accurate method; in fact, using red cell tagging, Faxclius found a 60% correlation between blood volume

and hematocrit in more than 290 neonatal intensive care unit admissions (68). However, it requires specialized equipment and more than 5 days to analyze, making the test of little use for clinical decision making (68,72). Albumin tagging with radioactive substances such as iodine (I^{125}) was used in several older studies (7,73–75); however, the practice is no longer considered ethical, now that danger of exposure to radioactive substances is known.

Capillary Leak Syndrome. Capillary leak syndrome occurs when hypoxia causes vascular endothelial integrity to be compromised (16). Failure of the capillary endothelium allows components of plasma such as salt, water, and albumin to leak from the intravascular circulation. Albumin leakage raises the colloid osmotic pressure on the extravascular side of the capillary membrane, pulling fluid out of the circulation and resulting in hemoconcentration that elevates hematocrit. Capillary leak syndrome masks hemoconcentrated hypovolemia, and, as a result, hematocrit can be an unreliable and misleading indicator of blood volume and adequacy of the blood for oxygen transport and tissue perfusion in the neonate (16,74).

RESULTS

Issues of Harm with Delayed Cord Clamping

The concerns regarding delayed cord clamping include the possibility of precipitating polycythemia, hyperviscosity, hyperbilirubinemia, and transient tachypnea of the newborn. Each of these variables is discussed in detail.

Polycythemia. Saigal and Usher (75) initially raised the concern about the potential for polycythemia with delayed cord clamping in 1977. They coined the phrase “symptomatic neonatal plethora” to describe a subgroup of babies with various times of cord clamping who either had hypervolemia or elevated hematocrit develop and were symptomatic. Polycythemia is defined as a venous hematocrit level greater than 65% to 70% (11,12) and has been associated with neurologic sequelae (9). Although clinical manifestations of polycythemia are nonspecific (76), Saigal reported such generalized symptoms as plethoric skin color, tachypnea, retractions, rales, cyanosis, grunting, hypotension, and hypoglycemia in addition to such neurologic symptoms as apneic spells, depression, and irritability (75). However, a 1992 randomized clinical trial found no differences in neurologic outcomes at 30 months when polycythemic infants and control infants returned for follow-up evaluation (77).

In the most extreme part of this protocol, term and preterm infants were held 30 cm below the introitus, and

cord clamping was delayed for 5 minutes. Hematocrit and blood volume were measured using radioactive iodine-tagged albumin at 4 hours of age. Of this group, none of the preterm infants had polycythemia develop, but two of the term infants had hematocrit levels greater than 70 at 4 hours, and one became symptomatic. Eleven preterm infants and three term infants were labeled “symptomatic,” although only one of the term and none of the preterm infants had an elevated hematocrit. The diagnosis of “hypervolemia” in the preterm infants was most likely due to capillary leak syndrome because the blood volumes listed for these infants were higher than plausible. This study is the only one found that suggests a link between delayed cord clamping and polycythemia and lacks the methodologic rigor found in later studies. The results have not been replicated.

Other causes for polycythemia are better documented than delayed cord clamping. Preexisting maternal conditions such as diabetes, preeclampsia, and hypertension increase the risk for chronic hypoxia in utero, and the resultant erythropoiesis may lead to polycythemia at birth. In a study of diabetic mothers, 5% of infants had polycythemia (78). Kurlat (79) found that the risk of polycythemia in appropriate-for-gestational-age infants of hypertensive mothers was 12.6-fold greater than that of the general population. Gruenwald (80) found higher residual placental blood volumes, despite higher hematocrits, in infants of preeclamptic mothers, indicating that preexisting hemoconcentration rather than placental transfusion was responsible.

Time of sampling and location of the blood draw may affect the results of hematocrit or hemoglobin studies. Shohat et al (81) assessed hematocrit over the first 16 hours in infants with cord clamping at 30 seconds and found a consistent elevation at 4 hours. However, all hematocrit levels returned to the birth level or lower by 16 hours. Oh and Lind (52) found that peripheral hematocrit was lower when drawn from warmed heels and remained higher than venous or arterial measurements.

The data from the randomized clinical trials and the “controlled trials” over the last two decades do not support the theory that delayed cord clamping causes symptomatic polycythemia, despite the fact that hematocrit levels are higher in late-clamped term and preterm infants. Symptomatic polycythemia was not found in the 531 late-clamped term infants in the studies or in any of the preterm infants. Only two infants, both asymptomatic, had hematocrit levels above 65%, and both had been lowered while clamping was delayed for 3 minutes (20). Other studies completed before 1980 reported no symptomatic polycythemia even when infants were held at the level of the perineum or lowered and cord clamping was delayed until pulsations ceased. One case report was found that attributed polycythemia to a water birth with delayed clamping (43). Because delayed cord clamping

occurs routinely at water births, this singular report requires more investigation. Currently, the American Academy of Pediatrics does not recommend routine examination of newborn’s hematocrit levels to check for polycythemia (82).

Hyperviscosity. Hyperviscosity, which often, but not always, accompanies polycythemia, is another concern raised by proponents of early cord clamping. Although earlier reports linked a hyperviscosity syndrome with poor neurologic outcomes (83), a later study failed to document any consistent pattern of damage (77). Blood transfusion and placental transfusion do increase whole blood viscosity in newborns. A marked rise in viscosity was found in late-clamped infants in two studies examining blood rheology (study of the flow of liquids and semisolids) (31,34). However, this increased viscosity was accompanied by a significant decrease in vascular resistance in the late-clamped newborn, resulting in increased pulmonary and generalized vasodilatation—essential components of a normal transition. Principles of physics governing flow of liquid through a tube state that viscosity must increase for a fluid to dilate the “tube” (in this case, arterioles and capillaries). Thus, an increased viscosity and a corresponding decrease in vascular resistance may be essential to effect the massive dilation of blood vessels required immediately after birth to adequately perfuse the lung and other organs. Examining only one parameter of blood rheology can be misleading, because checks and balances are essential to this intricate system.

Hyperbilirubinemia. Most infants experience some elevation of bilirubin. Elevated bilirubin levels are more common in preterm infants, whereas late-onset hyperbilirubinemia occurs frequently in term infants who are breastfed. Reports of hyperbilirubinemia from delayed cord clamping were found only in preterm infants in one older study (73); however, inclusion of some infants who were probably small for gestation age confounded the finding. Of note are the 409 term infants in four randomized clinical trials with delayed cord clamping who showed no significant differences in bilirubin levels compared with the babies with early clamping (20–23). In two of the trials, bilirubin levels of 12 mg/dL or more occurred more frequently in the late clamped infants but did not reach significance (22,23). The only trial to report any significantly elevated bilirubin levels was one of the “controlled trials,” which reported that 3 of 15 late-clamped babies had bilirubin levels greater than 15 mg/dL (34); all infants in both groups were breastfed, but no other information on age of the infants at the time of diagnosis, treatment plan, or outcomes was offered (34). Even for preterm infants, no significant differences are noted in bilirubin levels between the 123 babies in the

late-clamped groups versus the 124 babies in the early-clamped group in the seven randomized controlled trials (24–30).

Transient Tachypnea of the Newborn. Transient tachypnea of the newborn occurs soon after birth and is diagnosed by mild cyanosis, grunting, retracting, flaring, and tachypnea (84). The origin is believed to be from delayed reabsorption of lung fluid, because it is seen more commonly in infants born by cesarean section or after prolonged labor. The studies reviewed here show no indications of harm caused by transient tachypnea, although respiration rates are increased in babies with delayed cord clamping. The higher respiratory rates reported in late cord-clamped infants (59,61) are thought to be a result of greater pulmonary vascular filling, necessitating more shallow rapid breathing. Yao et al (63) found increased grunting in 7 of 33 late cord-clamped newborns but reported that it disappeared within 3½ hours in the infants without sequelae or treatment. It is important to note that these infants were observed away from their mothers and were not offered the opportunity to suckle during the first 2 hours of life, thus creating a less than ideal transition to extrauterine life. Allowing a newborn to suckle has been shown to improve oxygenation and lowering of the heart rate (85); thus, suckling should, theoretically, improve respiratory transition and reduce signs of grunting. Unfortunately, no studies on the effect of suckling on respiratory rates were found.

Beneficial Effects of Delayed Cord Clamping

Does delaying cord clamping at the time of birth lead to benefits for term or preterm infants compared with immediate or early cord clamping? Although most of the randomized controlled trials and “controlled trials” involve small numbers of subjects and need replication, several important findings are suggested.

Hematologic Benefits. Hematologic benefits were seen for delayed cord clamping in term and preterm infants. For term infants, improvements of higher hematocrit levels at 2 months of age and a trend toward increased ferritin levels are especially important findings (20,21). Anemia may have a larger impact on the normal development of infants than is currently realized. Lozoff and colleagues (86–88) report findings of altered central nervous system development in children who had iron deficiency anemia as infants. These results were evident in children as young as 6 months of age and persisted in these same children when reevaluated at 10 years of age (86–88). Lozoff (89) believes that iron is an important nutrient for myelination, which is occurring at a rapid pace during infancy and early childhood. Hematologic

improvements for preterm infants include higher hematocrit and hemoglobin levels and a corresponding reduction in the need for transfusions in the first 4 to 6 weeks of life.

The World Health Organization expert committee report (13), the American Academy of Pediatrics statement on cord blood collection (14), and one expert (41) stress prevention of anemia as a reason to delay cord clamping. Even with the small numbers in the current study on anemia, the findings indicate a beneficial effect of delayed cord clamping and support the need for further study.

Cardiopulmonary Benefits. Cardiopulmonary benefits of delayed cord clamping suggest better pulmonary and systemic vasodilatation and higher red blood cell flow to the brain, body, and intestines for all babies (26,32). For preterm infants, these findings support increased blood pressures (24,26,27), better cardiopulmonary adaptation with less need for oxygen and fewer days of ventilation (18), and decreased need for transfusions (24,25). Better capillary filling (58), higher peripheral temperatures (57), and greater urine output (56) have been documented in term infants because of increased perfusion from delayed cord clamping. Increased vasodilatation accompanies increased perfusion and is especially important in the hemodynamics of neonatal lung adaptation. Lack of adequate vasodilatation in the lungs of newborns is a characteristic of persistent pulmonary hypertension whose cause remains unknown. Increased vasodilatation supports increased blood pressure, adequate peripheral perfusion, and improved perfusion of organ systems.

Potential Behavior Effects. An important potential behavioral effect from delayed cord clamping is suggested in the finding of increased early breastfeeding duration in the Oxford Midwives’ study (22). This study was the first to look at breastfeeding duration in delayed and early clamped babies and did so only as a secondary dependent variable. More mothers in the delayed clamping group were still breastfeeding at 10 to 12 days postpartum ($p < .05$). It is important to note that of the 296 babies assigned to the delayed clamping in this study, 32 had early clamping because of intrapartum problems. Because the data were analyzed according to the intent-to-treat protocol, 32 babies with early clamping who were assigned to the late group were analyzed as part of the late group. This intent-to-treat analysis would reduce the significance of the differences in breastfeeding rates between groups.

This randomized controlled trial examined the differences in babies with cord clamping at 1 versus 3 or more minutes. At 1 minute, babies may have received 50% of their placental transfusion. The fact that the early group

had cord clamping at 1 minute, and thus potentially more blood volume, would also decrease significance of effects from cord clamping interval between babies in each group.

Based on a study that found better perfusion of and circulation to the gut after late clamping (32), further study is warranted to assess whether the improved perfusion results in better digestion with less abdominal discomfort and less crying. If so, fewer mothers may abandon breastfeeding in the early stages.

In summary, hematologic benefits found in the studies reviewed earlier include findings of increased hematocrit and hemoglobin levels (20,24,26), blood pressure (27), and blood volume (28), and the reduced need for transfusions in the first 4 to 6 weeks in preterm infants (24,25); cardiopulmonary benefits consist of better adaptation with fewer days of oxygen and ventilation needed for preterm infants and higher red blood cell flow to vital organs in the first few days of life for all babies (26,32); behavioral benefits suggested by the randomized controlled trials were increased duration of early breastfeeding for infants with delayed cord clamping of at least 3 minutes duration compared with early clamped infants (22).

Are There Harmful Effects of Immediate Clamping?

The studies reviewed did not reveal obvious or direct harm from immediate cord clamping in either term or preterm infants, except for an increase in anemia of infancy. It is important to note that none of the studies examine any long-term sequelae. The delay interval of 30 to 45 seconds in preterm infants may be too short to assess the full potential benefits and reduction of harm that may be achieved with a longer delay. A large multisite randomized controlled trial involving 300 preterm subjects has just been completed in Europe (Wardrop, Scotland, 2001, personal communication). This study's protocol involved a delay of 60 to 90 seconds with preterm infants lowered 30 cm. Analysis of the data will indicate whether a longer delay provides additional benefits. The analysis of the data should be completed and distributed by early 2002.

Does denial of 25% or more of an infant's blood volume create any damage? There is one study using an animal model that suggests harm from blood loss at birth. Rajnik and colleagues (90) removed approximately 25% of newborn rat pup's blood volume immediately after birth. There was no other intervention. The authors reported finding proinflammatory cytokines in the lungs and liver at 3 hours of age in the rat pups who had blood removed; rat pups with no loss of blood had no cytokines present in their organs. Proinflammatory cytokines are important markers for tissue damage and, thus, indicated

damage to the rat pup's lung and liver from removal of 25% of its blood volume. Figure 1 shows a reduction of approximately 30% in an infant's blood volume from immediately clamping. Proinflammatory cytokines have been found to be significantly higher in early blood samples from babies who later have cerebral palsy develop (91). Consequently, these cytokines may be important markers to use in examining the effect of various obstetric practices on infant outcomes. This study by Rajnik et al (90) documents that the denial of 25% of rat pup's blood volume alone, without any other intervention, elevated proinflammatory cytokines in the first 3 hours after birth. These findings lend support to the importance of reexamination of effects of immediate cord clamping in human infants.

DISCUSSION

For all but the last 50 to 100 years of human existence, it is highly likely that the umbilical cord of a newborn infant pulsated until it closed spontaneously. Along with important advances in obstetrics and neonatology, the current practice of immediate cord clamping has evolved in many institutions without adequate study of its potential short-term and long-term effects. The literature contains many unsubstantiated references to the fact that delaying cord clamping leads to a variety of harmful effects. Currently, the belief that delayed cord clamping causes polycythemia is so prevalent that one often finds it stated in the literature as an accepted fact not needing scientific references (10–12,76). The idea that delayed cord clamping is harmful is not supported by the findings from the 16 randomized controlled trials and 5 "controlled trials" completed over the last two decades involving term and preterm infants and reviewed here. See Appendices A and B.

Implications for Practice

Delayed cord clamping is consistent with gentle, physiologic birth. During the delay, the infant may be placed on the mother's abdomen with no obvious harm noted with a delay of 3 or more minutes (23,31–35). The trials verified that increased blood volume occurs even when the infant is placed on the maternal abdomen and cord clamping is delayed 3 or more minutes. Figure 1 shows that maximum transfusion occurs in 3 or more minutes. One other finding should be noted. A study was conducted in Israel to find how to maximize cord blood harvesting (92). The author found that if the infant was placed on the abdomen and the cord was clamped in 30 seconds, 80 mL of cord blood could be collected. If the infant was placed on the obstetrician's lap (lowered), only 30 mL was obtained when the cord was clamped at 30 seconds. The authors implied that no harm was done,

because hemoglobin levels were not significantly different at 24 hours. As stated earlier in the article, hemoglobin and hematocrit are not alone reliable indicators of harm or benefit from delayed cord clamping. However, if it is necessary to clamp the cord early and the CNM/CM wants to maximize the transfusion, then one should hold the infant lower than the placenta for the brief interval involved. This study has implications for placement of distressed babies who may be in greater need of blood volume (49). Any baby at risk for hypovolemia (very pale or mottled) can be lowered for 30 seconds to 1 minute before being placed on the abdomen or before the cord is clamped.

Implications for Research

Whether delayed cord clamping influences breastfeeding duration or other behavioral outcomes is an important question that needs to be examined in more detail, and the findings need to be replicated. The benefits to infants and mothers from breastfeeding are significant. Every effort should be made to ensure that birth practices are not contributing to breastfeeding difficulties.

Replication of the study by Grajeda et al (20) showing an association between immediate clamping and anemia in early infancy is important, and longitudinal follow-up should be added. The studies by Lozoff and colleagues (86–89) revealing behavioral and development problems in older children who experienced anemia in infancy adds urgency to the importance of repeating and lengthening this study to include examination of neurobehavioral development. Relatively noninvasive biologic research, such as measuring cytokines at birth, at 3 hours, and at later intervals in infants with immediate and delayed cord clamping, will tell us whether the rat pup's vulnerability is unique to that species or might affect our own.

All of the studies involving preterm infants have a relatively small number of subjects and need to be replicated and validated with larger samples of infants. Few deal with follow-up beyond 4 to 6 weeks. Studies examining progress and outcomes during the neonatal intensive care unit stay for preterm infants and follow-up beyond infancy are indicated on the basis of current findings.

CONCLUSIONS

Immediate clamping of the umbilical cord is an intervention that has developed in this country over the last century as birth moved into the hospital setting and represents the antipathy of the noninterventionist philosophy typical of midwifery care. None of the studies conducted before 1980 recommend immediate cord clamping—the most conservative recommendations

were to delay 1 to 1½ minutes even for preterm infants (55,73). However, in our well-intended haste to transfer an infant to the pediatric staff, we may be denying the infant a significant part of his vital blood supply while placing him or her at risk of hypovolemia and resulting damage.

In this review of the literature, no cause for concern of harm is shown in more than 500 term infants enrolled in randomized controlled trials and “controlled trials” whose cords were clamped between 3 and 10 minutes, or when pulsations ceased. Indeed, one finds that benefits are clearly documented for preterm infants and suggested for term infants. There is no evidence that early cord clamping is better, and evidence is lacking regarding long-term harm from immediate or delayed cord clamping. Until we have sufficient appropriate evidence showing otherwise, it is better to mimic nature than to interfere with the intricate, complex, and only partially understood design of the physiologic neonatal transition.

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APPENDIX A
LITERATURE ON CORD CLAMPING IN FULL-TERM INFANTS RANDOMIZED (4) AND NONRANDOMIZED (5) CONTROLLED TRIALS

<i>Authors, Year</i>	<i>Study Population</i>	<i>Cord Management Placement of Infant</i>	<i>Sample Size</i>	<i>Results</i>	<i>Comments</i>
Grajeda, Perez-Escamilla, & Dewey 1997 (20)	≥37 wks, ≥2,000 g, singleton vaginal deliveries. no GD, AP hemorrhage, CPD or other anomalies	EC: immediately LC: at end of pulsation, infant at level of placenta LC: after pulsations, infants held below introitus	21 26 22	At 2 mo, 88% of infants with delayed CC had Hcts > 0.33 versus 42% in the early group ($p = .001$). No differences between two late groups.	Recommends delay in CC as a feasible low-cost intervention that can reduce anemia in developing countries. No differences in polycythemia or jaundice. Two babies with Hcts > 65% were asymptomatic.
Geethanath, Ramji, Thirupuram, Rao, 1997 (21)	Term, vaginal births, mothers with Hgb >10 g/dL	EC: immediately LC: after placenta in vagina; infant lowered <10 cm	48 59	Mean ferritin higher in LC: 73.6 ng/mL vs 55.7 ng/mL but did not reach significance level as set by PI.	Set difference for significance at 30 ng/mL of ferritin. Did not report other variables.
Oxford Midwives Research Group-Healey, Greenish, Armstrong, & Ayers, 1991 (22)	37–42 wks, vertex, vaginal delivery, no AP complications	EC: stat or ≤1 min LC: after 3 min or when pulsations stopped, infant on abdomen	256 296	No significant difference in any variable except higher rates of continued BF at 10–12 days among mothers in LC group ($p = .05$).	Largest sample ever studied. No significant difference in jaundice. Highest BR levels = 12 mg/dL. 32 babies in LC group had early clamping (intent-to-treat analysis).
Nelson, Enkin, Saigal, Bennett, Milner, & Sackett, 1980 (23)	Low OB risk, >37 wks, wanted Leboyer birth, would attend prenatal classes	EC: <60 sec LC: after pulsations ceased, baby on maternal abdomen	26 28	No differences on any variable except mothers' opinion at 8 mo that the birth influenced the child's behavior ($p = .05$).	Found that Leboyer method was not unsafe. Found no differences in polycythemia or jaundice.
Nelle, Kraus, Bastert, & Linderkamp, 1996 (31)	30 FT neonates: from normal pregnancies and labors	EC: <10 sec LC: >3 min, infant on maternal abdomen	15 15	Hcts were higher in LC ($p < .05$). Preejection period ratios indicated higher systemic and pulmonary resistance on day 1 and same as EC babies on day 5.	Findings suggest more pronounced pulmonary vasodilatation in the LC group in the first 5 days.
Nelle, Zilow, Bastert, & Linderkamp, 1995 (32)	30 FT neonates: from normal pregnancies and labors	EC: <10 sec LC: >3 min, infant on maternal abdomen	15 15	LC: BV 32% higher. Blood viscosity increased at 4 h by 32%; vascular hindrance 25% lower; RBC flow to brain and intestines 25% higher day 1 and 10% higher on day 5.	Higher viscosity offset by lower vascular hindrance (marked vasodilation). Authors state EC deprives infants of placental transfusions and increase risk of hypovolemia and anemia.
Nelle, Zilow, Kraus, Bastert, & Linderkamp, 1993 (33)	Healthy, term, vaginal deliveries, pH ≥7.25, Apgar scores 9/10, all breastfed	EC: <10 sec LC: >3 min, infant on maternal abdomen (Leboyer method)	15 15	Residual placental blood volume higher in EC infants; Hct rose from 49% at birth to 58% at 2 h, 56% at 24 h, and 54% at 120 h. Viscosity increased by 32% in LC at 2 h with no further change.	Example: For 3-kg infant: EC = 135 mL in placenta, 210 mL in baby. LC = 75 mL in placenta, 270 mL in baby. See Nelle 1995 for discussion of viscosity.
Linderkamp, Nelle, Kraus, & Zilow, 1992 (34)	39–40 wks, normal EFM, pH >7.25, Apgars 9/10, AGA, 3,390–3,620 g	EC: <10 sec. LC: at 3 mins, infant held at introitus	15 15	RBPV = 15 vs 47 mL/kg in EC; Hct increased at 2 h; blood viscosity at 2 hs 40% higher; 3/15 with elevated BR over 15 mg/dL. All breastfed.	LC results in marked rise of blood viscosity caused by fluid shifting out of vascular space. No infants had any clinical symptoms. See Nelle 1995 re: viscosity.
Kliot & Silverstein, 1984 (35)	Normal FT infants, from private practice	EC: <60 sec LC: >10 min on maternal abdomen Control: CC <60 sec	39 40	No significant difference in temperature, heart rate, Hct, BR, pH, Apgar scores, or other variables.	Completed random assignment to two Leboyer groups. Validated safety of Leboyer-type delivery.

AP = antepartum; BF = breastfeeding; BR = bilirubin; BV = blood volume; CC = cord clamping; CL = lung compliance; CPD = cephalopelvic disproportion; C/S = cesarean section; EC = early clamping; FT = full term; GD = gestational diabetes; GFR = glomerular filtration rate; Hct = hematocrit; HR = heart rate; LC = late clamping; PT = preterm; RBC = red blood cell; RBPV = residual placental blood volume; RR = respiratory rate; VD = vaginal delivery.

APPENDIX B
LITERATURE OVERVIEW OF CORD CLAMPING IN PRETERM INFANTS (RANDOMIZED CONTROLLED TRIALS: 7 FOUND)

<i>Authors, Year</i>	<i>Study Population</i>	<i>Cord Management Infant Placement</i>	<i>Sample Size</i>	<i>Significant Results</i>	<i>Comments</i>
Ibrahim, Krouskop, Lewis, Dhanireddy, 2001 (24)	500–1,250 g, 24–29 wks, all vaginal births	EC: stat LC: at 20 sec; at introitus	16 16	LC: improved mean BP (.01); Less use of albumin (.03); Higher RBCs (.003), Hct (.01, mean = 50%), Hgb (.0002); Fewer transfusions (.001) over 4-wk period, higher 5-min Apgar scores.	No significant difference in BR in spite of higher hct; decrease in transfusions is cost effective and safer. Study was of 4 wks duration.
Rabe, Wacker, Hulskamp, Franz, Everding, 2000 (25)	Singleton, <33 wks	EC: 20 sec LC: 45 sec and lowered 20 cm + oxytocic	20 19	9 (LC) vs 16 (EC) transfused by day 42 ($p = .05$), OR 0.56 (CI .34– .94).	All mothers got oxytocic immediately after delivery; concludes that anemia of prematurity can be decreased by delayed cord clamping.
Nelle, Fischer, Conze, Beedgen, Linderkamp, 1998 (26)	C/S, \leq 1,200 g, \leq 30 wks	EC: stat LC: at 30 sec; infants held 30 cms below placenta	8 11	LC = higher mean BP, systemic vascular resistance, Hgb, systemic and cerebral Hgb transport. EC Group required more volume expansion in first 24 h.	LC resulted in sig. findings of most variables even with this small sample.
Rabe et al 1998 (27)	<33 wks	EC: 20 sec LC: 45 sec	15 15	BP: 10 (66%) of EC and 6 (40%) of LC had BP <30 mmHg in first 24 h.	LC can help prevent low BP and low microcirculation.
Narenda et al 1998 (28)	24–31 wks	EC: routine LC: \geq 30 sec; lowered 30 cm, + oxytocic	23 23	LC: BV increased by 8–19 mL/kg overall: Vaginal births = 10–28.4 mL/kg increase; C/S = 2–16.4 mL/kg increase.	BV increased by 30 sec delay, most pronounced in VD. Analyzed by actual treatment, not intent-to-treat, subgroup of larger RCT.
McDonnell & Henderson-Smart, 1997 (29)	NVD and C/S, 26–33 wks. twins	EC: stat LC: 30 sec: on maternal abdomen	24 22	Trend toward higher hct in LC infants but did not reach statistical significance. Delayed CC at C/S feasible.	Recommends to delay CC for more than 30 sec in trials and that infants be lowered in relation to the uterus.
Kinmond et al, 1993 (30)	SVDs 27–33 wks	EC: routine, stat or early, < 10 sec LC: 30 sec; 20 cm below introitus	19 17	Initial PCV higher in LC (.0013) and fewer RC Tfxs (.03). In ventilated infants: higher A-a O ₂ tension (.02), less supplemental O ₂ (.009). No difference in bilirubin levels.	Study is being replicated, and results should be available mid 2002. Overlapping outliers in each group.