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Policy Adherence and Neonatal Outcomes Following Implementation of a Delayed Cord Clamping Protocol for Premature Neonates

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Abstract

Objective: Delayed cord clamping (DCC) confers known benefits to premature infants; however, protocols often have variable adherence and exclusion criteria. This study evaluates adherence to a newly-implemented protocol, describes factors associated with DCC versus immediate cord clamping (ICC), and evaluates subsequent neonatal and maternal outcomes.

Methods: This is a retrospective cohort study of preterm singletons delivered between 24 and 37 weeks gestation over18 months following implementation of a DCC protocol. Neonates were categorized based on time from delivery to umbilical cord clamping: ICC (<30 seconds), DCC (>/= 30 seconds). The primary outcome is adherence to the implemented delayed cord clamping protocol (percent of eligible neonates receiving DCC). Secondary outcomes (neonatal hematocrit in the first 48 hours, peak bilirubin, phototherapy requirement, incidence of intraventricular hemorrhage, and maternal blood loss) were also evaluated. Data was analyzed with Stata version 15, using the chi-square or Student's t-test.

Results: Of 481 cases eligible, 466 met inclusion criteria. Forty-nine percent of eligible neonates received DCC. DCC was more common in vaginal than Cesarean deliveries (65.2% vs. 21.2%, p<0.01). A lower percentage of neonates born prior to 32 weeks received DCC (28.0% vs. 37.1%, p=0.06). The DCC cohort had higher 1-minute (6.8 vs. 5.5, p<0.01) and 5-minute APGAR scores (8.2 vs. 7.2, p<0.01). Neonatal hematocrit was higher following DCC than ICC (49.1vs. 47.9, p=0.10 respectively), without a significant difference in bilirubin or phototherapy requirement. DCC was not associated with increased blood loss at time of delivery.

Conclusion: Following protocol implementation, less than half of eligible neonates received DCC. A lower percentage of neonates born prior to 32 weeks received DCC, despite evidence supporting the benefits. There was a trend towards significance regarding increased hematocrit after DCC, without increased bilirubin or phototherapy requirement. Further investigation into the safety of exclusion criteria and efforts to support DCC during Cesarean deliveries is warranted.

Keywords: Delayed cord clamping; Premature neonates; Neonatal hematocrit; Neonatal bilirubin

Introduction

Delayed clamping of the umbilical cord has long been recognized for its beneficial effects on hemodynamic stability among preterm neonates. In 2017, the American College of Obstetricians and Gynecologists extended their recommendation for delayed cord clamping (DCC) to include full-term neonates as well as preterm infants [1]. In an era where high-tech, resource-intensive medical and surgical advances have allowed for the resuscitation of neonates at increasingly early gestational ages, DCC remains a relatively simple yet under-utilized intervention.

The benefits of 30-60 seconds of DCC following delivery of premature infants stems from the idea that following delivery a significant amount of blood, approximately 80cc, is retained in the placenta and flows into the neonate through the umbilical cord during the first minute of life [2]. Indeed, some of the strongest evidence supporting DCC is related to this enhanced hemodynamic stability: increased hemoglobin and hematocrit, increased mean arterial pressure, and decreased need for packed RBC transfusions through 9 weeks of life [3-5]. Perhaps one of the most important and well-supported benefits of DCC is a decrease in intraventricular hemorrhage (IVH), a devastating condition associated with high morbidity and mortality [6].

Evidence does not support many of the theoretical risks attributed to DCC. The most explored complication of DCC is an increased risk of hyperbilirubinemia secondary to the higher red blood cell load. Studies have consistently shown higher levels of bilirubin in neonates who received DCC; however, there is a lack of definitive data suggesting that this leads to an increased phototherapy requirement [3,5,7-9]. Other potential complications of DCC that have yet to be borne out in the literature include neonatal hypothermia, increased risk of maternal hemorrhage, and a delay in neonatal resuscitation [8].

However, despite strong evidence favoring the benefits of DCC and a dearth of proven risks, studies show that approximately 50% of preterm infants do not receive DCC [10]. The low frequency of this intervention is often due to reasons such as variation in guidelines, inconsistent policy implementation, and extensive and/or unclear exclusion criteria [11,12].

The aims of this study were 1) to assess patterns of adherence to a newly-implemented DCC protocol, 2) to describe factors associated with performance of DCC versus immediate cord clamping (ICC), 3) to evaluate neonatal outcomes, specifically hematocrit, bilirubin level, phototherapy requirement, intraventricular hemorrhage (IVH), and 4) to compare maternal blood loss at delivery following the implementation of a DCC protocol at a large academic center. Our primary outcome was neonatal hematocrit in the first 48 hours of life, and secondary outcomes included: percent of eligible neonates receiving DCC, peak bilirubin in the first 7 days of life, days of phototherapy, incidence of intraventricular hemorrhage, and maternal estimated blood loss at the time of delivery.

Materials and Methods

This is a retrospective cohort study of all preterm singleton infants born between 24 and 37 weeks gestation at a single tertiary care center between July 1, 2014 and December 31, 2015, immediately following the implementation of a DCC protocol. Outcomes for infants and mothers who underwent immediate cord clamping were compared to those who underwent delayed cord clamping during this time period. Prior to implementation, there was no formal DCC policy governing the attending, resident, or private-practice physicians who delivered at this academic center. The protocol for this study was approved by the Johns Hopkins Institutional Review Board.

The study population included women who delivered in the Johns Hopkins Labor & Delivery unit and their neonates. The collection time of 18 months was based on other implementation studies that support evaluation at or beyond 12 months [13,14]. The policy recommended initial assessment by the obstetric provider (and NICU provider, if present) to determine appropriateness of DCC, followed by30-60 seconds of delayed cord clamping at or below the level of the placenta (as timed by the bedside nurse) for neonates born between 24 and 37 weeks.

Exclusion criteria for DCC was jointly established by a group of obstetricians and neonatologists, and included the following: mono-chorionic twins, twins with growth discordance greater than 25%, IUGR less than the 10th percentile with evidence of circulatory compromise (e.g. absent or reverse end diastolic flow), neonates requiring immediate resuscitation, hydrops fetalis, red blood cell alloimmunization, congenital diaphragmatic hernia, abdominal wall defects, neonates receiving comfort care only after birth, infants of diabetic mothers with poor glycemic control (e.g. macrosomia with an estimated fetal weight greater than the 90th percentile), or history of a sibling with severe hyperbilirubinemia. Additionally, the obstetrician could consider performing ICC due to neonatal concerns (e.g. fetal distress, presence of meconium-stained amniotic fluid) or maternal complications (e.g. short umbilical cord, premature placental separation, significant maternal bleeding).

Data were manually extracted by the authors from the electronic medical record system. Data collection included demographics and outcome variables. Information regarding performance of delayed cord clamping as well as length of delay was recorded by nurses in the electronic medical record at the time of delivery. Additional data regarding demographics, prenatal and delivery information, and neonatal outcomes were obtained from hospital medical records as well as the Vermont Oxford Network database.

Data was analyzed with Stata version 15, using the chi-square test for dichotomous outcomes and a Student's t-test for continuous variables. Differences with $P<0.05$ were considered statistically significant and all tests were two-sided.

Results

Protocol adherence

A total of 481 singleton neonates met inclusion criteria for this study, of whom 15 were excluded due to cord milking or insufficient delay of cord clamping. Of the remaining466 neonates 64.4% met criteria for DCC, of whom 49.3% ultimately received DCC. All neonates were subsequently classified into one of the following groups: 1) DCC indicated and DCC received, 2) DCC indicated and ICC received, 3) ICC indicated and ICC received, 4) ICC indicated and DCC received (Figure 1).

Baseline characteristics

Maternal characteristics including age, parity (nulliparity vs. multiparity), and use of antenatal steroids or assisted reproductive technology were not significantly different between those who received immediate vs. delayed cord clamping (Table 1). Mode of delivery was predictive of immediate vs. delayed cord clamping. Neonates born by spontaneous vaginal delivery (including operative vaginal delivery) were significantly more likely to receive DCC than those born by Cesarean delivery (65.2% vs. 21.2%, respectively, $p<0.01$) (Table 1).

There was a trend towards significance with regards to gestational age at delivery, where neonates born on or after 32 weeks 0 days

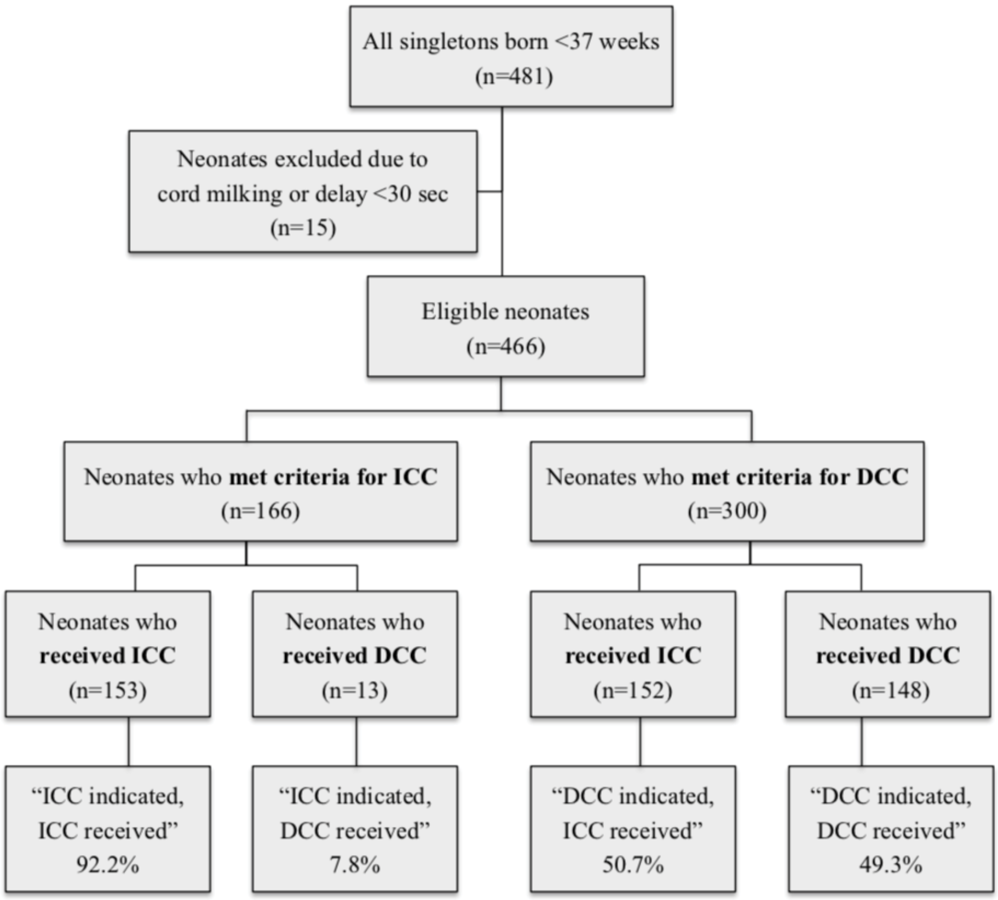

Figure 1: Flowchart of study population and type of cord clamping performed.

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Table 1: Baseline characteristics of study population and type of cord clamping performed.

Characteristic	Immediate (ICC) n=305	Delayed (DCC) n=161	*p* value
Maternal age (years)	29.1	30.1	0.12
Multiparous	155 (50.8%)	75 (46.6%)	0.25
Gestational age	-	-	-
24w0d – 31w6d	90 (72.0%)	35 (28.0%)	
32w0d – 36w6d	214 (62.9%)	127 (37.1%)	0.06
Mode of delivery	-	-	-
Vaginal (spontaneous or operative)	97 (31.8%)	105 (65.2%)	
Cesarean	208 (78.8%)	56 (21.2%)	<0.01
Received antenatal steroids	157 (51.6%)	74 (46.3)%)	0.27
Assisted reproductive technology	14 (4.6%)	9 (5.6%)	0.64
Weight (g)	-	-	-
<1000	40 (13.1%)	9 (5.6%)	
1000-1500	38 (12.5%)	15 (9.3%)	
>1500	227 (74.4%)	137 (85.1%)	0.02
Apgar score (1 minute)	5.5	6.8	<0.01
Apgar score (5 minute)	7.2	8.2	<0.01

Data are reported as mean or as n (%).

Reasons cited for deferring DCC	N
Fetal distress or immediate resuscitation	68
Apgar 0-2, infant appearance	21
Neonatologist/pediatrician's request	5
Not feasible (en caul delivery, immediate placental delivery)	4
Congenital anomaly or planned immediate intervention	3
General anesthesia	1
Reason not given	4
Intrauterine growth restriction (IUGR)<10th percentile	23
IUGR with circulatory compromise	18
IUGR without circulatory compromise	5
Infant of diabetic mother	23
Abruption or maternal bleeding	30
Alloimmunization	2
Abdominal wall defect	7
Reason not documented	155
Other	21

Figure 2: List of justifications cited by providers for deferring delayed cord clamping (DCC), with some providers providing more than one such justification.

gestation were more likely to receive DCC than those born before 32 weeks (37.1% vs. 28.0%, respectively, p=0.06). Neonates with birth weights >1500g were also significantly more likely to receive DCC (p=0.02). Average 1-minute and 5-minute Apgar scores were higher among neonates who received DCC (p<0.01) (Table 1).

The most commonly cited reasons for immediate cord clamping included fetal distress, need for immediate resuscitation, abruption or excessive maternal bleeding, IUGR, and infant of a diabetic mother (Figure 2). Among cases where DCC was deferred due to fetal distress or need for immediate resuscitation, low Apgar score and infant appearance accounted for 31%.

Neonatal outcomes

Mean hematocrit for neonates receiving DCC was higher than ICC (49.1 ± 7.4 vs. 47.9 ± 6.9, respectively), however, the observed difference is not statistically different as we observed from the p-value(p=0.1). There was no difference in peak bilirubin levels or days of phototherapy requiredfor neonates who received DCC vs. ICC (Table 2). The incidence of intraventricular hemorrhage was lower among neonates receiving DCC than (4.9% vs. 9.5%, respectively, p=0.085); however, this did not reach statistical significance.

Table 2: Comparison of selected neonatal and maternal outcomes among cases of immediate cord clamping (ICC) vs. delayed cord clamping (DCC).

	ICC	DCC	P
Neonatal hematocrit (%)	47.9 ± 7.4	49.1 ± 6.9	0.10
Peak bilirubin (mg/dL)	9.5 ± 8.0	9.7 ± 7.7	0.81
Days of phototherapy	6.7 ± 21.3	5.9 ± 20.1	0.69
Intraventricular hemorrhage	29 (9.5%)	8 (4.9%)	0.085
EBL, vaginal delivery (mL)	323 ± 181	309 ± 142	0.57
EBL, Cesarean delivery (mL)	1168 ± 1517	824 ± 274	0.10

EBL, estimated blood loss.
Data are reported as "mean ±standard deviation" or as n (%).

Subgroup analysis of neonatal outcomes was then performed based on type of cord clamping indicated by protocol and type of cord clamping ultimately performed. The following cohorts were defined: 1) DCC indicated and DCC received, 2) DCC indicated and ICC received, 3) ICC indicated and ICC received, 4) ICC indicated and DCC received (Table 3).

In cases where DCC was indicated, there was no significant difference with regards to neonatal hematocrit, peak bilirubin level, or phototherapy requirement between neonates who ultimately received ICC vs. DCC.

In cases where ICC was indicated, hematocrit among neonates who ultimately received DCC was higher than hematocrit among those who appropriately received ICC (52.1 vs. 48.4, respectively, p=0.08), though this did not reach statistical significance. Furthermore, when ICC was indicated but DCC was performed, there was no significant increase in peak bilirubin or phototherapy requirement (Table 3).

Maternal blood loss

For both vaginal deliveries and Cesarean deliveries, delayed cord clamping was not associated with an increase in estimated blood loss (EBL) at time of delivery (Table 2).

Discussion

Delayed cord clamping has proven health benefits for premature neonates; however, theoretical concerns regarding increased hematocrit and risk of hyper bilirubinemia, as well as lack of data regarding

Table 3: Select neonatal and maternal outcomes in cases where ICC vs. DCC was indicated, further stratified by whether ICC or DCC was ultimately performed.

	Immediate cord clamping (ICC) indicated			Delayed cord clamping (DCC) indicated		
	ICC performed n=153	DCCperformed n=13	P	ICC performed n=152	DCC performed n=148	P
Neonatal Hct (%)	48.4	52.1	0.08	47.4	48.8	0.10
Peak bilirubin (mg/dL)	9.3	8.7	0.80	9.6	9.7	0.90
Apgar score (5 min)	6.6	7.4	0.24	7.8	8.3	<.01
Phototherapy (# days)	6.2	2.3	0.50	7.28	6.2	0.67
Intraventricular hemorrhage (n, %)	18 (11.8%)	2 (15.4%)	0.70	11 (7.2%)	6 (4.1%)	0.23
EBL SVD (mL)	314	250	0.13	328	314	0.63
EBL CS (mL)	1145	867	0.57	1197	819	0.15

Hct, hematocrit.

specific conditions that may make neonates poor candidates for DCC, have contributed to gaps in DCC performance even among those preterm neonates for whom DCC data and recommendations have been longstanding. Furthermore, these vulnerable premature neonates may stand to gain significant benefit from additional transplacental blood transfusion. This study aimed to explore these gaps by assessing patterns of adherence to the new DCC protocol, exploring factors associated with DCC performance, and evaluating neonatal outcomes following DCC during the period following implementation. Although we did not demonstrate a statistically significant increase in hematocrit of infants undergoing DCC, our study supports the safety of expanding DCC protocols to include frequently excluded neonates, and highlights factors associated with significantly lower rates of DCC, including Cesarean delivery, birth weight <1500g, and lower Apgar scores

In the 18 months following protocol implementation, only 34.5% of neonates born between 24 and 37 weeks' gestation received DCC. Furthermore, 35.4% of neonates did not receive the type of cord clamping for which they met criteria. These numbers are lower than those reported by a similar study by Liu et al, which reported DCC in over 50% of neonates born before 32 weeks' gestation following protocol implementation [10]. This is likely due, in part, to our institution's broader exclusion criteria. Non-adherence to protocol occurred most commonly when DCC-eligible neonates received ICC.

Our findings suggest that delayed cord clamping of 30 to 60 seconds following delivery is associated with higher neonatal hematocrit (though this did not reach statistical significance) without increased rates of polycythemia, echoing previously published data [3,10]. Furthermore, DCC is not associated with significantly increased bilirubin levels or need for phototherapy.

Neonates weighing less than 1500g were significantly less likely to receive DCC. These findings may be partially explained by a higher incidence of fetal anomalies (either necessitating or triggering a preterm delivery) or a higher likelihood that a premature neonate may appear in distress or otherwise in need of immediate resuscitation, both of which could lead to ICC. Nonetheless, our results suggest that premature infants who may benefit the most from DCC are less likely to receive it.

Apgar scores were significantly higher in the DCC group; however, this is likely a reflection of more vigorous infants being granted the delay in resuscitation needed for DCC while more pale or hypotonic infants were not. Low Apgar score and poor neonatal appearance were commonly cited reasons for deferring DCC. Further investigation is warranted into the relative benefits of DCC versus immediate neonatal resuscitation in such cases.

The rate of DCC was significantly higher among vaginal deliveries (including operative vaginal deliveries) than among Cesarean deliveries. This highlights a key area for improvement in implementation. Efforts should be made to ensure that the policies and environment of an operating room are supportive of, and conducive to, DCC. Lastly, although "excessive maternal bleeding" was one of the most commonly cited reasons for ICC, there was no significant increase in estimated blood loss when DCC was performed.

A unique strength of this study was the ability to evaluate outcomes among neonates who received DCC despite meeting DCC exclusion criteria per our protocol. In this cohort, there was no evidence of polycythemia or hyperbilirubinemia, suggesting that the practice of DCC may be safely expanded, and that revision of existing exclusion criteria may be warranted.

An important limitation of this study was frequent poor documentation regarding reasons for excluding eligible neonates from DCC. Providers frequently omitted this information from delivery notes; however, this was often found elsewhere in provider documentation. Further implementation efforts should highlight the importance of explicit documentation in this area.

In summary, our study shows that DCC was performed in approximately one-third of deliveries occurring between 24 and 37 weeks' gestation following implementation of a DCC protocol with extensive exclusion criteria. Our cohort of neonates who received DCC despite meeting exclusion criteria was small; however, we did demonstrate an increase in hematocrit (though not reaching statistical significance) without an increase in polycythemia, hyperbilirubinemia, or phototherapy requirement. This data supports the safety of DCC in a wide cohort of premature neonates, argues for minimizing exclusion criteria among institutional DCC protocols, and highlights key areas for improvement in DCC implementation, including premature infants as well as those born by Cesarean delivery (Appendix A).

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Declaration of Interest

The authors report no conflict of interest.

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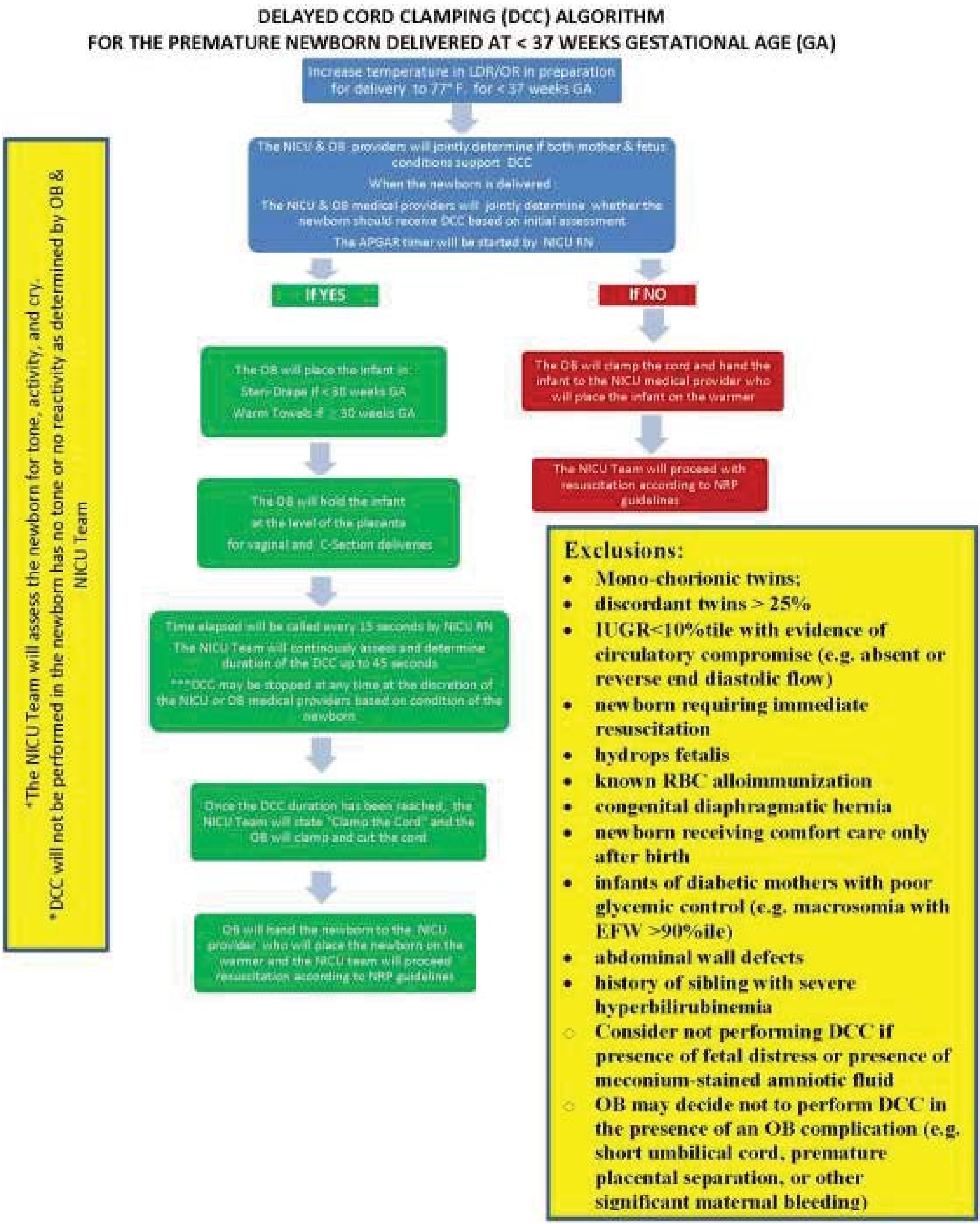

Appendix A. Delayed Cord Clamping Protocol