Milking versus Deferred Cord Clamping in Preterm delivery:
A Randomized Controlled Trial

Thesis

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List of Abbreviations

Abbr.	Title
AAP	: American Academy of Pediatrics
ACOG	: American College of Obstetricians and Gynecologists
BMI	: Body Mass Index
BMI	: Body mass index
CCT	: Controlled cord traction
CI	: Confidence interval
DCC	: Deferred cord clamping
DM	: Diabetes mellitus
Hb	: Haemoglobin
HS	: Highly significant
ICC	: Immediate cord clamping
ICM	: Inner Cell mass
ICU	: Intensive care unit
IVH	: Intra-ventricular haemorrhage
NEC	: Necrotizing enterocolitis
NS	: Non significant
PPH	: Post-partum haemorrhage
RBC	: Red blood cell
RBC	: Red blood cell
RCOG	: Royal college of obstetrics and gynecology
RR	: Relative risk
RR	: Relative risk
SD	: Standard deviation
SVC	: Superior vena cava
TE	: Trophoectoderm
UCM	: Umbilical cord milking
UK	: United kingdom
USA	: United stated of America
VD	: Vaginal delivery
WHO	: World health organization

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Introduction

Anemia of newborns is a common problem seen in most neonates. The placenta is a reservoir of fetal blood, which could be useful to the neonate. Effective placental transfusion depends on multiple factors including the timing of cord clamping, position of the infant relative to the placenta, the infant's respiratory effort and uterine contraction ***(Song et al., 2015).***

Clamping is followed by cutting of the cord, which is painless due to the lack of any nerves. The cord is extremely tough, and so cutting it requires a suitably sharp instrument. Negative effects of delayed cord clamping include an increased risk of polycythemia. Still, this condition appeared to be benign in studies ***(Hutton and Hassan, 2007).***

When clamping is delayed for more than one minute it is known as "deferred cord clamping" ***(Royal College of Obstetricians and Gynecologists, 2015).***

Deferred cord clamping (DCC) in premature neonates improves neonatal morbidity; however the impact on long-term outcomes remains limited ***(Brocato et al., 2016).***

The timing of the clamping of the cord has been the subject of much debate ***(Mercer et al., 2006).*** Measurements of increasing infant weight have provided additional evidence supporting the concept of placental to

infant blood transfusion (**Hooper *et al.*, 2016).** Each milliliter of blood weighs 1.05 gram (**Farrar *et al.*, 2011).**

Delayed cord clamping (DCC) has been associated with increased placenta-to-neonate transfusion, leading to an increase in neonatal blood volume at birth. This increases iron stores and hemoglobin concentration, decreasing in the risk of anemia, intraventricular hemorrhage and late onset sepsis ***(Mathew, 2011).***

DCC decreases postnatal exchange transfusion needs, with an improvement in the hemoglobin level at birth and longer delay between birth and first transfusion with no severe hyperbilirubinemia ***(Garabedian et al., 2016)***.

It also allows time for a transfer of the fetal blood in the placenta to the infant at the time of birth. This placental transfusion can provide the infant with an additional 30% more blood volume and up to 60% more red blood cells ***(Airey et al., 2010)***.

The American College of Obstetricians and Gynecologists recommended a 30- to 60-seconds deferred cord clamping for all preterm deliveries ***(American College of Obstetricians and Gynecologists Committee on Obstetric Practice, 2012).***

Umbilical cord milking (UCM), in which the unclamped umbilical cord is milked before it is clamped, may influence Superior Vena Cava flow by improving perfusion immediately after birth. During the first 30 seconds after delivery, blood volume in the newborn increases by 12 mL/kg this early

placental transfusion does not occur if the cord is clamped immediately ***(Aladangady et al., 2006).***

When UCM is done usually the umbilical cord is cut and clamped at the placental end, 25 cm from the umbilical stump. The umbilical cord is raised and milked from the cut end towards the infant three times at 10 cm over 1 second or 20 cm over 2 seconds and then clamped 2–3 cm from the umbilical stump to provide maximum benefit to the neonate ***(Shivam et al.,2016)***

Katheria et al., demonstrate greater systemic blood flow with umbilical cord milking in preterm neonates compared with immediate cord clamping (ICC) ***(Katheria et al., 2014).***

Currently, insufficient evidence exists to support or refute the benefits from DCC for term infants. Although a delay in umbilical cord clamping for up to 60 seconds may increase total body iron stores and blood volume, which may be particularly beneficial in populations in which iron deficiency is prevalent, these potential benefits must be weighed against the increased risk for neonatal phototherapy ***(American Academy of Pediatrics, 2013).*** Within few hours, the additional plasma from the placental transfusion is lost to the circulation, leaving a high red cell mass. This is quickly broken down and the iron stores increase. Immediate cord clamping reduces placental transfusion and potentially deprives the term baby of 20–30 mg/kg of iron, sufficient for the needs of a newborn baby for around 3 months (**Duley *et al.*, 2015).**

Aim of the work

To evaluate deferred cord clamping as compared to umbilical cord milking in enhancement of placenta-fetal blood transfusion among full term vaginally delivered new born.

The Human Umbilical Cord

Embryology of the Human Umbilical Cord (funiculus umbilicalis)

The fertilization and the first 4 days of cleavage up to the early blastocyst stage takes place in the Fallopian tubes in the human. On day 5, the early blastocyst descends down into the uterus, continues its divisions, undergoes expansion to the fully expanded blastocyst stage and then implants in the uterine endometrium around day 7 to 9. The migration of cells within the expanded blastocyst results in the laying down of two distinct cell layers, a peripheral layer of trophectoderm destined to become the placenta and a cluster of approximately 30-50 cells inner cell mass (ICM) that protrude from the inner wall of the polar trophectoderm (TE)and destined to form the entire fetus ***(Pappa and Anagnou, 2009).***

The ICM later develops into the hypoblast and epiblast. The hypoblast gives rise to the yolk sac and allantois which eventually degenerates and the epiblast cells which are pluripotent give rise to the three germ layers (ectoderm, mesoderm and endo-derm) from which the various organs and extra-embryonic membranes (amnion, chorion, placenta and UC) are formed. During further development the amnion forms an outer covering for the UC and the UC carries within it three

umbilical blood vessels (two arteries and a vein) to shuttle nutrients between mother and fetus. The amnion comprises of three layers: inner epithelial cell layer, an intermediate non-cellular basement membrane and outer mesenchymal layer ***(Pappa and Anagnou, 2009).***

The TE forms the cytotrophoblast and syncytiotrophoblast of the placenta while the blastocoelic cavity eventually produces the exocoelom. The part of the UC closest to the fetus may therefore contain remnants of the yolk sac and allantois **(*Haneline et al., 1996*)**

The umbilical cord function, composition and development:

The exterior surface of the cord is dull white in colour and moist, and normally comprises two umbilical arteries and one umbilical vein which are continuous with the blood vessels in the chorionic villi of the placenta. These vessels are encased in a protective, gelatinous substance known as Wharton's jelly (a form of connective tissue), which is covered by amnion ***(Raymond and Redline, 2015).***

The umbilical cord is attached to the placenta which transfers oxygen, nutrients and waste products, such as carbon dioxide to and from the maternal blood circulatory system without any direct contact between fetal and maternal blood. The blood vessels in the umbilical cord operate

differently from what would normally be expected, with the umbilical vein providing the fetus with a supply of oxygenated blood and nutrients (which it carries to the fetal heart), and the umbilical arteries carrying away the deoxygenated and nutrient-depleted blood. The only other example of this within human physiology occurs with the pulmonary veins and arteries which connect the lungs to the heart ***(Kluckow and Hooper, 2015).***

It is around 50-60 cm in length, with a diameter of approximately 1-2 centimeters in the full-term healthy neonate although this diameter reduces significantly once the cord inserts itself into the fetal surface of the placenta). The cord has a spiral twist, (twisting or coiling of UC vessels is either sinistral (left) or dextral (right) or random, with the left twisting more common than right). The length of the umbilical cord enables the baby to pass down the birth canal and deliver vaginally without any traction being applied to the placenta. Where the umbilical cord is of an above average length, although not of clinical significance, there is an increased risk that it could become wrapped around the fetal body/neck, prolapse, or become knotted (known as a true knot). A 'true knot' results from active fetal movements, where the fetus moves through a loop of its cord, so that it literally forms a knot, which can be clearly seen on examination of the cord at birth. The obstetric concern where

the cord becomes knotted or is compressed, relates to the potential for the blood vessels to become blocked and deprive the fetus of sufficient oxygen in utero, especially during labour and birth ***(Vance, 2009).***

By contrast, a 'false knot' is caused by varicosities of the umbilical vessels and/or insignificant lumps of Wharton's jelly that cause additional twists and protrusions on the surface of the cord. The false knots of the umbilical cord are more common than true knots. False knot occurs due to increased length of the umbilical vein in comparison to arteries, and has no known clinical significance ***(Elghazaly et al., 2016).***

True knot can be associated with fetal growth restriction, congenital malformations, early separation of the placenta from the uterine wall, fetal distress and in the worst case, fetal death ***(Raymond and Redline, 2015).***

The umbilical cord and fetal circulation

The umbilical cord enters the developing fetus through the lower abdominal wall, at the level which, following cord separation, becomes the umbilicus or navel. Once inside the fetus, the umbilical vein continues towards the transverse fissure on the visceral surface of the liver (i.e. where the portal vein and hepatic artery enter and the hepatic ducts leave). At this point it separates into two branches; the first joins with the hepatic portal vein, connecting to its left

branch. The other, which is known as the ductus venosus, allows the majority of the incoming blood (around 80% of blood volume) to bypass the liver and flow via the left hepatic vein into the inferior vena cava, which carries blood towards the fetal heart. The two umbilical arteries branch from the internal iliac arteries, passing on each side of the urinary bladder of the fetus before joining the umbilical cord ***(Abraham and Rudolph, 2009).***

Umbilical cord insertion

In the majority of cases the umbilical cord is inserted at, or close to, the center of the fetal surface of the placenta. However, abnormalities in the development and site of insertion of the umbilical cord can cause problems which have the potential to affect maternal and fetal health and well-being ***(Vance, 2009).***

Battledore insertion- this is where the cord is attached at the edge of the placenta and can separate during delivery of the placenta and membranes by controlled cord traction (CCT). Velamentous insertion - in around 1% of cases, the cord originates in membranes that are distanced from the placental margin, so the cord vessels run through the membranes to reach the placenta. There is a danger that spontaneous rupture of the membranes can be accompanied by tearing of a cord vessel which will lead to severe hemorrhage and fetal exsanguination ***(Pathak et al., 2010).***

Susceptibility of the umbilical cord

The umbilical cord fulfils a vital role in pregnancy but because of its inherent characteristics is susceptible to entanglement, prolapse, compression and occlusion. While some events tend to be of less concern, others can have serious implications for both short and longer-term perinatal outcome ***(Ferguson and Dodson, 2009)***.

- Nuchal cord-occurs in around 20-30% of births .this is where the cord is wrapped 360o around the baby's neck. A tight nuchal cord is associated with some short term fetal morbidity ***(Reed et al., 2009).***
- Umbilical cord 'true' knot, results from active fetal movements, where the fetus moves through a loop of its cord, so that it literally forms a knot, which can be clearly seen on examination of the cord at birth. The obstetric concern where the cord becomes knotted or is compressed, relates to the potential for the blood vessels to become blocked and deprive the fetus of sufficient oxygen in utero, especially during labor and birth***(Cunningham et al.,2005)***
- Umbilical cord prolapse - this refers to the descent of the umbilical cord, following rupture of the membranes, through the cervix so that it lies either alongside the fetal presenting part or descends beyond it. Where the forewaters are still intact, this is defined as a 'cord presentation***(Vance, 2009).***