Milking versus Delayed Cord Clamping in Preterm Delivery:
A Randomized Controlled Trial

A Thesis
Submitted for the partial fulfillment of MSc. Degree
in Obstetrics & Gynecology

By

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Introduction

In developing countries, up to 50% of children become anemic by 12 months of age. Risk factors for iron deficiency anemia include low birth weight, maternal iron deficiency during pregnancy, and male sex ***(Domellof et al., 2002)*** Iron deficiency anemia during infancy and childhood is of particular concern because of potentially detrimental effects on development, some of which might be irreversible even after iron treatment ***(Grantham and Ani, 2001).*** Prevention of iron deficiency anemia during infancy is therefore a priority.

Anemia of prematurity, a common problem seen in almost all preterm neonates younger than 34 weeks of gestation, often requires transfusion of donor red blood cells. The placenta is a reservoir of fetal blood, which could be equally useful to the neonate. Consequently, the timing of the clamping of the cord has been the subject of much debate. Recent reviews ***(Rabe et al., 2008)*** of the data from 10 randomized trials involving a total of 454 preterm neonates found that a delay of cord clamping time of at least 30 seconds stabilizes the circulatory system of neonates during the first day of life, leading to less requirement for volume therapy, transfusion, and inotropic support, reduced the need for donor red cell transfusions, decreased the incidence of intraventricular hemorrhage.

Preterm infants are often anemic and typically experience heavy blood losses from frequent laboratory testing in the first few weeks of life. Although their anemia is multifactorial, repeated blood sampling and reduced erythropoiesis with extremely low serum levels of erythropoietin (EPO) are major determining factors ***(Adams et al., 2005).*** Blood sampling done for laboratory testing can easily remove enough blood to produce anemia. During the first weeks of life, all infants experience a decline in circulating red blood cell (RBC) volume generally expressed as blood hemoglobin concentration (Hb) ***(Strauss, 2007).*** As anemia develops, there is even more of a significant reduction in the concentration of hemoglobin ***(Boxwell, 2000).*** Normally this stimulates a significant increased production of erythropoietin (EPO), but this response is diminished in premature infants.

General hospital-based obstetric practice introduces artificial clamping as early as 1 minute after the birth of the child. In birthing centers, this may be delayed by 5 minutes or more, or omitted entirely. 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).***

Aim of the Work

To compare Milking versus Delayed Cord Clamping to enhance placento-fetal blood transfusion in preterm neonates.

Patients and Methods

Setting:

The study will be carried out in the casualties of Ain-Shams University Maternity Hospital.

Study group:

Recruiting 60 women at risk of preterm deliveries All will deliver before 37 completed weeks of gestation they Will be randomized to either delayed cord clamping for 30 seconds after delivery or repeated (four times) milking of the cord toward the neonate either vaginal delivery or cesarean section

Study design:

Randomized controlled trial Randomization of the two groups based on computer-created tables, The randomization allocation cards will be kept on the labor ward in sealed opaque envelopes and will be consecutively numbered.

Statistical analysis:

Descriptive statistics for measured variables will be expressed as range, mean and standard deviation (for metric data); range, median and interquartile range(for discrete data);and number and proportions(for categorical data). Demographic data and outcomes of all women will be

compared using t-test (for quantitative parametric measures), Mann-Whitney's U-test (for quantitative non-parametric measures) and chi-squared (for metric variables) will be used to estimate association between variables. Microsoft Excel (version 2007)and SPSS for Windows version 15.0 will be used for data presentation and statistical analysis. P<0.05 considered as significant change, P>0.05 considered as non significant change.

Sample size estimation:

Estimation of standard deviation of mean hematocrit value= 0.07 (from previous study ***(Rabe et al., 2011).***

- Sig. level 5%
- Power: 80%
- Difference to be detected 0.04
- The smallest interest: standardized difference from paper (=0.57)

Required sample size: =16/ (standardized difference 0.57)^2 =49

As we need two groups the figure will be rounded to **60** the smallest not less than **18**)

Data are expressed as mean ± SD (range) or as number (%) of cases. Comparison of proportions and means between both groups was made by using the $\chi 2$ test and independent t-test, respectively. Non parametric data will be analyzed using

Mann-Whitney test (data presented as median and IQR. The Fisher's exact test was used when applicable. Analysis was performed by using the Statistical Package for the Social Sciences (SPSS, version15)

Population:

Includes **60 patients** women were randomized to either:

Group A - delayed cord clamping for 30 seconds for women at risk of preterm deliveries delivered before 37 completed weeks of gestation.

Group B - Repeated (four times) milking of the cord toward the neonate for women at risk of preterm deliveries; delivered before 37 completed weeks of gestation.

Inclusion criteria for both groups:

Women at risk of preterm deliveries will be recruited. All will deliver before 37 completed weeks of gestation either vaginal delivery or cesarean section.

Exclusion criteria for both groups:

1. Inadequate time to obtain consent before delivery.
2. Known congenital abnormalities of the fetus.
3. Rhesus sensitization.
4. Fetal hydrops.

5. Severe preclamptic patients.
6. Multiple pregnancies

Methods:

Before delivery, the fetuses will be randomized into two groups. Those randomized to the delayed clamping group will be positioned 20 cm below the level of the placenta, between their mother's thighs (vaginal delivery, with active management of third stage of labor) or to the mother's side (cesarean delivery). The umbilical cord then will be clamped at 30 seconds. In the milking group, the neonates will be positioned 20 cm below the level of the placenta, between the mother's thighs (vaginal delivery) or to the mother's side (cesarean delivery), with the cord being milked toward the neonate four times. This involving holding the cord at the introitus or cesarean delivery wound with one hand and milking the umbilical cord for its remaining accessible whole length toward the neonate four times. The cord will be clamped after the fourth milking.

Complete prelabour maternal assessment includes:

- **History**
- **Examination**
- **Investigation**

Then each patient in the study will be tested for the following endpoints:

1-Maternal:

- Hospital stay
- Urinary retention
- Any postoperative complications including:
- 1ry hemorrhage
- 2ry hemorrhage
- Need for blood transfusion.
- Puerperal pyrexia.

2-Neonatal:

- Birth weight
- Sex
- Gestational age
- Apgar score (1 min,5 mins)
- Intubation
- Maximum serum bilirubin (mmol/l)
- Initial [hematocrit (%), hemoglobin (g/dl)]
- Neonatal complications and ICU admission

Ethical and Legal Aspects:

Delegation of investigator responsibilities:

The investigator will ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, their trial-related duties and functions. The investigator will maintain a list of sub-investigators and other appropriately qualified person to whom he or she has delegated significant trial-related duties.

Patient information and informed consent:

Before being admitted to the clinical study, the patient must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to her. An informed consent document, in Arabic language, contains all locally required elements and specifies who informed the patient [form 1]. After reading the informed consent document, the patient must give consent in writing. The patient's consent must be confirmed at the time of consent by the personally dated signature of the patient and by the personally dated signature of the person conducting the informed consent discussions. If the patient is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to patients must take place in the presence of an impartial witness [form 2]. Consent must be confirmed at the time of consent orally and by the personally dated signature of the

patient or by a local legally recognized alternative *(*e.g., the patient's thumbprint or mark*)*. The witness and the person conducting the informed consent discussions must also sign and personally date the consent document. The original signed consent document will be retained by the investigator. The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

Confidentiality:

Only the patient number and patient initials will be recorded in the CRF, and if the patients name appears on any other document *(e.g.*, pathologist report*)*, it must be kept in privacy by the investigators. The investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

Protocol approval:

Before the beginning of the study and in accordance with the local regulation followed, the protocol and all corresponding documents will be declared for ethical and research approval by the council of ob/gyn department, Ain Shams University.

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العصر مقابل الربط المتأخر للحبل السرى فى حالات الولادة المبتسرة (المبكرة)
(دراسة عشوائية معتمدة على مجموعة ضابطة)

خطة رسالة

توطئة للحصول على درجة الماجستير فى أمراض النساء والتوليد

مقدمة من

الطبيب/ إســـــلام حسن إبراهيم محمد ســـــالم

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كلية الطب – جامعة عين شمس، ٢٠٠٨
طبيب مقيم بقسم النساء والتوليد
مستشفى النساء والتوليد بجامعة عين شمس

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